Is the required therapeutic effect always achieved by racemic switch of proton-pump inhibitors?

Quan Zhou, Xiao-Feng Yan, Wen-Sheng Pan, Su Zeng

Abstract

Many of the drugs currently used in medical practice are racemates. The enantiomers of a racemic drug differ in pharmacodynamics and/or pharmacokinetics, thus in some cases it is preferable to develop pure enantiomers by racemic switch. In a recent study by Pai et al., dexrabeprazole [R(+)-rabeprazole] (10 mg) was found to be more effective than rabeprazole (20 mg) in the treatment of gastroesophageal reflux disease. We read with great interest in this study and discussed whether such racemic switch would be applicable to other proton-pump inhibitors (PPIs). A literature review indicates that stereoselective pharmacokinetics, rather than stereoselective pharmacological activity, is the main cause of differences in clinical efficacy between pure enantiomer and racemic PPI. Racemic switches of PPI provide the therapeutic advantages such as reducing metabolic load on the body, simplifying pharmacokinetics, providing benefit to the non-responders to standard dose of racemate, more homogenous response to treatment providing benefit to the non-responders to standard dose of racemate, more homogenous response to treatment. Further studies in quantitative structure-activity relationships (QSARs) are needed to address the fact that the preferred enantiomer of PPI is not always in the same absolute configuration, i.e., S-form is for omeprazole, pantoprazole and tenatoprazole whereas R-form is for lansoprazole and rabeprazole.

Key words: Proton-pump inhibitors; Enantiomer; Racemate; Stereoisomerism; Racemic switch; Pharmacokinetics; Pharmacodynamics; Cytochrome P450; Genotype

TO THE EDITOR

We read with great interest in the study by Pai et al., who compared the therapeutic outcomes of dexrabeprazole (10 mg) with rabeprazole (20 mg) in the treatment of gastroesophageal reflux disease (GERD). The results showed that efficacy of dexrabeprazole (10 mg) is better than rabeprazole (20 mg), with regards to improvement/healing of endoscopic lesions and relief from symptoms of regurgitation. Rabeprazole is a racemic mixture of two enantiomers, R(+)-enantiomer and S(-)-enantiomer in 1:1 proportion. Dexrabeprazole is the chirally pure R(+)-enantiomer which is more effective than the racemate and S(-)-rabeprazole in inhibiting acid-related gastric lesions in rats. A superior pharmacokinetic profile, i.e., higher maximal plasma concentrations (Cmax) and area under the curve (AUC), was observed with R(+)-rabeprazole compared to its S(-)-enantiomer. Dexrabeprazole was launched as Dexpure® by Emcure Pharmaceuticals Ltd in September 2007.

Racemic switch stands for the development in single-enantiomer form of a drug that was first approved as a raceme. We have reported that the enantiomers of a racemic drug differ in pharmacodynamics and/or pharmacokinetics as a consequence of stereoselective interaction with optically active biological macromolecules, and the decision to perform racemic switch should be based on enough evidence. As far as proton-pump inhibitors (PPIs) are concerned, is the required therapeutic effect always achieved by racemic switch of proton-pump inhibitors?
effect achieved by racemic switch? We would discuss and share our perspectives below.

Omeprazole, lansoprazole, pantoprazole and rabeprazole possess asymmetric sulfur in their chemical structure and have been typically used in clinical practice as a racemic mixture. Esomeprazole, S(-)-enantiomer of omeprazole, is the first enantiomerically pure PPI and the compound is now marketed as Nexium®. The enantiomers of omeprazole produce similar pharmacological effects. The metabolic profile of S(-)-omeprazole is distinct from that of R(+)-omeprazole. Both enantiomers are metabolized by CYP2C19, but the enzyme plays a lower role (73% vs 98%) in the metabolism of the S(-)-enantiomer. As a result, the pharmacokinetic profile of the S(-)-enantiomer is less dependent on CYP2C19 genotype, hence leading to a less interpatient variability in clearance than omeprazole. \( \frac{AUC_{\text{po(PM)}}}{AUC_{\text{po(EM)}}} \), the ratio of \( AUC \) after oral administration (\( AUC_{\text{po}} \)) derived from poor metabolizers (PM) and extensive metabolizers (EM), is 3.0 and 7.4 for esomeprazole and omeprazole, respectively. Moreover, S(-)-omeprazole is cleared more slowly and has an improved oral bioavailability (81%-98% vs 35%-65%), leading to the greater inhibition of gastric acid secretion compared to omeprazole.

Lansoprazole is extensively metabolized by CYP2C19 and CYP3A4 in the liver. CYP2C19 genotype influences the disposition of S(-)-lansoprazole to a greater extent than the R(+)-enantiomer, resulting in less interpatient variability in clearance with R(+)-lansoprazole compared to lansoprazole. Both enantiomers of lansoprazole possess equal potency. Therefore, the use of R(+)-lansoprazole alone would be highly desirable for clinical application.

Pantoprazole is a racemic mixture of two enantiomers. Animal studies confirmed that S(-)-pantoprazole is more potent than R(+)-enantiomer in inhibiting acid-related lesions. Pantoprazole is metabolized mainly by CYP2C19 followed by sulfation and, to a lesser extent, by CYP3A4. The enantiomers of pantoprazole are differentially affected by CYP2C19 genotype. The \( \frac{AUC_{\text{po(PM)}}}{AUC_{\text{po(EM)}}} \) ratio is 11, 2.5 and 6.0 for the R(+)-enantiomer, S(-)-enantiomer and pantoprazole, respectively. The pharmacokinetics of S-pantoprazole depend less on CYP2C19 genotype, resulting in uniform therapeutic plasma levels of the drug, thus providing benefit to the non-responders to standard dose of racemate, more homogenous response to treatment and better efficacy with equal safety.

In conclusion, stereoselective pharmacokinetics, rather than stereoselective pharmacological activity, is the main cause of differences in clinical efficacies between pure enantiomer and racemic PPI (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole and tenatoprazole). Racemic switches of PPIs provide therapeutic advantages such as reducing metabolic load on the body, simplifying pharmacokinetics, providing benefit to the non-responders to prior standard dose of racemate, more homogenous response to treatment and better efficacy with equal safety. Further studies on the quantitative structure-activity relationships (QSARs) are needed to address the fact that the preferred PPI enantiomer is not always in the same absolute configuration, i.e., S-form is for omeprazole, pantoprazole and tenatoprazole whereas R-form is for lansoprazole and rabeprazole.

REFERENCES

1 Pai V, Pai N. Randomized, double-blind, comparative study of dexrabeprazole 10 mg versus rabeprazole 20 mg in the treatment of gastroesophageal reflux disease. World J Gastroenterol 2007; 13: 4100-4102
2 Bodhankar SL, Jain BB, Ahire BP, Daude RB, Shirole PP. The effect of rabeprazole and its isomers on aspirin and histamine-induced ulcers in rats. Indian J Pharmacol 2006; 38: 357-358
3 Miura M. Enantioselective disposition of lansoprazole and rabeprazole in human plasma. Yakugaku Zasshi 2006; 126: 395-402
4 Zhou Q, Yao TW, Yu YN, Zeng S. Concentration dependent stereoselectivity of propafenone N-depropylation metabolism with human hepatic recombinant CYP1A2. Pharmazie 2003; 58: 651-653
5 Zhou Q, Yao TW, Zeng S. Effects of stereochemical aspects on drug interaction in pharmacokinetics. Acta Pharmacol Sin 2002; 23: 285-292
6 Andersson T, Rohss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther 2001; 15: 1563-1569
7 Rodrigues AD, Rushmore TH. Cytochrome P450 pharmacogenetics in drug development: in vitro studies and clinical consequences. Curr Drug Metab 2002; 3: 289-309
8 Miura M, Tada H, Yasui-Furukori N, Uno T, Sugawara K, Tateishi T, Suzuki T. Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, www.wjgnet.com
5-hydroxylansoprazole, in relation to CYP2C19 genotypes. *Eur J Clin Pharmacol* 2004; 60: 623-628

9 Cao H, Wang MW, Sun LX, Ikejima T, Hu ZQ, Zhao WH. Pharmacodynamic comparison of pantoprazole enantiomers: inhibition of acid-related lesions and acid secretion in rats and guinea-pigs. *J Pharm Pharmacol* 2005; 57: 923-927

10 Tanaka M, Yamazaki H, Hakusui H, Nakamichi N, Sekino H. Differential stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor in extensive and poor metabolizers of pantoprazole—a preliminary study. *Chirality* 1997; 9: 17-21

11 Pai VG, Pai NV, Thacker HP, Shinde JK, Mandora VP, Erram SS. Comparative clinical trial of S-pantoprazole versus racemic pantoprazole in the treatment of gastro-esophageal reflux disease. *World J Gastroenterol* 2006; 12: 6017-6020

12 Charbit S, Cohen A, Ficheux H, Homerin M, Schutze F, Taccoen A, inventor; SIDEM PHARMA (LU), assignee. Enantiomer (-) of tenatoprazole and the therapeutic use thereof. United States Patent 7034038. 2006 April 25