Studies on the Evidence Base in Support of Digoxin Therapeutic Drug Monitoring

Sepehr Shakib
MBBS (Hons), FRACP

Department of Clinical and Experimental Pharmacology
University of Adelaide

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Abstract

Despite being available for over 3 decades, there is a dearth of high level evidence for the benefit of digoxin therapeutic drug monitoring (TDM) on clinical endpoints. A pilot randomised controlled trial of digoxin TDM was conducted in hospital inpatients. Clinical endpoints were difficult to collect without considerable additional resources. The main barrier to performing a full-scale randomised trial of digoxin TDM would be the required sample size, which would be over 1,500 patients for a hard endpoint such as incidence of toxicity.

The benefit of the knowledge of the serum digoxin concentration (SDC) in determining the likelihood of digoxin toxicity was assessed by presenting blinded clinicians clinical and SDC data using a computerised interface. The main benefit of the knowledge of the SDC was to reduce the percentage of patients classified as "possibly toxic", and to increase the agreement between clinicians. Those who were assessed as being more likely to be toxic after the knowledge of the SDC were also more likely to have symptoms of digoxin toxicity.

The impact of determining the SDC on all patients prescribed digoxin admitted to medical units of a tertiary referral hospital was assessed. Approximately one fifth of all patients had their management altered as a result of the knowledge of the SDC. In patients, in whom there was no indication for a digoxin assay, and the intended management was to "continue the same", approximately one tenth had a change in their management as a result of the knowledge of the SDC. It is possible to predict, on clinical grounds, patients who are more likely to have such an alteration, and in whom the test has greater clinical utility.

A systematic survey of symptoms and electrocardiographic changes associated with digoxin toxicity was conducted in hospital inpatients. The only symptoms found to be significantly associated with higher SDCs were anorexia, nausea, vomiting, fatigue, and subjective changes in colour vision. Although some colour vision tests can also identify patients with high SDCs, the only symptoms which are clinically useful for the assessment of toxicity, in current clinical practice, are assessment of digoxin's emetic effects. The predominant effect of increasing SDCs on the electrocardiogram was increasing prevalence and severity of bradycardic rhythms, without an increase in automaticity.

An increase in the prevalence of cardiac and non-cardiac manifestations of digoxin toxicity became clear at approximately 1.0 ng/ml which is at the lower end of the currently quoted therapeutic range. In light of these findings the current therapeutic range for digoxin should be revised.

Declaration

I hereby declare that this is my own work and contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. Any contribution made to the research by others is explicitly acknowledged in the thesis.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Sepehr Shakib

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Dedication

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Without you, I may have finished this thesis, but like all other things, the journey would not have been worthwhile.

Chapter 1

INTRODUCTION

1.1 Overview of Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) or applied pharmacokinetics is the strategy by which the dosing regimen for a patient is guided by repeated measurements of plasma drug concentration (Spector, Park et al. 1988). If the plasma drug concentration is not within a previously determined "target concentration range" the dose is adjusted (based on a mathematical model) to bring the patient's plasma drug concentration within the target concentration range. In this way the dose is individualized according to the patient's own pharmacokinetic parameters (absorption, distribution, elimination) in order to achieve a target drug concentration in plasma. This target concentration is derived from studies of other patients, identifying concentration ranges that produce efficacy and but not toxicity in the majority of patients.

Therapeutic drug monitoring arose as a practice at a time when there was concern about drug dosing and the need to individualize therapy. In the 1960s, there was concern that drug therapy was very much a case of trial and error (Schumacher 1995). Koch-Weser et al (Koch-Weser, Sidel et al. 1969) revealed that more than half of the adverse reactions in a major teaching hospital resulted from standard dosages that were too high for the patient. He later wrote "Perhaps no other concept has been as detrimental to

good pharmacotherapeutics as that of the 'usual' or 'average' dose". (Koch-Weser 1981), a criticism which is still being reiterated today (Begg 2004). Koch-Weser argued that when given in an unvarying dosage schedule, most important drugs are ineffective in many patients and cause serious toxic effects in others. When the usual dose is too low for a given patient, the drug may be falsely considered ineffective for that patient. When too high, the patient may be mistakenly considered intolerant to the drug. This view was supported by others who argued that the effectiveness and safety of almost all potent drugs can be increased by individualization of their dosage (Reidenberg 1974), and that the time had come "when each patient might need an individualised dosage regimen" (Brodie 1967). A typical example of the lack of dosage individualisation was the use of phenytoin which was prescribed in a dose of 300mg daily in virtually all patients, despite the fact that there was lack of efficacy in some patients, and toxicity in others (Kutt and McDowell 1968).

There are many sources of variability in dosage requirements resulting in this need for individualization. Once a dose is prescribed, there may be compliance issues resulting in variability in the amount of medication taken. Once administered, then a number of pharmacokinetic factors such as absorption from the site of administration, distribution, and elimination can influence the concentration of the drug in serum. This concentration is in equilibrium with the concentration of the drug at the site of action, which then interacts with the receptor to produce the desired or toxic effect.

Although there is great heterogeneity in the pharmacokinetic factors resulting in the serum concentration (dose-concentration relationship), there is less variability in the factors contributing to the concentration-effect relationship. Hence, it was argued that drug effects should be related to the plasma level rather than the dosage (Brodie 1967). It was thought that for some types of drugs, the serum concentration would be a better index to guiding treatment than dose (Schumacher 1995), because serum levels were expected to be a better indicator of drug concentration at receptor sites, and therefore more predictive of patient response.

1.1.1 Principles of Appropriateness of TDM

TDM is not necessarily appropriate for all drugs, however. In order for a drug to qualify for TDM it must have as a minimum the following characteristics (Spector, Park et al. 1988; Schumacher 1995):

1. *An appropriate assay is available*. This should be accurate, precise and specific, and ideally require a small sample volume, yield results quickly and be relatively inexpensive.

2. *There is significant inter-individual variability in drug absorption, elimination and distribution and adequate pharmacokinetic data concerning the drug are available*

3. *The pharmacological effect is proportional to the plasma drug concentration.*

4. *A constant effect over an extended period of time exists between plasma drug concentration and effect in an individual.* The implications of this criterion are twofold: firstly, TDM is not useful for acute, short or

intermittent drug effects. Secondly, the relationship between plasma concentrations, concentration at the receptor site and effect needs to be stable such that there is little intra-patient variability in the concentration-effect relationship.

5. *There is a stronger concentration-response than a dose-response relationship.* If this were not the case, then the drug could simply be dosed on clinical grounds alone. This criterion also applies to situations where the dose-response relationship may be difficult to assess e.g. use of anti-epileptic or anti-arrhythmic medication in the prophylactic setting, where one does not want for an event to occur to realise that the dose was inappropriately low.

6. *The drug has a narrow therapeutic index.* If a drug has a broad therapeutic index, yet fulfils all of the criteria above, TDM would not be necessary, as despite concerns of inter-individual variability in pharmacokinetics, the drug could be given in a sufficiently high dosage as to ensure efficacy in all patients, without the risk of toxicity.

7. *Toxicity or lack of effectiveness puts the patient at risk.* Most of the drugs for which TDM has been developed are indicated for serious conditions e.g. epilepsy, immunosuppression, cardiac arrhythmias, and septicaemia, and often have quite significant toxicities. Hence, given their narrow therapeutic indices as well, it is very important to ensure that the dosing regimen achieves adequate efficacy whilst minimising the risk of toxicity.

8. *Clinical studies exist that define the therapeutic and toxic ranges of the drug.*

1.1.2 History of Development of TDM

Research in the 1950s showed that serum levels could be used to determine individual patient differences in pharmacokinetics, and could also guide responses to treatment (Schumacher 1995). Sokolow and Edgar assayed the serum of patients prescribed quinidine for atrial fibrillation and found that reversion occurred at a range of peak concentrations, but that the majority of patients who reverted had a peak concentration between 4 and 9 mg/L (Sokolow and Edgar 1950). The reversion rate was poor at higher concentrations. Hence he argued against strategies with higher doses aiming for higher concentrations. Buchtal et al (Buchtal, Svensmark et al. 1960) investigated the concentration effect relationship of phenytoin in newly diagnosed epileptics, as well as inpatients with severe grand mal epilepsy and outpatients with other forms of epilepsy. They compared phenytoin concentrations to control of epilepsy as well as looking for the signs of toxicity and activity on an electroencephalogram. In the newly diagnosed epileptics, they found that although patients were receiving a range of doses (200-700 mg or 3.1-13.7 mg/kg per day), clinical improvement was not seen with serum concentrations below 10 mg/L. A similar finding was seen in the outpatient group with greater clinical improvement in those with concentrations greater than 10 mg/L than those below. This finding was supported by the improvement in electroencephalographic activity seen in those with concentrations greater than 10 mg/L. None of the patients with a concentration less than 14 mg/L had any adverse effects, but pronounced side effects began to occur at serum levels exceeding 30 mg/L. For this reason 20 mg/L was chosen as the upper limit of the therapeutic range for

phenytoin, and this range (10-20mg/L) has remained as the standard for phenytoin since. Similar studies were conducted with the antibiotic vancomycin (Geraci, Heilman et al. 1957) as well as with lithium (Talbott 1950).

By the end of the 1960s initial work on determining pharmacokinetic parameters and therapeutic serum concentration ranges for some cardiac drugs, antiepileptics, bronchodilators, and antibiotics was being published (Beller, Smith et al. 1971; Koch-Weser and Klein 1971; Jenne, Wyze et al. 1972; Lund 1973; Noone, Parsons et al. 1974). The 1970s and 80s were a period of extensive investigation and application of therapeutic drug monitoring, particularly with the emergence of organ transplantation and the need for careful immunosuppression, as well as the development of new technologies allowing more automated and rapid drug assays.

The practice of TDM has grown and the test volume has increased 500-fold over the last 25 years (Barr and Schumacher 1995). Determination of serum drug concentrations is listed as part of the usage guidelines in the product information of many of the drugs for which assays exist including theophylline, digoxin, phenytoin, carbamazepine, gentamicin and cyclosporine. In fact, many clinicians consider therapeutic drug monitoring an essential component of therapeutic practice and would consider omission of its routine use for certain drugs as unethical or even negligent (McCormack and Jewesson 1992; Tonkin and Bochner 1994).

1.1.3 Impact of TDM on Clinical Practice

Concurrent with the growth of TDM has been the emergence of concerns about the lack of studies evaluating the impact of TDM on patient centred outcomes (Hvidberg 1980; Vozeh 1987; Spector, Park et al. 1988). In a review of the literature, Barr and Schumacher (Barr and Schumacher 1995) were able to find only approximately 250 studies, conducted between 1974 to 1994, which assessed any clinical outcomes. Of these, almost 75% reported system-related measures for assessing the value of TDM. These included measures such as whether the assay was clinically indicated, whether the timing was appropriate, whether the result was appropriately interpreted and acted upon, the percentage of appropriate TDM tests per patient, and the number of TDM results within the therapeutic range. A minority assessed patient-centred outcomes such as the incidence of toxic effects, impact on symptoms, quality of life, or mortality.

Of the studies which assessed patient centred outcomes the majority compared therapeutic drug monitoring in conjunction with a clinical pharmacokinetic service compared to therapeutic drug monitoring alone. Only four studies compared the conduct of any therapeutic drug monitoring with no TDM (Duhme, Greenblatt et al. 1974; Koch-Weser, Duhme et al. 1974; Arroyo, Milligan et al. 1986; Eisenberg, Koffer et al. 1987), and none of these were randomised trials. This dearth of literature has led some to conclude that "there is little direct evidence that titrating drug doses to target plasma concentration ranges improves therapeutic outcome" (Tonkin and Bochner 1994), and that the application of the theory of plasma drug level monitoring and clinical pharmacokinetics improving patient care is a

"hypothesis in need of testing" (McInnes 1989). For this reason I was interested in conducting studies in order to test the hypothesis that TDM improves patient-centred outcomes.

1.2 Principles of Evidence Based Medicine

Evidence based medicine is defined as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett, Rosenberg et al. 1996). It arose initially as an approach to continuing medical education in Clinical Epidemiology, and the name Evidence Based Medicine or EBM was coined in 1992 (Evidence-Based Medicine Working Group 1992). There are many who criticise EBM for placing too much emphasis on large randomised "mega-trials" (Charlton and Miles 1998) and ignoring other rich sources of evidence (Smith 1996) such as clinical skill, anecdotes and qualitative research. Other criticisms include concerns regarding the inability of EBM to answer many clinical questions due to the lack of appropriate "evidence" (Dearlove, Sharples et al. 1995), the emphasis on large databases and an implicit belief in the primary role of information and statistics (Charlton and Miles 1998), that it represents a danger to scientific progress (Wu 2005), that EBM is being used to take over the clinical consultation by managers who are now empowered to define "best practice" (Charlton and Miles 1998), and most commonly that it represents "cookbook" medicine (Sackett, Rosenberg et al. 1996). Much of this criticism ignores the fact that the practice of EBM means "integrating individual clinical expertise with the best available external clinical evidence" (Sackett, Rosenberg et al. 1996). Despite this ongoing debate, the evidence

based approach has been increasingly taken up by clinicians, medical educators, and journals, as well as policy makers, governments, third-party payers, and most importantly, consumers.

1.2.1 Levels of Evidence

One of the key elements of EBM is the concept that there is a hierarchy of evidence and that the best available, i.e. highest level, of evidence should be used in clinical decision making. Table 1.1A and 1.1B list the hierarchies of evidence as described by the Oxford Centre for Evidence Based Medicine for therapy and diagnosis, respectively (Centre for Evidence-Based Medicine 2005)

Although different classification schemes are used by different institutions (Appendix A), there is a consistent approach in placing greater importance on randomised trials and systematic reviews with lesser degrees of bias, than on observational data and expert opinion.

TABLE 1.1A CENTRE FOR EVIDENCE-BASED MEDICINE LEVELS OF EVIDENCE FOR THERAPEUTIC STUDIES

1. **a.** Systematic review with homogeneity of randomised controlled trials
   b. Individual randomised controlled trial
   c. All or none criterion: (Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it)
2. **a.** Systematic review with homogeneity of cohort studies
   b. Individual cohort study or low quality randomised controlled trial e.g. less than 80% follow up

c. Outcomes research, ecological studies

3. **a.** Systematic review with homogeneity of case-control studies

b. Individual case-control study

4. Case series and poor quality cohort and case-control studies

5. Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

TABLE 1.1B CENTRE FOR EVIDENCE-BASED MEDICINE LEVELS OF EVIDENCE FOR DIAGNOSTIC STUDIES

1. **a.** Systematic review (with homogeneity) of Level 1 diagnostic studies;

b. Validating cohort study with good reference standards

2. **a.** Systematic review with homogeneity of Level >2 diagnostic studies

b. Exploratory cohort study with good reference standards

3. **a.** Systematic review with homogeneity of 3b and better studies

b. Non-consecutive study or without consistently applied reference standards

4. Case-control study, poor or non-independent reference standard

5. Expert opinion without explicit critical appraisal or based on physiology, bench research or "first principles"

1.3 Application of EBM Principles to TDM

A review of the TDM literature reveals that the vast majority of clinical studies which have been performed are of a low level of evidence according to all of the EBM classification schemes, and that they are dominated by descriptive observational studies. Unfortunately, all observational studies have built-in biases (Grimes and Schulz 2002), and bias in research undermines its internal validity and "denotes a deviation from the truth" (Grimes and Schulz 2002). TDM studies frequently suffer from not having an adequate control group, and are more akin to case series than true cohort studies. In fact, case-control studies are very rare (Gill, Cheetham et al. 1986; Weiner, Burman et al. 2003), and matching with a control is more often conducted for assessing pharmacokinetics and financial rather than clinical outcomes (Eisenberg, Koffer et al. 1987; Battino, Croci et al. 2003; Battino, Croci et al. 2005; Messina, Battino et al. 2005).

In a typical study, a group of patients with a particular disorder and prescribed a specific medication have their plasma drug concentrations assayed and have their outcome assessed. The dosing regimen may or may not be altered to achieve a previously determined therapeutic range. It is then found that patients who achieve a particular concentration range are more likely to have improved outcomes compared to the remainder who do not, and it is then recommended that therapeutic drug monitoring should be performed for patients prescribed this medication in this setting. Such typical TDM observational studies underlie the use of current assays (Buchtal, Svensmark et al. 1960; Smith, Butler et al. 1969; Schneider 1975; Kahan, Wideman et al. 1984; Moore, Smith et al. 1984) and have been used to

support TDM for a number of other drugs including antivirals (Rendon, Nun~ez et al. 2005), antineoplastics (Rubie, Doz et al. 2003 ; Kisanga, Gjerde et al. 2004), antidepressants (Lundmark, Reis et al. 2000), antipsychotics (Perry, Sanger et al. 1997; Odou, Levron et al. 2000; Ulrich, Baumann et al. 2003; Riedel, Schwarz et al. 2005), immunosuppressants (Llinares-Tello, Hernandez-Prats et al. 2004), anxiolytics (Greenblatt, Harmatz et al. 1993) and others.

In some cases a circular argument is created where drug concentrations are interpreted in light of pre-existing therapeutic concentration ranges, and it is then concluded that therapeutic drug monitoring was useful because of the changes in the dosing regimen which occurred as a result of the conduct of the assay (El Desoky, Kandil et al. 1999; Duong, Golzi et al. 2004; Rendon, Nun~ez et al. 2005). A recent example is a trial of a new immunosuppressant everolimus which was dosed at starting doses of 0.75 or 1.5 mg twice daily, but the doses were then individualized based on trough concentrations aiming to maintain the trough concentration above 3 ng/mL (Kovarik, Tedesco et al. 2004). As the study demonstrated good outcomes with respect to rejection and toxicity, the authors concluded that "maintaining everolimus troughs in the range 3 to 8 ng/mL in the first post-transplant year with reduced-exposure cyclosporine is associated with good efficacy and safety profiles". It could equally be argued that the study was not really designed to draw any other conclusions.

The difficulty with these observational studies is twofold. Firstly, they do not acknowledge the existence of the inherent biases within their data. There are several different classifications of bias, but they can generally be grouped

into the categories of selection, information and confounding biases (Grimes and Schulz 2002). As the majority of TDM clinical studies are cohort studies, they are particularly prone to selection bias (Grimes and Schulz 2002). Since the majority of the observational cohort studies are not inception cohorts (Morris, Black et al. 1998; El Desoky, Kandil et al. 1999; Le Bloc'h, Woggon et al. 2003; Ulrich, Baumann et al. 2003; Bergemann, Frick et al. 2004), patients who have drug concentrations outside the therapeutic range are more likely to represent new patients who may be more likely to have initial toxicity and not yet achieved efficacy with treatment. Alternatively, patients who have remained in the cohort and had dosage modifications resulting in a therapeutic plasma drug concentration, are more likely to be drug responders, and to tolerate the medication, quite independent of the role of TDM. There are also likely to be biases in the types of patients referred to tertiary referral centres where these studies are often conducted, or selection of patients for intensive compared to trough drug monitoring.

Information bias is also likely to occur as very few of the studies have a blinded assessment of the outcome. Although it may be argued that the laboratories may be blinded to the patient's condition when the specimen is analysed, and that frequently hard endpoints are used such as histological evidence of rejection, ongoing bacteremia, or recurrence of seizures, the authors who analyse and review the data are often involved in the laboratory analysis, and many of the endpoints are subjective such as symptoms of toxicity, response to treatment on the basis of patient questionnaire or clinician global impression.

Confounding bias is also very likely in TDM studies: a patient who has a drug concentration within a therapeutic range may be more likely to be compliant with their medication, and to attend follow-up and have subsequent dosage adjustments. These confounding factors would be independently associated with an improved outcome. A typical example is the observational study by Ulrich et al which found that serum concentrations of clozapine less than 250ng/mL in maintenance treatment of schizophrenia was associated with a higher rate of relapse, and which concluded that "the TDM of clozapine is recommended during maintenance treatment" (Ulrich, Baumann et al. 2003). Schizophrenia is a condition in which non-adherence with drug treatment can be a cause as well as a symptom of relapse, and hence it is not surprising that low drug concentrations were associated with this outcome.

The drugs for which TDM is available are frequently not prescribed as monotherapy, and it may be that the patient characteristics that result in inadequate or excessive concentrations of the drug whose concentration is being measured result in similar effects on the co-prescribed medication, which ultimately results in the clinical outcome seen. For example it has been shown that poor absorption of cyclosporine is associated with a poorer graft survival and a higher incidence of acute rejection in renal transplant recipients (Lindholm and Kahan 1993). However, cyclosporine is always administered with other immunosuppressants which may also be affected by poor absorption and which are not monitored by drug assays, such as prednisolone and azathioprine.

The other difficulty, apart from the presence of bias, is that all of these studies draw an association between a certain range of drug concentrations

and specific outcomes. They then frequently argue that TDM in such cases is justified on the assumption that modification of the dosing regimen in order to bring a patient whose drug concentration is outside of this range, into the therapeutic range, is likely to be associated with a greater likelihood of the desired outcome. In most cases, however, no direct evidence for the validity of this approach is provided.

In many cases the results of the initial observational data form the basis of further studies, and the therapeutic range for the drug and the routine conduct of drug assays becomes entrenched in the literature. An example is the threshold concentration for efficacy for olanzapine derived by Perry et al (Perry, Sanger et al. 1997). This was a secondary analysis of a Phase II study of olanzapine conducted in 79 patients with schizophrenia who were randomised to 1 or 10mg of olanzapine, and blood samples were obtained weekly for olanzapine concentration determination. A receiver operated characteristics (ROC) curve demonstrated a concentration of 9.3 ng/mL as being able to discriminate between good (≥20% reduction in Brief Psychiatric Rating Scale score) and poor (<20% reduction in score) responders. The authors concluded that "use of olanzapine plasma concentrations of > 9 ng/mL as a predictor for treatment response in acutely ill schizophrenic patients is practicable because this therapeutic marker significantly increases the likelihood of a patient responding to olanzapine". Caution should always be exercised with such secondary analyses, as it is likely that by chance alone a single concentration can be predictive of response in the sample cohort, while concentrations nearby may not have any predictive effect (Schulz and Grimes 2005; Scott and Greenberg 2005). The threshold

concentration may also only hold true for the sample cohort, and may not be valid when extrapolated to the whole population. Such secondary analyses should only really be hypothesis generating, and should prompt the conduct of further trials to specifically test these hypothesis e.g. randomised controlled trials. Instead, the study by Perry et al (Perry, Sanger et al. 1997) has been used as the basis for the conduct of olanzapine TDM as well as the basis of further research (Bergemann, Frick et al. 2004).

Comparative trials, which are ascribed a higher level of evidence in EBM classification schemes, are generally between different types of TDM (Chandler, Clifton et al. 1990; Burton, Ash et al. 1991; Andres, Lopez et al. 1997; Cantarovich, Latter et al. 1997; Pea, Bertolissi et al. 2002), and the majority of controlled trials involve comparison of TDM in addition to a clinical pharmacokinetic service compared to TDM alone (Barr and Schumacher 1995). Hence these do not really contribute to the evidence base for TDM compared to not doing TDM.

Apart from these, other concerns undermine the evidence base for TDM. Many articles do not comply with the recommendations for the suitability of conduct of TDM (Section 1.1.1), and advocate drug assays merely on the basis of the presence of variability in pharmacokinetics and/or the presence of a concentration-effect relationship (Palao, Arauxo et al. 1994; Kurowski, Muller et al. 1999; Lundmark, Reis et al. 2000; Kisanga, Gjerde et al. 2004; David-Neto, Pereira et al. 2005), whilst ignoring many of the other criteria. The TDM literature has many examples of incomplete compliance with the other criteria for the appropriateness of TDM. Hence these should not just be taken for granted. Examples of these include: interference by endogenous

(Smith and Morse 1999; Dasgupta 2002) and exogenous compounds (Yosselson-Superstine 1984; Rayner, Ioannides-Demos et al. 1999; Dasgupta, McNeese et al. 2004; Karamperis, Koefoed-Nielsen et al. 2005); poor quality control in laboratory standards and variability in drug concentration determination (Krogstad, Eveland et al. 1991; Sallustio and Morris 1999; Holt, Johnston et al. 2000; Bell, McLaren et al. 2001; Morris and Lam 2002; Staatz, Taylor et al. 2002; Morris 2005); non-standardisation of interpretation of drug concentration results (Markowitz, Morton et al. 1997; Paterson, Robson et al. 1998; Tobin, Darville et al. 2002); variability in the free concentration fraction which is not routinely measured but which contributes to the drug effect (Banh, Burton et al. 2002; Atcheson, Taylor et al. 2004); intra-patient variability in drug concentrations (Birnbaum, Hardie et al. 2003); lack of consistency in the concentration-effect relationship (Bigger 1985; Wildin, Pleuvry et al. 1993; Cohen-Mansfield, Taylor et al. 2000). TDM is also recommended and therapeutic ranges exist for drugs for which there is a good dose response relationship and/or lack of any concentration effect relationship e.g. vigabatrin (Johannessen, Battino et al. 2003).

In the TDM literature negative studies are frequently ignored, including studies evaluating associations between concentration and effect (Schumacher, Barr et al. 1991; Lindberger, Luhr et al. 2003; Einecke, Schutz et al. 2005), assessing the outcomes associated with different types of TDM (Cantarovich, Latter et al. 1997; International Neoral Renal Transplantation Study Group 2002), assessing the impact of TDM on compliance (Akerblad, Bengtsson et al. 2003), assessing the effect of achieving a therapeutic concentration (Woo, Chan et al. 1988) and even randomised controlled trials

of TDM compared to patients not having TDM (Fröscher, Eichelbaum et al. 1981; Kemme and Daniel 1993; Joos, Blaser et al. 1995; Fletcher, Acosta et al. 1998; Jannuzzi, Cian et al. 2000; Clevenbergh, Garraffo et al. 2002; Muller, Dragicevic et al. 2003; Bossi, Peytavin et al. 2004). In fact, the few high level evidence studies that have been performed have nearly all been negative with a few exceptions (Fernandez de Gatta, Calvo et al. 1996; Fletcher, Anderson et al. 2002; Burger, Hugen et al. 2003).

Instead, it is very common to find literature based on consensus reports, expert opinions and personal practices. In a review of TDM practices for immunosuppressive drugs, Shaw et al reviewing the evidence for cyclosporine concluded that "Considering such potential for high inter- and intra-patient variability, therapeutic drug monitoring of cyclosporine has become integral to the task of achieving optimal immunosuppression". This quote was followed by six references, all of which were for previous consensus documents published by the same or similar authors (Shaw, Holt et al. 1999).

Despite these criticisms and concerns regarding TDM, it could equally be argued that the absence of high quality evidence of benefit is not necessarily the same as evidence of the absence of benefit, and that to be consistent with EBM ideology the best available evidence for TDM should be used. This supporting evidence is currently predominantly in the form of observational studies, case reports, and consensus reports. Hence it can be concluded that the best available evidence would support the conduct of TDM.

This argument unfortunately ignores two important issues. Firstly it assumes that TDM is always potentially useful and beneficial. Hence it assumes that if there is an association between a certain range of drug concentrations and a desired outcome, it can be concluded that altering the dosing regimen to bring an individual's concentration into this range would always potentially be beneficial, without the necessity of conducting a randomised trial to test this hypothesis, as no harm is likely to come to the patient from this strategy. Unfortunately, there is some high level evidence that such an approach in a stable patient can be associated with a higher incidence of toxicity (Woo, Chan et al. 1988). Secondly, this argument forgets the cost associated with TDM, not just in terms of the cost of the assays, but in terms of the patient inconvenience, particularly with area-under-the-curve determination strategies which require multiple assays at specific times after dosing. In the current health care environment, it is important that any intervention demonstrates clinical benefit, particularly ones which are costly. Although many cost-effectiveness studies have been conducted with TDM, once again they nearly always have compared TDM with a clinical pharmacokinetic service compared to TDM alone, and one review of the literature concluded "Do the improved outcomes of TDM justify the cost? From a societal perspective, the data are inconclusive in terms of routine use in today's environment" (Schumacher and Barr 2001). The other issue affecting cost-effectiveness is that, although TDM may be shown to be cost-effective in a trial environment, there is considerable evidence for the inappropriate use of assays in clinical practice (Wing and Duff 1987a; Wing and Duff 1987b; Wing and Duff 1989; Schoenenberger, Tanasijevic et al. 1995; Bowhay 1996; Paul

and Ikwuagwu 1997; Thapar, Richens et al. 2001; Affolter, Krahenbuhl et al. 2003; Walters, Hutchings et al. 2004). Inappropriate use of assays would tend to dilute any potential benefits of TDM, increase the likelihood of harm, and reduce cost-effectiveness.

1.3.1 Evidence Base for Therapeutic Drug Monitoring of Different Drug Classes

Although this has been a general overview of the evidence base for TDM, it is important to appreciate that the quality of the evidence does vary across different drug classes for which TDM is available.

The highest quality evidence (Level 1b according to Centre for Evidence Based Medicine classification scheme) is available for the traditional antiepileptics (phenytoin, carbamazepine, and valproate) and the protease inhibitors used for Human Immunodeficiency Virus infections. Of all of the medications for which drug assays are available, in theory, phenytoin would be the one whose clinical use would benefit most from TDM. This is because it has saturable kinetics, with non-linearity in its clearance, which is seen within therapeutic concentrations (Aronson, Hardman et al. 1992). As a result, there is a great deal of variability between individuals in the steady-state concentration which is achieved at the same dose. Furthermore, for an individual patient, an increase in the dose can result in different increases in the concentration, depending on the initial concentration. It also fulfils many of the criteria listed above as requirements for TDM as it has a narrow therapeutic index, is used to treat the serious condition of epilepsy, and the pharmacological effect appears to be proportional to its plasma concentration

(Buchtal, Svensmark et al. 1960; Lund 1973; Aronson, Hardman et al. 1992). Perhaps more importantly, the concentration dependent toxicity of phenytoin such as nausea, vomiting, obtundation, and ataxia, can also be mimicked by the underlying pathology which has caused the seizures (e.g. brain tumours). Furthermore, phenytoin can cause a paradoxical increase in seizures with toxic concentrations (Troupin and Ojemann 1975; Stilman and Masdeu 1985).

Although an initial therapeutic range of 10-20 mg/L was proposed for phenytoin, it has become apparent that a wide range of concentrations can be therapeutic for the individual patient, with evidence of benefit from concentrations below (Feldman and Pippenger 1976; Shorvon, Chadwick et al. 1978; Hayes and Kootsikas 1993) and above (Schmidt, Einicke et al. 1986; Cobos 1987) the therapeutic range listed above.

It is a surprise then that randomised trials of TDM for phenytoin have been conducted, and that they have all been found to be negative. Woo et al (Woo, Chan et al. 1988) studied a group of 79 well stabilised epileptics with idiopathic generalised tonic-clonic seizures treated as monotherapy with phenytoin or phenobarbitone, but who had subtherapeutic concentrations. The patients were randomly assigned either to continuing with the same dose, or increasing the dose until the concentration reached and stayed at the "therapeutic range". Over a mean period of 24 months there was no difference between the groups with regard to occurrence of seizures, but the group having adjustments based on serum levels had a higher incidence of neurotoxicity. Two further trials have assessed patients with epilepsy who were prescribed a variety of traditional antiepileptics randomised to TDM or

management by clinical judgement alone (Fröscher, Eichelbaum et al. 1981; Jannuzzi, Cian et al. 2000). Both studies involved a randomised, controlled, open-label design in which drug assays were performed, but the results were made available to the clinicians in one group and not the other. Both of these studies failed to show an advantage of the TDM strategy, either in terms of efficacy or toxicity, despite a sample size of 127 and 180 patients. Although there are several criticisms of both studies, including a high drop-out rate, a minority of the patients being prescribed phenytoin, and heterogeneity in the patient populations, they do represent the highest level of evidence for TDM for the traditional antiepileptics.

The highest level of evidence available for the new antiepileptics such as lamotrigine, gabapentin, or topiramate is Level 4 evidence. Despite the negative high level studies for the traditional antiepileptics, and the low level of evidence for TDM for the new antiepileptics, review articles do advocate TDM for some of these drugs (Perucca 2000; Neels, Sierens et al. 2004), or do report a therapeutic concentration range (Johannessen, Battino et al. 2003), and there is evidence of routine monitoring of the new antiepileptics (Morris, Black et al. 1998) despite review articles recommending against this (Chong and Dupuis 2002).

Another class of drugs for which high level evidence for TDM exists is antivirals used for Human Immunodeficiency Virus infection. These agents are also good candidates for TDM as it is important to ensure that the trough drug concentration does not fall below that which will confer selective pressure for the survival of mutant viral isolates with reduced susceptibility to one or more drugs (Aarnoutse, Schapiro et al. 2003). TDM may be

particularly useful for this drug class, as they are often used in combination with other antiviral agents, with the resulting drug interactions increasing the inter-individual variability in their pharmacokinetics. Although these agents do not consistently have a narrow therapeutic index, some of their toxicity is concentration-dependent, and any lack of efficacy would certainly place the patient at risk.

On the basis of these theoretical considerations a number of randomised controlled trials (Level 1b evidence) have been performed to assess a concentration controlled strategy compared to conventional dosing (Fletcher, Acosta et al. 1998; Clevenbergh, Garraffo et al. 2002; Fletcher, Anderson et al. 2002; Burger, Hugen et al. 2003; Bossi, Peytavin et al. 2004). Although some of these studies have been negative, these have generally been those with a shorter duration of follow-up (Fletcher, Acosta et al. 1998; Clevenbergh, Garraffo et al. 2002; Bossi, Peytavin et al. 2004), whereas those with a duration of up to 52 weeks have shown positive results (Fletcher, Anderson et al. 2002; Burger, Hugen et al. 2003).

This contrasts with the situation with immunosuppressive drugs where there is a dearth of high level evidence for TDM. Cyclosporine was the first immunosuppressant for which TDM was developed as it became apparent that fixed doses of cyclosporine were not the best way to use the drug as no relationship could be found between administered doses and clinical effects (Citterio 2004). Kahan et al were able to demonstrate a relationship between trough cyclosporine concentrations and outcomes in human renal transplantation (Kahan, Wideman et al. 1984), and since then a variety of methods of monitoring have been proposed including a pharmacokinetic

approach (area-under-the curve determination), absorption profiling, and single sample C2 (sample taken 2 hours post-dose) monitoring (Citterio 2004). Unfortunately, this progression has occurred on the basis of observational data demonstrating a greater association between outcomes and some forms of monitoring compared to others e.g. pharmacokinetic monitoring compared to trough monitoring (Lindholm and Kahan 1993), or variability seen during pharmacokinetic monitoring compared to trough monitoring (Kahan, Welsh et al. 1996). Unfortunately, there are only a few randomised trials supporting the benefit of these more recent approaches over trough concentration determination (Cantarovich, Barkun et al. 1998; Levy, Burra et al. 2002). Whilst other randomised studies have been conducted, some have only demonstrated a reduction in the cyclosporine dosage (Cantarovich, Latter et al. 1997), and others have shown no difference in outcomes (International Neoral Renal Transplantation Study Group 2002) in comparison to trough monitoring alone.

Whilst it might be understandable that a randomised trial of empirical compared to TDM-based dosing of cyclosporine may no longer be ethical, this is certainly not the case with newer immunosuppressants such as mycophenolate, which are marketed with standard dosage recommendations (CellCept Product Information). Despite this, there is a plethora of review and consensus documents arguing for mycophenolate TDM (Nicholls 1998; Shaw, Korecka et al. 1998a; Shaw, Korecka et al. 1998b; Shaw, Nicholls et al. 1998; Shaw, Holt et al. 1999; Mourad, Wallemacq et al. 2002) but no randomised trials testing this strategy compared to standard dosing. This is despite one author reporting a required sample size of only approximately

200 patients for an adequately powered study to test this hypothesis (Nicholls 1998).

The evidence base for TDM for other drugs lies between these extremes. The data for vancomycin are largely observational (Level 4) However, there appears to be at least one randomised trial of TDM in patients with haematological malignancies which demonstrated a reduction in nephrotoxicity in the TDM arm. However, the management of the control group is not well described in this study, and it is not clear when discussing "monitoring" whether the authors imply the conduct of a drug assay, or a review by a clinical pharmacokinetic service.

The literature for aminoglycosides includes a single randomised controlled trial (Level 1b) which produced a negative result (Kemme and Daniel 1993), but which was under-powered to show any difference between the treatment groups, and a well conducted case-control study (Level 3b) with a positive result (Gill, Cheetham et al. 1986). Although there are numerous randomised trials of aminoglycosides and even several meta-analyses (Level 1a) (Galloe, Graudal et al. 1995; Barza, Ioannidis et al. 1996; Hatala, Dinh et al. 1996; Ali and Goetz 1997; Bailey, Little et al. 1997), these involve comparison of once-daily with multiple-daily doses of aminoglycosides.

Although TDM of the tricyclic antidepressants (TCAs) has been available for some time, the majority of the data, once again, is observational. One systematic review (Level 2a) of the concentration-effect relationships with different TCAs has been conducted (Perry, Pfohl et al. 1987), as well as a comparison of TDM compared to clinical dosage adjustment alone (Muller,

Dragicevic et al. 2003). This latter study produced no differences between the groups, either in clinical response, or the incidence of adverse reactions. The authors found, however, that therapeutic drug concentrations during initial dosing were associated with significantly better outcomes, and that adverse reactions occurred significantly more often when the serum concentrations were above the therapeutic range. As a result they concluded that "treating depression with TCA can be optimised by early TDM, which is superior to clinical judgment on its own". Clearly this is contrary to the appropriate interpretation of an intention-to-treat trial.

1.4 Therapeutic Drug Monitoring of Digoxin

When I first commenced work on this thesis, there were virtually no randomised trials of TDM compared to a dosing strategy without drug assays (Tonkin and Bochner 1994). The purpose of this research was to choose a widely used drug, which was an appropriate candidate for TDM, but for which no Level 1 evidence in support of TDM existed. I chose digoxin as it fulfils nearly all of the criteria for the conduct of TDM, listed above, is widely used, and at the time was the second most common drug assayed at our clinical pharmacology laboratory.

1.4.1 Clinical Pharmacology of Digoxin

Digoxin is a cardiac glycoside used for the treatment of supraventricular tachycardias, such as atrial fibrillation or flutter, and cardiac failure. Its mechanism of action is by inhibition of the Na^+/K^+ ATPase in the myocardium resulting in a positive inotropic effect, as well as increasing vagal tone to

control heart rate, and by regulation of sympathetic nervous activity (Ooi and Colucci 2001). This latter action is thought to be of particular use in heart failure (Gheorghiade and Pitt 1997).

The symptoms of digoxin intoxication are generally non-specific and can be categorized as gastrointestinal (anorexia, nausea, vomiting, diarrhoea, and abdominal pain), neuropsychiatric (manifesting as lethargy, bad dreams, restlessness, agitation, nervousness, and diminished muscle strength as well as others), visual (presenting as reversible red-green colour blindness, chromatopsia, scotoma, blurred vision), as well as disturbances of cardiac rhythm (Lely and van Enter 1972). Although virtually any arrhythmia can occur, they typically involve disorders of conduction and increased irritability.

In the 1960s and early 70s dosing with digoxin was made difficult by a number of factors including: variable and uncertain bioequivalence between different preparations; large inter-patient variability in the required maintenance dose; poor understanding of its pharmacokinetics, clearance mechanisms, and interacting medications; narrow therapeutic index; non-specificity of non-cardiac symptoms; and difficulty in differentiating some cardiac arrhythmias, seen during treatment, as representing toxicity from lack of efficacy.

1.4.2 Development of Digoxin TDM

At this time there was ample evidence that many patients on digoxin were inadequately dosed or overdosed with a rate of toxicity of 10-20% being reported in a number of studies (Rodensky and Wasserman 1961; Schott 1964; Dubnow and Burchell 1968). Hence, there was much interest in

methods which could help improve the individualisation of dosing. At this time assays had been developed for other drugs (Sokolow and Edgar 1950; Geraci, Heilman et al. 1957; Buchtal, Svensmark et al. 1960) and attempts were made to develop methods to assay digoxin, in order to better understand the variability in bioavailability and dosing, and to develop a better indicator of efficacy and toxicity than dose or clinical findings.

Early assays for digoxin involved embryonic duck heart bioassays, double isotope dilution, spectrophotometric techniques, and assays based on inhibition of erythrocytic cation transport (Aronson 1981). These assays were either too cumbersome, insensitive or both. The radioimmunoassay technique first described by Smith et al in 1969, however, rapidly became the standard in digoxin assays (Smith, Butler et al. 1969).

Smith et al described a technique for determination of digoxin concentrations using competitive binding of tritiated digoxin to an anti-digoxin antibody, and then comparison to a standard curve. In their initial study, they compared the serum digoxin concentrations (SDCs) of 10 patients taking 250µg of digoxin per day, with 11 taking 500µg, and another group of 18 patients in whom there was electrocardiographic evidence of digoxin toxicity according to predefined criteria. They found mean digoxin concentrations of 1.1 ng/mL and 1.4 ng/mL in those on 250µg, and 500µg of digoxin respectively, and a mean concentration of 3.3 ng/mL in the toxic group. This was the first time that a difference in digoxin concentrations between groups of patients with and without toxicity had been demonstrated.

Smith and Haber followed up this work in 1970 with a further study on the relationship between digoxin concentrations and electrocardiographic evidence of toxicity (Smith and Haber 1970). They defined the presence or absence of digoxin toxicity in the following manner:

Absence of toxicity was defined as:

- electrocardiographically documented stable sinus rhythm with PR interval 0.20 seconds or less,
- atrial fibrillation with ventricular response rate between 70 and 100 beats/minute,
- atrial flutter with degree of atrioventricular block in the 2:1 to 4:1 range.

Presence of digoxin intoxication as one or more of the following disturbances of impulse formation or conduction (and disappearance of the rhythm disturbance when digoxin was withheld):

- supraventricular tachycardia with atrioventricular block,
- frequent or multifocal ventricular premature beats, ventricular bigeminy, or ventricular tachycardia,
- atrial fibrillation with high grade atrioventricular block (ventricular response less than 50/minute) and ventricular premature beats,
- sinus rhythm with second or third degree atrioventricular block.

Questionable digoxin excess was defined as the presence of one or more of the following disturbances of impulse formation or conduction:

- occasional ventricular premature beats (less than 5/min),
- first degree atrioventricular block in the absence of other drugs capable of impairing conduction and in the absence of a prior history of this finding when off digoxin,

- atrial fibrillation with occasional atrioventricular junctional escape beats,
- marked sinus bradycardia (less than 50/min) without prior history of this finding off digoxin,
- atrial fibrillation with a relatively slow ventricular response (50-65 beats/min).

They then surveyed their hospital over a 6 month period and found 131 patients who had been on a maintenance dose of digoxin for 5 days, and who had no evidence of toxicity. They also collected data for 48 patients with signs of toxicity over a 15 month period. An additional group of 48 patients was defined by the questionable toxicity criteria. They collected data regarding the patient's dosing, as well as blood for SDC, sodium, potassium, and blood urea nitrogen estimation. Samples were drawn more than 8 hours after the dose of digoxin was administered. Each patient was also interviewed to collect data regarding the patient's non-cardiac symptoms of toxicity such as anorexia, nausea, and chromatopsia, and an electrocardiogram was performed within 24 hours of the serum digoxin sample being drawn.

Overall, patients in the toxic group tended to be older and to have a greater degree of renal impairment than those in the non-toxic group ($p<0.005$). There was also a highly significant difference in the mean SDCs of the toxic and non-toxic groups (3.7 ± 1.0 ng/mL vs 1.4 ± 0.7 ng/mL , $p<0.001$). The range of concentrations in the toxic group was 1.6-13.7 ng/mL, compared to 0.3-3.0 ng/mL in the non-toxic group. However, although the overlap extended from serum concentrations of 1.6 to 3.0 ng/mL, 90% of patients with no evidence of intoxication had levels of 2.0 ng/mL or below, while 87% of the toxic group

had concentrations above 2.0 ng/mL. They found those with questionable digoxin toxicity to have concentrations in the intermediate range (mean 1.9±0.8 ng/mL).

In their discussion, they concluded that decisions regarding cardiac glycoside dosing in patients with toxic ECGs would be straightforward, and knowledge of the SDC would be "chiefly of investigative interest". They argued that since a wide range of SDCs was found, no arbitrary level could be chosen below or above which digoxin should or should not be continued. They concluded that concentrations below 1.5 ng/mL are unlikely to be associated with significant digoxin intoxication, while levels above 3.0 ng/mL carry a high probability of digoxin induced rhythm disturbance. Despite these comments, the accepted therapeutic range for digoxin has an upper limit of 2.0 ng/mL and this cut-off is frequently used in clinical practice to diagnose digoxin toxicity.

Disappointingly, although information was collected regarding non-cardiac symptoms of digoxin toxicity, the only data reported were that patients with electrocardiographic evidence of toxicity had a higher incidence of these symptoms. The number of patients who had only extracardiac manifestations of toxicity and were excluded was not reported.

1.4.3 Evaluation of Digoxin TDM

This initial study was followed up by a number of similar papers evaluating the digoxin concentrations in toxic and non-toxic patients. Beller et al evaluated 931 consecutive admissions to a medical service for evidence of toxicity using similar ECG criteria to those above (Beller, Smith et al. 1971). They found 23% of all patients to have definite evidence of toxicity, and that

these patients had a mean SDC of 2.3±1.6 ng/mL compared to 1.0±0.5 ng/mL in the non-toxic group. They similarly found a large degree of overlap in the concentrations of those with toxic and non-toxic ECGs. The prevalence of nausea or vomiting was not different in the groups but 61% of toxic compared to 25% of non-toxic patients had anorexia. The prevalence of mental state changes was reported as being the same in both groups. They also found an increased mortality rate in those found to be digoxin toxic (41%) compared to the non-toxic group (17% $p<0.01$). This higher mortality was only associated with the presence of toxicity evident on the electrocardiogram, and was not associated with high digoxin concentrations alone. In fact, no study has demonstrated any adverse prognostic value of high digoxin concentrations alone or in association with non-cardiac symptoms of toxicity.

Interestingly, because of the large numbers of patients studied Beller et al (Beller, Smith et al. 1971) were able to assess some factors that may affect the patient's sensitivity to digoxin: those with New York Heart Association class III and IV heart failure, pulmonary disease, ischemic heart disease, and underlying atrial fibrillation were more likely to have evidence of toxicity. Other workers have similarly found that the sensitivity to digoxin is altered by patient characteristics such as thyroid function, electrolytes, hypoxia, acidosis, and age (George 1983; Sonnenblick, Abraham et al. 1983; Aronson and Hardman 1992; Kelly and Smith 1992). These factors increase the inter- and intra-individual variability in the plasma concentration-effect relationship, such that it may approach or even exceed that of the dose-concentration

relationship. This, of course, challenges an essential principle of therapeutic drug monitoring (Spector, Park et al. 1988).

Similar work by others showed the same pattern of electrocardiographically defined toxicity being associated with higher digoxin concentrations (Singh, Rai et al. 1975; Aronson, Grahame-Smith et al. 1978; Narayanan Nampoory, Abraham et al. 1978) while others demonstrated no difference in the SDC between toxic and non-toxic patients (Fogelman, La Mont et al. 1971; Howard, Smith et al. 1973). In all of the positive studies there was a large degree of overlap in the concentrations of the toxic and non-toxic patients, and with the exception of Nampoory et al (Narayanan Nampoory, Abraham et al. 1978) ECG evidence of toxicity alone was used to define the toxic group.

Ingelfinger and Goldman in 1976 reviewed the literature regarding the use of digoxin assays to diagnose toxicity (Ingelfinger and Goldman 1976). They proposed that an investigation of the serum digitalis concentration as a test for digitalis toxicity should (1) study patients with similar toxic manifestations, (2) obtain control concentrations from non-toxic patients with symptoms suggesting toxicity, (3) define criteria for toxicity and non-toxicity, (4) select representative patients, (5) describe the study population and (6) analyse how much diagnostic information the serum digitalis concentration provides that cannot be inferred from other observations (Ingelfinger and Goldman 1976). They reviewed 27 reports and found that no investigation adhered to all 6 elements of study design. Of the five studies most consistent with their requirements only three demonstrated higher mean serum digitalis concentrations in toxic patients. Whether knowledge of the digitalis concentrations was diagnostically more useful than knowledge of the digitalis

dosage, renal function, serum potassium concentration and cardiac status was not determined in any study. After their review of the literature, they concluded that on the basis of the principles of study design used in this analysis, the ability of the SDC to distinguish between toxic and non-toxic patients remained unproven (Ingelfinger and Goldman 1976).

Hence, even though digoxin assays were increasingly being used to diagnose digoxin toxicity, the evidence that digoxin assays could be used to diagnose toxicity was not conclusive, and it was unclear whether they added anything to what the clinician already knew about the patient's dosing, electrolytes, and cardiac condition. Even if digoxin assays could be used to diagnose toxicity, the authors of the original articles cautioned against using an arbitrary cut-off to diagnose toxicity, emphasized the overlap between toxic and non-toxic patients, and that assays were unnecessary in straightforward cases of clinical toxicity. There is some evidence, however, that clinicians do regulate digoxin therapy by using SDCs (Schapel and Read 1980), and I wanted to assess whether the SDC contributes any additional information to the clinical diagnosis of digoxin toxicity in current practice.

There was other evidence supporting the notion that digoxin assays had utility in reducing toxicity. Duhme et al compared the incidence of digoxin toxicity in two hospitals in Boston. In one hospital (Massachusetts General Hospital MGH), digoxin assays were done daily and in the other (Peter Bent Brigham Hospital PBBH) they were performed once a week (Duhme, Greenblatt et al. 1974). Both hospitals were affiliated with Harvard Medical School and drew their house staff from that medical school. They both used the same brand of digoxin, and appeared to be similar in every way, except

for the availability of digoxin assays. In this study, all patients receiving digoxin during the study period were monitored for adverse reactions occurring after admission. Adverse reactions were attributed to digoxin if the patient's physician and the reviewing pharmacologist agreed that it was the probable cause. If there was disagreement, then the case was reviewed by other clinicians blinded to the originating hospital.

The study demonstrated that during the survey period, dose related adverse reactions to digoxin were reported in 9.9% of those at PBBH and 4.1% of those at MGH ($p<0.02$), even though dose and admission blood urea nitrogen were not significantly different between the two institutions. The paper argues that since 39.5% of patients at MGH had a digoxin assay, compared to 14% at PBBH, but the concentrations from the latter hospital were higher, then this suggests that at PBBH assays were done primarily in patients already suspected of being digoxin toxic, whereas at MGH they were being performed for therapeutic guidance. On the basis of these data, the authors argue that prompt and appropriate use of serum digoxin assays can reduce the frequency of digoxin toxicity.

Although this study is frequently quoted as demonstrating the utility of digoxin assays articles (Spector, Park et al. 1988; Mahdyoon, Battilana et al. 1990; Ried, Horn et al. 1990; Barr and Schumacher 1995), it has a number of faults. Firstly, it was not randomised. Hence, although the only apparent difference between the institutions is the digoxin assay availability, there could be other differences in the culture of drug prescribing, clinical drug monitoring, attention paid to and or even the documentation of possible symptoms of toxicity, which could account for the differences between the

institutions. Secondly, although the patients were matched in their admission blood urea nitrogen, there is no information about subsequent tests of renal function, particularly given that toxicity had to occur during the admission and could not be diagnosed on admission. Thirdly, there is no information regarding possible interacting drugs, and given the fact that the mean dose and blood urea nitrogen were the same in both groups, the difference in toxicity could be explained by differences in interacting medications. One hospital may have had a culture of using quinidine for supraventricular arrhythmias, for example, and this could easily explain the differences between the institutions (Leahey, Reiffel et al. 1978; Hager, Fenster et al. 1979). Lastly, it is unclear from the article whether the assessors who determined the prevalence of digoxin toxicity were blinded to the serum digoxin concentration or not. This is important, because the availability of digoxin assays may have only influenced the perception of digoxin toxicity. For example, patients at MGH may have been deemed not to be toxic if they had manifestations of toxicity but were found to have a serum digoxin concentration within the therapeutic range. Conversely, patients at PBBH developing symptoms and signs of digoxin toxicity, but whose therapeutic digoxin concentrations were not known, would be more likely to be labelled toxic, in the absence of this assay information.

Despite the limitations of the above study, a widely held view is that digoxin assays are responsible for a greater awareness of the issues involved in digoxin dosing and have contributed to a reduction in the incidence of toxicity (Kelly and Smith 1992). In fact, recent surveys of digoxin toxicity in hospital populations (Mahdyoon, Battilana et al. 1990; Marik and Fromm 1998) have

demonstrated much lower incidences of digoxin toxicity than those quoted above, but it needs to be remembered that other factors other than the availability of digoxin assays have also contributed to this trend. These include better understanding of the pharmacokinetics and bioavailability of digoxin, reduction in maintenance doses prescribed, awareness of drug interactions, as well as readier access to the measurement of electrolytes, renal function, and thyroid function (Mahdyoon, Battilana et al. 1990). Jelliffe et al were able to demonstrate similar reductions in the incidence of toxicity using a computer assisted glycoside dosage regimen, without any input of glycoside assays (Jelliffe, Buell et al. 1972).

Given that the patient populations treated, and the use of digoxin has changed since these early studies in the 1970s, it appeared that it would be useful to revisit the issue of the electrocardiographic toxicity of digoxin. I have attempted to do this in Chapter 6. Despite the considerable research into the electrocardiographic toxicity of digoxin, the concentration-toxicity relationship had not been described, and the utility of the upper limit of the therapeutic range which designates toxic concentrations, had not been demonstrated.

In most previous studies of digoxin TDM, toxicity was typically defined by ECG criteria, and little attention was paid to the extracardiac manifestations of toxicity. Although, some studies did mention these, there is no information regarding the concentration-toxicity profile of these symptoms. In fact, the only study to specifically review extracardiac manifestations of digoxin toxicity found a very weak association between extracardiac symptoms and the serum glycoside concentration (Ochs, Greenblatt et al. 1980). In practice, if a patient has a suspicious cardiac rhythm, there is some literature on the

usefulness of a digoxin assay in determining whether it can be attributed to digoxin toxicity. However, when a patient has the more common non-cardiac symptoms of toxicity, there is virtually no literature on whether an assay can contribute to the diagnosis of toxicity. Hence, although the evidence for cardiac toxicity is arguable, the evidence for the more frequently problematic non-cardiac symptoms is negligible. I felt it was important to explore the concentration-toxicity of digoxin with respect to its non-cardiac toxicity as well, and to understand which symptoms most likely to be reliably indicative of digoxin toxicity.

The prevalence of factors which alter the sensitivity to digoxin also would have changed since these early studies. Given that one of the assumptions of TDM is that the concentration-effect relationship is consistent, I wanted to explore the prevalence of these factors in current clinical practice, and to assess their influence on the manifestations of cardiac and non-cardiac toxicity (see Chapter 5 and 6).

In summary, although a number of papers have shown a difference in the mean concentrations of patients with and without ECG evidence of toxicity, the evidence is not conclusive, there is a wide area of overlap between toxic and non-toxic concentrations, and an arbitrary cut-off cannot be used to define toxicity. Furthermore, the patient's sensitivity to a particular digoxin concentration has been shown to be influenced by a number of factors, and is potentially quite variable. This evidence relates only to ECG toxicity, and there is little evidence on the usefulness of assays in diagnosing toxicity in patients with the more common extracardiac manifestations. Finally, the only

evidence for the utility of digoxin assays in toxicity is from a non-randomised observational study, with many flaws.

If the case for toxicity is inconclusive, what about the use of assays to improve the efficacy of digoxin? In terms of control of rate in atrial fibrillation, in a review by Masuhara and Lelonde (Masuhara and Lalonde 1982), nine studies are quoted demonstrating a poor correlation between SDCs and ventricular rate. Part of the difficulty is that patients have quite variable conduction through their atrioventricular node and variable amounts of sympathetic stimulation, and so cross-sectional studies assessing the correlation between rate and concentration frequently show a lack of a relationship. Redfors (Redfors 1972) examined eleven patients at various predetermined digoxin doses, and found a strong relationship in individual patients between increased digoxin concentration and decreasing heart rate. Aronson et al (Aronson, Grahame-Smith et al. 1977) were also able to demonstrate a correlation between percent change in ventricular rate and the digoxin concentration within the range 0.8-3.2 ng/mL. Hence it appears that, although digoxin concentrations bear a poor relationship to the ventricular rate in atrial fibrillation across the population, in an individual patient, higher concentrations are likely to be associated with lower ventricular rates.

Investigators have attempted to relate concentrations of digoxin to its clinical effects in heart failure. Some found a relationship between plasma levels and systolic time intervals, but others did not (Aronson 1981). More recently two studies have assessed the concentration effect relationship of digoxin and its effect on heart failure. Gheorghiade et al (Gheorghiade, Hall et al. 1995) studied a group of twenty-two patients with heart failure and increased their

dose of digoxin, resulting in an increase in mean concentration from 0.67 to 1.22 ng/mL. This resulted in a statistically significant improvement in their radionuclide ejection fraction, but not their markers of neurohumoral activity such as plasma noradrenaline, renin, or atrial natriuretic factor. However, in a another study of similar design, nineteen patients were treated with initially low dose (125µg per day), then moderate dose (250µg per day) of digoxin for a period of 2 weeks each (Slatton, Irani et al. 1997). This resulted in mean digoxin concentrations of 0.8 ng/mL at the low dose and 1.5 ng/mL at the moderate dose. There was an improvement in echocardiographic performance with low dose digoxin, but no further improvement with moderate dose digoxin. However, because echocardiography was used to assess left ventricular function, compared to radionuclide scanning in the previous study, this trial was less able to detect a difference in left ventricular function if, in fact, it was there. It was found, however, that the benefit of digoxin in ameliorating autonomic dysfunction occurred at the low dose and that there was no further benefit at the higher dose. It was hence argued that lower doses should be used in clinical practice.

The largest source of data regarding the concentration-effect relationship for digoxin in heart failure comes from a subgroup analysis of the DIG study (The Digitalis Investigation Group 1997). This was a large study of approximately 7000 patients with chronic heart failure (CHF) and sinus rhythm who were randomised in a double-blind fashion to either digoxin or placebo and were followed-up for a period of three years. The main outcome of the study was a modest reduction in the rate of hospitalisation particularly for worsening CHF, although no difference in mortality was observed. Drug

assays were not necessarily part of the therapeutic strategy for this study, the investigators instead choosing a dosing nomogram devised by Jelliffe and Brooker in 1974 (Jelliffe and Brooker 1974).

A random selection of patients in that study did have SDCs assayed approximately 1 month after randomisation (Rathore, Curtis et al. 2003). As these researchers had previously reported an interaction between gender and outcomes with digoxin (Rathore, Wang et al. 2002), and few of the females had had an SDC determined, their analysis was limited to males only. They found a significant association between the SDC at 1 month and mortality, with patients with SDC of 0.5-0.8 ng/mL having a 29.9% mortality compared to 38.8% for those with SDC of 0.9-1.1 ng/mL, and 48.0% for those with SDC ≥1.2 ng/mL.

As that study did not randomise patients to different serum digoxin categories, the baseline characteristics of the patients in the various SDC categories were quite different. Those in the highest SDC group were significantly older, more likely to have New York Heart Association grade III or IV heart failure, a lower estimated glomerular filtration rate, and were more likely to be taking diuretics. As these factors alone are likely to be associated with a worse mortality the authors conducted a multivariate analysis to adjust for these factors. Their conclusion was that there was still a significant association between SDCs and mortality. However, the association was greater for the crude than for the adjusted analysis (Rathore, Curtis et al. 2003).

Although the data presented in that study are compelling, it is important to remember that they do represent a *post hoc* secondary analysis of a

subgroup of patients (males who had digoxin assays). The role of confounders should also not be underestimated: the baseline characteristics of the groups differed, and all of the characteristics in which the groups were significantly different such as age, severity of CHF, and degree of renal function are independently associated with worse mortality.

Patients with worse CHF were over-represented in the highest SDC category. Severe heart failure can artificially elevate the SDC due to interference with digoxin-like immunoreactive substances (Dasgupta 2002), as well as the likelihood that the patients' clinicians were using higher digoxin doses, or aiming for higher concentrations in order to treat patients with more severe disease. The use of other drugs which can elevate SDCs such as amiodarone, and spironolactone are also not reported. As these would have been prescribed for ventricular tachycardias and severe biventricular failure, respectively, their use would have been associated with a worse prognosis. Hence, although the results suggest that patients with CHF should have their digoxin dose titrated to a narrow range at the lower end of the current therapeutic range, these data can only generate a hypothesis, which should then be tested in a randomised trial.

In summary, in terms of the relationship between digoxin concentrations and efficacy, in atrial fibrillation there appears to be a relationship in individual patients that extends linearly at least to a concentration of 3.2 ng/mL. Given the fact that there is a ready marker of efficacy available, namely the patient's heart rate, the utility of assays is not in determining efficacy, but the likelihood of toxicity if the dose is further increased. For CHF, a well designed and conclusive study elucidating the concentration-effect relationship is lacking,

but the best available evidence would suggest that most of the benefit from digoxin is realised at the lower end of the therapeutic range, and that higher concentrations may, in fact, be associated with additional harm.

1.5 Summary and Aims of Thesis

On reviewing the data presented, the case for digoxin TDM does not appear compelling. Nevertheless some authors have attempted to create evidence-based appropriateness criteria for digoxin TDM (Canas, Tanasijevic et al. 1999; Mordasinia, Krähenbühl et al. 2002), which include performing assays in patients who are admitted to hospital and who have not had a recent SDC determination. Although this appears to be a common occurrence in clinical practice, there is very little literature to support it. I wanted to assess the utility of conducting routine digoxin assays on all patients admitted to general medical units of a hospital, in order to address this gap in the evidence.

The absence of high level evidence for digoxin TDM is of particular concern given the documented high prevalence of the inappropriate digoxin assays (Copeland, Thorpe et al. 1992; Canas, Tanasijevic et al. 1999; Mordasinia, Krähenbühl et al. 2002). It is important to consider, however, that although no randomised trial has assessed the utility of a digoxin TDM strategy, digoxin assays have a number of different roles in clinical practice, and different study designs will be necessary to answer these different questions. Certainly in CHF, digoxin TDM may be used as part of a target concentration range strategy, and a randomised trial of this strategy could be compared to empirical dosing according to an established nomogram. In other contexts, however, a digoxin assay may be used as a diagnostic test for toxicity or

non-adherence. In such cases, diagnostic utility of the assay would need to be compared to a "gold standard", and sensitivity and specificity of a particular concentration range for this diagnosis would need to be determined (Sackett, Haynes et al. 1991). In the management of atrial fibrillation, the digoxin assay may be used to indicate the likelihood of a patient experiencing symptoms of toxicity with an increase in the dose. In such a case, a description of the concentration-toxicity relationship across the population would be the most appropriate data source.

The aim of this thesis is to:

- contribute to the evidence base for digoxin TDM, particularly by attempting to provide higher levels of evidence e.g. randomised controlled trial data, than is currently available. Hence, I will assess the feasibility of conducting a randomised controlled trial of a digoxin therapeutic concentration strategy in hospital inpatients.
- address other gaps in the evidence such as:
    - determination of the concentration-toxicity relationship of digoxin with respect to its cardiac and non-cardiac manifestations,
    - developing a greater understanding of the impact of factors which alter the sensitivity to digoxin in current clinical practice,
    - determine the utility of the knowledge of the sdc in the diagnosis of digoxin toxicity,
    - determine utility of performing routine digoxin assays on patients admitted to hospital.

Chapter 2

RANDOMISED CONTROLLED TRIAL OF DIGOXIN THERAPEUTIC MONITORING - PILOT STUDY

2.1 Introduction

Digoxin therapeutic drug monitoring (TDM) was introduced in the early 1970s as a tool to assist the diagnosis of digoxin toxicity (Smith, Butler et al. 1969; Smith and Haber 1970; Beller, Smith et al. 1971; Singh, Rai et al. 1975; Aronson, Grahame-Smith et al. 1978; Narayanan Nampoory, Abraham et al. 1978). Since then it has become one of the most widely used drug assays (Mutnick 1995; Gheorghiade and Pitt 1997) representing a major medical care cost. There is some evidence for the benefit of digoxin TDM in reducing the incidence (Duhme, Greenblatt et al. 1974; Ried, Horn et al. 1990) and assisting in the diagnosis of digoxin toxicity (Abad-Santos, Carcas et al. 2000), as well as evidence for titrating the dose to a narrow therapeutic range in the management of congestive cardiac failure (Rathore, Curtis et al. 2003). However, to date, no prospective, randomised, controlled trials of the usefulness of employing the TDM strategy in the management of patients on digoxin have been performed (Tonkin and Bochner 1994) despite several authors arguing that they should be conducted (Hvidberg 1980; Spector, Park et al. 1988; McInnes 1989).

There are several potential barriers to conducting such a trial. Ethics committees, clinicians and patients may no longer consider it ethical to deny

patients TDM. The sample size of such a study may be prohibitive, given the size of previous studies required to demonstrate the efficacy of digoxin (The Digitalis Investigation Group 1997). The ready availability of TDM may present practical difficulties in maintaining a control (non-TDM) arm.

The ideal design of how TDM should be performed in such a study is also uncertain. If the design is too prescriptive regarding when and how assays should be performed, it would have limited applicability outside of such use. However, if the decisions regarding the performance of TDM are left up to all of the clinicians whom the patient may encounter, it will be impractical to assess necessary endpoints.

My aim was to study the feasibility of a prospective, randomised, controlled trial of the usefulness of digoxin TDM in a hospital and community setting. I intended to determine the practical difficulties of performing such a study, the sample size required for a study of adequate power, the feasibility of collecting a range of efficacy, toxicity, and quality-of-life endpoints, and the necessary resources associated with such data collection.

2.2 Methods

The study was conducted amongst patients admitted to the general medical and cardiology units of the Royal Adelaide Hospital, a tertiary referral institution, and was approved by the Human Research Ethics Committee. All patients admitted during a 3-month period, who were receiving ongoing digoxin therapy were included. Patients unable to give consent, or whose life expectancy was less than 4 months, or who were unlikely to be available for

follow up were excluded. Agreement for inclusion by the patient's general practitioner (GP) was sought before the patient was approached. The study was called DART: The Digoxin Assay Randomisation Trial.

Randomisation was on a 1:1 basis. Patients in the TDM arm were allowed to have digoxin assays at the discretion of their clinicians. The assay results were reviewed by the clinical pharmacology service so as to provide the best TDM outcome (Barr and Schumacher 1995).

A multifaceted intervention was used to educate the clinicians involved in the study. The hospital units involved in the study were those in whom there were clinical champions who supported the concept of the study. An initial information session was held for all of the senior and junior medical hospital staff involved in the conduct of the study, and the study was further discussed at individual unit meetings. Information sessions were also held for the clinical pharmacists, as they were in a position of being able to identify potential patients for enrolment. Written information was also sent to each clinician involved in the study including the general practitioners.

Extensive steps were taken to ensure that patients randomised to the non-TDM arm did not have an assay performed without my knowledge, and that clinicians were informed of the patient's involvement in the study to facilitate the collection of study endpoints. Each set of casenotes had a pink A4 cardboard sheet placed in its plastic sleeve to inform clinicians of the patient's participation in the trial (Figure 2.1). This was in addition to the hospital's requirements for patients participating in clinical trials having a separate stickers on the front of their casenotes. There were different sheets for patients randomised to the TDM or the non-TDM arm, with the latter

including a warning that the patient should not have a digoxin assay performed without contacting myself. A number of bright red stickers were developed which were similarly placed on the casenotes as well as the front of the medication chart and on each page next to the digoxin order to inform clinicians of the patient's participation in the study (Figure 2.2A-B). Patients randomised to the non-TDM arm had an additional sticker asking clinicians to page me before performing an assay. Patients involved in the study were given a carry card which included contact information for clinicians who may be involved in their care (Figure 2.3). A mobile phone and toll-free service were also set up for clinicians to be able to access the study coordinator when required. Although the clinicians involved in the study were given extensive written and verbal information regarding the study, a "short guide" was also made available which was customised to different practice settings and was sent to the patient's general practitioner, and was placed in all ward stations, resident offices, and outpatient areas (Figure 2.4A-C).

FIGURE 2.1 PINK CARDBOARD A4 SHEET PLACED IN PLASTIC SLEEVE IN CASENOTES OF ALL PATIENTS ENROLLED IN STUDY

FIGURE 2.2A STICKERS USED IN CASENOTES AND MEDICATION CHART

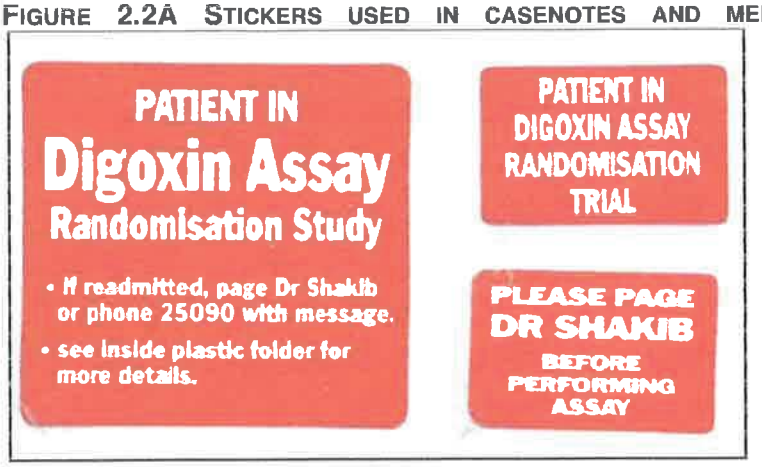

FIGURE 2.2B EXAMPLE OF MEDICATION CHART WITH STICKERS

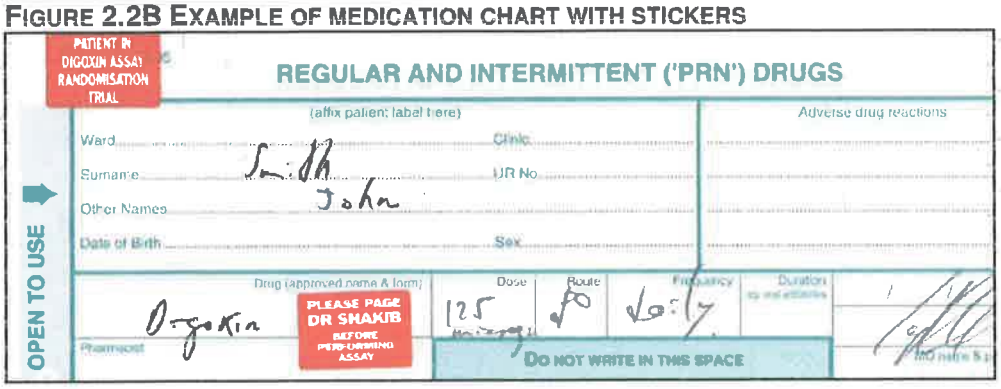

FIGURE 2.3 PATIENT CARRY CARD

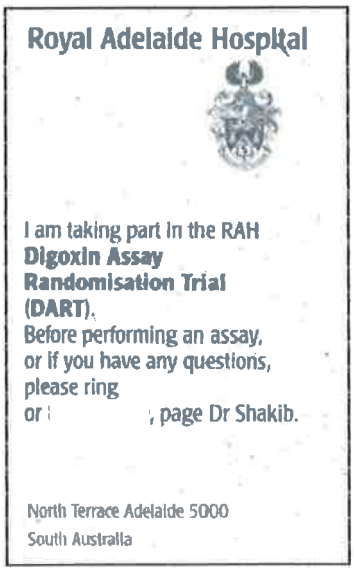

FIGURE 2.4A. SHORT GUIDE TO DART STUDY FOR GENERAL PRACTITIONERS

Short Guide to DART

Digoxin Assay Randomisation Trial

SUSPECTED TOXICITY: Fill out pink feedback sheet, and specify the type of toxicity

UNSURE ABOUT TOXICITY → **contact us urgently**

ADVICE ON MANAGING TOXICITY → **contact us urgently**

SERIOUS TOXICITY: eg. life-threatening arrhythmia, resulting in hospital admission or death, please → **contact us urgently**

ASSAY REQUESTED: Assay arm → pink feedback sheet.

Non assay arm: → please fill out a pink sheet if you would like to do an assay, even if you actually don't (this allows us to compare similar groups in the tdm arm)

If you do an assay on a patient in the non-assay arm of the study, then contact us urgently

DRUG DOSAGE CHANGE: → pink feedback sheet.

OTHER MAJOR EVENTS: eg death, **contact us urgently or leave message on free call number**

OTHER MINOR CHANGES: eg. moving into nursing home, becoming terminal care etc... → pink sheet or free-call

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The numbers you need:

TO CONTACT URGENTLY: RING
or PAGE VIA RAH **Dr Shakib**

TO LEAVE MESSAGES, ROUTINE: fax 8222 4189 or
FREE CALL

FIGURE 2.4B SHORT GUIDE TO DART STUDY FOR INPATIENT AREAS

Short Guide to DART

(Digoxin Assay Randomisation Trial)

Patients in DART will be identified with:

on plastic folder in case notes

on blue folder

on drug chart if in non-therapeutic drug monitoring arm

To let us know of:

- **routine** information fill out **pink sheet or ring 25090** and leave message
- **urgent** matters: Page **SHAKIB (1231)** or ring **0418 859 474**

In case of

- **suspected toxicity** ⟶ Pinksheet or ring 25090
- **serious toxicity** ⟶ **Please contact urgently**
  eg. arrhythmia
- **dosage change** ⟶ Pinksheet or ring 25090
- **Assays** (this bit a little more complicated):
  if: ordering for TDM patient ⟶ just write reason on request form (eg. routine, toxicity, lack of effect, other)

  if: ordering for non-TDM patient ⟶ **Contact urgently**
  (constitutes a withdrawal from study)

  if you would like to do an assay in non-TDM patient, but chose not to ⟶ Fill out pinksheet
- **any other events** eg. deaths, dramatic change in condition, etc... page 1231 or ring 25090 and leave message

FIGURE 2.4C SHORT GUIDE TO DART STUDY IN OUTPATIENT AREAS

Short Guide to DART

(Digoxin Assay Randomisation Trial)

Patients in DART will be identified with:

on plastic folder
in case notes

Sheet inside plastic folder tells if in TDM or non-TDM arm

Every time you see a patient please fill out a pink sheet, and put in box provided

Found inside plastic folder or on your desk (somewhere)

Please fill in the **date, digoxin dose patient has been on, current heart rate, and weight** (if available)

Then tick boxes for:

- **suspected toxicity**-regardless of how mild
- **dosage change** - for digoxin or drugs interacting with it
- **assays** (this bit a little more complicated):
  if ordering for **TDM** patient ⟶ tick reason
  if ordering for **non-TDM** patient ⟶ Contact us urgently (constitutes a withdrawal from study)
  if you would like to do an assay in **non-TDM** patient, but chose not to ⟶ tick reason
- **any other events** eg. deaths, admission, withdrawal, etc... page 1231 or ring 25090 and leave message

If URGENT: Page SHAKIB 1231 or ring

Patients were followed up for 4 months during subsequent readmissions, outpatient, and GP visits. I attempted to assess the following endpoints: number of assays, number of dosage changes, efficacy (measured by resting heart rate for patients in atrial fibrillation (AF) at the end of each admission and during ambulatory care visits), readmission rate and length of stay, incidence and duration of episodes of toxicity (as diagnosed by treating clinicians) and quality of life (QoL) using Short Form (SF)-36 (Ware Jr, Snow et al. 1993), as well as the Minnesota Living with Heart Failure Questionnaire (Rector, Kubo et al. 1987) for patients with cardiac failure. The latter was chosen as there is strong evidence that it is responsive to changes in health-related QoL that follow from the administration of effective medication (Guyatt 1993). The methods used for the collection of each endpoint are listed in Table 2.1.

TABLE 2.1 METHODS AND RELIABILITY OF ENDPOINT COLLECTION

Endpoint	Method of data collection	Reliability of data collection†
Therapeutic drug monitoring (TDM) related		
Number of TDM events	Pharmacology laboratory for inpatients	Very good
	Review of GP* notes at end of study	Moderate
Digoxin prescribing		
Dosage changes	Case note review for inpatients	Very good
	Encounter feedback sheets for ambulatory care	Very poor
	Review of GP notes at end of study	Poor
Efficacy		
Resting heart rate for atrial fibrillation patients	Observation chart for inpatients	Very good
	Encounter feedback sheets	Very poor
	Review of GP notes at end of study	Poor
Readmission rate	Hospital database	Very good
Quality of life	Questionnaires at enrolment and end of study	Very good
Toxicity		
Clinical toxicity	Review of hospital and GP notes	Poor
	Encounter feedback sheets	Very poor
Length of stay	Hospital database	Very good

*GP: general practitioner

†Very good, >80% of data reliably collected; good, 60–80% of data reliably collected; moderate, 30–60% of data reliably collected; poor, 10–30% of data reliably collected; very poor, <10% of data reliably collected

Encounter feedback sheets were used for ambulatory care visits to record, in a tick-box fashion, details of the patient, dosage changes, evidence of toxicity, lack of efficacy, or non-compliance, and whether an assay was performed (Figure 2.5A-B). For general practice visits, these were sent as part of a pack along with the information regarding the study, study contact details, the short guide, and a sufficient number of reply paid envelopes. In all of the outpatient areas where participating patients would be seen a prominent pink folder was placed with a large "DART study" label, which included the encounter feedback sheets.

FIGURE 2.5A ENCOUNTER FEEDBACK SHEETS USED IN HOSPITAL OUTPATIENT AREAS

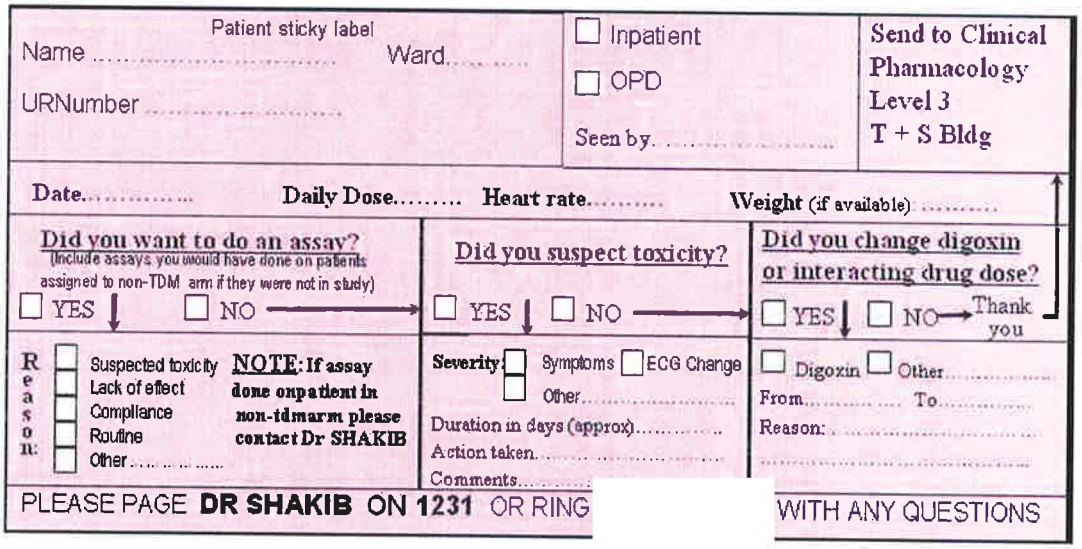


FIGURE 2.5B ENCOUNTER FEEDBACK SHEETS USED FOR GENERAL PRACTICE APPOINTMENTS

DART Feedback Sheet

Patient : Dr

Date: ...../...../..... Current dose of digoxin.....

1. Did you want to do an assay?

☐ YES → REASON:
☐ NO

☐ Suspected Toxicity
☐ Lack of effect
☐ Non-compliance
☐ Routine
☐ Other

If you did an assay please notify study coordinator urgently (see numbers at bottom)

2. Did the patient have any evidence of toxicity?

☐ YES → SEVERITY :
☐ NO

☐ Symptoms .....
☐ ECG Changes
☐ Other.....

DURATION (days).....
ACTION TAKEN:.....

3. Did you change the patient's digoxin dose?

☐ YES → Changed To .....Reason:.....
☐ NO

4. Did you change or add a drug that interacts with digoxin?

☐ YES → DRUG:.....DOSE.....
☐ NO

5. Any other event you would like to notify us of? (use back if necessary)

In case of serious toxicity, death, or patient withdrawal please contact us by mobile or paging RAH 8222 4000 Dr Shakib, or leave message on free-call 1800 688 245

Thank You

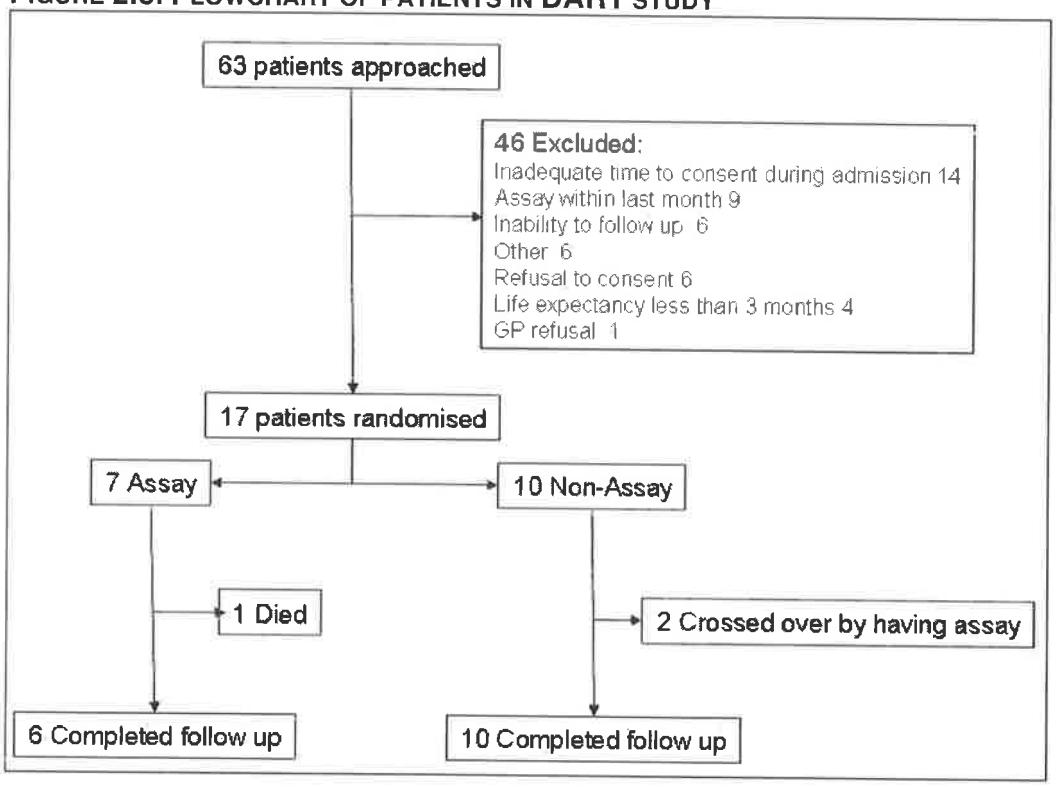
As readmissions in the enrolled patients were infrequent, I interrogated the hospital pharmacy and admission database and identified a list of patients who were known to have been admitted on chronic digoxin therapy one year prior to this pilot, to assess the readmission rate and length of stay in this population.

Sample size calculations were performed using SAS software (SAS Institute Inc., Cary, NC, USA) using a p value of 0.05 and 80% power.

2.3 Results

Sixty-three patients were approached and 17 were randomised (7 in TDM arm and 10 controls). One GP and 6 patients refused to take part in the study (see flowchart in Figure 2.6). The majority of non-enrolments were due to delays in obtaining consent from both the GP and the patient during the admission, hence patients were discharged before they could be approached. The median duration of follow-up was 129 days. There was one death unrelated to digoxin, and one episode of digoxin toxicity in the non-TDM arm. This patient was managed successfully with careful dose adjustments, without the conduct of a digoxin assay. Two patients from the non-TDM arm crossed-over by having assays performed. These were routine follow-up assays ordered by GPs who had forgotten about the patients' participation in the trial.

FIGURE 2.6. FLOWCHART OF PATIENTS IN DART STUDY



The encounter feedback sheets were very poorly utilised, with 14 out of 105 ambulatory care visits resulting in a form being forwarded to the study coordinator. Table 2.1 lists the reliability of the collection of different endpoints. Information from existing databases was more reliable than clinical information. The readmission rate for patients prescribed digoxin a year previously was 0.12 readmissions per patient per month.

Sample sizes for a randomised trial of TDM for different effect sizes for the endpoints which were reliably collected are listed in Table 2.2. As a comparison, the median improvement in the Minnesota Living with Heart Failure Questionnaire score of 7.5 and 5 points has been demonstrated with pimobendan (Rector and Cohn 1992) and enalapril (Rector, Kubo et al. 1993), respectively. The DIG sub-study observed a 7.3% relative risk reduction in all-cause hospitalisation in patients with a trough serum digoxin concentration of 0.5–0.8 ng/mL performed after 1 month of therapy,

compared to the overall digoxin group (Rathore, Curtis et al. 2003). Mortality improvements, used for the calculation of sample size, were taken from the sub-study of the DIG study, as the mortality in our sample was too small for accurate estimation.

TABLE 2.2 REQUIRED SAMPLE SIZE PER GROUP TO DETECT SPECIFIED DIFFERENCES IN VARIOUS ENDPOINTS IN A RANDOMISED TRIAL OF DIGOXIN THERAPEUTIC DRUG MONITORING IN PER-PROTOCOL ANALYSIS

Endpoint	Difference between groups	Sample size per group
Mortality reduction	Absolute risk reduction*	
	6.7%	2325†
	3%	11919†
Readmission	Relative risk reduction‡	
	10%	1146†
	6%	3120†
	3%	12296†
Incidence of toxicity (assuming a 3% baseline rate)	6% toxicity rate	749
	9% toxicity rate	245
Minnesota Living with Heart Failure Questionnaire	2 points	2837
	5 points	454
	10 points	114
Short Form-36 Physical Functioning	5 points	442
	10 points	111
Short Form-36 Role Physical	5 points	275
	10 points	70
Short Form-36 General Health	5 points	158
	10 points	40

*Based on Digoxin Investigator Group sub-study (Rathore, Curtis et al. 2003)

†Patient years of follow up.

‡Based on data from local population of patients.

2.4 Discussion

Although TDM has been available for many decades, it has not been subjected to many controlled trials (Tonkin and Bochner 1994; Barr and Schumacher 1995). The evidence supporting the utility of digoxin TDM is derived from studies of its use in reducing the incidence of toxicity (Koch-Weser, Duhme et al. 1974) as well as evidence for a narrow therapeutic range in the management of cardiac failure (Rathore, Curtis et al. 2003) suggesting that optimisation of dosing using TDM should be useful. To date no randomised trials of digoxin TDM have been reported in the literature, and the current study demonstrates some reasons for this.

The research ethics committee was concerned about the ethics of managing patients without digoxin assays, and only approved the protocol when I agreed to educate all clinicians involved in the trial about the manifestations of digoxin toxicity with written and verbal information. The study was well received by clinicians with only one GP refusing to take part. Approximately 60% of patients admitted on digoxin have an assay performed during their inpatient stay in this hospital, and clinician acceptability of not performing TDM may be lower at institutions where this value is closer to 100%.

One of my aims was to determine our ability to assess a range of endpoints and to determine the resource implications associated with such data collection. The data which could be determined most reliably with limited resources were those derived from hospital databases or patient questionnaires (Table 2.1). I found that clinicians' compliance with encounter feedback sheets was poor, and that routine clinical documentation was not

useful for the purpose of endpoint determination. These issues could be resolved with greater funding involving payment to the GPs for each patient's involvement. However, as digoxin assays are ubiquitously available, there would still be difficulties with data collection related to visits to other GPs, specialists, and emergency room visits.

Two patients from the non-TDM arm had digoxin assays performed. In both cases the GPs had overlooked the patient's participation in the trial. The rate of cross-over in our trial was relatively low as many patients had had a recent assay upon admission to hospital, and would have been on a stable dose of digoxin for the duration of the follow-up. With a longer follow-up period it would be anticipated that many more clinicians would request digoxin assays in order to determine the effects of drug interactions and alterations in renal function, or in cases of suspected digoxin toxicity or lack of efficacy. Given the reliance that clinicians have on TDM in answering these questions, many such protocol violations would be expected to occur. These unstable patients, however, are the very ones in whom a serum digoxin determination would be anticipated to have a clinical impact, and the cross-over of such patients would considerably reduce the power of such a study.

The main barrier to a randomised trial of the usefulness digoxin TDM, however, is the required sample size. The sub-study of the DIG study observed a benefit in hospitalisation and mortality in heart failure patients who had a trough serum digoxin concentration of 0.5–0.8 ng/mL performed 1 month after the start of therapy (Rathore, Curtis et al. 2003). Assuming that the full benefits of this observation would be realised by randomisation to this target range or empirical dosing, approximately 3000 patient years of follow

up would be required per group in a per-protocol analysis to demonstrate the benefit in each of these endpoints. The actual sample size in an intention-to-treat analysis would be much greater due to crossing over between groups, because of the ready availability of digoxin assays.

A stronger argument may be made that TDM reduces the rate of digoxin toxicity. The incidence of hospitalisation for toxicity in the DIG sub-study was 1.6% in all patients on digoxin and 1.2% in those with digoxin concentrations between 0.5 and 0.8 ng/mL. A randomised trial of sufficient power to detect this difference would need to enrol approximately 27,000 patients. The toxicity rate in clinical practice is described as between 0.8 and 6.7% (Mahdyoon, Battilana et al. 1990; Howanitz and Steindel 1993; Kernan, Castellsague et al. 1994; Marik and Fromm 1998; Williamson, Thrasher et al. 1998). If a baseline rate of 3% is assumed with TDM and the rate is expected to be double without TDM, approximately 1500 patients would still need to be randomised.

The required sample sizes are smaller for questionnaire based quality of life endpoints (Table 2.2). However, it is unclear whether digoxin TDM could result in a 5 point improvement in some of the sub-scores, and the sample size for a more realistic 2 point improvement in the Minnesota Living with Heart Failure Questionnaire is still over 2,500 patients per group.

A study of adequate statistical power would require enormous resources, particularly if clinician participation in the data collection was an important part of the outcomes to be assessed. It is very unlikely that such a study would be financially supported by a commercial agency as digoxin TDM is already in common use, and the cost would be prohibitive for a third-party.

It is likely that the ideal time for the conduct of a randomised trial of the usefulness of digoxin TDM has passed. In the years following the first use of digoxin assays, they were only available in restricted centres, little was known about digoxin pharmacokinetics or drug interactions, and much higher doses of digoxin were in use. This would have provided the ideal scenario in which to test whether digoxin TDM improved clinical outcomes. Since then, through the use of dosing nomograms, better understanding of drug interactions, and possibly because of the use of TDM, the incidence of toxicity has become much lower (Dubnow and Burchell 1968; Beller, Smith et al. 1971; Mahdyoon, Battilana et al. 1990; Kernan, Castellsague et al. 1994; Marik and Fromm 1998). Because of the ready availability of TDM, the conduct of a randomised trial is made more difficult and less fruitful.

In this era of evidence-based clinical practice, it is a concern that the highest level of evidence does not exist, nor is ever likely to exist, for the usefulness of a test as commonly utilised as digoxin TDM. Consumers and third-party payers are increasingly demanding justification for the performance of investigations and approaches to management that are evidence-based, and which have been demonstrated in clinical trials to be effective in improving patient centred outcomes. As this study demonstrates, the prospects for an improved evidence base for decision making for digoxin TDM, and many other similar automated assays, are very poor.

2.5 Conclusion

In conclusion, it is possible to perform a randomised trial of the clinical usefulness of digoxin assays, and such a trial is likely to have the approval of ethics committees, clinicians and patients. However, such a study would require a very large sample size and resources, and there is uncertainty about whether patients in such a trial could remain in their allocated groups sufficiently long for the trial to produce meaningful results. Hence, it is unlikely that the highest level of evidence will ever be available for TDM for digoxin.

Chapter 3

UTILITY OF DIGOXIN ASSAYS IN THE DIAGNOSIS OF DIGOXIN TOXICITY

3.1 Introduction

Given that a randomised controlled trial of digoxin TDM is virtually impossible to conduct, I wished to study whether higher levels of evidence could be developed for specific, common indications for digoxin assays. Two of the most common indications for digoxin assays are concerns regarding toxicity and as a routine assay upon admission to hospital (Hladik and Dujovne 1979; Mordasinia, Krähenbühl et al. 2002). The next two chapters study these specific indications for digoxin assays.

Digoxin TDM was originally developed as an aid in the diagnosis of digoxin toxicity. Numerous studies have been performed to assess the utility of digoxin assays in the diagnosis of toxicity by comparing serum concentrations of patients with and without manifestations of toxicity. Although most studies have demonstrated that patients with manifestations of toxicity have higher serum digoxin concentrations (SDC) than those without (Chamberlain, White et al. 1970; Smith and Haber 1970; Beller, Smith et al. 1971; Evered and Chapman 1971; Park, Chen et al. 1973; Singh, Rai et al. 1975; Huffman, Crow et al. 1976; Aronson, Grahame-Smith et al. 1978; Narayanan Nampoory, Abraham et al. 1978; Waldorff and Buch 1978; Bernabei, Perna et al. 1980), others have not (Fogelman, La Mont et al.

1971; Howard, Smith et al. 1973; Carruthers, Kelly et al. 1974; Ochs, Greenblatt et al. 1980). Ingelfinger and Goldman (Ingelfinger and Goldman 1976) reviewed many of these studies and after applying strict methodological criteria concluded that "the usefulness of serum digitalis concentration as a test for digitalis toxicity was not established". Other authors have also concluded that the digoxin assay should not be used as a sole test for digoxin toxicity (Smith 1975; Selzer 1985). Despite this, there is evidence that clinicians alter digoxin dosing largely on the basis of the serum concentration rather than on the consideration of clinical findings, e.g. presence of symptoms of toxicity and ancillary predictors (Schapel and Read 1980; Schapel, Jones et al. 1981).

The therapeutic role of digoxin and our understanding of the factors that lead to toxicity have changed considerably since these early studies. Initially, the ability to demonstrate the utility of TDM in the diagnosis of toxicity may have been hampered by the non-specific nature of the assay, and the lack of understanding that distribution phase assays do not correlate with therapeutic or toxic effects. Digoxin is now available in a consistent formulation with predictable bioavailability, is used at much lower doses, and there is a clearer understanding of its clearance, and drug-drug interactions. Hence, the usefulness of digoxin TDM in the determination of digoxin toxicity may have changed since these early studies.

The appropriate study design for the determination of the usefulness of digoxin assays in the diagnosis of digoxin toxicity would be to compare different SDC cut-offs compared to an existing gold standard of toxicity

(Sackett, Haynes et al. 1991). Unfortunately, no gold standard for the diagnosis of digoxin toxicity exists. In previous studies a range of symptoms and signs associated with high digoxin concentrations have been used as the definition of toxicity. However, these definitions have varied between different studies, and many of the manifestations, such as anorexia, nausea, and ECG changes, were non-specific and could also have been caused by the patient's underlying illness or other medications. These factors may have partly accounted for the variability in results observed by Ingelfinger and Goldman.

Some studies have sought to develop more specific definitions of digoxin toxicity by including only symptoms that resolve upon cessation of digoxin (Smith and Haber 1970; Singh, Rai et al. 1975; Aronson, Grahame-Smith et al. 1978; Waldorff and Buch 1978; Bernabei, Perna et al. 1980; Abad-Santos, Carcas et al. 2000). However, given digoxin's long half-life and the non-specific nature of the manifestations of toxicity, an underlying condition which may have precipitated an increase in serum digoxin concentrations, as well as given rise to manifestations of toxicity can be a potential confounder. Examples include the development of acute renal failure or the addition of amiodarone, both of which can increase serum digoxin concentrations as well as independently give rise to nausea and heart block respectively. Variation of factors which can alter the sensitivity to digoxin e.g. serum potassium, calcium or magnesium, acid-base balance, hypoxia or ischaemia (Davis, Vanderveen et al. 1983) would also need to be kept stable or adjusted for in such a study design.

Another approach would be to rapidly remove digoxin from its binding sites by administering digoxin Fab fragments to determine whether or not the symptoms settled simultaneously. This approach would be appropriate for patients with SDCs above the therapeutic range, however, may not be ethically justifiable in patients at therapeutic concentrations or those who do not have any manifestations of toxicity. This is because of the inherent risks of the administration of Fab fragments such as allergic reactions, precipitation of congestive cardiac failure, and possible hypokalemia (Antman, Wenger et al. 1990; Hickey, Wenger et al. 1991; Kirkpatrick 1991). Furthermore, in case of clinical deterioration such patients could not be re-administered digoxin until the Fab fragments were eliminated.

An alternative method of establishing the utility of digoxin TDM in the diagnosis of toxicity is to assess its impact on decisions made by clinicians managing patients (Schapel, Jones et al. 1981). Although this approach would not determine the sensitivity and specificity of digoxin TDM in the diagnosis of toxicity, such a design does give information about the utility of an investigation in clinical decision making.

The aim of this study was to determine:

- the impact of the knowledge of the digoxin assay result on clinicians' assessment of whether a patient was digoxin-toxic or not,
- whether the knowledge of the digoxin assay result contributed to the assessment of toxicity over and above clinical information alone.

3.2 Methods

3.2.1 Patient Data Collection

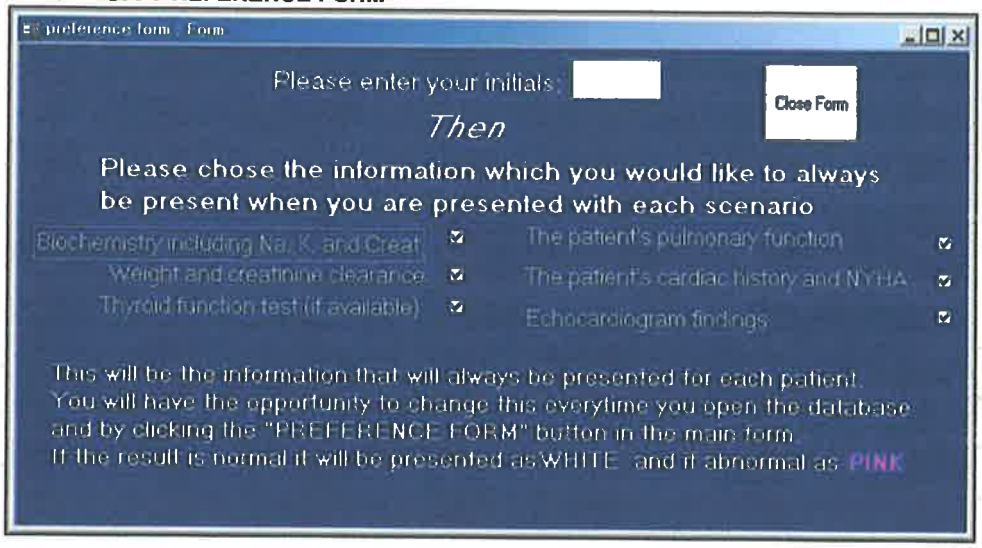
The methods for patient data collection are explained in more detail in Chapter 5. Data from the first 151 consecutive patients enrolled in the study described in Chapter 5 were used for this study. These were inpatients at the Royal Adelaide Hospital, a tertiary referral hospital, who were able to give consent and spoke English, were interviewed regarding potential symptoms of digoxin toxicity within 24 hours of having a trough serum digoxin concentration performed. Each patient was questioned regarding the presence or absence of a large number of symptoms of digoxin toxicity derived from the literature (Lely and van Enter 1972) including anorexia, nausea, vomiting, abdominal pain, diarrhoea, tiredness, difficulty thinking, dizziness, weakness and confusion. Colour vision was tested using Ishihara plates, and a modified "mini-mental" state examination was used to test orientation, short term memory and concentration (Folstein, Folstein et al. 1975). A 12-lead electrocardiogram (ECG) was performed within 24 hours of the assay to detect cardiac rhythm disturbances. For each patient, details of their digoxin dosing history, the presence of any potentially interacting drugs, renal function (as calculated creatinine clearance) (Cockcroft and Gault 1976), factors that are known to alter sensitivity to digoxin including serum sodium and potassium concentrations performed on the day of the assay, thyroid function, pulmonary disease, and history of cardiac disease such as a history of ischaemic heart disease or cardiac failure, as well as indication for digoxin and echocardiographic findings, if available, were recorded.

One hundred and three of these patients had a complete dataset and represented a wide range of digoxin concentrations. The information regarding these patients was then presented to 5 different expert clinicians (a geriatrician, clinical pharmacologist, cardiologist, general physician and specialist cardiology pharmacist) individually in a Microsoft Access database for their judgment as to whether each patient was toxic or not.

3.2.2 Computerised Form

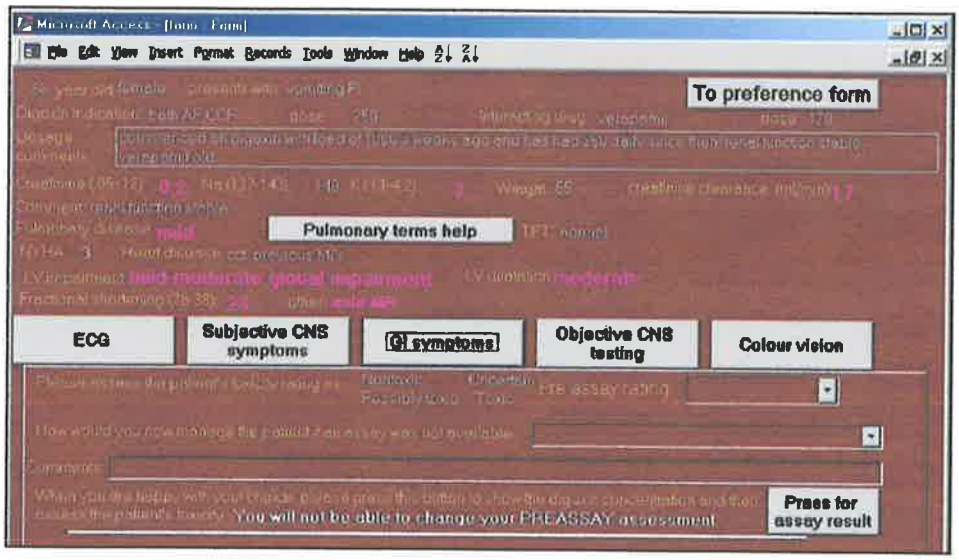
I wrote the Microsoft Access database which displayed the clinical information and also recorded the results of the clinicians' interpretation of the likelihood of digoxin toxicity. The database was designed such that upon opening it, a preference form asked each judge to specify the additional information they wished to see along with the patient's clinical findings (Figure 3.1). This additional information was related to factors which can alter the sensitivity to digoxin, and the clinicians could choose whether they were presented with this information or not.

FIGURE 3.1 PREFERENCE FORM



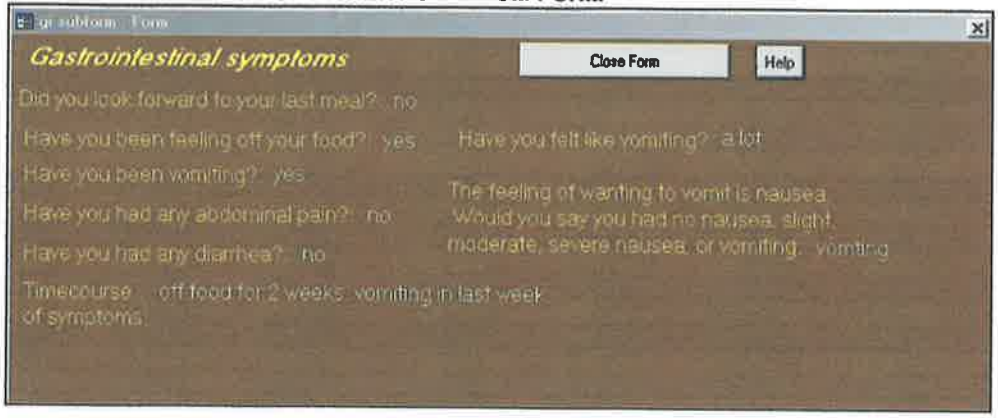
Subsequently, for each patient a form was presented which included basic information such as age, presenting complaint and digoxin dosing history. The additional information which was requested by the judges such as renal function, thyroid function, echocardiographic data was also presented, with abnormal results highlighted in bold and pink, with normal reference ranges, where appropriate (Figure 3.2)

FIGURE 3.2 PATIENT ASSESSMENT FORM



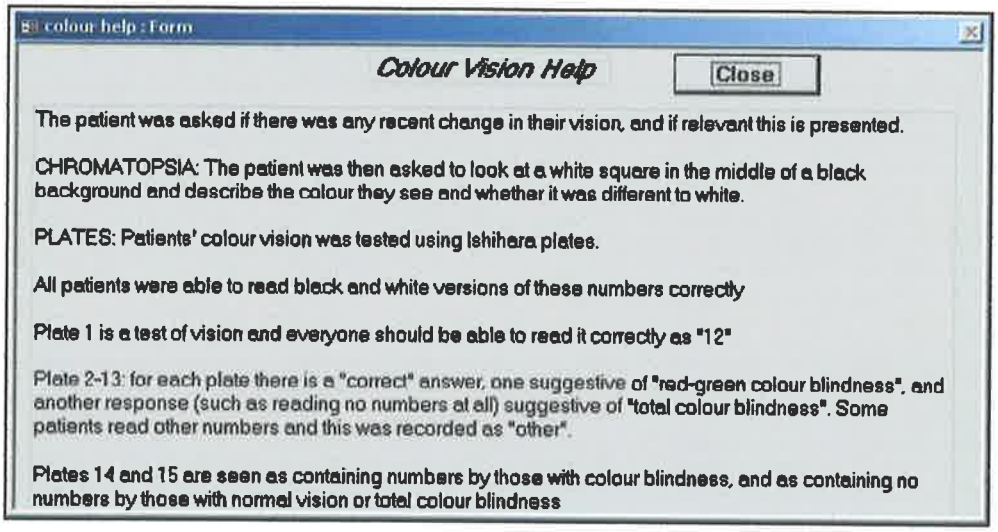
Below this information, 5 buttons were presented, each of which was able to launch a separate form which presented the relevant clinical information such as the 12-lead electrocardiogram, gastrointestinal symptoms, and colour vision test results (Figure 3.3). The order of the way these buttons were presented on the screen varied for each consecutive patient so that the same information was not always presented on the left most button, which might be the first one pressed by the clinician.

FIGURE 3.3 EXAMPLE OF PATIENT SYMPTOM FORM



In each of the forms with the clinical information a help button was provided, which launched a separate form describing the methods used for the data collection, and any of the definitions which were used (Figure 3.4)

FIGURE 3.4 EXAMPLE OF HELP AVAILABLE ON THE FORMS



After reviewing this information, judges were asked to categorise the patient as "non-toxic", "possibly toxic", "toxic" or "uncertain" (Figure 3.2). This judgement was defined as their assessment of the patient's toxicity prior to the knowledge of the SDC. The interpretations of the first three categories were left up to the individual judges. The "uncertain" category was defined as a case in which the judges felt that there was insufficient information to allow them to make an assessment of the patient's toxicity. On the electronic form the judges were also asked how they would manage the patient without knowledge of the SDC.

Once this information was entered, the judges were asked to press a button to reveal the assay result. The therapeutic range for digoxin for the institution was not presented on the form. They were again asked how they would rate the toxicity of the patient and manage the patient's digoxin dosing now with the knowledge of the SDC, using the same categories as above (Figure 3.5). Once the assay result was revealed, the fields for the pre-assay determination of toxicity were locked so that they could not be changed after the knowledge of the SDC.

FIGURE 3.5 ASSESSMENT OF TOXICITY PART OF PATIENT ASSESSMENT FORM

The judges were trained on the use of the database and 3 sham patients including an obviously toxic and a non-toxic patient were used at the beginning for training purposes. The patients' ECGs were reviewed by an independent cardiologist, who was blinded to the patient's identity, SDC and clinical data, in order to determine electrocardiographic toxicity, using previously published criteria (Beller, Smith et al. 1971).

3.2.3 Digoxin Concentration Determination

SDCs were determined by a laboratory accredited by the Australian National Association of Testing Authorities using the Syva enzyme immunoassay (Lane Cove, New South Wales). The limit of quantification was 0.2 ng/mL. The therapeutic range for digoxin provided by the laboratory was 0.5-2.0 ng/mL.

3.2.4 Statistical Analysis

Reliability analysis was assessed using Cronbach's alpha where a value of 0 indicates no agreement, a value of 1 perfect agreement, and values above 0.7 are regarded as indicating strong agreement. Association between ordinal measures was analysed using the Gamma statistic, which ranges between -1 and 1. Values close to an absolute value of 1 represent a very close association, and values close to zero represent little or no association. Statistical tests were performed using SPSS software (SPSS for Windows, Release 10.0.7 2000. Chicago: SPSS Inc.) with a p value of less than 0.05 set as significant.

3.3 Results

Table 3.1 lists the characteristics of the patients included for review by the judges. These characteristics would be representative of patients prescribed digoxin at the institution in which the study was conducted. However, the range of concentrations is skewed to include a greater prevalence of patients with concentrations above the therapeutic range. The values for SDC, creatinine and creatinine clearance were not normally distributed, hence median rather than mean values are presented.

TABLE 3.1 CHARACTERISTICS OF PATIENTS (N=103) PRESENTED TO FIVE JUDGES

CHARACTERISTIC	VALUE
Age (mean ± standard deviation, range)	73.2 ± 11.8 (15-97)
Male	50%
Serum creatinine (mmol/L) (median and range)	0.10 (0.04-1.00)
Calculated creatinine clearance[1] (ml/min) (median and range)	38.0 (7.8 –140.0)
Concurrent interacting medication[2]	24%
Indication for digoxin therapy	
- Cardiac failure alone	17 (16.5%)
- Atrial fibrillation alone	30 (29.1%)
- Both cardiac failure and atrial fibrillation	55 (53.4%)
- Unknown	1 (1%)
Digoxin concentrations ng/mL[3] (median with range)	0.75 (0.2-5.3)
- 0-0.5 ng/mL	7 (6.8%)
- 0.6-1.0 ng/mL	32 (31.1%)
- 1.1-1.5 ng/mL	25 (24.3%)
- 1.6-2.0 ng/mL	13 (12.6%)
- 2.1-2.5 ng/mL	12 (11.7%)
- 2.6-3.0 ng/mL	10 (9.7%)
- 3.1+ ng/mL	4 (3.9%)

1. Using method of Cockcroft and Gault (Cockcroft and Gault 1976),
2. Amiodarone, verapamil, quinidine, and/or spironolactone,
3. Therapeutic range at our institution is 0.5-2.0 ng/mL. Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

A summary of all of the judges' assessments are listed in Table 3.2. There were 5 judges each assessing the same 103 cases resulting in a total of 515 assessments of toxicity. In two of the cases, the judges felt that there was insufficient information to allow them to make an assessment of toxicity ("uncertain" category) and these were excluded from subsequent analysis.

TABLE 3.2 DISTRIBUTION OF ASSESSMENTS OF TOXICITY BEFORE AND AFTER THE KNOWLEDGE OF THE SERUM DIGOXIN CONCENTRATION*

	Assessment of toxicity after knowledge of SDC			
Assessment of toxicity prior to knowledge of SDC	Non-toxic	Possibly toxic	Toxic	Total (Percent)
Non-toxic	235	15	4	254 (49.5%)
Possibly toxic	82	78	59	219 (42.7%)
Toxic	3	5	32	40 (7.8%)
Total	320 (62.4%)	98 (19.1%)	95 (18.5%)	513 (100%)

* Excluding 2 cases where toxicity assessment was "uncertain"

Nearly half (42.7%) of the pre-assay assessments were considered to be "possibly toxic" and this was reduced to 19.1% ($p<0.0001$ for the difference in percentage) once the assay result was revealed. The clinical assessment of the patient, i.e. prior to the knowledge of the SDC, as "toxic" or "non-toxic" had poor sensitivity for the final assessment of toxicity, (32/95 or 34% for "toxic" and 235/320 or 73% for "non-toxic") principally because of the large number of cases categorised clinically as being "possibly toxic". However, the

pre-assay diagnosis of "toxic" had a good positive predictive value for the final assessment of toxicity with 80% (32 of 40) of patients diagnosed as "toxic" clinically having the final assessment of "toxic" with the knowledge of the SDC. Similarly in 92.5% (235 of 254) cases where the patient was thought clinically to be "non-toxic", the final diagnosis with the knowledge of the SDC was "non-toxic".

Agreement between the judges prior to the assay was good (Cronbach's alpha= 0.74), and this improved further once the assay result was revealed (alpha= 0.92). Figures 3.6 and 3.7 graphically represent the distribution of toxicity assessment between the categories of "non-toxic", "possibly toxic", and "toxic" across ascending assay categories before and after the knowledge of the SDC, respectively. As can be seen by the comparison of these figures, the impact of the knowledge of the SDC result was largely to reduce the percentage of cases where the toxicity was assessed as being "possible". Figure 3.8 displays the percentage of cases where there was any change in the assessment of toxicity after the knowledge of the SDC according to ascending assay categories.

FIGURE 3.6 DISTRIBUTION OF TOXICITY ASSESSMENT BY ASSAY CATEGORY PRIOR TO KNOWLEDGE OF THE SERUM DIGOXIN CONCENTRATION

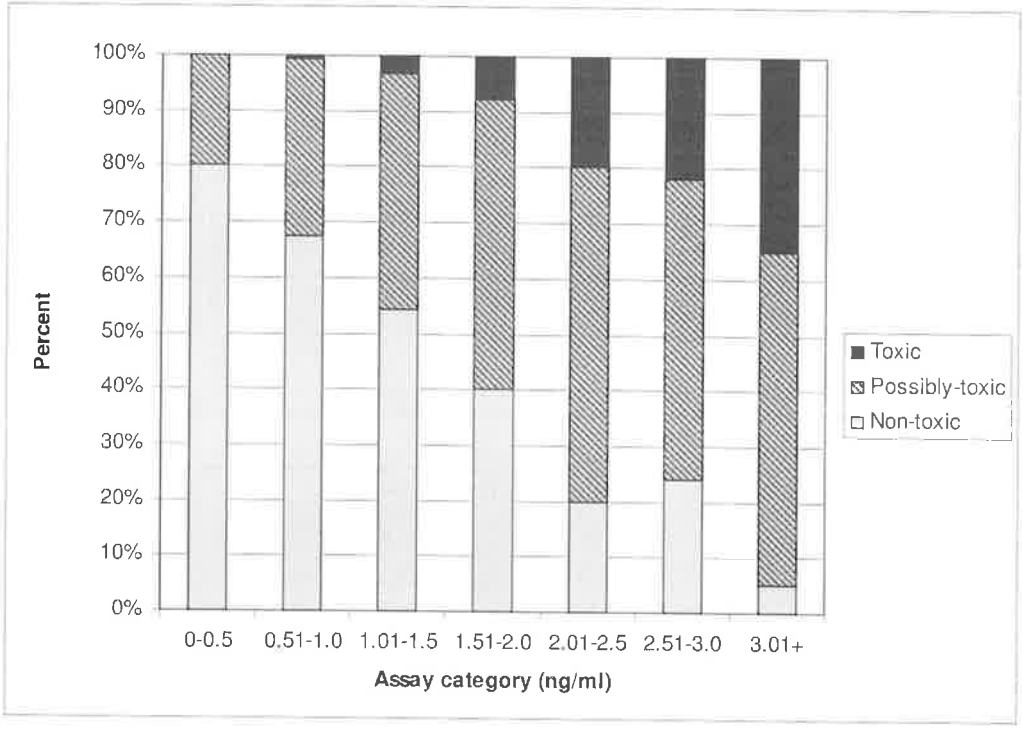


FIGURE 3.7 DISTRIBUTION OF TOXICITY ASSESSMENT BY ASSAY CATEGORY AFTER KNOWLEDGE OF THE SERUM DIGOXIN CONCENTRATION

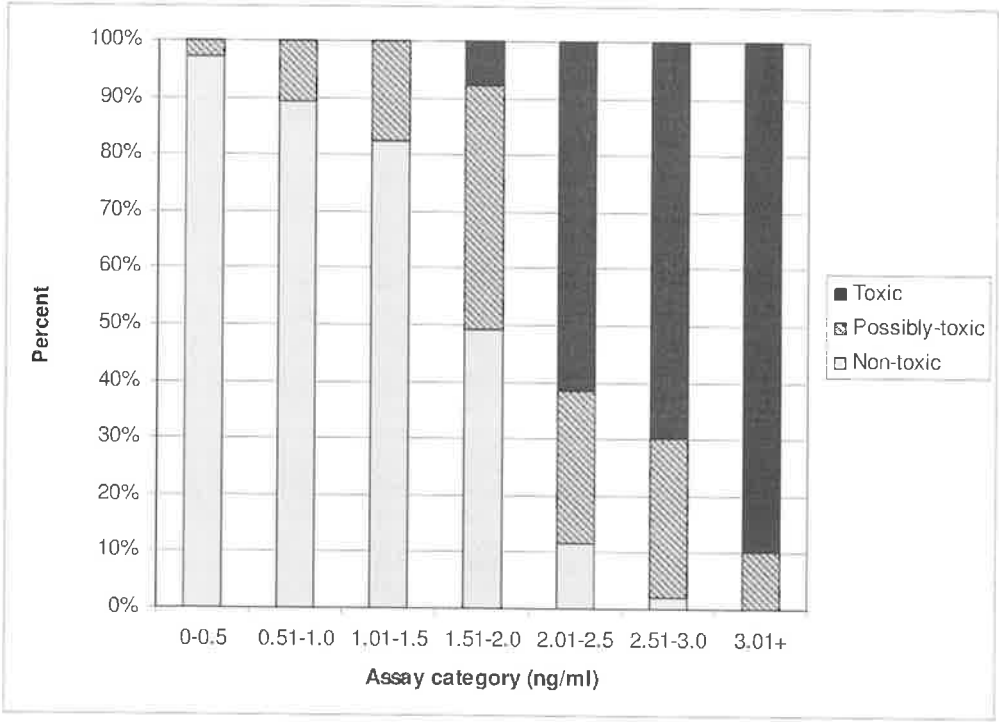


FIGURE 3.8 PERCENTAGE OF CASES HAVING ANY CHANGE IN ASSESSMENT OF TOXICITY AFTER KNOWLEDGE OF SERUM DIGOXIN CONCENTRATION

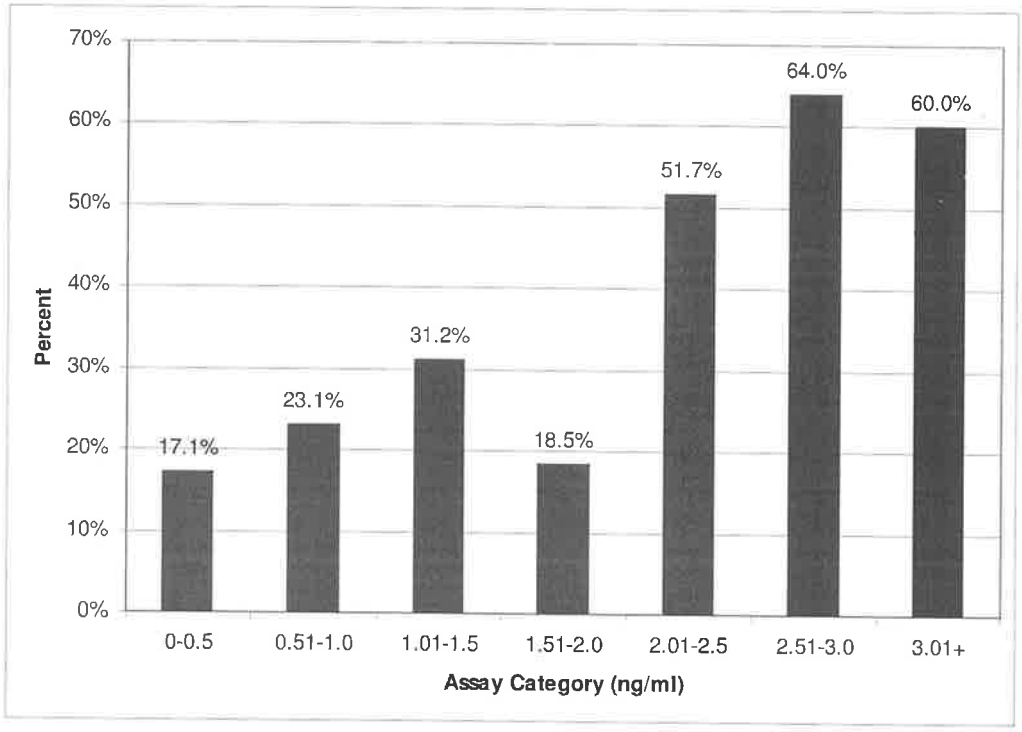


Table 3.3 shows the individual categories of assessment of toxicity before and after knowledge of the SDC, and the median assay concentrations for each category. Overall 32.7% (168 of 513 excluding 2 "uncertain" cases) of cases had an alteration of their assessment as a result of the knowledge of the SDC. Of these 168 cases only 7 (4%) involved a change from "toxic" to "non-toxic" or the converse.

TABLE 3.3 DISTRIBUTION OF ASSESSMENT OF TOXICITY BEFORE AND AFTER THE KNOWLEDGE OF THE SERUM DIGOXIN CONCENTRATION AND ASSOCIATED ASSAY CONCENTRATIONS

Pre-assay toxicity determination	Post assay toxicity determination	Count	Percent of total	Assay Median (ng/mL)*	Assay Interquartile range (ng/mL)*
Possibly toxic	Toxic	59	11.5%	2.74	2.42-2.83
Non-toxic	Possibly toxic	15	2.9%	2.58	2.25-2.75
Non-toxic	Toxic	4	0.8%	2.58	2.52-2.71
Toxic	Toxic	32	6.2%	2.58	2.19-2.92
Toxic	Possibly toxic	5	1.0%	1.83	1.42-2.04
Possibly toxic	Possibly toxic	78	15.1%	1.63	1.08-2.00
Toxic	Non-toxic	3	0.6%	1.25	0.83-1.42
Possibly toxic	Non-toxic	82	15.9%	1.04	0.81-1.33
Non-toxic	Non-toxic	235	45.6%	0.92	0.75-1.33

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

The cases which were determined as being "toxic" after the knowledge of the SDC were associated with a higher median SDC (3.1 ng/mL) than those deemed to be "possibly toxic" (2.0 ng/mL), and these were higher than those determined as being "non-toxic" (1.1 ng/mL). The difference across the 3 groups was significant ($p<0.0001$) as was the difference between any of the two groups ($p<0.001$).

Because of the large number of different categories, and the small numbers of cases in some of these, they were collapsed into the following toxicity assessment categories:

- Less toxic- assessment of toxicity after the knowledge of the SDC less toxic than assessment prior to knowledge of SDC i.e. change from "toxic" to "possibly toxic", "possibly toxic" to "non-toxic" or "toxic" to "non-toxic".

- No change- assessment of toxicity after the knowledge of the SDC same as assessment prior to knowledge of SDC.

- More toxic- assessment of toxicity after the knowledge of the SDC more toxic than assessment prior to knowledge of SDC i.e. change from "non-toxic" to "possibly toxic", "possibly toxic" to "toxic", or "non-toxic" to "toxic".

This enabled analysis of the relationship between changes in assessment of toxicity after the knowledge of the SDC and the patient's symptoms. All of the symptoms of toxicity that were available were assessed, and only those for which there was a significant association between the prevalence of the symptom, and toxicity assessment change category are presented in Table 3.4. For most of the symptoms presented, there was little difference between those in whom there was no change in assessment of toxicity, or who were assessed as being less toxic after the knowledge of the SDC. However, the prevalence of the symptoms of toxicity was higher in cases where the patient was assessed as being more toxic after the knowledge of the SDC.

Although the p values for the symptoms in Table 3.4 were significant, the values for Gamma suggest a modest association between the toxic assessment change categories and prevalence of symptoms of toxicity. This is largely due to the prevalence of symptoms in the "less toxic" and "no change" categories being similar. The p value for Gamma was only significant for anorexia, nausea and ECG changes of toxicity.

TABLE 3.4 PREVALENCE OF SYMPTOMS OF DIGOXIN TOXICITY IN DIFFERENT TOXICITY ASSESSMENT CHANGE CATEGORIES

Symptom	Symptom Prevalence in Toxicity Assessment Change Category:			P[4]	Gamma[5]	P for Gamma[6]
	Less toxic[1]	No change[2]	More toxic[3]			
Anorexia	52.2%	43.5%	84.6%	<0.001	0.316	<0.001
Nausea	26.7%	23.8%	48.7%	<0.001	0.259	0.007
ECG toxicity[7]	11.1%	15.4%	28.2%	0.007	0.317	0.006
Muscle weakness	24.4%	21.2%	37.2%	0.012	0.164	0.105
Restlessness	20.0%	20.3%	33.3%	.0037	0.192	0.064

1. Less toxic- assessment of toxicity after the knowledge of the SDC less toxic than assessment prior to knowledge of SDC i.e. change from "toxic" to "possibly toxic", "possibly toxic" to "non-toxic" or "toxic" to "non-toxic"
2. No change- assessment of toxicity after the knowledge of the SDC same as assessment prior to knowledge of SDC
3. More toxic- assessment of toxicity after the knowledge of the SDC more toxic than assessment prior to knowledge of SDC i.e. change from "non-toxic" to "possibly toxic", "possibly toxic" to "toxic", or "non-toxic" to "toxic"
4. P value for difference between prevalence of symptom across toxicity assessment change categories
5. Gamma: assessment of strength of relationship between ordinal measures in a cross-tabulation
6. Significance of Gamma
7. ECG toxicity- Electrocardiographic toxicity, according to literature based criteria of toxicity (Beller, Smith et al. 1971)

3.4 Discussion

The diagnosis of digoxin toxicity remains a difficult management problem in patients prescribed digoxin: most studies have been based on cardiac toxicity, and there is considerable overlap between toxic and non-toxic SDCs in these studies (Smith, Butler et al. 1969; Smith and Haber 1970; Beller, Smith et al. 1971; Howard, Smith et al. 1973; Singh, Rai et al. 1975; Aronson, Grahame-Smith et al. 1978; Waldorff and Buch 1978; Bernabei, Perna et al. 1980). A large number of factors including electrolyte changes, thyroid function, underlying heart disease, acid-base abnormalities, pulmonary disorders (Davis, Vanderveen et al. 1983) and possibly even age (Wofford, Hickey et al. 1992; Pahor, Guralnik et al. 1993; Miura, Kojima et al. 2000) influence the sensitivity to digoxin concentrations. Furthermore, the manifestations of digoxin toxicity are non-specific and can frequently be similar to those of the underlying illness, another cause and/or concurrent medications.

Ingelfinger and Goldman (Ingelfinger and Goldman 1976), in reviewing the literature, concluded that no study had examined whether the SDC provided diagnostic information in addition to that obtained from clinical observations. Since their work in the mid 1970s, little further research has been conducted in this area, but there is anecdotal and literature-based (Schapel and Read 1980) evidence that clinicians frequently use the SDC as the main determinant in the diagnosis of digoxin toxicity.

In the current study, the knowledge of the digoxin assay result, after consideration of clinical factors, did result in changes in the diagnosis of digoxin toxicity in approximately a third of the cases. Knowledge of the digoxin concentration primarily resulted in greater certainty regarding the diagnosis of toxicity, as the number of cases deemed "possibly toxic" was significantly reduced from 42.7% to 19.1%. In clinical practice this could have resulted in fewer patients having their doses inappropriately held for a period of observation, which could result in a shorter period of diagnostic uncertainty regarding the patient's management and potentially shorter hospital stays. This would be particularly useful in cases of suboptimal digoxin efficacy, where once the possibility of toxicity has been ruled out, the approach may be to increase the dose of digoxin, or to, for example, add another medication such as amiodarone or verapamil for the control of the ventricular rate in atrial fibrillation, which may increase the digoxin concentration.

The knowledge of the SDC also resulted in greater agreement between the judges regarding the patient's assessment of toxicity. Given that digoxin has a narrow therapeutic index, is a well recognized cause of medication related harm (ISMP High Alert Medications; LaPointe and Jollis 2003; Roughead and Semple 2002; Pirmohamed, James et al. 2004) , and communication error between health care professionals is a common cause of medication incidents (Roughead and Semple 2002), greater clinician agreement regarding the diagnosis of toxicity could potentially reduce the amount of harm associated with digoxin in a potentially toxic patient. This is particularly relevant as digoxin toxicity as the principal diagnosis for hospital admission has been decreasing in the last decade (HCUPnet 2005; AIHW 2005) and is

substantially lower than historical values (Mahdyoon, Battilana et al. 1990; Kernan, Castellsague et al. 1994). Hence patients are more likely to have manifestations of putative digoxin toxicity associated with other active problems for which they were admitted, rather than as the sole reason for hospital admission. For this reason, reduced uncertainty and greater agreement between clinicians regarding the diagnosis of digoxin toxicity becomes more important.

Analysis of the distribution of assessment of digoxin toxicity prior to and after the knowledge of the SDC reveals that the clinical diagnosis of a patient being "non-toxic" or "toxic" was an insensitive indicator of the patient's final toxicity assessment. However, the clinical assessment of "toxic" and "non-toxic" did have good positive predictive value for the final assessment of toxicity, with 80% and 92.5% of such patients having the same toxicity assessment after the knowledge of the SDC, respectively. In clinical practice, this could be interpreted in the following way. If a patient is thought to be "possibly toxic" on the basis of their clinical assessment, they should have a digoxin concentration determination performed, as in 64% of cases (141 of 219, Table 3.2), the assessment of toxicity would be altered on the basis of the SDC result. In cases where the patient is assessed clinically as being "non-toxic", in the majority of cases the assessment will remain the same after the knowledge of the SDC. However, in approximately 6% of the cases (15 of 254) the assessment will change to "possibly toxic", and in approximately 2% of cases (4 of 254) to "toxic" after the knowledge of the SDC. Whether such yields are sufficient to justify the routine conduct of assays in all patients depends on a large number of factors including the cost

and availability of the assay, and the consequences of missed cases of toxicity for the patient as well as the health care system, and is beyond the scope of this chapter. In cases where the patient is thought to be clinically toxic, the results of the present study suggest that in the vast majority of cases, the final assessment of toxicity after knowledge of the SDC remains unchanged. This is particularly pertinent as many patients present to clinicians with symptoms and signs of toxicity during the day, after having taken their morning dose of digoxin. In such circumstances, if the assay is drawn immediately then the SDC is artificially high and unreliable as it would be taken during the distribution phase (Mutnick 1995). Hence, if the patient is thought clinically to be "toxic", they should be treated as such, as in the majority of cases, the post-distribution digoxin concentration would confirm this clinical suspicion.

The final assessment of toxicity was closely correlated with SDC (Table 3.3). Hence those cases which were assessed as "toxic" had a higher SDCs than those who were "possibly toxic", and these in turn had higher SDCs than cases assessed as "non-toxic". This is an expected finding and does not necessarily signify the usefulness of serum digoxin measurement in the assessment of a patient's toxicity. The findings of this study suggest, however, that patients assessed after the knowledge of the SDC to have a higher degree of toxicity than that based on clinical assessment alone, do have a higher prevalence of symptoms typically associated with toxicity such as anorexia, nausea, electrocardiographic evidence of toxicity, muscle weakness and restlessness (Table 3.4). This would suggest that, in the context of this study, the assay was able to help correctly attribute these

symptoms to digoxin toxicity, which was missed by clinicians when they relied on symptoms alone.

Figures 3.6 and 3.7 demonstrate graphically the observation that the main effect of the knowledge of the SDC was to reduce the number of cases which were assessed as "possibly toxic". Figure 3.8 summarises the percentage of cases which had a change in their assessment of toxicity for ascending assay categories. It might be expected that this percentage would be lowest at the extremes of the SDC range, with low and high values being obviously non-toxic and toxic, respectively, based on clinical assessment alone. However, the results of this study suggest that the influence of assay in the assessment of toxicity is greatest at the highest SDCs. It is likely that the impact of the knowledge of the SDC on altering the assessment of toxicity would be less at much higher SDCs, at which patients would be expected to be universally manifesting symptoms of toxicity. However, such concentrations are rarely seen in current clinical practice.

Schapel et al (Schapel, Jones et al. 1981) assessed the influence of digoxin TDM on patient management and found that it did provide "extraordinary information to clinicians above clinical and ancillary predictors" to guide the adjustment of digoxin dose. They interviewed requesting doctors before and after the availability of the SDC result, and assessed the impact of this information on their intended action concerning future digoxin therapy. The same authors had previously found, however, that clinicians relied largely on the SDC to diagnose toxicity (Schapel and Read 1980). Hence the diagnostic utility of digoxin assays may reflect the lack of ability to interpret clinical and dosage information, rather than the intrinsic utility of TDM in this setting.

Since in this study the patient information was collected and presented systematically, it is likely to be a better arbiter of the utility of assays compared with clinical information alone than the study reported by Schapel et al. Furthermore these authors did not show any evidence of potential for improved patient outcome, such as greater detection of the manifestations of toxicity, in the group diagnosed as being digoxin "toxic".

The use of a computerised form in this study to present clinical information is artificial, and may not reflect clinical decision making very well. Although it may have been possible to interview individual clinicians regarding the impact of a digoxin assay on their management, this was the only way of presenting the information on a broad range of patients systematically to an expert panel.

There was a relatively small number of cases that were changed from "toxic" to "non-toxic" or the converse as a result of the knowledge of the SDC (7 of 513 assessments or 1.4%, Table 3.2). This may reflect the true influence of the knowledge of the SDC, or may reflect the fact that the clinicians performing the assessment did not want to document that they had assessed the patient's state of toxicity as toxic or non-toxic when their assessment after the knowledge of the SDC was the converse. This could have been avoided by presenting all of the cases to the judges twice, in a randomised fashion, once with and once without the assay result. This approach would have doubled the requirements of the judges, and may have influenced their compliance with the protocol and the quality of their assessments.

This was a retrospective study, and since the decision of the judges did not impact on the management of the patient, clinical outcomes were not evaluated in the patients involved. Hence, it is not possible to determine whether the benefits of the knowledge of the SDC demonstrated in this study translate into actual clinical benefits for patients.

It would have been desirable to have reached a summary assessment from the judges as to their collective assessment of the toxicity of each case before and after the presentation of the SDC. This could have been performed using a number of different methods of collating their individual assessments. However, any method chosen would necessarily have been arbitrary and may not have reflected the true summary assessment of the patient's toxicity.

The range of SDCs of the cases included in this study was higher than that seen in a general population of patients prescribed digoxin. This was done so that a larger number of patients would have evidence of toxicity than in usual practice, as the influence of the knowledge of the SDC on this assessment was the primary aim of this study. In routine clinical practice, a greater percentage of assays would be in the range of 0.5-1.5 ng/mL (0.6-1.8 nmol/L). Hence, the overall influence of the knowledge of the SDC in altering the assessment of toxicity would be expected to be less (Figure 3.8).

3.5 Conclusion

In conclusion, I individually presented five expert clinicians with all pertinent clinical information regarding 103 patients prescribed digoxin using a computerised form, and asked them to assess whether the patient was digoxin toxic before and after knowledge of the drug assay result. Knowledge of the assay result helped to reduce uncertainty regarding the diagnosis in individual judges, and increased agreement among them regarding this diagnosis. As expected, patients who were assessed as being more likely to be toxic after the knowledge of the SDC had higher digoxin concentrations than those who were assessed as being equally or less likely to be toxic. These patients were, in fact, more likely to have symptoms of digoxin toxicity than those in whom the assay did not alter their diagnosis. Hence this study provides further evidence that the digoxin assay is useful in diagnosing digoxin toxicity, particularly in those patients with clinical features suggesting "possible toxicity", both in helping to manage patients on digoxin, as well as being able to correctly attribute symptoms to digoxin toxicity over and above clinical features alone.

Chapter 4

THE USEFULNESS OF ROUTINE DIGOXIN ASSAYS ON ADMISSION TO MEDICAL UNITS

4.1 Introduction

Apart from assisting with the diagnosis of digoxin toxicity, another common indication for conducting serum digoxin assays is as a routine test upon admission to a hospital or other institution (Hladik and Dujovne 1979; Mayan, Bloom et al. 2002; Mordasinia, Krähenbühl et al. 2002). Although some authors consider it appropriate to perform such routine assays in patients who have not had a recent assay (Michalko and Blain 1987; Canas, Tanasijevic et al. 1999; Mordasinia, Krähenbühl et al. 2002), there has, in fact, been little research into the usefulness of digoxin assays in this setting.

A number of investigators have studied the role of routine assays in different practice settings including outpatient clinics (Savill J 1985), a nursing home (Dimant and Merrit 1978), and on admission to a rehabilitation institution (Goldstein, Stanton et al. 1985). Only in the latter setting was there a potential benefit, in that clinicians were more likely to alter management if the test result was above the "therapeutic range".

These studies were all conducted in a population of clinically stable patients. The usefulness of routine serum digoxin concentration (SDC) determination might be expected to be higher in patients admitted acutely to hospital, as

they would be more susceptible to alterations in the SDC due to potential alterations of renal function, and/or co-prescription of interacting drugs, as well as the difficulty in diagnosing over- or under-digitalisation due to intercurrent illnesses and co-prescription of other medications.

The aim of the study in this chapter was to:

- assess the usefulness of routine digoxin determination in patients admitted acutely to medical units of a tertiary referral hospital,
- assess factors that could be used to predict which patients would benefit most from such routine SDC measurements,
- determine the required sample size for different study designs to provide higher levels of evidence for the use of digoxin assays in this setting.

4.2 Methods

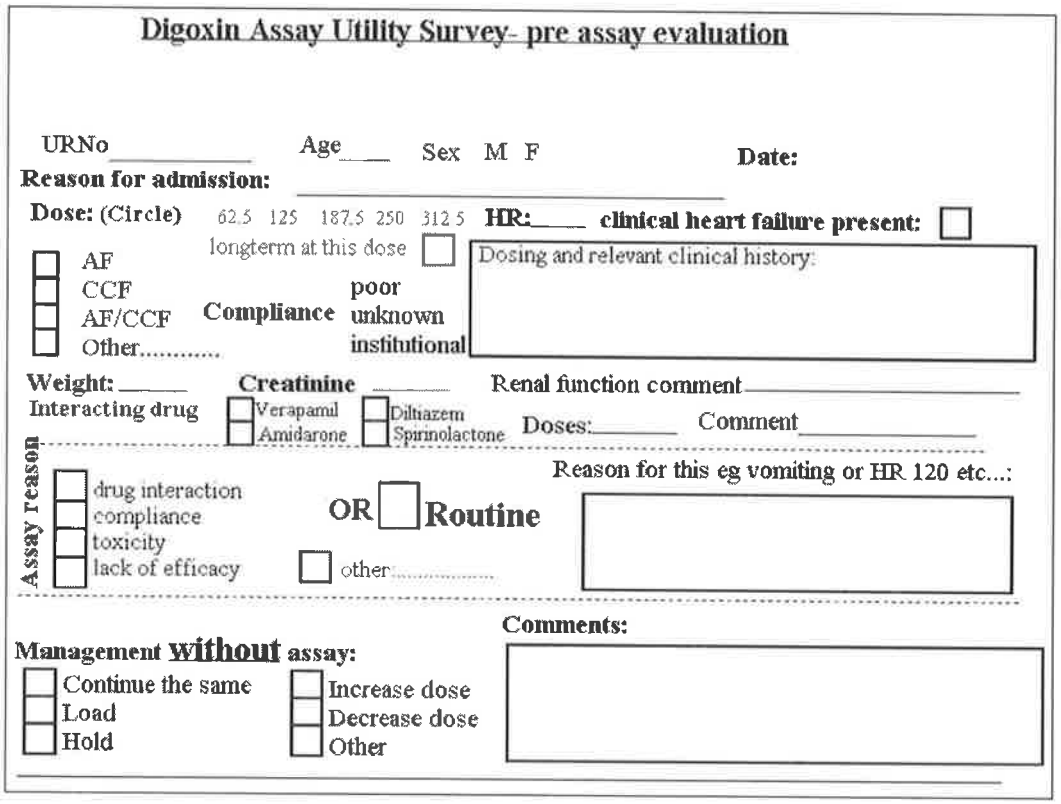
The study was performed within specific internal medical units of two metropolitan tertiary referral hospitals between 1997 and 2002. All patients admitted to these units through the emergency department, who were to have ongoing digoxin therapy were included. Patients in whom a digoxin assay could be of no possible benefit e.g. imminent death, or where a digoxin assay was conducted in the last 72 hours before admission and the result was known, or in whom a loading dose had been given in the emergency department prior to the assay being performed, were excluded. Enrolled patients had a serum digoxin assay performed as soon as practicable during the admission, at least 6 hours after the previous dose.

Clinicians on these units were recruited to collect data and to document their management regarding the patient's digoxin dosing. The clinicians recruited were the investigator, as well as resident staff who were approached and who were willing to participate in the study.

4.2.1 Data Collection Tool

Data collection was performed by the clinicians managing the patients using a double-sided A5 data sheet (Figure 4.1 and 4.2). The following data were collected prior to the availability of the digoxin assay result: age, gender, reason for admission, indication for digoxin therapy, details of dosing, factors relating to digoxin clearance such as renal function, weight, and details of interacting medications, as well as presence of clinical cardiac failure (e.g. presence of raised jugular venous pressure, respiratory crepitations, third heart sound), the heart rate, and the details of the reason for requesting the assay e.g. evidence of vomiting when assay performed for suspicion of toxicity.

FIGURE 4.1 FRONT OF DATA COLLECTION SHEET



Digoxin Assay Utility Survey- pre assay evaluation

URNo_____ Age____ Sex M F **Date:**

Reason for admission: _____

Dose: (Circle) 62.5 125 187.5 250 312.5 **HR:**____ **clinical heart failure present:** ☐

longterm at this dose ☐

☐ AF
☐ CCF
☐ AF/CCF
☐ Other.....

Compliance poor / unknown / institutional

Dosing and relevant clinical history:

Weight: ____ **Creatinine** ____ Renal function comment _____

Interacting drug ☐ Verapamil ☐ Amidarone ☐ Diltiazem ☐ Spirinolactone **Doses:**____ Comment _____

Assay reason

☐ drug interaction
☐ compliance
☐ toxicity
☐ lack of efficacy

OR ☐ **Routine**

☐ other.....

Reason for this eg vomiting or HR 120 etc...:

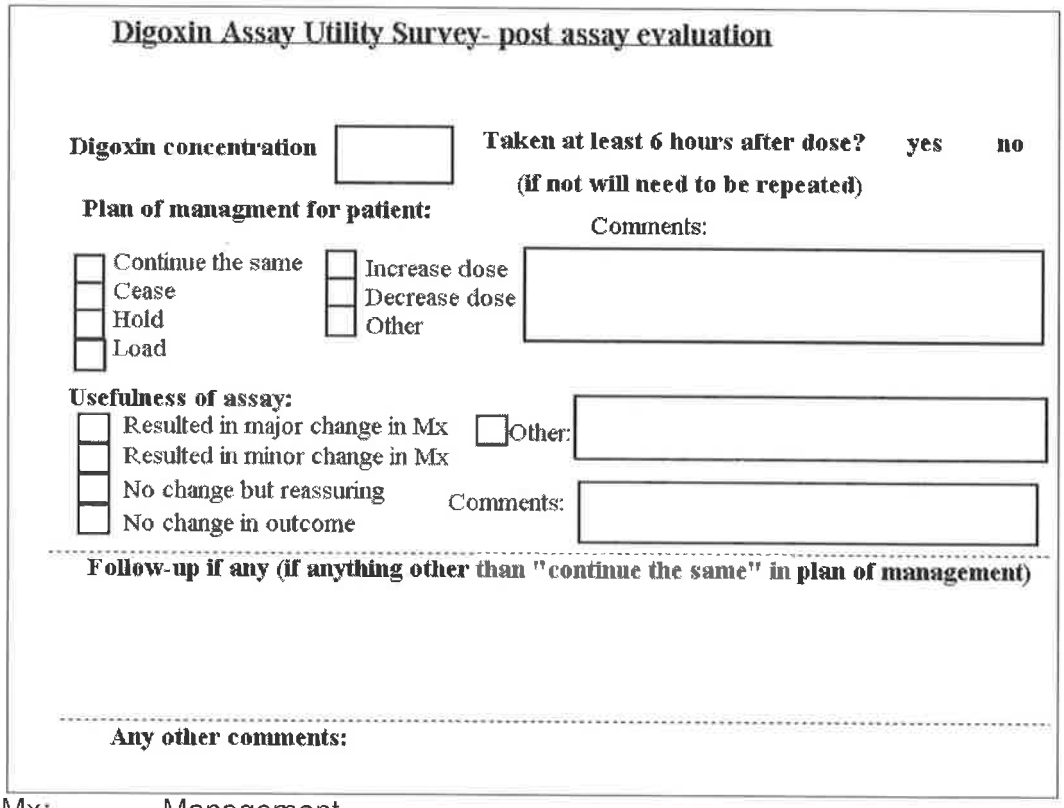
Comments:

Management without assay:

☐ Continue the same
☐ Load
☐ Hold
☐ Increase dose
☐ Decrease dose
☐ Other

M:	Male
F:	Female
AF:	Atrial Fibrillation
CCF:	Congestive Cardiac Failure
HR:	Heart Rate
URNo:	Unit Record Number

FIGURE 4.2 BACK OF DATA COLLECTION SHEET



Digoxin Assay Utility Survey- post assay evaluation

Digoxin concentration ☐ **Taken at least 6 hours after dose?** **yes** **no**

(if not will need to be repeated)

Plan of managment for patient:

Comments:

☐ Continue the same
☐ Cease
☐ Hold
☐ Load
☐ Increase dose
☐ Decrease dose
☐ Other

Usefulness of assay:

☐ Resulted in major change in Mx
☐ Resulted in minor change in Mx
☐ No change but reassuring
☐ No change in outcome
☐ Other:

Comments:

Follow-up if any (if anything other than "continue the same" in plan of management)

Any other comments:

Mx: Management

For each assay the clinician also recorded the reason for the assays as one of the following: "toxicity", "lack of efficacy", "drug interaction", "compliance", or "routine". The clinicians were given instructions on how to fill out the form and the definitions of the different categories. The "routine" category was defined as the situation in which the clinician deemed that the assay was not clinically necessary, and not thought to contribute to the management of the patient's current problem.

The clinicians were then asked to categorise their intended management of digoxin dosing without the knowledge of the SDC according to the following: "continue the same", "hold", "increase", "decrease" or "other". The "other" category could be used when alteration in another medication which may

influence concentration of digoxin, or combination of 2 or more of the above categories. For any intended action which would alter the digoxin concentration, the clinician was asked to indicate further details of dosing e.g. by how much the dose was to be altered, or for how long the dose should be withheld.

Once the SDC became available, the clinician recorded the concentration (Figure 4.2), and categorised how they would manage the patient with the knowledge of the digoxin concentration. The category "cease" could also be chosen, once the SDC was known. The difference in the planned management of the patient with and without knowledge of the SDC was categorised as "major" if there was a difference in the categories chosen, or "minor" if the categories were the same but the details of the management were different e.g. reduction of dose by differing amounts. The "utility" of the assay was determined on the basis of whether or not the assay resulted in a change in the management pertinent to digoxin dosing. "Yield" was defined as the percentage of assays which resulted in a change in management.

4.2.2 Digoxin Concentration Determination

SDCs were determined by laboratories accredited by the Australian National Association of Testing Authorities using the Syva enzyme immunoassay (Lane Cove, New South Wales) and the Abbott AxSYM system (North Ryde, New South Wales, Australia). The limit of quantification was 0.2 ng/mL for both methods. The therapeutic range for digoxin provided by the laboratory was 0.5-2.0 ng/mL and 0.6-2.3 nmol/L for the institutions that used mass and

molar units, respectively. A conversion factor of 1.2 was used for the conversion of concentrations from mass to molar (*systeme international*) units (Schumacher 1995).

4.2.3 Statistical Analysis

The data were subsequently entered into a Microsoft Access database, and were analysed using SPSS software (SPSS for Windows, Release 10.0.7 2000. Chicago: SPSS Inc.). Student's T test was used for normally distributed scale data, the Mann Whitney test for data that was not normally distributed, and the Fisher's Exact Test was used for analysis of dichotomous data. A p value of <0.05 was used for significance. Log binomial regression was performed for multivariate analysis using SAS software (Version 9.2, SAS Ins. Inc, Cary, NC). Due to the small numbers in each of the individual categories, "increase dose" and "load", and "decrease dose" and "hold" were pooled together for the univariate and multivariate analyses. Sample size calculations were performed using Compare 2 (v1.47 WinPEPI, 2006) using a p value of 0.05 and 80% power.

4.3 Results

Table 4.1 lists the characteristics of the 202 study patients. All patients enrolled completed the study and were included in the final analysis.

TABLE 4.1 CHARACTERISTICS OF STUDY PATIENTS

Characteristic	
Age (mean years ± standard deviation)	77.1 ± 9.4 (range 38-99)
Male	57%
Indication for digoxin: (number and percent)	
- Congestive cardiac failure	51 (25%)
- Atrial fibrillation	60 (30%)
- Both	90 (45%)
- Unknown	1 (0.5%)
Calculated creatinine clearance* (mean ± SD ml/min)	47 ± 28 (range 5-150)
Digoxin concentration measured at steady state**:	
- Yes	152 (75%)
- No	50 (25%)
Alteration in renal function:	
- Stable	144 (71%)
- Deteriorating	34 (17%)
- Improving	2 (1%)
- Unknown (no previous creatinine estimation available)	22 (11%)
Dosage change in last 4 weeks	17 (8%)
Medication compliance:	
- Unknown	165 (81.7%)
- Non-compliant	2 (1.0%)
- Supervised	35 (17.3%)
Co-prescription of interacting medication***	32 (16%)
Seniority of clinician:	
- Intern	19 (9.4%)
- Resident	73 (36.1%)
- Registrar	8 (4%)
- Consultant	102 (50.5%)

* Using equation by Cockcroft and Gault (Cockcroft and Gault 1976)

** The patient's digoxin concentration being measured at steady state was defined as being on an unchanged dose, with no alteration in renal function, nor the addition of interacting medications for 5 half lives, which was taken as being approximately 8 days (Roden 1996)

*** Amiodarone, spironolactone, verapamil, quinidine, erythromycin (Mutnick 1995)

TABLE 4.2 DISTRIBUTION OF DIGOXIN CONCENTRATIONS

Concentration Range (ng/mL)*	Number of Assays (percent)
≤0.5	17 (8%)
0.6-1.0	92 (46%)
1.1-1.5	55 (27%)
1.6-2.0	24 (12%)
2.1-2.5	9 (5%)
2.6+	5 (2.5%)

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

The population studied was elderly (mean age 77.1 ± 9.4), had moderate renal impairment (mean calculated creatinine clearance 47 ± 28 ml/min) and 25% of the patients (50/202) were not considered to be at steady state, due to a combination of altered renal function or dosage change prior to presentation. A substantial proportion (16%) was on interacting medications, and for 22 patients (11%) there were no previous creatinine measurements available, further adding to the uncertainty regarding the prediction of SDC on admission.

Table 4.3 lists the stated reasons for the assays, as well as their mean and median SDCs (as the SDCs were not normally distributed), and statistical comparison between the concentrations found in patients with the different reasons for assay. Despite the difficulty in predicting the digoxin concentration upon presentation, the majority of cases were deemed to be "routine" assays. Comparison of the median concentrations between groups

was highly significant ($p<0.0001$, Kruskal-Wallis nonparametric ANOVA), and patients for whom the assay was performed for reasons of suspicion of toxicity had significantly higher SDCs than for other indications. Patients who had assays performed for reasons of "compliance" had lower concentrations than for other indications, but this difference did not reach significance (Dunn's Post-Hoc Multiple Comparison Test).

TABLE 4.3 SERUM DIGOXIN CONCENTRATIONS BY REASON FOR ASSAY

Assay reason	Count (Percent of total)	SDC (ng/mL)* (Mean±SD) and Range	SDC (ng/mL)* (Median and IQR**)	P value for comparison of SDCs between groups:		
				Routine	Toxicity	Lack of efficacy
Routine	136 (67%)	0.95±0.44 (0.2-2.7)	0.90 (0.70-1.17)	N/A	<0.001	NS
Toxicity	37 (18%)	1.64±0.95 (0.5-5.2)	1.45 (0.90-2.0)	<0.001	N/A	<0.001
Lack of Efficacy	24 (12%)	0.84±0.35 (0.2-1.5)	0.85 (0.58-1.17)	NS	<0.001	N/A
Compliance	4 (2%)	0.37±0.34 (0.2-0.8)	0.29 (0.25-0.33)	NS	<0.001	NS
Drug Interaction	1 (0.5%)	1.42	1.42	N/A	N/A	N/A

NS= Not significant, N/A= Not applicable

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

** IQR: Inter-quartile range

Patients with "lack of efficacy" as an indication had very similar concentrations to patients having assays performed for "routine" reasons. Objective assessment of lack of efficacy was made retrospectively using the data recorded on the data collection forms (Figure 4.1): patients with an indication of cardiac failure who were documented as having clinical signs of cardiac failure on presentation, and patients with atrial fibrillation who were documented as having a heart rate ≥100, were defined as having objective evidence of lack of efficacy. Seventy-one patients fulfilled these criteria and

they had a mean SDC of 1.03 ± 0.58 ng/mL (1.24 ± 0.70 nmol/L), and median SDC of 0.92 ng/mL (1.1 nmol/L) compared to the remainder who had a mean SDC of 1.10 ± 0.74 ng/mL (1.32 ± 0.89 nmol/L) and median SDC of 0.94 ng/mL (1.13 nmol/L). This comparison was not significant (p=0.48), and based on the sample size and the standard deviation (assuming a normal distribution), there was 80% power to detect a 0.3 ng/mL difference in the means. Those patients who were suspected of non-compliance tended to have a lower SDC than all other groups, but because of the small number in this group (n=4) these comparisons were not statistically significant.

Table 4.4 lists the intended management without the knowledge of the SDC according to the assay indication. In most but not all cases, the intended management without the knowledge of the SDC was consistent with the assay reason e.g. 114 of 136 (84%) instances of routine assays, the intended management was to continue the same, and in 33 of 37 (89%) instances of suspected toxicity the intended management was to decrease or withhold the dose.

Table 4.5 lists the percentage of assays that resulted in a change in management by assay indication. As the majority of the changes were major (37 of 50), the major and minor changes were pooled. Overall 50 of 202 assays (24.8%) resulted in a change in management including 26 (19.1%) of the 136 "routine" assays. This percentage was lower than for other indications such as suspected toxicity, lack of efficacy, or suspected non-compliance. However, the difference was only statistically significant for the indication of toxicity, possibly due to the small numbers for the other reasons

resulting in a low statistical power. Of the 26 routine assays that resulted in a change in management, the majority (22/26) were defined as major changes.

TABLE 4.4 PROPOSED MANAGEMENT WITHOUT KNOWLEDGE OF THE SDC BY REASON FOR ASSAY

Assay	Proposed Management (Number and percent of assay reason)					
Reason (Count)	Continue the Same	Decrease	Withold	Increase	Load	Other
Routine (136)	114 (84%)	4 (3%)	8 (6%)	7 (5%)	1 (1%)	2 (2%)
Toxicity (37)	4 (11%)	2 (5%)	31 (84%)	0 (0%)	0 (0%)	0 (0%)
Lack of Efficacy (24)	12 (50%)	0 (0%)	0 (0%)	5 (21%)	1 (4%)	6 (25%)
Compliance (4)	3 (75%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)
Drug Interaction (1)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

TABLE 4.5 CHANGE IN MANAGEMENT AS A RESULT OF THE SDC DETERMINATION BY ASSAY INDICATION

Assay Reason	Total	Any Change in Management*	Percent of Patients with Change in Management (95% CI)**	P of Comparison to Routine***
Routine	136	26	19.1% (13.4-26.5%)	N/A
Non Routine	66	24	36.4% (25.8-48.4%)	0.009
- Toxicity	37	13	35.1% (21.8-51.2%)	0.047
- Lack of Efficacy	24	9	37.5% (21.2-57.3%)	0.06
- Compliance	4	2	50% (15.0-85.0%)	NS
- Drug Interaction	1	0	0%	NS
Overall	202	50	24.8% (19.3-31.1%)	N/A

*Includes major and minor changes

**CI: Confidence intervals

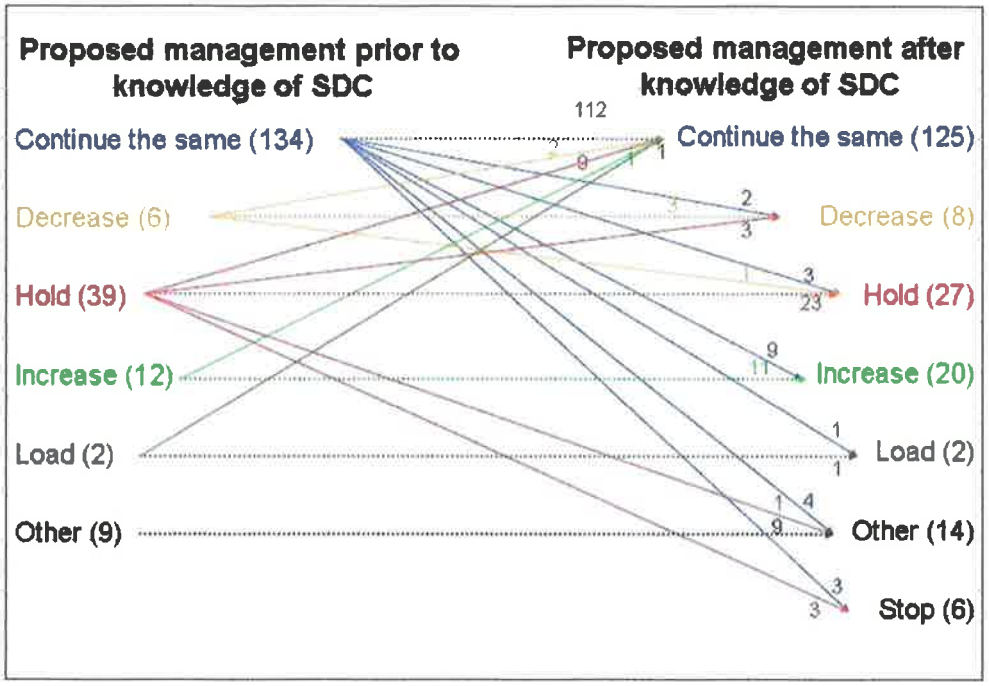
***Routine defined by the managing clinician as assay that was deemed as clinically unnecessary and not thought to contribute to patient management

NS: Non significant

N/A: Not applicable

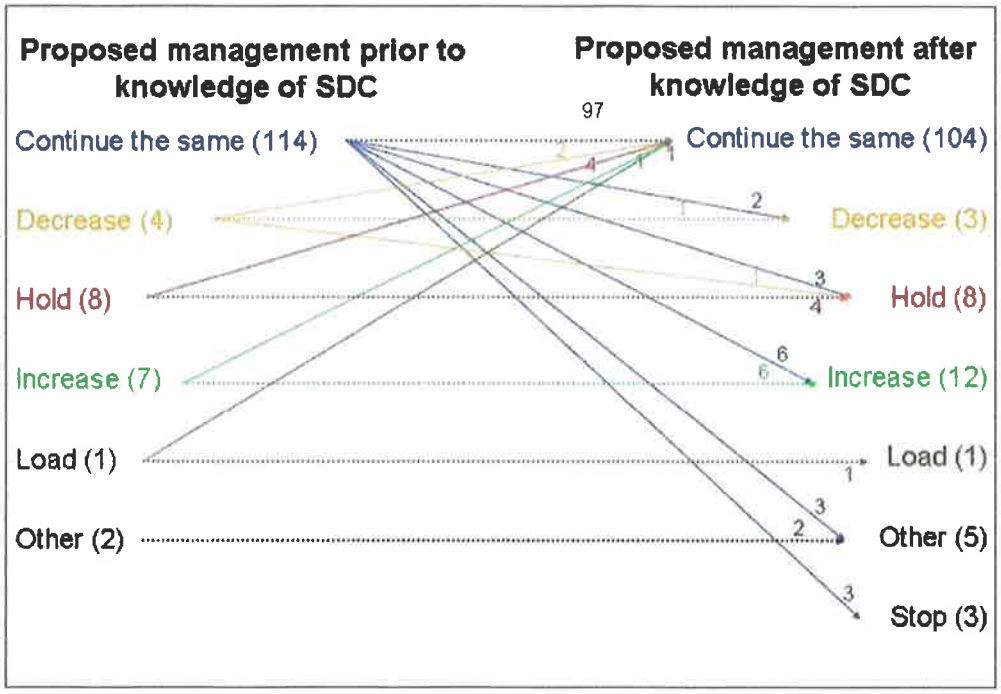
Figure 4.3 illustrates the changes in management as a result of the knowledge of the SDC for all patients, and Figure 4.4 illustrates the changes for patients with a routine assay indication.

FIGURE 4.3 ALTERATIONS IN MANAGEMENT AS A RESULT OF KNOWLEDGE OF SDC IN ALL PATIENTS



The numbers after the plan of management indicate the number of patients.

FIGURE 4.4 ALTERATIONS IN MANAGEMENT AS A RESULT OF KNOWLEDGE OF SDC IN PATIENTS HAVING ROUTINE ASSAYS ONLY



The numbers after the plan of management indicate the number of patients.

The routine assays were analysed in order to determine which factors were associated with greater utility. The following variables were assessed: gender and age of patient, seniority of clinician, indication for digoxin (AF, CCF, both or other), daily dose, duration at current dose, creatinine, calculated creatinine clearance, stability of creatinine, presence of clinical signs of cardiac failure on admission, heart rate (including presence of tachycardia (heart rate >100) or bradycardia (heart rate <60)), presence of interacting drugs such as amiodarone, spironolactone or verapamil, whether at steady state (yes or no), category of intended management, weight and the SDC.

On univariate analysis, the factors associated with a greater utility of the assay were lower calculated creatinine clearance (p=0.042), the category of intended management without knowledge of the SDC result (p=0.003), and subtherapeutic SDC (<0.5 ng/mL, and <0.6 nmol/L) (p<0.001). As the clinician cannot know the digoxin concentration at the time of ordering the assay, the subtherapeutic SDC variable was not included in the multivariate analysis. On log-binomial regression the only variable found to be independently associated with a greater likelihood of a change in management as a result of the assay was the category of the intended management without the knowledge of the SDC result. Those in whom the intended management was to decrease or withold the dose were 3.5 times (95% confidence interval 1.4-9.0) more likely to have a change in management as a result of the assay than those in whom the intended management was to continue the same, after adjustment for other factors.

The yields of routine assays by the intended management is demonstrated in Table 4.6.

TABLE 4.6 RATE OF CHANGE OF MANAGEMENT FOR ROUTINE ASSAYS BY INTENDED MANAGEMENT PRIOR TO KNOWLEDGE OF SERUM DIGOXIN CONCENTRATION

Intended management	Number of Patients	Major Changes	Minor Changes	Any Change	Rate of Change in Management (95% Confidence Intervals)
Continue the Same	114	16	1	17	14.9% (9.5-22.6%)
Any Alteration in Dosing	22	6	3	9	40.9% (23.3-61.3%)
- Decrease or Withold	12	5	2	7	58.3% (32.0-80.7%)
- Increase or Load	8	1	0	1	12.5% (2.2-47.1%)
- Other	2	0	1	1	50% (9.5-90.5%)

The intended management of 114 patients within the routine group was to continue the same, and this group was also analysed to determine the characteristics associated with a greater yield. Using the same variables in the model except for intended management, on univariate analysis subtherapeutic SDC ($p<0.0001$), and the patient having clinical signs of cardiac failure on presentation ($p=0.02$) were found to be significant. Once again, as the clinician cannot know the digoxin concentration at the time of ordering the assay, this variable was not included in the multivariate analysis. On log-binomial regression clinical signs of cardiac failure at presentation remained significant after adjustment for other variables, with patients having signs of cardiac failure being 2.6 (95% confidence intervals 1.1-6.1) times more likely to have a change in their management as a result of the digoxin assay, than patients not in cardiac failure at presentation. Of the 84 patients who did not have clinical signs of cardiac failure on presentation, 8 had a change in their management as a result of knowledge of the SDC (9.5%, 95% confidence intervals 4.9-17.7%), compared to 9 out of 30 patients (30%,

95% confidence intervals 16.7-47.9%) who did have clinical signs of cardiac failure on presentation.

The univariate and multivariate analyses were performed for patients having a major change in management as opposed to any change in management, and the results were similar.

The yields of the different assays categories is summarised in Figure 4.5.

FIGURE 4.5 BREAKDOWN OF ASSAY CATEGORIES AND YIELDS

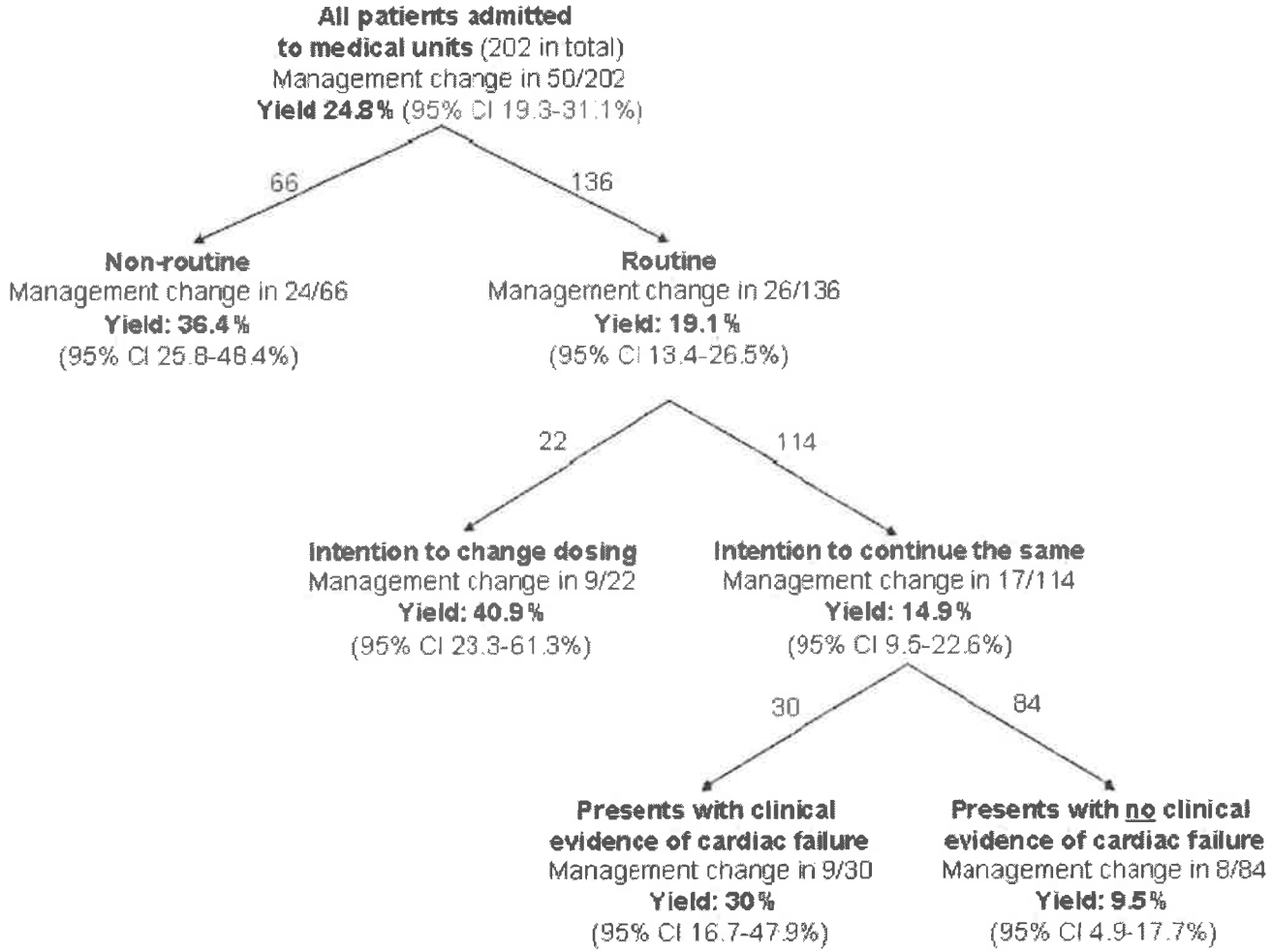


Table 4.7 lists the concentrations in the final category on the lower right of Figure 4.5, in the 8 patients who had a change in their management as a result of the knowledge of the SDC.

TABLE 4.7 DISTRIBUTION OF ASSAY CONCENTRATIONS IN PATIENTS WITH ROUTINE ASSAYS, INTENDED MANAGEMENT OF "CONTINUE THE SAME", AND WHO DID NOT HAVE CLINICAL EVIDENCE OF HEART FAILURE ON PRESENTATION, BUT WHO DID HAVE A CHANGE IN MANAGEMENT

Assay Concentration (ng/mL)*	Number
0.2	4
0.5	1
0.6	1
0.9	1
2.25	1

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

The data were also analysed according to the subgroup analysis by Rathore et al (Rathore, Curtis et al. 2003) from the DIG study which demonstrated a worse prognosis associated with trough SDCs of ≥1.2 ng/mL (≥1.5 nmol/L). The 84 patients with only cardiac failure as the indication for digoxin and in whom the intended management after the knowledge of the SDC was to continue the same were assessed to determine whether their management would have been different if the target SDC was to be in the range of 0.5-1.2 ng/mL (0.6-1.5 nmol/L). Twenty-two patients were identified as meeting these criteria. Of these, 7 (31.8%, 95% confidence intervals 16.4-52.7%) had concentrations of ≥1.2 ng/mL (≥1.5 nmol/L), the remainder had concentrations between 0.5–1.2 ng/mL, and none had a concentration of ≤0.5 ng/mL (≤0.6 nmol/L). Of those patients with SDCs above 1.2 ng/mL, 6 should have had a reduction in their dosage according to the recommendations by Rathore et al but the seventh patient was not at steady state at the time of the assay.

The data from the current study and the results of the study by Rathore et al (Rathore, Curtis et al. 2003) were used to calculate the required sample size of a case-control study to assess whether patients with SDCs within the range recommended by that paper, would be less likely to be admitted to hospital with evidence of cardiac failure. Table 4.8 lists the prevalence of clinical evidence of cardiac failure for patients in whom cardiac failure was the indication for digoxin therapy, and who were at steady state at different SDC ranges. As can be seen, such patients constitute 52% (106 of 202) of all of the presenting patients. Table 4.9 lists different potential sample sizes which would have 80% power at a p value of 0.05, assuming that the ratio of patients presenting in the concentration range of 0.5-0.8 ng/mL (0.6-1.0 nmol/L) to those at higher concentrations is 1:1.83 as was seen in this study. These data take into account the fact that 9.4% of eligible patients in this study had concentrations less than 0.5 ng/mL (0.6 nmol/L) and the Rathore paper did not provide any information as to their readmission rate, hence they would be excluded from the analysis.

TABLE 4.8 PREVALENCE OF SIGNS OF CARDIAC FAILURE IN PATIENTS WITH CONGESTIVE CARDIAC FAILURE (CCF) AS AN INDICATION FOR DIGOXIN THERAPY AND WHO WERE AT STEADY STATE BY ASSAY CONCENTRATION RANGE

Concentration range (ng/mL)*	Count (percent of total)	Percent of patients in each assay category presenting with signs of CCF
Less than 0.5	10 (9.4%)	40%
0.5-0.8	34 (32.0%)	41%
0.8-1.2	34 (32.0%)	29%
Greater than 1.2	28 (26.4%)	57%
Total	106 (100%)	42%

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

TABLE 4.9 SAMPLE SIZES FOR A CASE-CONTROL STUDY TO ASSESS THE IMPACT OF A THERAPEUTIC CONCENTRATION OF DIGOXIN IN CARDIAC FAILURE (0.5-0.8 NG/ML, 0.6-1 NMOL/L)*

Relative risk reduction	Prevalence of signs of heart failure in control group		
	30%	41%**	50%
0.40	325	228	138
0.32	840	486	309
0.25	1594	943	623

*Assuming that 50% of all patients presenting who are prescribed digoxin have heart failure as an indication and are at steady-state, using 80% power and significance at 0.05.

**41% of patients with cardiac failure as indication for digoxin therapy and who were at steady state presented with clinical evidence of cardiac failure in current study

4.4 Discussion

Despite the fact that digoxin assays are frequently performed (Mutnick 1995; Canas, Tanasijevic et al. 1999), and that the commonest indication is "routine" (Hladik and Dujovne 1979; Mayan, Bloom et al. 2002; Mordasinia, Krähenbühl et al. 2002), there has been little study of the utility of serum digoxin determinations in this setting. This is despite some authors considering a routine assay upon admission to hospital being appropriate

(Michalko and Blain 1987; Canas, Tanasijevic et al. 1999; Mordasinia, Krähenbühl et al. 2002), and others making a plea for such routine monitoring (Derkx, Bryson et al. 1983).

Most research into the utility of routine assays has been carried out in settings with stable digoxin dosing and elimination (Dimant and Merrit 1978; Kuhn, Hohenwallner et al. 1980; Savill J 1985) , where it would be expected that SDC determination would be unlikely to alter patient management. The current study, however, was performed in patients admitted in an emergency setting with many factors potentially contributing to unstable digoxin concentrations: the patients had moderate renal impairment, and many had either recent change in dosing, alteration in renal function, or were on an interacting medication, such that 25% were known not to be at steady-state upon presentation to hospital. The stability of renal function was unknown in 11%, and the details of previous dosing, and particularly medication compliance were unknown in many patients, further contributing to uncertainty of the predicted SDC. Furthermore, the majority of patients (70%) had congestive cardiac failure, where there is some evidence that the maintenance of the SDC in a narrow range is associated with improved outcomes (Rathore, Curtis et al. 2003).

It is difficult to compare the range of concentrations observed in this study with previous studies of routine digoxin concentration estimations, as the latter concentrations were only reported as being below, within, or above the therapeutic range and this range varied among the studies (Dimant and Merrit 1978; Goldstein, Stanton et al. 1985; Savill J 1985). The percentage of

assay results above the therapeutic range, which was universally defined as being above 2.0 ng/mL (2.4 nmol/L), varied between 10 and 17% in the previous studies, and was 7.5% in this current study. This is likely to reflect the fact that the former studies were performed in an era when much higher doses, and resulting concentrations of digoxin, were utilised.

Other audits of digoxin assays in the literature, which do not represent the routine conduct of digoxin assays on all patients prescribed digoxin, also reveal higher rates of concentrations above 2.0 ng/mL (2.4 nmol/L) (Hladik and Dujovne 1979; Ordog, Benaron et al. 1987; Howanitz and Steindel 1993; Canas, Tanasijevic et al. 1999; Mayan, Bloom et al. 2002; Mordasinia, Krähenbühl et al. 2002). However, there would be sampling bias in these studies, with patients having higher concentrations suggestive of symptoms of toxicity, being more likely to have an assay performed.

In the present study, the majority of assays were "routine", with most of the remainder being performed due to concerns about toxicity, which is similar to previous reports (Hladik and Dujovne 1979; Canas, Tanasijevic et al. 1999). Comparison of the SDCs performed for the different reasons reveals that there were significant differences in the concentrations between the different indications. Patients having assays conducted for suspicion of toxicity had significantly higher SDCs, and those patients having assays for suspicion of poor compliance had lower SDCs, although this result did not achieve statistical significance in comparison with the routine assays, probably due to low statistical power. Overall this analysis would suggest that clinicians are reasonable judges of the state of a patient's level of digitalization without

knowledge of the SDC, even in the setting of acute hospital admission where the digoxin concentration is often unstable.

The SDCs of patients having assays performed due to lack of efficacy were not different to the routine category, and analysis of the patients with objective evidence of lack of efficacy reveals that such patients tend not to have lower SDCs than the patients for whom the assay is performed as a routine. This is not surprising, given the fact that the majority of patients had cardiac failure as the indication for digoxin use, and it is certainly possible to present with cardiac failure with therapeutic digoxin concentrations. For patients with atrial fibrillation as the indication for digoxin therapy, the assays were performed when patients were first admitted for a variety of different reasons, not necessarily related to atrial fibrillation. Such patients would have presented with common medical conditions such as infections, chest pain, or exacerbation of chronic obstructive airways disease. Digoxin is not very efficacious at reducing the ventricular rate in atrial fibrillation in such situations of increased sympathetic tone (Roden 1996; Campbell and MacDonald 2003). Hence, those with lack of efficacy as the assay reason had similar SDCs to those for whom the assay reason was "routine".

Analysis of the intended plan of management according to the assay reason (Table 4.4) reveals that in most but not all cases, they are consistent with each other. Hence, in the majority of those having assays for routine reasons, the intention was to continue the same, but in 16% of cases (22 of 136) the plan of management was to alter the dose, and in those having assays performed for suspicion of toxicity, the intended management was to

reduce the dose in 89% of patients (33 of 37). This suggests that clinicians are confident to trust their judgement and to make changes to digoxin dosing in many cases without the knowledge of a digoxin assay result. Unfortunately, due to the small numbers involved, and the lack of detailed data recorded on the data collection forms it was not possible to analyse the management of these patients further.

In approximately half of the cases of lack of efficacy as the assay indication, the clinicians intended to continue their management. This is consistent with the above observation that objective evidence of lack of efficacy does not necessarily indicate SDCs below the therapeutic range. In many cases the clinicians would have waited for the SDC in order to determine whether the dosage should be increased or not. In such cases the main benefit of the SDC is to assist in determining the likely risk : benefit ratio in regard to the risk of toxicity compared to increased efficacy if the digoxin concentration is increased.

The above observations have to be viewed in the context in which the study was conducted, that is, in tertiary referral institutions where the assay results were generally available within 24 hours. In this setting, the questions asked on the data collection form may not readily reflect actual practice with respect to the intended management without the assay result, as the clinicians filling the form out would be aware that regardless of what they documented, it is likely that they would have the assay result available before the decisions that they had documented had been implemented.

Once the assay result became available, the patient's management with respect to digoxin dosing was altered in approximately a quarter of the patients (Table 4.5). In those patients having a digoxin assay for routine reasons, approximately 20% (26 of 136) had an alteration in their management as a result of the knowledge of the SDC. This is a surprisingly high value given that these are, by definition, assays which the clinicians felt were unnecessary and in usual clinical practice may not be performed. Furthermore, 22 of these 26 resulted in a difference in the category of management and were defined as major changes.

The other assay indications had a significantly higher yield, with approximately 1 in 3 assays results leading to a change in the patient's digoxin management. When the clinicians were educated regarding the data collection tool, it was made explicit that if they felt that the patient should have an assay performed, that the reason had to be specifically stated, and that if they felt that the assay was unnecessary then the reason should be documented as "routine". Hence it can be safely assumed that in normal clinical practice, all of the non-routine assays would usually be performed. The number of assays involved was insufficient to allow comparison of the differences in utility according to the various non-routine reasons.

Figures 4.3 and 4.4 illustrate the changes that were made according to the intended management prior and after the knowledge of the SDC. These data reveal that, although the knowledge of the SDC not infrequently results in a change in management, the clinical judgment of the clinicians is often correct. As can be seen from Figure 4.3, although there are numerous

changes as a result of the knowledge of the SDC, none of the patients who were thought to be under-digitalised and for whom the intended management was to load or increase the dose, subsequently had their doses held or decreased as a result of the knowledge of the SDC. Similarly, although a large number of patients, who were thought to require their digoxin dosing to be held or decreased prior to the knowledge of the SDC, had different management after the SDC was known, none had a load or increase in dosage. Hence, it appears that although the SDC result may frequently be different to that anticipated, it complements rather than contradicts clinical suspicion. This observation has occurred in the context of patients whose digoxin concentrations are frequently unstable, and by a group of clinicians about half (45%) of whom were junior hospital staff (interns or residents).

Because it was assumed that the non-routine assays would be clinically indicated, they were not analysed to assess the factors associated with greater yield. For routine assays, surprisingly, a number of factors that one would assume would be associated with greater yield, such as unstable renal function, recent dosage change, not being at steady state, or lack of seniority of clinician were not significant. There are many possible reasons for this, but a likely explanation is that the category of intended management was very significant ($p=0.003$) with a large relative risk (3.5), and it is likely that the influence of these other factors was captured by this variable. In fact, this variable was the only significant independent predictor of yield in routine assays on multivariate analysis.

As can be seen in Table 4.6, if the intended management was to decrease or withold the dosage in "routine" assays prior to the knowledge of the SDC, nearly half resulted in a change in management as a result of the knowledge of the SDC. Commonly the intended management after the knowledge of the SDC was to "continue the same" (Figure 4.4). In fact, the yield of assays performed for "routine" reasons for which the intended management was to alter dosing is very similar to the yield of assays performed for non-routine indications. These data suggest that if the clinicians intend to change the management of the patient, particularly if they intend to reduce or withold the dosage, and feel that the conduct of the assay is unnecessary, in many circumstances they are incorrect, and the assay would result in a change in management. Most commonly it would be to continue dosing, when the intended management would take action which would have reduced the SDC.

The definition of a routine assay used in this study was an assay considered to be unnecessary on clinical grounds. As seen above, in approximately 16% of such assays, the intended management without knowledge of the SDC was to alter the dosage, and in such patients the yield of the assay is similar to patients in whom the assay is performed for another reason. A tighter definition of routine assays would be ones where the clinician considers the assay to be unnecessary, and the intended treatment is to continue the same. As can be seen from Table 4.4, such assays make up the majority of routine assays (84%), but the yield of a digoxin assay in this population is still approximately 15% (Table 4.6). Hence even if the clinician feels that the assay is unnecessary, does not intend to perform an assay, and does not

intend to change the dosing regimen, if an assay were to be performed, one in seven would result in a change in dosing. Analysis of factors associated with greater yield in this population revealed clinical signs of cardiac failure on admission as the only factor that is independently associated with a greater yield, with approximately 30% of those with evidence of cardiac failure on presentation having a change in their management compared to 10% in those without.

It is surprising that the presence of clinical cardiac failure on admission was associated with a greater yield, compared to having any history of previous cardiac failure as the indication for heart failure. One possible explanation is that during the conduct of the study (1997-2002), some small experimental studies were published suggesting that most of the benefit of digoxin in cardiac failure was achieved with concentrations at the lower end of the therapeutic range (Gheorghiade, Hall et al. 1995; Slatton, Irani et al. 1997), but more convincing data, such as subgroup analysis from the DIG study (Rathore, Curtis et al. 2003), were not published until after completion of this study. For this reason, it is likely that the clinicians managing the patients would not have necessarily used the narrow therapeutic range for digoxin in heart failure that is currently recommended, and as a result, the presence of a history of cardiac failure would have been less likely to have resulted in a change in management.

These different categories of yields are summarized in Figure 4.5. It can be seen that the role of the conduct of digoxin assays on admission of medical patients can be broken up into 2 categories:

Category A: Patients with any of the following:

1. with a specific reason for having an assay performed e.g. lack of efficacy, suspicion of toxicity, compliance or concern about drug interactions,
2. for whom the intention is to alter the dosing regardless of the reason for performing the assay,
3. who present with clinical signs of cardiac failure.

Category B: Patients in whom the assay is not thought to be necessary, the intention is to continue dosing the same, and who do not have clinical signs of heart failure.

Category A constitutes approximately 60% (95% confidence interval 51.5-65.0%) of assays, and the conduct of a digoxin assay on admission in this group results in a change in management in 35.6% (95% confidence interval 27.5-44.6%). Performing an assay would be considered mandatory in patients in the first subgroup within this category, but has a similar yield for the other two subgroups, and hence should also be performed for these patients.

Category B represents the remainder of the assays (41.6%, 95% confidence interval 35.0-48.5%) and the yield in this group is 9.5% (95% confidence interval 4.9-17.7%). It could be debated whether there is a sufficient yield for performing assays in all of such patients on admission However, given that the assay is readily available, is relatively inexpensive, and is not a great burden for patients who are often having blood drawn for other tests in the first few days of their admission, this yield would be justified in most Western

health care institutions. Furthermore, as seen in Table 4.7, the distribution of assays in this sample included 4 patients who were possibly non-compliant, and one patient with a toxic concentration, suggesting that the assay result reveals information that is critical to the patient's management. The fact that digoxin has a narrow therapeutic index, its manifestations of toxicity are very variable, and it is listed amongst the medications associated with a high risk of adverse drug events (Roughead and Semple 2002; Pirmohamed, James et al. 2004), would further provide support for performing the assay in such patients despite the low yield.

Analysis of the data according to the study by Rathore et al into the association of trough SDCs performed 1 month after initiation of digoxin therapy in the DIG trial (Rathore, Curtis et al. 2003) revealed a further group of patients who would have a higher yield of routine digoxin assays on admission, i.e. patients who have a history of cardiac failure. The data were analysed including only those patients in whom the management would have been to "continue the same", as insufficient data were collected to be able to retrospectively assess what management would have been appropriate in other circumstances. The analysis was limited to patients with cardiac failure as the only indication for digoxin therapy i.e. those without a history of atrial fibrillation, as the DIG study did not address such patients (The Digitalis Investigation Group 1997). Furthermore, concentrations of >1.2ng/mL were used as there was an association between these concentrations and increased mortality, whereas the concentration range 0.9-1.1 ng/mL was associated with mortality similar to that of placebo treatment (Rathore, Curtis et al. 2003). Hence, although a fairly conservative approach was used, a

further 22 of 202 patients (10.9%) were identified in whom the yield was approximately 30%. The inclusion of this population of patients in category A above would result in a larger group with a similar yield, but would result in category B having an even lesser yield. The exact yield and benefit of the conduct of digoxin assays in patients with cardiac failure as the indication for digoxin is somewhat speculative as the information regarding the target SDCs in cardiac failure was not well known to most of the clinicians during the conduct of the study. It would be reasonable to conclude, however, on the basis of this analysis that a proportion of patients with a history of heart failure as the only indication for digoxin therapy would have their management changed as a result of the knowledge of the SDC, as has been demonstrated in this study.

Numerous previous studies have evaluated the appropriateness of digoxin SDC determination (Hladik and Dujovne 1979; Copeland, Thorpe et al. 1992; Howanitz and Steindel 1993; Piergies, Worwag et al. 1994; Canas, Tanasijevic et al. 1999; Mayan, Bloom et al. 2002; Mordasinia, Krähenbühl et al. 2002). The majority have found a high incidence of inappropriate therapeutic drug monitoring. Although premature sampling is a common cause in some studies (Howanitz and Steindel 1993; Piergies, Worwag et al. 1994), in others it is described as being due to a high incidence of "routine" assays (Hladik and Dujovne 1979; Mayan, Bloom et al. 2002; Mordasinia, Krähenbühl et al. 2002). The data from the current study reveal that approximately 1 in 5 patients having so-called "routine" assays upon admission to a hospital medical unit, may have a change in their management as a result of the drug assay, that it is possible to predict which

patients have a higher yield from the conduct of the assay, and gives evidence for the hitherto poorly supported recommendation that such patients should indeed have digoxin assays performed (Canas, Tanasijevic et al. 1999; Mordasinia, Krähenbühl et al. 2002). This result is in contrast to other studies of routine investigations in general (Hubbell, Greenfield et al. 1985; Hubbell, Frye et al. 1988), as well as specific (Aronson, Gennis et al. 1989; Namias, McKenney et al. 1996; Sherard and Newton 2001) patient populations, which have not demonstrated a change in the management of patients as a result of routine testing.

At both institutions at which the study was conducted, attempts were made to ensure that all patients, who were prescribed digoxin therapy on admission to the pre-specified units, had digoxin assays performed. It is possible, however, that some patients, particularly those with short durations of admission, may have been missed. Unfortunately the hospital pharmacy information systems in both institutions were unable to guarantee capture of all patients prescribed digoxin, as it was available on ward imprest stock. As a result, it is not possible to estimate the percentage of patients who may have been missed. In such patients, particularly those with short admission lengths, it might be assumed that the assay would be less likely to influence their management, hence the yields described above may overestimate the percentage of the total number of patients who may benefit from the conduct of a routine digoxin assay. However, given the fact that many of the patients who would have been missed from the study, may have had overnight admissions or admissions over a weekend, the data can be said to apply to

patients in whom it is "practicable" to perform routine digoxin assays on admission.

Another deficiency of the study was that requiring the clinicians to fill out the data collection sheets may have introduced bias, and made them think more about their assessment of the patient's digoxin status, and their prescribing. Unfortunately, this form of bias is inherent in such an observational study. It is likely that in usual clinical practice the clinicians, particularly the more junior staff, would have been less observant of clinical factors, and more reliant on the information from the digoxin assay, resulting in a higher yield from the conduct of the assay. However, by asking the clinicians to document the reason for the assay, and their intended management prior to the knowledge of the SDC, it is more likely to reflect the usefulness of the assay in a situation where the assay is not available and clinicians are required to make clinical judgements without the ready availability of the assay.

The outcome assessed in this study was alteration in management as a result of the knowledge of the SDC. It is uncertain what clinical impact this information would have on the patient. If the observations by Rathore et al (Rathore, Curtis et al. 2003) hold true, then it would be expected that the benefit may be manifest in terms of reduced mortality and readmission to hospital. Unfortunately, as described in earlier chapters, a study that is sufficiently powered to be able to detect changes in readmission, mortality or quality of life would have to be substantially larger, and there is no reliable clinical tool for the assessment of digoxin toxicity. This is particularly significant given that no study has yet demonstrated that patients randomised

to a particular serum digoxin concentration range have better outcomes (Spector, Park et al. 1988; McInnes 1989; Tonkin and Bochner 1994; Barr and Schumacher 1995). Hence, although clinicians would have altered the digoxin dosing in this study in order to maintain the SDC within a pre-specified range, the impact on patient outcomes may be expected to be less.

The results of this study can be used, however, to inform the sample size and the conduct of a randomized trial of digoxin assays. It can be seen from Figure 4.5 and categories A and B above, that if a randomised trial of the utility of digoxin assays on admission to hospital were to be performed in all patients, according to this study approximately 40% of patients (95% confidence interval 35-50%), are unlikely (<10% chance) to have a change in their management as a result of the conduct of the drug assay. However, if the study is performed in patients fulfilling the criteria in Category A, half as many patients would be enrolled but there is a 1 in 3 chance of alteration in management as a result of the assay. Hence, the sample size can be substantially reduced.

Alternatively, the results of the range of SDCs, the presence or absence of signs of cardiac failure on presentation, and whether the patients were at steady-state or not, can be used to determine the required sample size for a case-control study where the cases are patients admitted to hospital on digoxin with clinical signs of cardiac failure, and the controls are patients admitted without clinical signs of cardiac failure. Such a design could be used to address the question of whether patients whose digoxin concentrations are targeted to a particular concentration range are less likely to be admitted to

hospital with clinical evidence of cardiac failure. A case-control design would be susceptible to confounding bias in that patients who have closer attention paid to their digoxin concentrations may also have closer attention paid to other factors, e.g. angiotensin converting enzyme inhibitor or diuretic dosage, which may also contribute to the likelihood of hospital admission. It may also be more appropriate to use, as the control group, patients in the community who are not admitted to hospital. However, there are insufficient data available from this study to be able to inform the required sample size for such a study.

4.5 Conclusion

In summary, despite the fact that the conduct of routine assays on admission is advocated by some, there was previously little evidence to support this practice. In the current study, patients prescribed ongoing digoxin therapy who were admitted to medical wards had digoxin assays performed on admission, and in many cases the circumstances surrounding the SDC were unstable and hence the concentration was not predictable. This study reconfirmed other reports that routine assays were the commonest reason for conducting digoxin assays, and the majority of the remainder were conducted due to concerns about toxicity. Analysis of the reasons for the assays and the intended management suggests that clinicians are reasonable judges of the state of the patient's digitalisation. The exception to this is in cases of suspected lack of efficacy, a finding that was confirmed by objective assessment of lack of efficacy.

In approximately a quarter of the cases management was changed as a result of the assay being performed, and this yield was significantly higher in patients having assays performed for non-routine reasons. In general, the results of these assays tend to complement rather than contradict the plan of management that was determined prior to the knowledge of the SDC.

Analysis of routine reasons for digoxin assays revealed that the intended management was the only independent predictor of higher yield, with patients whose intended management was to alter dosing, having a significantly higher yield, which was similar to patients who had an assay performed for non-routine reasons.

Analysis of patients who had routine assays with the intended management of continuing the same dosing, showed that there was a change in management in approximately 15% of cases. The independent predictor of increased yield in this population was the presence of clinical evidence of cardiac failure on admission. Retrospective analysis of the data for patients with cardiac failure as the indication for digoxin therapy, aiming for a steady-state concentration of <1.2 ng/mL (<1.5 nmol/L) reveals that this is a further group of patients that may possibly have a higher yield from the conduct of admission digoxin assays.

As a result of this analysis it is possible to establish criteria for patients in whom the conduct of an admission digoxin assay is likely to result in a change in management (Category A). These include patients in whom the assay reason is suspicion of toxicity, lack of efficacy, non-compliance or drug interactions; patients in whom the plan of management prior to the

knowledge of the SDC is to alter management; patients with evidence of clinical cardiac failure on admission, and possibly patients with cardiac failure as the indication for digoxin therapy. Such patients would constitute approximately 60% of all patients prescribed digoxin admitted to medical units, and yield of a digoxin assay would be approximately 35%. The remainder (Category B) would constitute approximately 40% of patients, and the digoxin assay would have a yield of approximately 10%. In Western societies where access to the assay is readily available, and there is documented evidence of harm associated with medications with narrow therapeutic indices such as digoxin, the conduct of assays in this population would seem justified.

A randomised trial of digoxin assays should target patients admitted to hospital in Category A, as such patients have a higher incidence of alteration of their management as a result of the conduct of the assay, resulting in a smaller required sample size. A case-control study to assess whether patients whose digoxin concentration is targeted to a particular concentration range are less likely to be admitted to hospital with clinical evidence of cardiac failure, would require fewer patients. However, the study design would not be as appropriate as a randomised trial. Nevertheless, there is now at least some observational data supporting the conduct of routine digoxin assays in patients admitted to hospital, and the yield of this strategy can be increased with the application of appropriate patient selection criteria.

Chapter 5

SYSTEMATIC SURVEY OF SYMPTOMS OF DIGOXIN TOXICITY AND CORRELATION WITH SERUM DIGOXIN CONCENTRATIONS IN HOSPITAL INPATIENTS

5.1 Introduction

In the previous 2 chapters I have studied the impact of the knowledge of the SDC on clinical decision making. In both studies, the utility of the assay was largely dependent on an understanding of the therapeutic range for digoxin, particularly the upper limit of this range which represents the threshold for toxic concentrations. The upper limit of the therapeutic range for digoxin is used not only for determination of whether a patient is toxic or not, but also for providing guidance on how much the digoxin dosage can be increased, without the patient developing toxicity.

Over 200 years ago, Withering gave an account of the effects of "foxglove when given in large doses" (Withering 1785), and since then many similar descriptive accounts of the effects of cardiac glycoside toxicity have been written (Hurwitz and Wade 1969; Shapiro, Slone et al. 1969; Lely and van Enter 1970; Beller, Smith et al. 1971; Lely and van Enter 1972). These effects include a variety of cardiac rhythm disturbances as well as gastrointestinal (nausea, anorexia, vomiting, abdominal pain, diarrhoea) (Lely and van Enter 1970; Lely and van Enter 1972), neuropsychiatric (fatigue,

depression, confusion, dizziness, delirium) (Lely and van Enter 1970; Gorelick, Kussin et al. 1978; Shear and Sacks 1978; Varriale and Mossavi 1995), and visual (chromatopsia, reversible red-green colour blindness) (Lely and van Enter 1970; Aronson and Ford 1980; LeSage and Chuman 1986) manifestations. Studies on digoxin toxicity are important as, despite decreasing popularity, digoxin is a commonly recognised cause of medication adverse events, (LaPointe and Jollis 2003; Roughead and Semple 2002; Pirmohamed, James et al. 2004) due to its narrow therapeutic index. A number of studies performed in the 1970s assessed the relationship between serum digoxin concentrations (SDCs) and toxicity. Toxicity in these studies was defined empirically, and was based on electrocardiographic criteria with or without extracardiac manifestations(Smith, Butler et al. 1969; Beller, Smith et al. 1971; Evered and Chapman 1971; Singh, Rai et al. 1975; Aronson, Grahame-Smith et al. 1978). These studies aimed to demonstrate that SDCs were higher in patients with clinical toxicity, a fact that is now well accepted.

Since then no study has critically reassessed the individual symptoms and signs commonly ascribed to digoxin toxicity, in order to evaluate their relationship to serum SDCs, prevalence in a group of inpatients treated with digoxin, or predictiveness for digoxin toxicity. Given that the manifestations of digoxin toxicity are non-specific, this information would be useful in determining whether a patient's symptoms are likely to indicate digoxin toxicity, or are more likely to be due to another condition. This is particularly pertinent given that digoxin doses are less today, and patients are exposed to much lower serum concentrations, than in the era in which these studies were performed (Marik and Fromm 1998; Williamson, Thrasher et al. 1998).

Hence, the likelihood that an individual symptom is associated with digoxin toxicity is also lower than in previous decades.

Furthermore many studies have assessed the influence of factors which can alter a patient's sensitivity to SDCs. Some of those described include age (Pahor, Guralnik et al. 1993; Miura, Kojima et al. 2000), electrolyte changes (Aronson, Grahame-Smith et al. 1978; Davis, Vanderveen et al. 1983; Sonnenblick, Abraham et al. 1983; Young, Goh et al. 1991), acid-base disturbances (Sonnenblick, Abraham et al. 1983), type of underlying heart disease (Ooi and Colucci 2001; Braunwald 2005), pulmonary disease (Beller, Smith et al. 1971), and hypoxaemia (Braunwald 2005) Much of this literature is based on studies performed at a time when the prevalence of some of these such as hypokalemia, hypothyroidism, and type of heart disease, would have been different to clinical practice today.

The aim of the study in chapter was to:

- determine which symptoms demonstrated a concentration-effect relationship with SDCs,
- determine the concentrations at which these symptoms are likely to become manifest in hospital inpatients,
- assess the factors which alter the sensitivity to digoxin in this population.

5.2 Methods

The study was performed at three university teaching hospitals, and the protocol was approved by each Clinical Research Ethics Committee. The

study utilised a questionnaire-based approach in two groups of patients: patients taking digoxin who had trough SDCs performed (Group 1) and patients with indications for digoxin therapy (atrial fibrillation, and cardiac failure) but who were not receiving such therapy (Group 2). Data were collected from the latter group in order to determine the background prevalence of the relevant symptoms

5.2.1 Patients

Eligible patients were those who had adequate comprehension of English to be able to give informed consent and answer a questionnaire. For Group 1, each day the clinical pharmacology laboratory identified 3-5 patients who had digoxin assay results covering the range of results for SDCs assayed for that day, including all of the assays above the therapeutic range for the laboratory (SDC >2.0 ng/mL). I, who was blinded to the digoxin assay result, then approached each patient, confirmed that the assay was taken as a trough, and applied the questionnaire. This approach allowed assessment of a higher proportion of patients with SDCs above the therapeutic range than would be seen in routine clinical practice, whilst maintaining the blinding of the investigator to the assay result.

Patients in Group 2 were identified by approaching clinicians on general medical and cardiology units, who were blinded to the purpose of the study, regarding potential patients in whom digoxin therapy would be indicated but who were not receiving the drug. Patients were then approached and a questionnaire similar to that used in Group 1 was applied.

5.2.2 Questionnaire

The questionnaire is shown below in Table 5.1. The questions were selected to reflect the manifestations of digoxin toxicity that had been described in the literature, in a manner that was simple for clinicians to apply and for patients to answer. Manifestations that have been previously described as cardinal symptoms of digoxin toxicity e.g. nausea, vomiting and fatigue (Lely and van Enter 1972) were sought in a number of different ways, in order to determine the most reliable method of assessment. As questions 3 and 4, and question 7 addressed the same symptoms in different ways, the order in which they were administered was randomised so that asking questions 3 and 4 first did not consistently influence the responses to question 7. Many of the fatigue questions were derived from the Fatigue Severity Scale (Krupp, La Rocca. et al. 1989), which can be used to assess the level of fatigue and to monitor its change over time or in response to therapeutic interventions. Objective testing of mental state was based on a modified "mini-mental state" examination (Folstein, Folstein et al. 1975).

TABLE 5.1 QUESTIONNAIRE UTILISED

Gastrointestinal symptoms:
1. Did you look forward to your last meal?
In the last 1-2 days would you say that you:
2. Felt off your food?
2a. If you have felt off your food, would you describe this as a little or a lot?
3. Felt like vomiting?
4. Vomited?
5. Had any abdominal pain?
6. Had any diarrhoea?
7. The feeling of wanting to vomit is nausea. Would you say you had no nausea, slight, moderate, severe nausea, or vomiting?
Neuropsychiatric:
In the last 1-2 days have you had any
8. Difficulty thinking?
9. Muscle weakness?
10. Dizziness?
11. Agitation?
12. Tiredness?
Regarding the last 1-2 days: (reported as not at all, a little, or a lot)
13. Does thinking require effort?
14. Have you been easily tired?
15. Does tiredness cause you frequent problems?
16. Does tiredness interfere with your functioning?
17. Do you feel more confused in your thinking?
Objective testing of mental state:
18. Day?
19. Date?
20. Month?
21. Year?

Objective testing of mental state (Continued):
22. Place?
23. Ward?
24. Registration of 3 objects
25. Number of registration attempts
26. Counting backwards from 100 using 7s (scored out of 5)
27. Spelling "world" backwards (scored out of 5)
28. Recall of 3 objects
Colour vision changes:
Have you noticed any:
29. Changes in colour vision?
30. Blurred vision?
31. Haloes around lights?

5.2.3 Colour Vision Testing

All of the colour vision testing was performed using available ward lighting rather than standardised lighting conditions, as the latter would not reflect the utility of these tests in routine clinical practice. Chromatopsia was assessed by asking the patient to describe the colour of a 2.5 cm square of white paper presented on a black background. The reporting of any colour other than white indicated chromatopsia. Colour vision was also assessed using a 15 plate Ishihara test as well as the City University colour vision test.

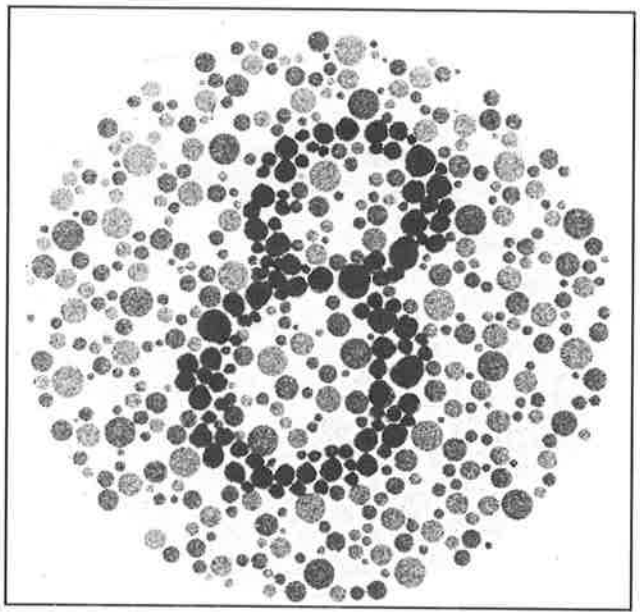
Colour vision testing was performed by initially asking whether the patient could read the number in Figure 5.1. This first plate was a black and white reproduction of one of the Ishihara plates (Plate 3) of the same size with the

number in solid format, and was used in order to test whether the patient had sufficient visual acuity to be able to read the numbers of this size.

FIGURE 5.1 PLATE TESTING ADEQUATE VISUAL ACUITY TO PERFORM ISHIHARA PLATE TESTING (ISHIHARA PLATE 3 DEMONSTRATED)

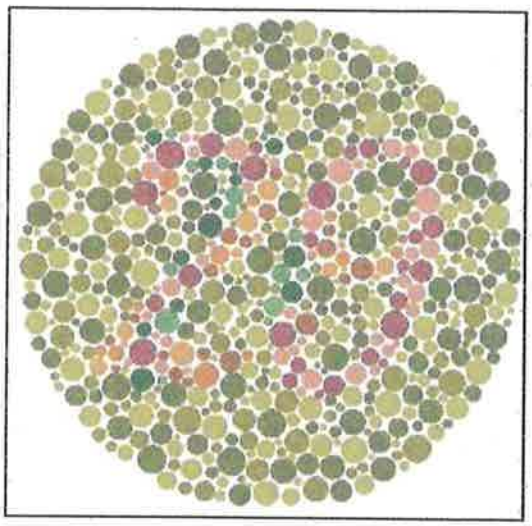
The next image presented to patients was a black and white version of one of the Ishihara plates with the number represented as dots rather than as a solid numeral (Figure 5.2). As many of the patients were elderly and some had cognitive impairment, the purpose of this plate was to determine whether the patient understood the task of being able to read a number amongst a series of dots, without the influence of colour discrimination. A different Ishihara plate was used to Figure 5.1, so that the patient did not simply repeat the number they had previously read.

FIGURE 5.2 PLATE TESTING ABILITY TO UNDERSTAND TASK OF READING NUMBERS WITHIN ISHIHARA PLATE TESTING (PLATE 5 DEMONSTRATED)



If the patient was able to perform these tasks, the 15 plate Ishihara plate test was performed (Figure 5.3). The results were analysed for the individual plates, as well as for the overall number of correct interpretation for the 15 plate set. For the purposes of a large scale examination the test may also be simplified to an examination of 6 plates only: Plate 1, one each of plates 2 or 3, 4-7, 8 or 9, 10-13 and 14 or 15 (Ishihara 1996).

FIGURE 5.3. EXAMPLE OF ISHIHARA PLATE (PLATE 3)



The City University colour vision test has been designed as a test to identify those with significant difficulties with colour vision and to be less sensitive than the Ishihara test. Subjects who pass the City University test, while failing the Ishihara test, are likely to have practical difficulties with only the most demanding of tasks involving colour discrimination (Fletcher and Voke 1985; Birch 1997; Fletcher 1998). This test consists of two parts, the first is a screening aid for detecting defective colour vision (Figure 5.4), and the second uses a different task to search for the sort and degree of any defect. In Part 1 patients are asked to determine for each column of dots whether they are all the same colour or whether one is a different colour. There are 10 rows which have different coloured dots, and the patient is scored according to how many of these they correctly identify. A score of 9 or 10 suggests normal vision. For Part 2, patients are asked which dot looks most like the colour of the dot in the centre. If the subject correctly identifies all dots correctly in the 6 plates, then this suggests that colour vision is at least adequate for most every-day purposes (Fletcher 1998).

FIGURE 5.4 CITY UNIVERSITY COLOUR VISION TEST PLATE 1 (PART 1)

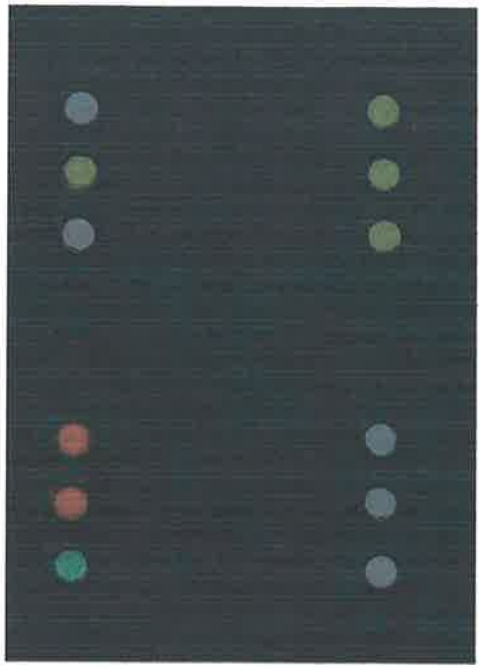
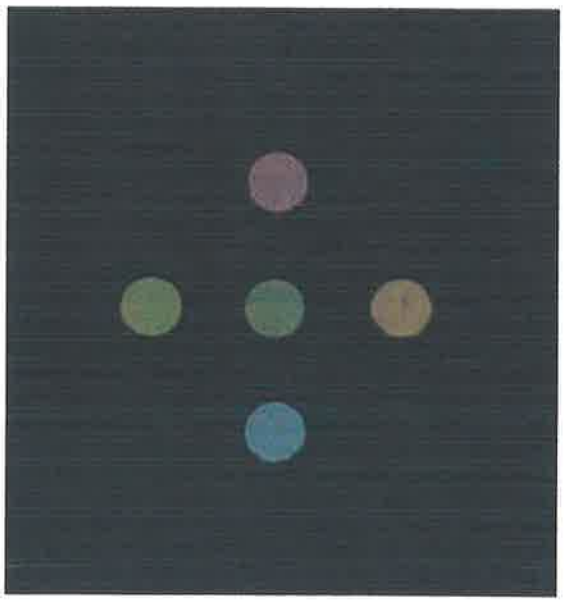


FIGURE 5.5 CITY UNIVERSITY COLOUR VISION TEST PLATE 7 (PART 2)



5.2.4 Factors Altering Sensitivity to Digoxin

In order to assess the factors which may alter the sensitivity to digoxin, the following information was also collected for each patient: gender, age, presenting complaint, type of cardiac disease as defined by the presence of any of the following in the problem list: atrial fibrillation, clinical heart failure, any ischaemic heart disease, previous myocardial infarction, history of revascularisation procedure (coronary artery bypass grafting or percutaneous coronary intervention), clinically significant valvular heart disease, history of hypertension requiring drug treatment, or idiopathic cardiomyopathy. If the patient had a history of cardiac failure, their New York Heart Association status was determined by questioning them about their symptoms in the week prior to admission.

Serum sodium, and potassium estimations were documented if collected within 24 hours of the SDC. Serum creatinine was also documented and the creatinine clearance was estimated using the equation by Cockcroft and Gault (Cockcroft and Gault 1976). If the patient had had a thyroid function test performed within 6 months of the SDC, the free T4, Thyroid Stimulating Hormone (TSH) concentrations as well as a summary of the results as euthyroid, hypothyroid, or hyperthyroid were documented. The majority of patients had not had calcium or magnesium determinations performed, but if these were available, they were also recorded.

If the patient had had an echocardiogram the details of this were also documented. Of particular interest were the degree of left ventricular enlargement and dysfunction as a 6 item ordinal measure from normal to

severe, left ventricular ejection fraction, fractional shortening, left atrial size, presence of left ventricular hypertrophy, and regional wall motion abnormalities suggestive of previous myocardial infarction.

Pulmonary function was assessed in the following manner: if the patient had no history of pulmonary disease and no history of smoking and / or had normal pulmonary function tests, they were described as having normal pulmonary function. If the patient had evidence of pulmonary disease or had previous pulmonary function testing the following categorisation was used (if a patient's symptoms and spirometry corresponded to more than one category, the more severe category was chosen):

- Mild: little or no breathlessness and / or forced expiratory volume in 1 second (FEV_1) between 60-80% of predicted,
- Moderate: breathlessness on moderate exertion and / or FEV_1 between 40-59% of predicted,
- Severe: breathlessness on mild exertion and / or at rest or $FEV_1 \leq 40\%$ of predicted.

The influence of concurrent medications which may alter sensitivity to digoxin was also documented. Medications known to alter either digoxin pharmacokinetics or pharmacodynamics were recorded if they were prescribed concurrently with digoxin, or if they were prescribed within the previous week and within 5 half-lives of the interacting drug. The medications considered were amiodarone, verapamil, diltiazem, and spironolactone.

5.2.5 Digoxin Concentration Determination

SDCs were determined by laboratories accredited by the Australian National Association of Testing Authorities using the Syva enzyme immunoassay (Lane Cove, New South Wales) for 70% of samples and the Abbott AxSYM system (North Ryde, New South Wales, Australia) for 30% of samples. The limit of quantification was 0.2 ng/mL for both methods.

5.2.6 Statistical Analysis

As the SDCs were not normally distributed, the data are presented as medians with inter-quartile ranges, and were log-transformed prior to statistical analysis. In order to assess whether patients with a particular symptom had significantly higher SDCs than those without (and thus whether there was a likely concentration-effect relationship for that symptom), the means of the log serum concentrations for the possible responses were compared using T-tests for questions with only two possible responses, and analyses of variance for questions with more than two possible responses. Statistical analysis was performed using SPSS software (SPSS for Windows, Release 10.0.7 2000. Chicago: SPSS Inc.), setting the threshold for significance at $p=0.05$. Comparison of the prevalence of toxicity symptoms at different concentration ranges was performed using Chi-squared tests for independence and trend.

For the determination of factors which may alter the sensitivity to digoxin a log-binomial model was utilised using generalized estimating equations methodology with SAS software (SAS Institute Inc., Cary, NC, USA). All of

the potential variables were assessed individually with univariate analysis, and those with p values less than 0.2 were analysed in the final multivariate model. Interactions were also sought between the SDC and other variables. For thyroid and pulmonary function if values were missing, a dummy variable was created where missing values were assumed to be normal. Although this assumption may not have been accurate, it did allow the inclusion of a larger number of patients with complete datasets into the multivariate analysis. This was not done with missing electrolyte or echocardiographic data, as the assumption of these values being normal could not be made in this population.

An interim analysis was performed after the initial 150 patients. Symptoms which did not show any evidence of a concentration-effect relationship in patients in Group 1 were removed, in order to simplify and shorten the questionnaire. For other symptoms the interim analysis revealed a trend for a significant difference between the median SDCs of patients with and without the symptom. In such instances, either further questions were added e.g. question 30 and 31 in Table 5.1, or the City University Colour Vision test, in order to address these symptoms more extensively.

5.3 Results

5.3.1 Patient Characteristics

Table 5.2 shows the demographic and clinical characteristics of the 256 patients enrolled in the two groups. The only significant difference between the groups was the indication for digoxin therapy ($p<0.001$).

TABLE 5.2 CHARACTERISTICS OF PATIENTS

	Group 1 (N=222)		Group 2 (N=34)	
		Percent Missing		Percent missing
Age, years		0.5%		0%
- Mean (SD)	74.1 (10.9)		74.5 (10.7)	
- Median (IQR) †	75.0 (70-81.5)		74.5 (68.8-84.3)	
- Range	15-97		48-93	
Male	113 (51)%	0%	22 (65)%	0%
Indication for digoxin[1]		0%		0%
- Atrial fibrillation	75 (34%)		5 (15%)	
- Cardiac failure	51 (23%)		24 (71%)	
- Both atrial fibrillation and cardiac failure	94 (42%)		5 (15%)	
- Other/Unknown	2 (1%)		0 (0%)	
New York Heart Association Class (Median)	2	2.3%	2	2.9%
- Class 1	46 (20.7%)		4 (11.8%)	
- Class 2	59 (26.6%)		14 (41.2%)	
- Class 3	90 (40.5%)		12 (35.3%)	
- Class 4	22 (9.9%)		4 (8.8%)	

	Group 1 (N=222)		Group 2 (N=34)	
		Percent Missing		Percent missing
Serum creatinine (mmol/L),		0.9%		0%
- Mean (SD)	0.152 (0.146)		0.113 (0.056)	
- Range	0.04-1.0		0.06-0.27	
Calculated creatinine clearance[2] (ml/min)		1.8%		5.9%
- Mean (SD)	49.8 (31.5)		57.2 (25.8)	
- Range	3-176		12-133	
Serum sodium (mmol/L)		1.4%		0%
- Mean (SD)	137.8 (4.4)		139.3 (3.4)	
- Range	111-147		131-145	
Serum potassium (mmol/L)		0.9%		0%
- Mean (SD)	4.1 (0.6)		4.0 (0.5)	
- Range	2.7-5.9		3.0-5.2	
Thyroid function:		47.7%		55.9%
- Overall status[3]				
- Hyperthyroid	4 (1.8%)		0 (0%)	
- Euthyroid	104 (46.8%)		14 (41.2%)	
- Mild hypothyroidism	8(3.6%)		1 (2.9%)	
- TSH		62.7%		67.6%
- Median (IQR)	1.6 (1.0-2.7)		1.9 (1.1-3.0)	
- Range	0.01-18.0		0.3-20.0	
- FT4		71.6%		76.5%
- Median (IQR)	15 (13-17)		18 (15.3-18.3)	
- Range	1-90		11-22	
Respiratory disease[4]		40.5%		41.2%
- Normal	48 (21.6%)		7 (20.6%)	
- Mild	25 (11.3%)		5 (14.7%)	
- Moderate	30 (13.5%)		3 (8.8%)	
- Severe	29 (13.1%)		5 (14.7%)	

	Group 1 (N=222)		Group 2 (N=34)	
		Percent Missing		Percent missing
Echocardiographic left ventricular dysfunction[5]		28.4%		38.2%
- None	63 (28.4%)		4 (11.8%)	
- Mild	21 (9.5%)		5 (14.7%)	
- Mild-moderate	15 (6.8%)		2 (5.9%)	
- Moderate	16 (7.2%)		1 (2.9%)	
- Moderate-severe	17 (7.7%)		2 (5.9%)	
- Severe	27 (12.2%)		7 (20.6%)	
Interacting medications		0%		0%
- Amiodarone	29 (13.1%)		6 (17.7%)	
- Spironolactone	17 (7.7%)		1 (2.9%)	
- Verapamil	10 (4.5%)		1 (2.9%)	
- Diltiazem	20 (9.0%)		2 (5.9%)	

Group 1: patients on digoxin

Group 2: patients with an indication for digoxin therapy (atrial fibrillation or cardiac failure) but not prescribed digoxin

For normally distributed values, the data presented are means and standard deviations. For non-normally distributed values, the data presented are medians and inter-quartile ranges

1. $p<0.001$ for difference in indication for digoxin between Group 1 and 2
2. Based on the equation by Cockcroft and Gault (Cockcroft and Gault 1976)
3. Based on assessment documented on pathology report

4. Based on following classification: Mild = little or no breathlessness and / or FEV_1 between 60-80%; Moderate=breathlessness on moderate exertion and/or FEV_1 between 40-59% of predicted; Severe= breathlessness on mild exertion or at rest and/or $FEV_1 \leq 40\%$ of predicted
5. Based on summary of left ventricular function by reporting cardiologist as the left ventricular ejection fraction or fractional shortening was not available on all reports

SD = Standard deviation

TSH: Thyroid stimulating hormone

FT4: Free thyroxin concentration

IQR: Inter-quartile range

Table 5.3 reveals the distribution of SDCs. As discussed above, in order to collect more information about potential symptoms of toxicity, the study surveyed a greater proportion of patients with SDCs above 2.0 ng/mL than would be seen in clinical practice.

TABLE 5.3 FREQUENCY OF TROUGH SERUM DIGOXIN CONCENTRATIONS FOR PATIENTS ON DIGOXIN THERAPY (GROUP 1)

Serum Digoxin Concentration (ng/mL)*	Number	Percent
<0.3	14	6.3%
0.31-0.6	20	9.0%
0.61-0.9	48	21.6%
0.91-1.2	33	14.9%
1.21-1.5	33	14.9%
1.51-1.8	19	8.6%
1.81-2.4	25	11.3%
2.41-3.0	21	9.5%
3.01-8.0	9	4.1%

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

5.3.2 Questionnaire Results

Table 5.3 shows the median SDCs associated with the different responses to the questions asked for patients in Group 1, together with the results of the statistical analysis. As can be seen, the patients with most of the previously described manifestations of digoxin toxicity did not have higher SDCs than those patients without. Symptoms which represented different grades of the emetic effects of digoxin were associated with higher SDCs, but otherwise other gastrointestinal symptoms were not. The presence of subjective and objective neuropsychiatric manifestations were generally not associated with higher SDCs, and of the questions assessing the patient's visual symptoms, only colour vision changes were associated with higher SDCs.

TABLE 5.4 SUMMARY OF RESPONSES FOR GASTROINTESTINAL SYMPTOMS

	P for difference between responses	Median concentration (ng/mL)* (Inter-quartile range)	
		"Yes" response	"No" response
1. Did you look forward to your last meal?	0.002	1.17 (0.75-1.60)	1.58 (0.92-2.46)
In the last 1-2 days would you say that you:			
2. Felt off your food?	<0.001	1.50 (1.0-2.31)	0.90 (0.70-1.42)
2a. If you have felt off your food, would you describe this as a little or a lot?	<0.001	Little: 1.58 (0.81-2.10) A lot: 2.00 (1.60-2.73)	
3. Felt like vomiting?	<0.001	1.75 (0.90-2.42)	1.01 (0.75-1.50)
4. Vomited?	0.001	1.70 (1.17-2.58)	1.08 (0.75-1.67)
5. Had any abdominal pain?	NS	1.33 (0.83-2.33)	1.38 (0.83-2.02)
6. Had any diarrhoea?	NS	1.33 (0.83-1.88)	1.17 (0.83-2.08)
7. The feeling of wanting to vomit is nausea. Would you say you had no nausea, slight, moderate, severe nausea, or vomiting?	NS	No nausea: 1.33 (0.81-1.67) Slight nausea: 1.38 (.83-2.17) Moderate nausea: 2.25 (0.83-2.58) Severe nausea: 1.33 (N/A†) Vomiting: 1.42 (0.83-1.83)	

NS= Not significant

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

† Not applicable as too few values to determine inter-quartile range

TABLE 5.5 SUMMARY OF RESPONSES FOR NEUROPSYCHIATRIC SYMPTOMS

	P for difference between responses	Median concentration (ng/mL)* (Inter-quartile range)		
In the last 1-2 days have you had any				
8. Difficulty thinking?	NS	1.29 (0.92-2.33)	1.33 (0.77-2.00)	
9. Muscle weakness?	NS	1.23 (0.80-2.00)	1.05 (0.75-1.67)	
10. Dizziness?	NS	1.33 (0.83-2.02)	1.25 (0.83-2.08)	
11. Agitation?	NS	1.25 (0.69-2.27)	1.50 (0.83-2.00	
12. Tiredness?	0.036	1.25 (0.83-1.95)	1.05 (0.68-1.50)	
Regarding the last 1-2 days,		Not at all	A little	A lot
13. Does thinking require effort?	NS	1.33 (0.83-2.08)	1.25 (0.75-1.96)	1.50 (0.96-2.33)
14. Have you been easily tired?	NS	1.25 (0.63-1.92)	1.33 (0.79-1.96)	1.33 (0.83-2.21)
15. Does tiredness cause you frequent problems?	NS	1.33 (0.75-2.08)	1.08 (0.88-2.21)	1.38 (0.83-1.73)
16. Does tiredness interfere with your functioning?	NS	1.21 (0.75-2.08)	1.33 (0.83-2.00)	1.33 (0.83-1.88)
17. Do you feel more confused in your thinking?	NS	1.33 (0.83-2.06)	1.33 (0.88-2.38)	1.25 (0.81-2.6)

NS= Not significant

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

TABLE 5.6 SUMMARY OF RESPONSES FOR OBJECTIVE TESTING OF MENTAL STATE

	P for difference between responses	Median concentration (ng/mL)* (Inter-quartile range)	
		Correct	Incorrect
18. Day?	NS	1.33 (0.83-2.08)	1.29 (0.83-2.08)
19. Date?	NS	1.33 (0.83-2.13)	1.25 (0.75-1.81)
20. Month?	NS	1.50 (0.83-2.21)	1.25 (0.83-2.04)
21. Year?	NS	1.29 (0.83-1.71)	1.33 (0.83-2.08)
22. Place?	NS	1.38 (0.81-2.21)	1.33 (0.83-2.04)
23. Ward?	NS	1.25 (0.83-2.08)	1.33 (0.83-2.08)
23b. Combinations of orientation questions			NS
24. Registration of 3 objects			NS
25. Number of registration attempts			NS
26. Counting backwards from 100 using 7s (scored out of 5)			NS
27. Spelling "world" backwards (scored out of 5)			NS
28. Recall of 3 objects			NS

NS= Not significant

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

TABLE 5.7 SUMMARY OF RESPONSES FOR COLOUR VISION CHANGES

	P for difference between responses	Median concentration (ng/mL)* (Inter-quartile range)	
Have you noticed any:			
		Yes response	No response
29. Changes in colour vision?	0.002	1.90 (1.20-2.70)	1.10 (0.7-1.50)
30. Blurred vision?	NS	1.10 (0.70-2.20)	1.00 (0.70-1.60)
31. Haloes around lights?	NS	1.00 (0.70-1.62)	0.75(0.60-2.1)
32. Testing for chromatopsia	NS	1.17 (0.75-1.80)	1.41 (0.78-3.1)

NS= Not significant

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

Table 5.8 summarises the results of the Ishihara colour vision testing. Plate 1 is a test plate and is expected to be correctly read by all subjects. For each Plate, there were a number of several possible responses e.g. for Plate 2 the number could have been read correctly as "8", or incorrectly as "3". However, the patient may have seen no numbers ("none") or read a different number ("other'). Rather than presenting the median SDCs associated with each of these responses, the data are summarised simply as correct or incorrect responses. Although generally the incorrect responses were reported by patients having higher SDCs, these differences are only significant for some of the plates (Plates 2, 3, 4, 5, 8, 9, 11, 12, 13).

TABLE 5.8 ASSESSMENT OF ISHIHARA COLOUR VISION TESTING

Plate	Incorrect response (Median SDC and IQR (ng/mL))	Correct response (Median SDC and IQR (ng/mL))	P value for difference
2	1.25 (0.90-1.87)	1.10 (0.70-1.80)	0.032
3	1.44 (0.98-2.05)	1.01 (0.70-1.64)	0.001
4	1.33 (0.90-1.88)	1.10 (0.70-1.80)	0.027
5	1.50 (1.01-2.19)	1.10 (0.70-1.70)	0.004
6	1.21 (0.88-1.76)	1.17 (0.70-1.80)	0.249
7	1.22 (0.79-1.78)	1.10 (0.70-1.86)	0.202
8	1.25 (0.80-1.90)	1.09 (0.70-1.70)	0.021
9	1.25 (0.86-1.89)	1.10 (0.70-1.61)	0.021
10	1.20 (0.81-1.89)	1.10 (0.70-1.70)	0.241
11	1.25 (0.89-1.93)	1.10 (0.70-1.80)	0.043
12	1.35 (0.9-1.86)	1.01 (0.70-1.80)	0.005
13	1.25 (0.79-1.98)	0.97 (0.70-1.46)	0.006
14	2.42†	1.19 (0.78-1.87)	0.257
15‡	0.92 (0.60-1.25)	0.78 (1.20-1.93)	0.515

† Too few values for determination of inter-quartile range

‡ Values for this plate lower as not all of the patients able to complete all plates

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

Table 5.9 presents some of the aggregate data for the Ishihara colour vision testing as recommended by the instruction booklet (Ishihara 1996). Although, overall there was no significant relationship between the number of plates correctly read and SDC, it can be seen that patients who were unable to read 13 or more plates correctly from the complete 15 plate set, or had any inaccuracies with the more limited 6 plate set, had higher SDCs than subjects who were able to read these plates correctly.

TABLE 5.9 SUMMARY SCORES FOR ISHIHARA PLATES

Plate summary	SDC (Median and IQR; ng/mL)*	P value for comparison
15 plate summary as total score (1 point for each correct response)	**N/A**	**0.285[1]**
15 plate summary as binary assessment		**0.002[2]**
- **13 or more correct**	**1.01 (0.70-1.70)**	
- **12 or less correct**	**1.40 (0.86-2.03)**	
6 plate summary score (1 point each for Plates 1, 3, 5, 8, 13 and 14)		**0.001[3]**
- **2[4] correct**	**1.53 (1.13-3.51)**	
- **3 correct**	**1.25 (0.78-2.03)**	
- **4 correct**	**1.48 (1.02-2.34)**	
- **5 correct**	**1.00 (0.70-1.56)**	
- **6 correct**	**1.02 (0.60-1.73)**	
6 plate (1, 3, 5, 8, 13 and 14) as binary assessment		**0.013**
- **All 6 plates correct**	**1.01 (0.6-1.73)**	
- **Less than 6 plates correct**	**1.20 (0.78-1.95)**	

N/A: Not applicable as there were too many values

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

1. P value for comparison of median SDCs for number of correct plates
2. P value for comparison between median SDCs associated with 12 or less, and 13 or more correct
3. P value for comparison between median SDCs for the number of correct plates
4. All patients were able to correctly interpret at least 2 of these 6 plates

The results of the City University Colour Vision Tests are summarised in Table 5.10. The patients who interpreted the majority of the plates correctly and incorrectly had similar SDCs. Hence, only results for those plates where there was a significant difference in the median SDCs of patients interpreting the plates correctly and incorrectly are presented. It should be noted that for Plate 2 the median SDC in patients giving the incorrect response was lower than that for patients giving the correct response. An assessment of the summary score was carried out using the instructions in the accompanying booklet. There was no significant difference in SDC between subjects with normal colour vision (9 or 10 correct) compared to those with abnormal colour vision (8 or less correct) (p=0.74).

TABLE 5.10 SUMMARY OF CITY UNIVERSITY COLOUR VISION TESTS

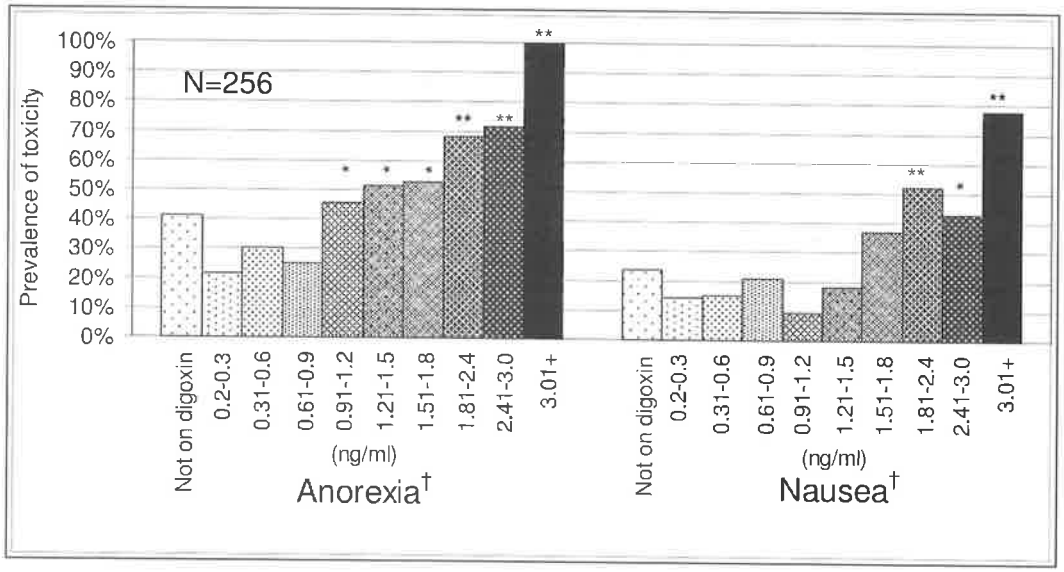
City Plate	Incorrect Response (Median SDC and IQR; ng/mL)	Correct Response (Median SDC and IQR; ng/mL)	P Value for Difference
2	0.40 (0.20-0.60)	1.20 (0.80-1.91)	0.01
6	1.90 (1.40-2.70)	1.06 (0.70-1.68)	0.004
7	1.60 (1.02-2.63)	1.10 (0.70-1.80)	0.017
16	1.45 (1.01-2.60)	1.10 (0.70-1.80)	0.011

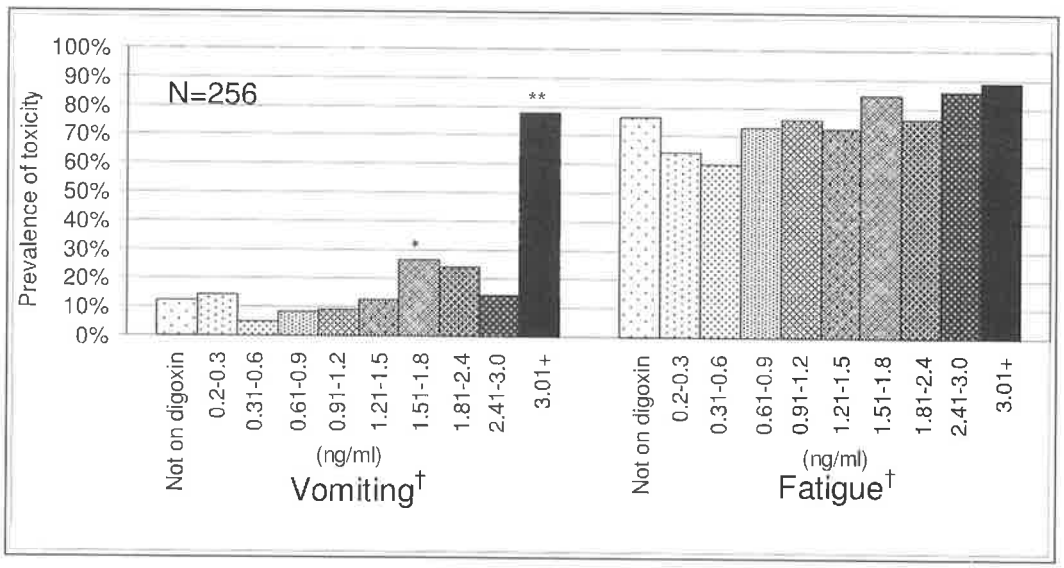
* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

5.3.3 Prevalence of Symptoms at Increasing SDCs

Figures 5.6-5.10 demonstrate the prevalence of the symptoms and signs identified as being associated with higher SDCs at increasing concentration categories. Figure 5.6 demonstrates that the prevalence of symptoms such as anorexia, nausea and fatigue increases progressively with increasing digoxin concentration, whereas the prevalence of vomiting only appears to be substantially higher at concentrations greater than 3.0 ng/mL. Anorexia appears to be the most sensitive symptom of digoxin toxicity with its prevalence being significantly higher in concentration groups above 0.9 ng/mL (15/33 or 45.5% for concentration range 0.91-1.2 ng/mL) compared to those below (21/82 or 25.6% for concentration range 0.2-0.9 ng/mL, p=0.047 for difference). The prevalence of vomiting at a concentration of 1.51-1.8 ng/mL was 26.3% (5/19) compared to 8.5% (7/82) at concentrations up to 0.9 ng/mL (p=0.047). The prevalence of vomiting is then similar at concentrations between 1.5 to 3.0 ng/mL, but increases substantially at concentrations above 3.0 ng/mL (77.8% or 7/9, p<0.001 for comparison with prevalence below 0.9 ng/mL). The prevalence of fatigue in the inpatient population was very high in all groups, and although its prevalence was not significantly higher than baseline in any of the concentration categories, the trend for higher prevalence with higher concentration was significant (p=0.03). Figure 5.6 also demonstrates the background prevalence of these symptoms in inpatients who had an indication for digoxin therapy, but who were not prescribed digoxin. It can be seen that amongst the gastrointestinal symptoms, although anorexia is the most sensitive symptom, it is also the least specific, and the converse is true for vomiting. Fatigue had a prevalence of nearly 80% in our inpatient population.

FIGURE 5.6. PREVALENCE OF SYMPTOMS SIGNIFICANTLY ASSOCIATED WITH HIGHER SERUM DIGOXIN CONCENTRATIONS AT INCREASING CONCENTRATION CATEGORIES





* p<0.05 in comparison to prevalence of symptom at range 0.2-0.9 ng/mL

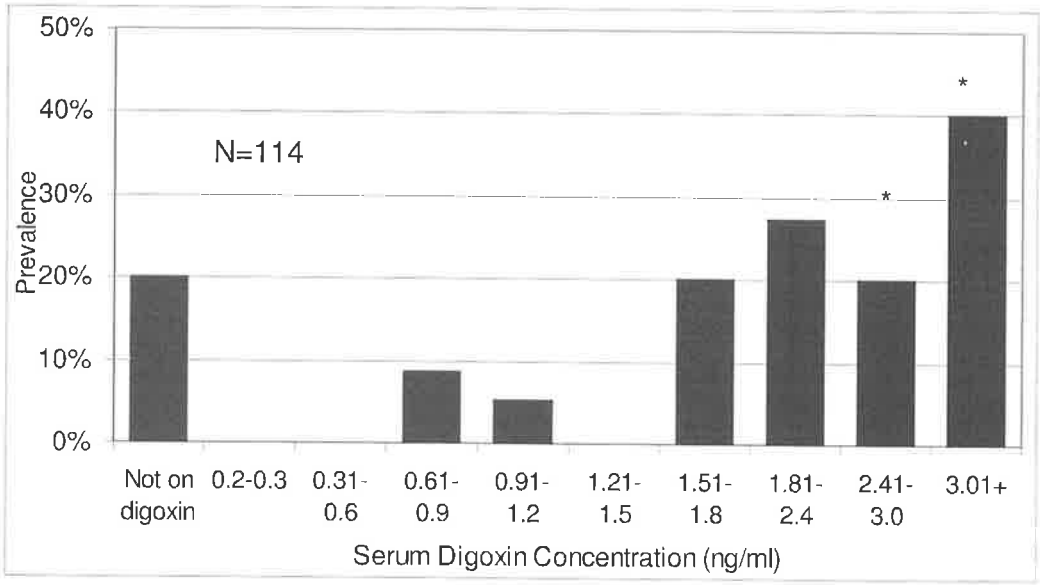
** p<0.01 in comparison to prevalence of symptom at range 0.2-0.9 ng/mL

† Significant linear trend among the ordered categories (p<0.05)

N= Total count of patients

Figure 5.7 demonstrates the prevalence of subjective symptoms of changes in colour vision at increasing concentration categories. Although the trend for increasing prevalence at increasing concentrations was significant (p=0.0018), the prevalence at each of the individual concentration categories above 1.5 ng/mL was not consistently significantly different to the prevalence at lower concentrations (p=0.11 for comparison of prevalence at concentration of 1.51-1.8 ng/mL, p=0.028 for 1.81-2.4 ng/mL, p=0.24 for 2.41-3.0 ng/mL, and p=0.031 for 3.01+ ng/mL, compared to prevalence at concentrations of 0.2-1.5 ng/mL).

FIGURE 5.7 PREVALENCE OF SUBJECTIVE SYMPTOMS OF CHANGES IN COLOUR VISION AT INCREASING CONCENTRATION CATEGORIES



* p<0.05 in comparison to prevalence of symptom at range 0.2-1.5 ng/mL

N= Total count of patients

Figure 5.8 displays the prevalence of incorrect responses for the individual Ishihara plates, for which there was a significant difference in the SDC between correct and incorrect responses, at increasing SDC categories. Figure 5.8A demonstrates the Ishihara plates for which the p values were

between 0.01 and 0.05, and Figure 5.8B for those with $p<0.01$. It can be seen that none of the plates demonstrates a consistently increasing prevalence of incorrect interpretation with increasing SDC, as was seen with the prevalence of the gastrointestinal symptoms in Figure 5.6. As seen with gastrointestinal symptoms, the overall prevalence of incorrect interpretation varied widely across different plates with 16.6% of patients interpreting Plates 11 incorrectly, compared with 74.1% with Plate 13. In general the Ishihara test was less sensitive than other symptoms with fewer than 50% of all patients demonstrating incorrect interpretation of the plates at even the highest SDC category of >3.0 ng/mL.

FIGURE 5.8A PREVALENCE OF INCORRECT RESPONSE TO INDIVIDUAL ISHIHARA PLATES ACROSS INCREASING SERUM DIGOXIN CONCENTRATION CATEGORIES

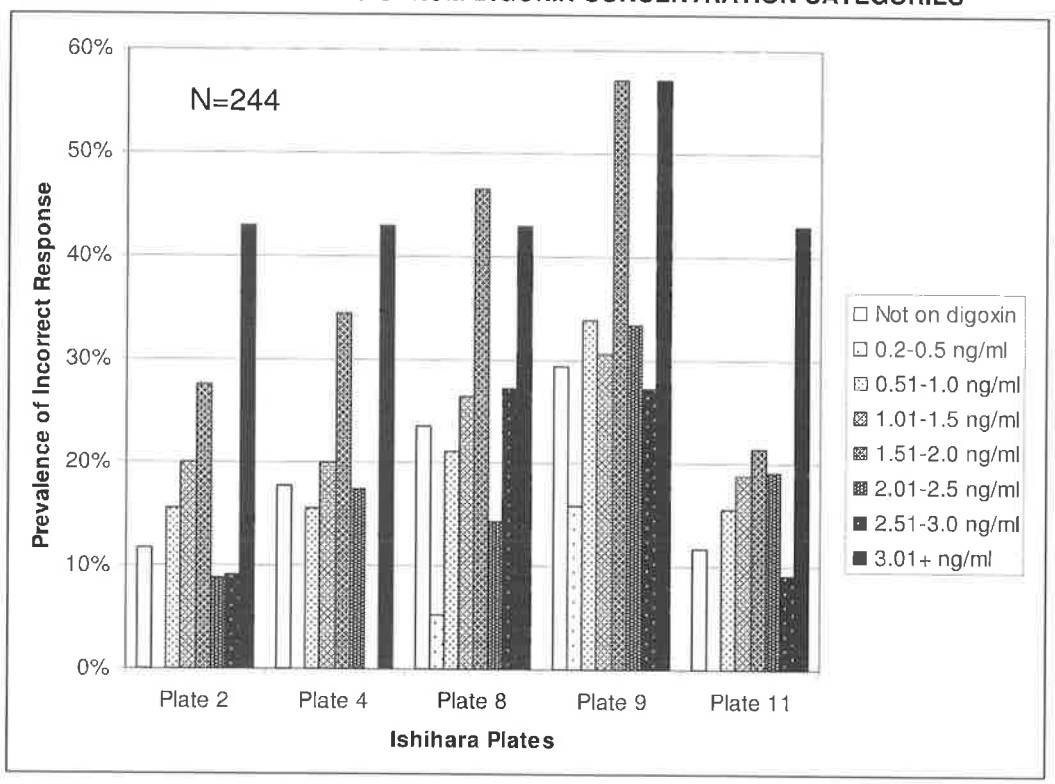


FIGURE 5.8B PREVALENCE OF INCORRECT RESPONSE TO INDIVIDUAL ISHIHARA PLATES ACROSS INCREASING SERUM DIGOXIN CONCENTRATION CATEGORIES

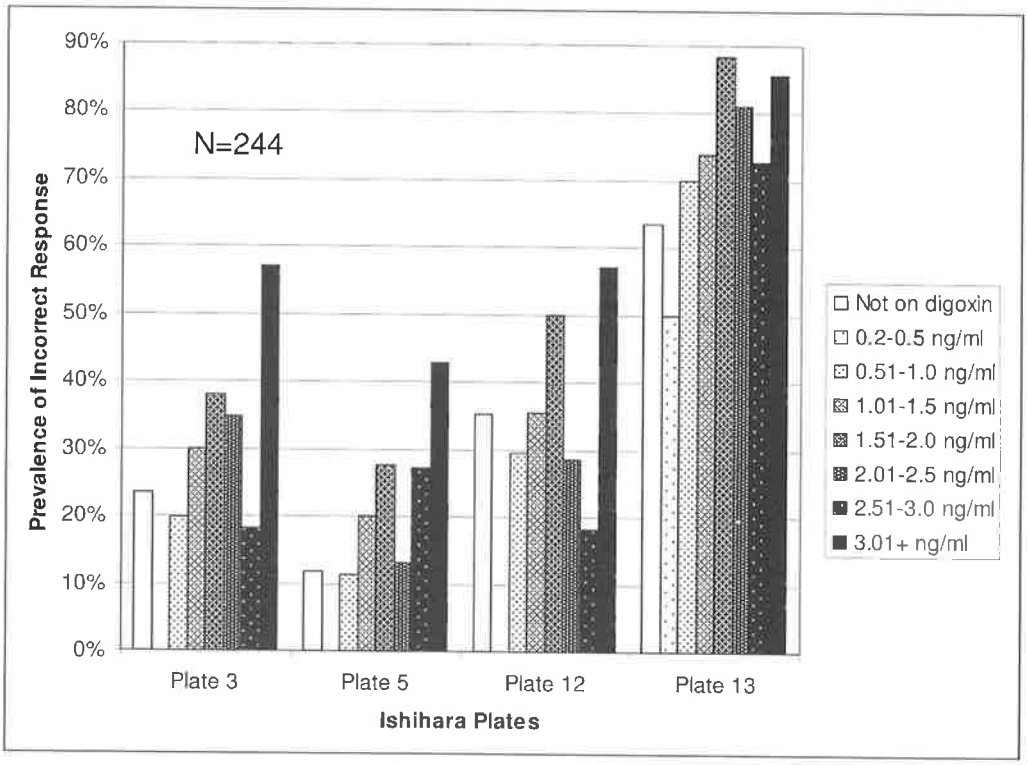
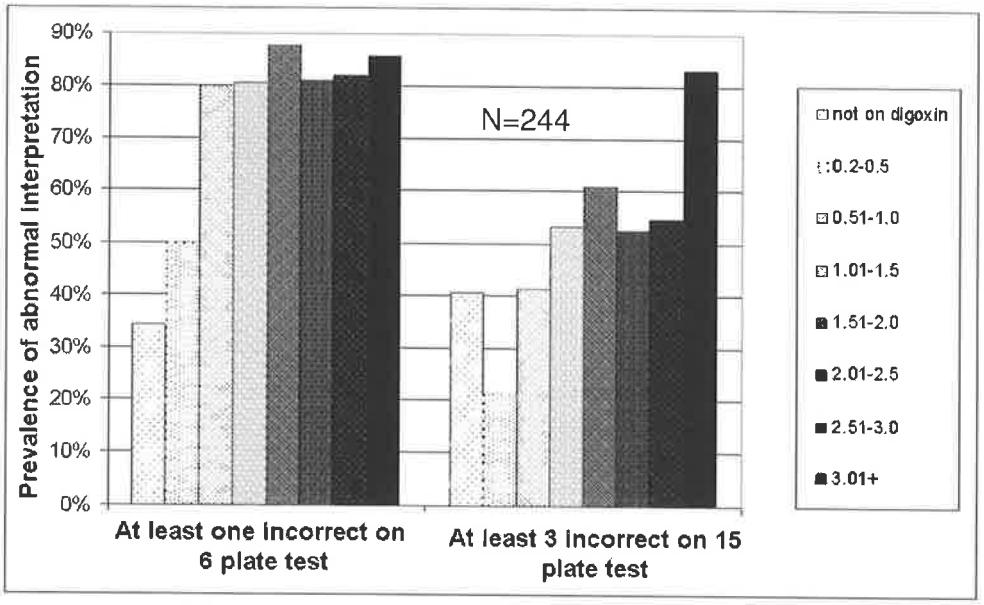


Figure 5.9 demonstrates the prevalence of abnormalities on summary assessments of Ishihara plates at increasing assay SDC categories. It can be seen that the difficulty with being able to read all 6 out of 6 plates correctly can occur in approximately 30% of patients not on digoxin, in 50% at subtherapeutic concentrations (0.2-0.5 ng/mL) and in over 80% of patients at higher concentrations. The inability to interpret 13 or more plates correctly out of 15 shows a gradual increase in prevalence with increasing concentration, but once again occurs in a high proportion of patients not on digoxin, as well as in over 40% of patients at the lower end of the therapeutic range (0.51-1.0 ng/mL).

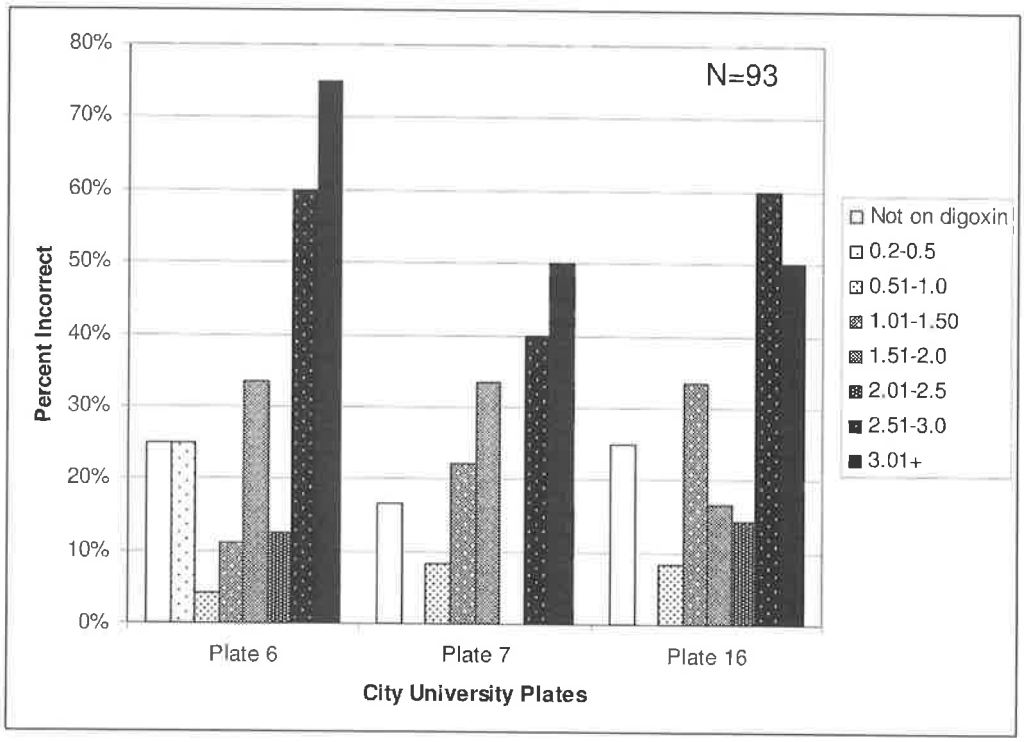
FIGURE 5.9 PREVALENCE OF INCORRECT INTERPRETATION ON SUMMARY ASSESSMENTS OF ISHIHARA PLATES AT INCREASING SERUM DIGOXIN CONCENTRATION CATEGORIES[1]



1. Data derived from Table 5.9

Figure 5.10 demonstrates the prevalence of incorrect interpretation of City University Colour vision plates across increasing SDC categories for those plates associated with a significantly higher SDC for incorrect compared to correct interpretation. As was seen with the Ishihara plates, the prevalence of abnormal interpretation does not consistently rise with increasing serum digoxin concentration.

FIGURE 5.10 PREVALENCE OF INCORRECT INTERPRETATION OF CITY UNIVERSITY COLOUR VISION PLATES ACROSS INCREASING ASSAY CONCENTRATION CATEGORIES



5.3.4 Influence of Factors Which May Alter Sensitivity to Digoxin

Factors which potentially could have influenced sensitivity to digoxin for the symptoms of anorexia, nausea, vomiting, and tiredness were analysed.

5.3.4.1 Anorexia

On univariate analysis, the SDC and co-prescription of verapamil were positively associated with the presence of anorexia, and serum sodium concentration, co-prescription of diltiazem, and the presence of atrial fibrillation were negatively associated. Table 5.11 displays the results of the log-binomial multivariate regression analysis.

TABLE 5.11 LOG-BINOMIAL REGRESSION OF FACTORS ASSOCIATED WITH PRESENCE OF ANOREXIA

Factor	Parameter Estimate (95% Confidence Limits)	P Value Of Individual Parameter	P Value in Overall Model
Serum Na^+	-0.038 (-0.060 to -0.016)	0.0008	0.0106
Digoxin Concentration	0.219 (0.102 to 0.336)	0.0003	<0.0001
Co-Prescription of Diltiazem	-1.093 (-0.178 to -2.009)	0.0193	0.0015
Co-Prescription of Verapamil	0.664 (0.190 to 1.137)	0.0061	0.0837
Presence of Atrial Fibrillation	-0.315 (-0.019 to -0.611)	0.0370	0.0504

Because of the known influence of factors such as the serum potassium concentration and thyroid function on altering the sensitivity of the pharmacodynamic response to digoxin, analysis of interactions between these and digoxin concentrations was also performed. On univariate analysis the combination of low serum potassium concentration and digoxin concentration was found to be significantly associated with the presence of anorexia. However, combination of other factors with SDCs were not. The results of the multivariate analysis including this interaction term are displayed in Table 5.12. It can be seen that, although the SDC is no longer significant, the interaction term is just above significance. Hence the model described in Table 5.11 without the interaction term appears to be a better model describing the factors associated with the presence of anorexia.

TABLE 5.12 LOG-BINOMIAL REGRESSION OF FACTORS ASSOCIATED WITH PRESENCE OF ANOREXIA INCLUDING ANALYSIS OF INTERACTION TERMS

Factor	Parameter Estimate (95% Confidence Limits)	P Value of Individual Parameter	P Value in Overall Model
Serum Sodium Concentration	-0.039 (-0.060 to -0.017)	0.0004	0.0066
Digoxin Concentration	0.066 (-1.051 to 1.183)	0.9074	0.9073
Co-Prescription of Diltiazem	-1.111 (-0.182 to -2.040)	0.0191	0.0020
Presence of Atrial Fibrillation	-0.310 (-0.010 to -0.610)	0.0427	0.0531
Interaction Between Serum Digoxin Concentration and Potassium	0.155 (0.009 to 0.302)	0.0378	0.0523

5.3.4.2 Nausea

On univariate analysis SDC, serum creatinine, and female gender were positively associated with the presence of nausea, and serum sodium concentration was negatively associated. Table 5.13 displays the results of the log-binomial multivariate regression analysis. Once again the role of interaction terms was explored. However, none of these contributed significantly to the model for the prevalence of nausea.

TABLE 5.13 LOG-BINOMIAL REGRESSION OF FACTORS ASSOCIATED WITH PRESENCE OF NAUSEA

Factor	Parameter Estimate (95% Confidence Limits)	P Value of Individual Parameter	P Value in Overall Model
Serum Sodium Concentration	-0.071 (-0.110 to -0.032)	0.0003	0.0234
Serum Creatinine Concentration	0.936 (0.024 to 1.848)	0.0444	0.1042
Serum Digoxin Concentration	0.227 (0.106 to 0.346)	0.0002	0.0149
Female Gender	0.589 (0.106 to 1.073)	0.0169	0.0142

5.3.4.3 Vomiting

On univariate analysis SDC, female gender, cardiac failure only as the indication for digoxin therapy, co-prescription of amiodarone, and New York Heart Association rating were positively associated with the occurrence of vomiting, and serum sodium and potassium concentrations were negatively associated. Table 5.14 displays the results of the log-binomial multivariate regression analysis. Once again the role of interaction terms was explored and found to be non-contributory to the overall model.

TABLE 5.14 LOG-BINOMIAL REGRESSION OF FACTORS ASSOCIATED WITH PRESENCE OF VOMITING

Factor	Parameter Estimate (95% Confidence Limits)	P Value of Individual Parameter	P Value in Overall Model
Serum Sodium Concentration	-0.100 (-0.147 to -0.052)	<0.0001	0.0319
Serum Potassium Concentration	-0.640 (-1.250 to -0.030)	0.0397	0.0320
Serum Digoxin Concentration	0.383 (0.192 to 0.574)	<0.0001	0.0138
Female Gender	0.673 (0.034 to 1.313)	0.0391	0.0417
Presence of Atrial Fibrillation	0.867 (0.052 to 1.682)	0.0371	0.0667
Co-Prescription of Amiodarone	1.037 (0.250 to 1.823)	0.0098	0.0448

5.3.4.4 Tiredness

On univariate analysis SDC, serum creatinine, and respiratory disease were found to be associated with the presence of tiredness. On multivariate analysis the p value for SDC became non-significant (p=0.0792) and the only factor independently associated with tiredness was the presence of respiratory disease. Once again interaction terms did not contribute to the overall model.

5.4 Discussion

To my knowledge, this is the first study to thoroughly explore the prevalence of the various symptoms of digoxin toxicity and their relationship to serum digoxin concentrations. My findings, in patients managed by contemporary clinical practices are that anorexia, nausea, vomiting, fatigue, and subjective colour vision changes are the only symptoms that exhibited a concentration-

response relationship to digoxin. Many of the previously described manifestations of digoxin toxicity did not exhibit such a relationship. There was an increase in the prevalence and severity of the manifestations of digoxin toxicity with increasing SDCs. The concentration at which gastrointestinal manifestations of digoxin toxicity became more prevalent than baseline was above a concentration of 0.9 ng/mL (1.1 nmol/L) which is in the lower half of the frequently quoted therapeutic range of 0.5-2.0 ng/mL (0.6-2.4 nmol/L).

Although the gastrointestinal symptoms of cardiac glycosides are well documented, an early editorial stressed the importance of abdominal pain (Chamberlain, White et al. 1970), and other authors noted an incidence of 65% in a case series of large scale digitalis intoxication (Lely and van Enter 1970). In this study, abdominal pain was not related to SDC and the ability of digoxin to induce emesis was the only gastrointestinal symptom associated with higher SDCs. Similarly, neuropsychiatric symptoms are described as common occurrences in patients with digoxin toxicity, with fatigue being a cardinal symptom (Lely and van Enter 1970; Lely and van Enter 1972). In this study, although patients who reported experiencing tiredness had significantly higher SDCs than those who did not, a number of other questions assessing fatigue and other neuropsychiatric manifestations were not associated with higher SDCs. None of the objective tests of mental state which addressed orientation (questions 18 to 23), attention (question 26 and 27) or short term memory (questions 24, 25, or 28) showed a relationship with SDCs. Table 5.6 describes the simple analysis of these data. Furthermore, even when the questions were combined in a number of

different ways, in none of the analyses was an abnormal result associated with higher SDCs.

Although some authors have suggested using bedside colour assessment tools for routine monitoring or screening (Aronson and Ford 1980; LeSage and Chuman 1986) of digoxin toxicity, others have found a high incidence of abnormal findings at therapeutic concentrations (Lawrenson, Kelly et al. 2002) and suggested that this approach would have a limited value in the detection of digoxin toxicity. This study would appear to be the largest study of colour vision abnormalities associated with digoxin, and the results support the latter view. Although the incorrect interpretation of a number of different plates within the Ishihara and City University tests, and subjective reporting of colour vision changes were associated with higher SDCs, these assessments present a number of difficulties which would prohibit their routine use in the clinical assessment of digoxin toxicity. Firstly, a number of practical issues apply to the use of the plate tests including access to the plates, and training in their use. Furthermore, many elderly patients had difficulty maintaining their concentration in performing the tests, and had difficulty following the instructions, particularly for the City University test. For the purpose of this study, all patients had to have sufficient cognitive functioning so as to be able to give informed consent. In clinical practice, however, the tests would be more useful if they could be applied to patients who are more unwell or with greater cognitive impairment, who would have even greater difficulty in completing the tests.

The results of Figures 5.7 to 5.10 also demonstrate some of the difficulties in using colour vision testing for the assessment of digoxin toxicity. For the

majority of the Ishihara plates there was a background incidence of abnormal interpretation of test results, and even at the highest SDC category less than half of patients interpreted the plates incorrectly. Given that in current clinical practice the incidence of SDCs greater than 2 ng/mL is less than 5% (Howanitz and Steindel 1993), the vast majority of abnormal colour vision detected would be false positives. Few patients reported subjective changes of colour vision at subtherapeutic concentrations or concentrations in the lower part of the therapeutic range. However, this symptoms is not sufficiently sensitive as only 40% of patients reported this symptom even at concentrations greater than 3.0 ng/mL (Figure 5.7).

The prevalence of abnormal test results across increasing SDC categories was also highly variable, even for Ishihara plates for which the difference in median SDC between correct and incorrect interpretation was highly significant (Plates 3, 5, 12 and 13). Although part of the reason for this observation associated with the City University test could be the smaller number of patients studied (93 patients), this does not apply to the Ishihara plate testing (244 patients). This is in contrast to the consistent increase in prevalence and severity of gastrointestinal symptoms observed.

LeSage and Chuman (LeSage and Chuman 1986) observed that the results from individual Ishihara plates were not as useful as scoring of a total test. In my analysis, the results of the summary score for both the 15 and 6 plate tests were highly significant. However, for the 15 plate test, if the subject is able to correctly interpret 13 or more plates, this should be scored as a positive result for the test, and if the subject is able to interpret 9 or fewer plates correctly, this should be scored as a negative result. Subjects who

score between 10 and 12 plates (inclusive) correctly should not be scored (Ishihara 1996). In this study, this comprised 48 of 210 patients (23%). Figure 5.9 demonstrates that although the Ishihara total score can be useful, the 6 plate test is far too sensitive with over 30% of patients not prescribed digoxin, and 50% of subjects having subtherapeutic concentrations (0.2-0.5 ng/mL) not able to read all 6 plates correctly. The results of the 15 plate test is more specific, but as it utilises the full 15 plates, it would be less practical in routine clinical care.

The results of the City University test are similar in many ways to the Ishihara plates. Firstly, only for a limited number of plates were the median SDCs of patients who interpreted the plates incorrectly higher than those who interpreted them correctly, and with the overall score there was no significant difference in the SDCs between patients who interpreted the plates correctly and incorrectly. Plate 2 demonstrated that patients who interpreted the test incorrectly, paradoxically, had significantly lower SDCs than those who interpreted the plate correctly. This probably reflects the alpha error associated with the large number of questions which were asked as part of this study. Figure 5.10 shows that the 3 plates associated with significantly different median SDCs for correct and incorrect interpretation (Plates 6, 7 and 16) demonstrate quite variable but increasing prevalence of abnormal colour vision across increasing SDC categories. Although these results are promising and might suggest a role for the City University test in the clinical diagnosis of digoxin toxicity, the main barrier to this is the great difficulty which many elderly patients had in understanding and following the instructions associated with the test.

There are two likely explanations for the difference in results between the current study and others studies which have assessed the utility of colour vision testing for the clinical diagnosis of digoxin toxicity. Firstly, previous studies have used standardised lighting for testing (LeSage and Chuman 1986), or even ensured adequate daylight (Lawrenson, Kelly et al. 2002), whereas the current study was performed using the available ward lighting. This included daylight, and halogen lighting, but in many circumstances the lighting source was fluorescent or tungsten lighting which can be associated with green and orange hues, respectively (Freeman 1993).

Secondly, previous reports have either been case reports (Robertson, Hollenhorst et al. 1966; Weleber and Shults 1981), case series (Manninen 1974), or studies specifically assessing digoxin toxic patients (Aronson and Ford 1980; LeSage and Chuman 1986). The patients in those reports have either been chosen because they have manifested colour vision abnormalities associated with high digoxin concentrations, or alternatively their SDCs were sufficiently high to give rise to colour vision abnormalities, or both. In the current study, a very broad range of patients was chosen, either randomly or on the basis of their SDC. As there was no bias towards the selection of patients with colour vision abnormalities, the relationship between SDC and colour vision defects was less reliable.

In descriptions of digoxin toxicity, many different symptoms are described as being equally important in making the diagnosis. In this study, hospital inpatients taking digoxin were systematically interviewed using a structured questionnaire and the presence of many of these symptoms was not related to SDCs. The likely explanation for this is twofold. Firstly, in current clinical

practice and in this study, patients on digoxin are older and present with more comorbidities than in the earlier studies, accounting for a higher frequency of symptoms ascribed to digoxin excess which are, in fact, caused by other conditions. For example, difficulty with mentation, agitation, and mental state abnormalities would be more likely to be due to dementing illnesses in inpatients now than in the 1970s (Lyketsos, Sheppard et al. 2000), and colour vision defects could be due to a greater prevalence in an aging population of cataracts, which absorb more light at the blue end of the spectrum (Chitkara and Colin 2004). Secondly, such patients are exposed to much lower SDCs than in the past (Mahdyoon, Battilana et al. 1990; Williamson, Thrasher et al. 1998). Hence these symptoms are less likely to be due to digoxin excess. Furthermore, the prevalence of hypokalemia and hypothyroidism, which enhance the toxicity of digoxin (Smith and Haber 1970; Aronson, Grahame-Smith et al. 1978; Davis, Vanderveen et al. 1983; Sonnenblick, Abraham et al. 1983), is lower, due to the greater use of angiotensin converting enzyme inhibitors in patients with heart disease and the greater availability of biochemical testing. The only other similar study, in which a minority of patients received digoxin (Ochs, Greenblatt et al. 1980), was performed in patients with permanent pacemakers and demonstrated a weak relationship between the occurrence of extra-cardiac symptoms of digitalis toxicity and SDCs.

This study challenges the traditional binary view of digoxin toxicity i.e. that patients are either "toxic" or "non-toxic". It is apparent that, with increasing digoxin concentrations, both the prevalence and severity of gastrointestinal adverse effects increase. Patients experiencing vomiting have higher SDCs

than those with nausea and anorexia, and those describing their anorexia as "a lot" have higher SDCs than those describing it as "a little". Furthermore, the prevalence of anorexia, nausea, and fatigue progressively increases with increasing concentration, with little evidence of a threshold.

The concentration at which anorexia is significantly more common than baseline appears to be 0.9 ng/mL (1.1 nmol/L), which is in the lower part of the frequently quoted therapeutic range of 0.5-2.0 ng/mL (0.6-2.4 nmol/L). Although this is a *post hoc* analysis which is subject to multiple comparisons, this study demonstrates that compared to baseline, the increase in the prevalence of anorexia occurs at concentrations below the upper end of the therapeutic range. Furthermore, many patients with concentrations above 2.0 ng/mL did not have any manifestations of toxicity in this study, demonstrating that this cut-off is neither sensitive nor specific.

Analysis of the factors influencing the sensitivity to digoxin concentrations revealed that many of the factors which are described in the literature had little role in influencing the sensitivity to SDCs in this study, and appear to be less important in clinical practice today. For all of the gastrointestinal symptoms, serum sodium concentration was negatively associated with the prevalence of the symptom. There are a number several potential explanations for this. It may be that high SDCs cause lower serum sodium concentrations through digoxin's inhibitory action on Na^+-K^+ ATPase. However, the correlation between serum sodium and SDCs was very weak. Alternatively, the effect of serum sodium may be truly independent of the SDC, and may be an independent contributor to the gastrointestinal symptoms. Vomiting can also cause hyponatraemia by increasing the release

of anti-diuretic hormone (Singer and Brenner 2005), hence hyponatraemia may be the effect rather than the cause of the symptoms. If that were the case, one would expect a greater association between more severe gastrointestinal symptoms such as vomiting and hyponatraemia, than with anorexia. Given that this was not seen, it is most likely that hyponatraemia independently contributed to the symptoms.

Serum potassium concentration was negatively associated only with the occurrence of vomiting and not with the other gastrointestinal symptoms. It may be that, when hypokalemia is present, it results in patients vomiting rather than having milder gastrointestinal symptoms. However, in the majority of cases, vomiting was attended by anorexia and nausea. A more likely explanation is that anorexia and nausea were more prevalent in the study population than vomiting, and hypokalemia was a rare event. Hence, although hypokalemia is known to influence the sensitivity to digoxin, because of its low prevalence, it would have played a role in the occurrence of a minority of cases of anorexia and nausea. Hence, it was not revealed as a significant factor on multivariate analysis. Analysis of an interaction between SDC and serum potassium concentrations also did not become significant in any of the models, and the explanation for this would be the same as above.

Female gender was an independent predictor of the occurrence of nausea and vomiting but not anorexia. This may reflect a higher prevalence of these symptoms in females or a greater sensitivity to the effects of digoxin. Little is known about gender based differences in sensitivity to digoxin. Rathore et al (Rathore, Wang et al. 2002) in a *post-hoc* analysis of the DIG trial (The

Digitalis Investigation Group 1997) demonstrated an association between female gender and increased adverse outcomes with digoxin, independent of serum concentration and other patient characteristics.

Co-prescription of some medications contributed to the symptoms of digoxin toxicity. Amiodarone was found to be independently associated with an increased likelihood of the occurrence of vomiting, but diltiazem co-prescription was found to be associated with a lower prevalence of anorexia. The influence of amiodarone may be explained by its independent effects in causing vomiting, or alternatively by blocking p-glycoprotein, and hence resulting in a greater concentration of digoxin within the cerebrospinal fluid (Ieiri, Takane et al. 2004), which may result in a greater prevalence of symptoms. The apparent protective effect of diltiazem on anorexia remained inexplicable. It may be postulated it may be blocking the calcium influx associated with the effects of digoxin. However, verapamil was associated with a greater prevalence of anorexia, and was nearly significant in the multivariate model.

The only factor significantly associated with tiredness on multivariate analysis was respiratory disease. Fatigue is a cardinal symptom of patients with cardiac disease, especially if there is coexistent respiratory disease. Hence given the high prevalence of this symptom at all digoxin concentrations, it is not surprising that only a non-significant trend was found in the association between fatigue and SDCs on multivariate analysis.

The lack of association of many factors previously documented as influencing the sensitivity to digoxin in this study has many explanations. In the case of thyroid disease, and hypokalemia the main reason was the low incidence of these abnormalities in the study population. With the more ready availability of biochemical testing for these abnormalities, as well as the greater use of agents acting on the renin-angiotensin system, which increase potassium concentrations, it is likely that these factors do not play a large role in altering the sensitivity to digoxin in today's clinical practice. Some of the factors which have previously been described as altering digoxin sensitivity, such as hypoxemia or acid-base disturbances, can vary from hour to hour, and it was not possible to reliably assess these at the same time as the patient was being interviewed and having a serum digoxin assay determination performed. As this was an observational study, an insufficient number of patients had routine serum calcium or magnesium estimations performed for these factors to be analysed in this study.

This study demonstrated no association between age and the manifestations of digoxin toxicity. The literature in this area has been conflicting (Wofford, Hickey et al. 1992; Pahor, Guralnik et al. 1993; Miura, Kojima et al. 2000; Rich, McSherry et al. 2001, Lecointre, Pisante et al, 2001). Prospective studies with robust methodology and large sample sizes (Miura, Kojima et al. 2000; Rich, McSherry et al. 2001) have been able to demonstrate a relationship between age and digoxin toxicity, suggesting that the lack of a relationship found in the current study may reflect the fact that the majority of patients were elderly.

The results of this study have a number of implications for the management of hospital inpatients on digoxin therapy in the 2000s. Firstly, only a few symptoms are consistently associated with higher serum digoxin concentrations, and the presence of other symptoms such as diarrhoea, abdominal pain, difficulty thinking, or disorientation is unlikely to indicate digoxin toxicity in clinical practice. The presence of subjective changes of colour vision is specific for digoxin toxicity in a patient prescribed digoxin. However, it is not sufficiently sensitive, as the majority of patients with concentrations above 3.0 ng/mL, which is rarely seen in clinical practice today, did not complain of this symptom. Although an individual patient may have these other symptoms such as abdominal pain, diarrhoea, difficulty thinking or disorientation as a manifestation of digoxin toxicity, routine enquiry of these symptoms is an unreliable discriminator of clinical toxicity. Of the symptoms associated with higher SDCs, fatigue occurs at such a high prevalence in patients with low or absent SDCs that it has little utility in determining whether the patient's symptoms are due to digoxin excess or not. On the other hand, asking the patient about graded severity of anorexia, nausea and vomiting is the most reliable method of eliciting whether the patient has clinical evidence of toxicity.

The strengths of this study are that it includes the largest number of patients reported so far, and the fact that the patients were interviewed by a single investigator who was blinded to the assay result. The study was also performed at three different institutions using two different validated digoxin assays. Hence, the findings should have wide applicability in hospital inpatients having digoxin assays performed. The main weakness is that it

was conducted on hospital inpatients having digoxin assays. It may not be possible to extrapolate the results to other populations such as inpatients not having assays, ambulatory patients or inpatients of residential care facilities. Although it would be anticipated that the prevalence of the symptoms examined in this study would be lower in these populations, the concentration-effect relationship demonstrated here would be expected to be similar. It should be noted that those with higher concentrations are over-represented in this study compared to routine clinical practice. The impact of this would be to make the potential symptoms of toxicity observed in routine clinical practice even less likely to be due to digoxin excess and more likely to be due to another cause.

The results in Table 5.3 also highlight the difficulties in this type of research, in that the responses to Question 7 were not consistent with the responses to Questions 3 and 4. Similarly although there was a significant difference in the median SDCs of patients complaining of tiredness in the last 1 to 2 days compared to those who did not (Question 12), there was no significant difference in the median SDCs associated with the responses to Questions 14 to 16.

The results of this study have important implications for the therapeutic concentration range for digoxin. There is experimental evidence (Gheorghiade, Hall et al. 1995; Slatton, Irani et al. 1997) to suggest that low SDCs between 0.5-0.8 ng/mL are sufficient for efficacy in management of congestive cardiac failure. In atrial fibrillation, there is evidence for a relationship between SDCs and a reduction in heart rate up to a concentration of 3.2 ng/mL (Redfors 1972; Aronson, Grahame-Smith et al.

1977) but my data indicate that such concentrations are likely to be associated with a high frequency of gastrointestinal adverse effects. The observational study by Rathore et al (Rathore, Curtis et al. 2003) suggested that increased mortality may be associated with digoxin concentrations above 0.8 ng/mL in patients with cardiac failure in sinus rhythm, although this conclusion is prone to selection bias as patients were not randomised to different target concentration ranges. My study confirms the suspicion that adverse effects can occur at relatively low SDCs.

These findings have considerable implications for medication safety. Firstly, the therapeutic index for digoxin appears to be even narrower than previously thought, particularly in atrial fibrillation. Secondly, the reference range for digoxin concentrations on clinical laboratory reports should be altered, as many patients with adverse reactions to digoxin are falsely reassured that their digoxin concentrations are "therapeutic" using the current range.

5.5 Conclusion

In conclusion, this is the first study to systematically examine the relationship between the subjective manifestations of digoxin toxicity and SDCs in hospital inpatients. Of all of the symptoms which have traditionally been regarded as having a concentration-response relationship with digoxin, only anorexia, nausea, vomiting, and fatigue are significantly associated with high serum digoxin concentrations. The background prevalence of fatigue in the population taking digoxin is so high that it renders it not clinically useful in the assessment of digoxin toxicity. The most sensitive symptom appears to be anorexia, followed by nausea, and vomiting. Many of the factors which have previously been described as increasing the sensitivity of digoxin toxicity were not found to be associated with greater toxicity in this study. This largely reflects the fact that the prevalence of many of these such as hypokalemia, and hypothyroidism is much less in today's clinical practice.

This would also appear to be the largest study of colour vision abnormalities associated with digoxin, and it suggests that, although reversible colour vision abnormalities are associated with digoxin toxicity, bedside colour assessment tools are not useful for monitoring of or screening for digoxin toxicity. This is due to the fact that none of the individual or combination of plates have sufficient sensitivity and specificity, and the difficulties which many patients had in interpreting the plates, particularly the City University Test.

Chapter 6

ELECTROCARDIOGRAPHIC CHARACTERISATION OF DIGOXIN TOXICITY

6.1 Introduction

Although the previous chapter examined the relationship between patient reported symptoms and digoxin concentrations, the main concern regarding digoxin toxicity is its cardiac manifestations. Several studies in the early 1970s evaluated the relationship between serum digoxin concentrations and electrocardiographic manifestations of toxicity (Grahame-Smith and Everest 1969; Chamberlain, White et al. 1970; Smith and Haber 1970; Beller, Smith et al. 1971; Evered and Chapman 1971; Fogelman, La Mont et al. 1971; Howard, Smith et al. 1973). Seminal observations by Smith and Haber (Smith and Haber 1970) established a serum concentration of 2.0 ng/mL (2.6 nmol/L) as the best discriminator of toxic and non-toxic patients, and this value is still used as the upper margin of the therapeutic range (Mutnick 1995; Gibbs, Davies et al. 2000; Campbell and Williams 2001; Dec 2003). In experimental studies (Grahame-Smith and Everest 1969; Chamberlain, White et al. 1970; Smith and Haber 1970; Beller, Smith et al. 1971; Evered and Chapman 1971; Fogelman, La Mont et al. 1971; Howard, Smith et al. 1973), the diagnosis of digoxin toxicity was determined by the presence of a number of electrocardiographic changes. These emphasised the presence of atrioventricular block and increased automaticity, and remain the basis for descriptions of the electrocardiographic manifestations of digoxin toxicity in

textbooks (Mutnick 1995 ; Goldberger 1999; Hack and Lewin 2002; Ford 2004; Katzung and Parmley 2004; Bristow, Linas et al. 2005; Linden and Burns 2005), review articles (Ma, Brady et al. 2001; Eichhorn and Gheorghiade 2002), some drug information databases (Gold Standard Multimedia 2005), and online sources of drug information (eMedicine 2005; RxList 2005; GP Notebook 2005) . Although some of the these highlight the early appearance of ventricular ectopy and bigeminy (Ma, Brady et al. 2001; Katzung and Parmley 2004), and the specificity of bidirectional ventricular tachycardia (Bristow, Linas et al. 2005; Linden and Burns 2005), there is little consensus as to the rhythms that constitute digoxin cardiotoxicity.

There is also some literature supporting the use of quantitative electrocardiographic measurements to assess digoxin toxicity (Joubert, Muller et al. 1975). The electrical effects of digoxin on the heart can result in a prolongation of the PR interval, shortening of the QT interval (Katzung and Parmley 2004) and T inversion resulting in ST segment sagging (Goldberger 1999). Joubert et al (Joubert, Muller et al. 1975) proposed combining these into a PTQ score, and their preliminary study of 70 patients demonstrated a significant linear correlation with serum digoxin concentrations. Furthermore, PTQ scores of more than 3.0 were in all instances associated with toxic SDCs. Although other authors have used calculated electrocardiographic indices such as the PTQ score for assessment of the effect of digoxin (Joubert, Kroening et al. 1976; Joubert, Muller et al. 1978; Sziegoleit, Weiss et al. 1986; Weiss, Sziegoleit et al. 1986; Sziegoleit, Weiss et al. 1987), there has been no further assessment of this approach in assisting in the diagnosis of digoxin toxicity.

The population of patients treated with digoxin today differs from that in whom the original descriptions of digoxin cardiotoxicity were derived. Patients are now considerably older, with a greater frequency of ischemic heart disease, lesser frequency of rheumatic valvular disease and are more likely to be treated with multiple drug therapies. In addition, the serum concentrations of digoxin to which today's patients are exposed are also lower (Mahdyoon, Battilana et al. 1990; Williamson, Thrasher et al. 1998), and, as discussed in the previous chapter, the prevalence of hypokalemia and hypothyroidism which enhance digoxin's effect would be expected to be lower due to the use of angiotensin converting enzyme inhibitors and the greater availability of biochemical testing. Hence, an electrocardiographic abnormality legitimately attributed to digoxin toxicity 30 years ago is more likely to be caused by other conditions today.

The aim of this study was to:

- determine the relationship between electrocardiographic changes and serum digoxin concentrations,
- determine the utility of specific electrocardiographic changes in predicting digoxin toxicity in the current prescribing environment,
- assess the factors which alter the sensitivity to the electrocardiographic manifestations of digoxin in this population,
- assess the utility of the PTQ score in the diagnosis of electrocardiographic digoxin toxicity in current clinical practice.

6.2 Methods

6.2.1 Patient Selection and Data Collection

The patient selection methods for this study were similar to those in the previous chapter, with the exception that informed consent was not required in order to collect a patient's data. The study comprised patients undergoing serum digoxin assays at three university hospitals. The study was approved by each participating institutional Clinical Research Ethics Committee. Each day the clinical pharmacology laboratory identified 3-5 patients who had digoxin assay results that covered the range of results for SDCs assayed for that day, including all of the assays above the therapeutic range for the laboratory (>2.0 ng/mL). I was blinded to the digoxin assay result and the subsequent ECG appearance, and approached each patient to collect the ECG performed within 24 hours of the serum assay and the results of continuous cardiac monitoring (if performed).

Patients were excluded from the analysis if:

1. the SDC was not a trough result,
2. the patient received a loading dose of digoxin after the assay determination and prior to acquisition of an ECG,
3. cardiac pacing precluded determination of the cardiac rhythm.

Each patient was included only once in the analysis. Data were collected for each patient regarding factors which may alter sensitivity to digoxin as in the previous chapter.

6.2.2 Digoxin Concentration Determination

SDCs were determined by laboratories accredited by the Australian National Association of Testing Authorities using the Syva enzyme immunoassay (Lane Cove, New South Wales) for 53% of samples and the Abbott AxSYM system (North Ryde, New South Wales, Australia) for 47% of samples. The lower limit of quantification was 0.2 ng/mL for both methods.

6.2.3 Electrocardiographic Assessments

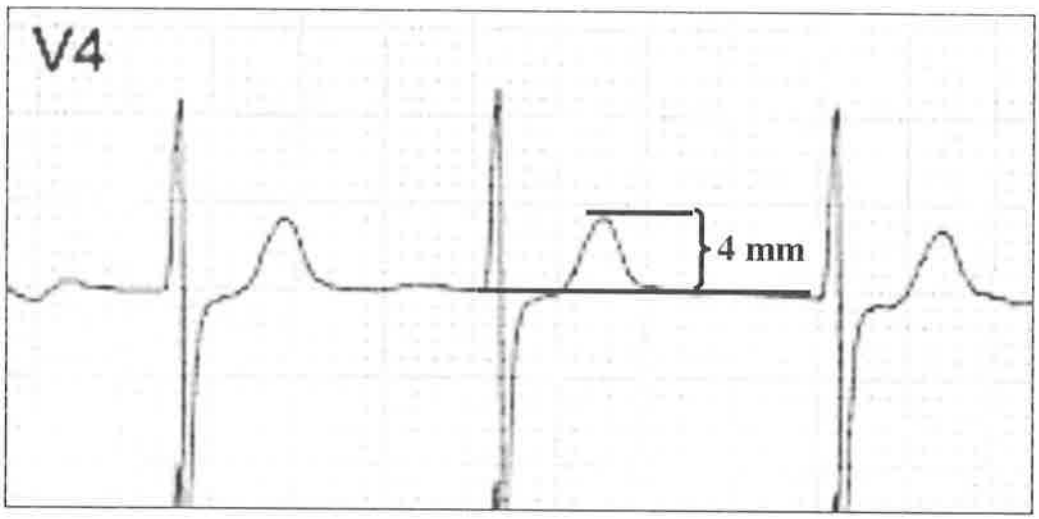
Each ECG was evaluated by 3 independent investigators, comprising myself and/or cardiologists, who were blinded to the patient's history and SDC. Differences between qualitative variables were resolved by consensus. Quantitative variables were determined on conventionally recorded ECGs at a sweep speed of 25mm/s (amplitude 10 mm:1 mV) using manual callipers, and an average between the investigators was utilised.

The following variables were determined:

1. Heart rate was defined as the mean ventricular rate over the duration of the recording;
2. PR interval in sinus rhythm was defined as the duration from the initial deflection from the isoelectric baseline during atrial activity to the commencement of ventricular activation. The PR interval was evaluated on lead 2,
3. Cardiac rhythm was determined for both the atria and ventricles. Where there was evidence of multiple rhythms (e.g. atrial flutter with complete heart block), each rhythm was analysed separately,
4. Premature ventricular complexes (PVCs): total number and number of morphologies were determined,

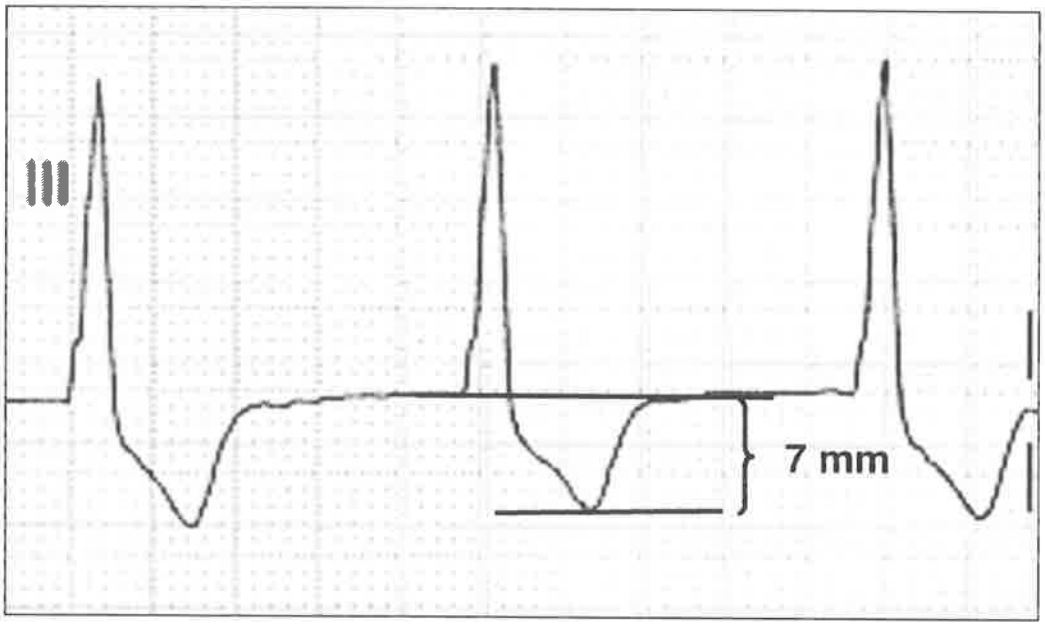
5. ST segment was classified by the presence or absence of sagging (Goldberger 1999),
6. T score was determined using the method by Joubert et al (Joubert, Muller et al. 1975). The T wave in the standard lead showing the largest net positive QRS deflection was scored as follows: an upright T wave of 3 mm or more was given a baseline score of 1; if a T wave was inverted or flattened, the distance in mm from the apex to 3 mm above the isoelectric line was added to 1. Examples of determination of the T score are given in Figures 6.1A-6.1C

FIGURE 6.1A DETERMINATION OF T SCORE EXAMPLE WITH POSITIVE T WAVE GREATER THAN 3 MM



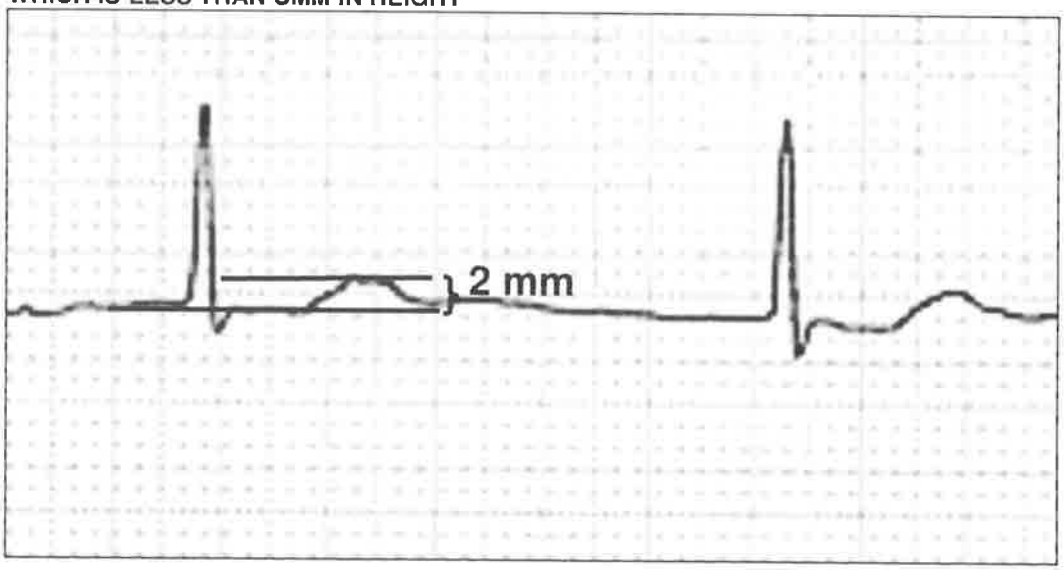
Height of T wave is 4 mm. As this is above the maximum 3 mm above the isoelectric line, this is scored as 1 point.

FIGURE 6.1B DETERMINATION OF T SCORE EXAMPLE WITH NEGATIVE T WAVE



Apex of T wave is 7mm below the isoelectric line. The distance from the apex of the T wave and 3mm above the isoelectric line is 10mm. This is added to 1 to give a T score of 11.

FIGURE 6.1C DETERMINATION OF T SCORE EXAMPLE WITH POSITIVE T WAVE WHICH IS LESS THAN 3MM IN HEIGHT



Distance from height T wave apex and 3 mm above the isoelectric line is 1 mm. This is added to 1 giving a T score of 2.

7. QT interval was measured from the beginning of the QRS complex to the end of the T wave in the lead with the longest interval and without prominent U waves (Mirvis and Goldberger 2005),

8. QTc interval was determined using the equation by Bazett (Mirvis and Goldberger 2005),

$$QTc = \frac{QT}{\sqrt{R-R}}$$

Where R-R is the average difference between consecutive R defections of the QRS complex,

9. PTQ score was calculated as (Joubert, Muller et al. 1975).

$$PTQ = \frac{PR \times T}{QTc}$$

6.2.4 Determination of Toxic Rhythms

ECGs with rhythms for which digoxin would be prescribed such as atrial fibrillation, atrial flutter and sinus rhythm in patients with cardiac failure, were considered to be baseline rhythms. The SDCs of patients with these ECGs were compared to the SDCs of patients with all other rhythms with particular interest in those previously attributed to digoxin toxicity (Smith and Haber 1970; Packer 2004; Bristow, Linas et al. 2005). Rhythms that were associated with statistically significantly higher SDCs than the baseline rhythms were defined as "toxic rhythms".

6.2.5 Statistical Analysis

All variables are presented as mean ± standard deviation, except for the serum digoxin concentration that is presented as the median and range. Comparison between groups was performed with either Student's t-test or Wilcoxon Rank-Sum test. Proportions were compared using the Fisher's exact test. Statistical analysis was performed using SPSS (SPSS for Windows, Release 10.0.7 2000. Chicago: SPSS Inc.), setting the threshold for significance at $p=0.05$.

For the determination of factors which may alter the sensitivity to digoxin, a log-binomial model was utilised using generalized estimating equations methodology with SAS software (SAS Institute Inc., Cary, NC, USA). The methodology and the assumptions were the same as in the previous chapter.

6.3 Results

6.3.1 Patient Characteristics

Data were collected from 616 patients with 657 rhythms. Forty-one ECGs exhibited more than one rhythm. The demographics of the population studied are shown in Table 6.1.

TABLE 6.1 CHARACTERISTICS OF 616 PATIENTS

Characteristic	Value
Age, (mean, ±SD) (years)	76.3 ± 10.9
Male	320 (52.0%)
Indication for Digoxin	
Atrial fibrillation	199 (32.3%)
Cardiac failure	122 (19.8%)
Both atrial fibrillation and cardiac failure	246 (40.0%)
Other/Unknown	49 (8.0%)
Potential Pharmacodynamic Interactions*	
None	433 (70.3%)
One drug	145 (23.5%)
Two drugs	9 (1.5%)
Unknown †	29 (4.7%)
Serum Potassium (mean ±SD) (mmol/L)	4.17 ± 0.69

SD= Standard Deviation

* Drugs which have similar effects to digoxin on heart rhythm: amiodarone, verapamil, sotalol and other beta-blockers

† Unknown due to the lack of availability of casenotes

The potential confounding effect of the co-administration of drugs that could have similar effects on the ECG to digoxin, e.g. amiodarone, verapamil, sotalol, was examined on the SDCs of patients who were and were not co-prescribed such medications. There was no statistically significant difference in the mean SDC of patients who were co-administered such medications,

and those who were not, suggesting that the observation of a relationship between high SDCs and ECG findings was unlikely to be influenced by a greater prevalence of co-administered medications in such patients.

The SDCs ranged from 0.2 to 8.0 ng/mL (0.3-10.3 nmol/L) and their distribution is demonstrated in Table 6.2.

TABLE 6.2 DISTRIBUTION OF TROUGH SERUM DIGOXIN CONCENTRATIONS

Concentration Range (ng/mL)*	Number of Patients	Percent of Total
0.2-0.5	62	10.1%
0.51-1.0	185	30.0%
1.01-1.5	109	17.7%
1.51-2.0	86	14.0%
2.01-2.5	87	14.1%
2.51-3.0	36	5.8%
3.01-3.5	26	4.2%
3.51-8.0	25	4.1%

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

6.3.2 Rhythm Analysis

Table 6.3 reveals the cardiac rhythms that were observed more than once with the associated digoxin concentrations and comparison with baseline rhythms. The following rhythms were found to be associated with significantly higher SDCs than baseline and were defined as toxic: ventricular and junctional escape ($p=0.04$ and $p=0.003$ respectively), atrial fibrillation with rate less than 60 ($p<0.001$), ventricular tachycardia ($p=0.025$), junctional rhythm ($p=0.003$), and sinus rhythm with heart block ($p=0.003$ for first degree heart block and $p=0.09$ for third degree heart block). The lack of significance of sinus rhythm with third degree heart block ($p=0.09$) is largely due to the limited number of patients with this diagnosis ($n=3$).

TABLE 6.3 FREQUENCY OF RHYTHMS OBSERVED MORE THAN ONCE AND CORRESPONDING MEDIAN TROUGH SERUM DIGOXIN CONCENTRATIONS

Rhythm	Frequency of Rhythm	Median SDC* (ng/mL)† and Range	P of Comparison to Caseline Rhythm
Baseline Rhythm‡	458 (70.0%)	1.10 (0.2-5.2)	Not Applicable
Sinus Bradycardia	35 (5.4%)	1.42 (0.4-3.2)	0.18
Sinus Rhythm with 1st Degree Block	68 (10.4%)	1.57 (0.2-5.1)	0.003
Sinus Rhythm with 3rd Degree Block	3 (0.5%)	1.75 (1.6-3.9)	0.09
Multifocal Atrial Tachycardia	7 (1.1%)	1.33 (0.3-3.6)	0.67
Atrial Fibrillation Rate 50-59	23 (3.5%)	1.80 (0.7-4.6)	0.001
Atrial Fibrillation Rate <50	20 (3.1%)	2.57 (0.6-5.0)	<0.0001
Junctional Rhythm Rate >70	7 (1.1%)	2.10 (1.4-3.7)	0.003
Junctional Escape	18 (2.8%)	1.80 (0.2-8.0)	0.003
Ventricular Bigeminy	6 (0.9%)	1.31 (0.7-2.4)	0.81
Ventricular Tachycardia	6 (0.9%)	2.52 (0.5-5.1)	0.025
Ventricular Escape	3 (0.5%)	3.58 (1.3-3.6)	0.04

* SDC= Serum digoxin concentration

† Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

‡ Rhythms for which digoxin would be prescribed: atrial fibrillation, atrial flutter, and sinus rhythm in patients with heart failure

As there was a trend for patients with sinus bradycardia to have higher SDCs than the baseline rhythm, and many of these patients had concurrent first degree heart block, the relationship between these two rhythms and SDC was explored further, and the results are displayed in Table 6.4.

TABLE 6.4 RELATIONSHIP BETWEEN SINUS BRADYCARDIA AND FIRST DEGREE HEART BLOCK AND SERUM DIGOXIN CONCENTRATIONS

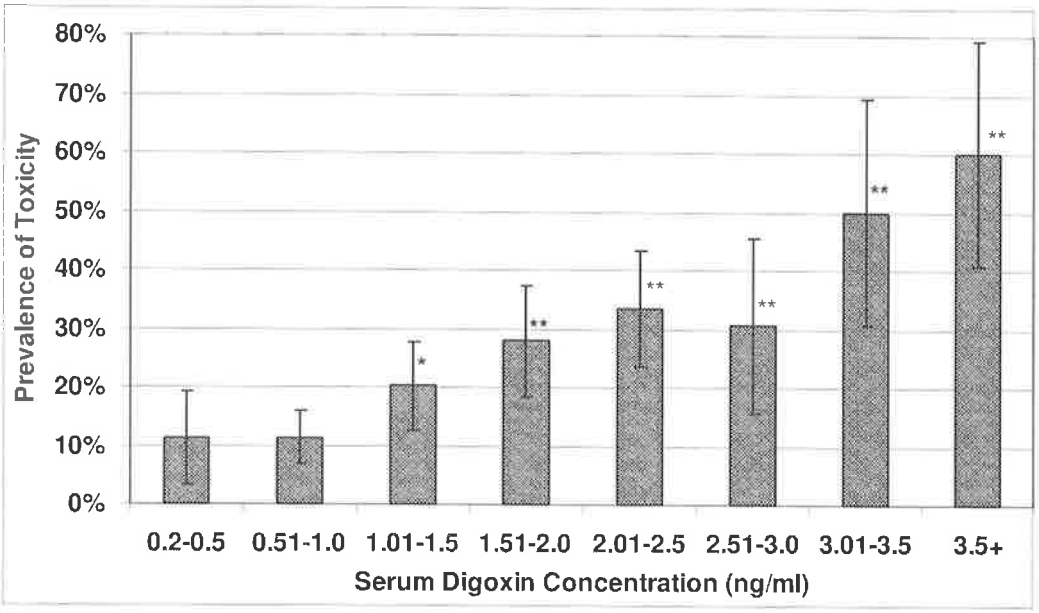
Rhythm	Count	Median SDC (ng/mL)*	P of comparison to sinus rhythm	Co-prescription of medication with pharmacodynamic interaction†
Sinus Rhythm	157	1.02	N/A	20.7%
Sinus with First Degree Heart Block	54	1.56	0.0025	42.3%
Sinus Bradycardia	21	1.10	0.47	42.1%
Sinus Bradycardia and First Degree Heart Block	14	1.57	0.053	50.0%

† Pharmacodynamic drug interaction: medications which have a similar effect on the ECG as digoxin including amiodarone, sotalol, other beta blockers, and verapamil.

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

Figure 6.2 demonstrates the prevalence of the occurrence of any of these rhythms plotted against the digoxin concentration, demonstrating the concentration-dependent increase in the prevalence of digoxin toxicity. At a concentration up to 1.0 ng/mL, the prevalence of cardiac toxicity was 11.3% (28/247), and at a concentration of 1.01-1.50 ng/mL the prevalence was 20.2% (22/109, p=0.032 for difference). The prevalence of toxicity at higher digoxin concentrations was also significantly higher than at concentrations up to 1.0 ng/mL.

FIGURE 6.2 PREVALENCE OF TOXICITY AT INCREASING CONCENTRATIONS CATEGORIES



* P<0.05 in comparison to prevalence of toxicity at range 0.2-1.0 ng/mL

** P<0.01 in comparison to prevalence of toxicity at range 0.2-1.0 ng/mL

6.3.3 Analysis of Premature Ventricular Complexes

There was no significant difference between the SDCs of patients whose ECGs demonstrated monomorphic or polymorphic PVCs and those without any evidence of ventricular premature complexes (Table 6.5).

TABLE 6.5 MEDIAN SERUM DIGOXIN CONCENTRATION (SDC) OF PATIENTS WITH ELECTROCARDIOGRAMS WITH AND WITHOUT PREMATURE VENTRICULAR COMPLEXES (PVC)

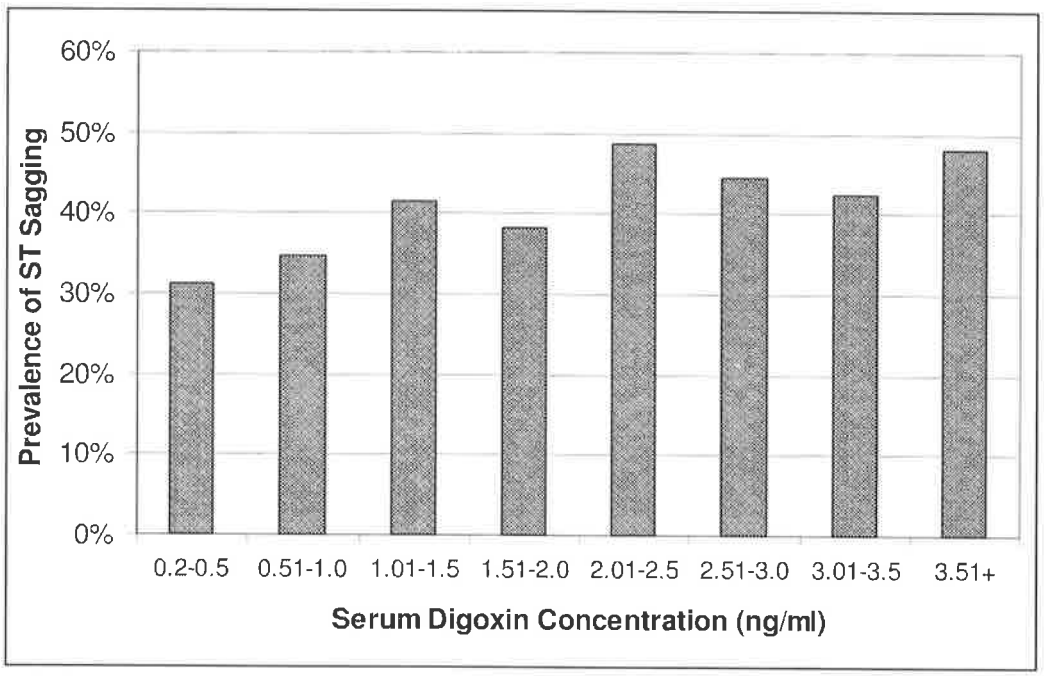
	Median SDC (ng/mL) and Range*	Frequency	P of Comparison with PVCs Absent
PVC Absent	1.25 (0.20-8.00)	496	N/A
PVC Present	1.25 (0.20-5.24)	120	NS
- Polymorphic PVCs	1.19 (0.31-5.24)	34	NS
- Monomorphic PVCs	1.29 (0.20-3.56)	86	NS

* Multiply by 1.2 for *systeme international* units (nmol/L) (Schumacher 1995)

6.3.4 Analysis of ST Segment Sagging

There was a small but significant difference between the SDCs of patients whose ECGs exhibited ST segment sagging (median concentration 1.4 ng/mL, range 0.2-5.2 ng/mL) compared to those which did not (median concentration 1.2 ng/mL, range 0.2-8.0 ng/mL, p=0.03). As can be seen from Figure 6.3, although the prevalence of ST segment sagging was higher at SDCs above 2.0 ng/mL, the increase in prevalence was only modest.

FIGURE 6.3 PREVALENCE OF ST SEGMENT SAGGING AT INCREASING CONCENTRATION CATEGORIES



6.3.5 Analysis of Quantitative Data

The Spearman correlation coefficients and significance of the relationships between the SDC and the quantitative ECG criteria are summarized in Table 6.6 and Figures 6.4A-D.

TABLE 6.6 RELATIONSHIP BETWEEN QUANTITATIVE ECG PARAMETERS AND SERUM DIGOXIN CONCENTRATION

ECG Parameter	Correlation coefficient	P value
Heart Rate	-0.173	<0.001
Machine Determined PR Interval	0.173	<0.001
Machine Determined QTc Interval	-0.075	0.069
Manual PR Interval	0.239	<0.001
Manual QTc Interval	-0.129	<0.001
T Score	0.168	<0.001
Machine Determined PTQ Score	0.208	0.002
Manual PTQ Score	0.217	0.001

FIGURE 6.4A SCATTERPLOT OF SERUM DIGOXIN CONCENTRATION AND HEART RATE

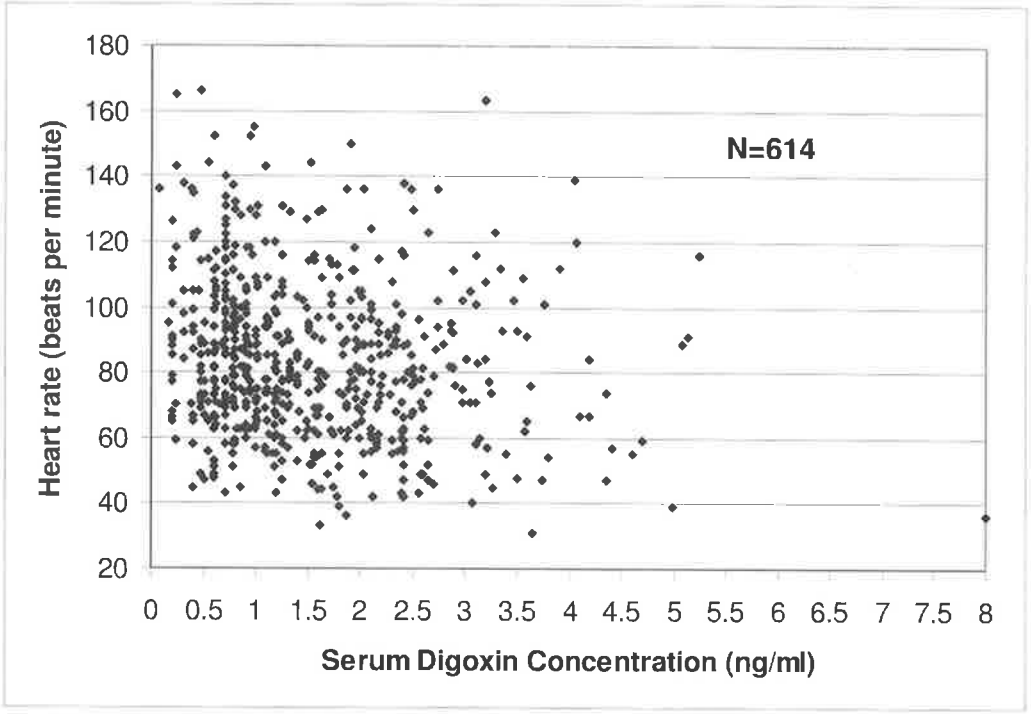


FIGURE 6.4B SCATTERPLOT OF SERUM DIGOXIN CONCENTRATION AND MANUALLY DETERMINED PR INTERVAL

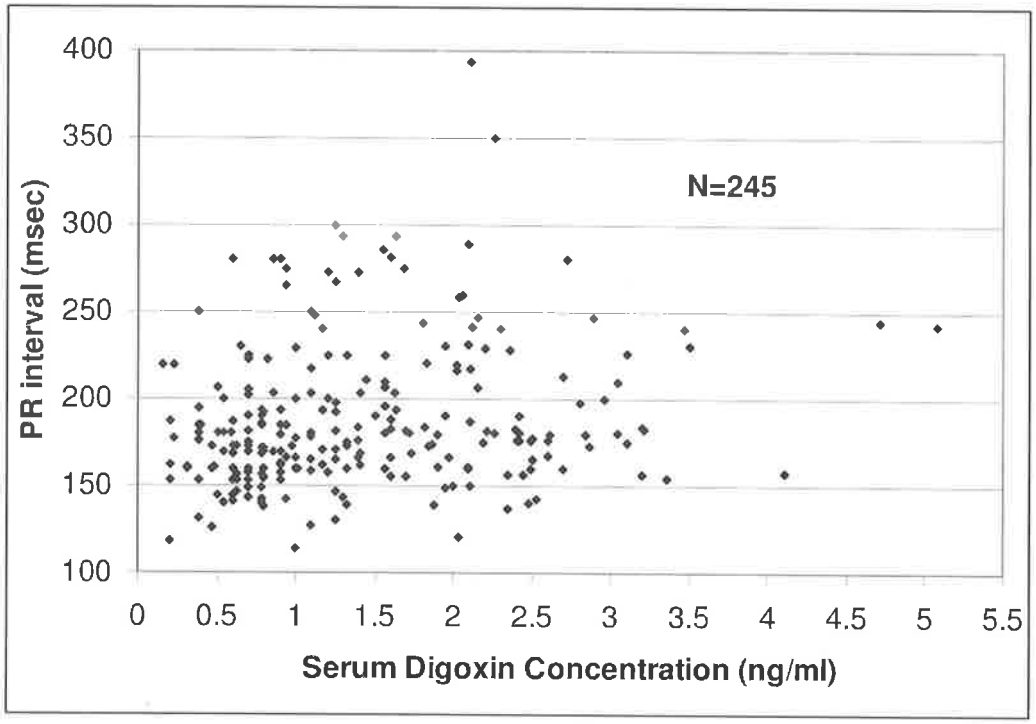


FIGURE 6.4C SCATTERPLOT OF SERUM DIGOXIN CONCENTRATION AND T SCORE

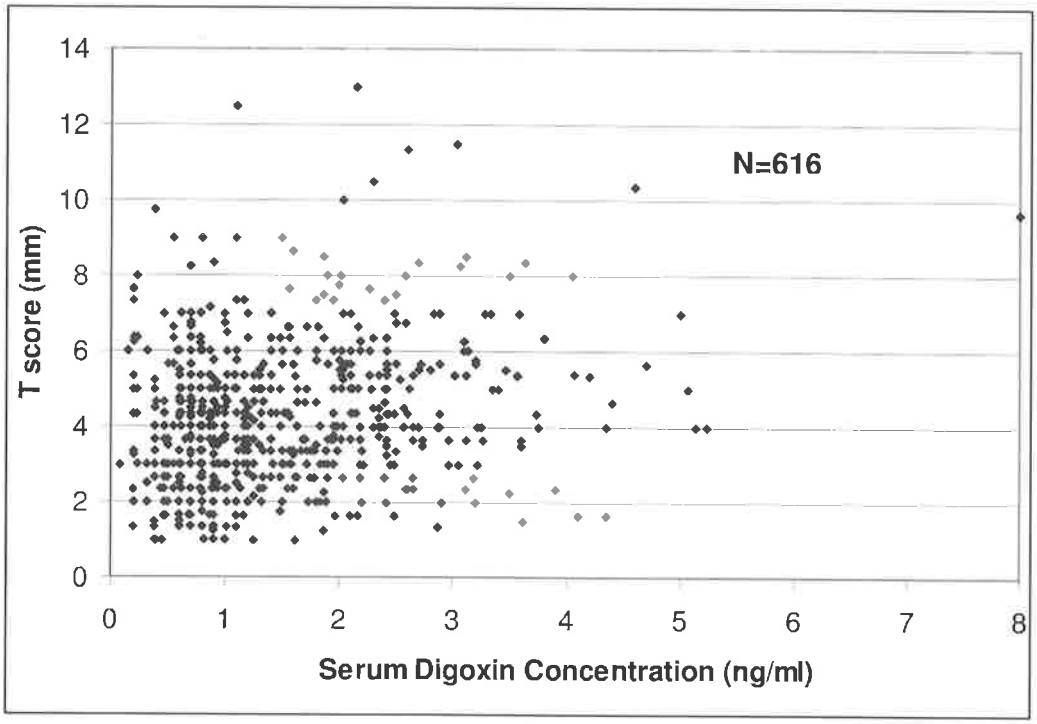
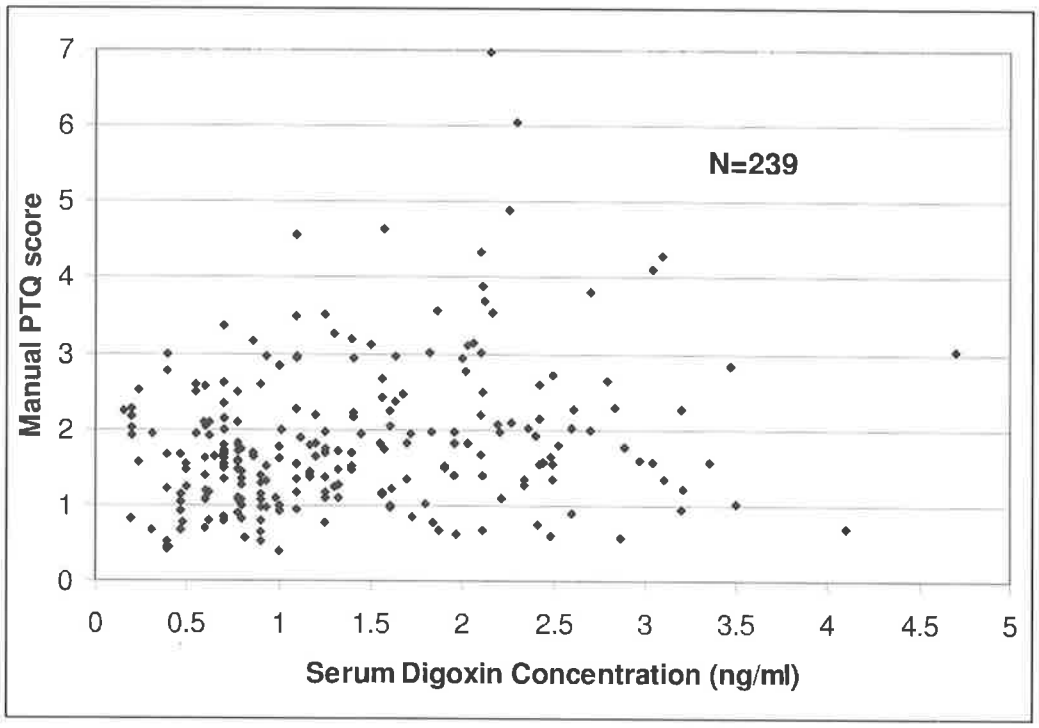


FIGURE 6.4D SCATTERPLOT OF SERUM DIGOXIN CONCENTRATION AND PTQ SCORE



Figures 6.5A-D present the relationship between the mean values for heart rate, PR intervals, T score and manually determined PTQ score represented against increasing assay concentration categories.

FIGURE 6.5A MEAN HEART RATE WITH STANDARD DEVIATION AT INCREASING SERUM DIGOXIN CONCENTRATIONS

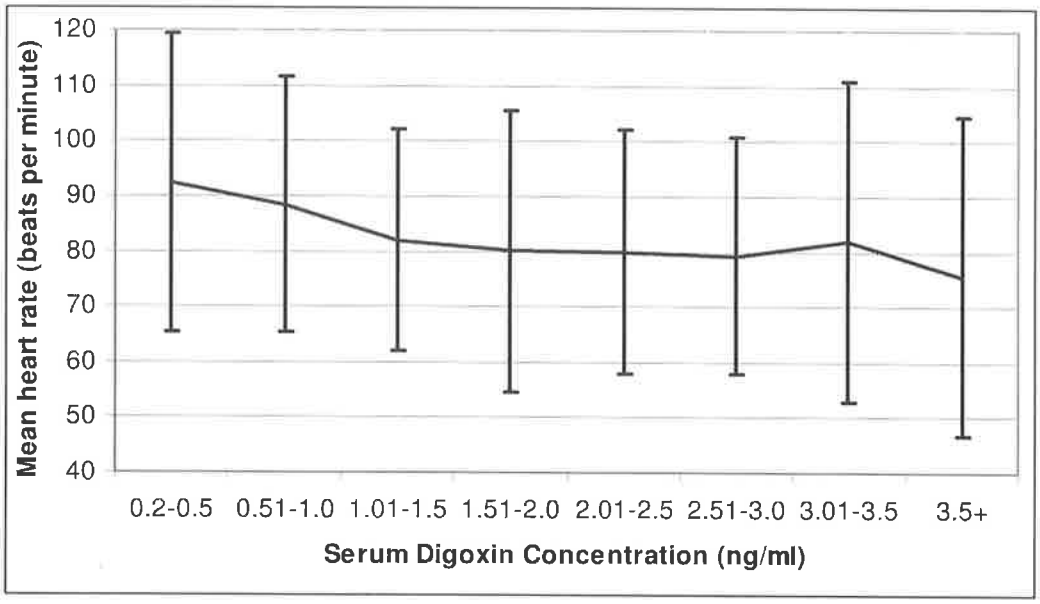


FIGURE 6.5B MEAN MANUALLY DETERMINED PR INTERVAL WITH STANDARD DEVIATION AT INCREASING SERUM DIGOXIN CONCENTRATIONS

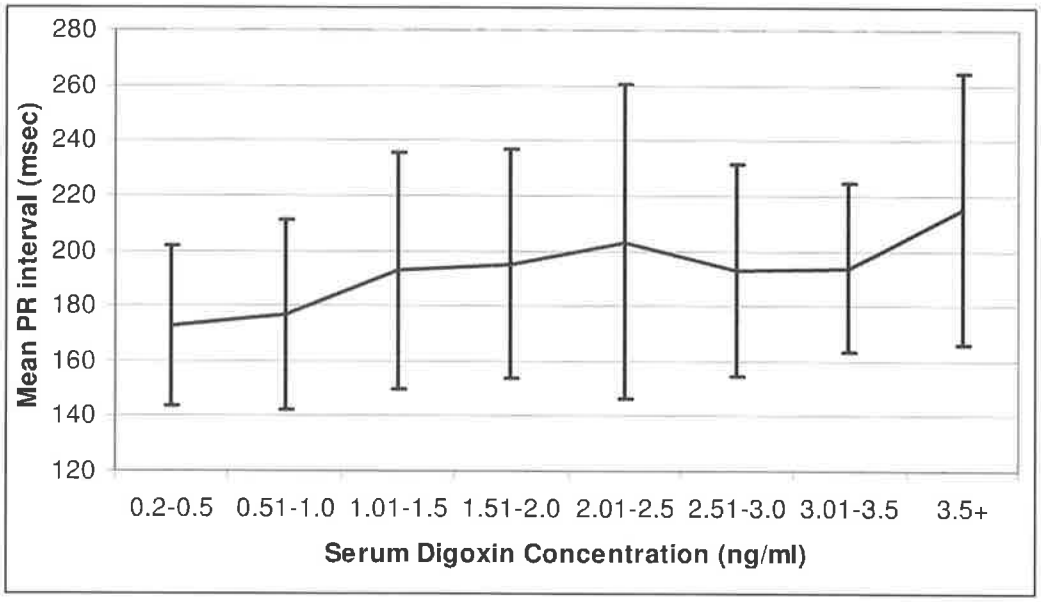


FIGURE 6.5C MEAN T SCORE WITH STANDARD DEVIATION AT INCREASING SERUM DIGOXIN CONCENTRATIONS

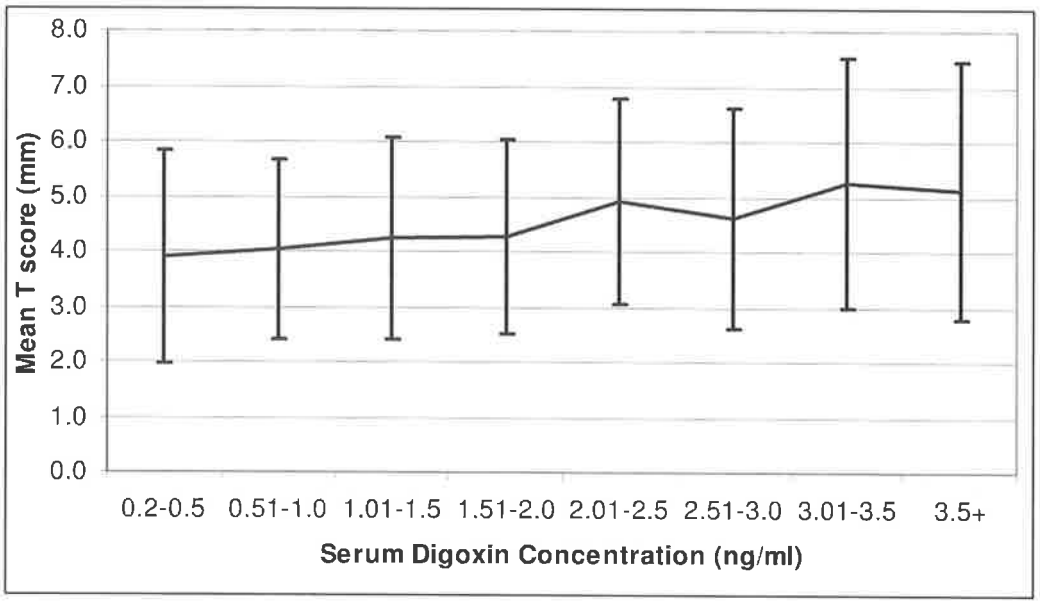
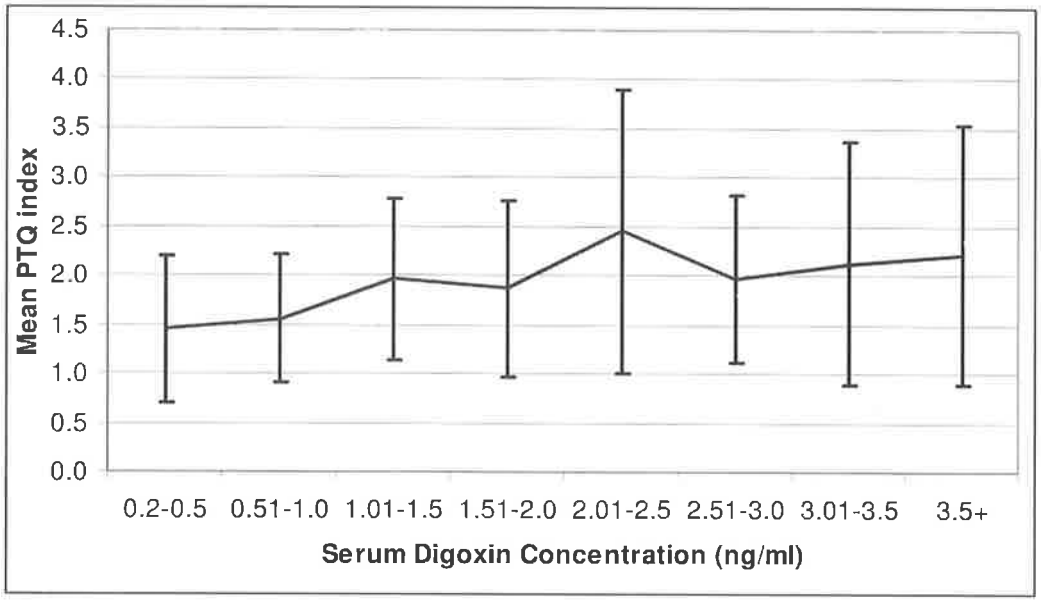
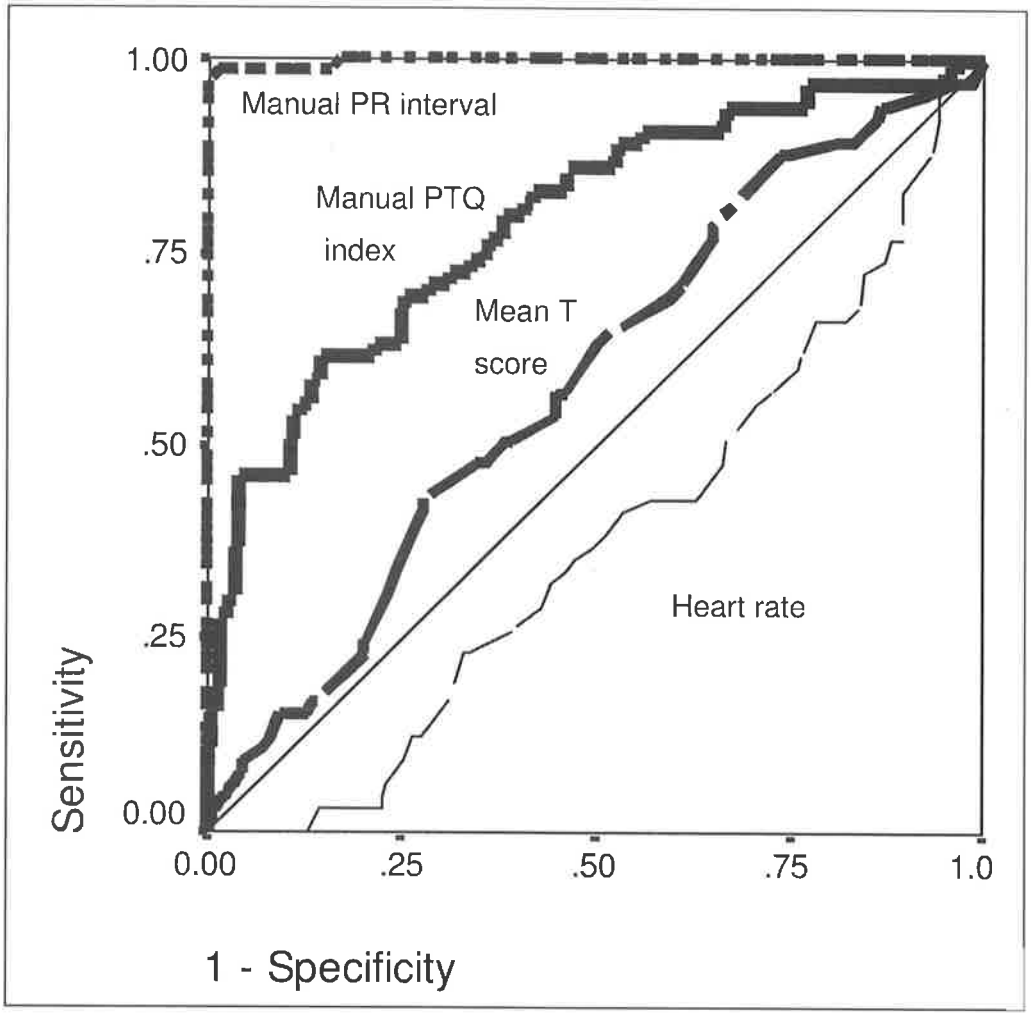


FIGURE 6.5D MEAN MANUALLY DETERMINED PTQ SCORE WITH STANDARD DEVIATION AT INCREASING SERUM DIGOXIN CONCENTRATIONS



A receiver operating characteristics curve was determined in order to assess each of the quantitative ECG parameters as a test for a toxic rhythm defined above.

FIGURE 6.6 RECEIVER OPERATING CHARACTERISTICS CURVE FOR QUANTITATIVE ECG PARAMETERS AND TOXIC RHYTHM†



† Defined as rhythms having significantly higher SDCs than baseline (Table 6.3).

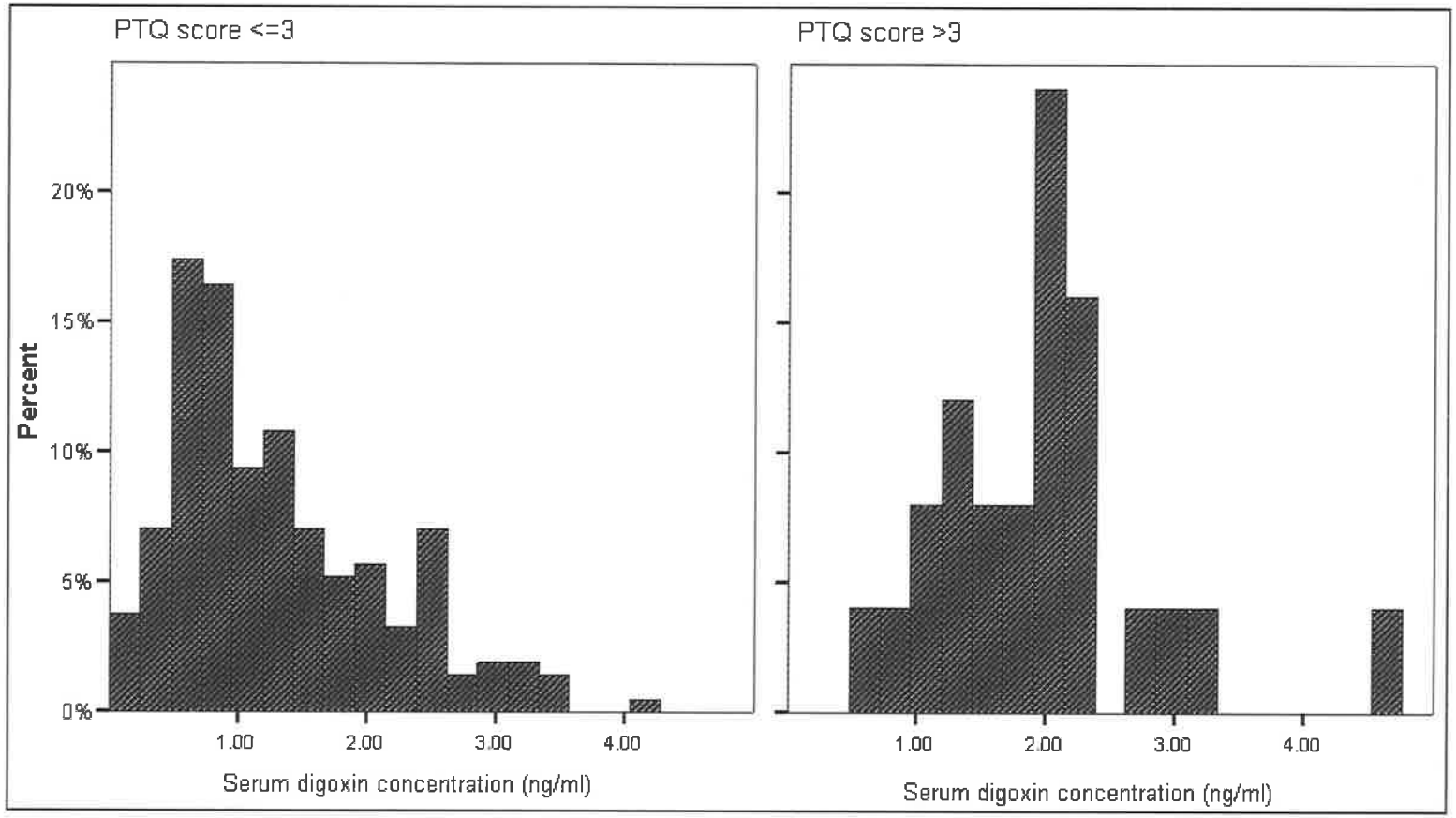
TABLE 6.7 AREA UNDER THE CURVE ANALYSIS OF RECEIVER OPERATING CHARACTERISTICS FOR QUANTITATIVE ECG PARAMETERS AND TOXIC RHYTHM

Parameter	Area (95% confidence intervals)	P Value
Manual PR Interval	0.997 (0.992-1.002)	<0.001
Manual PTQ Score	0.792 (0.725-0.859)	<0.001
T Score	0.586 (0.506-0.666)	0.041
Heart Rate	0.380 (0.303-0.457)	0.004

Because of the observed relationship between manually determined PTQ score and SDC (Table 6.6), and the relationship between SDC and electrocardiographic toxicity, the relationship between PTQ score and electrocardiographic toxicity was explored further in order to determine whether it could provide additional information regarding whether a patient was experiencing digoxin cardiotoxicity.

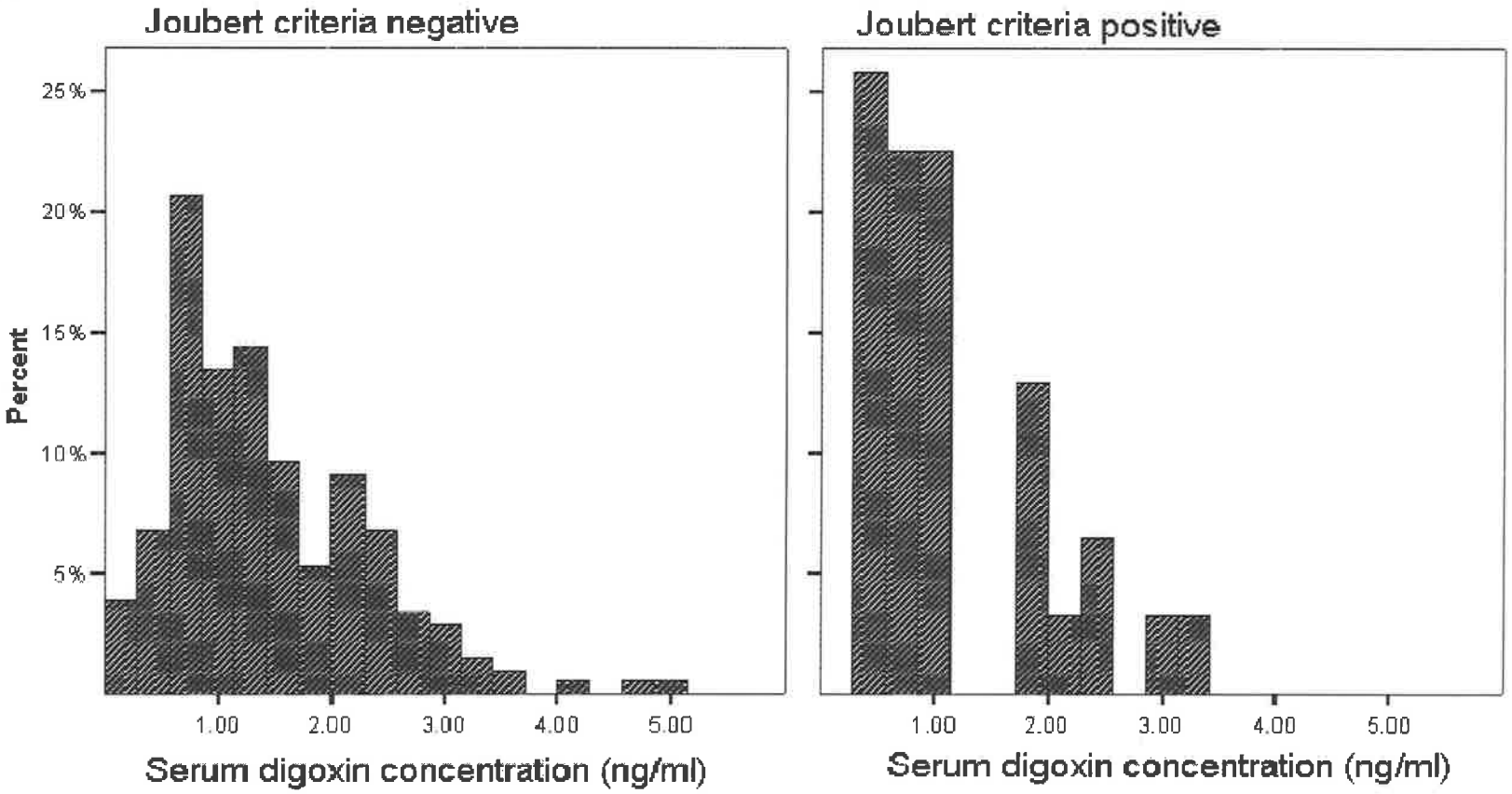
The potential ability of a PTQ score of greater than 3.0 to be able to discriminate between "toxic" and "non-toxic" digoxin concentrations (Joubert, Muller et al. 1975) was explored. Figure 6.7 demonstrates the histogram of SDCs for patients having PTQ scores of greater than and less than or equal to 3.0. As can be seen, this particular cut-off was not specific for digoxin concentrations greater than the accepted upper limit of the therapeutic range in this study, although it was associated with significantly higher median SDCs (1.1 ng/mL compared to 2.1 ng/mL, $p<0.001$). This cut-off was also significantly associated with a greater prevalence of toxic rhythms as defined above ($p<0.001$). Although a PTQ score of 3.0 had a poor sensitivity for detection of a toxic rhythm (20 of 65), the majority of those with a score greater than 3.0 had a toxic rhythm (20 of 25), suggesting good specificity but poor sensitivity.

FIGURE 6.7. HISTOGRAM OF SERUM DIGOXIN CONCENTRATIONS FOR PATIENTS HAVING PTQ SCORE GREATER AND LESS THAN OR EQUAL TO 3.0



The criteria developed by Joubert et al (Joubert, Muller et al. 1975) of absence of ST segment sagging, an upright T wave, and PTQ score less than or equal to one being specific for absence of toxicity was also assessed in this study population. Figure 6.8 describes the histogram of SDCs for patients whose ECGs fulfilled all of these criteria (Joubert criteria positive) and those were it did not (Joubert criteria negative). As can be seen from the histogram, the number of patients whose ECGs fulfilled all of these criteria was relatively small (31 of 239), and the SDC for a number of these patients exceeded the "toxic"' threshold on the current accepted therapeutic range for digoxin. The median concentration of patients whose ECGs fulfilled these criteria was slightly, though significantly, less than patients whose ECGs did not fulfil these criteria (0.90 ng/mL compared to 1.25 ng/mL, p=0.03).

FIGURE 6.8 HISTOGRAM OF SERUM DIGOXIN CONCENTRATIONS OF PATIENTS WITH ECGS DEMONSTRATING JOUBERT CRITERIA OR NOT[1]



1. Defined as present if all of the following fulfilled: PTQ score≤1, absence of ST segment sagging, and upright T wave

There was also a significant association between presence of the Joubert criteria and prevalence of toxicity as defined in Table 6.3 (6.5% compared to 30.2%, p=0.004). There were two patients whose ECGs did fulfil all 3 criteria, and whose electrocardiographic rhythm was deemed to be toxic by the criteria determined above. The SDCs of these patients were 0.82 and 0.90 ng/mL.

As might be expected, the median PTQ score for patients with electrocardiographic toxicity was higher than patients without (2.41 versus 1.51, p<0.001). However, when patients with electrocardiographic toxicity were excluded, the correlation between PTQ score and SDC was no longer significant (p=0.207), and the correlation coefficient was only 0.096.

6.3.6 Factors Altering Sensitivity to Serum Digoxin Concentration

Analysis of factors altering sensitivity to SDCs was performed in the same way as in the previous chapter with subjective symptoms of digoxin toxicity. On log-binomial regression (Table 6.8) the only factors found to independently influence the prevalence of digoxin toxicity using the definition above were the SDC (p<0.0001) and the co-prescription of a drug with a pharmacodynamic interaction with digoxin (p=0.0126). The latter included amiodarone, sotalol, other beta-blockers, and verapamil.

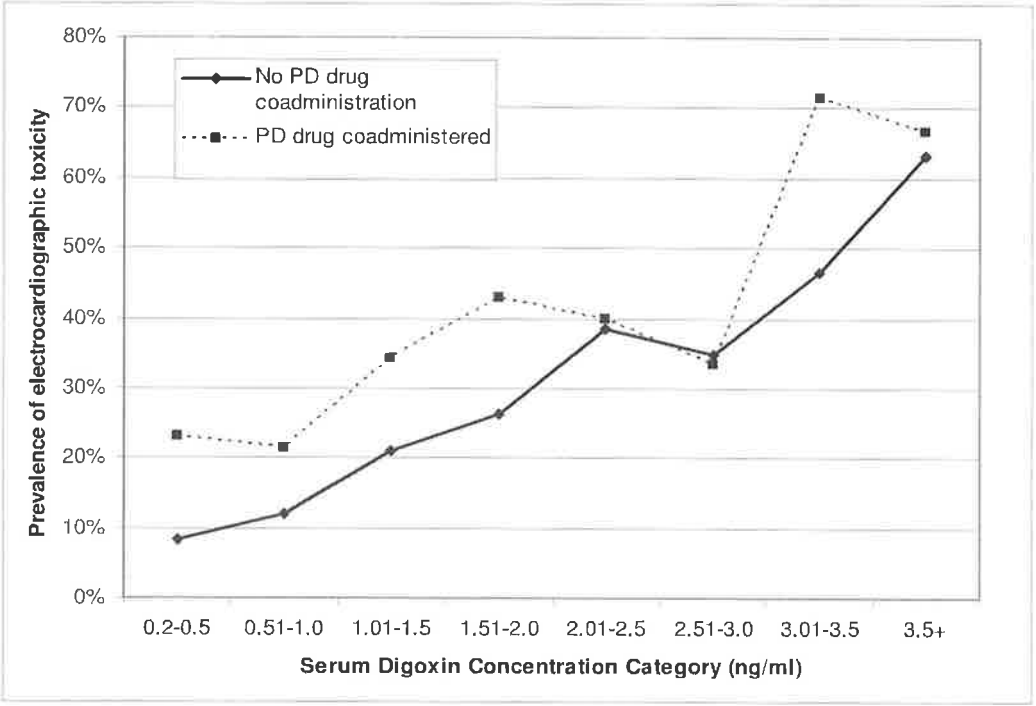
TABLE 6.8 LOG-BINOMIAL REGRESSION OF FACTORS ASSOCIATED WITH DIGOXIN ELECTROCARDIOGRAPHIC TOXICITY[1]

Factor	Parameter Estimate	P value
Serum Digoxin Concentration	**0.368 (0.231 to 0.505)**	**<0.0001**
Co-Prescription of Medication with Pharmacodynamic Interaction[2]	**0.471 (0.101 to 0.841)**	**0.0126**

1. As defined as those rhythms which have higher median serum digoxin concentrations than baseline (Table 6.3)
2. Includes amiodarone, verapamil, sotalol and other beta-blockers

Figure 6.9 demonstrates the influence of co-administration of medications with pharmacodynamic interactions on the concentration-toxicity relationship of digoxin.

FIGURE 6.9 PREVALENCE OF ECG TOXICITY AT INCREASING SDC CATEGORIES BY CO-ADMINISTRATION OF DRUGS WITH PHARMACODYNAMIC (PD) INTERACTIONS



6.4 Discussion

To my knowledge this is the largest study to use stringent criteria such as blinding of the investigator, confirmation of trough status of the assay, and blinded assessment by three independent assessors, to assess the relationship between SDCs and electrocardiographic manifestations of digoxin in contemporary practice. The findings of this study are that there was a concentration dependent increase in the prevalence and severity of bradycardic rhythms, but not increased automaticity. The concentration at which there was an increase in the prevalence of toxicity appeared to be at 1.0 ng/mL, which is at the lower end of the currently quoted therapeutic range (0.5-2.0 ng/mL, 0.6-2.4 nmol/L). The majority of rhythms associated with significantly higher serum digoxin concentrations demonstrated bradycardia. In addition, arrhythmias previously attributed to increased automaticity and digoxin toxicity were not observed to be associated with higher serum digoxin concentrations. These findings challenge long held dictums of the electrocardiographic manifestations of high digoxin concentrations.

Most of the current literature emphasises the importance of increased automaticity (Ma, Brady et al. 2001; Katzung and Parmley 2004), as manifested by ectopy with or without heart block (Packer 2004; Bristow, Linas et al. 2005; Linden and Burns 2005), as signs of toxicity. The literature also states that the prevalence of toxicity increases at SDCs above 2.0 ng/mL (Mutnick 1995; Campbell and Williams 2001; Campbell and MacDonald 2003; Dec 2003). The majority of rhythms associated with significantly higher SDCs in this study were bradycardias. Toxic rhythms

manifested as tachycardias, such as ventricular tachycardia and accelerated junctional rhythm, were rare, accounting for fewer than 10% of toxic rhythms. Furthermore, ECGs demonstrating PVCs or ventricular bigeminy were not associated with higher serum digoxin concentrations than ECGs without PVCs. My findings also indicate that the effect of digoxin in causing heart block demonstrates concentration dependency with increasing prevalence as well as severity with higher concentrations, such as ventricular escape occurring at higher concentrations than sinus rhythm with first degree heart block. This increasing prevalence appeared to be continuous with no evidence of a threshold effect at a concentration of 2.0 ng/mL, the currently accepted upper end of the therapeutic range in many laboratories. The toxicity rate at concentrations of 1.01-1.50 ng/mL was significantly higher than for concentrations up to 1.0 ng/mL. Although this is a *post hoc* analysis which is subject to multiple comparisons, it suggests that the prevalence of digoxin toxicity increases at values in the lower end of the current therapeutic range. This is supported by the recent finding from the DIG study, that patients with SDCs above 0.8 ng/mL had a worse outcome than those with lower serum concentrations.(Rathore, Curtis et al. 2003) Furthermore, as only approximately 50% of patients with concentrations above 2.0 ng/mL demonstrated electrocardiographic evidence of toxicity, this cut-off level was neither sensitive nor specific.

The findings were based on 12-lead ECG rather than continuous cardiac monitoring data. However, this reflects current practice in these institutions as a minority of the patients had electrocardiographic monitoring. In addition, while the study was performed using a blinded approach with the

determination of toxicity being based on the comparison of SDCs of rhythms to comparator rhythms, the gold standard method of determining toxicity by using digoxin Fab antibodies to remove the effect of digoxin on cardiac tissue within hours was not feasible. Despite the large number of patients studied, the prevalence of individual electrocardiographic rhythms was low and there was considerable variability in the SDCs at which they occurred. Hence it is not possible to conclude that an individual electrocardiographic manifestation is definitely diagnostic of digoxin toxicity. Nevertheless, the number of ECGs reviewed was far larger than in previous studies and the study was conducted across three institutions, broadening the applicability of the findings to general clinical practice.

ST segment sagging is traditionally described in the literature as being a drug effect of digoxin, and not associated with toxic concentrations (Goldberger 1999; Mirvis and Goldberger 2005), a statement that is supported by the findings of this study. Although patients whose ECGs demonstrated ST segment sagging had significantly higher SDCs than those who did not, the difference was modest (0.2 ng/mL difference in median values). Furthermore, Figure 6.3 demonstrates that the ECGs of patients with the lowest SDC category (0.2-0.5 ng/mL) had a prevalence of ST segment sagging of 30%, and this compares to only approximately 50% for those at the highest SDC category of greater than 3.51 ng/mL. Hence, although an association between ST segment sagging and SDCs has been demonstrated in this large scale study, in the evaluation of an individual patient, ST segment sagging could not by itself be considered as being caused by digoxin toxicity.

6.4.1 Analysis of Quantitative Variables

This cross-sectional study demonstrated a poor relationship between SDC and heart rate, which confirms the findings of other authors (Chamberlain, White et al. 1970; Goldman, Probst et al. 1975; Halkin, Kleiner et al. 1979). There is evidence, however, to support a better relationship between SDCs and a percentage improvement in heart rate in individual patients (Redfors 1972). My finding is not surprising as there are many influences on heart rate apart from the digoxin concentration, and the study patients were a broad cross-section of hospital inpatients. Although some of the patients were clinically stable, in many patients the digoxin assay would have been performed on admission for an acute medical condition e.g. pneumonia, cardiac ischemia, or in relation to a surgical procedures, where digoxin has limited efficacy in reducing the heart rate.

In practice, there is concern regarding whether a slow pulse rate is by itself a sign of digoxin toxicity (Williams, Aronson et al. 1978). This study indicates that in patients with sinus rhythm, heart rates less than 60 are by themselves not necessarily associated with higher median serum digoxin concentrations than patients with sinus rhythm and heart rates greater than 60 (Table 6.4). However, many of the patients with sinus bradycardia had coexistent evidence of first degree heart block, which is associated with higher SDCs than sinus rhythm alone. This degree of heart block, however, would not be detectable by an assessment of the pulse alone. In this study, 40% of patients with sinus rhythm and heart rate less than 60 had concurrent first degree heart block, suggestive of electrocardiographic evidence of digoxin toxicity.

In patients with atrial fibrillation, greater degrees of bradycardia were associated with higher SDCs (AF with heart rate less than 50 associated with higher median SDCs than heart rate between 50 and 59, and this was associated with higher concentrations than AF at rates greater than or equal to 60 beats per minute).

Amongst other rhythms observed to have a higher SDCs than baseline, some would be associated with heart rates less than 60 e.g. junctional and ventricular escape, whilst others such as ventricular tachycardia and "junctional rhythm with rate greater than 70 beats per minute" would be associated with faster rates. Of the escape rhythms, 75% (15 of 20) were associated with heart rates less than 60. Hence an artificial cut-off of 60 would not be able to readily distinguish between toxic and non-toxic rhythms.

In summary, patients taking digoxin having an irregular pulse of less than 60 beats per minute, are likely to have electrocardiographic digoxin toxicity. Patients with a slow pulse which is regular may have a number of rhythms, some of which are associated with electrocardiographic toxicity and others which are not. In all such circumstances the patient should have an electrocardiograph performed and be further assessed for other symptoms and signs of digoxin toxicity.

Although digoxin is reported to be associated with a shortening of the QTc interval, in this study, the relationship between SDC and QTc was poor. The explanation is likely to reflect, again, the multitude of influences on the QTc duration in such a population, including alterations in electrolytes, structural heart disease, and the concurrent use of other medications which can affect the QTc interval e.g. amiodarone, and sotalol.

Although there was a significant relationship between the T score and SDCs, the relationship was not very strong. As discussed above, a large number of different factors can influence the height of the T wave including electrolyte abnormalities, cardiac ischemia, co-administration of other medications, and structural heart disease. Another important influence on the height of the T wave which was not factored into this study was the presence of bundle branch block, which can cause dramatic T inversion.

Amongst the quantitative variables assessed, the best relationship was found between the manually determined PR interval and the PTQ score. A possible explanation is that PR prolongation is a relative contraindication to digoxin use. Hence patients who would have had other factors causing PR prolongation would have been excluded from the analysis. Despite this, from Figure 6.4B it can be seen that the relationship between PR interval and SDC in a cross-section of hospital inpatients is a continuous one, and it would be difficult to nominate a single value, above which all patients should be considered to be digoxin toxic. Nevertheless, a PR interval of 200msec is taken as a cut-off for first degree heart block, and in this study, patients with ECGs with PR intervals above this value were found to have higher median SDCs than patients with sinus rhythm and normal PR intervals. A more useful measure may be absolute or relative change in PR interval in an individual patient, but this study was not designed to address this question.

Figure 6.6 demonstrates the receiver operating characteristics curve for a number of the quantitative ECG parameters and toxic rhythm as defined by the rhythms shown to have a higher median SDC than baseline in Table 6.3. Table 6.7 summarises the area under the curve of these curves and the

associated p values. The tests were only undertaken for manual PR and PTQ determination as these had better correlations with the SDC than their machine derived values. It is not surprising to find the excellent relationship between PR prolongation and electrocardiographic toxicity, as ECGs demonstrating PR prolongation would be considered toxic by definition. Amongst the other quantitative assessments, it can be seen both graphically and from Table 6.7, that the manual determination of PTQ score was a better test of electrocardiographic toxicity than the T score or heart rate. However, once patients with documented electrocardiographic toxicity were excluded, there was a poor and non-significant relationship between PTQ and the SDC. This would suggest that the PTQ score does not provide any additional information regarding the likelihood of digoxin toxicity than the electrocardiographic rhythm alone.

The suggestions by Joubert et al (Joubert, Muller et al. 1975) of a PTQ score of greater than 3.0 being specific for digoxin toxicity, and a PTQ score less than or equal to one in combination with other electrocardiographic criteria being specific for non-toxicity was also assessed. Although a PTQ score greater than 3.0 was associated with a higher SDC and a greater prevalence of electrocardiographic toxicity, it had very poor sensitivity. This is not very important as patients should be considered to have digoxin cardiotoxicity if they have the rhythm disturbances defined in Table 6.3. The real benefit of a high PTQ score in the absence of one of the rhythms associated with cardiotoxicity would be its ability to stratify those patients who did not have a toxic rhythm initially, but then went on to develop one later on e.g. ventricular tachycardia. This study has not been able to address this question, however.

Although, the Joubert criteria for non-toxicity were associated with lower SDCs and a lesser likelihood of toxicity, the real benefit of such a criterion would be in being able to determine that the cause of an apparent digoxin toxic rhythm was, in fact, due to a cause other than digoxin, prior to the availability of the SDC. Unfortunately, in this study only two patients fulfilled the Joubert ECG criteria and also had evidence of electrocardiographic toxicity. Both patients had low SDCs (0.80 and 0.92 ng/mL), but because of the small number of patients involved, it is not possible to draw any conclusions about the clinical utility of this criterion.

There are other limitations to the use of the PTQ score in clinical practice. Firstly, it only has utility for patients in sinus rhythm, as it requires determination of the PR interval as part of its calculation. The percentage of patients with heart failure in sinus rhythm who are treated with digoxin would vary across different practices, but is likely to fall due to several concerns: greater toxicity in women (Rathore, Wang et al. 2002); a narrower therapeutic range than previously thought (Rathore, Curtis et al. 2003); increasing evidence for other agents, including beta-blockers (Packer, Bristow et al. 1996; Hjalmarson, Goldstein, et al 1999; Dargie, Lechat 1999), aldosterone antagonists (Pitt, Zannad et al. 1999; Pitt, Remme et al. 2003), and angiotensin II receptor antagonists (Cohn, Tognoni et al. 2001; Granger, McMurray et al. 2003; McMurray, Ostergren et al. 2003) having greater efficacy than digoxin for this indication.

Secondly, in this study I took an average value for the PR and QTc intervals and T score for the three assessors of each ECG. In clinical practice, there would be greater variability between individual clinicians in determining each

of these, resulting in a poorer relationship between manually determined PTQ score and SDC. The PTQ score could be determined using manually determined T score, and machine derived values for PR interval and QTc. However, there was a poorer relationship between this and the manually determined PTQ score and SDC (Table 6.6). Hence overall, it appears from this study that the PTQ score has little utility in assisting in the clinical diagnosis of digoxin toxicity.

6.4.2 Factors Altering Sensitivity to Serum Digoxin Concentration

Table 6.8 reveals the results of analysis of factors which are associated with digoxin electrocardiographic toxicity. It can be seen that the only significant factors were serum digoxin concentration and co-prescription of medications with a pharmacodynamic interaction with digoxin. This is not surprising as the main arrhythmias found to be associated with digoxin toxicity in this study demonstrated bradycardia, and these medications would have similar effects on the cardiac rhythm.

The sample size for this study was more than double than that for the symptoms associated with digoxin toxicity (Chapter 5), and the presence of electrocardiographic toxicity was more objectively documented than patient's subjective reporting of symptoms. Both of these factors should result in greater statistical power in being able to detect small influences on the prevalence of toxicity. Hence, it is surprising that some of the other factors which were associated with non-cardiac symptoms of digoxin toxicity were not found to be significant contributors to digoxin cardiotoxicity.

For example, hyponatraemia which was found consistently to be associated with a higher prevalence of all of the gastrointestinal symptoms (anorexia, nausea and vomiting), was not associated with an increased prevalence of digoxin cardiotoxicity. This would suggest a relationship between hyponatraemia and gastrointestinal symptoms, rather than an effect of serum sodium concentrations on the toxic effects of digoxin. Similarly, female gender which was associated with vomiting was not associated with an increased prevalence of digoxin cardiotoxicity. This raises some questions about the *post hoc* subgroup analysis by Rathore et al of an observed increased risk of mortality with the use of digoxin for heart failure in women (Rathore, Wang et al. 2002). It would be anticipated that if there was indeed a gender based increased risk of toxicity resulting in increased mortality, that it would manifest itself primarily as cardiac toxicity.

As with the analysis of factors contributing to symptoms of digoxin toxicity, previously documented factors such as age, hypokalemia and hypothyroidism were not found to be associated with a higher prevalence of digoxin cardiotoxicity in this study. This, again, most likely reflects the fact that the majority of patients were elderly, and very few had abnormalities of their serum potassium concentration or alterations of their thyroid function.

Figure 6.7 demonstrates the prevalence of digoxin cardiotoxicity at increasing SDC categories, by whether the patient was co-prescribed a medication with a pharmacodynamic interaction. As can be seen, at almost all concentration categories the prevalence of electrocardiographic toxicity is higher when a drug with a pharmacodynamic interaction is co-administered, which would be an anticipated effect. Furthermore, in patients prescribed digoxin alone, there

is a similar continuous increase in the prevalence of electrocardiographic toxicity that was seen in Figure 6.2 without any evidence of a clear threshold effect. Furthermore the increase in the prevalence of electrocardiographic toxicity becomes apparent at concentrations at the lower end of the current therapeutic range (0.5-2.0 ng/mL).

6.5 Conclusion

Digoxin caused an increase in the prevalence of bradycardic rhythms at concentrations above 1.0 ng/mL and this was the predominant electrocardiographic manifestation of digoxin toxicity. The only factors found to influence the prevalence of cardiotoxicity in this study were the SDC and the co-prescription of medications which had a pharmacodynamic interaction with digoxin. Exclusion of patients prescribed such medications reveals that there is still a continuous relationship between rising SDCs and increasing prevalence of digoxin cardiotoxicity, without evidence of a threshold effect.

PVCs and ventricular bigeminy did not indicate digoxin toxicity in current clinical practice. In a cross section of hospital inpatients there was a poor relationship between quantitative electrocardiographic parameters such as heart rate, PR, and QTc interval and SDC. Although there was a better relationship between manually derived PTQ score and SDC, in clinical practice this is likely to be of little value in the diagnosis of digoxin toxicity.

The concentration at which a higher prevalence of cardiotoxicity was seen, is similar to the concentration at which a higher prevalence of the non-cardiac

toxicity of anorexia occurred (Chapter 5). This strengthens the conclusion that a higher prevalence of the toxic manifestations of digoxin occurs at the lower end of the currently reported therapeutic range for digoxin (0.5-2.0 ng/mL). The therapeutic index for digoxin appears to be even narrower than previously described, and this raises additional safety concerns about digoxin.

In patients with cardiac failure in sinus rhythm, the SDC should be maintained in the range of 0.5-0.8 ng/mL, and in patients with atrial fibrillation with or without cardiac failure, the lowest dose which controls the resting rate should be used. If the concentration needs to be increased beyond 1.0 ng/mL, it needs to be appreciated that there is an increased prevalence of cardiac and non-cardiac toxicity associated with this, and the patient should be closely monitored for the occurrence of these adverse effects, with increasing dosage. In light of these findings, the reported therapeutic range for digoxin on TDM reports should be revised.

CONCLUSIONS AND FUTURE DIRECTIONS

7.1 Overview of thesis

Although digoxin assays have been available for over 3 decades, there has been little high level research published that evaluates clinical outcomes in relation to therapeutic drug monitoring of digoxin. In particular, there have not been any randomised controlled trials assessing the utility of digoxin TDM. This thesis explored the feasibility of conducting such studies, and provided some additional outcome-based data in support of digoxin TDM.

7.2 Conclusions

7.2.1 Randomised controlled trial of digoxin therapeutic monitoring - pilot study

The main findings of this chapter were:

1. It is possible to perform a randomised trial of the clinical usefulness of digoxin assays, and such a trial is likely to have the approval of ethics committees, clinicians and patients.

2. In the pilot study, the collection of questionnaire based data, and data from health care administration databases such as readmission rates, and number of digoxin assays, was more reliable than clinical data such as evidence of toxicity, heart rate, or indication for assay. The poor reliability in such data collection could be addressed with greater resources for the clinicians involved in the study.

3. To be adequately powered, such a trial would require a very large sample size and resources. The required sample size would range from 750 patients per group if there were a doubling of the incidence of toxicity in the non-TDM arm, to over 11,000 patients per group for a 3% absolute difference in the mortality rate, in a per-protocol analysis. The required sample sizes for questionnaire based endpoints such as quality of life could be smaller, but there is less certainty as to whether such improvements are realistic with digoxin TDM.

4. The cross-over rate from the non-TDM to the TDM arm of the study could be substantial, and is, in part, dependent on the resources applied to engage the clinicians in the study. As a result, the sample size for a randomised trial would be even greater than that described above.

7.2.2 Utility of digoxin assays in the diagnosis of digoxin toxicity

The main findings of this chapter were:

1. Five expert clinicians were provided, in the form of a Microsoft Access database, with all available patient information which might have influenced their diagnosis of a patient's likelihood of digoxin toxicity. The knowledge of the digoxin assay result, after consideration of clinical factors, did result in changes in the diagnosis of digoxin toxicity in approximately a third of the cases.

2. Knowledge of the SDC primarily resulted in greater certainty regarding the diagnosis of toxicity, as the number of cases deemed "possibly toxic" more than halved.

3. The knowledge of the SDC also resulted in greater agreement between the clinicians regarding the patient's likelihood of toxicity,

4. If a patient is thought to be "possibly toxic" on the basis of their clinical assessment, they should have a digoxin concentration determination performed, as in the majority of cases the assessment of toxicity would be clarified on the basis of the SDC result.

5. In cases where the patient is thought to be clinically "toxic", in the vast majority of cases (80%), the final assessment of toxicity after knowledge of the SDC remains unchanged; hence such patients should be treated as being toxic until proven otherwise.

6. In cases where the patient is thought clinically to be "non-toxic", the likelihood that knowledge of the SDC will change the diagnosis is small (<10%).

7. Patients assessed after knowledge of the SDC to have a higher likelihood of toxicity than that based on clinical assessment alone, do have a higher prevalence of symptoms typically associated with toxicity. This would suggest that, in the context of this study, the assay was able to help correctly attribute these symptoms to digoxin toxicity, which was missed by clinicians when they relied on symptoms alone.

7.2.3 The usefulness of routine digoxin assays on admission to medical units

The main findings of this chapter were:

1. If all patients admitted to general medical units, who are prescribed digoxin, have an assay conducted on admission, approximately 2/3 would be for a "routine" indication.

2. Approximately 20% of such patients having a routine assay will have a change in their management as a result of the knowledge of the SDC.

3. In multivariate analysis of routine assays, the only factor, found to be independently associated with a greater likelihood of a change in management as a result of the assay was the intention to change the digoxin dose prior to the assay. Those patients in whom the intended management was to decrease or hold the dose were 3.5 times (95% confidence interval 1.4-9.0) more likely to have a change in management as a result of the assay than those in whom the intended management was to continue the same dosing, after adjustment for other factors.

4. In routine cases where the intention prior to the knowledge of the assay was to continue the same dose, approximately 15% of patients had a change in their management as a result of the knowledge of the SDC.

5. On multivariate analysis, the only factor that predicted a greater likelihood of a change in management as a result of the knowledge of the SDC in this group of patients was the presence of clinical signs of

cardiac failure at presentation. Patients with evidence of cardiac failure were 2.6 times more likely to have a change in their management as a result of the knowledge of the SDC than patients without evidence of cardiac failure.

6. Using this information, it is possible to stratify patients on digoxin, who are admitted to general medical units, according to their likelihood of having a change in their management as a result of having a digoxin assay conducted. Patients in whom the assay is not for a routine indication, patients having a routine assay but in whom the plan of management is to alter the digoxin dose, and other patients with clinical evidence of cardiac failure on presentation are more likely (approximately 1 in 3 patients) to have a change in their management as a result of having a digoxin assay performed. A change in management as a result of performing a digoxin assay in all other patients occurs in approximately 1 in 10.

7. The data from this study can be used to determine the sample size required for a controlled trial of the utility of performing digoxin assays in all patients admitted to general medical units.

7.2.4 Systematic survey of symptoms of digoxin toxicity and correlation with serum digoxin concentrations in hospital inpatients

The main findings of this chapter were:

1. Of all of the symptoms of digoxin toxicity, which have traditionally been regarded as having a concentration-response relationship with digoxin, only anorexia, nausea, vomiting, fatigue, and changes in colour vision are significantly associated with higher serum digoxin concentrations.

2. The background prevalence of fatigue in the population taking digoxin is so high that it renders it not clinically useful in the assessment of digoxin toxicity.

3. The most sensitive symptom of digoxin toxicity appears to be anorexia, followed by nausea, and vomiting.

4. Many of the factors which have previously been described as increasing the sensitivity of digoxin toxicity were not found to be associated with greater toxicity in this study. This largely reflects the fact that the prevalence of many of these, such as hypokalemia and hypothyroidism, is much less in today's clinical practice.

5. Although incorrect responses on individual and combination of colour vision plates from the Ishihara and City University Colour Vision Tests are associated with significantly higher SDCs than correct responses, these bedside colour assessment tools are not useful for monitoring of or screening for digoxin toxicity. This is due to the fact that none of the individual or combination of plates have sufficient sensitivity and specificity, and many patients had difficulty interpreting the plates, particularly the City University Test.

7.2.5 Electrocardiographic characterisation of digoxin toxicity

The main findings of this study were:

1. There was a concentration-dependent increase in the prevalence and severity of bradycardic rhythms, but not increased automaticity .

2. The concentration at which an increase in the prevalence of cardiac toxicity first appeared was 1.0 ng/mL, which is at the lower end of the currently quoted therapeutic range (0.5-2.0 ng/mL, 0.6-2.4 nmol/L).

3. The increasing prevalence of cardiac toxicity appeared to be continuous with increasing SDC, with no evidence of a threshold effect at a concentration of 2.0 ng/mL, the currently accepted upper end of the therapeutic range in many laboratories.

4. The only factors found to influence the prevalence of cardiotoxicity in this study were the SDC and the co-prescription of medications which had a pharmacodynamic interaction with digoxin e.g. amiodarone, verapamil, sotalol. Exclusion of patients prescribed such medications reveals that there is still a continuous relationship between rising SDCs and increasing prevalence of digoxin cardiotoxicity, without evidence of a threshold effect.

5. ECGs demonstrating premature ventricular complexes (PVCs) or ventricular bigeminy were not associated with higher serum digoxin concentrations than ECGs without PVCs.

6. Although patients whose ECGs demonstrated ST segment sagging had significantly higher SDCs than patients whose ECGs did not, this difference was modest (0.2 ng/mL difference in median values), and in

the evaluation of an individual patient, ST segment sagging could not by itself be considered as being caused by digoxin toxicity.

7. In a cross section of hospital inpatients there was a poor relationship between quantitative electrocardiographic parameters such as heart rate, PR, and QTc interval and SDC. Although there was a better relationship between manually derived PTQ score and SDC, in clinical practice this is likely to be of little value in the diagnosis of digoxin toxicity.

8. The concentration at which a higher prevalence of cardiotoxicity was first seen is similar to the concentration at which a higher prevalence of anorexia first occurred. This strengthens the conclusion that a higher prevalence of the toxic manifestations of digoxin occurs at the lower end of the currently reported therapeutic range for digoxin. The therapeutic index for digoxin appears to be even narrower than previously described, and this raises additional safety concerns about digoxin.

9. In patients with cardiac failure in sinus rhythm, the SDC should be maintained in the range of 0.5-0.8 ng/mL, and in patients with atrial fibrillation with or without cardiac failure, the lowest dose which controls the resting rate should be used. If the concentration needs to be increased beyond 1.0 ng/mL, it needs to be appreciated that there is an increased prevalence of cardiac and non-cardiac toxicity associated with this, and the patient should be closely monitored for the occurrence of these adverse effects with increasing dosage.

10. In light of these findings, the reported therapeutic range for digoxin on TDM reports should be revised.

Hence Chapter 2 demonstrated that although randomised trials of digoxin TDM with clinical endpoints are feasible, due to the required sample size, they are virtually impossible to conduct. Chapters 3 and 4 demonstrated that knowledge of the SDC did result in changes in patients' management in some clinical situations. On their own, however, these two chapters could be seen as representing circular arguments, as the assay result would be evaluated against a therapeutic concentration range, and the change in management would aim to bring the concentration within this range. This would not by itself suggest that the conduct of the assay would necessarily benefit the patient.

The results of the following two Chapters, however, demonstrated that the upper limit of the therapeutic range for digoxin should be revised downward as symptoms such as anorexia and electrocardiographic toxicity first occur at a higher prevalence than background at a concentration of approximately 1.0 ng/ml. Given that many of the concerns which altered management in Chapters 3 and 4 were regarding the possibility of toxicity, then if these studies were to be conducted again in light of the data in Chapters 5 and 6, the impact of the knowledge of the SDC on the patients' management would be expected to be even more dramatic.

Although the studies in this thesis have contributed to the evidence base for digoxin TDM, and have helped clarify the role of digoxin assays in some common clinical situations, in terms of the hierarchy of the evidence presented, these studies would still be classified as low level observational studies. This appears to reflect the deficiency of the very rigid evidence based medicine classification schemes, which are more suited to specific

intervention or diagnostic studies, than to therapeutic drug monitoring which can be used in a several different clinical situations for different purposes.

This thesis also highlights another reason for the lack of high level outcome studies in TDM: the very characteristics of drugs which make them good candidates for TDM i.e. protean manifestations of toxicity, difficulty in clinically assessing efficacy, difficulty in distinguishing between drug toxicity or lack of efficacy, makes them very difficult to study clinically. If a toxicity or efficacy endpoint for a drug was readily assessable in a clinical trial, then it is likely that it would also be readily assessable clinically, and TDM would be less beneficial.

7.3 Future Directions

All of the studies conducted in this thesis were performed in tertiary referral metropolitan hospital inpatients. Hence, the obvious first step for future research would be to conduct some of the studies e.g. routine performance of digoxin assays, or systematic review of symptoms of digoxin toxicity in another population of patients such as those in residential care, or ambulatory community patients.

Conducting routine digoxin assays in all patients in different settings e.g. patients in ambulatory care presenting to general practitioners, would be expected to produce different results, and this would be important in determining the yield of routine digoxin assays in different settings, and which patients would particularly benefit from having such assays performed.

The signs and symptoms of digoxin toxicity would also be expected to produce different results in different clinical settings. Although the same concentration-response relationship would be expected, because of the different background prevalence of some of the symptoms in different clinical situations, the utility of each symptom in diagnosing digoxin toxicity would vary.

The symptoms and electrocardiographic abnormalities associated with significantly higher digoxin concentrations could be incorporated into a clinical tool for the diagnosis of digoxin toxicity. Such a tool should also take into account some of the factors which have been demonstrated to affect the prevalence of some of these symptoms e.g. hyponatremia, or drugs with pharmacodynamic interactions with digoxin. Such a tool could then be tested and validated in different patient populations.

If such a validated tool is developed, it may be a more sensitive indicator of the benefit of digoxin TDM than currently available endpoints e.g. mortality, readmission rates, or non-specific quality of life questionnaires. In this case, the required sample size for the studies discussed in this thesis e.g. randomised controlled trial of digoxin TDM as a therapeutic strategy, or randomised controlled trial of digoxin assays on admission to hospital, may make such trials a possibility.

Appendix A

EXAMPLES OF LEVELS OF EVIDENCE HIERARCHY USED BY DIFFERENT INSTITUTIONS

TABLE A1 AUSTRALIAN NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL DESIGNATIONS OF LEVEL OF EVIDENCE* (NH&MRC, 1998)

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

* It is generally accepted that Level V evidence is expert or consensus opinion

TABLE A2. U.S. PREVENTIVE SERVICES TASK FORCE LEVELS OF EVIDENCE (U.S. PREVENTIVE SERVICES TASK FORCE, 2005)

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well-designed controlled trials without randomization.

II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

TABLE A3. NATIONAL INSTITUTE OF CLINICAL EXCELLENCE (NATIONAL INSTITUTE OF CLINICAL EXCELLENCE, 2005) AND SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK LEVELS OF EVIDENCE (SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK, 2004)

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials with a high risk of bias*

2++ High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.

2– Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal

3 Non-analytic studies (for example, case reports, case series)

4 Expert opinion, formal consensus

Appendix B

ETHICS COMMITTEE PROTOCOLS

B1. Ethics committee protocol, information sheet and approval letter for study described in Chapter 2.

Common Research Protocol Application to Research Ethics Committee

Title:

A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin- pilot study.

Investigators:

Dr Sepehr Shakib Pager 1231
Professor F Bochner Work Phone 8303 5571
Dr A Tonkin Work Phone 8303 4696
Professor J Marley Work Phone 8303 3459
Dr J Faunt Pager 22550

Purpose of Study:

Our aim is to assess the feasibility of carrying out a study which comprehensively assesses whether the availability of digoxin therapeutic drug monitoring is useful.

During this pilot study, we will assess the practicality of the enrollment process, whether it is possible to recruit the patient numbers required for the full study, and the practicality of the data collection procedures for all of the end-points we are measuring for the full-scale study.

Background and Preliminary Studies:

Therapeutic drug monitoring is used extensively for patients on digoxin. In a recent survey of all patients administered digoxin over a two week period at the Royal Adelaide Hospital, approximately 60% of all patients had a drug assay performed, amounting to over 50 assays per week. This is despite the fact that there have been to date no randomised, prospective, controlled clinical trials that document the clinical usefulness of employing the therapeutic drug monitoring strategy [1]. There is some evidence for benefit in reducing toxicity[2,3] . However, no study has so far shown it to improve the effectiveness of digoxin, nor has it been proven as a surrogate marker for effectiveness in heart failure.

Despite the popularity of digoxin assays, there are many arguments against their routine use. Digoxin's effects in atrial fibrillation have been shown to be predictable and dose-responsive through the range 1.0-3.8 nmol/l[4] (well beyond the accepted therapeutic range of 0.6-2.3 nmol/l.) Hence if a larger effect is desired, the dose can be increased through a broad concentration range.

Toxicity, too, is dose-responsive and has been shown to occur at concentrations well within the accepted therapeutic range, and non-toxic values can occur well above it[5]. If a patient is thought to be toxic, their dose needs to be reduced regardless of the plasma concentration. Hence, it can be seen that the generally accepted therapeutic range is only an approximation for the population, and does not predict the concentration at which effect and toxicity will occur in an individual.

Digoxin pharmacokinetics are reasonably predictable in that it is mainly renally cleared. Hence by knowing the patient's age, weight and serum creatinine, a reasonable estimate of the drug's clearance, and hence its plasma concentration can be made. Therefore patients at the higher serum concentrations, who are more likely to be toxic and are less likely to benefit from further dosage increases, can be easily identified.

In a recent review of the toxic digoxin values, we found that **no** patient on 62.5 microgram of digoxin had a toxic value unless they had renal impairment ie creatinine clearance <40ml/min. Even in the group on 125 micrograms per day, the **mean** creatinine clearance was <30 mls/min. This suggests that toxic digoxin values are predictable ie the patient either has renal impairment, or is on a higher dose, or is on a drug which interacts with digoxin elimination.

A study assessing usefulness of digoxin therapeutic drug monitoring would have to involve quite a few hundred patients in each arm. It would have to have a long follow-up period to look at end-points which are affected by digoxin such as readmission rates. To be comprehensive, it would need to look at a variety of efficacy, safety, quality of life, and pharmacoeconomic end-points, some of which may be impractical or impossible to measure. Such a study would have to involve the patient's general practitioner to ensure compliance with the protocol and for data collection, and the general practitioner would need to give their consent to the patient's enrollment into the trial early in the admission before a digoxin assay is ordered. Because of these possible obstacles to the success of a full-scale study, we have decided to embark on a 3 month pilot study, to assess its feasibility.

If the pilot study is successful, then patients may wish to roll over to the full study.

Subjects:

All patients admitted to medical units C and D, GI Medicine, Cardiology, Geriatrics, and male patients on medical unit A who are on digoxin, and for whom a consent is possible to be obtained, and whose general practitioner agrees to the protocol will be eligible for the study. The pilot study will intend to enroll 100 such patients within a three month period.

Study Plan and Design:

This study will randomly assign eligible subjects to have digoxin therapeutic drug monitoring available to their clinicians or not. Once a patient has been assigned to an arm of the study, they are to remain in that arm until the study completion. The patients will be followed up through subsequent readmissions, outpatients and through their general practitioner, to assess the full impact of the digoxin monitoring strategy.

The pilot study will run for a total of three months, and will aim to recruit 100 subjects in that time

If a patient is thought to be eligible his/her general practitioner will first be contacted to seek their cooperation with the study. If the general practitioner is not willing to take part, the reason for exclusion will be documented.

Eligible patients, whose general practitioners have agreed to take part, will be approached regarding the study and their consent and permission to obtain information from their general practitioner about their digoxin treatment will be sought.

Details such as age, sex, weight, serum creatinine, calculated creatinine clearance, digoxin dose, reason for digitalisation, other medication use and doses, and reason for admission will be recorded.

On enrollment the patient's clinicians will be given information regarding the trial including information on the importance of assessing the patient regarding toxicity at each interaction, regardless of the dose of digoxin, or what arm of the study the patient is in.

Inpatient Management:

The patients offered therapeutic drug monitoring will be managed as they currently would be, except that they will be reviewed by the clinical pharmacology unit when digoxin assays are performed, in order to provide the best therapeutic drug monitoring strategy available. Those ordering the assays will be asked for the reason for requesting the assay.

Patients randomised not to receive therapeutic drug monitoring (non-TDM arm), will be managed clinically without any digoxin assays. The clinical pharmacology unit will be available for advice to help manage these patients without drug assays. If the unit responsible for the patient feels that an assay needs to be performed for the optimal care of the patient, the clinical pharmacology registrar can be contacted, the home unit will be asked what their management would be without an assay, the assay can be performed, the patient will be withdrawn, and the reason for the withdrawal will be noted. The patient will then be followed up, in order to assess whether the performance of the assay made any difference to the patient's management.

Some patients, particularly those admitted thorough casualty, may have serum assays requested before they are enrolled into the study. If the assay result is already known then the patient will not fulfill the entry criteria. If the assay has not been performed yet, then the patient will be enrolled and randomised as usual. If the patient is randomised to the non-TDM arm, the assay can be performed if the unit feels that it is necessary for the optimal management of the patient. Otherwise the lab can be instructed not to perform the assay, as would usually happen if an unnecessary test is requested by a resident.

During the orientation to the study, at its beginning and at every resident rotation, resident staff will be told of the importance of asking about symptoms of toxicity in all patients on digoxin. They will also be asked to contact the clinical pharmacology registrar with any cases where they have thought of performing a digoxin assay in patients in the non-TDM arm (even if they actually chose not to). In this way we will help ensure that all patients who **should** have an assay performed **do** have an assay performed, even if this means withdrawal from the study.

All patients entered into the trial will have a sticker attached to the front of their casenotes documenting this. Patients in the non-TDM arm, will also have stickers on their blue folders, drug charts, and casenotes explaining that they should not have assays performed, unless discussed with the clinical pharmacology registrar.

Upon discharge an information sheet will be placed in the case notes notifying which arm the patient is in, what that means, and whom to contact for assistance. Their general practitioner will also be contacted by phone to ensure understanding of the study, and the requirements for compliance with it. The general practitioner will be sent a pack containing details of the arm of the study the patient is in, an information sheet to go into their case records, and a card with phone numbers of whom and when to contact.

Outpatient management:

The general practitioner will be able to contact us by fax, phone, letter, pager, or mobile phone if there is any concern regarding the patient's management, or if they need advice managing the patients, particularly those in the non-TDM arm. We ask them to inform us and keep us updated if the patient has an assay performed, has a change in dosage, change in clinical circumstances or develops toxicity. It is not imperative that the GP contact us with this information, as it will also be collected at the end of the study. **However, it is imperative that a GP contact us if there is a withdrawal, the patient dies, or suffers toxicity.** At the end of the study period, the general practitioner will be contacted or the case records directly reviewed to assess the differences in outcome between the two study arms.

When a patient presents for an outpatient's appointment, we would similarly ask the medical officer to contact us if there is a change in the patient's management or if toxicity is suspected. Sheets will be available in outpatients which the medical officer can fill out simply, and put into the internal mail system informing us of any changes to the patient's condition.

Outcome measures:

A number of end-points will be measured as an inpatient and an outpatient. Our aim is to collect information about the efficacy, toxicity, pharmacoeconomic, and quality of life impact of a therapeutic drug monitoring strategy for digoxin. We envisage, however, that it may not be possible to collect all of the following data on all of the patients.

Whilst an inpatient, the patients will be reviewed regularly by the clinical pharmacists or clinical pharmacology registrar to collect the following data:

For all patients: number of drug assays, changes in drug dosing, evidence of toxicity and duration, the total number of hours on cardiac monitoring, if applicable, and length of stay. Once medically stable the patient will have a baseline quality of life assessment performed using the Minnesota "Living with Heart Failure" and SF-36 self administered questionnaire. The total cost of the admission can be derived from Trendstar.

patients in atrial fibrillation: the mean heart rate on discharge,

patients presenting with *rapid* atrial fibrillation: the number of hours until heart rate <100.

When presenting to outpatients or when readmitted: the number of drug assays, changes in drug dosing, evidence and duration of toxicity

Whilst visiting general practitioner: performance of drug assays, drug dosage changes or evidence of toxicity. If possible information will be collected regarding the number of general practitioner visits and the cost of each encounter.

At the end of the study: patients will be reassessed re their digoxin dosage, total number of assays performed, diuretic dose, and quality of life. The readmission and mortality rates, numbers and cost of combined general practitioner and outpatient visits will be collected.

The number and reasons for withdrawal will also be recorded. Those withdrawn due to crossing over to having a assay will be followed up to analyse the effect of the assay, and will continue in the long term follow up results.

In this way we will attempt to comprehensively collect data about a therapeutic drug monitoring strategy by assessing its impact on inpatients, its impact on hospital readmission rates and hospital outpatient visits, its effects on changes in drug dosing as outpatients and general practitioner visits, its impact on patients by way of subjective symptom scores, and its economic impact .

Ethical Considerations:

The patients randomised to the TDM arm will not have any change to their management. Those in the non-TDM arm, will have a strategy that is unproven not offered to them, and at the home unit's discretion the patient can, at any time, have a drug assay performed and be withdrawn from the study.

Patients will be consented if possible. However, a lot of the elderly patients, in whom we would be particularly interested, may be cognitively impaired. In this situation we would seek the consent of a relative. If this is not possible, at the time of entry into the study, we submit that because the TDM strategy is unproven, and because the clinician can perform a digoxin assay at their own discretion at any time, such patients should be entered to the study initially in the absence of a formal consent. Information sheets will be provided for relatives, who will be asked to give consent at a later time, if possible.

References:

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Information sheet for digoxin therapeutic drug monitoring study

Title: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin- Pilot Study

Investigators:

Dr Sepehr Shakib RAH 2224000 Pager1231 Home
Professor F Bochner Phone 8303 5571
Dr A Tonkin Phone work:8303 4696 home
Professor J Marley Phone 8303 3459
Dr J Faunt RAH 8222 4000 Pager 22550

You are currently being treated with a drug called digoxin for your heart. As with most drugs, if you do not have enough of it in your blood, it may not be fully effective, and if you have too much, it can cause side-effects.

It is possible to take a sample of your blood and measure the amount of digoxin in it (called a digoxin assay). Then your digoxin dose can be adjusted according to this level. This practice is called therapeutic drug monitoring, and you have probably had a digoxin blood level taken at some stage in the past. Therapeutic drug monitoring is routinely practiced when patients are on digoxin.

There is no evidence, however, that the availability of digoxin assays helps doctors to manage patients any better. Some argue that the amount of digoxin in the blood of one patient that is just right for them, may be too much for another patient, and that we should use clinical signs, for example how you feel, how fast your heart is beating etc. to determine how much digoxin you should take, rather than the result of a blood test.

We intend to do a large study to find out if doing digoxin assays are useful. Before then, though, we would like to do a pilot study to make sure that our study is on the right track. If you decide to take part, you will be assigned at random (like the toss of a coin) to either have or not have digoxin assays performed for the length of this study (until *date 3 months after starting date).* Your general practitioner has already been contacted and must also agree with the study before we go ahead.

If this pilot study is successful, then if you wish, you can go into our main study which will go for about 2 years. Both yourself and your general practitioner will be contacted, though, before enrolling you into the larger study.

If you are assigned to the group to have digoxin assays, your management will not be different in any way from usual. If you are assigned to the other group, then your doctors will manage you clinically, without using digoxin assays. If at any time any of your doctors feel that it would be best for your management to perform a digoxin assay, then this can be done, but you will then be withdrawn from the study.

If you choose to participate, as a part of the study we may ask you to fill out a health questionnaire, and we ask for information from your general practitioner about visits pertaining to the drug digoxin. All this information is confidential.

If you decide not to take part in the study, you will be managed in the usual manner by your doctors, and your care will not be affected in any way. You can withdraw from the study at any time, for any reason, and this will not affect your care in any way.

The possible benefits from the study are that your disease may be better managed, because more attention will be paid to your clinical signs than the result of blood tests. The main risk with the study is that the digoxin level in your blood may become too high, making you feel sick.. For this reason it is important that you report to your doctor any side effects of digoxin such as: unexplained nausea, vomiting, abdominal pain, visual changes, lethargy, palpitations or lethargy.

If you have any questions at any time, please do not hesitate to contact the investigators listed above. The chairperson of the Research Ethics Committee, Dr. Michael James (ph. 8222 4139) is also available to discuss general aspect of the project.

Consent form for: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin.

I have read the information sheet, and have had the study explained to me to my satisfaction.

I understand that I can withdraw from the study at any time, without this affecting my care in any way.

I understand the risks and possible benefits of the study for my health.

I understand that as part of the study, my general practitioner will be involved, and information regarding my visits pertaining to digoxin will be recorded for the study. I understand that this information will remain confidential.

I hereby consent to the study: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin.

Name.....

Signed..... Date.....

Witness.....

Information sheet for digoxin therapeutic drug monitoring study

Title: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin- Pilot Study

Investigators:

Dr Sepehr Shakib RAH 2224000 Pager1231 Home
Professor F Bochner Phone 8303 5571
Dr A Tonkin Phone work:8303 4696 home
Professor J Marley Phone 8303 3459
Dr J Faunt RAH 8222 4000 Pager 22550

Your relative is currently being treated with a drug called digoxin for his/her heart. As with most drugs, if you do not have enough of it in your blood, it may not be fully effective, and if you have too much, it can cause side-effects.

It is possible to take a sample of blood and measure the amount of digoxin in it (called a digoxin assay). Then the digoxin dose can be adjusted according to this level. This practice is called therapeutic drug monitoring, and your relative may have probably had a digoxin blood level taken at some stage in the past. Therapeutic drug monitoring is routinely practiced when patients are on digoxin.

There is no evidence, however, that the availability of digoxin assays helps doctors to manage patients any better. Some argue that the amount of digoxin in the blood of one patient that is just right for them, may be too much for another patient, and that we should use clinical signs, for example how the patient feels, how fast the heart is beating etc. to determine how much digoxin one should take, rather than the result of a blood test.

We intend to do a large study to find out if doing digoxin assays are useful. Before then, though, we would like to do a pilot study to make sure that our study is on the right track. If you decide for your relative to take part, he/she will be assigned at random (like the toss of a coin) to either have or not have digoxin blood tests performed for the length of this study (until *date 3 months after starting date)*. The general practitioner has already been contacted and must also agree with the study before we go ahead.

If this pilot study is successful, then if you wish, your relative can go into our main study which will go for about 2 years. Both your relative and the general practitioner will be contacted, though, before continuing into the larger study.

If your relative is assigned to the group to have digoxin assays the management will not be different in any way from usual. If he/she is assigned to the other group, then the doctors will make decisions clinically, without using digoxin assays. If at any time any of the doctors feel that it would be best for your relative's management to perform a digoxin assay, then this can be done, but he/she will then be withdrawn from the study.

If you choose to participate, as a part of the study, we will ask for information from the general practitioner about visits pertaining to the drug digoxin. All this information is confidential.

If you decide not to take part in the study, your relative will be managed in the usual manner by the doctors, and his/her care will not be affected in any way. You can withdraw from the study at any time, for any reason, and this will not affect your relative's care in any way.

The possible benefits from the study are that his/her disease may be better managed, because more attention will be paid to clinical signs than the result of blood tests. The main risk with the study is that the digoxin level in the blood may become too high, making him/her feel sick.. For this reason it is important that you report to doctors any side effects of digoxin such as: unexplained nausea, vomiting, abdominal pain, visual changes, lethargy, palpitations or lethargy.

If you have any questions at any time, please do not hesitate to contact the investigators listed above. The chairperson of the Research Ethics Committee, Dr. Michael James (ph. 8222 4139) is also available to discuss general aspect of the project.

Consent form for: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin.

Carer's consent

I have read the information sheet, and have had the study explained to me to my satisfaction.

I understand that I can withdraw from the study at any time, without this affecting the care of my relative in any way

I understand the risks and possible benefits of the study for the health of my relative.

I understand that as part of the study, the general practitioner will be involved, and information regarding visits pertaining to digoxin will be recorded for the study. I understand that this information will remain confidential.

I ..... being the ..... of
(Name) *(Relationship to patient)*

..... give consent to him/her being entered
(Name of patient)

into the study: A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin- pilot study.

Signed..... Date.....

Witness.....

Royal Adelaide Hospital

Medical & Allied
Health Services

Level 2 Eleanor Harrald Building
South Australia 5000

Telephone: (08) 8222 5345

Facsimile: (08) 8222 5936

222 4139
29th November, 1996

Dr S Shakib
PHARMACY DEPT.

Dear Dr Shakib,

Re: "A hospital and community based study of the usefulness of therapeutic drug monitoring for digoxin - Pilot Study." Protocol: 961106.

I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

As a matter of Human Ethics Committee Policy, copies of the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation adopted by the Human Ethics Committee, are attached for your information and guidance.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Dr M James
CHAIRMAN
RESEARCH ETHICS COMMITTEE

B2. Ethics committee protocol, and approval letter for study described in Chapter 4.

Common Research Protocol Application to Research Ethics Committee

Title:

Study of the usefulness of routine digoxin therapeutic drug monitoring in the management of general medical hospital inpatients.

Investigators:

Dr Sepehr Shakib Pager 1231

Purpose of study:

To investigate whether and how much routine performance of digoxin assays contributes to the management of inpatients in general medical units.

Background and preliminary studies:

Digoxin assays were first developed in the early 70's as a tool for the diagnosis of digoxin toxicity. Since then their popularity has grown such that currently over 60-80% of patients admitted to medical units at the Royal Adelaide Hospital have a digoxin assay performed at some stage during their admission. The vast majority of these have "routine" assays performed, where the indication is not toxicity, lack of efficacy, compliance etc...but rather the assay is performed to detect variation of the patient's plasma digoxin concentration from the therapeutic range.

Studies have shown that when a large number of digoxin assay concentrations are reviewed a large number lie outside of the therapeutic range for this drug [1] . This has been used as justification for routine monitoring of all patients. Other studies, however, have shown that such routine monitoring in the outpatient [2] and nursing home setting [3], does not offer any additional benefit in the management of patients over what is already known about the patient's ECG, electrolytes, dose etc... These studies were carried out on stable, chronic patients whose dosages had been previously adjusted according to their clinical condition, perhaps with the aid of previous plasma monitoring. Both studies were also of small size (25 and 51 patients, respectively) so they would not have picked up subgroups that may have benefited from routine monitoring.

The group of patients on digoxin seen in the general medical units at the Royal Adelaide Hospital is very different to those in the above studies. Patients are often acutely unwell with fluctuating renal function, and the dosage of digoxin and compliance to is often uncertain. Approximately 20% of patients on digoxin have had it started in hospital, hence the dosage has not been stabilised.

As digoxin is predominantly renally cleared, the patient's renal function is an important factor in determining the risk of developing toxicity. The mean creatinine clearance of our patients on digoxin is ~50 mmol/l being in the mild-moderate renal

impairment range, with ~25% having moderate to severe impairment. A further 30% are on drugs which interact with the concentration of digoxin making dosing more complicated.

Many clinicians perform routine digoxin assays on all of such patients to ensure that the risk of undiagnosed toxicity is minimised, and that the plasma concentration of digoxin is adequate.

The aim of this survey is to elucidate whether the performance of routine digoxin assays, in fact, makes any difference in the clinical management of the patient.

Patient selection:

Patients surveyed will be those taking digoxin on medical units A, C, D and E being cared for by one of the investigators in the study.
Patients will be excluded if it is felt that they would not benefit in any way from the performance of a digoxin assay eg dying patients, where digoxin is about to be ceased regardless of an assay, assay recently performed by GP, or patient given loading dose of digoxin before assay could be performed.
The study will continue for as long as the investigators are on these general medical rotations, and will involve approximately 120-140 patients.

Study plan and design:

Synopsis: all eligible patients will be reviewed prior to the performance of a digoxin assay and baseline data and proposed management without an assay will be documented. Then the assay is performed and when the results are available, the clinician will document the management that will be carried out in light of the assay result. The differences in outcomes before and after the assay will be compared to assess the utility of the test. At the end of the study, the clinical scenario of all of the patients will be reviewed by all of the other investigators, who will similarly document their management with and without the assay.

If a patient is admitted on digoxin, then the assay will be taken as a trough assay (where possible) at the earliest opportunity. If the patient is commenced on digoxin in hospital, then the assay will be taken as close as possible to the day of discharge or at steady-state, whichever is earliest.

If a patient is admitted on digoxin and the dose is significantly altered during the admission then the assay and survey process can be repeated in the same patient.

These practices of performing digoxin assays at these times are routine practice for many clinicians. The only difference in this study is the survey of the utility of the assay which is associated with it.

The following data will be gathered prior to the performance of the assay: patient's name, URno, age, ward, age, indication for digoxin use, dosing history, reason for assay, compliance, weight, interacting drugs and doses, serum creatinine, stability of

renal function, estimation of drug concentration and documentation of proposed management without knowledge of the digoxin assay result.

The assays will be performed through the clinical pharmacology laboratory of the IMVS in the usual fashion. Where possible trough (pre-dose) specimens will be collected.

After the assay is performed, the clinician documents the proposed plan of management with the light of this knowledge.

If the patient's management is changed as a result of the assay, then the clinician will be asked to comment on any follow-up relevant for the patient eg reduction in dose relieving symptoms of toxicity, better heart rate control as a result of increased dose etc...

Endpoint assessment:

The main endpoint of this study will be how often the performance of a digoxin assay leads to a change in the management of the patient, and then whether on follow-up this change in dosing results in an improved outcome for the patient in terms of the efficacy and toxicity of the drug.

The reasons for the performance of the assay will be divided into the traditional reasons for performance of therapeutic drug monitoring, (compliance, lack of efficacy, toxicity, drug interaction) but the main group of interest will be those for whom no specific indication exists who will have the assay performed for routine reasons. The main outcomes of interest in this group are the rate of occurrence of digoxin concentration outside of the therapeutic range, how many of these were clinically significant, and how many of these when they resulted in dosage adjustment, led to improved patient outcome.

At the end of the study, the clinical scenarios will be presented to all of the investigators individually without knowledge of the assay result, and expected management etc... will be similarly documented. In this way it may be possible to stratify the utility of digoxin assays according to the seniority of the clinician involved in the case.

Ethical considerations:

Most patients admitted to hospital have a digoxin assay performed at some stage during their admission, and in most cases there is no indication for this test other than that the patient is on this medication. In this study patients on digoxin will have an assay performed unless it is obvious that it will not be of any benefit to them, and this practice would be in keeping with the clinical practice of many clinicians.
The patient's management will not be altered in any way as a result of this survey. This survey simply aims to make clinicians think about and document their specific reasons for the assay if any, and then to consider how the assay may help them in the management of the patient.

Justification of patient numbers:

Over a 3 month period in medical units A and D, we would anticipate some 120-140 patients being admitted on digoxin, most of whom could be surveyed. If these results show a non-significant trend we would like to, if possible, extend the study to involve approximately 200 assays surveyed.

It is not possible to perform sample size calculation for a survey of this nature, but we feel that if between 100-200 assays are surveyed then this should give us a clear picture of the usefulness of assays and allow us to determine if certain subgroups deserve special consideration.

References:

1. Derkx FHM, Bryson SM, Kelman AW, Whiting B. A plea for routine monitoring of theophylline and digoxin palsma concentrations. *Pharmaceutisch Weekblad Scientific Edition.* Vol 5 1983 page 35
2. Savill J, Mitchell M, Wood D, Krikler D. Rapid plasma digoxin assay in outpatients- a useful routine technique? *Br Heart J.* 1985; 54:248-50
3. J Dimant. W Merritt. Serum digoxin levels in elderly nursing home patients: appraisal of routine period measurements. *Journal of the American Geriatrics Society.* Volume 26 378-79, 1978

Flinders Medical Centre
Bedford Park South Australia 5042

Telephone (08) 8204 5511
International 618 8204 5511

Committee on Clinical Investigation
AV:CMH

Telephone (08) 8204 4507
Facsimile (08) 8204 4006
email: Carol.Hakof@health.sa.gov.au

9 March 1999

MEMORANDUM

TO: Dr. S. Shakib, Clinical Pharmacology

FROM: Dr. A. Vedig, Chairman, Committee on Clinical Investigation

TOPIC: **Research Application 6/99**

I am pleased to advise that the Committee on Clinical Investigation has approved your research application in accordance with the following extract from the Minutes of its meeting held on 22 February 1999.

4460 RESEARCH APPLICATION 6/99 – DR. S. SHAKIB
Study of the usefulness of routine digoxin therapeutic drug monitoring in the management of general medical hospital inpatients.
Reviewer: Dr. J. Walsh

This application was approved. However, if the investigator wishes to access patient casenotes, consent would need to be obtained.

If conditional *('subject to' or 'in principle')* approval is granted, research involving human subjects **may proceed only after written acceptance of the conditions of approval** (including a copy of the modified research protocol) has been received by the Committee.

This approval is for a period of one year. Application for re-approval must be made annually. Please note that if this trial involves normal volunteers it will be necessary for you to keep a record of their names and you may be required to supply this list with your annual report.

You are reminded that the Committee on Clinical Investigation must approve the content and placement of advertisements for the recruitment of volunteers.

The Committee must be notified and approve any changes (e.g. additional procedures, modification of drug dosage, changes to inclusion or withdrawal criteria, changes in mode and content of advertising) in the investigational plan particularly if these changes involve human subjects.

The safe and ethical conduct of a trial is entirely the responsibility of the investigators. While the Committee on Clinical Investigation takes care to review and give advice on the conduct of trials, approval by the Committee is not an absolute confirmation of safety, nor does approval alter in any way the obligations and responsibilities of investigators.

It is the duty of the chief investigator to give prompt notification to the Committee on Clinical Investigation of matters which might affect continued ethical acceptability of the project, including:

1. Adverse effects of the project on subjects and of steps taken to deal with these.
2. Other unforeseen events.
3. A change in the base for a decision made by the Committee, e.g. new scientific information that may invalidate the ethical integrity of the study.

If patients are involved the chief investigator is also responsible for the process of notification, seeking approval or permission of Departments, Divisions or individual consultants.

A. Vedig
Critical Care Medicine Unit
Extension 65206

B3. Ethics committee protocols, informed consent forms and approval letters for study described in Chapter 3, 5 and 6.

Common Research Protocol Application to Research Ethics Committee

Title:

The development of a clinical tool for the diagnosis of digoxin toxicity.

Investigators:

Dr Sepehr Shakib	Pager 1231
Dr Steve Worthley	Pager 1745
Dr A Tonkin	Phone 8303 4696
Professor F Bochner	Phone 8303 5571

Purpose of Study:

To develop a simple and easy-to-use clinical tool for the diagnosis of digoxin toxicity.

Background and Preliminary Studies:

For most patients on digoxin, therapeutic drug monitoring is used to determine whether the daily dose of digoxin is insufficient, adequate, or toxic. The scientific basis for the toxic cut-off, however, has many flaws.

The digoxin concentration, above which a patient is considered toxic, was derived from comparing the levels in patients who did and did not have characteristic ECG changes of toxicity[1,2]. Patients we see on our daily therapeutic drug monitoring rounds with "toxic" values, however, mostly have normal ECG's . Biochemically toxic patients do complain of other manifestations of digoxin excess such as vomiting, abdominal pain, and confusion, but these have been assessed in only a few studies, and the authors have rarely specified their criteria for the diagnosis of toxicity.[2]

Although studies have shown that the mean digoxin level in the ECG toxic group is higher than those in the non-toxic group, there is a considerable overlap, with many toxic patients having "therapeutic values" and vice versa [3].

Also no study has thus far shown the utility of the digoxin assay in diagnosing toxicity beyond the knowledge of other factors such as digoxin dosage, renal function, serum K concentration[1].

In summary, although it is known that those who have evidence of digoxin toxicity on their ECG have a higher mortality [4], many clinicians are faced with the patients who have biochemically toxic values, but a normal ECG's. In this situation there is scant literature guidance, as most articles have analysed electrocardiographic toxicity, and there is no standardised way of diagnosing digoxin toxicity on the basis of its other more common toxic manifestations.

Although the symptomatic effects of digoxin excess and the characteristic ECG changes are well described[3,5] and it has also been shown that the acquired red-green colour blindness of digoxin toxicity can be reliably diagnosed with Ishihara plates [5], a clinical tool which brings together these varied aspects of digoxin toxicity into a validated questionnaire has never been described. Our aim is to develop a clinical tool for the diagnosis of digoxin toxicity, which is easy to use, can be readily applied in the clinical setting, requires the minimum of accessories to apply, has been validated, and carries prognostic significance for the patient. The aim of this initial project is the development of the appropriate questionnaire for such a tool.

Subjects:

A random sample of patients, who are on digoxin, and have therapeutic drug monitoring performed will be approached regarding the questionnaire. These patients will be divided into the subtherapeutic, therapeutic, and toxic categories on the basis of their digoxin assay results. Patients who are not on digoxin, but who have medical conditions the same as those which could be treated with digoxin will be approached as the control group.

As this work has never been attempted before there is no data on the variance seen in responses. Most studies looking at ECG criteria for toxicity or colour vision changes have used between 20 and 80 toxic subjects. Initially there will be approximately 20 patients in each group and 50 in the therapeutic digoxin concentration group. More patients may be approached if it appears that a trend is developing requiring more patients to reach significance.

Study Plan and Design:

Each day the investigator will acquire a list of hospital patients who have had a digoxin assay performed from the therapeutic drug monitoring laboratory. A random sample of patients will then be selected, and they will be approached within 24 hours of the sample having been taken, regarding the study.

The investigator will not be aware of the result of the serum digoxin assay, and will collect the data regarding dose, serum creatinine after the patient questionnaire has been performed. In this way the investigator will be blinded as to the possible digoxin level of the patient, when the patient is given the questionnaire.

During the study, resident staff will also be approached about patients who have conditions such as cardiac failure or atrial fibrillations, but who

are not on digoxin, and such patients will be enrolled as a control group into the study.

The questionnaire (Appendix A) consists of 4 components and an open ended question regarding the patient's worst symptoms at the start.. The first two components question gastrointestinal and CNS toxicity. There are many questions asked, in different ways, in order to ascertain which are the most useful questions to ask and how to best assess the symptom in question. The patient is questioned verbally by the investigator and the responses are noted. The time taken to complete each component and any additional comments will also be noted.

Visual acuity will then be tested, to assess whether the patient has greater than 6/60 corrected vision, and whether the patient can read black and white numbers the size of those on Ishihara plates. Whether the patient has their spectacles or not will also be recorded. Chromatopsia, the perception of white as a colour, will be tested using a white card on a black background. 6 Ishihara plates will be used to diagnose red-green colour blindness. The testing of colour vision is usually performed under standardised lighting. As we are deriving a tool to be used under normal ward conditions, the lighting will not be predetermined nor described.

The applicability of the questionnaire and the ability of subjects to answer it various components will be noted during this preliminary survey. Hence reasons for the inability to perform the questionnaire eg. poor English, poor hearing, dementia, will be noted, and will be one of the end-points studied. If it appears initially that some questions have no utility, but that others may prove to be more useful, then the questionnaire will be altered in response.

After the completion of the questionnaire, other relevant data will be gathered: name, UR Number, age, sex, renal function, serum potassium level, left ventricular function (by echocardiogram or nuclear study if available in last year), New York Heart Association grade, digoxin level, and likely duration at that level before measurement.

Finally, each patient's ECG and, if available, cardiac monitoring strips will be analysed by an independent investigator who will not be aware of any other information about the patient other than age, sex, and diagnosis. The ECG's will be diagnosed and categorised according to the criteria in Appendix B. If an ECG has not been performed during the current admission, the resident will be asked to request it, as this would be a part of good clinical practice.

Analysis and Statistics:

The patients will be categorised as either toxic, therapeutic, subtherapeutic, or not on digoxin. (In the analysis the latter two groups

will also be analysed pooled.) Each response in the questionnaire will be given a score, with the most toxic responses having the highest score. This will result in a certain digoxin toxicity score depending on which particular questions are selected and how the responses are weighted.

The data will then be manipulated by altering the weightings given to different responses, selection of different questions in each component of the questionnaire, and by changing the definition of the different groups in order to find a set of questions which have the best degree of internal consistency, and give the widest separation between the groups tested.

The data will be analysed with and without the use of the visual testing component as Ishihara plates are not readily available on wards.

Ethical Consideration:

This study is simply a structured survey of questions that should be routinely asked of patients who are on digoxin. It also includes visual testing using Ishihara plates, which are not particularly inconvenient for patients. One of the main objectives with this preliminary study is to assess the applicability of such a tool to the general medical inpatient.

We will seek to get written informed consent from all patients or from their next of kin or legal guardian. However, we will enrol patients, who are not able to give written informed consent, for example because of their confusion, as this may be one of the manifestations of digoxin toxicity being assessed, and the exclusion of such patients would bias our results. If a patient refuses to take part in our study, then this wish will naturally be respected.

References:

1. Ingelfinger JA and Goldman P. The serum digitalis concentration- does it diagnose digitalis toxicity? N Engl J Med 294: 867-870, 1976
2. Ried LD, Horn JR, McKenna DA. Therapeutic drug monitoring reduces toxic drug reactions: a meta-analysis. Ther Drug Monit 1990;12:72-8
3. Smith TW and Haber E. Digoxin intoxication: the relationship of clinical presentation to serum digoxin concentration. J Clin Inv 1970; 49: 2377-2386
4. Beller GA etal. Digitalis Intoxication. A prospective clinical study with serum level correlations. N Engl J Med 1971; 284: 989-997
5. Biddle TL, Weintraub M, Lasagna L. Relationship of serum and myocardial digoxin concentrations to electrocardiographic estimation of digoxin intoxication. J Clin Pharm
6. LeSage LA and Chuman M A. Colour vision tests to identify elevated digoxin levels. Research in Nursing and Health 1986; 9: 171-7

Appendix A

What is your most troubling symptom?

Time

Nausea/anorexia/vomiting

- Do you feel off your food? Yes No
- Have you felt like vomiting? Yes No
- Have you vomited? Yes No
- Do you have abdominal pain? Yes No
- The feeling of wanting to vomit is nausea. Would you say you had no nausea, mild, moderate, or severe nausea, or vomiting?

Discrete scale: 0=no nausea
1=slight nausea
2=moderate nausea
3=severe nausea
4=vomiting

Comments *Time*

Fatigue/depression/CNS changes

Would you say that in the last few days:

thinking requires effort (not at all a little a lot)
you are easily tired (not at all a little a lot)
tiredness causes you frequent problems (not at all a little a lot)
tiredness interferes with your f"ing (not at all a little a lot)
you feel more confused in your thinking (not at all a little a lot)

Orientation: day date monthyear
Place
Name date of birth

Can you count backwards from 100 using 7's?

Short term recall of 3 common objects of 3 different colours (score registration and recall out of 3 each)

Comments *Time*

Colour vision perception

- Are glasses present?
- Visual acuity
- Ability to read black and white numbers
- Chromatopsia
- Ishihara plates

Comments *Time*

Appendix B

ECG:
Category I (Definite): any of the following if no other aetiology of the arrhythmia is present:
- frequent (>5/min) or multifocal PVC's, VT
- AV junctional tachycardia
- atrial tachycardia with AV block
- AF with slow ventricular response (<50/ min) and PVC's
- sinus rhythm with Mobitz type I block or third degree block

Category 2: Definite arrhythmias but other medical illness may account for it

Category 3 (possible):
- Occasional VPC's (<5/min)
- 1^{o} AV block in absence of other drugs which may decrease conduction, and in absence of prior history off digoxin
- AF with occasional junctional escape beats
- sinus bradycardia in absence of history off digoxin
- AF with slow ventricular response (50-65)
- ventricular bigeminy

Information Sheet for Digoxin Toxicity Tool Development Study

Digoxin patients

Title: The development of a clinical tool for the diagnosis of digoxin toxicity.

Investigators:

Dr Sepehr Shakib 1231	Royal Adelaide Hospital 8222 4000 Pager
Dr Steve Worthley 1745	Royal Adelaide Hospital 8222 4000 Pager
Dr A Tonkin	Phone 8303 4696
Professor F Bochner	Phone 8303 5571

You are currently taking the drug digoxin for your heart. Like many drugs, if you have too much of it in your blood it can cause side-effects, and blood tests measuring the amount of digoxin are frequently done on patients on this drug.

We are keen to develop a questionnaire to see if it is possible to tell if a patient is taking too much digoxin by clinical means, rather than having to use a blood test. The questionnaire, we would like you to do, consists of questions about how you feel, as well as a test of colour vision. We will also be looking at the results of tests you have already had done such as your electrocardiogram (recording of your heart rhythm), blood test looking at your kidney function and blood potassium level, etc… All this information is confidential.

Your treatment will not be affected in any way as a result of this questionnaire .

If you decide not to take part, your management will not be affected in any way.

If you wish you can chose not to take part in some parts of the questionnaire, and you can withdraw from the study at any time without it affecting your management in any way.

If you have any questions, please do not hesitate to contact the investigators listed above. The chairperson of the Research Ethics

Committee, Dr Michael James (ph. 8222 4139) is also available to discuss general aspects of the project.

Information Sheet for Digoxin Toxicity Tool Development Study

Non-digoxin patients

Title: The development of a clinical tool for the diagnosis of digoxin toxicity.

Investigators:

Dr Sepehr Shakib	Royal Adelaide Hospital 8222 4000 Pager 1231
Dr Steve Worthley	Royal Adelaide Hospital 8222 4000 Pager 1745
Dr A Tonkin	Phone 8303 4696
Professor F Bochner	Phone 8303 5571

Patients with heart complaints are managed in different ways by different doctors. Some patients are treated with a drug called digoxin, but your doctors have currently chosen not to treat you with it.

Like many drugs, if you have too much of digoxin in your blood it can cause side-effects, and blood tests measuring the amount of digoxin are frequently done on patients on digoxin.

We are keen to develop a questionnaire to see if it is possible to tell if a patient is taking too much digoxin by clinical means, rather than having to use a blood test. We need the assistance of patients such as yourself, who do not have any digoxin in their blood, to serve as a control group.

The questionnaire, we would like you to do, consists of questions about how you feel, as well as a test of colour vision. We will also assess the results of tests you have already had done such as your electrocardiogram (recording of your heart rhythm) blood test looking at your kidney function and blood potassium level, etc… All this information is confidential.

Your treatment will not be affected in any way as a result of this questionnaire . If you decide not to take part, your management will not be affected in any way. If you wish you can chose not to take part in some parts of the questionnaire, and you can withdraw from the study at any time without it affecting your management in any way.

If you have any questions, please do not hesitate to contact the investigators listed above. The chairperson of the Research Ethics

Committee, Dr Michael James (ph. 8222 4139) is also available to discuss general aspects of the project.

Consent form for: The development of a clinical tool for the diagnosis of digoxin toxicity

I have read the information sheet, and have had the study explained to me to my satisfaction

I understand that I can withdraw from the study at any time, without this affecting my care in any way

I understand the risk and possible benefits of the study for my health

I understand that all information collected will remain confidential

I hereby consent to: The development of a clinical tool for the diagnosis of digoxin toxicity.

Name.....

Signed..... Date.....

Carer's Information Sheet for Digoxin Toxicity Tool Development Study

Title: The development of a clinical tool for the diagnosis of digoxin toxicity.

Investigators:

Dr Sepehr Shakib	Royal Adelaide Hospital 8222 4000 Pager 1231
Dr Steve Worthley	Royal Adelaide Hospital 8222 4000 Pager 1745
Dr A Tonkin	Phone 8303 4696
Professor F Bochner	Phone 8303 5571

Your relative is currently in hospital with a heart complaint, and he/she may be treated with a heart drug called digoxin. Like many drugs, if you have too much of digoxin in your blood it can cause side-effects, and blood tests measuring the amount of digoxin are frequently done on patients taking this drug.

We are keen to develop a questionnaire to see if it is possible to tell if a patient is taking too much digoxin by clinical means, rather than having to use a blood test. If your relative is on digoxin, we would like to see if they have any side-effects from it. If your relative is not on digoxin, then he/she will have no digoxin in their blood, and will make up an important control group for our study.

The questionnaire we would like you to do, consists of questions about how your relative feels, as well as a test of colour vision. We will also be looking at the results of tests he/she has already had done such as an electrocardiogram (recording of heart rhythm), blood test looking at kidney function and blood potassium level, etc… All this information is confidential.

Your relative's treatment will not be affected in any way as a result of this questionnaire. If you decide not to take part, your relative's management will not be affected in any way. If you or your relative wish, you can chose not to take part in some parts of the questionnaire, and you can withdraw from the study at any time without it affecting his/her management in any way.

If you have any questions, please do not hesitate to contact the investigators listed above. The chairperson of the Research Ethics

Committee, Dr Michael James (ph. 8222 4139) is also available to discuss general aspects of the project.

Consent form for: The development of a clinical tool for the diagnosis of digoxin toxicity

Carer's consent

I have read the information sheet, and have had the study explained to me to my satisfaction

I understand that I can withdraw my relative from the study at any time, without this affecting his/her care in any way

I understand the risk and possible benefits of the study for my relative's health

I understand that all information collected will remain confidential

I ..... being the .....of

(*Name*) (*relationship to patient)*

..... give consent to him/her being entered into the

(*Patient's name)*

study:The development of a clinical tool for the diagnosis of digoxin toxicity.

Signed..... Date.....

Witness.....

Flinders Medical Centre
Bedford Park South Australia 5042

Telephone (08) 8204 5511
International 618 8204 5511

Committee on Clinical Investigation
AV:CMH

Telephone (08) 8204 4507
Facsimile (08) 8204 4006
email: Carol.Hakof@health.sa.gov.au

9 March 1999

MEMORANDUM

TO: Dr. S. Shakib, Clinical Pharmacology

FROM: Dr. A. Vedig, Chairman, Committee on Clinical Investigation

TOPIC: **Research Application 5/99**

I am pleased to advise that the Committee on Clinical Investigation has approved your research application in accordance with the following extract from the Minutes of its meeting held on 22 February 1999.

4459 RESEARCH APPLICATION 5/99 – DR. S. SHAKIB
The development of a clinical tool for the diagnosis of digoxin toxicity.
Reviewer: Dr. C. McFarlane

This application was approved subject to amendments to the information sheet which have been conveyed to the investigator by Dr. McFarlane.

If conditional *('subject to' or 'in principle')* approval is granted, research involving human subjects **may proceed only after written acceptance of the conditions of approval** (including a copy of the modified research protocol) has been received by the Committee.

This approval is for a period of one year. Application for re-approval must be made annually. Please note that if this trial involves normal volunteers it will be necessary for you to keep a record of their names and you may be required to supply this list with your annual report.

You are reminded that the Committee on Clinical Investigation must approve the content and placement of advertisements for the recruitment of volunteers.

The Committee must be notified and approve any changes (e.g. additional procedures, modification of drug dosage, changes to inclusion or withdrawal criteria, changes in mode and content of advertising) in the investigational plan particularly if these changes involve human subjects.

The safe and ethical conduct of a trial is entirely the responsibility of the investigators. While the Committee on Clinical Investigation takes care to review and give advice on the conduct of trials, approval by the Committee is not an absolute confirmation of safety, nor does approval alter in any way the obligations and responsibilities of investigators.

It is the duty of the chief investigator to give prompt notification to the Committee on Clinical Investigation of matters which might affect continued ethical acceptability of the project, including:

1. Adverse effects of the project on subjects and of steps taken to deal with these.
2. Other unforeseen events.
3. A change in the base for a decision made by the Committee, e.g. new scientific information that may invalidate the ethical integrity of the study.

If patients are involved the chief investigator is also responsible for the process of notification, seeking approval or permission of Departments, Divisions or individual consultants.

A. Vedig
Critical Care Medicine Unit
Extension 65206

Research and Ethics
Committee

Telephone: 08 8275 1876
Fax: 08 8374 0225
Email: ssutca@rgh.sa.gov.au

Contact
eference

Please quote 24/99

A Teaching Hospital of Flinders University

July 27, 1999

Dr Sepehr Shakib
Department of Clinical Pharmacology
Flinders Medical Centre
Bedford Park SA 5042

Dear Dr Shakib

Re: The development of a clinical tool for the diagnosis of digoxin toxicity. Protocol No 24/99

Thank you for your letter of 16 June 1999, in which you answer the Committee's concerns about the above project. Your reply was discussed at the Research and Ethics Committee meeting held on 14 July 1999, but a final decision had to wait until Dr Craig Whitehead had an opportunity to comment. Ethical approval to proceed has now been given and I have enclosed the approved version of the information sheet and consent form.

A copy of a sticker which can be attached to medical records which are part of research records is enclosed. Supplies of these can be obtained from the Supervisor in Medical Records.

Ethical approval is given initially for a period of one year, and an annual report will be requested. As a condition of ethical approval you should report immediately anything which might affect ethical acceptance of the protocol, including adverse events, protocol changes, and unforeseen events which may affect continued ethical acceptability. The Committee is to be notified when the study is completed or discontinued.

Yours sincerely

Anne Sutcliffe
Executive Officer
Research and Ethics Committee

encl

Daws Road, Daw Park, South Australia 5041
Telephone: (08) 8276 9666, Facsimile: (08) 8277 9401

Royal Adelaide Hospital

Medical & Allied
Health Services

Level 2 Eleanor Harrald Building
South Australia 5000

Telephone: (08) 8222 5345

Facsimile: (08) 8222 5936

222 4139
19th December, 1996

Dr S Shakib
PHARMACY DEPT

Dear Dr Shakib,

Re: "The development of a clinical tool for the diagnosis of digoxin toxicity."
RAH Protocol No: 961205

I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

Human Ethics Committee deliberations are guided by the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation. Copies of these can be forwarded at your request.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Dr M James
Chairman
RESEARCH ETHICS COMMITTEE

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