Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue3abst090P.pdf

Effect of fluoxetine on the transplacental transfer of fexofenadine enantiomers in parturients

L PINTO[1], RC CAVALLI[2], MP MARQUES[1], EC MOISÉS[2], VL LANCHOTE[1]. [1]School of Pharmaceutical Sciences of Ribeirão Preto - University of São Paulo, Ribeirão Preto, Sao Paulo, Brazil, [2]Ribeirão Preto Medical School - University of São Paulo, Ribeirão Preto, Sao Paulo, Brazil

Placental P-glycoprotein (P-gp) is an ABC transporter with an important role on the transplacental pharmacokinetic of drugs during pregnancy (1). Fexofenadine, a second-generation H_1-antihistamine, is a substrate of P-gp and organic anion transporter polypeptides (OATPs). Fexofenadine is commonly proposed as a probe drug to assess the activity of P-gp, *in vivo* (2). Fluoxetine, a selective serotonine reuptake inhibitor, is considered as a competitive potent human P-gp inhibitor (3), but not an inhibitor of OATPs (4), *in vitro*. Drug-drug interactions on the placental P-gp may affect the fetus drug exposure (5). The aim of our study was to evaluate the effect of fluoxetine on the stereoselective transplacental transfer of fexofenadine in parturients. Healthy pregnant women at term received a single oral dose of 40 mg racemic fluoxetine and 3 hours later of 60 mg racemic fexofenadine (group B; n=6) or received only a single oral dose of 60 mg racemic fexofenadine (group A; n=8). After 2 hours of fexofenadine administration, blood samples (5 mL) from maternal and umbilical cord venous were simultaneously collected at delivery. Fexofenadine enantiomers plasma concentrations were measured using liquid chromatography–tandem mass spectrometry. The results, reported as median, were compared using the Mann-Whitney test ($p \leq 0.05$). Fetal-to-maternal plasma concentration ratios show limited transfer of *R*-(+)- and *S*-(-)-fexofenadine enantiomers across the human placenta, as evidenced by values of 0.175 and 0.155 for group B and 0.169 and 0.174 for group A (Table 1), respectively. No significant differences in the plasma concentration ratios with or without administration of fluoxetine was observed for both *R*-(+)- and *S*-(-)-enantiomers (Table 1), while plasma concentrations of *R*-(+)-fexofenadine were greater than *S*-(-)-enantiomer in both mother and fetus, with the *R*-(+):*S*-(-) ratios of approximately 1.75.

Table 1 Umbilical/maternal venous plasma fexofenadine concentration ratios following a single oral dose of 60 mg racemic fexofenadine associated (group B) or not (group A) with a single oral dose of 40 mg fluoxetine. Data are reported as median and IQR.

Without fluoxetine (group A)		**With fluoxetine (group B)**	
R-(+)	*S*-(-)	*R*-(+)	*S*-(-)
0.169	0.174	0.175	0.155
(0.11-0.21)	(0.10-0.20)	(0.14-0.22)	(0.14-0.21)

***** $p \leq 0.05$, Mann-Whitney test for unpaired data (with and without fluoxetine)

In conclusion, the results of this study demonstrate that a single oral dose of 40 mg fluoxetine does not affect the placental transfer of fexofenadine enantiomers in pregnant women at term. The limited transplacental passage of fexofenadine was stereoselective with or without fluoxetine administration, with umbilical and maternal plasma accumulation of the *R*-(+)-enantiomer.

(1) Staud F *et al.* (2012). *J Drug Target* **20**: 736-763.

(2) Miura M and Uno T (2010). *Expert Opin Drug Metab Toxicol* **6**: 69-74.

(3) Weiss J *et al.* (2003). *J Pharmacol Exp Ther* **305**: 197-204.

(4) Karlgren M *et al.* (2012). *J Med Chem* **55**: 4740−4763.

(5) Rubinchik-Stern M and Eyal S (2012). *Front Pharmacol* **3**: 1-7.