

Effects of stereochemical aspects on drug interaction in pharmacokinetics

ZHOU Quan^{1,2}, YAO Tong-Wei¹, ZENG Su^{1,3} (¹Department of Drug Metabolism & Pharmaceutical Analysis, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310031; ²Department of Clinical Pharmacy, the Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, China)

KEY WORDS stereoisomerism; drug interactions; pharmacokinetics

ABSTRACT

Recent literatures on enantiomer/enantiomer and enantiomer/coadministered drug interactions in pharmacokinetics were reviewed. The clinical significance of introducing the concept of stereoselectivity into pharmacokinetic interaction study cannot be overestimated, such as avoiding interaction-based adverse reactions, increasing therapeutic index, resolving the apparent anomaly in the plasma concentration-effect relationship and providing starting point of investigation into drug disposition, etc. Study in this respect should be enhanced.

INTRODUCTION

The majority of chiral synthetic or semisynthetic drugs are marketed as racemates. However, the enantiomers of a racemic drug generally differ in pharmacodynamic and/or pharmacokinetic properties as a consequence of stereoselective interaction with optically active biological macromolecules. Thus, the clinical significance of stereoselectivity cannot be overestimated^[1,2]. Although recently this issue has drawn adequate attentions from the biomedical community, relevant review has not been available with respect to stereochemical aspects of pharmacokinetic drug interaction, resulting in ignorances by most of clinicians and investigators. Racemate has been usually treated as a pure compound in the study of drug interaction, resulting in the discrepancy between the study conclusion and

clinical consequences and even mistake in guiding drug administration. Fortunately, there have been enormous advances in the analytical technology required to resolve racemic drugs. As a consequence, the requisite analytical skills are no longer the exclusive domain of "specialists." Perhaps the greatest obstacle to be overcome is one of adequate education. Thus, the intent of this review is to provide a comprehensive rather than exhaustive, appraisal of stereochemical aspect of pharmacokinetic drug interaction.

ENANTIOMER/ENANTIOMER INTERACTION

Absorption Stereoselectivity is not expected during passive absorption of enantiomers. However, this is not generally true if an active or receptor-mediated process is involved. Absorption may exhibit stereoselectivity, giving rise to the possibility of competitive interaction between enantiomers. For example, the intestinal absorption of *D*-cefalexin via dipeptide transport system can be inhibited by its *L*-enantiomer^[3]. Inversion from therapeutically "inactive" *R*-ibuprofen to the active antipode appears to take place presystematically in the gastrointestinal tract. Moreover, the extent of *R* to *S* inversion may be absorption rate dependent^[4].

Distribution Enantiomeric competition for plasma protein (HSA) or α -glycoprotein (AGP) binding sites has been suggested as the mechanism responsible for this type of interaction. For example, due to interactions in HSA binding, distribution volumes of ibuprofen enantiomers increase in the presence of their antipodes^[5]. (-)-*S*-propranolol, the more active enantiomer, can be displaced from HSA binding by its antipode, which increases the toxicity of racemate in rats^[6].

The enantiomer of *N*-demethyldisopyramide can competitively displace the parent drug from AGP binding. The plasma concentration of *N*-demethyldisopyramide is

³ Correspondence to Prof ZENG Su. Phn 86-571-721-7203.
Fax 86-571-721-7086. E-mail zengsu@zjuem.zju.edu.cn
Received 2001-10-23 Accepted 2002-01-31

more pronounced in patients with renal dysfunction, which gives rise to higher risk of toxicity due to the increase in plasma concentration of unbound (+)-disopyramide^[7]. This is a special example involving metabolite/parent interaction in distribution.

Metabolism It involves mutual interaction, unidirectional interaction, enantiomeric activation, and enantiomeric inversions *via* metabolite (Tab 1).

Type 1 is mutual interaction. In this case, both enantiomers mutually compete for the same catalytic site of the enzyme. For example, metabolism of *S*-propafenone seems to be retarded in the presence of *R*-propafenone *in vivo*^[8]. Furthermore, *in vitro* experiment also revealed that *R*-propafenone was a more potent inhibitor than the *S*-enantiomer with respect to CYP2D6-mediated 5-hydroxylation^[9]. Because beta-blocking properties of propafenone reside in the *S*-enantiomer, inhibition of metabolism of this enantiomer by *R*-propafenone may provoke side effects in patients who are intolerant of beta-blockade. In this case, developing the pure *R*-propafenone (eutomer) is necessary. The rate of racemic cisapride metabolism by human liver microsomes and recombinant CYP3A4 is slower compared with equimolar concentrations of each other. When incubated simultaneously, the enantiomers inhibit each other's metabolism, with (-)-cisapride being a more potent inhibitor than the (+)-enantiomer. This enantiomer/enantiomer interaction influences the prokinetic efficacy and cardiac safety of cisapride^[10]. Mutual inhibition of benidipine enantiomer in rat liver microsomes was also observed^[11]. The (-)- α -isomer acts as a more potent inhibitor than (+)- α -isomer and it is useful for reducing the dose of the pharmacologically potent (+)- α -isomer. In this case, dosing of racemate is preferable.

Type 2 is unidirectional interaction. The mechanism is that only one enantiomer acts as a competitive inhibitor of the other's metabolism. For example, the formation of *R*-desethylchloroquine at low concentration

(1–5 $\mu\text{mol/L}$) was strongly inhibited by *S*-chloroquine. This underlying mechanism explains the fact that the enantiomeric ratio (*R/S*) of desethylchloroquine was dependent on concentration, and ranged from 8 at 1 $\mu\text{mol/L}$ to 1 at 300 $\mu\text{mol/L}$ ^[12]. 4-Hydroxylation of (+)-bunitrolol (10 $\mu\text{mol/L}$) was markedly suppressed in the presence of its antipode (10 $\mu\text{mol/L}$) in rabbit liver microsomes, whereas (-)-bunitrolol 4-hydroxylation was not affected by the presence of its antipode, resulting in a change of the stereoselectivity from (+)-bunitrolol > (-)-bunitrolol for enantiomer to (+)-bunitrolol < (-)-bunitrolol for racemate^[13].

When the racemic nitrendipine was given, the extent of bioavailability and dose-normalized AUC and C_{max} values for the *S*-enantiomer were not different from the values after administration of the *S*-enantiomer. In contrast, those for *R*-nitrendipine doubled after administration of racemate as compared with *R*-nitrendipine, suggesting a metabolic enantiomer/enantiomer interaction with *S*-enantiomer acting as inhibitor of *R*-nitrendipine metabolism^[14].

The clearance of *S*(+)-ketamine was smaller in the racemate [(18.5 ± 0.7) mL · kg⁻¹ · min⁻¹, *P* < 0.05] than for the pure isomer [(26.3 ± 3.5) mL · kg⁻¹ · min⁻¹], demonstrating that *R*(-)-ketamine inhibited the elimination of *S*(+)-ketamine^[15].

Type 3 is enantiomer interaction with a cascade effect. The interaction between warfarin enantiomers is more interesting. *R*-Warfarin was shown to inhibit 7-hydroxylation of *S*-enantiomer^[16]. It was later demonstrated that 7-hydroxylation of *S*-enantiomer was catalyzed predominantly by CYP2C9 and *R*-warfarin was most likely binding to the active site, but was not metabolized to any appreciable extent by the enzyme. This raises the intriguing possibility of very complex drug interactions, including the situation where another drug with no direct effect on the clearance of the more pharmacologically active *S*-enantiomer might still elicit a

Tab 1. Types of enantiomer/enantiomer interactions in metabolism.

Type	Racemates
Mutual interaction	propafenone, cisapride, benidipine
Unidirectional interaction	chloroquine, bunitrolol, ketamine, propylisopropyl acetamide, nitrendipine
Enantiomer interaction with a cascade effect	warfarin
Enantiomer activation	zileuton
Enantiomer inversions <i>via</i> metabolite	flosequinan

clinically significant drug interaction by inhibiting the clearance of *R*-warfarin with a cascade effect on the metabolism of *S*-warfarin. And this underlying mechanism addressed the fact that the coadministration of cimetidine or zileuton with warfarin enhanced the anticoagulant effect, although both cimetidine and zileuton only interact with *R*-warfarin by inhibiting CYP1A2 and the accumulation of *R*-warfarin does not directly increase pharmacological effect^[17,18].

Type 4 is enantiomeric activation. Sweeny *et al* reported the enantiomeric activation of zileuton glucuronidation in dog hepatic microsomes^[19]. The glucuronidation of individual enantiomer was stereoselective, as dog hepatic microsomes glucuronidated the *S*-enantiomer but failed to generate conjugate of *R*-enantiomer. Amazingly, nonconjugated *R*-enantiomer competitively activates the glucuronidation of its enantiomer. This is the first demonstration of enantiomeric activation of an enzyme involved in hepatic drug metabolism.

Type 5 is enantiomeric inversions *via* metabolite. For example, the interconversions of flosequinan (FSO) occurred *via* formation of flosequinan sulphide^[20]. The amount of interconversion from *S*-FSO to *R*-FSO was greater than that from *R*-FSO to *S*-FSO. Moreover, the rate of interconversion after oral administration was higher than that after *iv* administration.

The observed decrease in liver blood flow caused by *S*-propranolol may also reduce the hepatic clearance of *R*-propranolol in monkeys.

In theory, the inhibition of clearance of a eutomer by a non-toxic distomer may support the development of the racemate (eg, benidipine) and offer an economic advantage not only during the development process, by avoiding the need to produce commercial quantities of an individual enantiomer, but also in the clinical use of a high unit cost drug. For ketamine, although *R*(-)-enantiomer inhibits the elimination of *S*(+)-enantiomer (eutomer), the incidence of emergence reactions reside in *R*(-)-enantiomer (distomer). Thus, developing *S*(+)-ketamine is preferable^[2]. It is also necessary to develop eutomers of warfarin, cisapride, and propafenone with respect to toxicological relevance and potential for complex drug interactions.

Renal excretion Stereoselective renal clearance may be observed as a result of active transport or renal metabolism. For example, (+)-terbutaline can competitively inhibit the reuptake of (-)-enantiomer in renal tubular, resulting in the increase in the latter renal excretion. Renal clearances of *S*-sotalol were signi-

ficantly reduced after administration of racemate due to the renal perfusion changes caused by the beta-bloking effects of *R*-sotalol. It suggested that the dosage of racemate be reduced if sotalol was applied in anti-arrhythmic therapy^[21].

ENANTIOMER-COADMINISTERED DRUG INTERACTION

The stereochemical process of chiral drug may be influenced by the other coadministered drugs, and *vice versa*.

Distribution The effect of phenylbutazone on the binding between warfarin and HSA is enantioselective^[22]. The unbound concentration of (*R*)-warfarin was significantly higher than that of (*S*)-enantiomer by 1.22-fold in solution containing warfarin and HSA. By addition of phenylbutazone, the unbound concentrations of *R*- and *S*-warfarin increased by 2.18- and 3.17-fold, respectively. As a result, the unbound concentration of the more potent enantiomer (*S*-form) became significantly higher than that of the antipode by 1.19-fold. Two possible hypotheses can be considered to explain the reversal of the enantioselectivity in warfarin-HSA binding by addition of phenylbutazone. One explanation is that phenylbutazone induces a conformational change in the warfarin binding site on the albumin molecule which produces a differential change in the affinities with warfarin enantiomers. Another hypothesis is that the binding sites on albumin for warfarin and phenylbutazone are not identical but overlap to some extent. If warfarin enantiomers are bound to the overlapping region with different affinities, phenylbutazone may induce a stereoselective change. This interaction, along with the inhibitory effect on *S*-warfarin metabolism by phenylbutazone, account for a serious side effect of warfarin (hemorrhagic complications).

S-Lorazepam acetate exhibited considerably enhanced binding, especially in the presence of (+)-*S*-ibuprofen. The phenomenon is an indication of cooperative allosteric interaction between different binding sites during multiple cobinding of two ligands. This is a special example with respect to interaction in distribution^[23].

Clofibrate may increase the proportion of *R*-ibuprofen incorporated into long-lived lipid ("hybrid" lipid) stores, resulting in a significant increase in volume of distribution at steady-state observed for *R*-enantiomer but

not *S*-enantiomer^[24].

Halothane enantioselectively reduces the relative uptake of *R*-thiopental into brain tissue, resulting in the fact that total body clearance of *R*-thiopental > *S*-thiopental^[25].

Metabolism Stereoselectivity would be altered due to drug interaction. For example, we reported that the phase I metabolic stereoselectivity of propranolol in rat liver microsomes was reversed by pretreatment of β -naphtho flavone and increased by phenobarbital^[26]. The stereoselectivity in metoprolol pharmacokinetics in human when metoprolol was given alone was abolished after multiple dose paroxetine dosing. The *S/R* AUC ratio decreased significantly from 1.72 to 1.07 ($P < 0.001$) after paroxetine treatment^[27].

Some enantiomer/coadministered drug interactions are of clinical relevance. Benzbromarone-warfarin and buclome-warfarin interactions are attributed to stereoselective inhibition of *S*-warfarin 7-hydroxylation *via* CYP2C9^[28,29]. The mechanism explains the intensified anticoagulant response and dosage reduction of warfarin by 30% – 60% when coadministered with benzbromarone or buclome.

Stereoselective interactions in phase II metabolism are less available. Previously, we observed that the glucuronidation of propranolol in rat hepatic microsome had stereoselectivity of *S*(-)-propranolol, and that the pretreatment of phenobarbital reduced this stereoselectivity^[30]. Combining the results shown by Laethem *et al* that probenecid preferentially decreased the formation clearance of *S*-glucuronide of oxprenolol than that of *R*-glucuronide^[31], we suppose that the glucuronosyl-transferases have different subfamilies with regio-selectivities and stereoselectivities for substrate.

If racemate metabolism involves more than one metabolic pathways, stereoselective effect of coadministered drug on each pathway should be examined. For example, paroxetine did not stereoselectively affect α -hydroxylation of metoprolol, but preferentially inhibited the *O*-demethylation of *R*(+)-metoprolol versus the *S*-enantiomer^[32].

Renal secretion Little information is available regarding stereoselective interactions in kidney, especially with respect to competition for active tubular secretion. Cimetidine, a potent inhibitor of the renal tubular secretion of organic cations, stereoselectively inhibited the renal secretion of *S*-enantiomer of D-617, a metabolite of verapamil. It was interpreted as there being different affinities of the enantiomers of D-617 for tubular

secretion, resulting in competitive displacement of the *S* but not *R* enantiomer from the transporter by cimetidine^[33]. Mikus *et al* also raised the possibility of enantiospecific subsystems for active tubular secretion. In contrast, probenecid decreased the renal clearance of both glucuronides of oxprenolol enantiomers to the same extent^[31]. Thus, stereoselective effect on the active tubular secretion of racemate including parent drug and its metabolites by coadministered inhibitors of organic cation transport system needs to be investigated.

SIGNIFICANCE OF STEREOSELECTIVE INTER-ACTION

Explain the discrepancy between kinetics and dynamics In the following examples, the reason for the discrepancy between kinetics and dynamics became clear when the stereochemical aspects of the situation were examined.

Coadministered phenylbutazone does not significantly alter the pharmacokinetics of racemic warfarin, but enhances the anticoagulant effect of warfarin. The paradoxical fact can be easily understood when individual enantiomers were considered. In fact, phenylbutazone increases the clearance of *R*-warfarin and decreases that of pharmacologically active *S*-enantiomer^[34]. In this case, the monitoring of the plasma concentration of *S*-warfarin is necessary.

An interaction between fluoxetine and carvedilol has little clinical significance in heart failure patients, although the elevated total carvedilol plasma concentrations were observed when coadministered with fluoxetine. A stereoselective inhibition of carvedilol metabolism by fluoxetine, with the *R*(+)-carvedilol increasing to a great extent than the active *S*(-)-enantiomer, may accounts for the absence of a significant change in the pharmacodynamics of racemic carvedilol^[35].

Enhance clinical therapy Interaction between enantiomer and coadministered drug in some occasions is beneficial for clinical therapy. For example, the effect of first-pass metabolism is more pronounced on (*S*)-verapamil than on the (*R*)-enantiomer. Coadministered cimetidine can decrease the first-pass metabolism of verapamil. However, the increase in bioavailability of the more active (*S*)-enantiomer was almost twice than that of (*R*)-enantiomer. Hence, at identical total concentrations of verapamil, coadministration of cimetidine

will enhance the therapy effect of verapamil^[36].

Bondolfi *et al* reported fluoxetine augmentation in citalopram non-responders^[37]. Eight of the 11 patients showed clinical improvement (reduction > 50 % of the MADRS score) without intolerance after the combined treatment of fluoxetine (10 mg/d) and citalopram (40 mg/d) for 7 weeks. The underlying mechanism is that fluoxetine stereoselectively increases the pharmacologically more active *S*-citalopram in comparison with *R*-enantiomer.

Provide starting point of investigation Some underlying disposition information have been acquired through studies of stereoselective drug interaction. For example, propafenone is mainly metabolized by CYP2D6. Stereoselective differences in plasma concentrations of propafenone enantiomers were observed in poor metabolizers. After coadministration of quinidine (a potent inhibitor of CYP2D6), the differences still existed. Thus, it strongly indicated that at least one possible pathway accounted for the differences^[9]. This provides a new starting point of investigation. In our laboratory, substrate concentration-dependent stereoselectivity in propafenone metabolism *via* CYP3A4 expressed in transgenic Chinese hamster cell lines was observed^[38].

Fluvoxamine, a specific inhibitor of CYP1A2, significantly increased the plasma concentrations of methadone enantiomers to the similar extent. Fluoxetine, a potent inhibitor of CYP2D6, markedly increased the plasma concentrations of more active *R*-enantiomer, without effect on (*S*)-methadone. The study indicated that metabolism *via* CYP2D6 exhibited stereoselectivity for *R*-enantiomer whereas metabolism *via* CYP1A2 had no stereoselectivity^[39].

Phenytoin induced significantly *N*-dechloroethylation of (*S*)-cyclophosphamide while having no effect on that of (*R*)-enantiomer. So it is concluded that different enzymes are responsible for the *N*-dechloroethylation of two enantiomers^[40].

Ketoconazole had a robust effect on the single dose pharmacokinetics of both reboxetine enantiomers. Furthermore, the fact that the AUC ratio for the two enantiomers was minimally affected by treatment shows similar affinities of the enantiomers for CYP3A4^[41].

Stereoselective drug interactions between nimodipine and propafenone were addressed in our laboratory^[42]. Nimodipine (CYP3A4 inhibitor) preferentially inhibited *R*-propafenone metabolism in rat liver microsomes induced by dexamethasone, which confirms the stereoselectivity for *R*-enantiomer in propafenone metabolism

via CYP3A4. Fluvoxamine has a more pronounced inhibitory effect on (*R*)-propafenone than that on (*S*)-propafenone *N*-dealkylation^[43]. It indicates the stereoselectivity (*R* > *S*) in propafenone metabolism *via* CYP1A2. This stereoselectivity was also observed by us using cDNA-expressed transgenic Chinese hamster CHL cell lines as *in vitro* model (unpublished data).

PATIENT FACTORS INFLUENCING ON STEREOSELECTIVE INTERACTION

Genetic factors Genetic factors are known to be significant in drug disposition and also influence the stereoselective aspects in drug metabolism. Stereoselective drug interactions in extensive metabolizers may not be observed in poor metabolizers (PM). For example, daily dosing with 600 mg rifampicin for 22 d caused a three to eight fold increase in the 0–8 h urinary *R/S* ratio of mephenytoin following oral administration (100 mg) of racemic drug to extensive metabolizers of the anticonvulsant. By contrast, rifampicin had no effect on mephenytoin metabolism in poor metabolizers^[44]. The underlying mechanism is that CYP2C19 induced by rifampicin only metabolizes *S*-enantiomer and this subfamily can not be induced by rifampicin in PM due to genetic deficiency.

Species The glucuronidation of *S*-zileuton was competitively inhibited by *R*-enantiomer in human liver microsomes^[45]. However, it was competitively activated by *R*-zileuton in dog hepatic microsomes^[19], indicating that there are species differences in enantiomer/enantiomer interaction.

Age Age-associated alternations in enzyme expression may influence the pharmacokinetics of the enantiomers of a racemic drug differently. Several stereoselective drug interactions are also age-associated. For example, rifampicin treatment (600 mg daily for 14 d) produced a larger and a differential increase in the oral clearance of *R*-(-)-hexobarbitone in young and elderly subjects, an 89-fold change in the young [(15.6 ± 16.4) mL · min⁻¹ · kg⁻¹ to (1146.7 ± 1478.0) mL · min⁻¹ · kg⁻¹] and a 19-fold change [(10.3 ± 3.0) mL · min⁻¹ · kg⁻¹ to (199.9 ± 98.1) mL · min⁻¹ · kg⁻¹] in the elderly^[46].

Sex Palylyk *et al* reported the influence of sex on the stereoselective probenecid-ketoprofen interaction in the rat^[47]. An increase of 182 % in the AUC of *S*-ketoprofen was observed in female whereas only an 88 %

increase in *S*-ketoprofen was observed in male rats. The mechanism is that there is the very efficient biliary clearance of *S*-ketoprofen conjugate in the male and that probenecid may be unable to compete for biliary excretion to the extent it can in the female.

METHODS FOR STEREOSELECTIVE PHARMACOKINETIC INTERACTION

Analytical methods for enantiomer discrimination in most occasions are necessary, including stable isotope technique and chiral chromatography. The former technique relies on the detection of the mass difference between the isotope-labelled and unlabelled enantiomer by GC-MS. It has been used in the studies of enantiomeric interactions of propafenone^[9], nitrendipine^[14], amphetamine, and benidipine^[11].

The latter chiral chromatography has also been applied widely in stereoselective pharmacokinetic interaction study, such as mutual enantiomeric interactions in 4-, 5-, and 7-hydroxylations of propranolol^[48], *N*-dealkylation of cisapride^[10], 4'-hydroxylation of flurbiprofen^[49] and interactions of paroxetine-metoprolol^[27], floxetine-carvedilol^[37], and bucolome-warfarin^[29], etc. In our laboratory, through manipulation of the enantiomeric composition of propafenone and a chiral HPLC analysis, we found that *S*-propafenone metabolism via recombinant CYP3A4 was inhibited by *R*-enantiomer, with the IC₅₀ value of 125 μmol/L^[38].

When enantiomer discrimination method was not employed, mutual competitive enantiomer/enantiomer interaction in metabolism could be examined by a mixed alternative substrates model suggested by Segal^[50]. The total rate of metabolism of a racemic mixture on the basis of V_{max} and K_m values obtained from experiments using the individual enantiomers are estimated according to the model, and then compared with the value experimentally obtained. If the experimental data were almost superimposable on those obtained by simulation, competitive inhibition-based enantiomer/enantiomer interaction may exist. The model was adapted to the 5-hydroxylation of (*S*)- and (*R*)-propafenone and *N*-dealkylation of (+)- and (-)-cisapride^[9,10].

In summary, enantiomer/enantiomer interaction in racemates and enantiomer/other drug interaction in coadministration may exist in pharmacokinetics. Some of these are associated with polymorphism, age, species, and sex. The clinical significance of introducing the

concept of stereoselectivity into pharmacokinetic interaction study cannot be overestimated, such as avoiding interaction-based adverse reactions, increasing therapeutic index, resolving the apparent anomaly in the plasma concentration-effect relationship, and providing starting point of investigation into drug disposition, etc. With analytical technology spreading and desires of rational drug use increasing, studies of stereoselective pharmacokinetic drug interaction would prosper.

REFERENCES

- 1 Nation RL. Chirality in new drug development. Clin Pharmacokinet 1994; 27: 249-55.
- 2 Hutt AJ, Tan SC. Drug chirality and its clinical significance. Drugs 1996; 52 Suppl: 1-12.
- 3 Tamai I, Ling HY, Timbul SM, Nishikido J, Tsuji A. Stereospecific absorption and degradation of cephalexin. J Pharm Pharmacol 1988; 40: 320-4.
- 4 Jamali F, Singh NN, Pasutto FM, Russell AS, Courts RT. Pharmacokinetics of ibuprofen enantiomers in human following oral administration of tablets with different absorption rates. Pharm Res 1988; 5: 40-3.
- 5 Itoh T, Maruyama J, Tsuda Y, Yamada H. Stereoselective pharmacokinetics of ibuprofen in rats; effects of enantiomer-enantiomer interaction in plasma protein binding. Chirality 1997; 9: 354-61.
- 6 Bode W, Toet AE, Stolker AA, Van-Ginkel LA, Groen K, Werner J, et al. Toxicokinetics of a single intravenous dose of Rac-propranolol versus optically pure propranolol in the rat. Chirality 1995; 7: 626-31.
- 7 Takahashi H, Ogata H, Seki Y. Binding interaction between enantiomers of disopyramide and mono-*N*-dealkyldisopyramide on plasma protein. Drug Metab Dispos 1991; 19: 554-7.
- 8 Li G, Gong PL, Qiu J, Zeng FD, Klotz U. Stereoselective steady state disposition and action of propafenone in Chinese subjects. Br J Clin Pharmacol 1998; 46: 441-5.
- 9 Kroemer HK, Fischer C, Meese CO, Eichelbaum M. Enantiomer/enantiomer interaction of (*S*)- and (*R*)-propafenone for CYP2D6 catalyzed 5-hydroxylation; *in vitro* evaluation of the mechanism. Mol Pharmacol 1991; 40: 135-42.
- 10 Desta Z, Soukhova N, Morochio AM, Flockhart DA. Stereoselective metabolism of cisapride and enantiomer-enantiomer interaction in human cytochrome P450 enzymes; major role of CYP3A. J Pharmacol Exp Ther 2001; 298: 508-20.
- 11 Kobayashi H, Kobayashi S. Enantiomer-enantiomer interaction of a calcium channel antagonist, benidipine hydrochloride, during liver metabolism in the rat. Eur J Drug Metab Pharmacokinet 1999; 24: 121-6.
- 12 Augustjns P, Peeters L, Croes K, Verbeeck RK. Stereoselective deethylation of chloroquine in rat liver microsomes. Eur J Drug Metab Pharmacokinet 1999; 24: 105-8.
- 13 Narimatsu S, Mizukami T, Huang Y, Masubuchi Y.

- Suzuki T. *In-vitro* metabolic interaction of bunitrolol enantiomers in rabbit liver microsomes. *J Pharm Pharmacol* 1996; 48: 1185-9.
- 14 Tokuma Y, Noguchi H. Stereoselective pharmacokinetics of dihydropyridine calcium antagonists. *J Chromatogr A* 1995; 694: 181-93.
- 15 Ihmsen H, Geisslinger G, Schuttler J. Stereoselective pharmacokinetics of ketamine; *R* (-)-ketamine inhibits the elimination of *S* (+)-ketamine. *Clin Pharmacol Ther* 2001; 70: 431-38.
- 16 Kunze KL, Eddy AC, Gibaldi M, Haynes BP, Breckenridge AM, Park BK. Metabolic enantiomeric interactions; the inhibition of human (*S*)-warfarin-7-hydroxylase by (*R*)-warfarin. *Chirality* 1991; 3: 24-9.
- 17 Choonara IA, Cholerton S, Haynes BP, Breckenridge AM, Park BK. Stereoselective interaction between the *R*-enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; 21: 271-7.
- 18 Awni WM, Hussein Z, Granneman GR, Patterson KJ, Dube LM, Cavanaugh JH. Pharmacodynamic and stereoselective pharmacokinetic interaction between zileuton and warfarin in humans. *Clin Pharmacol* 1995; 29 Suppl: 267-76.
- 19 Sweeney DJ, Nellans HN. Enantiomeric activation of glucuronidation in drug hepatic microsomes. *J Biol Chem* 1992; 267: 13171-4.
- 20 Kashiwara E, Todaka T, Odomi M, Tanokura Y, Johnson DB, Yokoi T, *et al*. Stereoselective pharmacokinetics and interconversions of flosequinan enantiomers containing chiral sulphoxide in rat. *Xenobiotica* 1994; 24: 369-77.
- 21 Carr RA, Pasutto FM, Foster RT. Stereospecific evaluation of sotalol pharmacokinetics in a rat model; evidence suggesting an enantiomeric interaction. *Biopharm Drug Dispos* 1994; 15: 109-20.
- 22 He J, Shibukama A, Tokunaga S, Nakagawa T. Protein binding high performance frontal analysis of (*R*)- and (*S*)-warfarin on HSA with and without phenylbutazone. *J Pharm Sci* 1997; 86: 120-5.
- 23 Fitos I, Visy J, Simonyi M, Hermansson J. Stereoselective allosteric binding interaction on human serum albumin between ibuprofen and lorazepam acetate. *Chirality* 1999; 11: 115-20.
- 24 Scheuerer S, William KM, Brugger R, McLachlan AJ, Brune K, Day RO, *et al*. Effect of clofibrate on the chiral disposition of ibuprofen in rats. *J Pharmacol Exp Ther* 1998; 284: 1132-8.
- 25 Mather LE, Edwards SR, Duke CC, Cousins MJ. Enantioselectivity of thiopental distribution into the central neural tissue of rats; an interaction with halothane. *Anesth Analg* 1999; 89: 230-5.
- 26 Li X, Liu Q, Zeng S. Influence of phenobarbital induction on the stereoselectivity of propranolol glucuronidation in rat hepatic microsomes. *J Zhejiang Univ (Medical Sciences)* 1999; 28: 202-5.
- 27 Hemeryck A, Lefebvre RA, De Vriendt C, Belpaire FM. Paroxetine affects metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. *Clin Pharmacol Ther* 2000; 67: 283-91.
- 28 Takahashi H, Sato T, Shimoyama Y, Shoda N, Shimizu T, Kubo S, *et al*. Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. *Clin Pharmacol Ther* 1999; 66: 569-81.
- 29 Matsumoto K, Ishida S, Ueno K, Hashimoto H, Iakada M, Tanaka K, *et al*. The stereoselective effects of bucolome on the pharmacokinetics and pharmacodynamics of racemic warfarin. *J Clin Pharmacol* 2001; 41: 459-64.
- 30 Li X, Zeng S. Stereoselective propranolol metabolism in two drug induced rat hepatic microsomes. *World J Gastroenterol* 2000; 6: 74-8.
- 31 Laethem ME, Belpaire FM, Wijnant P, Bogaert MG. Effect of probenecid on the enantioselective pharmacokinetics of oxprenolol and its glucuronides in the rabbit. *Pharm Res* 1995; 12: 1964-7.
- 32 Hemeryck A, De Vriendt CA, Belpaire FM. Metoprolol-paroxetine interaction in human liver microsomes; stereoselective aspects and prediction of the *in vivo* interaction. *Drug Metab Dispos* 2001; 29: 656-63.
- 33 Mikus G, Eichelbaum M, Fischer C, Gumulka S, Klotz U, Kroemer HK. Interaction of verapamil and cimetidine; stereochemical aspects of drug disposition, metabolism and drug action. *J Pharmacol Exp Ther* 1990; 253: 1042-8.
- 34 O'Reilly RA, Trager WF, Modley CH, Howald W. Stereoselective interaction of phenylbutazone with [¹²C/¹³C] warfarin pseudoracemates in man. *J Clin Invest* 1980; 65: 746-53.
- 35 Graff DW, Williamson KM, Pieper JA, Carson SW, Adams KF Jr, Cascio WE, *et al*. Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and an autonomic balance in heart failure patients. *J Clin Pharmacol* 2001; 41: 97-106.
- 36 Jamali F, Mahvar R, Pasutto FM. Enantioselective aspects of drug action and disposition; therapeutic pitfalls. *J Pharm Sci* 1989; 78: 695-714.
- 37 Bondolfi G, Lissner C, Kosel M, Eap CB, Baumann P. Fluoxetine augmentation in citalopram non-responders; pharmacokinetics and clinical consequences. *Int J Neuro-psychopharmacol* 2000; 3: 55-60.
- 38 Zhou Q, Yao TW, Yu YN, Zeng S. Stereoselective metabolism of propafenone by human liver CYP3A1 expressed in transgenic Chinese hamster CHL cells lines. *Acta Pharmacol Sin* 2001; 22: 944-8.
- 39 Eap CB, Bertschy G, Powell K, Baumann P. Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. *J Clin Psychopharmacol* 1997; 17: 113-7.
- 40 Williams ML, Wainer IW, Embree L, Barnett M, Granvil CL, Ducharme MP. Enantioselective induction of cyclophosphamide metabolism by phenytoin. *Chirality* 1999; 11: 569-74.
- 41 Herman BD, Heishaker JC, Brown MT. Ketoconazole inhibits the clearance of the enantiomers of the antidepressant reboxetine in humans. *Clin Pharmacol Ther* 1999; 66: 374-9.

42 Zhou Q, Yao TW, Zeng S. Chiral metabolism of propafenone in rat hepatic microsomes treated with two inducers. *World J Gastroenterol* 2001; 7: 830-5.

43 Hemeryck A, De Vriendt C, Belpaire FM. Effect of selective serotonin reuptake inhibitors on the oxidative metabolism of propafenone; *in vitro* studies using human liver microsomes. *J Clin Psychopharmacol* 2000; 20: 423-34.

44 Zhou HH, Anthony LB, Wood AJJ, Wilkinson GR. Induction of polymorphic 4-hydroxylation of *S*-mephenytoin by rifampicin. *Br J Clin Pharmacol* 1990; 30: 471-5.

45 Sweeny DJ, Nellans HN. Stereoselective glucuronidation of zileuton isomers by human hepatic microsomes. *Drug Metab Dispos* 1995; 23: 149-53.

46 Smith DA, Chandler MH, Shedlofsky SI, Wedlund PJ, Blouin RA. Age-dependent stereoselective increase in the oral clearance of hexobarbitone isomers caused by rifampicin. *Br J Clin Pharmacol* 1991; 32: 735-9.

47 Palylyk EL, Jamali F. Influence of sex on the stereoselective probenecid-ketoprofen interaction in the rat. *J Pharm Sci* 1994; 83: 1184-5.

48 Masubuchi Y, Yamamoto LA, Uesaka M, Fujita S, Narimatsu S, Suzuki T. Substrate stereoselectivity and enantiomer/enantiomer interaction in propranolol metabolism in rat liver microsomes. *Biochem Pharmacol* 1993; 46: 1759-65.

49 Tracy TS, Rosenbluth BW, Wrighton SA, Gonzalez FJ, Korzekwa KR. Role of cytochrome P450 2C9 and allelic variant in the 4'-hydroxylation of (*R*)- and (*S*)-flurbiprofen. *Biochem Pharmacol* 1995; 49: 1269-75.

50 Segel IH. Simple inhibition systems. In: *Enzyme kinetics*. New York: John Wiley & Sons; 1993. p 113-8

在药物动力学中立体选择性因素对药物相互作用的影响

R96 A

周 权^{1,2}, 姚彤炜¹, 曾 苏^{1,3}

(¹浙江大学药学院药物分析和药物代谢研究室, 杭州 310031; ²浙江大学医学院附属二院临床药理学研究室, 杭州 310009, 中国)

关键词 立体异构; 药物相互作用; 药物动力学

综述了近几年对映体/对映体、对映体/并用药物在药理学中的相互作用。提出药理学相互作用研究中考虑立体选择性因素具有十分重要的临床意义, 例如, 避免相互作用引起的不良反应、增加治疗效果、理解血药浓度量效关系不一致现象以及提供研究生长点以进一步探求代谢处置机理等。应加强对立体选择性药理学相互作用的研究。

(责任编辑 吴民淑)

The 12th China and Japan Joint Meeting on Pharmacology (CJP-2002)

2002, October 27-30

Shanghai, China

Info: The 12th CJP-2002 Secretariat
Department of Pharmacology
Kinki University School of Medicine
377-2 Ohno-Higashi, Osakasayama-shi,
Osaka 589-8511, Japan
E-mail pharm@med.kindai.ac.jp
Fax +81 723-66-0206