Effect of itraconazole on the pharmacokinetics of bupivacaine enantiomers in healthy volunteers†

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We studied seven healthy volunteers given itraconazole 200 mg orally or placebo, once daily for 4 days, in a crossover study. On day 4, racemic bupivacaine 0.3 mg kg\(^{-1}\) was given i.v. over 60 min and venous plasma samples were collected for 23 h. Plasma concentrations of R- and S-bupivacaine, itraconazole and hydroxyitraconazole were measured. Itraconazole reduced the clearance of R-bupivacaine by 21\% (P<0.05) and that of S-bupivacaine by 25\% (P<0.05), while it had no significant effect on other pharmacokinetic variables of the enantiomers. Reduction of bupivacaine clearance by itraconazole probably increases the steady-state concentration of bupivacaine enantiomers by 20–25\%. This should be taken into account in the concomitant use of bupivacaine and itraconazole, although the interaction seems to be of limited clinical significance.

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Bupivacaine is an amide-type local anaesthetic administered as a racemic mixture of two optically active enantiomers, R-bupivacaine and S-bupivacaine. R-bupivacaine is mainly responsible for the cardiotoxicity of bupivacaine, but it has also greater clearance compared with S-bupivacaine. The isoforms of the enzymes catalysing bupivacaine metabolism are still unknown, but bupivacaine is related structurally to another amide-type local anaesthetic, ropivacaine, which is metabolized by cytochromes P450 1A2 (CYP1A2) and CYP3A4. As the azole antimycotic itraconazole inhibits CYP3A4 and can increase the concentrations of drugs metabolized by CYP3A4, we investigated the possible effect of itraconazole on the metabolism of bupivacaine enantiomers.

Methods and results

We calculated that seven subjects would be required to demonstrate a 20% difference in values for clearance of the enantiomers at a level of significance of $P=0.05$ and power of 80\%. After obtaining institutional approval and informed written consent, we studied three women and four men, aged 21–27 yr, weighing 59–95 kg, in a randomized, double-blind, crossover study of two phases at intervals of 4 weeks.

The subjects were given itraconazole 200 mg (Sporanox, Janssen Pharma, Beerse, Belgium) orally or placebo, once daily for 4 days at 08:00. RS-bupivacaine hydrochloride (Marcain, Astra, Finland) 0.3 mg kg\(^{-1}\) was given i.v. over 60 min on day 4, starting exactly 1 h after ingestion of itraconazole or placebo. The ECG was monitored continuously for 6 h after the beginning of infusion of bupivacaine and symptoms of possible CNS toxicity were recorded by frequent questioning. Volunteers fasted for 2 h before the beginning of infusion of bupivacaine and had a standard meal 4 h and 7 h afterwards. Ingestion of alcohol, coffee, tea and cola was not allowed during the test days, nor was smoking permitted.

Venous blood samples (10 ml) were obtained into EDTA tubes immediately before and 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 23 h after the beginning of infusion of bupivacaine. Plasma concentrations of bupivacaine enantiomers were measured by high performance liquid chromatography (HPLC). The limit of detection for both enantiomers was 1.0 ng ml\(^{-1}\). Between-day coefficients of variation (cv) were 11.5\%, 7.5\% and 5.9\% for R-bupivacaine at plasma concentrations of 4.25, 24.4 and 106 ng ml\(^{-1}\), respectively ($n=6$ for all concentrations). Corresponding values for S-bupivacaine were 5.8\%, 8.2\% and 5% at plasma concentrations of 4.46, 25.4 and 103 ng ml\(^{-1}\), respectively ($n=6$ for all concentrations). Concentrations of itraconazole and hydroxyitraconazole were measured by liquid chromatography.

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trations of itraconazole and hydroxyitraconazole were measured by HPLC.\(^3\)

Values for plasma clearance (\(Cl\)) and steady state volume of distribution (\(V^{ss}\)) of bupivacaine enantiomers were calculated by non-compartmental methods. The elimination rate constant (\(k_{el}\)) was measured by regression analysis and the elimination half-life (\(T_{1/2}\)) was calculated from \(T_{1/2} = \ln 2 / k_{el}\). AUC\(_{0–23\, \text{h}}\) was determined for itraconazole and hydroxyitraconazole using the trapezoidal rule.

Pharmacokinetic variables between the phases were compared using Wilcoxon’s matched pairs test. The possible relationship between the ratio of the AUC\(_{0–23\, \text{h}}\) of bupivacaine enantiomers during the itraconazole phase to that during the placebo phase and the AUC\(_{0–23\, \text{h}}\) of itraconazole was investigated using the Pearson product moment correlation coefficient. Differences were regarded as statistically significant if \(P<0.05\).

None of the volunteers reported symptoms of toxicity and no ECG abnormalities were observed. Itraconazole reduced the clearance of R-bupivacaine from mean 6.6 (s.d 2.2) to 5.2 (1.8) ml min\(^{-1}\) kg\(^{-1}\) (\(P<0.05\)) and that of S-bupivacaine from 4.8 (1.4) to 3.6 (0.8) ml min\(^{-1}\) kg\(^{-1}\) (\(P<0.05\)). Values of \(V^{ss}\) and \(T_{1/2}\) for R-bupivacaine were 1.3 (0.3) litre kg\(^{-1}\) and 4.2 (1.7) h for placebo and 1.3 (0.5) litre kg\(^{-1}\) and 4.3 (2.2) h for itraconazole. Corresponding values for S-bupivacaine were 0.9 (0.2) litre kg\(^{-1}\) and 3.5 (1.3) h for placebo and 1.0 (0.3) litre kg\(^{-1}\) and 4.2 (1.6) h for itraconazole, respectively. The effects of itraconazole were not statistically significant (Fig. 1). The mean value of \(V^{ss}\) of R-bupivacaine was approximately 35% greater than that of S-bupivacaine during both phases (\(P<0.05\)). Mean plasma concentration of itraconazole 1 h after the end of infusion of bupivacaine was 328 (54) ng ml\(^{-1}\). There was no linear correlation between the AUC\(_{0–23\, \text{h}}\) values of itraconazole and itraconazole-induced changes in AUC\(_{0–23\, \text{h}}\) values of the bupivacaine enantiomers.

**Comment**

We have shown that itraconazole reduced the clearance of both enantiomers of bupivacaine by approximately 20–25% while other pharmacokinetic variables did not change significantly. The magnitude of the interaction was similar between R-bupivacaine and itraconazole and between S-bupivacaine and itraconazole.

Previous studies showed that propranolol reduced the clearance of racemic bupivacaine by 35%.\(^5\) However, there is no information on the effect of propranolol on individual bupivacaine enantiomers. _In vitro_, propranolol has an inhibitory effect on CYP2D6 and to a lesser degree on CYP1A2. Because propranolol reduces liver blood flow,\(^5\) and because bupivacaine is a drug with an extraction ratio of 0.2–0.4,\(^1\) both enzyme inhibition and reduction of liver blood flow may play a role in its interaction with bupivacaine. However, using the ‘well-stirred’ model of hepatic metabolism,\(^6\) it can be estimated that propranolol changes the clearance of bupivacaine mainly by enzyme inhibition.

Itraconazole is a potent and relatively specific inhibitor of CYP3A4 at concentrations measured in the present study,\(^3\) and it is not known to change liver blood flow in humans. Because itraconazole reduced the elimination of bupivacaine, we can conclude that CYP3A4 also contributes to elimination of bupivacaine. However, the relative importance of different CYP enzymes in the elimination of bupivacaine cannot be deduced on the basis of our and previous studies.\(^5\) Moreover, as CYP3A4-mediated metabolism may assume greater importance at higher bupivacaine doses, the low dose used may underestimate the magnitude of drug interaction after higher doses. For ethical reasons, however, we wished to use a small dose of bupivacaine.

The pharmacokinetics of the bupivacaine enantiomers during the placebo phase were in good agreement with earlier studies.\(^1\) Because of the smaller clearance and volume of distribution, concentrations of S-bupivacaine were higher than those of R-bupivacaine (Fig. 1). The difference in the volume of distribution between the enantiomers probably reflects the difference in plasma protein binding. We did not measure free concentrations of the enantiomers because that would have necessitated higher doses of bupivacaine. However, because bupivacaine is bound mainly to alpha\(_1\) acid glycoprotein at these concentrations, it is unlikely that itraconazole would have affected the protein binding of bupivacaine.

The cardiotoxicity of bupivacaine is greater than that of other local anaesthetics. The 20–25% decrease in clearance of bupivacaine enantiomers by itraconazole increases the steady-state plasma concentrations of the enantiomers by 20–25%. This should be taken into account when itraconazole is used concomitantly with bupivacaine, although the interaction seems to be of limited clinical significance.
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