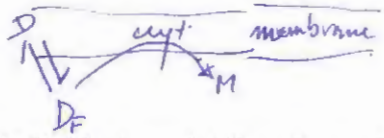
PL1 UNDERSTANDING AND PREDICTING INTERINDIVIDUAL VARIABILITY IN DRUG METABOLISM IN HUMANS

John O. Miners

Department of Clinical Pharmacology, Flinders Medical Centre and Flinders University, Bedford Park, SA 5042, Australia.



ABSTRACT

Wide interindividual variability is a characteristic of drug metabolism in humans, and the metabolic clearances of some drugs may vary 100-fold or more in the population. It is now recognised that this variability arises from differences in the activities of drug metabolising enzymes. Individual isoforms of cytochrome P450 (CYP) and UGT-glucuronosyltransferase (UGT), which are quantitatively the most important drug metabolising enzymes, exhibit distinct substrate and inhibitor specificities and each *CYP* and *UGT* gene is regulated independently. Thus, rationalisation and prediction of altered metabolic drug clearance requires knowledge of both the isoform(s) responsible for drug elimination and factors which regulate isoform activity *in vivo*. Studies *in vivo* and *in vitro* with isoform-specific substrates indicate that drug-drug interactions (inhibition and induction) and polymorphism in the coding regions of CYP and UGT genes are the major determinants of variability in the elimination of compounds metabolised by these enzymes. This will be illustrated using the isoforms CYP2C9 and UGT2B7 as examples. The characterisation of isoform-selective inhibitors in this and other laboratories together with the availability of recombinant enzymes allows the identification of the individual isoform(s) responsible for the metabolism of any given drug, a process referred to as reaction phenotyping. When factors altering the activity of the isoform(s) *in vivo* are known, causes of variability in the clearance of the drug in defined population groups may then be predicted. *In vitro* drug metabolism kinetic data may also be used to predict key *in vivo* pharmacokinetic parameters such as hepatic clearance and extraction ratio and the magnitude of inhibitory drug interactions. Understanding and predicting drug interactions and the consequences of genetic polymorphisms are essential components of rational drug therapy and important considerations in the clinical development of newly discovered drugs.