FACTORS AFFECTING ANTIPYRINE

METABOLISM

Thesis submitted to the University of Adelaide for the degree of
Doctor of Philosophy

by

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OCTOBER 1979

Awarded 13th July 1980
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GENERAL DISCUSSION

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ABSTRACT OF THESIS

The aims of this thesis were to assess the value of salivary antipyrine elimination kinetics in the study of factors that influence the activity of hepatic mixed function oxidase enzymes.

Antipyrine metabolism in patients with chronic liver disease was found to be impaired when compared with a control population of unmedicated volunteers. Chronic renal dysfunction did not appear to alter antipyrine elimination.

The half-life of antipyrine was significantly reduced in a group of epileptics on long-term phenytoin therapy. Used as a measure of enzyme induction, half-life was unable to discriminate those patients at risk from osteomalacia or to detect any additional enzyme inducing effect on the addition of a barbiturate to the therapeutic regimen. Antipyrine half-life did not correlate with either phenytoin dose or plasma level.

Patients receiving chlorpromazine therapy for psychotic illness metabolized antipyrine faster than control subjects; however, in patients receiving fluphenazine decanoate there was no change. The difference may be related to plasma levels attained by each agent after dosing, fluphenazine being given intramuscularly and achieving only very low plasma concentrations.

The effects of chronic ethanol intake on the elimination kinetics were determined in a group of male alcoholics. Antipyrine metabolism was impaired in this group when compared to controls.
These results demonstrated that a significant proportion of the alcoholics studied had impaired hepatic drug metabolizing capacity and that the activity of the hepatic microsomal enzymes may be related to the extent of ethanol induced liver damage in these subjects.

Antipyrine elimination kinetics were measured in anaesthetists during a period when they were giving general anaesthetics and a period when they were working in intensive care where they were not using volatile anaesthetic agents. During the anaesthetic work period there was a reduction in antipyrine half-life and the clearance of antipyrine was increased. Analysis of the data was performed using each anaesthetist as his/her own control. When the data was analysed on a group basis, no change in elimination kinetics was detected because of the wide variation in metabolism between subjects. Exposure to anaesthetic agents under operating theatre conditions appeared to enhance hepatic metabolism.

Many chemicals in the environment are known to alter the disposition of drugs. The effect of petrol on the activity of mixed function oxidase activity was investigated in man and the rat. Antipyrine half-lives in a group of male petrol station workers were shorter than in controls. The rates of oxidative metabolism of antipyrine, aminopyrine, ethylmorphine, aniline and benzo(a)pyrene were all increased by more than 45% in 10,000 x g hepatic microsomal supernatant preparations from rats exposed to petrol vapour over a period of three weeks. These results indicated that petrol vapour was a moderately potent inducer of microsomal mixed function oxidase
activity in rats, and that occupational exposure to petroleum may result in enhanced microsomal drug metabolism.

Isolated rat hepatocytes offer a useful in vitro model for the study of drug metabolism. They retain activity of Phase I and II reactions without the necessity for added cofactors and hence are more indicative of the metabolic activity of intact tissue than are microsomal preparations. Metabolic drug interactions between antipyrine and inhibitor concentrations of SKF525-A, phenobarbitone and chlormethiazole were investigated in rat hepatocytes isolated by a collagenase perfusion technique. Chlormethiazole and SKF525-A competitively inhibited antipyrine metabolism. Phenobarbitone produced a mixed-type inhibition. Chlormethiazole and phenobarbitone were found to be weak inhibitors and acute inhibitory drug interactions between these agents and antipyrine are unlikely to be observed at normal therapeutic blood concentrations. Pretreatment of rats with phenobarbitone prior to hepatocyte isolation resulted in induction of antipyrine metabolism. The results showed that classical microsomal induction and inhibition can be demonstrated in isolated hepatocytes.

The overall results of this thesis indicate that (i) the salivary elimination kinetics of antipyrine in man is a sensitive qualitative test for assessing those factors that can alter the activity of the hepatic mixed function oxidase enzymes; (ii) isolated hepatocyte preparations may be a useful in vitro model in which to study potential drug interactions.