Pharmacokinetic interaction between the opioid-analgesic Fentanyl and the CYP3A inhibitor Ketoconazole

INTRODUCTION

• Fentanyl is an opioid analgesic with high potency, a rapid onset and a short duration of action. It is widely used in the treatment of chronic and breakthrough pain in different formulations (e.g., transdermal fentanyl, oral transmucosal fentanyl citrate, nasal spray).

• Fentanyl is mainly metabolized by CYP3A4 and CYP2D6.

• Cytochrome P450 (CYP) 3A4, also known as CYP3A, is the most important of the cytochrome P450 enzyme family.

• The concomitant administration of Fentanyl and CYP3A inhibitors may cause dangerous drug interactions which can lead to severe and fatal side effects of Fentanyl (i.e., respiratory depression).

METHODS

3. Pharmacokinetic Assessment

• After Fentanyl administration, 10 blood samples were drawn and urine was collected for 24 hours.

• Concentrations of Fentanyl and its metabolites were determined by validated assays using high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS, Goss AR 400).

• The mean concentration-time curves and the area under the concentration-time curve (AUC) were calculated for Fentanyl and its metabolites in part A (F) and part B (F+K).

• Partial metabolic clearance of Midazolam as a measure of CYP3A activity was determined by using a limited sampling strategy (from 0 to 4 hours after midazolam administration) according to Katzenmair et al., 2011.

RESULTS

1. Study Population

12 male and 4 female volunteers, aged 22 to 49 years (mean 32.7 ± 8.8 years), participated in this study. Mean body weight was 74.1 ± 9.4 kg and mean body height was 178.0 ± 8.7 meters (m). Mean Body Mass Index (BMI) was 22.3 ± 2.2 kg/m².

Fentanyl dosing was based on body weight (5 µg/kg), resulting in a mean absolute Fentanyl dose of 25.1 ± 6.3 µg/kg (figure 2).

2. Study Design

The concomitant administration of Fentanyl and Ketoconazole during part B was started the day before the Fentanyl infusion.

Each study part was followed by a washout period of six days.

3. Fentanyl Pharmacokinetics

The total area under the Fentanyl plasma concentration time curve (AUC0-24h) was 13.0 ± 4.5 h·nmol/l. Ketoconazole increased the Fentanyl AUC0-24h to 20.2 ± 10.0 h·nmol/l (p < 0.05) and reduced the total body clearance of Fentanyl from 3.2 ± 1.3 h·nmol/l (50%) to 1.6 ± 0.8 h·nmol/l (60%). The renal clearance of Fentanyl was not affected by Ketoconazole (table 1).

4. Fentanyl Excretion

The total amount of excreted Fentanyl and metabolites from 0 to 24 hours was significantly altered during CYP3A inhibition. It decreased from 25.9 ± 12.5 % of the administered dose in part A to 9.8 ± 6.3 % in part B (p < 0.05).

The amount excreted of unchanged Fentanyl (from 0 to 24 hours, AUC0-24h) was not altered by concomitant administration of Fentanyl and Ketoconazole (table 2).

The mean plasma concentration of Norfentanyl was reduced from 0.78 ± 0.38 nmol/l to 0.19 ± 0.15 nmol/l during Ketoconazole administration (figure 3). The reduction of Norfentanyl (from 0 to 24 hours) was not altered by Ketoconazole administration (table 2).

The mean plasma concentration of Hydroxynorfentanyl was significantly reduced from 0.87 ± 0.58 % of the administered Fentanyl dose to 0.17 ± 0.38, p < 0.01 during Ketoconazole (figure 4).

CONCLUSIONS

Reduced plasma concentrations of Fentanyl and its metabolites were observed during the concomitant administration of Fentanyl and Ketoconazole. The inhibition of the CYP3A enzymes by Ketoconazole reduced the metabolism of Fentanyl, which resulted in an increase in its plasma concentrations and a decrease in the urinary excretion of the drug and its metabolites. The findings suggest that concomitant administration of Fentanyl and Ketoconazole may lead to a significant increase in plasma concentrations of Fentanyl and its metabolites, which could result in an increased risk of adverse effects, such as respiratory depression. Therefore, caution is advised when prescribing Fentanyl to patients who are taking CYP3A inhibitors, such as Ketoconazole. Further studies are needed to confirm these findings and investigate the clinical implications of these interactions.

REFERENCES


