Teijo I. Saari, Kari Laine, Mikko Neuvonen, Pertti J. Neuvonen, Klaus T. Olkkola

EFFECT OF VORICONAZOLE AND FLUCONAZOLE ON THE PHARMACOKINETICS OF INTRAVENOUS FENTANYL

T.I. Saari, K.T. Olkkola, Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Turku, Turku, Finland

K. Laine, Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Turku, Finland

M. Neuvonen, P.J. Neuvonen, Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland.

Corresponding author: Teijo Saari, Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine, University of Turku, P.O. Box 52 (Kiinamyllynkatu 4-8), FI-20520 Turku, Finland; Tel. +358-2-313 0596 (work); Fax +358-2-313 3960; E-mail: teijo.saari@tyks.fi

ABSTRACT

Objective: Fentanyl is a widely used opioid analgesic, which is extensively metabolized by hepatic cytochrome P450 (CYP) 3A. Recent reports suggest that concomitant administration of CYP3A-inhibitors with fentanyl may lead to dangerous drug interactions.

Methods: The potential interactions of fentanyl with triazole antifungal agents voriconazole and fluconazole were studied in a randomized crossover study in three phases. Twelve healthy volunteers were given 5 μg/kg of intravenous fentanyl without pre-treatment (control), after oral voriconazole (400 mg twice on the first day and 200 mg twice on the second day) or after oral fluconazole (400 mg once on the first day and 200 mg once on the second day). Plasma concentrations of fentanyl, norfentanyl, voriconazole and fluconazole were determined up to 24 h. Pharmacokinetic parameters were calculated using compartmental methods.

Results: The mean plasma clearance of intravenous fentanyl was decreased by 23% (range -22-48%; $p < 0.05$) and 16% (-34-53%; $p < 0.05$) after voriconazole and fluconazole administration, respectively. Voriconazole increased the area under fentanyl plasma concentration-time curve by 1.4-fold ($p < 0.05$). The initial plasma concentrations and volume of distribution of fentanyl did not differ significantly between the phases.

Conclusion: Both voriconazole and fluconazole delay the elimination of fentanyl significantly. Caution should be exercised especially in patients who are given voriconazole or fluconazole during a long-lasting fentanyl treatment because insidiously elevated fentanyl concentration may lead to respiratory depression.

Keywords: fentanyl, voriconazole, fluconazole, cytochrome P450, CYP3A, pharmacokinetics

INTRODUCTION

Fentanyl is a synthetic μ-opioid receptor agonist with a potent analgesic effect. Due to its cardiovascular stability and relatively rapid onset and termination of action, it is the most commonly used perioperative opioid analgesic in the world. Fentanyl is also popular in the treatment of chronic and breakthrough pain in cancer. Recently, transdermal fentanyl has also been used in the treatment non-malignant pain [1-3]. Fentanyl is eliminated mainly by metabolism in the liver and N-dealkylation to norfentanyl by cytochrome (CYP) P450 enzyme isoform CYP3A is the predominant pathway [4-7]. Fentanyl has a high extraction ratio of 0.8 to 1.0 [8], and its hepatic elimination should be more dependent on the liver blood flow than on the changes in its intrinsic clearance [9]. However, a strong CYP3A-inhibitor, ritonavir profoundly decreases the clearance of fentanyl in healthy volunteers [10].

Voriconazole is a novel, broad-spectrum triazole antifungal agent that is used to treat severe invasive fungal infections both orally and intravenously [11]. Voriconazole undergoes extensive oxidative metabolism involving CYP2C9, CYP2C19 and CYP3A [12]. *In vivo* studies have demonstrated that voriconazole also inhibits these enzymes [13, 11, 14], being a strong inhibitor of e.g. CYP3A [15, 16]. Fluconazole is another triazole antimycotic, which also inhibits CYP2C9 and CYP2C19, and to a lesser extent CYP3A [17-19]. It has clinically significant pharmacokinetic interactions with many substrates of CYP3A [20-22].

A recent case report, published in this journal, with fatal outcome described a possible drug interaction between fluconazole and fentanyl in a patient given transdermal fentanyl for pain in oral cavity due to tonsillar cancer [23]. As previous studies have demonstrated that both voriconazole and fluconazole can have clinically significant interactions with the substrates of CYP3A [15, 16,

20, 22], we found it important to study the possible effect of voriconazole and fluconazole on the pharmacokinetics of fentanyl.

MATERIALS AND METHODS

Subjects and ethics

The study protocol was approved by the Ethics committee of the Hospital District of Southwest Finland, as well as by the Finnish National Agency for Medicines, and was conducted according to the revised Declaration of Helsinki (http://www.wma.net/e/ethicsunit/helsinki.htm). Based on our previous works [9, 21], we calculated that 10 subjects would be required in order to demonstrate a 35% difference in fentanyl clearance values with a type I error of 5% and a statistical power of 80%. Written informed consent was obtained from 12 healthy volunteers, 7 men and 5 women. Before entering the study, the volunteers were ascertained to be in good health by medical history, clinical examination and standard haematological and blood chemistry tests. None of the volunteers was receiving any continuous medication, including contraceptive steroids, or natural products, nor was anyone a smoker.

Study design

We used an open, randomized, three-phase crossover study design at intervals of 4 weeks. Before fentanyl dosing, the volunteers were given in a randomized order either no pretreatment (control phase), oral voriconazole (voriconazole phase) or oral fluconazole for two days (fluconazole phase). The dose of voriconazole (Vfend 200 mg tablet, Pfizer Ltd, Sandwich, Great Britain) was 400 mg every 12 hours on the first day and 200 mg every 12 hours on the second day. The dose of fluconazole (Fluconazol Copypharm 100 mg tablet, Copypharm A/S, Odense, Denmark) was 400 mg once on the first day and then 200 mg on the second day. The last doses of voriconazole and fluconazole were given at 8 A.M. with 150 ml of water by the investigators in the research facility and those volunteers not receiving any pretreatment were given 150 ml of water. The volunteers had

been instructed to take the pretreatment at home with a meal and the adherence with the drug dosing schedule was assessed by using mobile phone short message service.

One hour after the last dose of voriconazole, fluconazole or water, all volunteers received 5 μg/kg of intravenous fentanyl (Fentanyl 0.05 mg/ml injection, Janssen Pharmaceutica N.V., Beerse, Belgium) in 2 minutes. To prevent the sedative and respiratory depressant effects of fentanyl, naloxone 0.1 mg (Narcanti 0.4 mg/ml, Bristol-Myers Squibb AB, Bromma, Sweden) was given intravenously 5 minutes before the fentanyl injection, and an additional dose of naloxone 0.1 mg was given with the fentanyl. Additional doses of naloxone were used if needed to counteract the side-effects of fentanyl. The volunteers fasted for 12 hours before the administration of fentanyl, and they were given standard meals 4 hours and 8 hours after fentanyl administration. The drinking of grapefruit juice, alcohol, coffee, tea or cola was forbidden on the test days and for 2 days prior to the study.

Blood sampling

For each session, an intravenous catheter was placed in both arms, one for drug administration and the other for blood sampling. A baseline venous blood sample was drawn into a EDTA-tube just before the last dose of pretreatment and timed blood samples (10 ml each) were drawn 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after the fentanyl administration. Plasma was separated within 30 minutes and stored at -40 ºC until analysis.

Bioanalysis of fentanyl and norfentanyl

Plasma concentrations of fentanyl and norfentanyl were quantified by use of an Agilent 1100 series liquid chromatography system (Agilent Technologies, Waldbronn, Germany) coupled to API 3000 tandem mass spectrometry (Sciex Division of MDS Inc, Toronto, Ontario, Canada) operating in

positive turbo ion spray mode at 380 °C. Plasma (0.5 ml), the internal standards fentanyl-D5 and norfentanyl-D5 (in 50 μl of water), and 200 μl of 5% phosphoric acid were vortexed and applied to an Oasis MCX solid-phase extraction cartridge (1 ml, 30 mg; Waters Corp, Milford, Mass) without prior conditioning. Cartridges were washed with 1 ml 0.1N HCl and 1 ml methanol, and finally eluted with 1 ml 5% ammonium hydroxide (v/v) in methanol. Samples were evaporated to dryness under a nitrogen stream, reconstituted with 100 μl of acetonitrile/water (20:80, v/v), and transferred to autosampler vials.

Chromatography was performed on a SunFire C18 analytic column (2.1 x 100 mm, 3.5 μm) with a Waters SunFire C18 guard column (2.1 x 10 mm, 3.5 μm; Waters Corp) by use of gradient elution. The mobile phase was (A) 10 mM ammonium formiate, pH 3.5, and (B) acetonitrile (0-5.5 min 20% B → 65% B, 5.5-15 min 20% B), and the flow rate was 0.19 ml/min. The retention times were 7 min 50 sec for fentanyl and fentanyl-D5, and 2 min 40 sec for norfentanyl and norfentanyl-D5. The ion transitions monitored were mass-to-charge ratio (m/z) 337 to m/z 188 for fentanyl, m/z 233 to m/z 84 for norfentanyl, m/z 342 to m/z 188 for fentanyl-D5, and m/z 238 to m/z 84 for norfentanyl-D5. The recovery of both fentanyl and norfentanyl was more than 90%, and the limit of their quantification was 0.02 ng/ml. For fentanyl, the interday coefficient of variation (CV) was 4.9%, 2.8%, and 2.6% at 0.1 ng/ml, 1.0 ng/ml, 20 ng/ml, respectively (n = 5). For norfentanyl, the CV was 2.4%, and 6.1% at 0.1 ng/ml, and 1.0 ng/ml, respectively (n = 5). Voriconazole and fluconazole did not interfere with the fentanyl or norfentanyl assay.

Bioanalysis of voriconazole and fluconazole

After a solid-phase extraction of voriconazole from plasma, its concentrations were determined by high pressure liquid chromatography (HPLC) with UV detection at 255 nm by using a fluconazole analog (UK 54373) as the internal standard [24, 25]. The limit of quantification was 50 ng/ml for

voriconazole and the interday CV was 2.9%, 5.4% and 2.9% at 50 ng/ml, 1000 ng/ml and 10000 ng/ml (n = 2), respectively. The plasma fluconazole concentrations were determined after a solid-phase extraction by HPLC with UV detection at 210 nm by using UK 54373 as the internal standard [26]. The limit of quantification for fluconazole was 0.2 mg/l. The CV was 1.1 % and 2.4% at 3 mg/l and 18 mg/l (n = 6), respectively. Trough concentrations (C_{trough}) of voriconazole and fluconazole were determined from the baseline samples.

Pharmacokinetic analysis

The individual plasma fentanyl concentrations were fitted to the following multiexponential function with the aid of a nonlinear regression program (WinNonlin version 4.1, Pharsight Corporation, California, USA) using iteratively reweighted least squares with reciprocal squared prediction weighting

$$C_{\text{Fentanyl}}(t) = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i \cdot t}$$

where $C_{Fentanyl}(t)$ is the plasma concentration of fentanyl at time t, C_i is a zero-time intercept, and λ_i is a disposition rate constant. The same program and reweighting scheme was also used to fit the plasma norfentanyl concentrations to the following exponential function

$$C_{\text{Norfentanyl}}(t) = A \cdot \lambda \cdot t \cdot e^{-\lambda \cdot t}$$

where $C_{Norfentanyl}(t)$ is the plasma concentration of norfentanyl at time t, A is a constant describing the ratio of the amount of norfentanyl formation to its apparent distribution volume, and λ is a disposition rate constant. The goodness of the fit was determined by Akaike's information criterion [27], and by assessment of randomness of "scatter" of actual data points about the fitted function. The plasma clearances (Cl) and steady-state volumes of distribution (V_{ss}) of fentanyl were calculated according to standard formulae [28].

Statistical analysis

Pharmacokinetic variables were compared with the analysis of variance for repeated measures, and *a posteriori* testing was performed using Tukey's test. Differences were regarded statistically significant if $p < 0.05$. Geometric mean ratios with 90% confidence intervals (CIs) were calculated and bioequivalence (i.e., the lack of an interaction) was concluded if the 90% CI of the geometric mean ratios for pharmacokinetic variables were within the acceptance limit of 0.8 to 1.25. The results are expressed as mean ± SD. All data were analysed with the statistical program Systat for Windows, version 10.2 (Systat Software, Richmond, California, USA).

RESULTS

All volunteers completed the study according to the protocol. Mean plasma concentrations of fentanyl and norfentanyl as a function of time are shown in the figure 1. During the voriconazole phase, the mean plasma concentration of fentanyl at 12 h after the injection was at the same level as at 6 h during the control phase. The pharmacokinetics of fentanyl was best described by a bioexponential function in all cases. Voriconazole decreased the mean plasma Cl of intravenous fentanyl by 23% (range -22-48%), and the mean $AUC_{0-\infty}$ of fentanyl was increased 1.4-fold by voriconazole (Fig. 1, Table 1). After fluconazole pretreatment, the plasma Cl of fentanyl was decreased by 16% (range -34-53%). The mean $t_{½}$ was not changed after voriconazole or fluconazole pretreatments. Voriconazole and fluconazole significantly decreased the $AUC_{0-\infty}$ of norfentanyl after intravenous fentanyl (Fig. 1, Table 1). The ratio of norfentanyl AUC_{0-24} to fentanyl $AUC_{0-\infty}$ was significantly higher during the control phase as compared with the voriconazole and fluconazole phases. During the voriconazole and fluconazole phases, the geometric mean ratios with 90% CI for all calculated pharmacokinetic variables for fentanyl were outside the bioequivalence acceptance limits. Mean C_{trough} of voriconazole and fluconazole before the last dose were 1.47 mg/l (range 0.46 to 3.92) and 4.97 mg/l (range 3.85 to 6.21), respectively. Visual adverse events were reported by five of the twelve volunteers during voriconazole pretreatment. Transient altered perception of light, chromatopsia and photophobia were experienced shortly after taking voriconazole. Fentanyl administration caused nausea and vomiting to 2 volunteers (1 woman) during the control phase, to 1 volunteer (woman) during the fluconazole phase and to 4 volunteers (1 woman) during the voriconazole phase. Additional doses of naloxone were not needed. There were no other observed or reported adverse effects during the study.

DISCUSSION

Voriconazole and fluconazole, administered at typically used clinical doses, significantly affected the pharmacokinetics of fentanyl. For ethical and safety reasons, only single doses of fentanyl were given in this study. Voriconazole reduced, on average, the clearance of fentanyl by 23%. The greatest individual reduction of the clearance was 52% in this group of twelve young healthy volunteers. The changes in pharmacokinetics were somewhat smaller after fluconazole, but the clearance of fentanyl was reduced in a statistically significant degree by it, too. Neither voriconazole nor fluconazole had an effect on the steady-state volume of distribution and as the initial concentrations were not altered, a difference in the volume of the central compartment was unlikely. The observed changes in fentanyl clearance appear to be due mainly to the inhibition of the predominant metabolic pathway, the CYP3A-mediated N-dealkylation of fentanyl to norfentanyl [6].

After antimycotic treatments, the AUC-ratios between norfentanyl and fentanyl were decreased substantially more than the corresponding clearances. Although we have no scientific proof, CYP-enzymes other than 3A may be involved in the metabolism of fentanyl in vivo, explaining the difference between the change in fentanyl clearance and AUC-ratio. About 7% of fentanyl is excreted unchanged normally [29], and the relative proportion of fentanyl excreted into the urine in unchanged form may increase as a result of inhibition of the CYP-mediated metabolism by voriconazole or fluconazole. This may partially compensate the effect of voriconazole and fluconazole on the CYP-mediated metabolism of fentanyl. Thus the total clearance of fentanyl may not be diminished as much as could be assumed by the inhibition of its metabolism.

Conventional pharmacokinetic theories anticipate that the rate of the hepatic elimination of a drug with high extraction ratio, like fentanyl, is more dependent on the liver blood flow than on the changes in its intrinsic clearance [9]. However, strong inhibitors of CYP3A, ritonavir and troleandomycin, profoundly decrease the clearance of fentanyl [10, 30], demonstrating that disposition of fentanyl can be affected by inhibiting its metabolism. It can be estimated by using the "well-stirred" model of hepatic elimination [9] that up to a 60% inhibition of intrinsic fentanyl clearance would be required to cause the observed decrease in the total clearance of fentanyl.

Theoretically, naloxone which was given with fentanyl to all subjects to prevent the effects of fentanyl, could have affected the results. However, because naloxone was given during all phases and it is metabolized by glucuronyltransferase [31], it is unlikely that naloxone would have invalidated our conclusions on the effect voriconazole and fluconazole on the pharmacokinetics of fentanyl. Also fentanyl might have affected the pharmacokinetics of voriconazole and fluconazole. Unfortunately, our study design does not allow any conclusions on the possible effect of fentanyl on these antimycotics. Nevertheless, the potential effect of fentanyl on voriconazole and fluconazole had no effect on our conclusions because therapeutic antimycotic levels were reached in all subjects.

Because both voriconazole and fluconazole were administered at typically used clinical doses, it is plausible to conclude that these antimycotics can reduce the elimination clearance of fentanyl also in a clinical setting. It is likely that the elimination of transdermally administered fentanyl is inhibited by voriconazole and fluconazole at the same magnitude as that of intravenous fentanyl. It can be calculated that in our volunteers voriconazole treatment during continuous use of transdermal fentanyl would have caused up to 100% increase in fentanyl concentrations, which is close to the previously reported toxic concentrations in forensic studies [32]. When the

interindividual variation in the pharmacokinetics of fentanyl is taken into account, also some individuals given fluconazole could have a similar up to 100% increase in the concentrations of fentanyl. Thus, the interactions between voriconazole and fentanyl as well as between fluconazole and fentanyl are clearly of clinical significance. There is a potential risk of respiratory depression if the dose of fentanyl during infusion or transdermal administration is not reduced and the patients are not monitored closely. Of note is that the transdermal absorption of fentanyl continues for several hours after release of a transdermal fentanyl patch [33]. This warrants a careful monitoring of patients, when voriconazole or fluconazole have been added to their drug regimen.

Although our study was done in healthy young volunteers, and the results may not be directly extrapolated to elderly patients or patients with critical illness, it seems reasonable to conclude, that care should be exercised if fentanyl is given concomitantly with voriconazole or fluconazole. If only small intravenous bolus doses of fentanyl are given, a dose adjustment of fentanyl is probably not needed, because the initial concentrations of fentanyl are not affected. However, during long-term administration of fentanyl, e.g. using the transdermal route, close monitoring of the patient and possibly a reduction of the dose is necessary.

ACKNOWLEDGEMENTS

We thank Mrs. Elina Kahra, Mrs. Eija Mäkinen-Pulli and Kerttu Mårtensson for technical assistance and skilful determination of the voriconazole and fluconazole plasma concentrations. The study was supported by the EVO grants #13821 and #13390 of the Hospital District of Southwest Finland, the Duocecim Foundation, Finland and the Sigrid Juselius Foundation, Finland. All experiments comply with the current laws in Finland, where the research was performed. There are no conflicts of interest.

REFERENCES

1. Muijsers, RB, Wagstaff, AJ (2001) Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 61 (15): 2289-2307

2. Mystakidou, K, Katsouda, E, Parpa, E, Vlahos, L, Tsiatas, ML (2006) Oral transmucosal fentanyl citrate: overview of pharmacological and clinical characteristics. Drug Deliv 13 (4): 269-276

3. Portenoy, RK, Messina, J, Xie, F, Peppin, J (2007) Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. Curr Med Res Opin 23 (1): 223-233

4. Tateishi, T, Krivoruk, Y, Ueng, YF, Wood, AJ, Guengerich, FP, Wood, M (1996) Identification of human liver cytochrome P-450 3A4 as the enzyme responsible for fentanyl and sufentanil N-dealkylation. Anesth Analg 82 (1): 167-172

5. Guitton, J, Buronfosse, T, Desage, M, Lepape, A, Brazier, JL, Beaune, P (1997) Possible involvement of multiple cytochrome P450S in fentanyl and sufentanil metabolism as opposed to alfentanil. Biochem Pharmacol 53 (11): 1613-1619

6. Labroo, RB, Paine, MF, Thummel, KE, Kharasch, ED (1997) Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual

variability in disposition, efficacy, and drug interactions. Drug Metab Dispos 25 (9): 1072-1080

7. Ibrahim, AE, Feldman, J, Karim, A, Kharasch, ED (2003) Simultaneous assessment of drug interactions with low- and high-extraction opioids: application to parecoxib effects on the pharmacokinetics and pharmacodynamics of fentanyl and alfentanil. Anesthesiology 98 (4): 853-861

8. Bower, S, Hull, CJ (1982) Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 54 (8): 871-877

9. Rowland, M, Tozer, TN (1995) Elimination. In: Rowland M, Tozer TN (Ed.s) Clinical Pharmacokinetics: Concepts and Applications, 3rd ed. Baltimore, Williams and Wilkins, pp. 156-183

10. Olkkola, KT, Palkama, V, Neuvonen, PJ (1999) Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. Anesthesiology 91 (3): 681-685

11. Theuretzbacher, U, Ihle, F, Derendorf, H (2006) Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet 45 (7): 649-663

12. Hyland, R, Jones, BC, Smith, DA (2003) Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. Drug Metabol Dispos 31 (5): 540-547

13. Hynninen, VV, Olkkola, KT, Leino, K, Lundgren, S, Neuvonen, PJ, Rane, A, Valtonen, M, Vyyrylainen, H, Laine, K (2006) Effects of the antifungals voriconazole and fluconazole on the pharmacokinetics of s-(+)- and R-(-)-Ibuprofen. Antimicrob Agents Chemother 50 (6): 1967-1972

14. Romero, AJ, Le Pogamp, P, Nilsson, L-G, Wood, N (2002) Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. Clin Pharmacol Ther 71 (4): 226-234

15. Saari, TI, Laine, K, Leino, K, Valtonen, M, Neuvonen, PJ, Olkkola, KT (2006) Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam Clin Pharmacol Ther 79 (4): 362-370

16. Saari, TI, Laine, K, Leino, K, Valtonen, M, Neuvonen, PJ, Olkkola, KT (2006) Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. Clin Pharmacol Ther 80 (5): 502-508

17. Morita, K, Konishi, H, Shimakawa, H (1992) Fluconazole: a potent inhibitor of cytochrome P-450-dependent drug-metabolism in mice and humans in vivo. Comparative study with ketoconazole. Chem Pharm Bull (Tokyo) 40 (5): 1247-1251

18. Wienkers, LC, Wurden, CJ, Storch, E, Kunze, KL, Rettie, AE, Trager, WF (1996) Formation of (R)-8-hydroxywarfarin in human liver microsomes. A new metabolic marker for the (S)-mephenytoin hydroxylase, P4502C19. Drug Metab Dispos 24 (5): 610-614

19. Niwa, T, Shiraga, T, Takagi, A (2005) Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. Biol Pharm Bull 28 (9): 1805-1808

20. Olkkola, KT, Ahonen, J, Neuvonen, PJ (1996) The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. Anesth Analg 82 (3): 511-516

21. Varhe, A, Olkkola, KT, Neuvonen, PJ (1996) Fluconazole, but not terbinafine, enhances the effects of triazolam by inhibiting its metabolism. Br J Clin Pharmacol 41 (4): 319-323

22. Palkama, VJ, Isohanni, MH, Neuvonen, PJ, Olkkola, KT (1998) The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. Anesth Analg 87 (1): 190-194

23. Hallberg, P, Marten, L, Wadelius, M (2006) Possible fluconazole-fentanyl interaction-a case report. Eur J Clin Pharmacol 62 (2): 491-492

24. Gage, R, Stopher, DA (1998) A rapid HPLC assay for voriconazole in human plasma. J Pharm Biomed Anal 17 (8): 1449-1453

25. Pennick, GJ, Clark, M, Sutton, DA, Rinaldi, MG (2003) Development and validation of HPLC assay for voriconazole. Antimicrobial Agents and Chemotherapy 47 (7): 2348-2350

26. Inagaki, K, Takagi, J, Lor, E, Okamoto, MP, Gill, MA (1992) Determination of fluconazole in human serum by solid-phase extraction and reversed-phase high-performance liquid chromatography. Ther Drug Monit 14 (4): 306-311

27. Akaike, H (1976) An information criterion (AIC). Math Sci 14: 5-9

28. Wagner, JG (1976) Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokin Biopharm 4 (5): 443-467

29. McClain, DA, Hug, CC (1980) Intravenous fentanyl kinetics. Clin Pharmacol Ther 28 (1): 106-114

30. Kharasch, ED, Whittington, D, Hoffer, C (2004) Influence of hepatic and intestinal cytochrome P4503A activity on the acute disposition and effects of oral transmucosal fentanyl citrate. Anesthesiology 101 (3): 729-737

31. Handal, KA, Schauben, JL, Salamone, FR (1983) Naloxone. Ann Emerg Med 12 (7): 438-445

32. Jung BF, Reidenberg MM (2005) Interpretation of opioid levels: comparison of levels during chronic pain therapy to levels from forensic autopsies. Clin Pharmacol Ther 77 (4): 324-334

33. Grond S, Radbruch L, Lehmann KA (2000) Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. Clin Pharmacokinet 38 (1): 59-89

Table 1. Pharmacokinetic parameters of fentanyl following intravenous administration of 5 μg/kg fentanyl without pretreatment (control) or following pretreatment with oral voriconazole or oral fluconazole, based on a compartmental analysis.

Parameter	Control phase	Voriconazole phase	Fluconazole phase	Geometric mean ratio (90% CI)	
				Voriconazole/ Control	Fluconazole/ Control
Fentanyl					
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$) % of control (range)	14.0 ± 2.5 100	10.7 ± 3.0* 77 (48-122)	11.6 ± 3.0* 84 (47-134)	0.75 (0.63, 0.89)	0.81 (0.69, 0.95)
V_{ss} ($l \cdot kg^{-1}$) % of control (range)	9.5 ± 2.4 100	8.4 ± 2.8 88 (68-106)	8.0 ± 2.4 87 (55-145)	0.84 (0.69, 1.01)	0.87 (0.73, 1.04)
$AUC_{0-\infty}$ ($ng \cdot ml^{-1} \cdot h$) % of control (range)	6.1 ± 1.1 100	8.5 ± 2.9* 139 (81-204)	7.7 ± 2.3 128 (75-211)	1.34 (1.12, 1.60)	1.23 (1.05, 1.45)
$t_{½}$ (h) % of control (range)	12.1 ± 4.7 100	12.9 ± 4.4 114 (66-169)	11.8 ± 3.7 111 (37-241)	0.82 (0.48, 1.41)	1.02 (0.56, 1.80)
Norfentanyl					
$AUC_{0-\infty}$ ($ng \cdot ml^{-1} \cdot h$) % of control (range)	1.8 ± 1.1 100	0.8 ± 0.5* 27 (19-44)	0.8 ± 0.7* 43 (16-72)	0.41 (0.24, 0.72)	0.46 (0.23, 0.91)
AUC ratio % of control (range)	0.3 ± 0.2 100	0.1 ± 0.1* 14 (10-21)	0.1 ± 0.1* 32 (20-48)	0.33 (0.22, 0.62)	0.24 (0.13, 0.44)

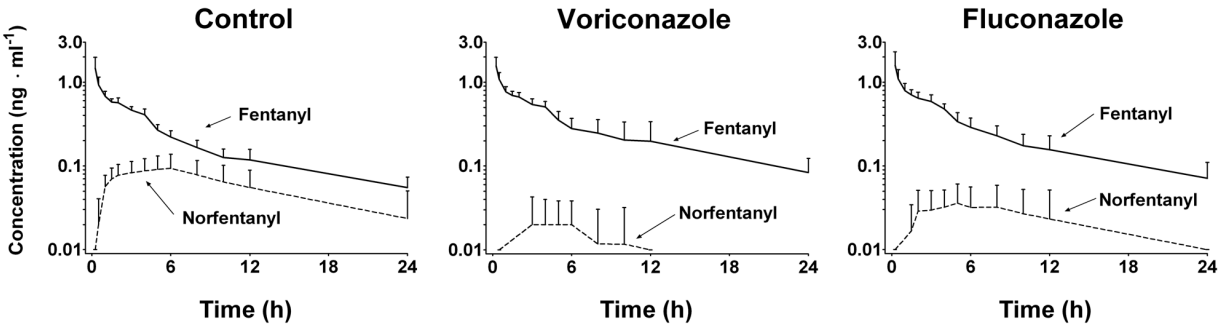
Values are mean ± SD. % of control was calculated individually for each subject, and the mean and range of these individual values are reported.

CI = confidence interval; Cl = plasma clearance of fentanyl; V_{ss} = steady-state volume of distribution; $AUC_{0-\infty}$ = area under the fentanyl plasma concentration-time curve extrapolated to infinity; AUC ratio = ratio of norfentanyl $AUC_{0-\infty}$ to fentanyl $AUC_{0-\infty}$; $t_{½}$ = terminal elimination half-live.

*Significantly ($p < 0.05$) different from control

Figure Legend:

Fig 1. Mean plasma (± SD) concentrations of fentanyl (*solid line*) and norfentanyl (*dashed line*) in 12 healthy volunteers after an intravenous dose of 5 μg/kg of fentanyl without pre-treatment (Control) or following pretreatment with oral voriconazole or oral fluconazole. Voriconazole was given 400 mg twice on the first day and 200 mg twice on the second day. Fluconazole was given 400 mg once on the first day and 200 mg once on the second day.


Control
Voriconazole
Fluconazole
Concentration (ng · ml-1)
3.0
1.0
0.1
0.01
Fentanyl
Norfentanyl
0
6
12
18
24
Time (h)