THE STEREOSELECTIVE PHARMACOKINETICS OF THE ENANTIOMERS OF PERHEXILINE IN POOR AND EXTENSIVE METABOLISERS OF THE CYTOCHROME P450 2D6

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ABSTRACT

Perhexiline maleate was first introduced for the prophylaxis of exertional angina in the 1970s but reports of adverse reactions, including potentially fatal hepatotoxicity, increasingly restricted its application. By 1988 Australia and New Zealand were the only countries permitting its use, limited to the treatment of refractory angina pectoris conditional upon the therapeutic monitoring of patients, due to recognition of the concentration dependent nature of its efficacy and toxicity. An understanding of the extreme interindividual variability in the pharmacokinetics of perhexiline due to metabolism by the polymorphic Cytochrome P450 2D6 (CYP2D6) has prompted a recent resurgence of its use in Australasia and Europe.

Perhexiline is a chiral molecule and is administered as a racemic mixture. Prior to the publication of the papers that are the topic of this thesis the characterisation of the clinical pharmacology of the enantiomers of perhexiline had been limited to one pharmacokinetic study that suggested that the (+) enantiomer of perhexiline may display a smaller polymorphic effect in its metabolism than its optical antipode. The four publications that comprise this thesis describe a comprehensive investigation of the pharmacokinetics and metabolism of the enantiomers of perhexiline in extensive and poor metabolisers (EM and PM, respectively) of CYP2D6 in both an *in vitro* model and clinically. The aim was to determine if the CYP2D6 polymorphism affects the metabolism of (+)-perhexiline significantly less than (-)-perhexiline, such that the inherent variability observed in the pharmacokinetics of the racemic preparation used clinically might be overcome by administration of only (+)-perhexiline.

Although both the *in vitro* and *in vivo* studies determined that the involvement of CYP2D6 was proportionately greater in the total clearance of (-)- than (+)-perhexiline, the empirical data also demonstrated that the role of CYP2D6 in the metabolism of (+)-perhexiline was simply too pre-eminent for a chiral preparation of this enantiomer to significantly reduce the difference in clearance observed between EM and PM. An unexpected finding was that the enantioselectivity observed in the clinical pharmacokinetics of perhexiline in EM was, in fact, significantly greater in PM. Whilst the enantioselectivity in EM was attributable to metabolism by CYP2D6, the mechanism responsible for this in PM could not be determined, but was postulated to involve enantioselective biliary excretion. Because PM are effectively exposed to greater concentrations of (+)-perhexiline and lower concentrations of (-)-perhexiline, when the relative pharmacodynamic activities of the individual enantiomers have been established therapeutic drug monitoring may be improved by the development of specific enantiomer target concentration ranges in plasma. What is certain is that perhexiline will remain an essential option in the armamentarium for the treatment of refractory angina pectoris and therapeutic drug monitoring will remain obligatory due to the inter- and intra-subject pharmacokinetic variability attributable to the respective polymorphic and saturable metabolism of both enantiomers by CYP2D6.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text.

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Publication 1

Enantioselective assay for the determination of perhexiline enantiomers in human plasma by liquid chromatography.

Davies BJ, Herbert MK, Culbert JA, Pyke SM, Coller JK, Somogyi AA, Milne RW, Sallustio BC.

J Chromatogr B Analyt Technol Biomed Life Sci. 2006 Feb 17;832(1):114-20.

Publication 2

Determination of the 4-monohydroxy metabolites of perhexiline in human plasma, urine and liver microsomes by liquid chromatography.

Davies BJ, Herbert MK, Coller JK, Somogyi AA, Milne RW, Sallustio BC.

J Chromatogr B Analyt Technol Biomed Life Sci. 2006 Nov 7;843(2):302-9.

Publication 3

CYP2B6, CYP2D6, and CYP3A4 catalyze the primary oxidative metabolism of perhexiline enantiomers by human liver microsomes.

Davies BJ, Coller JK, Somogyi AA, Milne RW, Sallustio BC.

Drug Metab Dispos. 2007 Jan;35(1):128-38.

Publication 4

Steady-state pharmacokinetics of the enantiomers of perhexiline in CYP2D6 poor and extensive metabolizers administered *Rac*-perhexiline.

Davies BJ, Herbert MK, Coller JK, Somogyi AA, Milne RW, Sallustio BC.

Br J Clin Pharmacol. 2008 Mar;65(3):347-54.

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