Pharmacokinetic Interaction Between Telaprevir and Methadone

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Running title: Telaprevir and methadone interaction
ABSTRACT

Hepatitis C virus (HCV) antibody is present in most patients enrolled in methadone maintenance programs. Therefore, interactions between the HCV protease inhibitor telaprevir and methadone were investigated. The pharmacokinetics of R- and S-methadone were measured after administration of methadone alone, and after 7 days of telaprevir (750 mg q8h) co-administration in HCV-negative subjects on stable, individualized methadone therapy. Unbound R-methadone was measured in pre-dose plasma samples before and during telaprevir co-administration. Safety and symptoms of opioid withdrawal were evaluated throughout the study. In total, 18 subjects were enrolled; 2 discontinued prior to receiving telaprevir. C_{min}, C_{max}, and AUC_{24h} for R-methadone were reduced by 31%, 29%, and 29%, respectively, in the presence of telaprevir. The AUC_{24h} ratio of S-/R-methadone was not altered. The median unbound percentage of R-methadone increased by 26% in the presence of telaprevir. The median (absolute) unbound C_{min} of R-methadone, was similar in absence (10.63 ng/mL) and presence of telaprevir (10.45 ng/mL). There were no symptoms of opioid withdrawal, and no discontinuations due to adverse events. In summary, exposure to total R-methadone was reduced by approximately 30% in the presence of telaprevir, while the exposure to unbound R-methadone was unchanged. No symptoms of opioid withdrawal were observed. These results suggest that dose adjustment of methadone is not required when initiating telaprevir treatment.
INTRODUCTION

Hepatitis C virus (HCV) infection is widespread among previous intravenous drug users who shared syringes and drug preparation equipment (1). Methadone is commonly used as a maintenance therapy for opiate dependence, and prevalence of HCV antibody of up to 96% has been reported among patients enrolled in methadone maintenance programs (2). Telaprevir is a novel agent for the treatment of genotype 1 chronic HCV infection in adults, as shown by significantly improved rates of sustained HCV RNA clearance in combination therapy with pegylated interferon/ribavirin compared with pegylated interferon/ribavirin alone (3–5). Use of telaprevir for treatment of HCV infection includes patients receiving methadone maintenance therapy.

Methadone is a synthetic narcotic analgesic that is administered as a combination of $R$- and $S$-isomers, with the $R$-isomer being mainly responsible for the opioid effect (6, 7), whereas the $S$-isomer has been linked to QTc prolongation (8). Methadone is primarily metabolized by $N$-demethylation to an inactive metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP). Cytochrome P450 enzymes, primarily CYP3A, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine (9). According to U.S. labeling for methadone, co-administration of a CYP3A inhibitor and methadone may potentiate the opioid effects of methadone (9).
As telaprevir has been shown to be a potent inhibitor of CYP3A (10), a study to evaluate the potential drug-drug interaction between telaprevir and methadone was initiated. The main objective of this Phase I clinical study was to investigate the effect of steady-state telaprevir on the steady-state pharmacokinetics (PK) and pharmacodynamics of methadone to guide dosing recommendations for concurrent use of these therapeutic agents.

MATERIALS AND METHODS

Subjects. Eligible subjects were HCV-negative adults (18–55 years old, male or female), on a stable methadone maintenance dose of 30 to 130 mg q.d. Females had to be at least 2 years post-menopausal. Body mass index (BMI) had to be between 18.0 and 30.0 kg/m². All subjects obtained approval for participation in this study from the physician treating their addiction, who agreed to provide medical care after discharge from the study center. Subjects were healthy at screening, as shown by physical examination, medical history (except drug abuse), electrocardiogram (ECG), vital signs, blood biochemistry, blood coagulation, hematology tests, and urinalysis.

Subjects were to be excluded following a positive result for any of the following infectious disease tests: hepatitis A IgM antibody, hepatitis B antigen, HCV antibody, or human immunodeficiency virus type 1 or 2 antibody. Subjects also had to comply with protocol requirements and restrictions, including abstinence from disallowed concomitant medications (i.e. drugs known or expected to interact with methadone or telaprevir) from Day -14 until Day 8.
Study design. This was an open-label, single-sequence, drug-drug interaction study of telaprevir and methadone, both at steady-state. The study was conducted in a single center in Canada, with approval from the Institutional Review Board Services (Aurora, ON, Canada), and registered at clinicaltrials.gov (NCT00933283). All subjects signed the Informed Consent Form prior to any study-related procedures. Subject enrollment started in July 2009, and the last visit was in December 2009.

Eligible subjects were receiving individualized stable methadone maintenance therapy prior to enrollment. In a run-in period, subjects received supervised oral methadone for 2 weeks (Days -14 to Day -1), with intensive blood sampling for PK analysis of methadone on Day -1. Subsequently, telaprevir (750 mg every 8 hours [q8h]) and methadone were co-administered for 7 days with supervised medication intake at the trial center (Days 1 to 7), with intensive blood sampling for PK analysis of methadone and telaprevir on Day 7.

Methadone was taken following breakfast, immediately after the morning dose of telaprevir, if applicable. Telaprevir was taken with food. On days of intensive pharmacokinetic sampling a standardized breakfast (containing about 21g fat, 533 kcal) was served prior to drug administration. After the co-administration period, subjects continued their individualized methadone maintenance therapy.

Objectives. The primary objective of the study was to evaluate the effect of steady-state telaprevir (750 mg q8h) on the steady-state PK of total R- and S-methadone. Blood samples for determination of R- and S-methadone plasma concentrations were taken immediately before intake of methadone on Days -4, -
3, -2, 2, 3, 4, 5, and 6, and on Day -1 (methadone alone, reference) and Day 7 (methadone co-administered with telaprevir, test). Blood samples were collected immediately pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24-hours post-dose.

Further objectives were to evaluate: the pharmacodynamic effects of methadone therapy; the steady-state PK profile of telaprevir; the short-term safety and tolerability of co-administered telaprevir and methadone; and the effect of telaprevir on the unbound pre-dose concentration of R-methadone in a post-hoc analysis. The pharmacodynamic effects of methadone therapy were collected using the Short Opiate Withdrawal Scale [SOWS] (11), Desires for Drugs Questionnaire [DDQ] (12), and pupillometry on Day -7 and daily from Day -2 until Day 7 within 2 hours before the intake of methadone; on Days -1, 2, 4, and 7 pupillometry was also performed 2 and 4 hours after the intake of methadone. The steady-state PK of telaprevir in subjects on stable methadone maintenance therapy were compared with historical control samples; blood samples for analysis of telaprevir plasma concentrations were collected on Day 7 immediately pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 hours post-dose. Short-term safety and tolerability of co-administration of telaprevir and methadone as indicated by adverse events (AEs), vital signs, ECG, physical examination, and clinical laboratory tests. Furthermore, the effect of telaprevir on the unbound pre-dose concentration of R-methadone was evaluated in a post-hoc analysis.
Bioanalysis. Telaprevir concentrations. Telaprevir concentrations were determined in acidified human K₂EDTA plasma using a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) method. In brief, human plasma was acidified directly after sampling by adding 5% (v/v) of a 10% aqueous formic acid solution to prevent epimerization of telaprevir. A 100-μL aliquot of acidified plasma containing telaprevir was mixed with 100-μL telaprevir-d₁₁ internal standard solution (300 ng/mL in acetonitrile) and extracted with 500 μL toluene. After evaporation of the organic layer under nitrogen, the residue was reconstituted in heptane:tetrahydrofuran:formic acid (80:20:1, v/v) and analyzed on a normal phase chromatographic system with a cyanopropyl silica Hypersil analytical column (250 x 2.1 mm, 5 µm) thermostated at -1°C, and an isocratic mobile phase of heptane:acetone:methanol (80:19:1, v/v) at 0.750 mL/min. Post-column addition of a make-up solvent, acetonitrile:acetone:methanol:formic acid (40:60:1:1, v/v), was performed at 0.250 mL/min and MS/MS (tandem mass spectrometry) detection was achieved using a Sciex API 3000 detector with electrospray ionization in the positive ion-mode (ESI+). Multiple reaction monitoring (MRM)-transitions were Q1 mass: 680.5, Q3 mass: 322.3 for telaprevir, and Q1 mass: 691.5, Q3 mass: 322.2 for telaprevir-d₁₁.

The method was validated prior to analysis of study samples and was found to be selective, precise, accurate, and reproducible for the quantitative determination of telaprevir. Telaprevir was separated chromatographically from its epimer. The calibration range for telaprevir was 2 to 1000 ng/mL, and up to
8000 ng/mL after 10-fold dilution. A linear, 1/concentration squared weighted regression algorithm was used to plot the peak area ratio of the analyte over the internal standard versus concentration. The correlation coefficients from the standard curves were >0.990. The accuracy (% bias) for the assay ranged from -4% to +4.2% across the calibration range. The average within-run precision (%CV) was less than or equal to 10.3%.

**Total R- and S-methadone concentrations.** Plasma concentrations of total (bound plus unbound) R- and S-methadone were determined in human K$_2$EDTA plasma samples using a validated LC-MS/MS method.

A 50-μL aliquot of human plasma containing R- and S-methadone was fortified with (R, S)-methadone-d$_9$ internal standard, extracted by liquid extraction using ISOLUTE 200 mg SLE+ plate, and eluted with dichloromethane. After evaporation under nitrogen, the residue was reconstituted with 1000 μL of 12% isopropyl alcohol in 10 mM ammonium acetate. The final extract was analyzed on a chiral chromatographic system with a Chiral-$\alpha$-1-acid glycoprotein (AGP) analytical column (50 x 2.0 mm, 5 μm), isocratic elution mixture of 12% isopropyl alcohol in 10 mM ammonium acetate at a flow rate of 0.4 mL/min, and MS/MS detection using Sciex API 4000 detector with ESI+.

MRM-transitions were Q1 mass: 310.3, Q3 mass: 265.4 for (R, S)-methadone, and Q1 mass: 319.3, Q3 mass: 268.2 for (R, S)-methadone-d$_9$.

The method was validated prior to analysis of study samples, and was found to be specific, selective, precise, accurate, and reproducible for the quantitative determination of R- and S-methadone. The calibration range was 5 to 1000
ng/mL for both R- and S-methadone. The ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate 4000 ng/mL quality controls as 20-fold dilutions. A linear, 1/concentration squared weighted, least-squares regression algorithm was used to plot the peak area ratio of the appropriate analyte to the internal standard versus concentration. The average correlation coefficient from four standard curves was >0.990 for each analyte. For R-methadone, the between-run accuracy (% bias) for the assay ranged from -0.749% to 2.27%, the within-run precision (%CV) was less than or equal to 5.64%, and the between-run precision (%CV) was less than or equal to 4.39%.

For S-methadone, the between-run accuracy (% bias) for the assay ranged from -0.628% to 1.92%, the within-run precision (%CV) was less than or equal to 6.16%, and the between-run precision (%CV) was less than or equal to 3.90%.

Unbound R-methadone. Unbound R-methadone, as well as AGP and albumin concentrations, were measured in individually pooled pre-dose plasma samples before co-administration of telaprevir (pre-dose samples were pooled from Days -4, -3, -2, and -1 per subject) and in the presence of co-administered telaprevir (pre-dose samples were pooled from Days 2, 3, 4, 5, 6, and 7 per subject). The pooled plasma samples were fortified with [3H]-R-methadone (radiochemical purity >99 %, specific activity 858 GBq/mmol) at a final concentration of 6.5 ng/mL (18 kBq/mL). The fortified plasma samples were subjected to equilibrium dialysis against 0.067 M phosphate buffer, pH 7.17, at
37°C for 6 hours in a Dianorm system with identical macro-1 Teflon cells and Diachema 10.17 dialysis membranes (M, cut-off of 10,000). After dialysis, the contents of the two compartments of the dialysis cells were collected separately. The contents of each buffer compartment were weighed, and 2.0 mL methanol was subsequently added to limit adsorption. Each sample was analyzed by liquid scintillation counting.

Statistical methods. PK statistical analysis was done using the validated computer program WinNonlin Professional (version 4.1; Pharsight Corporation, Mountain View, California, U.S.A.). The noncompartmental analysis model (extravascular input, plasma data) was applied to evaluate PK data. To assess the effect of telaprevir on R- and S-methadone, statistical analysis was performed for R- and S-methadone comparing Day 7 (test: methadone + telaprevir) versus Day -1 (reference: methadone alone). The primary PK parameters for R- and S-methadone were the minimum plasma concentration in the dosing interval (Cmin), the maximum plasma concentration (Cmax), and the area under the plasma concentration-time curve from time of administration up to 24 hours post-dose (AUC24h) on the logarithmic scale. Additionally, statistical analysis was performed on the ratios of the individual AUC24h value of S-methadone over the value of R-methadone (ratio AUC24h, S/R-methadone) comparing Day 7 (test: methadone + telaprevir) versus Day -1 (reference: methadone alone). All test and reference data, paired and unpaired, were included in the statistical analyses. The least squares (LS) means of the primary parameters for each treatment group (day) were estimated with a linear mixed
effects model, controlling for treatment as a fixed effect, and subject as a random

effect. A 90% confidence interval (CI) was constructed around the difference

between the LS means of test and reference data. Both the difference between

the LS means and the 90% CIs were transformed to the original scale.

The unbound fraction of R-methadone (fu) was calculated as the ratio of

the unbound concentrations (Cu) in the buffer compartment versus the total

concentrations (CED) in the plasma compartment of the dialysis cell (formula:

fu = Cu/ CED). The fu was multiplied by the Cmin on Day -1 and Day 7, based on
total concentration, to derive the absolute unbound Cmin or multiplied by 100 to
derive the unbound percentage R-methadone.

With an intra-subject variability of 0.22 for the AUC24h, Cmax, and Cmin of
total R- and S-methadone, and an estimated sample size of 12 subjects who
would complete the study, the point estimates of the primary PK parameters for
R- and S-methadone with and without co-administration of telaprevir were
anticipated to fall within 85% and 117% of the true ratio with 90% confidence.

RESULTS

Subject disposition. In total, 44 subjects were screened and 18 subjects fulfilled
all inclusion and exclusion criteria and proceeded to the run-in period. Three
subjects discontinued the study prematurely (all withdrew consent); one on
Day -2 (before blood sampling for methadone), one on Day 1 (before
co-administration of telaprevir with methadone), and one on Day 4 of the
co-administration of telaprevir. Consequently, full PK profiles of $R$- and $S$-methadone on Day -1 were available for 17 subjects, and full PK profiles of telaprevir and $R$- and $S$-methadone on Day 7 were available for 15 subjects.

Subjects treated with telaprevir were mainly male ($n = 14, 87.5\%$) and Caucasian ($n = 15, 93.8\%$). Median age was 33 years (range 23 to 45 years), median weight 78.5 kg (range 65 to 96 kg), and median BMI 25.25 kg/m$^2$ (range 20.7–30.0 kg/m$^2$). The median methadone dose was 85 mg q.d. (range 40–120 mg q.d.).

**PK of total $R$- and $S$-methadone.** The mean plasma concentrations of both enantiomers ($R$- and $S$-methadone) were lower when telaprevir was co-administered with methadone versus methadone alone (Fig. 1). Based on the LS mean ratios, the $R$-methadone $C_{\text{min}}$, $C_{\text{max}}$, and $\text{AUC}_{24h}$ were reduced by 31%, 29%, and 29%, respectively, and for $S$-methadone, the $C_{\text{min}}$, $C_{\text{max}}$, and $\text{AUC}_{24h}$ were reduced by 40%, 35%, and 36%, respectively, in the presence of telaprevir versus methadone alone (Table 1). Although the decrease in $\text{AUC}_{24h}$ in the presence of telaprevir versus methadone alone was numerically slightly greater for $S$-methadone than for $R$-methadone, the $S$/-$R$-methadone geometric mean ratio for $\text{AUC}_{24h}$ did not show a relevant difference (0.90, [90% CI: 0.86–0.94]), suggesting no stereo-specific effect of telaprevir on methadone (Table I). The mean pre-dose $R$-methadone concentrations were stable prior to Day -1, which confirms that steady-state conditions were achieved, while after 1 day of telaprevir co-administration a decrease was observed, which remained stable throughout the remainder of the co-administration period (Fig. 2).
PK of unbound $R$-methadone. A subset of 13 subjects provided consent for inclusion in this additional post-hoc analysis. The mean (± standard deviation [SD]) AGP and albumin concentrations in this subset were 98.8 (±27.7) mg/dL and 4.66 (±0.13) g/dL, respectively, in the samples collected before telaprevir co-administration and 91.6 (±24.7) mg/dL and 4.66 (±0.12) g/dL, respectively, in the samples collected during co-administration of telaprevir. The median unbound percentage of $R$-methadone in the pre-dose samples was 7.92% (range 5.27–9.94%) before co-administration of telaprevir and increased to 9.98% (range 8.17–13.20%) after co-administration of telaprevir. An analysis of covariance was applied to the unbound percentage of $R$-methadone controlling for AGP concentration and administration of telaprevir. A negative relationship was observed between the percentage free fraction of $R$-methadone and AGP (slope $\beta = -0.04329$, $P = 0.0006$) while the concomitant administration of telaprevir increased the percentage free fraction of $R$-methadone in absolute number by 2.1% ($P < 0.0001$) (Fig. 3). Although the median unbound percentage of $^3$H-$R$-methadone increased by 26% upon co-administration of telaprevir, the unbound minimum concentration of $R$-methadone was comparable before (median 10.63 ng/mL, range 5.63–15.04 ng/mL) and after (median 10.45 ng/mL, range 5.97–13.56 ng/mL) co-administration of telaprevir.

PK of telaprevir. The mean plasma concentration-time profile for 8 hours after co-administration of methadone and telaprevir on Day 7 is presented in Fig. 4. The median time to reach the maximum plasma concentration was 4 hours (range 2.5–8 hours) post-dose. The mean (±SD) AUC$_{8h}$ of telaprevir was 20,480.
(±7628) ng*h/mL, with a C$_{\text{min}}$ of 1894 (±905) ng/mL and a C$_{\text{max}}$ of 3376 (±1260) ng/mL.

**Pharmacodynamic assessment of methadone.** Based on clinical symptoms, no dose adjustments were required for the subjects’ stable, individualized methadone maintenance therapies during the study. When telaprevir and methadone were co-administered, fewer subjects experienced withdrawal symptoms than during treatment with methadone alone (as measured by SOWS). The largest difference between the treatments was observed for ‘insomnia/problems sleeping’; during the methadone + telaprevir co-administration period, none of the subjects had insomnia/problems with sleeping, whereas 7 (43.8%) subjects had mild or moderate insomnia/problems with sleeping when methadone was administered alone. One (6.3%) subject had a withdrawal symptom on Day 2 of methadone and telaprevir co-administration that was considered severe (i.e. feeling sick). This may have been secondary to gastrointestinal AEs, as Grade 1 abdominal pain and nausea were reported by this subject on the same day.

No changes in the desire for heroin, as measured by DDQ, were observed during telaprevir co-administration. The median resting pupil diameter prior to methadone or telaprevir intake on Day 1 was 5.60 mm (range 3.6 to 6.5 mm). A median decrease in resting pupil diameter was observed during methadone and telaprevir co-administration at all time points versus Day 1, except on Day 2, indicating that there were no symptoms of opioid withdrawal. The median change
in pupil diameter just before methadone intake ranged between -0.85 mm (on Day 3, range -1.8 to +1.1 mm) to +0.10 mm (on Day 2, range -1.8 to +1.0 mm).

**Safety.** No serious AEs (SAEs) occurred in this study. In addition, none of the subjects permanently discontinued study treatment prematurely due to an AE. The most frequently reported AEs were headache and nausea in 6 [37.5%] subjects each, euphoric mood in 5 [31.3%] subjects, and pruritus in 3 [18.8%] subjects. The incidence of headache in the methadone + telaprevir period was similar to the incidence in the run-in period (4 [25.0%] subjects). Nausea, euphoric mood, and pruritus were only reported during the methadone + telaprevir co-administration period. No clinically relevant trends or changes over time were observed in laboratory values. No clinically relevant changes in vital signs and ECG parameters were seen during the methadone + telaprevir co-administration period. None of the subjects had a QTcF value above 450 ms or a QTcF increase versus reference of more than 60 ms during the methadone + telaprevir co-administration period. No abnormal vital signs or ECG parameters were reported as AEs.

**DISCUSSION**

The results of this study showed that both R- and S-methadone total plasma concentrations were reduced to a similar extent after co-administration of telaprevir. The AUC$_{24h}$ of R- and S-methadone were reduced by 29% and 36%, respectively, indicating lack of a stereospecific effect. Exposure to telaprevir when co-administered with methadone in the current study was comparable with
historical data, suggesting the absence of an effect of methadone on telaprevir metabolism.

Steady-state telaprevir has been shown to be a potent inhibitor of CYP3A, as indicated by a 9-fold increase in the exposure to orally co-administered midazolam (10). Hence, the reduction in methadone exposure that we observed suggests that CYP3A plays a limited role in the metabolism of methadone, consistent with previous findings in a drug-drug interaction study of methadone and ritonavir (13). Specifically, Kharasch et al. (13) reported that, although steady-state ritonavir 400 mg twice daily resulted in >70% inhibition of hepatic CYP3A activity, the clearance of co-administered methadone increased by approximately 2-fold via induction of alternative metabolic pathways and renal clearance.

Evaluation of the individual pre-dose concentrations of R-methadone in the current study indicated a rapid onset of the effect of telaprevir on methadone exposure (first observation 24 hours after initiating telaprevir co-administration) without a further reduction upon continued co-administration (Fig. 2). As enzyme induction is generally caused by increased de novo synthesis of protein, it takes several days to weeks to reach its maximum effect and so cannot explain the pattern of reduction of pre-dose methadone concentrations observed in the current study (14). Furthermore, in vitro studies suggest that telaprevir has a low potential to induce CYP2C, CYP3A, or CYP1A (15). Based on these considerations and the absence of withdrawal symptoms despite about 30% lower methadone exposure during co-administration of telaprevir, protein
displacement of methadone by telaprevir was investigated as a potential
mechanism to explain the observed interaction.

Approximately 59% to 76% of telaprevir is bound to human plasma
proteins at concentrations ranging from 0.1 \( \mu \)M to 20 \( \mu \)M, mainly to AGP and
human serum albumin (16). About 85% of the methadone in blood plasma is
bound to AGP, and a much smaller proportion is bound to albumin (17). Since
AGP is present in plasma at much lower concentrations than albumin, the
potential for protein displacement is particularly high for drugs (e.g. methadone),
which are primarily bound to AGP. Indeed, protein displacement of methadone
has previously been observed during co-administration of the ritonavir-boosted
HIV protease inhibitors saquinavir and fosamprenavir, which both bind primarily
to AGP (19). Co-administration of saquinavir and ritonavir or fosamprenavir and
ritonavir reduced the AUC of total \( R \)-methadone plasma concentrations by 32%
and 18%, respectively, without a statistically significant change in the unbound
concentrations and without causing opioid withdrawal symptoms (18, 19).

In the current study, a negative relationship was observed between AGP
congentations and the unbound (active) percentage of \( R \)-methadone, similar to
previously reported findings (20). As shown by the parallel decreasing slopes of
the linear regression lines in Fig. 3, the effect of telaprevir on the percentage of
unbound \( R \)-methadone was similar across the range of AGP concentrations.

The median unbound percentage of \( R \)-methadone increased by 26%
during co-administration of telaprevir, indicating displacement of \( R \)-methadone
from its protein binding sites. However, changes in plasma protein binding for a
low clearance drug (such as methadone) do not influence unbound drug concentrations because the displaced drug will be distributed throughout the body and eliminated more rapidly, hence a new equilibrium is achieved where the unbound drug concentrations will return to the pre-displacement level (20, 21). Consistent with this theory, the median absolute unbound (active) concentration of $R$-methadone in the current study was indeed similar with (10.45 ng/mL) and without co-administration of telaprevir (10.63 ng/mL), which may explain why the approximate 30% reduction in methadone exposure based on total plasma concentrations did not result in clinically significant changes in withdrawal symptoms or heroin cravings (Fig. 5).

The combination of methadone and telaprevir was generally well tolerated, with no SAEs or discontinuations due to AEs reported in the current study. However, nausea, euphoric mood, and pruritus were observed during the methadone + telaprevir co-administration period. Euphoric mood and pruritus might be interpreted as typical symptoms of opioid use, whereas nausea can occur during the late stages of opioid withdrawal. Direct testing of withdrawal symptoms and desire for heroin with the SOWS, DDQ questionnaire, and pupillometry did not indicate signs of opioid withdrawal during co-administration of telaprevir and methadone. Hence, overall there were no clear symptoms of opioid withdrawal, despite the 30% reduction of methadone exposure, which is consistent with the observation that the unbound (active) concentrations of $R$-methadone were not affected by co-administration of telaprevir.
Median changes from reference values in vital signs and ECG parameters were generally small and none of the median changes were considered clinically relevant.

In conclusion, co-administration of telaprevir and methadone in subjects on stable methadone maintenance therapy did not result in changes in absolute unbound $R$-methadone concentrations. Moreover, there were no reports of serious AEs nor permanent discontinuations of treatment. The results of this study suggest that no adjustment of the methadone dose is required during co-administration of telaprevir.

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REFERENCES


TABLE 1 Pharmacokinetics of R- and S-methadone in the absence or presence of telaprevir

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Individualized methadone therapy + telaprevir 750 mg q8h (Test, Day 7)</th>
<th>LS mean ratio methadone only (Reference, Day -1)</th>
<th>(90% CI)</th>
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<tr>
<td><strong>R-methadone</strong></td>
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<td>17</td>
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<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>2.5 (1.5,16.0)</td>
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<td>( C_{\text{min}} ) (ng/mL)</td>
<td>139.2 ± 45.31</td>
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<td>( C_{\text{max}} ) (ng/mL)</td>
<td>257.7 ± 92.69</td>
<td>189.8 ± 113.8</td>
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<td>AUC(_{24h}) (ng·h/mL)</td>
<td>4334 ± 1542</td>
<td>2991 ± 959.6</td>
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<tr>
<td>( t_{\text{max}} ) (h)</td>
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<td>( C_{\text{min}} ) (ng/mL)</td>
<td>132.8 ± 57.12</td>
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</tr>
<tr>
<td><strong>Cmax (ng/mL)</strong></td>
<td>301.8 ± 114.4</td>
<td>211.9 ± 145.3</td>
<td>0.65 (0.60,0.71)</td>
</tr>
<tr>
<td><strong>AUC_{24h} (ng·h/mL)</strong></td>
<td>4562 ± 1982</td>
<td>2941 ± 1378</td>
<td>0.64 (0.58,0.70)</td>
</tr>
</tbody>
</table>

LS mean ratio S- vs. R-methadone

\[ \text{AUC}_{24h} \]

\[ \frac{S}{R} = 0.90 \ (0.86, 0.94) \]

\( ^a \) \( t_{max} \) shown as median (range), all other parameters shown as mean ± standard deviation.

\( ^b \) \( N = \) number of subjects.
FIG 1 Mean (standard deviation) plasma concentration-time profiles of R-methadone and S-methadone.

FIG 2 Mean (standard deviation) of pre-dose concentrations of R-methadone over time.

FIG 3 Relationship between α₁-acid glycoprotein concentrations and unbound R-methadone in pre-dose samples collected before and during methadone + telaprevir co-administration.

FIG 4 Mean (standard deviation) plasma concentration-time profile of telaprevir 750 mg q8h.

FIG 5 The effect of telaprevir co-administration on total and unbound concentrations of R-methadone.