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Voriconazole more likely than posaconazole increases plasma exposure to sublingual buprenorphine causing a risk of a clinically important interaction

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ABSTRACT

Purpose: This study aimed to determine possible effects of voriconazole and posaconazole on the pharmacokinetics and pharmacological effects of sublingual buprenorphine.

Methods: We used a randomized, placebo-controlled crossover study design with 12 healthy male volunteers. Subjects were given a dose of 0.4 mg (0.6 mg during placebo phase) sublingual buprenorphine after a 5-day oral pretreatment with either (i) placebo, (ii) voriconazole 400 mg twice daily on the first day and 200 mg twice daily thereafter or (iii) posaconazole 400 mg twice daily. Plasma and urine concentrations of buprenorphine and its primary active metabolite norbuprenorphine were monitored over 18 h and pharmacological effects were measured.

Results: Compared to placebo, voriconazole increased the mean area under the plasma concentration-time curve ($AUC_{0-\infty}$) of buprenorphine 1.80-fold (90% confidence interval 1.45-2.24; $P<0.001$), its peak concentration (C_{max}) 1.37-fold ($P<0.013$) and half-life ($t_{1/2}$) 1.37-fold ($P<0.001$). Posaconazole increased the $AUC0_{0-\infty}$ of buprenorphine 1.25-fold ($P<0.001$). Most of the plasma norbuprenorphine concentrations were below the limit of quantification (0.05 ng/ml). Voriconazole, unlike posaconazole, increased the urinary excretion of norbuprenorphine 1.58-fold (90% confidence interval 1.18-2.12; $P<0.001$) but there was no quantifiable parent buprenorphine in urine. Plasma buprenorphine concentrations correlated with the pharmacological effects but the effects did not differ significantly between the phases.

Conclusions: Voriconazole, and to a minor extent posaconazole, increase plasma exposure to sublingual buprenorphine, probably via inhibition of cytochrome P450 3A and/or P-glycoprotein. Care should be exercised in the combined use of buprenorphine with triazole antimycotics, particularly with voriconazole, because their interaction can be of clinical importance.

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INTRODUCTION

Buprenorphine is a semisynthetic partial µ-opioid receptor agonist. The analgesic efficacy of buprenorphine is 20−40 times higher than that of morphine [1]. Buprenorphine acts also as an antagonist at the κ-opioid receptor and as an agonist at the δ-opioid receptor and opioid receptor-like receptor. In low doses, it is used in the treatment of moderate acute and chronic pain whereas in high doses, it is used in the management of opioid withdrawal symptoms and opioid dependence [2, 3]. Buprenorphine can be administered in various formulations and there is a growing interest for its use as an alternative to methadone that could increase access to treatment and be more acceptable to patients [4, 5].

After an oral and sublingual administration of buprenorphine, variability in its absorption and disposition increases its susceptibility to drug interactions. Buprenorphine undergoes extensive metabolism, particularly during its first-pass and has an oral bioavailability of 15% only [6, 7]. Bioavailability following sublingual administration of buprenorphine is higher, but the estimates of absolute bioavailability vary from 15 to 30% [8, 9]. Some transporters such as P-glycoprotein can play a role in the pharmacokinetics of buprenorphine and/or its metabolites [10–12]. Peak plasma concentrations of buprenorphine are reached within 1-3 hours after sublingual administration [13–15]. Practically no unconjugated parent drug is excreted into urine [14]. The main metabolic pathway, N-dealkylation of buprenorphine, is catalyzed mainly by cytochrome P450 (CYP) 3A4, and also by CYP3A5 and CYP2C8, yielding an active metabolite norbuprenorphine [16], which is further glucuronidated to norbuprenorphine-3-glucuronide [6, 17–20]. In addition to the N-dealkylation, smaller fractions of buprenorphine are converted to other hydroxylated metabolites and to buprenorphine-3-glucuronide. Some *in vitro* data suggest that CYP2C9 and CYP2C19 are involved in

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smaller oxidative pathways of buprenorphine [19]. Overall, about 80−90% of buprenorphine-derived compounds are excreted by the biliary system and can be subject to enterohepatic circulation [21].

Voriconazole and posaconazole are triazole antifungal agents clinically used in the treatment of disseminated fungal infections. Voriconazole inhibits the activities of CYP3A, CYP2C19 and CYP2C9 enzymes [22] and it has greatly increased plasma concentrations of orally administrated CYP3A4 substrates, e.g., oxycodone [23] and midazolam [24]. Posaconazole also is a moderately strong inhibitor of CYP3A4 and CYP2C18, but is not a clinically relevant inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP2E1 [25, 26]. Concomitant use of posaconazole has increased the plasma concentrations of many drugs that are predominantly metabolized by CYP3A4 [27]. In addition, posaconazole is more potent than voriconazole as inhibitor of P-glycoprotein and breast cancer resistance protein [28].

Some interaction studies have been conducted using high-dose buprenorphine and antiretrovirals [29–32]. However, the effect of azole antifungals on the pharmacokinetics of buprenorphine is largely unknown. In particular, there seem to be no previous studies on the possible interaction of voriconazole and posaconazole with sublingual buprenorphine although their concomitant use is likely to occur commonly. We hypothesized that inhibition of CYP-mediated metabolism of buprenorphine by voriconazole or posaconazole leads to significant changes in the plasma concentrations of buprenorphine.

MATERIALS AND METHODS

Study participants

On the basis of our previous drug-drug interaction studies [33, 34], we calculated that 10 subjects

were needed to detect a 30% difference in the area under the concentration-time curve ($AUC_{0-\infty}$) of

buprenorphine at a power of 80% and a level of significance of *P*<0.05. To be

prepared for dropouts, 12 healthy non-smoking male volunteers were recruited in the study. All

subjects completed the study. Age and body mass index ranges were 19 to 23 years and 19.8 to 24.8

kg/m2, respectively. The inclusion criteria for the volunteers were age 18 to 40 years, body weight

within ±15% of the ideal weight, and blood pressure within normal limits. The criteria for exclusion

included a previous history of intolerance to the study drugs; concomitant drug therapy; past or

present significant disease or drug allergy, alcoholism, drug abuse, or psychological or emotional

problems; blood donation within the 4 weeks prior to the study; lifestyle habits that would

compromise the conditions of the study or interpretation of the results. Informed consent was

obtained from all individual participants included in the study and the eligible volunteers were

ascertained to be healthy by clinical examination, medical history, routine laboratory tests, and an

electrocardiogram. It was ensured that urine drug screening was negative. The risk of participants to

develop opioid dependency was considered low as evaluated by the Finnish translation of the Abuse

Questions [35].

Study outline and drug administration

The ethics committee of the Hospital District of Southwest Finland and by the Finnish National

Agency for Medicines approved the study protocol, and it was registered in the EudraCT clinical

trials register under code number 2010-020953-14. A placebo-controlled, single-blinded, randomized,

three-phase crossover study design with 5-day pretreatment periods was used, separated by intervals

of 4 weeks. The volunteers ingested orally one of the following treatments in a randomized order: (i)

voriconazole (Vfend 200 mg tablet; Pfizer, Sandwich, Great Britain) 400 mg at 8.00 and 20.00 on day

1, 200 mg at 8.00 and 20.00 on days 2-4, and 200 mg at 10.00 and 20.00 on day 5 (voriconazole

phase), (ii) posaconazole (Noxafil 40 mg/ml oral suspension; Merck Sharp & Dohme, Hoddesdon,

Great Britain) 400 mg at 8.00 and 20.00 for 4 days and on day 5, posaconazole was given at 10.00

and 20.00 (posaconazole phase), or (iii) placebo at 8:00 am and 8:00 pm for 4 days, and on day 5

placebo was given at 10.00 and 20.00 (control phase). We assessed the adherence to the

premedication schedule of mobile telephone text messages. On day 5, after

fasting overnight, the subjects ingested the premedication with 100 ml of water followed by a single

dose of 0.4 mg (0.6 mg during placebo phase) of sublingual buprenorphine (Temgesic 0.2 mg tablets;

RB Pharmaceuticals Limited, Slough, Great Britain) with 20 ml of water 1 h later. Standardized meals

were served 4 and 8 h after the buprenorphine challenge.

On the test days, a forearm vein was cannulated, and blood samples (10 ml) for

pharmacokinetic measurements were collected into ethylenediaminetetraacetic acid–containing tubes

immediately before and at the following time points after the administration of buprenorphine: 30 min

and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 18 h. Plasma was separated within 30 min and stored at −70 °C

until analysis. Another venous cannula was inserted to the opposite forearm for the possible

administration of naloxone (Naloxon B. Braun 0,4 mg/ml, B. Braun Melsungen AG, Melsungen,

Germany). Urine was collected up to 18 h after buprenorphine administration. Urine aliquots were

stored at − 70°C until analysis. Determination of drug concentrations has been described in detail in

Supplement file 1.

Pharmacokinetic measurements

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We observed the peak plasma concentration (C_{max}) and time to C_{max} (t_{max}) directly from the data. The area under the plasma concentration–time curve (AUC) values from 0 to 18 h (AUC_{0-18}), as well as from 0 h to infinity ($AUC_{0-\infty}$), were calculated for buprenorphine applying noncompartmental methods using the WinNonlin pharmacokinetics program (version 4.1; Pharsight, Mountain View, CA). After visual identification of the terminal log-linear part of each concentration–time curve the elimination rate constant (k_e) was determined using linear regression analysis. The $t_{1/2}$ was calculated using the equation $t_{1/2} = \ln2/k_e$. The AUC values were calculated using a combination of the linear and log-linear trapezoidal rules with extrapolation to infinity, when appropriate, by division of the last measured concentration by k_e. We also calculated the cumulative amount of free, unconjugated norbuprenorphine excreted into urine from 0 to 18h (A_e).

Measurement of pharmacological effects

Adverse effects were evaluated using a questionnaire before, and 3 and 6 hours after buprenorphine administration. Other subjective effects of buprenorphine were evaluated using 100-mm visual analog scales for the following items: drowsy/alert, very poor performance/very good performance, no drug effect/very strong drug effect, relaxed/anxious, no nausea/very strong nausea, calm/restless. The Maddox wing test [36] and Cogan's pupillometer [37] was used to measure the central coordination of extraocular muscles and pupil size, respectively. A digit symbol substitution test was used to estimate central processing of sensory information by recording the number of correct symbols substituted in 3 min [38]. The analgesic effect was evaluated using the cold pressor test as described earlier [33].

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Pharmacological effects were evaluated

prior to and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after buprenorphine administration. For each effect

variable, area under the response–time (AUEC) curve was determined using the trapezoidal rule.

Statistical analysis

The data were evaluated for normality of distribution with probit plots and the Shapiro–Wilk's

W-test. Log-transformed data were analysed but nontransformed

results are reported. The $AUC_{0-\infty}$ of buprenorphine was the primary outcome variable in the study,

and all other pharmacokinetic and all pharmacodynamic parameters were secondary variables.

Geometric mean ratios with 90% CIs were calculated for the pharmacokinetic variables. Lack of

interaction was assumed if the 90% CI of the geometric mean ratios for pharmacokinetic variables

were within the acceptance limit of 0.8–1.25. Pharmacokinetic variables were compared also using

repeated-measures analysis of variance with a posteriori testing was performed using the Tukey test.

Values for t_{max} were analyzed using the Wilcoxon signed-ranks test. Differences were regarded as

statistically significant when *P<0.05*. The Pearson product moment correlation coefficient was used

to investigate the possible relationship between the ratios of the $AUC_{0-\infty}$ of buprenorphine during the

treatment phases (voriconazole or posaconazole) to the $AUC_{0-\infty}$ of buprenorphine during the control

phase, as well as to the C_{trough} of voriconazole or posaconazole before the administration of

buprenorphine. The associations of plasma buprenorphine concentrations with psychomotor and

analgesic effects were also calculated using the Pearson's product moment correlation coefficient.

The results are expressed as mean values ± SD. All data were analyzed using SYSTAT for Windows

(version 10.2; Systat Software, Richmond, CA) and R software (version 3.2.0) ~~was also applied for~~

~~statistical analysis~~ [39].

RESULTS

Pharmacokinetics

The mean plasma concentrations of buprenorphine during the placebo, voriconazole and posaconazole phases are shown in Figure 1 and the individual amounts of norbuprenorphine excreted into urine in Figure 2. The concentrations of norbuprenorphine were around or below the LLQ in the most of the plasma samples during all three study phases. The effects of voriconazole and posaconazole on the pharmacokinetics of buprenorphine are summarized in Table 1 and Figure 3.

Effect of voriconazole: Compared to the placebo phase, voriconazole increased the mean $AUC_{0-\infty}$ of buprenorphine by 1.80-fold (90% confidence interval (CI) 1.45-2.24; $P<0.001$) and its C_{max} by 1.37-fold (90% CI 1.05-1.79; $P<0.001$). Voriconazole increased the mean $t_{1/2}$ of buprenorphine from 7.9 h to 11.0 h ($P<0.001$). The mean C_{trough} of voriconazole on day 5 was 1522 ng/ml (range 668-4162 ng/ml).

Effect of posaconazole: Compared to the placebo phase, posaconazole increased the mean $AUC_{0-\infty}$ of buprenorphine by 1.25-fold (90% CI 1.03-1.52; $p=0.016$) and its C_{max} by 1.20-fold (0.97-1.48) but the latter effect was not statistically significant ($p=0.206$). Posaconazole had no effect on the $t_{1/2}$ of buprenorphine. The mean C_{trough} of posaconazole on day 5 was 967 ng/ml (range 367-1758 ng/ml).

Effects on the renal excretion of buprenorphine and norbuprenorphine: Voriconazole increased the cumulative amount of norbuprenorphine excreted in urine by 1.6-fold (90% CI 1.18-2.12; $P<0.001$), when compared to placebo (Table 1). The concentrations of parent buprenorphine in urine were in no study phase reliably quantifiable being much lower than those of norbuprenorphine.

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Comparison of voriconazole and posaconazole*:* Voriconazole increased the mean plasma AUC_{0-18} and $AUC_{0-\infty}$ of buprenorphine significantly more than posaconazole (*P<0*.001). Similarly the cumulative amount of norbuprenorphine excreted to urine was significantly increased during voriconazole, compared to posaconazole (*P<0*.001).

3.2 Pharmacological effects

Almost every subject experienced some mild or moderate adverse effects (Supplementary Table S1). The most frequent adverse effect was sedation, followed by ataxia, dizziness and nausea. These effects were transient and did not require any treatment.

There was a linear correlation between plasma buprenorphine concentration and pharmacological drug effect (*P<0*.001). However, there were no statistically significant differences in the pharmacological effects of buprenorphine between the three phases (Supplementary Figure S1).

DISCUSSION

This study was designed to investigate the effect of voriconazole and posaconazole on the pharmacokinetics and pharmacodynamics of sublingual buprenorphine in healthy volunteers. The strong CYP3A and CYP2C inhibitor voriconazole markedly increased the C_{max} and $AUC_{0-\infty}$ of buprenorphine and prolonged its $t_{1/2}$. In some subjects, the exposure to buprenorphine was increased more than two-fold by voriconazole. On the other hand, the effects of posaconazole on buprenorphine exposure were minor.

We measured also the urinary excretion of norbuprenorphine. As an N-dealkylated metabolite, it is less lipophilic than the parent buprenorphine and can be excreted into urine to some extent also in the unconjugated form. Surprisingly, voriconazole caused a 58% increase in the amount of norbuprenorphine excreted into urine, although it is reasonable to assume that voriconazole as a strong inhibitor of CYP3A4 decreases the (CYP3A4-mediated) N-dealkylation of buprenorphine. On the other hand, the strong and more selective CYP3A4 inhibitor posaconazole actually tended to decrease the excretion of norbuprenorphine into urine, consistent with inhibition of its CYP3A4-mediated formation. Furthermore, norbuprenorphine is a substrate of P-glycoprotein [40]. Different effects of posaconazone (potent inhibitor) and voriconazole (weak inhibitor) on P-glycoprotein may partially explain their different effects on buprenorphine plasma concentrations and on urinary excretion of norbuprenorphine. Unfortunately, we could not determinate the renal clearances, due to low free, unconjugated concentrations of plasma norbuprenorphine and urine buprenorphine.

It is noteworthy that 400 mg posaconazole twice daily has increased the AUCs of sensitive CYP3A4 substrates several fold; for example, the AUC of oral midazolam was increased about 5-fold, consistent with roughly 80% inhibition of the total CYP3A4-mediated clearance of midazolam [41]. Thus, as posaconazole increased the AUC of buprenorphine by 25% only, equal to 20% reduction in

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oral clearance, it seems that after sublingual buprenorphine dosing, only a small fraction (less than 30-40%) of buprenorphine dose is metabolized by CYP3A4, and that other CYP-enzymes and UGTs play a larger role. Accordingly, strong inhibition of CYP2C9 and CYP2C19 mediated alternative pathways, in addition to inhibition of CYP3A4-mediated N-demethylation, by voriconazole may partially explain why voriconazole increased the urinary excretion of norbuprenorphine, and increased buprenorphine plasma concentrations more than did posaconazole. In addition, the increased urinary excretion of the metabolite may involve unidentified membrane transporter mechanisms.

Previous studies on drug-drug-interactions between CYP-inhibitors and buprenorphine are scarce. The effects of HIV protease inhibitors have been characterized most thoroughly on the pharmacokinetics of high-dose sublingual buprenorphine. Ritonavir increased the AUC of buprenorphine significantly (57%), while the other protease inhibitors studied had no effect [30–32, 42]. Similarly, the non-nucleoside reverse-transcriptase inhibitors efavirenz and delavirdine increased the AUC of buprenorphine [29]. Atazanavir alone or together with ritonavir increased buprenorphine AUC_{0-18} 93% and 67%, respectively, and lead to significant increase in sedative effect [31]. These interactions with buprenorphine are of the same order as those observed in our present study with voriconazole and might necessitate a decrease in the buprenorphine dose during concomitant treatment.

Compared to oral intake, sublingual administration has increased the bioavailability of buprenorphine considerably, from 15% to up to 30-60% [9, 43]. Our present results suggest that strong CYP-inhibitors may further increase the bioavailability of sublingual buprenorphine as both the C_{max} and AUC of buprenorphine were clearly increased after voriconazole pretreatment. Most probably, voriconazole caused increased exposure by inhibiting both the intestinal and hepatic

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CYP3A increasing both the C_{max} and $t_{1/2}$ of buprenorphine. In addition, other mechanisms may also be

involved. P-glycoprotein is an efflux transporter in the intestinal wall, blood–brain barrier and many

other tissues [44]. Several opioids, including morphine [45], fentanyl [46] and alfentanil [47], are

substrates of P-glycoprotein, and especially posaconazole P-glycoprotein inhibitor [28, 48, 49]. Previ-
ous studies conducted in transfected cells

and mice indicate that P-glycoprotein mediated drug efflux influences brain access and

antinociceptive effects of norbuprenorphine [12].

The majority of a buprenorphine dose is excreted as different metabolites into the bile and

circulates in enterohepatic system [21]. Voriconazole as a strong inhibitor of many CYP enzymes

alters the pharmacokinetics of several drugs metabolized by CYP3A, including oral hypnotics [24, 50,

51] and opioids [33, 52–54]. Voriconazole has decreased the clearance of alfentanil by 83% [49] and

that of fentanyl by 23% [53], and increased the $AUC_{0–24}$ of R-methadone by 47% [54]. In the present

study, voriconazole increased the exposure to sublingual buprenorphine by 1.8-fold, i.e., less than has

been its effect (10x-fold) on oral midazolam [24]. Sublingual buprenorphine partially bypasses the

intestinal first-pass metabolism and therefore seems to be less prone than, e.g., oral midazolam or

oxycodone to the effects of drugs affecting intestinal and hepatic CYP3A4 during the first-pass

metabolism [33, 55, 56].

The half-life of buprenorphine increased significantly after voriconazole, but not after

posaconazole pretreatment, which is likely to reflect a decrease in buprenorphine systemic clearance

by voriconazole, although an increase in the volume of distribution cannot be excluded without

intravenous buprenorphine dosing. The route of administration may affect the apparent half-life of

buprenorphine since the estimates appear to be longer after sublingual administration compared to

intravenous administration [57, 58]. Furthermore, longer half-lives than observed in the present study

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have been described after high doses of buprenorphine [15, 43, 57–59]. The terminal elimination

phase can continue for a longer time than was the sampling time in the present study, where the limit

of buprenorphine quantification after small doses did not allow a longer sampling. Thus, our studies

should be interpreted with care in this regard.

In our earlier studies, we have characterized previously unrecognized, drastic increases in the

AUC of several substrate drugs, which have a limited therapeutic index, such as midazolam, triazolam,

quinidine, tizanidine and oxycodone, when potent inhibitors of their metabolism have been

administered concomitantly [34, 56, 60–63]. Based on these experiences, and for ethical and safety

reasons in general, only a single clinically relevant, small dose of buprenorphine was employed,

because we studied healthy volunteers and we wanted to minimize the risk of adverse events. This

may be the reason that the values for the pharmacodynamic variables differed only slightly between

phases. Our study was designed mainly to evaluate the pharmacokinetics of buprenorphine, and its

power was not sufficient for more precise pharmacodynamic analysis. Nonetheless, we detected a

significant linear correlation between plasma buprenorphine concentrations and pharmacological

effects, which proves that our methodology was sensitive enough to measure the effects of

buprenorphine.

In conclusion, our results show that even a short treatment with clinically used doses of

voriconazole increases the exposure to sublingual buprenorphine and this interaction may have a

considerable clinical relevance in individual patients. When the interindividual variation in the

pharmacokinetics of buprenorphine is taken into account, some individuals given voriconazole may

have a more than 100% increase in the exposure to buprenorphine. Thus, at least the interaction

between voriconazole and sublingual buprenorphine can be of clinical significance. It has been

previously shown that the strong CYP3A-inhibitor ketoconazole had no effect on the

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pharmacokinetics of transdermal buprenorphine [64]. Our results warrant careful patient monitoring

when sublingual buprenorphine is used with triazole antifungals, especially voriconazole.

Posaconazole is less likely to cause a clinically significant interaction with sublingual buprenorphine.

Description of authors' roles

Mari Fihlman took care of the clinical phase of the study and data collection, participated in data analysis and statistical analysis and wrote the manuscript. Klaus Olkkola and Kari Laine designed the study, wrote the protocol, supervised and coordinated the clinical implementation of the study, and participated in data analysis. Tuija Hemmilä and Kristiina Kuusniemi participated the clinical phase and data collection. Janne T. Backman, Jouko Laitila and Pertti J Neuvonen performed the analytical assays. Teijo Saari designed the study, analysed the data, performed statistical analysis, and wrote the manuscript. All authors materially participated in the research and/or manuscript preparation. All authors have contributed to and approved the final manuscript.

Conflict of interest Declaration

The authors declare no conflict of interest.

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FIGURE LEGENDS

Figure 1. Mean plasma (SD) concentrations of buprenorphine in 12 healthy volunteers after 0.4 mg (0.6 mg in placebo phase) sublingual buprenorphine on the fifth day of pretreatment with placebo (*open circles*), voriconazole 400 mg twice on the first day, thereafter 200 mg twice daily (*filled triangles*) or posaconazole 400 mg twice daily (*filled circles*) for 5 days. Right panel shows the same concentrations in semilogarithmic scale. Values are normalized for a sublingual dose of 1.0 mg.

Figure 2. The individual amounts of urinary norbuprenorphine excreted during 18 hours after 0.4 mg (0.6 mg in placebo phase) sublingual buprenorphine on the fifth day of pretreatment with placebo, voriconazole (400 mg twice on the first day, thereafter 200 mg twice daily) or posaconazole (400 mg twice daily) for 5 days in 12 healthy volunteers. Values are normalized for a sublingual dose of 1.0 mg.

Figure 3. Individual pharmacokinetic parameters after sublingual buprenorphine. Values for maximum concentration (C_{max}), area under plasma concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) and elimination half-life ($t^{1/2}$) in 12 healthy volunteers after 0.4 mg (0.6 mg in placebo phase) sublingual buprenorphine on the fifth day of pretreatment with placebo, voriconazole (400 mg twice on the first day, thereafter 200 mg twice daily) or posaconazole (400 mg twice daily) for 5 days. Values are normalized for a sublingual dose of 1.0 mg.

Table 1. Pharmacokinetic parameters of buprenorphine after sublingual administration of 0.6 mg (control phase) or 0.4 mg (posaconazole and voriconazole phases) of buprenorphine on the fifth day of pre-treatment with oral posaconazole (400 mg twice daily for 5 days), voriconazole 400 mg twice daily on the first day and 200 mg for 4 days) or placebo to 12 healthy volunteers.

Parameter	Placebo	Posaconazole	Posaconazole / Placebo		Voriconazole	Voriconazole / Placebo		Voriconazole / Posaconazole	
			GMR (90% CI)	p-value		GMR (90% CI)	p-value	GMR (90% CI)	p-value
Buprenorphine									
C_{max} (ng/ml)	0.70 ± 0.20	0.84 ± 0.27	1.20 (0.95, 1.51)	0.159	0.96 ± 0.27	1.37 (1.05, 1.79)	0.013	1.15 (0.93, 1.42)	0.333
t_{max} (h)	2.0 (1.0-3.0)	2.0 (1.5-3.0)	-	0.667	2.0 (1.5-3.0)	-	0.40	-	0.40
AUC_{0-18} (ng· h/ml)	4.1 ± 1.2	5.0 ± 1.3	1.22 (1.05, 1.41)	0.026	6.5 ± 1.7	1.58 (1.28, 1.94)	<0.001	1.30 (1.10, 1.53)	0.003
$AUC_{0-\infty}$ (ng· h/ml)	4.9 ± 1.3	6.1 ± 1.6	1.25 (1.20, 1.43)	0.008	8.9 ± 2.5	1.80 (1.45, 2.24)	<0.001	1.44 (1.23, 1.68)	<0.001
Cl/F (l/min)	2.9 ± 0.9	2.3 ± 0.7	0.80 (0.70, 0.91)	0.007	1.7 ± 0.6	0.56 (0.48, 0.65)	<0.001	0.70 (0.60, 0.81)	<0.001
Vz/F (l)	32 ± 12	27 ± 11	0.82 (0.63, 1.10)	0.430	25 ± 11	0.76 (0.52, 1.12)	0.22	0.93 (0.64, 1.36)	0.892
$t_{1/2}$ (h)	7.9 ± 2.8	8.1 ± 2.9	1.02 (0.77, 1.35)	0.991	11.0 ± 3.9	1.37 (0.88, 2.12)	<0.001	1.34 (0.90, 2.00)	0.230
Norbuprenorphine									
A_e (μg)	5.7 ± 2.2	4.8 ± 2.2	0.81 (0.58, 1.14)	0.239	9.0 ± 3.1	1.58 (1.18, 2.12)	<0.001	1.95 (1.45, 2.61)	<0.001

GMR, geometric mean ratio; CI, confidence interval; C_{max}, peak plasma concentration; t_{max}, concentration peak time; AUC_{0-18} and $AUC_{0-\infty}$, area under curve from 0 to 18 h and from 0 to infinity, respectively; $t_{1/2}$, elimination half-life; A_e, amount excreted into urine within 18 h. Values are normalized for a sublingual dose of 1.0 mg. Data are shown as mean ± standard deviation (SD) and as the geometric mean ratios with the 90% confidence interval (CI) in parenthesis - except for t_{max}, which is given as median and range.
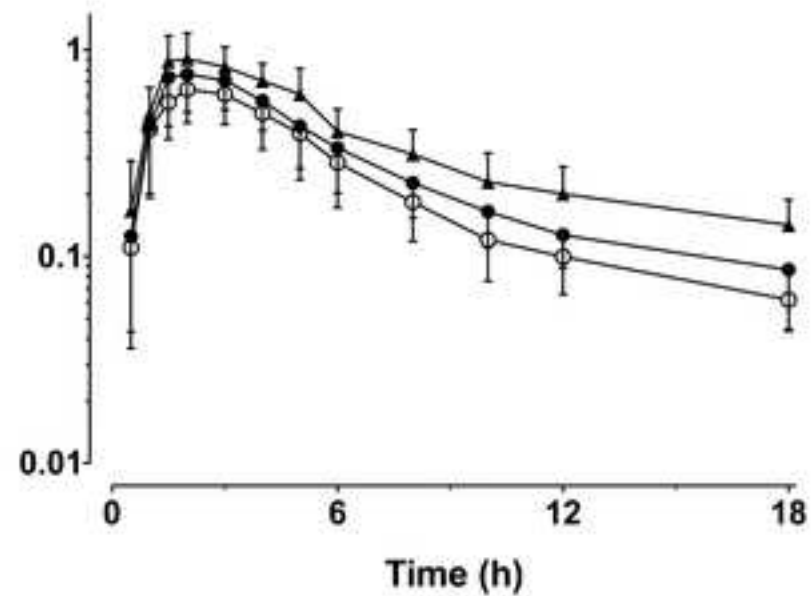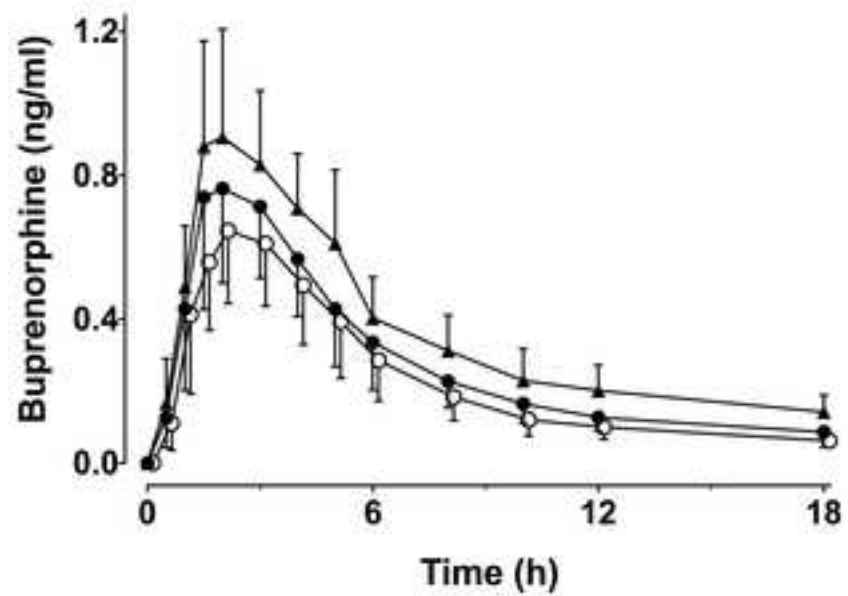
Legend:
- –O– Buprenorphine + placebo
- –●– Buprenorphine + posaconazole
- –▲– Buprenorphine + voriconazole

Figure_2

Figure_2