

ORIGINAL ARTICLE

Rifampicin decreases exposure to sublingual buprenorphine in healthy subjects

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Keywords

Cytochrome (P450) 3A4, first-pass metabolism, interaction, rifampicin, sublingual and intravenous buprenorphine.

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Abstract

Buprenorphine is mainly metabolized by the cytochrome P450 (CYP) 3A4 enzyme. The aim of this study was to evaluate the role of first-pass metabolism in the interaction of rifampicin and analgesic doses of buprenorphine. A four-session paired cross-over study design was used. Twelve subjects ingested either 600 mg oral rifampicin or placebo once daily in a randomized order for 7 days. In the first part of the study, subjects were given 0.6-mg (placebo phase) or 0.8-mg (rifampicin phase) buprenorphine sublingually on day 7. In the second part of the study, subjects received 0.4-mg buprenorphine intravenously. Plasma concentrations of buprenorphine and urine concentrations of buprenorphine and its primary metabolite norbuprenorphine were measured over 18 h. Adverse effects were recorded. Rifampicin decreased the mean area under the dose-corrected plasma concentration–time curve (AUC_{0-18}) of sublingual buprenorphine by 25% (geometric mean ratio (GMR): 0.75; 90% confidence interval (CI) of GMR: 0.60, 0.93) and tended to decrease the bioavailability of sublingual buprenorphine, from 22% to 16% ($P = 0.31$). Plasma concentrations of intravenously administered buprenorphine were not influenced by rifampicin. The amount of norbuprenorphine excreted in the urine was decreased by 65% ($P < 0.001$) and 52% ($P < 0.001$) after sublingual and intravenous administration, respectively, by rifampicin. Adverse effects were frequent. Rifampicin decreases the exposure to sublingual but not intravenous buprenorphine. This can be mainly explained by an enhancement of CYP3A-mediated first-pass metabolism, which sublingual buprenorphine only partially bypasses. Concomitant use of rifampicin and low-dose sublingual buprenorphine may compromise the analgesic effect of buprenorphine.

Abbreviations

A_e , The cumulative amount of free unconjugated buprenorphine and norbuprenorphine excreted into urine; AUC, The area under the plasma concentration–time curve; CI, confidence interval; C_{max} , The peak plasma concentrations; F%, relative bioavailability; GMR, Geometric mean ratios; MRM+, positive multireaction monitoring detection mode; SD, standard deviation; T_{max} , Time to the peak plasma concentration; UGT, UDP-glucuronosyl transferases.

Introduction

Buprenorphine is a widely used partial μ -opioid receptor agonist. In low doses, it is used as an analgesic and, in

moderate or high doses, it is used in the treatment of opioid withdrawal symptoms and maintenance therapy of opioid-dependent patients. In recent years, transdermal formulations have increased its use in the treatment of

moderate chronic pain (Fredheim *et al.* 2010; Zin *et al.* 2014). In the United Kingdom, use of buprenorphine for chronic noncancer pain in primary care has increased by 16.5-fold during the past decade (Zin *et al.* 2014).

Buprenorphine is extensively metabolized. Due to first-pass metabolism, the bioavailability of oral buprenorphine is very low (about 10–16%) and that of sublingual buprenorphine somewhat higher (30–55%), but data from different studies is very variable (Bullingham *et al.* 1982; Kuhlman *et al.* 1996; Mendelson *et al.* 1997; Nath *et al.* 1999; Cowan *et al.* 2005). After sublingual administration of buprenorphine, peak plasma concentrations are reached in 1–3 h (Bullingham *et al.* 1981; McAleer *et al.* 2003; Ciraulo *et al.* 2006).

The main metabolic pathway of buprenorphine is N-dealkylation to an active metabolite norbuprenorphine, catalyzed mainly (65%) by cytochrome P450 (CYP) 3A4, but also by CYP3A5 and CYP2C8 (Iribarne *et al.* 1997; Kobayashi *et al.* 1998; Moody *et al.* 2002; Picard *et al.* 2005; Chang *et al.* 2006). Buprenorphine and norbuprenorphine are further conjugated to buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide by UDP-glucuronosyl transferases (UGT) (Chang and Moody 2009), at least the first of which is pharmacologically active (Brown *et al.* 2011). Other metabolic pathways yield hydroxylated (M1–M5) and possibly other oxidative metabolites (Picard *et al.* 2005; Chang *et al.* 2006). Buprenorphine is mainly excreted as metabolites in bile (80–90%) and urine (10–30%) (Brewster *et al.* 1981; Cone *et al.* 1984).

Drug–drug interaction studies in opioid-dependent users of high-dose sublingual buprenorphine show that many CYP3A4 inhibitors such as atazanavir, ritonavir, and boceprevir increase plasma concentrations of buprenorphine (McCance-Katz *et al.* 2006, 2007; Hulskotte *et al.* 2015). Ketoconazole, however, has no effect on plasma concentrations of buprenorphine during transdermal administration in healthy subjects (Kapil *et al.* 2012). Although rifampicin has decreased greatly plasma buprenorphine concentrations causing opioid withdrawal symptoms in opioid-dependent persons on stable high-dose sublingual buprenorphine/naloxone treatment (McCance-Katz *et al.* 2011), its effect on low-dose buprenorphine has not previously been reported. Furthermore, most of the opioid-dependent patients in the above-mentioned study (McCance-Katz *et al.* 2011) were hepatitis C-positive and smokers, and many of them had used also other substances. In addition, effects of rifampicin on steady-state pharmacokinetics of buprenorphine are not necessarily identical with its effects on single-dose pharmacokinetics.

After sublingual administration, a part of buprenorphine dose bypasses the first-pass metabolism as it is

absorbed through the oral mucosa, and a part is swallowed and undergoes first-pass metabolism in the intestinal wall and liver. Enhancement of CYP3A4 activity by rifampicin (Niemi *et al.* 2003) may thus compromise the analgesic effects of buprenorphine. To our knowledge, neither the effect of rifampicin on intravenous administration of buprenorphine nor the role of first-pass metabolism in the magnitude of the rifampicin–buprenorphine interaction is known. Thus, we conducted a study to evaluate the effect of rifampicin on the pharmacokinetics of sublingual and intravenous buprenorphine in healthy subjects, using low doses applicable in the treatment of pain.

Materials and Methods

The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines. It was registered in the EudraCT clinical trials register under code number 2012-002871-32. Good Clinical Practice and International Council for Harmonisation regulations were followed in this study.

Subjects

Written informed consent was obtained from 12 healthy subjects, 5 women and 7 men (age range from 19 to 23 years and weight range from 57 to 95 kg). Their general health was good as assessed by their medical history, clinical examination, routine laboratory tests, and an ECG. Pregnancy tests for women and urine drug screening tests were negative. The subjects were not on any regular medication, including hormonal contraceptives. Female participants were instructed to use nonhormonal contraception throughout the study. Smoking was not allowed during the study. Participants abstained from any products with known effects on CYP enzyme activity such as herbal and grapefruit products for 4 weeks prior to the study. The risk of participants to develop opioid abuse was estimated low as evaluated by the Finnish translation of the Abuse Questions (Michna *et al.* 2004).

Study outline and drug administration

A four-session paired cross-over study design was used at intervals of 4 weeks. During each session, the subjects ingested as pretreatments either 600 mg oral rifampicin (Rimapen 600 mg[®] tabl, Orion, Finland) or placebo once daily at 8 P.M. for 7 days in randomized order. Adherence to the dosing schedule was assessed by use of mobile telephone text messages. In the first part of the study, subjects were given sublingually 0.6-mg or 0.8-mg buprenorphine (Temgesic 0.2 mg[®] resoriblets; RB

Pharmaceuticals Limited, Slough, Great Britain) after placebo or rifampicin, respectively, on day 7 at 11 A.M. after fasting overnight. In the second part of the study, subjects received an intravenous bolus of 0.4-mg buprenorphine (Temgesic 0.3 mg/mL[®] inj; RB Pharmaceuticals Limited, Slough, Great Britain) after rifampicin or placebo. Subjects were served standardized meals 4 and 8 h after buprenorphine. For nausea or vomiting, intravenous tropisetron was used, if clinically indicated. For itch or urticaria, cetirizine hydrochloride was used if indicated. Subjects consented to abstain from any products with known effects on CYP enzyme activity as well as alcohol, tea, coffee, cola, and energy drinks during the test days.

Blood samples (10 mL) were collected into ethylenediaminetetraacetic acid-containing tubes for pharmacokinetic measurements immediately before and 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 18 h after the administration of buprenorphine. Plasma was separated within 30 min and stored at -70°C until analysis. Urine was collected up to 18 h after buprenorphine administration. Urine aliquots were stored at -70°C until analysis. In the second part of the study, another venous cannula was inserted on the opposite forearm for intravenous administration of buprenorphine.

Adverse effects

Adverse effects were recorded before and 3 and 6 h after buprenorphine administration by a questionnaire.

Determination of buprenorphine and norbuprenorphine concentrations

Mass spectrometric detection of buprenorphine and norbuprenorphine was carried out using API 3000 Triple Quadrupole tandem mass spectrometer (Applied Biosystems MDS Sciex, Toronto, ON, Canada) as previously described (Ceccato *et al.* 2003), with minor modifications. The internal standards (buprenorphine-D4 and norbuprenorphine-D3) were added to samples, quality control samples, and reference standards before other preanalytical procedures. Plasma and urine samples (0.5 mL) were prepared by use of a Bond Elut C8 solid phase extraction (Agilent Technologies, Lake Forest, CA). Gradient chromatography was carried out using a Model 1100 Series liquid chromatograph (Agilent Technologies) equipped with a binary pump, a vacuum degasser, a thermostated column compartment, and an autosampler. Atlantis HILIC Silica analytical column (2.1 \times 100 mm; Waters, Milford, MA) with precolumn (2.1 mm \times 10 mm; Waters) were used at 30°C . The mobile phase A consisted of a mixture of acetonitrile: methanol: 10 mmol/L ammonium formate + 0.2% formic acid (90:5:5, v/v/v), and the mobile phase B of

10 mmol/L ammonium formate + 0.2% formic acid. The gradients were as follows: 0–0.5 min B = 0%, 0.5–5 min B \rightarrow 40%, 5–8 min B = 40%, 8.0–8.1 min B \rightarrow 0%, and 8.1–20 min B = 0%. The flow rate was 0.2 mL/min. The mass spectrometer was operated in positive multireaction monitoring (MRM⁺) detection mode with electro spray ionization. The selected ion transitions used for quantification were as follows: m/z 468.3 to m/z 55.1 for buprenorphine, m/z 414.3 to m/z 340.2 for norbuprenorphine, and m/z 472.3 to m/z 59.2 and m/z 417.3 to m/z 83.2 for the internal standards, respectively. The low limit of quantification (LLQ) for plasma buprenorphine was 0.02 ng/mL, and for norbuprenorphine 0.10 ng/mL. For urine buprenorphine and norbuprenorphine, the LLQ was 0.5 ng/mL. The inter-day coefficients of variation (CV%) were for plasma buprenorphine 8.0% at 5.3 ng/mL, 8.7% at 0.5 ng/mL, and 6.1% at 0.05 ng/mL, and for norbuprenorphine 3.7% at 4.8 ng/mL and 8.7% at 0.48 ng/mL.

Pharmacokinetic measurements

The peak plasma concentrations (C_{max}) and corresponding C_{max} times (t_{max}) of buprenorphine were observed directly from the data. After sublingual administration of buprenorphine, its plasma concentrations were not quantifiable at 18 h in eight subjects, from 8 h on in two subjects, and from 6 h on in one subject. Norbuprenorphine concentrations were below the quantitation limit in most of the plasma samples; therefore, its pharmacokinetics in plasma were not calculated. The area under the plasma concentration–time curve (AUC) values from 0 to 18 h (AUC_{0-18}) was calculated for buprenorphine by noncompartmental methods using the WinNonlin pharmacokinetics program (version 4.1; Pharsight, Mountain View, CA). We also calculated the relative bioavailability (F %) of buprenorphine, and the cumulative amount of free unconjugated buprenorphine and norbuprenorphine excreted into urine from 0 to 18 h (A_e). Pharmacokinetic parameters were normalized for a buprenorphine dose of 1.0 mg.

Statistical analysis

In view of our previous drug–drug interaction studies (Nieminen *et al.* 2009), we calculated that 10 subjects would be needed to detect a 30% difference in the area under the concentration–time curve (AUC_{0-18}) of buprenorphine at a power of 80% and a level of significance of $P < 0.05$. To be prepared for dropouts, we recruited 12 subjects.

The data were evaluated for normality of distribution using probit plots and the Shapiro–Wilk's W -test. Data were log transformed for analysis, but were reported as

nontransformed results. The AUC_{0-18} of buprenorphine was the primary outcome variable in the study. Geometric mean ratios (GMR) with 90% confidence intervals (CIs) were calculated for the pharmacokinetic variables. Lack of interaction was assumed if the 90% CI of the GMRs for pharmacokinetic variables were within the acceptance limit of 0.8–1.25. Differences in pharmacokinetic variables between rifampicin and placebo phases were analyzed using paired Student's *t*-test except for t_{max} which was analyzed using the Wilcoxon signed-ranks test. Differences were regarded as statistically significant at $P < 0.05$. The results are expressed as mean values \pm standard deviation (SD). All data were analyzed using R language for Statistical Computing, version 3.1.3 (R Core Team 2015), in RStudio, version 0.99.878 (RStudio 2015).

Results

Mean plasma concentrations of sublingual and intravenous buprenorphine during rifampicin and placebo phases are shown in Figure 1. Interindividual differences in pharmacokinetic variables were considerable (Table 1, Figs 2 and 3).

Rifampicin decreased the mean AUC_{0-18} of sublingual buprenorphine by 25% (GMR: 0.75; 90% CI of GMR: 0.60, 0.93) (Table 1, Figs. 1, 2). The bioavailability of sublingual buprenorphine decreased from the control value of 22 to 16% by rifampicin, but the change was not statistically significant (GMR: 0.84; 90% CI of GMR: 0.62, 1.13) (Table 1, Fig. 2). After intravenous buprenorphine administration, there were no statistically significant differences in plasma buprenorphine concentrations between

the placebo and rifampicin phases. Rifampicin decreased the cumulative excretion of free, nonconjugated norbuprenorphine in urine by 65% after sublingual (GMR: 0.35; 90% CI of GMR: 0.24, 0.51) and by 52% after intravenous (GMR: 0.48; 90% CI of GMR: 0.39, 0.58) administration, but the effect on buprenorphine excretion was less consistent (Table 1, Fig. 3).

All subjects experienced mild-to-moderate adverse effects during the study and needed medication (tropisetron) for nausea after buprenorphine. Nausea was more pronounced during the intravenous than sublingual part of the study. Eight subjects needed medication (cetirizine hydrochloride) for itch or urticaria during the intravenous part of the study.

Discussion

The results of this study show that rifampicin reduces the exposure to sublingual, but not to intravenous buprenorphine. Although this finding is most likely caused by an induction of CYP3A4 activity by rifampicin in the intestinal wall and liver, other mechanisms such as enhancement of UGT or P-glycoprotein activities may also be involved. The sublingual route of administration of buprenorphine is more vulnerable to the effects of an interaction with rifampicin than the intravenous one, as sublingual buprenorphine only partially avoids the induction of CYP3A4-mediated gastrointestinal metabolism by rifampicin.

CYP3A4 is involved in several steps in the metabolic pathways of buprenorphine. It catalyzes not only *N*-dealkylation of buprenorphine to norbuprenorphine but also

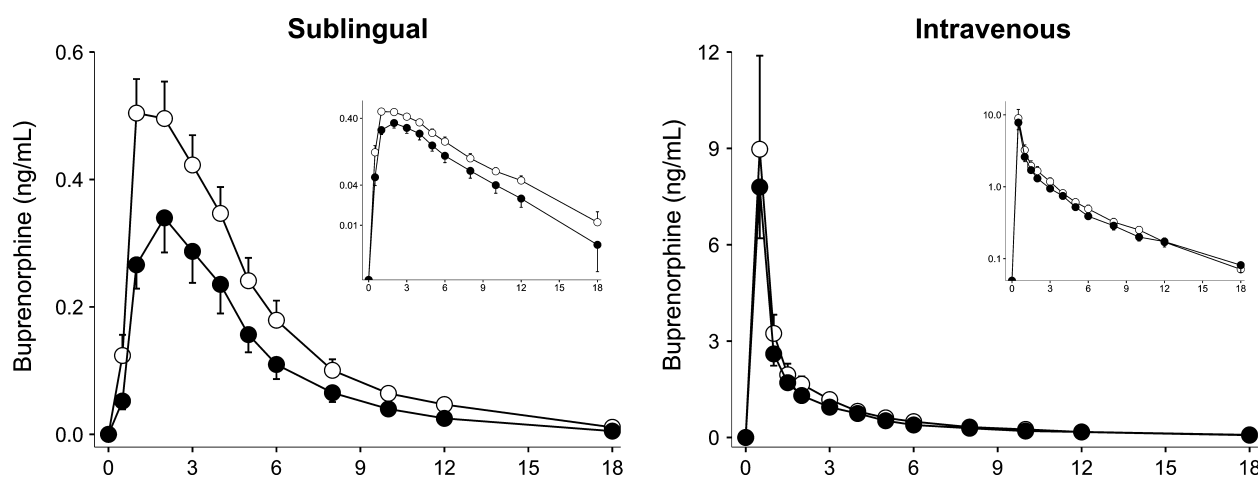


Figure 1. Mean plasma (SD) concentrations of buprenorphine in 12 healthy subjects after 0.6-mg (placebo phase) or 0.8-mg (rifampicin phase) sublingual buprenorphine or 0.4-mg intravenous buprenorphine on the seventh day of pretreatment with placebo (open circles) or rifampicin (filled circles) 600 mg once daily for 7 days. Values are normalized for a buprenorphine dose of 1.0 mg. Buprenorphine concentrations are shown both on an arithmetic and a semilogarithmic scale (inset).

Table 1. Dose-normalized pharmacokinetic parameters of buprenorphine and norbuprenorphine after sublingual administration of 0.6 mg (placebo phase) or 0.8 mg (rifampicin phase), or intravenous administration of 0.4 mg buprenorphine on the seventh day of pretreatment with rifampicin (600 mg once daily for 7 days) or placebo in 12 healthy subjects.

Parameter	Placebo	Rifampicin	P-value	Geometric mean ratio (90% CI)
<i>Sublingual phase</i>				
Buprenorphine				
C_{max} (ng/mL)	0.36 ± 0.15	0.30 ± 0.17	0.041	0.78 (0.64, 0.94)
t_{max} (h)	1.5 (1–3)	2 (1–3)	—	—
AUC _{0–18} (ng h/mL)	1.64 ± 0.74	1.36 ± 0.87	0.035	0.75 (0.60, 0.93)
F (%)	22 ± 10	16 ± 11	0.31	0.84 (0.62, 1.13)
A_e (μg)	0.21 ± 0.20	0.17 ± 0.20	0.82	0.71 (0.04, 12.52)
Norbuprenorphine				
A_e (μg)	4.35 ± 1.85	1.47 ± 0.66	<0.001	0.35 (0.24, 0.51)
<i>Intravenous phase</i>				
Buprenorphine				
AUC _{0–18} (ng h/mL)	5.32 ± 3.18	4.53 ± 1.64	0.37	0.92 (0.77, 1.08)
A_e (μg)	1.5 ± 0.7	2.7 ± 2.3	0.67	1.18 (0.59, 2.39)
Norbuprenorphine				
A_e (μg)	4.6 ± 1.9	2.3 ± 1.1	<0.001	0.48 (0.39, 0.58)

Values are normalized for a buprenorphine 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.

CI, confidence interval; C_{max} , peak plasma concentration; t_{max} , concentration peak time; AUC_{0–18}, area under curve from 0 to 18 h; A_e , amount excreted into urine within 18 h, F % relative bioavailability.

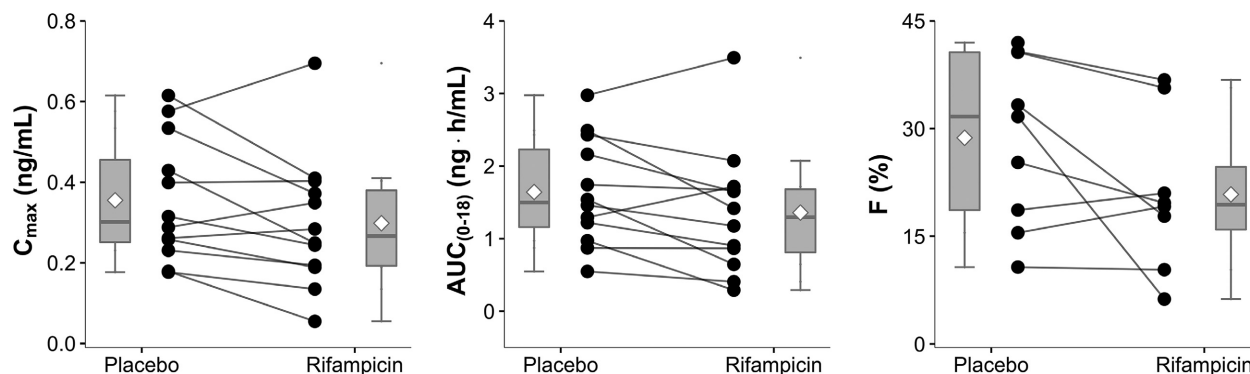


Figure 2. Box-plot analysis and individual parameters for maximum concentration (C_{max}), area under plasma concentration–time curve values from 0 to 18 h (AUC_{0–18}), and relative bioavailability (F %) in 12 healthy subjects after 0.6 mg (placebo phase) or 0.8 mg (rifampicin phase) sublingual buprenorphine on the seventh day of pretreatment with placebo or rifampicin 600 mg once daily for 7 days. The horizontal line in the box represents the median, white diamonds show the mean, the box shows the interquartile range, and whiskers show the 10th and 90th percentiles. Range of fold increase for AUC_{0–18} was 0.3–10 ng h/mL during the sublingual part and 0.62–1.50 ng h/mL during the intravenous part of the study. Values are normalized for a buprenorphine dose of 1.0 mg.

hydroxylation of buprenorphine to M1, and conversion of norbuprenorphine into M3 (Chang et al. 2006; Moody et al. 2009). In this study, rifampicin decreased the mean AUC_{0–18} of sublingual buprenorphine by 25% in healthy subjects. A previous study shows that when opioid-dependent subjects on stable, high doses of sublingual buprenorphine/naloxone were treated with rifampicin 600 mg daily for 15 days, a 70% decrease in the mean AUC of buprenorphine was detected, and withdrawal symptoms were frequent (McCance-Katz et al. 2011). It is

possible that the smaller effect of rifampicin on the exposure to sublingual buprenorphine in this study was due to shorter duration of rifampicin administration, that is, that the induction was not yet at its maximum within 7 days (Niemi et al. 2003). However, also different study populations, and a single, small buprenorphine dose versus over 10 times higher daily doses, administered up to steady state (McCance-Katz et al. 2011) may explain quantitatively different effects of rifampicin. Induction of CYP3A4 by rifampicin reduces the exposure also to several other

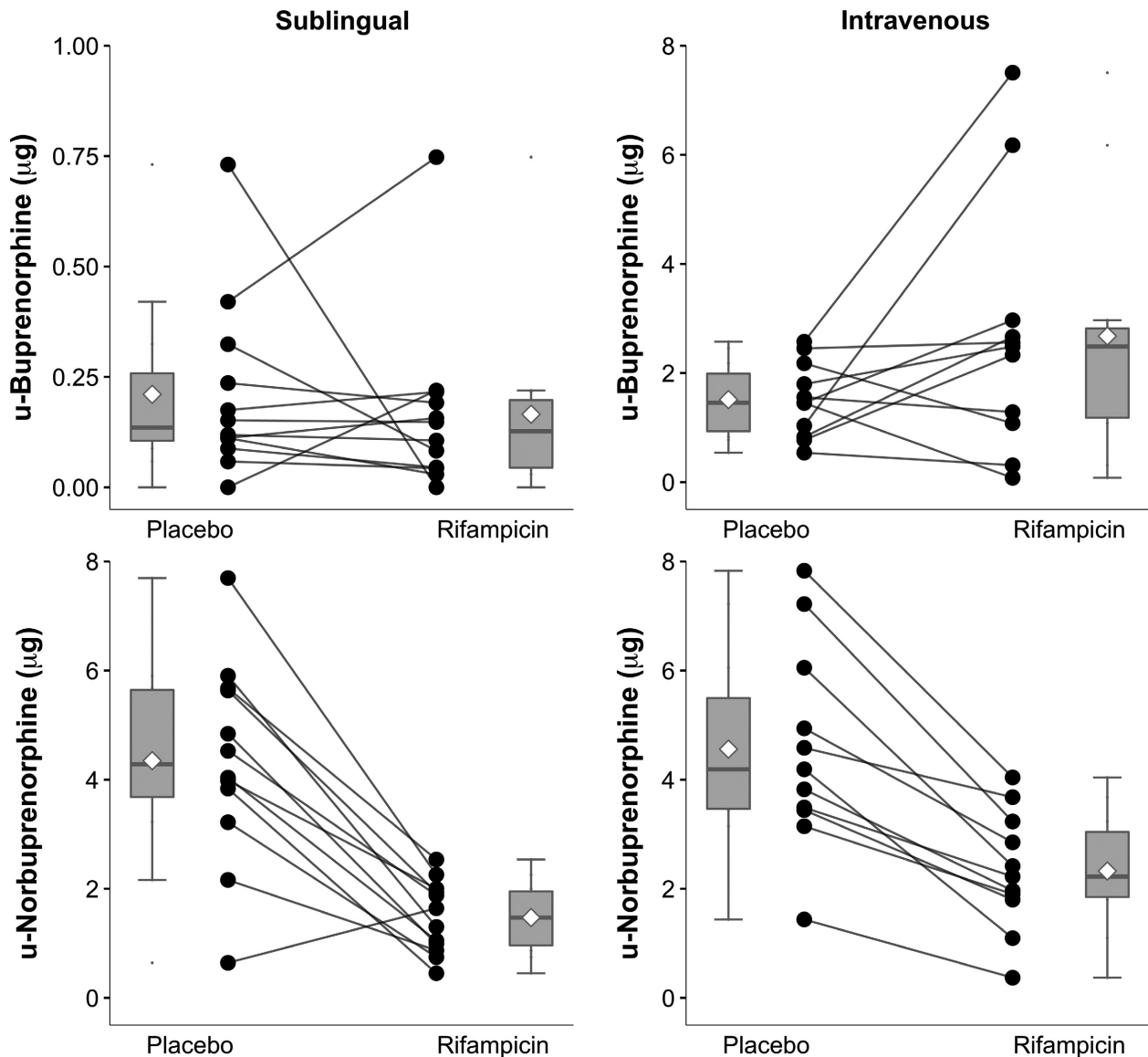


Figure 3. The individual amounts of urinary buprenorphine and norbuprenorphine excreted during 18 h in 12 healthy subjects after 0.6 mg (placebo phase) or 0.8 mg (rifampicin phase) sublingual buprenorphine or 0.4 mg intravenous buprenorphine on the seventh day of pretreatment with placebo or rifampicin 600 mg once daily for 7 days. The horizontal line in the box represents the median, white diamonds show the mean, the box shows the interquartile range, and whiskers show the 10th and 90th percentiles. Values are normalized for a buprenorphine dose of 1.0 mg.

opioid substrates of CYP3A4, such as methadone, alfentanil, oxycodone, and tramadol (Kharasch *et al.* 1997, 2004; Nieminen *et al.* 2009; Saarikoski *et al.* 2013). Although rifampicin can also act as a competitive inhibitor of organic anion transporting polypeptide (OATP) 1B1 and possibly of CYP2C8/CYP3A4 (Bidstrup *et al.* 2004; Kajosaari *et al.* 2005), this effect was avoided in this study by administering buprenorphine 15 h after the last dose of rifampicin.

Rifampicin enhances the activities of UGTs and P-glycoprotein (Greiner *et al.* 1999; Niemi *et al.* 2003; Soars

et al. 2004). As buprenorphine and norbuprenorphine are conjugated to buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide by UGTs (Chang and Moody 2009), it is possible that enhanced activity of UGTs by rifampicin contributed to the pharmacokinetic changes seen in this study. The role of P-glycoprotein in the transport of buprenorphine is less clear. *In vitro* studies in rodents suggest that norbuprenorphine, but not buprenorphine, is a substrate for P-glycoprotein, but its role in the transport of buprenorphine in humans is yet to be solved (Hassan *et al.* 2009; Brown *et al.* 2012).

CYP2C8 is involved in the formations of norbuprenorphine and M1 from buprenorphine (Moody *et al.* 2002; Chang *et al.* 2006). As rifampicin is an inducer and inhibitor of CYP2C8 (Kajosaari *et al.* 2005), it is possible that this enzyme may have contributed to the findings of this study. However, its role in the metabolism of buprenorphine is probably less important than that of CYP3A4, as *in vitro* studies suggest that the potency of rifampicin to induce CYP3A4 exceeds that of CYP2C8 (Dixit *et al.* 2007).

Bioavailability of oral buprenorphine is only approximately 10–16% due to its extensive first-pass metabolism in the intestinal wall and liver (Cowan *et al.* 2005). Sublingual administration of buprenorphine increases bioavailability to about 30–55% (Bullingham *et al.* 1982; Kuhlman *et al.* 1996; Mendelson *et al.* 1997; Nath *et al.* 1999; Cowan *et al.* 2005) as buprenorphine is markedly absorbed transmucosally from the oral cavity (Weinberg *et al.* 1988). Even though the participants in this study were well informed about how to use the sublingual tablet, they most likely ingested a part of the dose with saliva predisposing sublingual buprenorphine to enhanced intestinal and hepatic first-pass metabolism by rifampicin. This was reflected by a decrease in bioavailability of buprenorphine from 22% to 16% after pretreatment with rifampicin.

Only 10–30% of a buprenorphine dose is excreted in urine, mainly as metabolites (Cone *et al.* 1984). As norbuprenorphine is less lipophilic than the parent drug, its excretion into urine occurs, to some extent, also in the unconjugated form. After the sublingual administration of buprenorphine, the excretion of unconjugated norbuprenorphine was about 10-fold greater than that of buprenorphine, whereas after the intravenous administration, this difference did not exist. Rifampicin decreased the amount of unconjugated norbuprenorphine in urine after both sublingual and intravenous buprenorphine dosing, which may reflect a shift in the metabolic pathway toward hydroxylation of buprenorphine or norbuprenorphine by CYP3A4, or possibly, induction of further metabolism of norbuprenorphine by UGTs after rifampicin pretreatment (Chang *et al.* 2006; Chang and Moody 2009). Similarly, pretreatment with the CYP3A4 inducer/inhibitor efavirenz decreased urinary excretion of norbuprenorphine in subjects treated with buprenorphine/naloxone combination for opioid dependency (Moody *et al.* 2009).

The reduction in the AUC_{0-18} of buprenorphine by rifampicin pretreatment was significant after sublingual, but not after intravenous administration. This is a clinically important finding, as sublingual buprenorphine is more commonly used in the treatment of opioid dependence, opioid withdrawal symptoms, and pain than the

intravenous formula. The interaction of low-dose sublingual buprenorphine and rifampicin (or any other strong CYP3A4 inducer) may predispose a patient to diminished analgesic effects of buprenorphine or, on the other hand, to enhanced side-effects if rifampicin treatment is abruptly discontinued without a dose adjustment of buprenorphine.

There were some strengths and limitations in our study. The four-phase cross-over study design in healthy volunteers under strictly controlled conditions was used to confirm compliance with, for example, blood sampling and urine collection. Buprenorphine was given without naloxone to avoid any possible pharmacokinetic interferences of naloxone with buprenorphine and rifampicin. For safety reasons, we used single small doses of buprenorphine. Consistent with previous studies (Harris *et al.* 2004; Escher *et al.* 2007), adverse effects such as nausea and itch were frequent. Nausea and changes in saliva excretion may explain a part of the interindividual variability after sublingual administration. Nausea was treated with tropisetron which, theoretically, might have affected the results. However, as tropisetron is a very weak inhibitor of CYP2D6, and its concentrations achieved *in vivo* are at least one order of magnitude lower than its K_i -value (16 μM) needed for inhibition of CYP2D6 (Firkusny *et al.* 1995; Ho and Gan 2006), its effect on our results was most likely minimal. Itch and urticarial were treated with cetirizine. As cetirizine has a negligible interaction with liver enzymes (Chen 2008), this most likely did not influence the results of this study. Theoretically, the use of different doses of buprenorphine during various phases of the study might have biased dose-corrected results if buprenorphine had nonlinear pharmacokinetics. However, although the pharmacokinetics of buprenorphine appears to be nonlinear in rats (Gopal *et al.* 2002), there is no indication for nonlinear buprenorphine pharmacokinetics in humans (McAlear *et al.* 2003). Thus, there is no evidence that the dose of buprenorphine would affect the magnitude of its interaction with rifampicin.

Low-dose buprenorphine is increasingly used in the treatment of chronic pain but drug–drug interaction studies have mainly been conducted in subjects using intermediate or high doses for opioid dependency. In this study, rifampicin decreased the exposure to a low dose of sublingual buprenorphine, but did not affect intravenous buprenorphine exposure indicating that the sublingual route of administration is more vulnerable to the effects of an interaction with CYP3A4 inducers than the intravenous one. This is most likely explained by the fact that sublingual buprenorphine only partially avoids the enhanced first-pass metabolism by rifampicin. In clinical use, this interaction may be associated with diminished

analgesic effects of low-dose sublingual buprenorphine. Buprenorphine interaction with rifampicin can be avoided by choosing an intravenous route of administration when appropriate.

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Disclosure

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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