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PHARMACOKINETIC AND PHARMACODYNAMIC CONSEQUENCES OF STEREOSELECTIVE DRUG METABOLISM IN MAN

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Abstract—The examples discussed demonstrate the importance of stereoselective drug metabolism and raise the question of whether the therapeutic use of racemic drugs is still justified.

There is no straightforward answer to this question. If only quantitative differences in therapeutic activity exist and the less active enantiomer is not predominantly responsible for side effects, the therapeutic benefit gained by using the more active enantiomer is only marginal and does not justify the substantial increase in costs involved in manufacturing such a drug preparation. However, if stereoselectivity in therapeutic activity is pronounced and adverse drug reactions are caused mainly by the less active isomer then an isomeric pure drug preparation should be used.

In contrast to chiral drugs of natural origin which usually contain only one of two possible enantiomers, chemical synthesis generally results in the formation of both configurations unless stereospecific drug synthesis is employed. It is interesting to note that only 41 out of 266 racemic drugs are marketed as drug preparations containing only one isomer. Stereoisomers contained in racemic drug preparations quite often exhibit pronounced differences in their pharmacological and toxicological properties both in quantitative and qualitative terms. In addition to stereoselectivity of drug action, various aspects of drug disposition exhibit stereoselectivity. Although known for years, it was not until recently that the importance of stereoselective drug metabolism in man and its therapeutic consequences have been appreciated. In view of the pronounced differences in activity and toxicity as well as the different pharmacokinetic behaviour of stereoisomers one is administering in fact two drugs when giving a racemate. However, most physicians are not aware of this fact [1].

This article will focus on three aspects of stereoselective drug metabolism in man: (1) stereoselective first-pass metabolism; (2) stereochemical considerations of drug interaction; (3) stereochemical aspects of polymorphic drug oxidation.

1. STEREOSELECTIVE FIRST-PASS METABOLISM

We became interested in stereoselective first-pass metabolism and its pharmacokinetic and pharmacodynamic consequences during our work with the calcium channel blocker verapamil. Since its introduction more than 20 years ago, clinicians realized that an i.v. dose of 5–10 mg was effective in terminating various supraventricular tachyarrhythmias, whereas an oral dose of 80–160 mg was required in order to elicit a therapeutic effect comparable to i.v. administration. The cause of this pronounced difference in dose requirement became apparent when we demonstrated that despite its almost complete absorption, bioavailability was only 20–30% due to extensive hepatic presystemic elimination [2]. Based on a bioavailability of 20–30%, an oral dose of 25–50 mg should suffice to elicit a therapeutic effect comparable to an i.v. dose of 5–10 mg. However, analysis of the concentration–effect relationship revealed that after oral administration verapamil had less negative dromtropic potency at the same plasma concentration than after a single intravenous bolus injection. On average, verapamil plasma concentrations three times higher were required after oral administration in order to produce the same PR-prolongation as after i.v. administration. As the most plausible explanation for the different slopes of the plasma concentration–effect relationship, we proposed that the more active *l*-isomer is preferentially metabolized during hepatic first-pass metabolism [3]. Recent studies carried out in our laboratory have demonstrated that *l*-verapamil in agreement with animal experiments is on average 8–10 times more potent than *d*-verapamil with regard to its negative dromotropic activity [4]. In addition to these differences in pharmacodynamic activity of the *l*- and *d*-isomers, pronounced differences in the various pharmacokinetic parameters and bioavailability were observed between *d*- and *l*-verapamil. Systemic and oral clearance of *l*-verapamil was substantially higher than that of *d*-verapamil. The bioavailability of *d*-verapamil (50%) was 2.5 times greater than that of *l*-verapamil (20%) [5, 6]. The *d*- to *l*-isomer ratio of plasma verapamil following i.v. administration was approximately 2, whereas after oral administration the *d* to *l* ratio was 5. These differences in the *d*- to *l*-isomer ratio of plasma verapamil concentration in relation to the route of administration explain the observed differences in the slopes of the concentration–effect curves [7].

The metabolism of verapamil involves several *N*-dealkylation and *O*-demethylation reactions. So far 12 metabolites have been identified [8]. With regard to the metabolic reactions exhibiting

enantioselectivity in studies carried out *in vitro* with human hepatic microsomal fraction and *in vivo* after oral administration of the isomers, no difference in K_m and V_{max} could be observed for the various *N*-dealkylated metabolites. A threefold difference in clearance to these metabolites (*l*: 118, *d*: 40 l/hr) was seen *in vivo*. However, the formation of the *O*-demethylated metabolites exhibited a high degree of enantioselectivity. *l*-Verapamil had 2–3-fold higher V_{max} (K_m *l*: 60 μM; *d*: 48 μM; V_{max} (pmol/mg/min): *l*: 333; *d*: 153) and a 30-fold higher metabolic clearance compared to *d*-verapamil (*l*: 43.6 l/hr; *d*: 1.32 l/hr).

A much enhanced therapeutic effect can be anticipated for highly cleared drugs in patients with liver cirrhosis. In patients with liver cirrhosis hepatic first-pass metabolism is substantially decreased and bioavailability increased due to extra- and intrahepatic shunting of the portal blood supply as well as a reduced capacity of the functioning liver cell mass. In a previous study we observed an increased pharmacodynamic response of verapamil in patients with liver cirrhosis at the same verapamil concentration as compared to subjects with normal liver function [9]. Recent studies in this laboratory could demonstrate, that this enhanced negative dromotropic response was not due to an altered sensitivity of the AV-node in liver disease but rather changes in stereoselective first-pass metabolism. The differences in bioavailability of *l*- and *d*-verapamil normally observed are no longer present in patients with liver cirrhosis. If the differences in the *d*/*l* verapamil plasma concentration ratio are taken into account and the concentration effect curves are based on *l*-verapamil concentrations these curves are almost superimposable. Thus in patients with liver cirrhosis dose recommendations should not only be based on pharmacokinetic data but also pharmacodynamic response taking into account the impact of liver disease on the stereoselective first-pass metabolism.

2. STEREOCHEMICAL CONSIDERATIONS OF DRUG INTERACTIONS

Stereoselective drug metabolism may have important therapeutic implications in the case of drug interactions if pronounced differences in potency exist between enantiomers and their disposition is differently affected by the causative drug.

The following example with warfarin will illustrate the importance of studying the enantiomeric disposition of drugs in drug interactions. In a very elegant study O'Reilly *et al.* [10] elucidated the mechanism responsible for the augmented hypoprothrombinemia of warfarin caused by the coadministration of phenylbutazone. Although total warfarin plasma concentrations decreased during phenylbutazone treatment, yet an augmented pharmacodynamic response of warfarin was observed. In order to evaluate whether or not phenylbutazone had a differential effect on the disposition of the more potent *S*-isomer they studied the biological fate of the *R*- and *S*-enantiomers. During phenylbutazone a highly significant increase in the plasma clearance of *R*-warfarin and significant decrease in the clearance of *S*-warfarin was observed compared with the administration of warfarin alone. Thus phenylbutazone augmented the hypoprothrombinemic action of warfarin by inhibiting the metabolism of the more hypoprothrombinemic *S*-warfarin, yet reduced total warfarin plasma concentrations by greatly augmenting the clearance of *R*-warfarin. Recently Toon *et al.* [11] investigated the warfarin–sulfinpyrazone interaction. An enhanced hypoprothrombinemia was observed when warfarin and sulfinpyrazone were taken together. This study illustrates even more the necessity of monitoring the individual enantiomers of racemic drugs. Whereas some of the subjects showed an increase warfarin elimination, $t_{\frac{1}{2}}$, consistent with the enhanced pharmacologic response, other subjects showed a 25% decrease in warfarin elimination, $t_{\frac{1}{2}}$, a result seemingly in contradiction with the observed enhanced pharmacologic response. Based on these data alone, conclusions regarding plasma concentration response relationship are meaningless, if the $t_{\frac{1}{2}}$ for the individual enantiomer are not considered and the paradox is resolved. Thus for instance in one subject the $t_{\frac{1}{2}}$ of *S*-warfarin increased from 25 to 49.5 hr, while that of the *R*-enantiomer decreased from 46 to 38 hr with sulfinpyrazone dosing. In the case of another subject the $t_{\frac{1}{2}}$ of *S*-warfarin increased from 49 to 58 hr while that of *R*-warfarin was so greatly decreased from 87 to 25 hr with sulfinpyrazone dosing so that the $t_{\frac{1}{2}}$ of total warfarin decreased relative to the control value. But in both cases the *S*-warfarin concentrations increased, a result in agreement with the observed enhanced pharmacologic response.

3. STEREOCHEMICAL ASPECTS OF POLYMORPHIC DRUG OXIDATION

Genetic factors play an important role in stereoselective metabolism of certain drugs. The oxidative metabolism of several drugs (debrisoquine, sparteine, mephenytoin) exhibits a genetic polymorphism [12–14].

The metabolism of several racemic drugs is controlled by the debrisoquine/sparteine polymorphism and marked genetic determined differences in stereoselectivity of certain metabolic reactions are observed.

The metabolism of the β-adrenoreceptor antagonists, metoprolol and bufuralol, which are administered as racemates, is controlled by the debrisoquine/sparteine polymorphism [15, 16]. Whereas in EM subjects the first-pass metabolism of these drugs exhibits enantioselectivity, PMs are characterized by an increased bioavailability and a loss of stereoselectivity. Most of the β-blocking activity of metoprolol resides with the *S*(−)-enantiomer. Following oral administration the *R*(+)-enantiomer has a lower bioavailability in EM subjects. In contrast to EMs bioavailability of *R*(+)- and *S*(−)-metoprolol is almost identical in PM subjects leading to a shift in the concentration–effect curve to the right in this phenotype.

Recently Siddoway and coworkers [17] have demonstrated that the metabolism of the class I antiarrhythmic drug propafenone cosegregates with

the polymorphic debrisoquine/sparteine metabolism. Large interindividual differences in the various pharmacokinetic parameters and C_{ss} were observed. Propafenone is used as a racemate. With regard to the antiarrhythmic effect, no difference exists between the *S*-(+) and *R*-(−)enantiomer. However, the *R*-(−)-isomer has weak β-blocking activity corresponding to 2–5% of propranolol. In a recent study in our laboratory, we have investigated the stereoselective metabolism of propafenone in EMs and PMs of sparteine. In EMs we observed not only a substantial first-pass metabolism but also a high degree of enantioselectivity leading to the preferentially presystemic elimination of *R*-(−)-propafenone. In contrast PMs show a decreased first-pass metabolism and loss of enantioselectivity. Based on single dose pharmacokinetic parameters during multiple dosing of 600 mg daily *R*(−)-propafenone concentrations in the order of 1000–1500 ng/ml will be achieved in PMs. These concentrations would be equivalent to propranolol concentrations of 25–50 ng/ml, which are associated with complete β-blockade. Thus it is very likely that PMs will achieve *R*-(−)-propafenone concentrations during chronic treatment which could elicit β-blockade. These findings could explain the observation of Siddoway and coworkers that in 67% of PMs central nervous system side effects such as visual blurring and dizziness were present, whereas these adverse drug reactions occurred only in 14% of EM patients.

Even more pronounced genetic determined differences in the stereoselectivity of certain metabolic reactions are observed, if stereoselectivity of product formation is considered. Although debrisoquine has no chiral centre, hydroxylation in position 4 introduces a chiral centre into the molecule giving rise to two possible enantiomers. Recent studies from this laboratory have elucidated the absolute configuration of the *R*- and *S*-enantiomers of 4-hydroxydebrisoquine, being *R*(−) and *S*(+)-4-hydroxydebrisoquine [18]. The enantioselectivity of 4-hydroxydebrisoquine has been investigated in this laboratory in panels of EMs and PMs. Without any exception in all of the EMs a high degree of enantioselectivity in the 4-hydroxylation of debrisoquine favouring the *S*(+)-enantiomer was observed. In 80% of EMs (N: 32) the *S*(+) enantiomeric excess was 100. In the remaining 20% EMs (N: 9) trace amounts of *R*(−)-4-hydroxydebrisoquine were formed resulting in a *S*(+) enantiomeric excess ranging from 99.4 to 97.6. In contrast PMs are not only characterized by a marked decreased formation of total 4-hydroxydebrisoquine, but also by a loss of product stereoselectivity of this reaction. Between 5 and 36% of total 4-hydroxydebrisoquine formed corresponded to the *R*(−)enantiomer. The *S*(+)-enantiomeric excess ranged from 90 to 28. Within the PMs (N: 41) a significant negative correlation between the urinary metabolic ratio and the *S*(+) enantiomeric excess was observed (r^2: 0.71; $P < 0.001$), indicating that product enantioselectivity is related to 4-hydroxylation capacity. The less 4-hydroxydebrisoquine is being formed the less product enantioselectivity is observed [19].

The use of drugs exhibiting substrate and product enantioselectivity in their metabolism might offer a tool to elucidate the mechanisms responsible for impaired drug oxidation in PMs. Meyer *et al.* have used the stereoselective hydroxylation of (+) and (−)-bufuralol as a model reaction to characterize the cytochrome P-450 isozyme involved in the polymorphic oxidation of debrisoquine and sparteine [20]. The formation of *l'*-hydroxy-bufuralol in liver microsomes of *in vivo* phenotyped EMs had a substantially higher V_{max} when (+)-bufuralol was used as a substrate. In liver microsomes from PMs, however, a loss of stereoselectivity together with a marked increase in K_m and decrease in V_{max} was observed. A cytochrome P-450 isozyme, which was isolated from human kidney donor livers using this reaction for purification metabolized bufuralol in a highly stereoselective fashion. Since the formation of *l'*-hydroxy-bufuralol and α-hydroxymetoprolol creates a new chiral centre, it would certainly be of interest to see whether the generation of these metabolites proceeds with the same degree of product enantioselectivity and exhibits phenotypic differences similar to the ones observed for 4-hydroxydebrisoquine. The decreased rate of metabolite formation together with the loss of enantioselectivity seem to indicate that besides a decreased amount of cytochrome $P\text{-}450_{bufl}$ the catalytic properties of this isozyme are altered in the PM phenotype.

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