STUDIES OF NORMAL AND DISORDERED GASTRIC MOTILITY IN HUMANS

A Thesis submitted by
Karen Louise Jones

For the Degree of
Doctor of Philosophy

Department of Medicine
University of Adelaide

November 1997
# TABLE OF CONTENTS

Summary .................................................................................................................. 1
Statement of originality ......................................................................................... 6
Dedication ................................................................................................................ 7
Acknowledgements ................................................................................................. 8
Publications arising from the thesis ...................................................................... 12

## CHAPTER 1: GASTRIC MOTOR FUNCTION

1.1 Introduction ........................................................................................................ 14

1.2 Motor functions of different regions of the stomach ........................................... 14
   1.2.1 Proximal stomach ...................................................................................... 16
   1.2.2 Distal stomach ......................................................................................... 17
   1.2.1 Pylorus ..................................................................................................... 20

1.3 Patterns of gastric emptying ............................................................................... 21
   1.3.1 Digestible solids ...................................................................................... 23
   1.3.2 Non-digestible solids ............................................................................... 24
   1.3.3 Nutrient and non-nutrient liquids .............................................................. 24
   1.3.4 Interaction between solids and liquids .................................................... 25
   1.3.5 Fats .......................................................................................................... 26

1.4 Conclusions ......................................................................................................... 28

## CHAPTER 2: REGULATION OF APPETITE

2.1 Introduction ......................................................................................................... 29

2.2 Control of appetite ............................................................................................. 29

2.3 Role of the gastrointestinal tract in appetite regulation .................................... 31
   2.3.1 Gastric distension .................................................................................... 31
   2.3.2 Small intestinal mechanisms .................................................................. 32
2.3.3 Interaction between gastric and small intestinal mechanisms ........................................... 33
2.3.4 Gastrointestinal hormones ........................................... 35

2.4 Conclusions .......................................................... 37

CHAPTER 3: ASSESSMENT OF GASTRIC MOTOR FUNCTION

3.1 Introduction .......................................................... 38

3.2 Measurement of gastric emptying ........................................... 40
  3.2.1 Scintigraphy ........................................... 40
  3.2.2 Ultrasound ........................................... 44
  3.2.3 Radiological measurement ........................................... 46
  3.2.4 Radioisotopic breath tests ........................................... 47
  3.2.5 Magnetic Resonance Imaging (MRI) ........................................... 48
  3.2.6 Applied potential tomography and epigastric impedance .............. 48
  3.2.7 Pharmacokinetics of oral drug absorption ........................................... 49
  3.2.8 Intubation/aspiration techniques ........................................... 49

3.3 Measurement of intraluminal pressures and contractions .............. 49
  3.3.1 Manometry ........................................... 50
  3.3.2 Barostat ........................................... 52
  3.3.3 Scintigraphy ........................................... 52
  3.3.4 Ultrasound ........................................... 53
  3.3.5 Radiological measurement ........................................... 53
  3.3.6 Magnetic Resonance Imaging (MRI) ........................................... 53

3.4 Measurement of gastric electrical activity ........................................... 54
  3.4.1 Serosal electrogastrography ........................................... 54
  3.4.2 External electrogastrography ........................................... 54

3.5 Conclusion .......................................................... 54
CHAPTER 4: CLINICAL MANIFESTATIONS OF DISORDERED GASTRIC EMPTYING

4.1 Introduction ........................................................................................................... 56

4.2 Gastrointestinal symptoms ................................................................................. 56
4.2.1 Treatment of gastrointestinal symptoms in patients with gastroparesis .......... 58
4.2.2 Treatment of symptoms associated with more rapid gastric emptying ............ 61

4.3 Glycaemic control ............................................................................................... 61

4.4 Oral drug absorption ........................................................................................... 62

4.5 Postprandial hypotension .................................................................................... 63

4.6 Conclusions .......................................................................................................... 64

CHAPTER 5: GASTRIC MOTOR FUNCTION IN DIABETES MELLITUS

5.1 Introduction .......................................................................................................... 65

5.2 Prevalence of disordered gastric emptying in diabetes mellitus ................. 66

5.3 Gastric motility in diabetes mellitus ................................................................... 69

5.4 Gastrointestinal symptoms in diabetes mellitus .............................................. 70

5.5 The effect of blood glucose concentration on gastro-duodenal motor and sensory function .................................................................................................................. 71
5.5.1 Gastric emptying .............................................................................................. 72
5.5.2 Gastro-duodenal motility ............................................................................... 72
5.5.3 Gastrointestinal symptoms ............................................................................ 73
5.5.4 Mechanisms mediating the effects of the blood glucose concentration on motility and sensation .......................... 74

5.6 Conclusions ........................................................................................................... 76

CHAPTER 6: EVALUATION OF ANTRAL MOTILITY IN HUMANS USING MANOMETRY AND SCINTIGRAPHY

6.1 Summary ........................................................................................................... 78

6.2 Introduction ....................................................................................................... 79

6.3 Materials and Methods ..................................................................................... 81
   6.3.1 Experimental protocol ............................................................................... 81
   6.3.2 Intraluminal manometry ........................................................................... 81
   6.3.3 Radionuclide evaluation of gastric emptying and contractile activity .......... 83

6.4 Data analysis ..................................................................................................... 84
   6.4.1 Manometry ............................................................................................... 84
   6.4.2 Scintigraphy ............................................................................................. 85
   6.4.3 Statistical analysis ..................................................................................... 86

6.5 Results .............................................................................................................. 86
   6.5.1 Scintigraphy ............................................................................................. 86
   6.5.2 Manometry ............................................................................................... 87
   6.5.3 Relationship between scintigraphic and manometric measurements .......... 88

6.6 Discussion ......................................................................................................... 95
CHAPTER 7: SCINTIGRAPHIC MEASUREMENT OF GASTRIC EMPTYING AND ULTRASONOGRAPHIC ASSESSMENT OF ANTRAL AREA - RELATIONSHIP TO APPETITE

7.1 Summary ........................................................................................................... 98
7.2 Introduction ......................................................................................................... 99
7.3 Materials and Methods ..................................................................................... 101
  7.3.1 Experimental protocol .................................................................................. 101
  7.3.2 Scintigraphic measurement of gastric emptying ........................................... 102
  7.3.3 Ultrasound measurement of antral area ...................................................... 103
  7.3.4 Assessment of appetite .............................................................................. 104
  7.3.5 Statistical analysis ...................................................................................... 104
7.4 Results ............................................................................................................... 104
  7.4.1 Scintigraphic measurements of gastric emptying and intragastric distribution .................................................. 105
  7.4.2 Relationship and limits of agreement between scintigraphic and ultrasound measurements .............................................. 105
  7.4.3 Hunger and fullness .................................................................................... 106
  7.4.4 Relationships between hunger, fullness and gastric emptying ..................... 106
7.5 Discussion ......................................................................................................... 115

CHAPTER 8: RELATIONSHIP BETWEEN POSTPRANDIAL SATIATION AND ANTRAL AREA IN NORMAL SUBJECTS

8.1 Summary .......................................................................................................... 119
8.2 Introduction .................................................................................................... 120
## CHAPTER 8: MATERIALS AND METHODS

8.3 Materials and Methods ......................................................... 122
8.3.1 Experimental protocol ....................................................... 122
8.3.2 Assessment of appetite ....................................................... 123
8.3.3 Scintigraphic measurement of gastric emptying .................. 123
8.3.4 Ultrasound measurement of antral area ............................. 124
8.3.5 Statistical analysis .............................................................. 125

8.4 Results .............................................................................. 125
8.4.1 Appetite ........................................................................... 125
8.4.2 Gastric emptying ............................................................... 126
8.4.3 Relationships of appetite to antral area and gastric emptying ...................................................................... 126

8.5 Discussion ........................................................................ 134

## CHAPTER 9: EFFECTS OF MEAL VOLUME AND POSTURE ON GASTRIC EMPTYING OF SOLIDS AND APPETITE

9.1 Summary ........................................................................... 137

9.2 Introduction ........................................................................ 138

9.3 Materials and Methods ......................................................... 139
9.3.1 Experimental protocol ....................................................... 139
9.3.2 Measurement of gastric emptying ..................................... 140
9.3.3 Assessment of appetite ....................................................... 141
9.3.4 Statistical analysis .............................................................. 141

9.4 Results .............................................................................. 141
9.4.1 Gastric emptying ............................................................... 142
9.4.2 Appetite ........................................................................... 143
9.4.3 Relationships between appetite and gastric emptying ........ 143

9.5 Discussion ........................................................................ 147
CHAPTER 10: THE EFFECT OF POSTURE ON GASTRIC EMPTYING AND INTRAGASTRIC DISTRIBUTION OF OIL AND AQUEOUS MEAL COMPONENTS AND APPETITE

10.1 Summary ........................................................................................................... 151

10.2 Introduction ....................................................................................................... 152

10.3 Materials and Methods ....................................................................................... 154
  10.3.1 Experimental protocol .................................................................................. 154
  10.3.2 Measurement of gastric emptying ............................................................... 155
  10.3.3 Assessment of appetite ................................................................................ 157
  10.3.4 Statistical analysis ...................................................................................... 157

10.4 Results ................................................................................................................ 157
  10.4.1 Gastric emptying of oil and aqueous phases .............................................. 158
  10.4.2 Relationship between gastric emptying and intragastric distribution ....... 160
  10.4.3 Hunger and fullness ..................................................................................... 160
  10.4.4 Relationships between hunger and gastric emptying ......................... 161

10.5 Discussion ........................................................................................................... 167
  10.5.1 Gastric emptying and intragastric distribution of extracellular fat .......... 167
  10.5.2 Effect of gravity on gastric emptying ......................................................... 170
  10.5.3 Relationship between hunger and gastric emptying ......................... 171

CHAPTER 11: GASTRIC EMPTYING OF OIL AND AQUEOUS MEAL COMPONENTS IN PANCREATIC INSUFFICIENCY - EFFECTS OF POSTURE AND ON APPETITE

11.1 Summary ........................................................................................................... 174

11.2 Introduction ....................................................................................................... 175
CHAPTER 12: EFFECTS OF CISAPRIDE ON GASTRIC EMPTYING OF OIL AND AQUEOUS MEAL COMPONENTS, HUNGER AND FULLNESS

12.1 Summary ................................................................. 196

12.2 Introduction ............................................................ 197

12.3 Materials and Methods ................................................ 199
  12.3.1 Experimental protocol ........................................... 199
  12.3.2 Measurement of gastric emptying ............................ 200
  12.3.3 Assessment of hunger and fullness .......................... 201
  12.3.4 Statistical analysis .............................................. 201

12.4 Results .......................................................................... 202
  12.4.1 Gastric emptying of oil and aqueous phases ................ 204
  12.4.2 Relationship between retention in the total, proximal and distal stomach ................................... 204
  12.4.3 Hunger and fullness ................................................. 204
  12.4.4 Relationships between hunger and fullness and gastric emptying ........................................... 205

12.5 Discussion ..................................................................... 210
CHAPTER 13: RELATIONSHIPS BETWEEN GASTRIC EMPTYING, INTRAGASTRIC MEAL DISTRIBUTION AND BLOOD GLUCOSE CONCENTRATIONS IN DIABETES MELLITUS

13.1 Summary ................................................................. 214
13.2 Introduction ............................................................ 215
13.3 Materials and Methods ............................................. 216
   13.3.1 Experimental protocol ....................................... 217
   13.3.2 Assessment of gastrointestinal symptoms ............... 218
   13.3.3 Assessment of autonomic neuropathy, peripheral neuropathy and retinopathy ........................................ 218
   13.3.4 Assessment of glycaemic control ......................... 219
   13.3.5 Measurement of gastric emptying ....................... 219
   13.3.6 Statistical analysis ......................................... 221
13.4 Results ...................................................................... 221
   13.4.1 Gastrointestinal symptoms, diabetic complications and glycaemic control ..................................................... 221
   13.4.2 Gastric emptying .............................................. 222
   13.4.3 Relationships between total stomach gastric emptying and intragastric distribution ........................................... 224
   13.4.4 Relationships between diabetic complications, gastrointestinal symptoms and gastric emptying ......................... 225
   13.4.5 Relationships between plasma glucose concentrations, gastric emptying and gastrointestinal symptoms ................ 225
13.5 Discussion .............................................................. 235

CHAPTER 14: GASTRIC EMPTYING IN “EARLY” NON-INSULIN DIABETES MELLITUS

14.1 Summary ................................................................. 240
CHAPTER 14: ANALYSIS OF GASTROINTESTINAL SYMPTOMS AND GLUCOSE CONTROL IN DIABETES MELLITUS

14.2 Introduction .............................................................................. 241

14.3 Subjects and Methods ................................................................. 243
14.3.1 Experimental protocol ......................................................... 244
14.3.2 Assessment of upper gastrointestinal symptoms ................. 244
14.3.3 Measurement of gastric emptying and intragastric distribution ......................................................... 245
14.3.4 Measurement of blood glucose concentrations ................. 246
14.3.5 Assessment of appetite ......................................................... 246
14.3.6 Assessment of autonomic nerve function ......................... 246
14.3.7 Statistical analysis ............................................................... 247

14.4 Results ..................................................................................... 247
14.4.1 Gastric emptying and intragastric distribution ..................... 248
14.4.2 Relationships between total stomach emptying and intragastric distribution ............................................. 248
14.4.3 Relationships between gastrointestinal symptoms, autonomic nerve function and gastric emptying ................. 249
14.4.4 Relationships between blood glucose concentrations and gastric emptying ..................................................... 249
14.4.5 Hunger and fullness ............................................................. 249
14.4.6 Relationships between appetite, gastric emptying and blood glucose concentrations ................................. 250

14.5 Discussion ................................................................................. 257

CHAPTER 15: THE BLOOD GLUCOSE CONCENTRATION INFLUENCES POSTPRANDIAL FULLNESS IN INSULIN DEPENDENT DIABETES MELLITUS

15.1 Summary .................................................................................. 262

15.2 Introduction .............................................................................. 263
15.3 Materials and Methods ......................................................... 265
  15.3.1 Experimental protocol ................................................. 265
  15.3.2 Assessment of upper gastrointestinal symptoms ................. 266
  15.3.3 Measurement of gastric emptying .................................... 266
  15.3.4 Measurement of blood glucose concentrations ...................... 267
  15.3.5 Assessment of autonomic nerve function ............................ 268
  15.3.6 Statistical analysis .................................................... 268

15.4 Results ............................................................................. 268
  15.4.1 Gastric emptying .......................................................... 269
  15.4.2 Relationships between gastric emptying and other variables ... 269
  15.4.3 Hunger and fullness ..................................................... 270

15.5 Discussion ........................................................................ 276

CHAPTER 16: THE RATE OF GASTRIC EMPTYING IS A SIGNIFICANT DETERMINANT OF POSTPRANDIAL HYPOTENSION IN NON-INSULIN DEPENDENT DIABETES MELLITUS

16.1 Summary .......................................................................... 280

16.2 Introduction ...................................................................... 281

16.3 Materials and Methods ...................................................... 283
  16.3.1 Experimental protocol ................................................... 284
  16.3.2 Measurement of gastric emptying ..................................... 284
  16.3.3 Measurement of blood glucose concentrations .................... 285
  16.3.4 Measurement of blood pressure ....................................... 285
  16.3.5 Assessment of autonomic nerve function ......................... 285
  16.3.6 Statistical analysis ....................................................... 286

16.4 Results ............................................................................. 286
  16.4.1 Gastric emptying .......................................................... 287
16.4.2 Relationships between mean arterial pressure, gastric emptying autonomic nerve function and blood glucose .................................................. 287

16.5 Discussion .............................................................................. 292

CHAPTER 17: HYPERGLYCAEMIA ATTENUATES THE GASTROKINETIC EFFECT OF ERYTHROMYCIN AND AFFECTS THE PERCEPTION OF POSTPRANDIAL HUNGER IN NORMAL SUBJECTS

17.1 Summary .................................................................................. 296

17.2 Introduction ........................................................................... 297

17.3 Materials and Methods .............................................................. 300
17.3.1 Experimental protocol ......................................................... 300
17.3.2 Stabilisation of blood glucose concentrations ...................... 301
17.3.3 Measurement of gastric emptying ......................................... 302
17.3.4 Hunger and fullness ............................................................. 303
17.3.5 Statistical analysis ............................................................... 303

17.4 Results ..................................................................................... 303
17.4.1 Gastric emptying ................................................................. 303
17.4.2 Hunger and fullness ............................................................. 304

17.5 Discussion .............................................................................. 308

CHAPTER 18: CONCLUSIONS ................................................................. 313

REFERENCES .................................................................................. 322
SUMMARY

This thesis presents studies relating to normal and disordered gastric motility and the role of the gastrointestinal tract in appetite regulation in humans. Three broad areas have been addressed: (i) methodological approaches to the evaluation of gastric motility, (ii) gastric emptying of oil in normal subjects and patients with pancreatic insufficiency and (iii) the prevalence, clinical significance and treatment of disordered gastric emptying in patients with insulin dependent (IDDM) and non-insulin (NIDDM) diabetes mellitus. All of the studies have been either published, accepted for publication or submitted for publication and are presented as complete manuscripts.

There are many techniques available to assess gastric motility, including manometry, which measures pressure changes caused by gastric contractions, and scintigraphy which can be used to quantify gastric emptying and antral contractile activity. Concurrent measurements of antral pressure waves by manometry and antral contractions by fast frame scintigraphy (2 sec) were performed in normal volunteers. The frequency of contractions was substantially greater than the number of lumen occlusive pressure waves detected by manometry. Manometric measurements, however, unlike scintigraphy, reflected events occurring with a 0.1 sec resolution. Complimentary information about gastric motility, therefore, arises from the simultaneous use of scintigraphy and manometry.

While most information about disordered gastric emptying has been derived from studies using scintigraphy, the technique is not always readily available and involves exposure to radiation. Concurrent scintigraphic and ultrasound measurements of gastric emptying of liquid were performed in normal volunteers. There was a close correlation between measurements of nutrient and non-nutrient
liquid meals between the two techniques, indicating that ultrasound can be used to quantify gastric emptying of liquids in normal subjects.

There is relatively little information about the mechanisms which control appetite in humans, although signals from the gastrointestinal tract are important. The relationship between appetite and antral area, measured with ultrasound, was evaluated in normal volunteers after a liquid meal. The score for fullness and the width of the antrum were related both before and after the drink, supporting the concept that antral distension is an important mechanism mediating postprandial satiation.

The effects of volume and posture on gastric emptying and intragastric distribution of a solid meal and appetite were evaluated in normal volunteers. Meal volume had a major effect on gastric emptying and intragastric distribution of a digestible solid meal; in particular the rate of solid emptying (kcal/min) was faster in the sitting than the left lateral position. In contrast posture had only a minor impact on intragastric meal distribution, and no effect on gastric emptying. These observations indicate that gastric emptying of digestible solids is load-dependent.

Studies which have evaluated gastric emptying in patients with upper gastrointestinal symptoms, have characteristically used bland test meals, however, such symptoms are often precipitated by fatty meals. The effect of posture on gastric emptying of a meal containing oil and aqueous components and the relationship between appetite and gastric emptying was evaluated in normal volunteers. Gastric emptying of the oil phase was initially faster in the lying than the sitting position, but, the overall rate of emptying of oil was similar in the two postures. In contrast, emptying of the aqueous phase was much faster in the
sitting position when compared to the lying position. Hunger was inversely related to gastric emptying of oil, ie subjects were less hungry when more oil emptied from the stomach. These observations suggest that the interaction of fat with small intestinal receptors plays a major role in the regulation of gastric emptying and appetite in normal volunteers.

To evaluate the hypothesis that fat must be digested to fatty acids in order to slow gastric emptying the effect of posture on gastric emptying of a meal containing oil and aqueous components was evaluated in patients with cystic fibrosis who had exocrine pancreatic insufficiency. Gastric emptying of oil was faster than normal in both positions and much faster in the lying than the sitting position. In contrast, hunger did not decrease after the meal. These observations indicate that gastric emptying of oil is accelerated in pancreatic insufficiency and that digestion of fat is required for suppression of appetite.

Cisapride is arguably the optimum drug for the treatment of gastrointestinal symptoms in patients with gastroparesis. The effects of cisapride on gastric emptying of a meal containing oil and aqueous meal components and appetite were evaluated in a group of normal volunteers. Cisapride accelerated gastric emptying of oil by shortening the lag phase and did not affect the post-lag emptying rate. The retention of oil in the distal stomach was increased by cisapride. Preprandial hunger was greater, and postprandial fullness less on cisapride. These observations indicate that cisapride may influence appetite in humans.

30-50% of patients with longstanding diabetes mellitus have delayed gastric emptying of solid or liquid meals and this may be associated with gastrointestinal symptoms, poor control of blood glucose concentrations and impaired oral drug
absorption. The prevalence of abnormal intragastric meal distribution was assessed in patients with longstanding diabetes mellitus. Intragastric meal distribution was often abnormal with increased retention of both solids and liquids in the proximal stomach but the relationships with the rate of emptying from the total stomach and gastrointestinal symptoms were poor.

The prevalence of abnormal gastric emptying in patients with recently diagnosed non insulin-dependent diabetes mellitus (NIDDM) and the relationship between postprandial blood glucose concentrations and gastric emptying in NIDDM are poorly defined. The prevalence of disordered gastric emptying of a nutrient liquid meal and the relationship between the rise in blood glucose concentration and gastric emptying of a 75g glucose load were assessed in patients with "early" NIDDM. There was no overall difference in gastric emptying between patients with "early" NIDDM and normal volunteers. There was a significant relationship between the magnitude of the increase in plasma glucose after the glucose load and the rate of gastric emptying. This study indicates that during hyperglycaemia gastric emptying of a nutrient liquid meal is similar in patients with "early" NIDDM to normal subjects and a significant determinant of the glycaemic response.

Gastrointestinal symptoms occur frequently in patients with diabetes mellitus, but the relationship with gastric emptying is weak, suggesting that other factors are important. Recent studies have suggested that the blood glucose concentration influences sensations arising from the gut. The relationships between gastric emptying, gastrointestinal symptoms and the blood glucose concentration were evaluated in patients with longstanding insulin dependent diabetes mellitus. There was a significant relationship between both pre- and postprandial fullness and the blood glucose concentration, consistent with the concept that the latter is a
significant determinant of gastrointestinal symptoms in patients with diabetes mellitus.

Postprandial hypotension is a major clinical problem in the elderly and in patients with autonomic failure; including patients with diabetes mellitus. The relationship between the postprandial fall in blood pressure and the rate of gastric emptying was evaluated in patients with "early" NIDDM and both young and older normal volunteers. In the NIDDM group the area under the change in mean blood pressure curve between was related to the rate of gastric emptying, accounting for approximately 45% of the variance. There was no significant relationship between the change in blood pressure and gastric emptying in the normal subjects. These observations suggest that the rate of gastric emptying has a significant impact on the change in blood pressure after a meal in patients with diabetes.

Recent studies have demonstrated that acute changes in the blood glucose concentration may effect gastrointestinal motor function. The effects of erythromycin (3mg/kg IV) on gastric emptying of a solid meal and, postprandial hunger and fullness were assessed in normal subjects during both hyperglycaemia (~15mmol/L) and euglycaemia. Hyperglycaemia markedly slowed gastric emptying after both saline and erythromycin administration. Erythromycin accelerated gastric emptying during euglycaemia, but had little effect during hyperglycaemia. Postprandial hunger was less during hyperglycaemia after administration of saline but not erythromycin. This study indicates that the prokinetic effect of erythromycin on gastric emptying of solids is attenuated during hyperglycaemia and that the hyperglycaemia-induced changes in gastrointestinal sensation may be altered by erythromycin.