SHORT COMMUNICATIONS

The CYP 3A4 inhibitor itraconazole has no effect on the pharmacokinetics of i.v. fentanyl†

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Summary

We studied 10 healthy volunteers given itraconazole 200 mg orally, once daily or placebo for 4 days in a crossover study. i.v. fentanyl 3 µg kg\(^{-1}\) was given on day 4. Plasma concentrations of fentanyl were measured by radioimmunoassay and ventilatory frequency and peripheral arterio-lar oxygen saturation were also measured. Fentanyl-induced subjective effects (drowsiness, itching, nausea, performance, feeling of drug effect) were measured by visual analogue scales. The pharmacokinetics and pharmacodynamics of fentanyl were similar after both itraconazole and placebo. Thus although itraconazole is a strong inhibitor of the cytochrome 3A enzymes responsible for metabolism of fentanyl in vitro, it did not affect the i.v. pharmacokinetics of fentanyl in humans. (Br. J. Anaesth. 1998; 81: 598–600).

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Fentanyl is a synthetic opioid and its metabolism is mediated by CYP 3A4. As there is no information on the effect of CYP 3A4 inhibitors on the metabolism of fentanyl in humans, we have studied the possible interaction of the CYP 3A4 inhibitor, itraconazole, with i.v. fentanyl.

Methods and results

Based on previous studies, we calculated that eight subjects would be required to demonstrate a 20% difference in values for fentanyl clearance (which was regarded as the primary pharmacokinetic end-point) at a level of significance of \(P = 0.05\) and a power of 80%. Thus after obtaining approval from our institute and written informed consent, we studied 10 healthy volunteers (five women), aged 19–24 yr, weighing 53–75 kg. None was receiving regular medications except for two females who were using contraceptive steroids.

A randomized, double-blind, cross-over study design was used at intervals of 4 weeks. Subjects were given either itraconazole 200 mg (Sporanox, Janssen, Belgium) orally, once daily at 0700 or placebo for 4 days. On day 4, fentanyl (Fentanyl 50 µg ml\(^{-1}\), Janssen, Belgium) 3 µg kg\(^{-1}\) was given i.v., 1 h after oral administration of itraconazole/placebo over 2 min.

Venous blood samples were obtained immediately before injection of fentanyl and 0.25, 0.5, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 24 h after administration. Fentanyl concentrations were analysed by a specific radioimmunoassay method. The sensitivity of the method for fentanyl was 0.1 ng ml\(^{-1}\) and the coefficient of variation (cv) was 11.8% at mean 0.179 ng ml\(^{-1}\), 8.1% at mean 0.596 ng ml\(^{-1}\) and 7.6% at mean 2.98 ng ml\(^{-1}\) (\(n = 6\) at each concentration). Concentrations of itraconazole were analysed by HPLC.

Standard non-compartmental methods were used to calculate plasma clearance (\(Cl\)) and apparent steady state volume of distribution (\(V_{ss}\)) of fentanyl. Elimination half-lives (\(T_{1/2}\)) were calculated using log-linear regression. Peripheral arteriolar oxygen saturation (\(S_{\text{aO}}\)) was measured continuously during the first 2 h after administration of fentanyl, and thereafter \(S_{\text{aO}}\) was recorded at blood sampling together with ventilatory frequency and heart rate until 10 h after administration of fentanyl. Subjective effects were recorded on five horizontal visual analogue scales for 10 h at blood sampling (no effects of the drug—very strong effects of the drug; alert—drowsy; very good performance—very poor performance; no nausea—lots of nausea; no itching—lots of itching).

Pharmacokinetic and pharmacodynamic variables between phases were compared using the Wilcoxon matched pairs test. Differences were regarded as statistically significant if \(P < 0.05\).

There were no statistically significant differences in any of the pharmacokinetic or pharmacodynamic variables between phases (fig. 1). Values of \(Cl\), \(V_{ss}\) and \(T_{1/2}\) for fentanyl during the placebo phase were mean 23.9 (SD 9.9) ml kg\(^{-1}\) min\(^{-1}\), 5.2 (1.9) litre kg\(^{-1}\) and 4.4 (2.3–6.9) h (median (range)). The corresponding values during the itraconazole phase were 22.0 (12.7) ml kg\(^{-1}\) min\(^{-1}\), 5.4 (1.9) litre kg\(^{-1}\) and 4.8 (2.4–18.2) h, respectively. The elimination half-life was not calculated when fentanyl concentration decreased to less than the detection limit but then exceeded this limit later (one subject in the placebo phase and one subject in the itraconazole phase). The concentration of itraconazole at the time of administration of fentanyl during the itraconazole phase was
Interaction of itraconazole with fentanyl

Itraconazole at a concentration of 80 ng ml\(^{-1}\) effectively inhibits CYP 3A4.5

Comment

In our study, itraconazole had no statistically significant effects on the pharmacokinetics or pharmacodynamics of fentanyl. The mean value for \(V^\infty\) was virtually unchanged by concomitant administration of itraconazole, and the small 9% decrease in mean fentanyl \(Cl\) was not statistically significant. All pharmacological effect vs time curves were essentially the same between the two phases.

Fentanyl is metabolized by the CYP3A4 isoenzyme in human liver.1 Itraconazole is a strong inhibitor of CYP3A4 \textit{in vitro} and it has been shown to markedly reduce the clearance of substrates of CYP3A4, such as midazolam\(^2\) in humans. We were unable to identify any effects of itraconazole on fentanyl elimination. Compared with alfentanil, the elimination of which is strongly inhibited by, for instance, concomitant therapy with the macroline antibiotic troleandomycin,\(^6\) there appears to be some discrepancy between fentanyl studies \textit{in vitro} and in humans. In contrast, similar results have also been obtained with sufentanil, which is metabolized \textit{in vitro} by CYP3A4 but whose pharmacokinetics in humans are also virtually unaffected by prior administration of the enzyme inhibitor, erythromycin.\(^1\)

The different effects of the inhibitors of CYP3A4 on the pharmacokinetics of fentanyl, alfentanil and sufentanil in humans can be explained by the differences in the pharmacokinetics of these opioids. Fentanyl, alfentanil and sufentanil are eliminated mainly by metabolism,\(^2\) but hepatic extraction ratios vary greatly. Alfentanil has an extraction ratio of 0.3–0.5 and the corresponding values for fentanyl and sufentanil are 0.8–1.0 and 0.7–0.9, respectively.\(^5\) Because fentanyl has a very high extraction ratio, it can be estimated that even rather large changes in the activity of the enzymes metabolizing fentanyl are unlikely to significantly affect its pharmacokinetics. However, clearance of alfentanil is readily altered when the activity of CYP3A4 enzymes change.\(^6\)

In our study, small doses of fentanyl were used. Because healthy volunteers were studied, higher doses would have necessitated the use of opioid antagonists or alternatively the study could have been performed during clinical anaesthesia. However, both of these alternatives might have disturbed the assessment of the possible interaction between itraconazole and fentanyl, as all drugs administered concomitantly may interact with each other. Therefore, we chose to study healthy volunteers using a fentanyl dose which is commonly used during induction of general anaesthesia. Although our study did not allow definitive conclusions on the possible effect of oral itraconazole on higher doses of fentanyl, it can be anticipated that itraconazole causes no major changes in the pharmacokinetics of the usual doses of fentanyl administered during surgery. In these instances, fentanyl can be used in normal doses with itraconazole and probably also with other CYP3A4 inhibitors. Further studies are needed to evaluate the effect of itraconazole on high-dose fentanyl anaesthesia.
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References


