THE MYOCARDIAL METABOLIC AND HAEMODYNAMIC EFFECTS OF PERHEXILINE IN IN VIVO AND IN VITRO MODELS

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SUMMARY

Perhexiline is an effective anti-anginal agent without clinically significant haemodynamic effects which is postulated to have a primary “metabolic” mechanism of action. Recent in vitro work in isolated cardiac mitochondria suggested that inhibition of the key enzyme in the regulation of fatty acid catabolism, carnitine palmitoyltransferase (CPT-1), may play a key role in the action of perhexiline. The experiments described in this thesis are primarily aimed at investigating the postulated metabolic effects of perhexiline in the heart, and correlating these to changes in haemodynamics. Secondary aims are the assessment of the time-dependence of such changes, and the investigation of haemodynamic changes induced by parenteral perhexiline in a conscious animal model.

**Haemodynamic effects of parenteral perhexiline**

An experimental model of chronically catheterised sheep enabled the monitoring of haemodynamics during and after intravenous perhexiline administration in conscious animals. The major haemodynamic effects of brief intravenous infusions of perhexiline were vasoconstriction, followed by bradycardia. There was no evidence of negative inotropy to suggest any significant calcium channel antagonism at the dosages used.

**Metabolic effects of perhexiline in vivo**

Nuclear medicine imaging of the heart following injection of a radio-iodinated fatty acid (IPPA) enabled assessment of the effects of parenteral perhexiline administration
on myocardial fatty acid utilisation in an *in vivo* animal model. The use of a known CPT-1 inhibitor, etomoxir, resulted in a significant delay in myocardial clearance of IPPA, indicating inhibition of beta oxidation. However no significant changes in the uptake or clearance kinetics of IPPA were seen following either short-term or long-term (24 hours) perhexiline infusions.

**Metabolic effects of perhexiline in vitro**

The working rat heart model was used to assess both substrate utilisation and haemodynamics in response to perhexiline and the known CPT-1 inhibitors, etomoxir and oxfenicicine. Although there were no significant effects of acute *in vitro* perhexiline exposure on myocardial energetics of efficiency, *ex vivo* experiments following 24 hours of transdermal perhexiline administration demonstrated an increase in cardiac work performed per unit of fatty acid consumption, associated with improved myocardial efficiency.

In conclusion, perhexiline's effects on cardiac metabolism are not as striking as those of oxfenicicine *in vitro* and etomoxir *in vivo*. However it appears that any such effects of perhexiline are related to total duration of perhexiline exposure, and further work is required in more suitable models of chronic perhexiline administration.