Deakin Research Online

This is the published version:


Available from Deakin Research Online:

http://hdl.handle.net/10536/DRO/DU:30035592

Reproduced with the kind permission of the copyright owner.

Copyright : 2000, Cambridge University Press
The antidepressant mirtazapine (1,2,3,4,10,14b-hexahydro-2-methylpyrazolo[2,1-
a]-pyrido[2,3-c][2]benzazepine) is administered clinically as a racemate. This study examined the metabolism of enantiomers of mirtazapine by CYP450 isoenzymes expressed in human lymphoblast microsomes transfected with human cDNA and by HLM (human liver microsomes) from pooled human livers. The cDNA enzymes used were CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Pooled human liver microsomes were from ten different donors, enzyme activity of the pooled microsomes had previously been demonstrated by the supplier (Genentech corporation, USA). Drug, enzymes, co-factors and buffer were incubated at 370°C. Drugs were extracted into hexane/ethylacetate and assayed by HPLC using a hexane-ethanol-isopropanol 98:1:1 mobile phase at a flow rate of 1.5 ml/min, with a Chiralpak AD column and pre-column. Detection was by UV at 290 nm and retention times were (+)-mirtazapine 11 minutes and (-)-mirtazapine 12.5 minutes.

Enzyme kinetic parameters were calculated from untransformed mirtazapine concentration data using EZ-Fit (version 5.03; Perrella Scientific Inc, Amhurst, NH) assuming a linear Michaelis-Menten fit. Linear competitive inhibition was used as the model for the analysis of inhibition data. Incubations of the racemate and the individual enantiomers demonstrated that CYP2D6 is the enzyme with the strongest activity in the metabolism of mirtazapine. (+)-Mirtazapine is metabolised by CYP2D6 (Km = 9.26 ± 3.27 μmol/L, Vmax = 40.86 ± 7.68 % mol/h/mg, intrinsic clearance = 4.41 L/hr/mg) whereas (-)-mirtazapine is a weak competitive inhibitor of CYP2D6 (Ki = 1.88 ± 0.91 μmol/L) and is not metabolised by it. CYP1A2 and CYP3A4 had metabolic effects on mirtazapine, but they were too weak for pharmacokinetic parameters to be calculated. Neither CYP2C9 or CYP2C19 appeared to be involved in the metabolism of mirtazapine.

When (+)-mirtazapine was incubated with HLM for one hour both enantiomers were found to have been extensively metabolised. This is probably due to the high levels of 3A4 in the liver. However, when plasma from patients treated with mirtazapine was assayed for the enantiomers of mirtazapine, typically the concentration of (+)-mirtazapine measured approximately one third of the concentration of (-)-mirtazapine after oral administration of the racemate.