Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst216P.pdf

Effect of fluoxetine on the enantioselective pharmacokinetics of fexofenadine in parturients including *in vivo* and *ex vivo* placental transfer models.

P-glycoprotein (P-gp) develops an important role on absorption, distribution and elimination of drugs that are its substrates (1). Fexofenadine, market as a racemic mixture, is used to treat seasonal allergic rhinitis and chronic urticarial during pregnancy (2). (S)-(-)-fexofenadine has a greater affinity to P-gp as compared with the (R)-(+)-fexofenadine. It is commonly proposed as a probe drug to assess *in vivo* the activity of P-gp (3). Fluoxetine, a chiral drug used to treat depression during pregnancy, is considered as a competitive potent human P-gp inhibitor, *in vitro* studies (4). The aim of our study was to assess the effect of fluoxetine on the enantioselective pharmacokinetic of fexofenadine in parturients and their relationships with *in vivo* and *ex vivo* placental transfer.

Eight healthy pregnant women at term received a single oral dose of 60 mg racemic fexofenadine 2-3 h before delivery (control group) and another group of eight parturients received 40 mg racemic fluoxetine 3 h before 60 mg racemic fexofenadine administration (interaction group). Serial blood and urine samples were collected for 48 h following fexofenadine administration. Maternal and umbilical cord blood samples were collected at delivery in order to evaluate the placental transfer. The placental transfer of fexofenadine enantiomers was also assessed in 4 placental lobule using the *ex vivo* placental perfusion model. Fexofenadine enantiomers in plasma, urine and placental perfusate and fluoxetine and norfluoxetixe enantiomers in plasma were measured using liquid chromatography–tandem mass spectrometry. The results, reported as median and IQR, were compared using the Mann-Whitney and Wilcoxon tests ($p \leq 0.05$).

In the Control group, fexofenadine pharmacokinetics is enantioselective with higher $AUC_{0-\infty}$ (423.20 vs. 267.67 ng.h/mL) and lower Vd/F (621.37 vs. 889.83 L), oral clearance (CL/F) (66.20 vs. 105.05 L/h) and renal clearance (CL_R/F) (5.25 vs. 8.78 L/h) for (R)-(+)-fexofenadine than those of (S)-(-)-fexofenadine. There was limited placental transfer of fexofenadine enantiomers, as evidenced by fetal-to-maternal ratio of 0.16. R-(+)/S-(-) ratios were 1.7 in maternal and fetal compartments, which suggests that placental P-gp does not have the ability of chiral discrimination. Fluoxetine administration significantly increased $AUC_{0-\infty}$ (376.09 vs. 267.67 ng.h/mL) and reduced both CL/F (74.37 vs. 105.05 L/h) and CL_R (3.50 vs. 8.78 L/h) only for the (S)-(-)-fexofenadine eutomer as compared to Control group. Fluoxetine does not alter umbilical vein/maternal vein ratios and fetal and maternal R-(+)/S-(-) ratios. Fexofenadine enantiomers had slow and limited placental perfusion as characterized by fetal-to-maternal ratios of 0.18. R-(+)/S-(-) ratios were 1.0 (maternal and fetal compartments), which confirm that P-glycoprotein does not possess the ability of chiral discrimination. Fluoxetine does not affect fetal-to-maternal ratios, placental transfer rate and R-(+)/S-(-) ratios in maternal and fetal reservoirs. The *ex vivo* model predict *in vivo* placental fexofenadine enantiomers transfer as shown by similar fetal-to-maternal ratios.

In conclusion, fluoxetine enantioselectively inhibits intestinal P-gp and yet does not inhibit placental P-gp. This study indicates that the enantioselective pharmacokinetics of fexofenadine in parturients is due to intestinal P-gp-mediated transport and its enantioselectivity is altered by fluoxetine, a P-gp inhibitor.

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