

Chiral Relevance of Stereoselective Disposition of Proton Pump Inhibitors: Comparison of Lansoprazole to Omeprazole and Pantoprazole

Jae-Gook Shin

Department of Pharmacology, Inje University College of Medicine and Clinical Pharmacology Center

It has been well known for the stereoselectivity in pharmacodynamic effects of many xenobiotics including therapeutic agents, which have led to the development of enantiomer drugs. Compared to pharmacodynamic stereoselectivity, stereoselective pharmacokinetics of each enantiomer has not been seriously considered in the development of enantiomer drugs although many reports have been demonstrated the stereoselective absorption and metabolism of racemic drug (e.g verapamil).

Esomeprazole is the first single isomer proton pump inhibitor (PPI) and is on the market as an enantiomer drug of omeprazole, a prototype PPI. It has developed mainly because of its favorable pharmacokinetic characteristics compared to its R-form and raceamte. The formation rate of hydroxy metabolite from S-omeprazole is lower than fro R-omeprazole, and the sum if intrinsic clearance of the 3 major metabolites for S-omeprazole is one-third of that for R-form *in vitro*, suggesting lower clearance of omeprazole *in vivo*. Since the formation of hydroxyomeprazole is mainly mediated by cytochrome P450 2C19 (CYP2C19), a representative CYP isomer showing genetic polymorphism, it has been well known for the interindividual variation if disposition and clinical effects of racemate omeprazole. Regarding this issue, esomeprazole is superior to R-omeprazole, because the S-form is minimally converted to it hydroxy metabolite by genetically polymorphic CYP2C19 compared to R-form. There hence, S-omeprazole produces greater and more consistent clinical effects in the suppression of gastric acid and secretion tan those of R-form.

Lansoprazole is a structural analogue of omeprazole, but its catalytic sites are different to those of omeprazole, which suggests stereoselective disposition of lansoprazole should be evaluated and compared to those of omeprazole in order to understand the clinical meaning of stereoselectivity of lansoprazole. we evaluated the effects of CYP2C19 genetic polymorphism on the disposition of lansoprazole enantiomer in order to evaluate the contribution of lansoprazole enantiomers in order to evaluate the contribution of CYP2C19 in the stereoselective metabolism of lansoprazole. From this study, we found that the stereoselective disposition of lansoprazole was influenced by CYP2C19 genetics polymorphism, but the effects of CYP2C19 activity seemed to be less significant than that of omeprazole and pantoprazole. Of interesting, the disposition of lansoprazole enantiomers appeared to

be caused by stereoselective protein binding, as well as stereoselective metabolism of lansoprazole. Omeprazole has not reported to show stereoselective protein binding.

Our *in vitro* microsomal incubation studies demonstrated the stereoselective formation of major metabolites such as hydroxylansoprazole and lansoprazolesulfone catalyzed by CYP2C19, CYP3A4, and CYP2C9. However, the CYP2C19-catalyzed metabolite formation was not so significantly different between two enantiomers (mean Clint of S- and R-forms : 179.6 vs. 143.3 ml/min), but the intrinsic clearance for CYP3A4 catalyzed sulfone formation from S-form was 5.5 fold greater than that from R-form (79.2 vs 14.4 ml/min). These results suggest that the disposition of lansoprazole is less influenced by CYP2C19 genetic polymorphism, and support the clinical data in which the plasma concentration of R-form was consistently higher than that of S-form regardless of CYP2C19 genotype (EM or PM). In addition, lansoprazole enantiomers showed stereoselective inhibition of CYP2C19 *in vitro*, suggesting different effects of both enantiomers on the drug interaction potential and the accumulation of lansoprazole in the body after repeated dose.

In conclusion, the stereoselective disposition of lansoprazole seems to be less significant compared to omeprazole, and the development of enantiomer drug seems not to improve significantly the pharmacokinetics of racemic lansoprazole in comparison to the case of omeprazole.