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Rifampin, but not Rifabutin, May Produce Opiate Withdrawal in Buprenorphine-Maintained Patients*

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Abstract

Background—This series of studies examines the pharmacokinetic/pharmacodynamic interactions between buprenorphine, an opioid partial agonist increasingly used in treatment of opioid dependence, and rifampin, a medication used as a first line treatment for tuberculosis; or rifabutin, an alternative antituberculosis medication.

Methods—Opioid-dependent individuals on stable doses of buprenorphine/naloxone underwent two, 24-hour blood sampling studies: 1. for buprenorphine pharmacokinetics and 2. following 15 days of rifampin 600 mg daily or rifabutin 300 mg daily for buprenorphine and rifampin or rifabutin pharmacokinetics.

Results—Rifampin administration produced significant reduction in plasma buprenorphine concentrations (70% reduction in mean area under the curve (AUC); p=<0·001) and onset of opiate withdrawal symptoms in 50% of participants (p=0·02). While rifabutin administration to buprenorphine-maintained subjects resulted in a significant decrease in buprenorphine plasma concentrations (35% decrease in AUC; p<0·001) no opiate withdrawal was seen. Compared with historical control data, buprenorphine had no significant effect on rifampin pharmacokinetics, but was associated with 22% lower rifabutin mean AUC (p=0·009), although rifabutin and its active metabolite concentrations remained in the therapeutic range.

Conclusions—Rifampin is a more potent inducer of buprenorphine metabolism than rifabutin with pharmacokinetic and pharmacodynamic adverse consequences. Those patients requiring

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Contributors Elinore McCance-Katz designed the study. David E. Moody managed all buprenorphine analysis, while Petrie M. Rainey directed all pharmacokinetics analyses. Elinore McCance-Katz and Sudha Prathikanti carried out clinical implementation, and Gerald Friedland performed consultation on treatment of tuberculosis. All authors contributed to and have approved the final manuscript.

Informed consent was obtained from all subjects who participated in this study and the US Department of Health and Human Services guidelines for human experimentation were followed in the conduct of this clinical research.

Conflict of Interest David E. Moody, has consulted for and received funding from Reckitt Benckiser, the manufacturer of buprenorphine, to perform research unrelated to this study. All other authors declare that they have no conflicts of interest.

rifampin treatment for tuberculosis and receiving buprenorphine therapy are likely to require an increase in buprenorphine dose to prevent withdrawal symptoms. Rifabutin administration was associated with decreases in buprenorphine plasma concentrations, but no clinically significant adverse events were observed.

Keywords

buprenorphine/naloxone; rifampin; rifabutin; tuberculosis; opioid addiction; drug interactions

1. Introduction

Tuberculosis is among the most common infectious diseases worldwide, with an estimated 9 million incident cases and 2-3 million deaths per year (World Health Organization, 2010). It is a major cause of morbidity and mortality in those with HIV/AIDS worldwide (Friedland, 2010; World Health Organization, 2010) and also has a considerably increased incidence in individuals with opioid addictions (Rich et al., 2005; Wang et al., 2006; Conover et al., 2001; Friedland, 2010; Altice, et al., 2010). In the United States, close to 30% of incident TB cases occur within the drug using population (Centers for Disease Control and Prevention, 2000).

Rifampin is a first-line agent for treatment of tuberculosis. It is a potent inducer of metabolism of cytochrome P 450 (CYP 450) hepatic enzymes (Centers for Disease Control and Prevention, 1998; Centers for Disease Control and Prevention, 2000; Burman et al., 2001) and its use is associated with induction of methadone metabolism, significant reduction in methadone exposure, and onset of opiate withdrawal (Kreek et al., 1976). As a result, methadone-maintained individuals requiring treatment for tuberculosis preferentially receive rifabutin, which is significantly more costly than rifampin and less widely available globally, but has not been associated with opiate withdrawal.

Buprenorphine (BUP) is an opioid partial agonist that offers an alternative to methadone treatment of opioid addiction (McCance-Katz, 2004) and has shown fewer adverse drug interactions with antiretroviral medications than has methadone (McCance-Katz et al., 2010). Although methadone and BUP share a common route of metabolism in CYP 450 3A4 (Iribarne et al.,1996; Iribarne et al., 1997) several other aspects of their metabolism differ. Methadone is metabolized to an inactive metabolite (EDDP) in a stereoselective manner. The contribution of CYP2B6 to methadone N-demethylation accounts for much of the stereoselective metabolism; while other enzymes (CYP2C9 and 2D6) can perform the metabolism, they do not appear to be clinically significant in the clearance of methadone (Totah et al., 2008; Chang et al., 2010). BUP is metabolized to norbuprenorphine (norBUP) and both the parent compound and metabolite are glucuronidated (Cone et al., 1984). Besides CYP3A4, CYP2C8 also forms norBUP (Moody et al, 2002). NorBUP is a potentially active metabolite with mu opioid agonist activity which may be protective from opiate withdrawal when drugs that are inducers of CYP 3A4 are co-administered (Kuhlman et al., 1998).

Because of the high incidence of tuberculosis as an opportunistic infection in those with opioid addiction, particularly those with comorbid HIV/AIDS, and because BUP is increasingly used in the treatment of opioid dependence, it is important to understand whether clinically significant drug-drug interactions occur between BUP and commonly used tuberculosis medications. The following were the goals of the current studies: 1) To determine whether the pharmacokinetics of the opioid dependence medication, BUP (administered in this study as the buprenorphine/naloxone [BUP/NLX] combination sublingual tablet that is used in the clinical setting for the treatment of opioid dependence),

are affected by co-administration of either of the tuberculosis medications, rifampin or rifabutin; 2) to determine whether the pharmacokinetics of these tuberculosis medications are affected by co-administration of BUP/NLX by comparison with the pharmacokinetics of historical controls receiving only rifampin or rifabutin, and 3) to determine whether clinically significant pharmacodynamic effects or toxicities occur when BUP/NLX is administered simultaneously with either tuberculosis medication. Answers to these questions could make a significant contribution to optimizing clinical care for tuberculosis-infected, opioid-dependent patients.

2 Methods

2.1 Procedures

Twenty-one individuals participated in this project (12 in the BUP/rifampin study and nine in the BUP/rifabutin study), which was reviewed and approved by the Institutional Review Board at the University of California San Francisco (UCSF). The study is registered at ClinicalTrials.gov (NCT00877591). Participants received treatment for opioid dependence with BUP/NLX in the Addiction Medicine Treatment Research Program at San Francisco General Hospital and provided voluntary written informed consent for study participation. Study samples were based on a power analysis showing that nine opioid-dependent individuals were needed for within-subjects analyses aimed at determining the effect of rifampin or rifabutin on BUP. The study design has been previously reported (McCance-Katz et al., 2006). Briefly, stabilized BUP/NLX-treated individuals underwent a 24-hour study to determine BUP pharmacokinetics and a second 24-hour study for BUP and either rifampin or rifabutin pharmacokinetics, following 15 days of either rifampin 600 mg daily or rifabutin 300 mg daily. The co-administration periods of 15 days for BUP/NLX and rifampin or rifabutin were chosen because 1 week is required for full induction of CYP 3A4 by rifampin (Niemi et al., 2003) and it could take several days to observe opiate withdrawal following full induction of metabolic enzymes. Rifabutin, while an inducer of CYP 3A4 (Benedetti, 1995), does not appear to be as potent an inducer of CYP 3A4 as rifampin, given that it has been reported not to produce opiate withdrawal in methadone-maintained individuals in contrast to rifampin (Brown et al., 1996). The elimination half-life of rifabutin is 36 hours (Skinner et al. 1989); steady state is achieved in 7.5 days. We therefore postulated that a 15 day dosing period would be sufficient to assure that full induction of metabolic enzymes would have occurred and steady state was reached for rifampin and rifabutin and that opiate withdrawal, if it were to occur, would be observed within this period of time for both medications with BUP/NLX. Stabilization was defined as at least two weeks on a stable dose of BUP/NLX with no illicit opioid use as confirmed by urine toxicology screen (which included an expanded opioids panel that tested for heroin, morphine, codeine, oxycodone, hydrocodone, methadone and buprenorphine). Participants had observed dosing of medications and were clinically evaluated daily throughout the study period for onset of opiate withdrawal. If this occurred, the medication administration was terminated early and participants were admitted to the UCSF Clinical and Translational Science Institute Clinical Research Center for the second 24-hour pharmacokinetics study. In those cases, the BUP dose was increased as clinically indicated following the completion of the pharmacokinetics study. We used existing historical control data to examine the effect of BUP on the pharmacokinetics of rifampin and rifabutin. When available, data in the published literature (Loos et al., 1985; Sekar et al., 2010) were used to compare area under the curve (AUC), oral clearance (CL/F), maximum concentration in plasma (C_{max}), time of C_{max} (T_{max}), trough values (C_{24}), and half-life values with those observed in the presence of BUP in our subjects.

Study procedures included standardized and validated measures of opioid withdrawal by clinician rating using the Clinical Opiate Withdrawal Scale (COWS) (Wesson and Ling,

2003) and cognitive impairment using the Mini-Mental State Examination (Folstein et al., 1975) for opioid-dependent participants (maximum score=30; scores of <27 are indicative of cognitive impairment with severity proportional to decrease in score). Adverse symptoms were recorded for all participants using an Adverse Symptoms Checklist (McCance-Katz et al., 2006) that queried for a wide range of adverse experiences including changes in energy, gastrointestinal symptoms, central nervous system effects, genitourinary symptoms, and other somatic complaints scored for severity on an ordinal scale (0-3, with 0=not present, 1=mild, 2=moderate, and 3=severe, maximum possible score=87). These ratings were administered at baseline, following stabilization on BUP (prior to rifampin or rifabutin administration), and at completion of the rifampin or rifabutin dosing period.

2.2 Analytical Assays

Buprenorphine assay—Plasma BUP and metabolite concentrations were determined using a previously described liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (Huang et al., 2006) except that BUP-d_4 and norBUP-d_3 were used as the internal standards for their respective glucuronides.

Rifampin assay—Samples were analyzed at National Jewish Hospital, Denver, CO using their standard procedures. Briefly, samples were extracted by adding acidified methanol and centrifugation. Samples were analyzed by reverse phase isocratic HPLC employing UV detection at 275 nm. A six-point calibration curve and three levels of quality control samples were extracted and analyzed in parallel with each group of study samples. The calibration curve ranged from 0·5 to 50 mcg/mL.

Rifabutin assay—Samples were analyzed at National Jewish Hospital, Denver, CO, using their standard procedures. Briefly, samples were analyzed by isocratic HPLC with UV detection at 275 nm. Samples were extracted by liquid/liquid extraction of a 1-mL aliquot, concentrated to a final volume of 300 μL. An eight-point calibration curve and three levels of quality control samples were extracted and analyzed in parallel with each group of study samples. The calibration curve ranged from 10 - 2000 ng/mL.

2.3 Pharmacokinetics Analysis

The pharmacokinetic parameters of BUP, norBUP, buprenorphine-3-glucuronide (BUP-3-glucuronide), norbuprenorphine-3-glucuronide (norBUP-3-glucuronide), rifampin, and rifabutin were evaluated as appropriate for each subject. BUP and metabolite pharmacokinetics were calculated following sublingual administration of BUP/NLX alone and again following administration of either rifampin or rifabutin. Pharmacokinetic parameters were determined by non-compartmental analysis. For statistical analysis and comparison, all BUP concentrations were normalized to a standard dose of 16 mg by multiplying each concentration by the factor, 16/(administered dose). Normalized steady-state AUC was calculated using the trapezoidal rule over the dosing interval ($AUC_{0\text{-}24}$). Sublingual (BUP) or oral (rifampin or rifabutin) clearance (CL/F) was determined as AUC/standard dose. Apparent half-life was determined as ln2/kel, where the elimination rate constant, kel, was determined as the negative slope of the linear segment of a plot of ln (concentration) versus time. Maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and trough concentration (C_{24}) were determined directly from the normalized timed concentration measurements. For metabolites, concentrations were also normalized to a 16 mg BUP dose and CL/F was calculated based on the standard16 mg dose. The F term thereby represents the fraction of parent drug ultimately converted to the metabolite. For purposes of non-compartmental analysis, drug concentrations that were less than the detection limit were expressed as one-half of the detection limit. All pharmacokinetic parameters were summarized and displayed by treatment period.

2.4 Statistical Analysis

Previous experience with drug interaction studies examining BUP in combination with antiretroviral medications indicated that the within-subject coefficient of variation (CV) for the AUC would be approximately 40%. We also assumed that a 40% change or greater in BUP AUC would be of clinical importance, as we observed in our study of atazanavir/ritonavir with BUP (McCance-Katz et al., 2007) which required a sample size of ten with alpha of 0·05 and beta of 0·80 for a within-subject comparison. The rifabutin study was originally planned for ten subjects, but was terminated before enrollment of the last subject after interim analysis demonstrated a highly significant decrease in AUC of BUP ($p < 0·001$). The paired *t*-test was used to test the significance of the differences in pharmacokinetic parameters for BUP and metabolites (within-subject analyses). The unpaired t-test was used for between-subjects comparisons of rifampin and rifabutin parameters with historical control data. The Wilcoxon test was used for the within-subject comparison of the nonparametric values of Tmax and the Mann-Whitney test was used for between-subjects comparison of Tmax. Comparisons of subject characteristics were made by single factor ANOVA. Comparisons of severity of opiate withdrawal were made using paired t-tests. A difference was considered statistically significant if the p value was $\leq 0·05$ (two-tailed).

3 Results

3.1 Study Participants

Table 1 summarizes the characteristics of study participants in each of the two pharmacokinetics studies. Mean age was 45 years in both groups and mean number of years of heroin use was 20·9 (4·5) [mean (standard error, SE)]. Women comprised 58% of the rifampin/BUP sample and 56% of the rifabutin/BUP sample. The mean dose of BUP/NLX was 14/3·5 mg daily. Other current substance use disorders included cocaine abuse (three participants) and cannabis abuse (five participants) in the BUP/rifampin sample and in the BUP/rifabutin study cocaine abuse (two participants), methamphetamine abuse (one participant) and cannabis abuse (one participant). Cigarette smoking was common, but use for both samples was less than one pack daily. No participants met diagnostic criteria for an alcohol use disorder or had a diagnosis of an acute mental disorder. Injection drug use was reported by 75% of the BUP/rifampin sample and 89% of the BUP/rifabutin sample and all injection drug users also showed evidence of Hepatitis C infection. However, indices of hepatic function (ALT, AST) remained within normal range throughout the study period (Table 2).

3.2 Pharmacokinetic results

Pharmacokinetic parameters for BUP and metabolites before and after either rifampin or rifabutin administration are shown in Tables 3 and 4, respectively. Figures 1 and 2 graphically represent mean concentrations of BUP (1a, 2a), the active metabolite, norBUP (1b, 2b), and the inactive glucuronides of BUP (1c, 2c) and norBUP (1d, 2d) over a 24-hour dosing interval for BUP/rifampin and BUP/rifabutin, respectively. Both rifampin and rifabutin significantly altered the pharmacokinetics of BUP with a 70% decrease in $AUC_{0\text{-}24}$ following rifampin administration ($p<0·001$), and a lesser, albeit significant, effect of rifabutin with a 35% decrease in AUC ($p<0·001$). Decreases were also observed in maximum plasma concentration (Cmax) and trough plasma concentrations (C_{24}), with C_{24} more affected than Cmax, and rifampin having greater effects than rifabutin. The sublingual clearance of BUP (Cl/F) was proportionately increased for each medication.

Rifampin administration was associated with significant decreases in norBUP AUC (88%), Cmax (77%) and C_{24} (92%) (all with $p < 0·001$). This was also accompanied by proportionate increases in norBUP clearance. The effects of rifampin on norBUP were

substantially greater than its effects on BUP (Table 3). In contrast, rifabutin administration produced no significant effects on norBUP PK (Table 4).

There were few significant effects of rifampin or rifabutin on pharmacokinetic parameters of BUP-3-glucuronide. Because it is an inactive metabolite, the statistically significant effects on Tmax and C_{24} are unlikely to be of clinical significance. The pharmacokinetics of norBUP-3-glucuronide were significantly altered with rifampin administration (Table 3), but not with rifabutin (Table 4). This is likely to be a reflection of the differing effects of the two drugs on the precursor molecule, norBUP, and again is unlikely to have clinical significance.

3.3 Clinical results

The clinical manifestations of these pharmacokinetic interactions differed for the two medications. Rifampin administration was associated with a significant increase in opiate withdrawal symptoms in 50% of study participants as measured by the COWS (p=0·02), while rifabutin did not show an association with increased opiate withdrawal symptoms (Fig 3). Opiate withdrawal symptoms in participants receiving rifampin were of sufficient severity that five study participants, were terminated from the study prior to completing the 15 day rifampin administration period and one participant showed evidence of opiate withdrawal on the day of the final pharmacokinetics study (day 15). Opiate withdrawal symptoms were observed as early as 6 days after starting rifampin (range of onset of opiate withdrawal symptoms following initiation of rifampin was 6-15 days). These individuals were all admitted to the CRC following clinical evaluation in which significant opiate withdrawal symptoms were observed. Following completion of the 24-hour pharmacokinetics study, participants were offered BUP/NLX dose increases and four participants accepted a dose increase. Doses were increased 25-100% for a period ranging from one to five days, after which time the dose was decreased to the former maintenance dose on which the participant had been stable (Table 5). The participant able to complete the 15 day study period, but who experienced mild withdrawal at the time of the second pharmacokinetics study, received a BUP/NLX dose increase of 25% for two days followed by resolution of symptoms and a return to the previous dose on which this individual had been stable (16/4 mg daily) (Table 5). In contrast, none of the nine participants receiving rifabutin experienced clinically important opioid withdrawal symptoms.

3.4 Effect of Buprenorphine on Rifampin or Rifabutin

BUP effect on rifampin or rifabutin pharmacokinetics was determined by comparing pharmacokinetics for those medications in the presence of BUP with existing data from historical controls who had steady-state pharmacokinetic measurements made during chronic administration of standard clinical doses of either rifampin 600 mg daily (Loos et al., 1985) or rifabutin 300 mg daily (Sekar et al., 2010). Figures 4a and 4b show rifampin and rifabutin plasma concentrations, respectively, in the presence of BUP. Tables 6a and 6b compare the pharmacokinetic parameters observed during coadministration of BUP with parameters that were determined from the historical studies. The AUC, oral clearance and half-life of rifampin were not significantly different from those in the historical control study (Table 6a). On the other hand, AUC for rifabutin in BUP-treated participants was significantly decreased, as was Cmax, while Tmax was significantly increased, relative to historical controls receiving rifabutin alone (Table 6b). Conversely, the active metabolite, desacetylrifabutin had a significantly greater AUC and Cmin when administered in combination with BUP/NLX. A statistically significant decrease in AUC for the sum of rifabutin and desacetylrifabutin was also observed (Table 6b).

3.5 Adverse Symptoms

Concurrent administration of BUP and either rifampin or rifabutin had no significant effect on cognition (as measured by Mini Mental State Examination), hepatic function (as measured by AST, ALT and bilirubin), cardiac conduction (as measured by cardiac QTc and PR interval), or lipids (as measured by cholesterol and triglycerides). While there was a statistically significant increase in cholesterol and a statistically significant decrease in PR interval in the BUP/rifampin sample, the values remained within normal limits and the changes were not clinically significant (Table 2).

Adverse symptoms were infrequently reported by study participants receiving BUP, BUP/rifampin, or BUP/rifabutin. The only statistically significant increase in adverse symptoms occurred in those receiving BUP and rifampin concurrently. Those adverse symptoms included headaches (p=0·05), drowsiness (p=0·05), sweating (p=0·01), and early morning awakening (p=0·01). All of these symptoms were mainly attributed to those participants who experienced significant opiate withdrawal. No other adverse symptoms reported by study participants reached statistical significance.

4 Discussion

Rifampin, a medication used worldwide as part of the first line regimen for the treatment of tuberculosis, was associated with significant reductions in BUP and norBUP concentrations when administered at a standard clinical dose to individuals stably maintained on BUP/NLX for treatment of opioid dependence. The $AUC_{0\text{-}24}$ for BUP was reduced by 70%, while that of norBUP was reduced 88%. C_{max} was decreased by 39% and 77%, respectively, and trough concentrations (C_{24}) were lowered by 87% and 92%, respectively. These observed reductions in BUP and norBUP concentrations were presumably a consequence of induction of BUP metabolism. Consistent with the observed reductions in BUP and norBUP exposure, opiate withdrawal symptoms of moderate severity were observed in 50% (6 of 12) study BUP/NLX-maintained participants. Opiate withdrawal symptoms occurred in some participants after as little as six days of simultaneous administration. These findings are similar to those observed when methadone-maintained, opioid-dependent individuals were given rifampin (Kreek et al., 1976). Although significant decreases in BUP AUC, Cmax, and Cmin were observed with rifabutin co-administration, in contrast to rifampin, this was not associated with opiate withdrawal symptoms.

The induction of BUP metabolism by rifampin appears to be readily reversible upon rifampin discontinuation, as most participants experiencing opiate withdrawal received only brief increases in BUP/NLX dose (up to five days) with complete resolution of opiate withdrawal symptoms and a return to the previous dose of BUP/NLX on which they had been stable. In this study, most experienced resolution of withdrawal with a BUP/NLX dose increase of 25-50%. These increased doses remained within the dose range approved by the FDA for this drug (up to 24/6 mg daily). Subjects in this study were followed clinically by the investigators after terminating study participation until they were restabilized on BUP/NLX.

It is difficult to predict which patients will develop adverse drug interactions and opiate withdrawal with concomitant administration of BUP and rifampin. In this study, 50% of the sample developed opiate withdrawal. There were no significant differences in participants who developed opiate withdrawal versus those who did not when compared by age, weight, or cigarette smoking. Five of the six participants who developed opiate withdrawal were women. In our previous study in which we reported the onset of opiate withdrawal in those receiving methadone with lopinavir/ritonavir (McCance-Katz et al., 2003), we were able to correlate symptoms with lower baseline methadone doses, as well as higher body weight,

older age, and moderate alcohol intake (five drinks or more weekly). In the current study, only one affected participant had been stabilized on a low dose of BUP/NLX (8/2 mg daily). The remaining participants who experienced withdrawal had stabilized on a standard clinical dose of 16/4 mg daily. Alcohol use was modest in this sample overall, and in the subgroup that developed opiate withdrawal symptoms, the highest alcohol use reported was 1-2 drinks weekly. Chronic cocaine use has been shown to be associated with lower BUP plasma concentrations (McCance-Katz et al., 2010), but in this sample cocaine use was minimal.

The study of the interaction of BUP and rifabutin showed no evidence of symptoms of opiate withdrawal indicating that rifabutin might possibly be substituted for rifampin should a BUP/NLX-treated patient requiring tuberculosis treatment have difficulty tolerating the combination of rifampin and BUP/NLX. The finding for rifabutin with BUP may be explained by the pharmacokinetics data showing that trough BUP and norBUP concentrations following rifampin co-administration were significantly lower than those observed when BUP/NLX was given in combination with rifabutin. Plasma concentrations of combined BUP and norBUP that exceed 0·7 ng/ml have been reported to be associated with suppression of withdrawal symptoms (Kuhlman et al., 1998). For rifampin, mean trough BUP concentration (C_{24}) decreased by 87% from 1·46 (0·22) ng/mL (BUP alone) to 0·19 (0·03) ng/mL, while mean norBUP decreased by 92% from 3·57 (0·48) ng/mL to 0·29 (0·05) ng/mL. These are substantially lower than those observed for BUP and norBUP when rifabutin was administered. With rifabutin treatment, mean trough levels were 0·72 (0·15) for BUP and 1·8 (0·2) for norBUP. In our previous study of the interaction of efavirenz and BUP, we reported that mean trough BUP concentration was reduced by 51% and norBUP was decreased by 66%. We previously speculated that the combined concentrations of BUP and norBUP in those receiving efavirenz were sufficient to prevent the onset of opiate withdrawal. Rifampin administration was associated with more marked decrements in BUP and norBUP trough concentrations, such that the combined trough levels fell below the previously reported minimum trough concentration needed to prevent the onset of opiate withdrawal.

Rifampin has been reported to be among the most potent inducers of CYP3A4 (Centers for Disease Control and Prevention, 1998; Centers for Disease Control and Prevention, 2000; Burman et al., 2001) and, further, it is an inducer of glucuronidation (Oesch et al., 1996; Gallicano et al., 1999). These are two of the major pathways of BUP and norBUP elimination (Cone et al., 1984; Chang and Moody, 2009). This combination of effects may work in concert to greatly reduce exposure to BUP and its active metabolite, norBUP, thus rendering vulnerable individuals more susceptible to development of opiate withdrawal symptoms. Further, two mechanisms may be involved in the marked decrease in norBUP. First, it has been shown that norBUP can be further metabolized by CYP3A4 to hydroxyl metabolites (Chang et al., 2006). We have shown that some antiretrovirals impact this pathway (Moody et al., 2009), and rifampin may induce further metabolism of norBUP via this route. NorBUP is also a substrate for p-glycoprotein (Hassan et al., 2009) and rifampin is an inducer of p-glycoprotein (Paine et al., 2002). Either or both of these pathways may contribute to the significant decrease in norBUP which along with decreased BUP contributes to the adverse effect of rifampin.

In contrast to findings for BUP with rifampin, mean trough BUP concentration while receiving rifabutin decreased by only 43% and norBUP trough concentrations decreased by 18%, and no withdrawal symptoms were observed in this sample. Although rifabutin induces CYP 3A4 activity (Benedetti, 1995), it had no clinically significant effect in precipitating opiate withdrawal in BUP/NLX-maintained individuals, despite lower BUP exposure. This relationship is similar to that reported when methadone is administered with rifabutin (Brown et al., 1996). While no opiate withdrawal was observed in this small

sample, it should be noted that if opiate withdrawal symptoms, increased opioid craving or relapse to opioid use are observed when rifabutin is administered simultaneously with BUP during long-term treatment, an increase in BUP dose should be considered.

In comparing the effects of BUP/NLX administration on rifampin pharmacokinetics, as compared with a historical control (Table 6a), no significant effects were observed. On the other hand, BUP/NLX treatment produced statistically significant reductions in mean AUC_{0-24}, and Cmax, but not in C_{24} of rifabutin (Table 6b). The very similar half-lives observed for rifabutin are consistent with similar clearance and imply decreased bioavailability as the primary cause for lower AUC. Tmax was delayed, consistent with delayed absorption, possibly caused by decreased gastric motility in the presence of BUP. Both decreased bioavailability and delayed absorption would be expected to contribute to the lower observed Cmax. The paradoxically higher Cmin in the presence of BUP is presumably due to the shorter elimination phase resulting from the delayed Cmax, since the mean half-lives were similar for both groups.

Desacetylrifabutin is the active metabolite of rifabutin, and is thought to be equipotent in its antituberculosis effects. Overall drug effects may be best correlated with the sum of rifabutin and desacetyrifabutin. Increased metabolism of rifabutin might be expected to lead to increased desacetylrifabutin concentrations, as observed here. However, the increases in desacetylrifabutin were not sufficient to offset the decreases in rifabutin, as reflected in the net decrease in AUC for the total of rifabutin and desacetylrifabutin of 18%. Nonetheless, this drop in AUC_{0-24} is unlikely to be clinically significant.

Rifampin containing regimens have been first line treatments of tuberculosis for decades, but the findings from this study, in combination with those previously demonstrating a potent rifampin-induced pharmacokinetic and pharmacodynamic effect on methadone metabolism with opioid withdrawal, call attention to the risks of rifampin administration with opioid dependence therapy. However, we also note that we were able to relieve opiate withdrawal symptoms rapidly with an increase in buprenorphine dose. Studies indicate equivalent therapeutic success for tuberculosis with rifabutin, although these studies were not conducted in opioid-maintained individuals (Brogden and Fitton, 1994). Therefore, while in this study rifabutin administered at standard, clinical doses used in the treatment of tuberculosis were not associated with opiate withdrawal, further study is needed to determine the effectiveness of rifabutin for tuberculosis in buprenorphine-treated patients.

There are several limitations to these studies. The first is that these studies enrolled small samples who received study medications for a short period, which is not fully comparable to what would occur in a clinical situation where a BUP/NLX-maintained participant would receive tuberculosis treatment for a much longer period of time. Therefore, we cannot comment on long-term adverse events that might occur with chronic co-administration of these medications. Neither rifampin nor rifabutin has been systematically studied for effectiveness of treating tuberculosis in BUP/NLX-maintained patients; therefore we cannot comment on possible treatment recommendations based on the data from these studies. While we made an estimate as to length of time necessary to allow for induction of CYP3A4 by rifampin and rifabutin, based on existing literature and based on the length of time judged to be feasible to obtain participant adherence to the study protocols, it is possible that longer co-administration of these medications might have revealed additional information of clinical importance. Another limitation is that we were did not conduct any studies using alternate administration regimens for BUP; for example, every other day dosing or every third day dosing of BUP. Further studies are needed to better address these continuing clinical questions.

In summary, in the study of the interaction of BUP with rifampin, we present the first reported drug-drug interaction with BUP to be associated with opiate withdrawal. To date, although other medications have lowered BUP plasma concentrations, the magnitude of those effects was insufficient to produce adverse clinical events. As rifampin is among the most potent inducers of hepatic enzymes (Centers for Disease Control and Prevention, 1998; Centers for Disease Control and Prevention, 2000; Burman et al., 2001), this finding is not surprising, but needs to be widely known among clinicians caring for patients with opiate addiction and tuberculosis. The production of opiate withdrawal syndromes or other drug toxicities can lead to non-adherence to prescribed medications with a risk of tuberculosis treatment failure. Ineffective treatment of tuberculosis is responsible for continued ongoing transmission as well as the development of drug resistance (Shenoi et al., 2009). Increased abuse of other illicit substances or alcohol in an attempt to alleviate the discomfort resulting from withdrawal symptoms may also occur and represent additional risks to patients. Among opioid addicted persons, treatment of both tuberculosis and HIV/AIDS is best accomplished if therapy for substance abuse is addressed (Altice et al., 2010; World Health Organization, 2008; McCance-Katz, 2005). Although readily available in the United States, rifabutin is not available in most countries in Eastern Europe, the former Soviet Union, and Asia, where both opioid addiction and tuberculosis are most common. In these settings, rifampin use remains necessary and careful attention to opioid withdrawal symptoms in those receiving opioid dependence therapies is critically important. It appears that management of such symptoms among those receiving BUP need not be difficult and can be accomplished by informed clinicians. These findings underscore the need to continue to perform drug-drug interaction studies in humans that examine BUP in combination with other frequently prescribed medications. Such studies will help to inform patient care, reduce the likelihood of adverse events, and improve clinical outcomes in those with opioid dependence and other co-occurring diseases.

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References

Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. 2010; 376:367–387. [PubMed: 20650518]

Benedetti MS. Inducing properties of rifabutin, and effects on the pharmacokinetics and metabolism of concomitant drugs. Pharmacol. Res. 1995; 32:177–187. [PubMed: 8866833]

Brogden RN, Fitton A. Rifabutin: a review of its antimicrobial activity, pharmacokinentic properties and therapeutic efficacy. Drugs. 1994; 47:983–1009. [PubMed: 7521834]

Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rifabutin and methadone in HIV-infected former injecting drug users. Drug Alcohol Depend. 1996; 43:71–77. [PubMed: 8957145]

Burman W, Gallican K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin. Pharmacokinet. 2001; 40:327–341. [PubMed: 11432536]

Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR. 1998; 47:11–15.

Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR. 2000; 49:185–189. [PubMed: 11795500]

Chang Y, Fang WB, Lin SN, Moody DE. Stereo-selective metabolism of methadone by human liver microsomes and cDNA-expressed cytochrome P450s: a reconciliation. Basic Clin. Pharmacol. Toxicol. 2010 DOI:10.1111/j.1742-7843.2010.00628.x.

Chang Y, Moody DE, McCance-Katz EF. Novel metabolites of buprenorphine in human liver microsomes and human urine. Drug Metab. Dispos. 2006; 34:440–448. [PubMed: 16381669]

Chang Y, Moody DE. Glucuronidation of buprenorphine and norbuprenorphine by human liver microsomes and UDP-glucuronosyltransferases. Drug Metab. Lett. 2009; 3:101–107. [PubMed: 19601871]

Cone E, Gorodetzky C, Yousefnejad D, Buchwald W, Johnson R. The metabolism and excretion of buprenorphine in humans. Drug Metab. Dispos. 1984; 12:577–581. [PubMed: 6149907]

Conover C, Rizdon R, Valway S, Schoenstadt L, McAuley J, Onorato I, Paul W. Outbreak of multi-drug resistant tuberculosis at a methadone treatment program. Int. J. Tuberc. Lung Dis. 2001; 5:59–64. [PubMed: 11263518]

Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975; 12:189–198. [PubMed: 1202204]

Friedland G. Infectious disease comorbidities adversely affecting substance users with HIV: hepatitis C and tuberculosis. J. Acquir. Immune Defic. Syndr. 2010; 55:S37–S42. [PubMed: 21045598]

Gallicano KD, Sahai J, Shukla VK, Seguin I, Paluts A, Kwok D, Foster BC, Cameron DW. Induction of zidovudine glucuronidation and amidation pathways by rifampicin in HIV-infected patients. Br. J. Pharmacol. 1999; 48:168–179.

Hassan HE, Myers AL, Coop A, Eddington ND. Differential involvement of P-glycoprotein (ABCB1) in permeability, tissue distribution, and antinociceptive activity methadone, buprenorphine, and diprenorphine: in vitro and in vivo evaluation. J. Pharm. Sci. 2009; 98:4928–4940. [PubMed: 19370547]

Huang W, Moody DE, McCance-Katz EF. The in vivo glucuronidation of buprenorphine and norbuprenorphine determined by liquid chromatography-electrospray ionization-tandem mass spectrometry. Ther. Drug Monit. 2006; 28:245–251. [PubMed: 16628138]

Iribarne C, Berthou F, Baird S, Dréano Y, Picart D, Bail JP, Beaune P, Ménez JF. Involvement of cytochrome P450 3A4 enzyme in the n-demethylation of methadone in human liver microsomes. Chem. Res. Toxicol. 1996; 9:365–373. [PubMed: 8839037]

Iribarne C, Picart D, Dreano Y, Bail JP, Berthou F. Involvement of cytochrome P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. Life Sci. 1997; 60:1953–1964. [PubMed: 9180349]

Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N. Engl. J. Med. 1976; 294:1104–1106. [PubMed: 1256526]

Kuhlman JJ, Levine B, Johnson RE, Fudala PJ, Cone EJ. Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, maintenance and withdrawal from sublingual buprenorphine. Addiction. 1998; 93:549–559. [PubMed: 9684393]

Loos U, Musch E, Jensen JC, Mikus G, Schwabe HK, Eichelbaum M. Pharmacokinetics of oral and intravenous rifampicin during chronic administration. Klin Wochemschr. 1985; 163:1205–1211.

McCance-Katz EF, Moody DE, Morse GD, Friedland G, Pade P, Baker J, Alvanzo A, Smith P, Ogundele A, Jatlow P, Rainey PM. Interactions between buprenorphine and antiretrovirals I: nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. Clin. Infect. Dis. 2006; 43:S224–S234. [PubMed: 17109309]

McCance-Katz EF, Moody DE, Morse GD, Ma Q, DiFrancesco R, Friedland G, Pade P, Rainey PM. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend. 2007; 91:269–278. [PubMed: 17643869]

McCance-Katz EF, Rainey P, Friedland G, Jatlow P. The protease inhibitor lopinavir/ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin. Infect. Dis. 2003; 37:476–482. [PubMed: 12905130]

McCance-Katz EF, Rainey PM, Moody DE. Effect of cocaine use on buprenorphine pharmacokinetics in humans. Am. J. Addict. 2010; 19:38–46. [PubMed: 20132120]

McCance-Katz EF, Sullivan LS, Nallani S. Drug interactions of clinical importance between the opioids, methadone and buprenorphine, and frequently prescribed medications: a review. Am. J. Addict. 2010; 19:4–16. [PubMed: 20132117]

McCance-Katz EF. Office based treatment of opioid dependence with buprenorphine. Harv. Rev. Psychiatry. 2004; 12:321–338. [PubMed: 15764468]

McCance-Katz EF. Treatment of opioid dependence and HIV/HCV co-infection in opioid dependent patients: the importance of drug interactions between opioids and antiretroviral medications. Clin. Inf. Dis. 2005; 41:S89–S95.

Moody DE, Chang Y, Huang W, McCance-Katz EF. The in vivo response of novel buprenorphine metabolites, M1 and M3, to antiretroviral inducers and inhibitors of buprenorphine metabolism. Basic Clin. Pharmacol. Toxicol. 2009; 105:211–215. [PubMed: 19500085]

Moody DE, Slawson MH, Strain EC, Laycock JD, Spanbauer AC, Foltz RL. A liquid chromatographic-electrospray ionization-tandem mass spectrometric method for determination of buprenorphine, its metabolite, norbuprenorphine, and a coformulant, naloxone, that is suitable for in vivo and in vitro metabolism studies. Anal. Biochem. 2002; 306:31–39. [PubMed: 12069411]

Nieimi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin. Clin. Pharmacokinet. 2003; 42:819–850. [PubMed: 12882588]

Oesch F, Arand M, Benedetti MS, Castelli MG, Dostert P. Inducing properties of rifampicin and rifabutin for selected enzyme activities of the cytochrome P-450 and UDP-glucuronosyltransferase superfamilies in female rat liver. J. Antimicrob. Chemother. 1996; 37:1111–1119. [PubMed: 8836814]

Paine MF, Wagner DA, Hoffmaster KA, Watkins PB. Cytochrome P450 and P-glycoprotein mediate the interaction between an oral erythromycin breath test and rifampin. Clin. Pharmacol. Ther. 2002; 72:524–535. [PubMed: 12426516]

Rich JD, McKenzie M, Shield DC, Wolf FA, Key RG, Poshkus M, Clarke J. Linkage with methadone treatment upon release from incarceration: a promising opportunity. J. Addict. Dis. 2005; 24:49–59. [PubMed: 16186082]

Sekar V, Lavreys L, Van de Casteele T, Berckmans C, Spinosa-Guzman S, Vangeneugden T, De Pauw M, Hoetelmans R. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. Antimicrob. Agents Chemother. 2010; 54:4440–4445. [PubMed: 20660678]

Shenoi S, Heysell S, Moll T, Friedland G. Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community. Curr. Opin. Infect. Dis. 2009; 22:11–17. [PubMed: 19532076]

Skinner MH, Hsieh M, Torseth J, Pauloin D, Bhatia G, Harkonen S, Merigan TC, Blaschke TF. Pharmacokinetics of rifabutin. Antimicrob. Agents Chemother. 1989; 33:1237–1241. [PubMed: 2552902]

Totah RA, Sheffels P, Roberts T, Whittington D, Thummel K, Kharasch ED. Role of CYP 2B6 in human methadone metabolism. Anesthesiology. 2008; 108:363–374. [PubMed: 18292673]

Wang W, Xiao H, Lu L. Case-control, retrospective study of pulmonary tuberculosis in heroin abusing patients in China. J. Psychoactive Drugs. 2006; 38:203–205. [PubMed: 16903459]

Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J. Psychoactive Drugs. 2003; 35:253–259. [PubMed: 12924748]

World Health Organization. Global Tuberculosis Control. WHO Rep.; Geneva: 2010.

World Health Organization. Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach. WHO Rep.; Geneva: 2008.

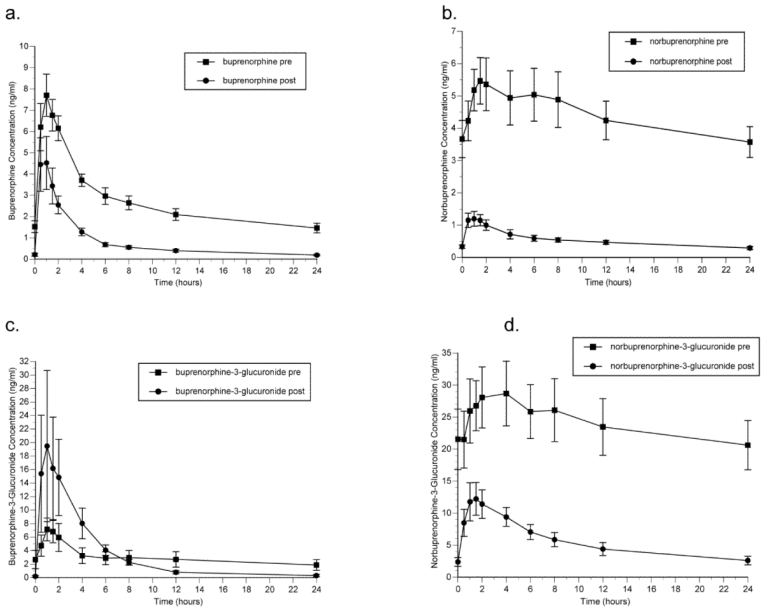

Figure 1.
Effect of rifampin on a. buprenorphine, b. norbuprenorphine, c. buprenorphine-3-glucuronide, and d. norbuprenorphine-3-glucuronide

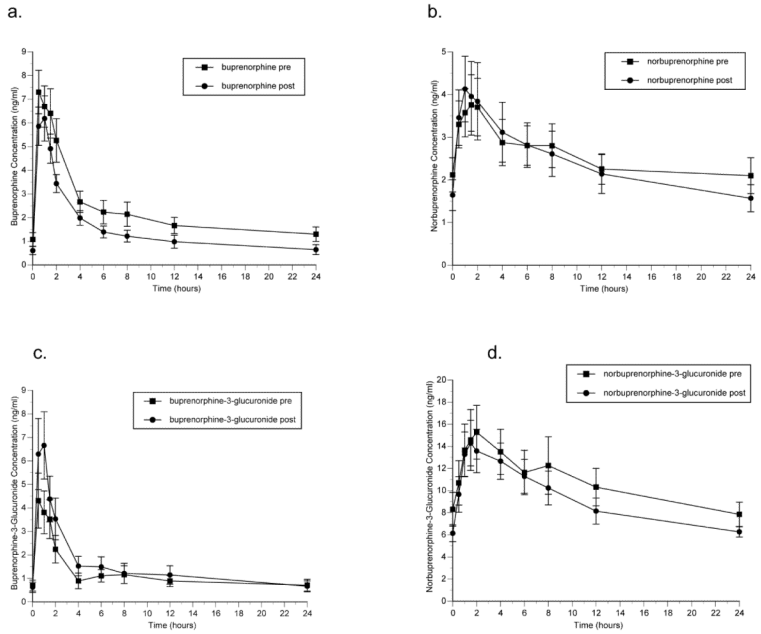

Figure 2.
Effect of rifabutin on a. buprenorphine, b. norbuprenorphine, c. buprenorphine-3-glucuronide, and d. norbuprenorphine-3-glucuronide

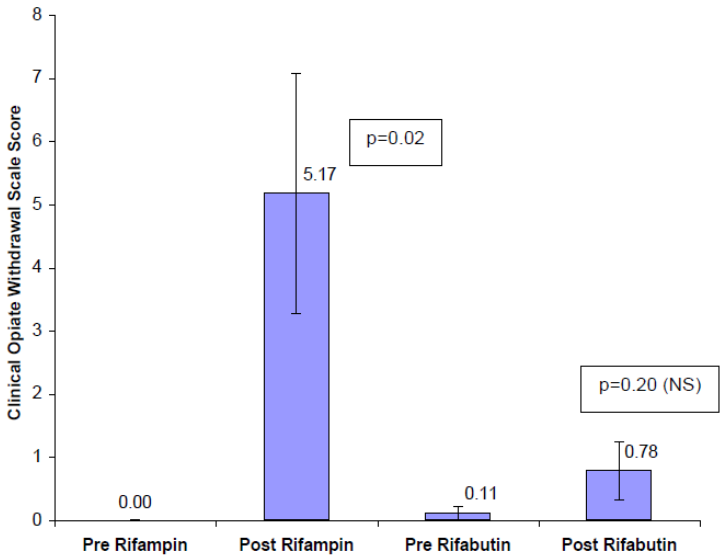

Figure 3.
Effect of rifampin or rifabutin on ratings of opiate withdrawal severity

Figure 4a.

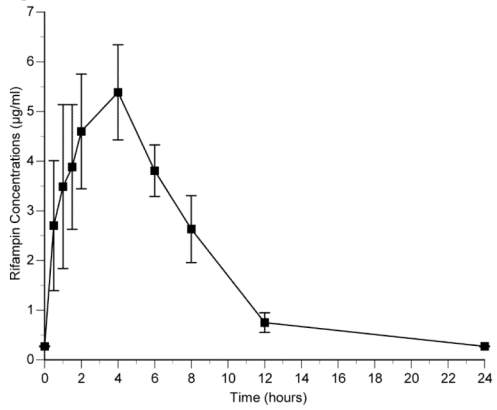

Figure 4b.

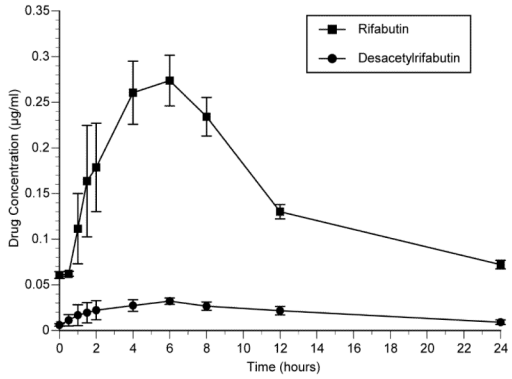

Figure 4.
Effect of buprenorphine on a. rifampin concentrations, b. on rifabutin and desacetylrifabutin concentrations

Table 1

Participant demographics and characteristics

	Rifampin n = 12	**Rifabutin n = 9**
Age (yrs)	44.8 (2.7)[#]	45.2 (3.4)
Weight (kg)	69.1 (3.8)	70.0 (3.8)
Buprenorphine/Naloxone Dose (mg/day)	14.2 (1.0)/ 3.5 (0.2)	14.0 (1.1)/ 3.5 (0.3)
Female	7 [58%]	5 [56%]
Race:		
African-American	2 [17%]	0 [0%]
Caucasian	7 [58%]	7 [78%]
Hispanic	2 [17%]	2 [22%]
Pacific Islander	1 [8%]	0 [0%]
Substance Use Disorders:		
Opioid Dependence	12 [100%]	9 [100%]
Cocaine Abuse	3 [25%]	2 [33%]
Marijuana Abuse	5 [42%]	1 [22%]
Amphetamine Abuse	0 [0%]	1 [11%]
Injection Drug Use	9 [75%]	8 [89%]
Nicotine Use Packs/Day	0.6 (0.1)	0.7 (0.1)
Hepatitis C Positive	9 [75%]	8 [89%]

[#] mean (SE)

[ ] percent of sample affected

Table 2

Physiological and Cognitive Responses Prior to and Following Rifampin or Rifabutin Administration

	Rifampin Pre/Post n=12	**Rifabutin Pre/Post n=9**
AST (U/L)	28.6 (4.0)[#]/ 29.5 (4.4)	34.2 (8.4)/ 35.7 (6.0)
ALT (U/L)	27.5 (5.0)/ 37.8 (8.5)	37.6 (12.8)/ 33.9 (9.4)
Total Bilirubin (mg/dL)	0.4 (0.1)/ 0.3 (0.0)	0.4 (0.1)/ 0.3 (0.0)
Cholesterol (mg/dL)	173.3 (10.3)/ 199.7 (11.1)[*]	180.1 (10.4)/ 165.6 (10.5)
Triglycerides (mg/dL)	80.9 (9.3)/ 81.3 (8.2)	87.1 (9.4)/ 102.8 (13.4)
QTc Interval (msec)	421.5 (5.8)/ 425.2 (5.0)	415.8 (6.0)/ 418.8 (8.8)
PR Interval (msec)	157.0 (5.4)/ 146.7 (5.6)[†]	163.6 (7.9)/ 166.2 (6.4)
Mini-Mental State Examination Score	28.7 (0.3)/ 28.6 (0.4)	28.9 (0.3)/ 28.3 (0.2)
Adverse Symptom Checklist Score	7.8 (1.5)/ 14.4 (4.2)	4.1 (1.3)/ 7.2 (2.3)
Clinical Opiate Withdrawal Scale Score	0.0 (0.0)/ 5.2 (1.9)[§]	0.1 (0.1)/ 0.8 (0.5)

[#] mean (SE)

[*] p = 0.002

[†] p = 0.05

[§] p = 0.02

Table 3

Effect of rifampin on buprenorphine and buprenorphine metabolite pharmacokinetic parameters (all parameter values adjusted to a standard dose of 16 mg buprenorphine)

Pharmacokinetic Parameter	Pre-rifampin (n = 12)	With rifampin (n = 12)	p value
Buprenorphine			
AUC_{0-24} (ng-h/ml)	65.2 (6.7)	19.3 (2.9)	<0.001
Cl/F (L/h)	274 (27)	1010 (119)	<0.001
C_{max} (ng/ml)	8.1 (0.9)	5.0 (1.3)	0.009
T_{max} (h)	1.0 (1.0–2.0)	1.0 (0.5–1.5)	n.s.
C_{24}	1.46 (0.22)	0.19 (0.03)	<0.001
Norbuprenorphine			
AUC_{0-24} (ng*h/ml)	105 (15.2)	12.7 (1.7)	<0.001
Cl/F (L/h)	195 (28)	1527(203)	<0.001
C_{max} (ng/ml)	6.0 (0.8)	1.4 (0.2)	<0.001
T_{max} (h)	1.5 (1–12)	1.0 (0–2)	<0.02
C_{24}	3.57 (0.48)	0.29 (0.05)	<0.001
Buprenorphine-3-Glucuronide			
AUC_{0-24} (ng*h/ml)	71.4 (26.2)	83.3 (23.7)	0.73
Cl/F (L/h)	565 (144)	449 (127)	0.42
C_{max} (ng/ml)	8.6 (2.1)	26.2 (10.4)	0.14
T_{max} (h)	1.25 (1–2)	2.0 (0.5–6)	<0.05
C_{24}	1.87 (0.79)	0.31 (0.17)	0.036
Norbuprenorphine-3-Glucuronide			
AUC_{0-24} (ng*h/ml)	576 (104)	132 (25)	<0.001
Cl/F (L/h)	37 (5)	183 (37)	0.001
C_{max} (ng/ml)	32.5 (5.3)	13.4(2.6)	0.003
T_{max} (h)	1.75 (1-8)	1.5 (0.5–6)	n.s.
C_{24}	20.6 (3.8)	2.60 (0.67)	<0.001

Note: Values are the mean (standard error of the mean), except that T_{max} is given as median (range). The paired t-test was used to determine p-values for all parameters except T_{max}, where the Wilcoxon test was used.

Table 4

Effect of rifabutin on buprenorphine pharmacokinetic parameters (all parameter values adjusted to a standard dose of 16 mg buprenorphine)

Pharmacokinetic Parameter	Pre-rifabutin (n = 9)	With rifabutin (n = 9)	p value
Buprenorphine			
AUC_{0-24} (ng-h/ml)	57.5 (6.7)	37.6 (5.58)	<0.001
Cl/F (L/h)	304 (29)	498 (66)	0.004
C_{max} (ng/ml)	9.0 (1.3)	7.1 (1.7)	0.007
T_{max} (h)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	n.s.
C_{24}	1.26 (0.23)	0.72 (0.15)	0.02
Half-life (h) (n=6)	28.5 (8.2)	24.9 (5.5)	0.76
Norbuprenorphine			
AUC_{0-24} (ng*h/ml)	65 (6.7)	62 (8.4)	0.63
Cl/F (L/h)	269 (31)	301 (41)	0.67
C_{max} (ng/ml)	4.4 (0.4)	4.6 (0.7)	0.80
T_{max} (h)	1.0 (0.5 – 2)	1.0 (0.5 – 1.5)	n.s.
C_{24}	2.2 (0.3)	1.8 (0.2)	0.31
Half-life (h) (n=6)	42.1 (5.5)	36.5 (10.2)	0.75
Buprenorphine Glucuronide			
AUC_{0-24} (ng*h/ml)	37 (7.1)	40 (7.5)	0.61
Cl/F (L/h)	618 (139)	625 (163)	0.95
C_{max} (ng/ml)	6.3 (1.0)	9.1 (2.0)	0.30
T_{max} (h)	0.5 (0.5 – 1.5)	0.5 (0.5 – 1.0)	n.s.
C_{24}	0.82 (0.21)	0.75 (0.18)	0.45
Norbuprenorphine Glucuronide			
AUC_{0-24} (ng*h/ml)	290 (35)	249 (24)	0.14
Cl/F (L/h)	61 (5.9)	70 (7.2)	0.20
C_{max} (ng/ml)	17.8 (2.0)	16.3 (1.7)	0.44
T_{max} (h)	2.0 (1.5 – 2)	1.5 (1.0 – 4.0)	n.s.
C_{24}	8.9 (0.9)	7.3 (0.5)	0.11

Note: Values are the mean (standard error of the mean), except that T_{max} is given as median (range). The paired t-test was used to determine p-values for all parameters except T_{max}, where the Wilcoxon test was used.

Table 5

Opiate Withdrawal with Rifampin Administration

Subject	Bup/Nlx Dose (mg/d)	COWS (pre)	COWS (post)	Days of Rifampin Administration	Increase in Buprenorphine Dose (%) Number of Days at Increased Dose ( )
1	16/4	0	2	15	0
2	16/4	0	0	15	0
3	16/4	0	7	10	0
4	16/4	0	23	12	50 (5)
5	16/4	0	1	15	0
6	8/2	0	1	15	0
7	16/4	0	4	15	25 (2)
8	16/4	0	0	15	0
9	10/2.5	0	0	15	0
10	8/2	0	7	6	100 (1)
11	16/4	0	10	8	25 (1)
12	16/4	0	7	11	0

Table 6a

Effect of Buprenorphine on Rifampin Pharmacokinetics

Pharmacokinetic Parameter	Buprenorphine (n=12)	Historic Controls (n=12)	p value
AUC (mcg-h/mL)	44.8 (4.2)	53.2 (8.7)	0.39
Cl/F (L/h)	15.2 (8.8-35.0)	16.4 (2.9)	0.75
Half-Life (h)	2.04 (0.13)	1.64 (0.14)	0.06

Table 6b

Effect of Buprenorphine on Rifabutin Pharmacokinetics

Pharmacokinetic Parameter	Buprenorphine (n=9)	Historic Controls (n=15)	p value
Rifabutin			
AUC_{0-24} (ng-h/mL)	3622 (203)	4659 (250)	0.009
C_{max} (ng/mL)	351 (44)	565 (34)	<0.001
T_{MAX} (h)	6 (1.5-8)	2.5 (1-6)	0.009
C_{24} (ng/mL)	72 (5)	62 (4)	n.s.
Half-Life (h)	13.3 (1.2)	12.7 (0.8)	n.s.
Desacetylrifabutin			
AUC_{0-24} (ng-h/mL)	477 (81)	339 (30)	0.07
C_{max} (ng/mL)	43.6 (9.0)	41.0 (4.1)	n.s.
C_{24} (ng/mL)	9.0 (2.5)	3.7 (0.3)	0.01
Rifabutin+desacetyl-rifabutin			
AUC_{0-24} (ng-h/mL)	4100 (276)	5015 (258)	0.03