

Pharmacokinetic interaction between the opioid-analgesic fentanyl and the CYP3A inhibitor ketoconazole

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Purpose

Fentanyl is an opioid analgesic with high potency which is widely used in pain management as transdermal fentanyl. It is metabolized by cytochrome P450 3A4 (CYP3A4) to inactive metabolites. The concomitant administration of CYP3A inhibitors may cause dangerous drug interactions and can lead to severe and fatal side effects of fentanyl (eg, respiratory depression) in chronic pain patients (Mercadante 2002, Hallberg 2006, Horton 2009). Fentanyl has also been suggested a minor inhibitor of CYP3A (Hase 1997). The purpose of this mechanistic study was to investigate the influence of CYP3A inhibition by ketoconazole on the pharmacokinetics of fentanyl in healthy volunteers.

Method

We conducted a prospective, open-label, randomized, crossover study (EudraCT-No: 2010-019171-29) with 16 healthy volunteers. Fentanyl was administered intravenously using a dose adapted to bodyweight (5 µg per kg). The opioid antagonist naloxone (2 x 0.2 mg iv) was given simultaneously to avoid the side effects of fentanyl (especially respiratory depression). The potent CYP3A inhibitor ketoconazole (200 mg bid) was given orally over two days starting the day before the fentanyl infusion. Midazolam (3 mg orally) was administered as CYP3A probe drug in order to monitor CYP3A activity during fentanyl and fentanyl plus ketoconazole. Each study part was followed by a wash-out period of 6 days. The 24-hour concentration-time curves and clearances of fentanyl and its metabolites were calculated using noncompartmental models. The partial metabolic clearance of midazolam as a measure of CYP3A activity was determined according to Katzenmaier 2011.

Results

The area under the fentanyl plasma concentration time curve (AUC_{0-24h}) was 13.0±4.5 h*nmol/l. Ketoconazole increased the fentanyl AUC_{0-24h} to 16.8±6.6 h*nmol/l ($P<.05$) and reduced the total body clearance of fentanyl (0-24 h) from 1522±427 ml/min (20.9±6.0 ml/min*kg) to 1223±435 ml/min (16.7±5.5 ml/min*kg), $P<.05$. The metabolic clearance of fentanyl to the main metabolite norfentanyl was significantly reduced from 322±201 ml/min to 60.9±34.3 ml/min by ketoconazole ($P<.001$). The renal clearance of fentanyl was not affected by ketoconazole. Maximal plasma concentration of norfentanyl was reduced from .78±.38 nmol/l to .19±.15 nmol/l and norfentanyl AUC_{0-24h} was reduced from 10.3±6.3 h*nmol/l to 2.4±1.8 h*nmol/l under ketoconazole (both $P<.001$). The amounts excreted of the metabolites norfentanyl and hydroxynorfentanyl (from 0-24 h) were significantly decreased during ketoconazole from 21.4±11.5% of the administered fentanyl dose to 5.4±3.7% (norfentanyl, $P<.001$) and from .87±0.58% of the administered fentanyl dose to .17±.38 (hydroxynorfentanyl, $P<.01$). The renal clearance of norfentanyl (from 0-24 h) and the amount excreted of the metabolite despropionylfentanyl were not altered by ketoconazole administration. There was no statistically significant influence of fentanyl on the pharmacokinetics of midazolam suggesting that fentanyl is not an inhibitor of CYP3A, whereas ketoconazole significantly inhibited midazolam clearance by 88%. Additional doses of .2 mg Naloxone were needed in 6 cases of moderate respiratory depression (one during fentanyl and 5 during fentanyl plus ketoconazole) that could not be controlled by behavioral measures/ somatic treatment.

Conclusions

Fentanyl metabolism was significantly altered by coadministration of the CYP3A inhibitor ketoconazole leading to an increased exposure to fentanyl and reduced clearance. Ketoconazole decreased the formation of the metabolites norfentanyl and hydroxynorfentanyl significantly. Therefore physicians should adapt and monitor the dosage of fentanyl in each patient when prescribing drugs with inhibitory effects on CYP3A to chronic pain patients who are treated with fentanyl, in order to avoid life-threatening side effects, eg, respiratory depression. Fentanyl did not show inhibitory effects on CYP3A.