Relevance of genetic polymorphism in drug metabolism in the development of new drugs

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Summary. Drugs whose principal metabolic pathways are under polymorphic genetic regulation may show considerable interindividual pharmacokinetic variability. This could lead to clinically significant differences in the pharmacological responses of some patients and so might lead the pharmaceutical industry to stop development of the drug. This can be prevented and there are several measures that can be taken to avoid such premature termination of development. They include studies in vitro with human liver samples, and clinical pharmacological experiments designed specifically to examine possible genetic polymorphism in the disposition of the drug.

Key words: genetic polymorphism, drug development; pharmacokinetic variability

Amongst the factors which hinder introduction of a drug into the market, a narrow therapeutic range combined with large interindividual variation in pharmacokinetics is of major concern. For a compound with these qualities it can be assumed that a proportion of the patient population receiving a "standard dose" will develop unwanted effects related to "higher than normal" blood concentrations of the active principle, whereas other patients might show an "apparent nonresponse" due to unusually low concentrations.

It is well recognised that drugs are eliminated by metabolic routes that are under genetic control. Some of these metabolic pathways show a distribution of their activity that allows patients and/or healthy volunteers to be classified into distinct subpopulations. Among the best studied routes showing such genetic polymorphism are sulphonamide-type acetylation and debrisoquine-type hydroxylation. The latter is known as the "debrisoquine-sparteine-type polymorphism of drug oxidation", and 5 to 10% of Caucasians fall into the category of "poor hydroxylators" [1-3]. Other oxidative reactions seem to be independently polymorphically regulated, including mephenytoin hydroxylation.

The clinical relevance of such genetic variability is strongly dependent on the therapeutic class of the compound and on the concentration-effect relationships of the desired and unwanted effects. Thus, beta-adrenoceptor antagonists, which have a large therapeutic margin, can be used almost regardless of the phenotype of the patient; large interindividual variations in steady-state plasma concentrations are probably of minor clinical significance, and certainly do not warrant plasma concentration monitoring. In contrast, it is now recognised that for tricyclic antidepressants, plasma concentration monitoring is important in preventing unwanted effects and therapeutic failures, although this point of view is still not universally held.

In the present pharmaco-political context, the benefit-to-risk ratio of a new drug must be very stringently assessed. This may lead the pharmaceutical industry to stop the development of potentially important new chemical entities for which early studies in man indicate the possibility of a "higher than expected" incidence of adverse effects, or difficulties in managing differences in the dose requirements between different patients. The present paper discusses the question of whether genetic polymorphism in drug metabolism represents an important factor in determining the overall benefit-to-risk ratio, and it includes proposals about how this problem can be handled during the development of a new drug. For practical reasons, examples will be limited to drugs associated with the debrisoquine-sparteine polymorphism of oxidative drug metabolism.
Interindividual variability in drug response linked to genetic polymorphism in drug metabolism

Any kind of genetic polymorphism in the disposition of a drug has the potential to increase interindividual variability in the pharmacokinetics of that drug. The dispersion of any relevant kinetic variable is likely to be greater when the overall variation is due to the existence of more than one discrete sub-population than in the polygenic case, where there is a single population. As a rule, distributions in the former case tend to be highly skewed, whereas in the latter they tend to normality. However, the likely extent and consistency of the variability are difficult to predict from published information.

As an example, in one study of bufuralol (a beta adrenoceptor antagonist with small therapeutic index), the systemic clearance was found to be about 371. h\(^{-1}\) in extensive metabolizers and only about 151. h\(^{-1}\) in poor metabolizers [4]. It was also shown that polymorphic metabolism had a major influence on the extent of hepatic first-pass elimination, as judged by the large variability in systemic availability. Since the intravenous doses used in the study were smaller than the oral doses, the calculated apparent absolute availability even exceeded 1 in a healthy volunteer phenotyped as a “very poor” metabolizer, reflecting the fact that non-linear kinetics probably occur at the higher dose levels used orally in this type of subject. Depending on the values of \(V_{\text{max}}\), \(K_M\) and the drug concentration, it is conceivable that extensive metabolizers might also exhibit non-linear kinetics. Further work in suitably planned studies is required before the practical relevance of these findings can be fully assessed.

Non-linear kinetics has also been reported for the hydroxylation of imipramine. Such dose-dependent behaviour contributes substantially to the known variability in the steady-state concentrations of imipramine and desipramine [5], although its relationship to the hydroxylation status of the patients has not been established. Thus, under certain circumstances genetic polymorphism may transform the elimination of a compound from linear into non-linear kinetics, which could have important clinical implications.

Pre-clinical investigations

Determination of the main metabolic pathways

It is now customary early in the development of a new drug, to perform preliminary metabolic studies in animals. The data from such investigations (together with theoretical considerations) may help in determining whether a given compound is likely to be metabolized by pathways known to be under polymorphic genetic control in man. It must be kept in mind, however, that a given enzyme may metabolize a substrate in different positions. It is also possible, as demonstrated in the rabbit model of the acetylation polymorphism, that two drugs may be handled by the same enzyme, one in a polymorphic and the other in a non-polymorphic fashion. Accordingly, extrapolation from in vitro or animal data to man must be done cautiously. At this stage, it might be useful to extend the predictability of such findings for man by using in vitro studies with human hepatocytes or liver microsomes. The trend towards the establishment of human liver banks, comprising well characterized samples stored under defined conditions [6–8] should prove invaluable in the application of such an approach. Currently, when neither pure cytochrome P-450 isoenzymes nor specific inhibitory antibodies against the isoenzymes are readily available, most reliance has to be placed on experiments with samples from subjects of defined phenotype, or in which competitive inhibition of drug substrates is assessed. Thus, by using liver from subjects identified as poor metabolizers, or by performing inhibition studies with marker drugs, valuable predictive information on the qualitative and quantitative importance of a polymorphic enzyme in the metabolism of a new compound can be obtained. Many clinically important drug metabolic interactions could probably also be detected by using such techniques.

If the in vitro experiments indicate that polymorphic differences are to be expected in man, it would be prudent to perform, as soon as possible, pharmacokinetic experiments in healthy volunteers, phenotyped as extensive and poor metabolizers for the metabolic pathway under consideration. This is quite feasible at present using relatively simple methods for the debrisoquine-sparteine and the mephenytoin types of polymorphism. Even a combination of probes to phenotype can be employed to phenotype volunteers for different polymorphisms in one session [9]. In addition, studies with specific inhibitors of a polymorphic enzyme, such as quinidine, might be performed in extensive metabolizers [10, 11]. Such single-dose studies can be performed at a time when only minimal animal toxicological data are available (i.e. mutagenic potential, one- or two-week toxicity studies in two animal species, and safety pharmacology). The aim of such an investigation would be to confirm the findings in animals and in vitro, and to determine the contribution of the polymorphic metabolic pathway to overall elimination of the drug. If the