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DRUG METABOLISM AND INTERINDIVIDUAL
DIFFERENCES IN DRUG RESPONSIVENESS

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Interindividual differences in drug responsiveness between patients are often quite pronounced and frequently reflect differences in the processes of disposition. Countless studies have identified numerous environmental and disease-related factors contributing to such variability, particularly that related to drug metabolism, which generally occurs in the liver. In addition, it has become increasingly apparent that an individual's genetic constitution, both familial and racial, may be of considerable importance in determining their response to a particular drug. This is especially the case when drug metabolism involves the P450 super-gene family of enzymes.

A major genetic effect in drug metabolism occurs when a single individual P450 gene and its product is largely responsible for the majority of a drug's overall elimination and several allelic forms exist. In which case, drug metabolizing enzyme activity is polymorphically distributed within the population and generally two phenotypes can be characterized by the administration of probe substrates - extensive metabolizers (EM), who possess the enzyme, and poor metabolizers (PM), where the enzyme is functionally absent and metabolism is impaired. The resulting interphenotypic differences in pharmacokinetics lead to predictable clinical consequences, although their magnitude varies for each individual drug. For example, concentration-related therapeutic and adverse effects are exaggerated in PMs. By contrast, EMs are susceptible to drug:drug interactions involving the affected enzyme, whereas PMs are not. For racemic drugs, interphenotypic differences in the stereoselectivity of metabolism may also be present. Furthermore, if the polymorphically distributed enzyme mediates the formation of an active metabolite, different pharmacokinetic-pharmacodynamic relationships will be present in the two phenotypes.

Two independent polymorphisms of drug oxidation are now well characterized and are associated with P4502D6 (debrisoquine/sparteine type) and P4502C_{MP} - tentatively identified as P4502C18 - (mephenytoin type), respectively. Importantly, P4502D6 mediates the oxidation of a large number (>30) of commonly used drugs including, β -adrenoceptor blockers, antiarrhythmic agents, tricyclic antidepressants, and neuroleptics. The specificity of P4502C_{MP} appears to be narrower - initially only certain anticonvulsant drugs related to mephenytoin, such as mephobarbital and hexobarbital, were identified as substrates. More recently, however, P4502C_{MP} has been shown to be important in the metabolism of structurally dissimilar compounds; for example, propranolol, imipramine, omeprazole, proguanil and possibly diazepam.

The frequency distributions of the PM phenotype for both polymorphisms exhibit considerable global heterogeneity probably reflective of racial background. Thus, P4502D6 activity is absent in 7-10% of Caucasians; by contrast, populations of Mongoloid-origin (Chinese, Japanese, Koreans) consist almost entirely of EMs. The reverse situation applies to the P4502C_{MP} polymorphism - the frequency of the PM phenotype is 5 to 6-fold higher in Asian populations compared to the 3-5% present in Caucasians. It is also becoming apparent that racially-based differences in drug metabolizing ability may also be present in EM populations. Thus, the pharmacokinetics of propranolol, omeprazole and diazepam, for example, are substantially different between EM Caucasians and EM Chinese/Japanese. The relative contributions of genetics and environment to such differences remain to be determined.

Interindividual differences in drug responsiveness not only arise because of factors related to drug disposition/pharmacokinetics but may also be due to differences in pharmacodynamics - the relationship between drug concentration and its elicited effect. Race appears to be a potentially important contributing factor to such differences. For example, Chinese subjects are 3 to 10-fold more sensitive to several propranolol-induced, β -adrenoceptor effects, regardless of any differences in drug disposition. Presumably, such differences reflect fundamental, but currently unknown, factors in the post-receptor-effect cascade.

It is likely that racial differences in drug disposition and/or pharmacodynamic sensitivity occur with drugs that are metabolized by P450s other than 2D6 and 2C_{MP} as well as other enzyme families such as the glucuronosyltransferases. The increasing international nature of drug development and clinical use, along with the increased racial diversity of many national populations, requires that these and other aspects of pharmacogenetics continue to be further investigated.

Reference

Pharmacogenetics of Drug Metabolism. W. Kalow, editor, Pergamon Press, New York, 1992.