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Pharmacokinetic Interaction between Telaprevir and Methadone

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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 every 8 h [q8h]) coadministration in HCV-negative subjects on stable, individualized methadone therapy. Unbound *R*-methadone was measured in predose plasma samples before and during telaprevir coadministration. Safety and symptoms of opioid withdrawal were evaluated throughout the study. In total, 18 subjects were enrolled; 2 discontinued prior to receiving telaprevir. The minimum plasma concentration in the dosing interval (C_{min}), the maximum plasma concentration (C_{max}), and the area under the plasma concentration-time curve from h 0 (time of administration) to 24 h postdose (AUC_{0-24}) for *R*-methadone were reduced by 31%, 29%, and 29%, respectively, in the presence of telaprevir. The AUC_{0-24} ratio of *S*-methadone/*R*-methadone was not altered. The median unbound percentage of *R*-methadone increased by 26% in the presence of telaprevir. The *R*-methadone median (absolute) unbound C_{min} values in the absence (10.63 ng/ml) and presence (10.45 ng/ml) of telaprevir were similar. 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. (This study has been registered at ClinicalTrials.gov under registration no. NCT00933283.)

Hepatitis C virus (HCV) infection is widespread among previous intravenous drug users who share syringes and drug preparation equipment (1). Methadone is commonly used as a maintenance therapy for opiate dependence, and a 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 prolongation of the corrected QT (QTc) (where QT represents the time between the start of the Q wave and the end of the T wave) (8). Methadone is primarily metabolized by *N*-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (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, coadministration 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 to 55 years old, male or female) on a stable methadone maintenance dose of 30 to 130 mg once a day (q.d.). Females had to be at least 2 years postmenopausal. Body mass index (BMI) had to be between 18.0 and 30.0 kg/m^2. All subjects obtained approval for participation in this study from the physician who was treating their addiction and who agreed to provide medical care after discharge of the subject 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 virus IgM antibody, hepatitis B virus antigen, HCV antibody, or human immunodeficiency virus type 1 (HIV-1) or HIV-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 the steady state). The study was conducted in a single center in Canada, with approval from the

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Institutional Review Board Services (Aurora, Ontario, Canada), and registered at http://clinicaltrials.gov/ (NCT00933283). All subjects signed an 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 (day −14 to day −1), with intensive blood sampling for PK analysis of methadone on day −1. Subsequently, telaprevir (750 mg every 8 h [q8h]) and methadone were coadministered for 7 days of 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 21 g fat [533 kcal]) was served prior to drug administration. After the coadministration 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 coadministered with telaprevir [test]). Blood samples were collected immediately predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 h postdose.

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 coadministered telaprevir and methadone, and the effect of telaprevir on the unbound predose 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 h before the intake of methadone; on days −1, 2, 4, and 7, pupillometry was also performed 2 and 4 h after the intake of methadone. The steady-state PK of telaprevir in subjects on stable methadone maintenance therapy were compared with those of historical control samples; blood samples for analysis of telaprevir plasma concentrations were collected on day 7 immediately predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h postdose. The short-term safety and tolerability of coadministration of telaprevir and methadone as indicated by adverse events (AEs), vital signs, ECG, physical examination, and clinical laboratory tests were assessed. Furthermore, the effect of telaprevir on the unbound predose concentration of *R*-methadone was evaluated in a *post hoc* analysis.

Bioanalysis. (i) Telaprevir concentrations. Telaprevir concentrations were determined in acidified human K_2EDTA 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% (vol/vol) of a 10% aqueous formic acid solution to prevent epimerization of telaprevir. A 100-μl aliquot of acidified plasma containing telaprevir was mixed with a 100-μl telaprevir-d_{11} 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 [vol/vol]) and analyzed on a normal phase-chromatographic system with a cyanopropyl siloxane Hypersil analytical column (250 by 2.1 mm; 5 μm pore size) thermostated at −1°C and an isocratic mobile phase of heptane:acetone:methanol (80:19:1 [vol/vol]) at 0.750 ml/min. Postcolumn addition of a makeup solvent, acetonitrile:acetone:methanol:formic acid (40:60:1:1 [vol/vol]), 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 as follows: for telaprevir, Q1 mass was 680.5 and Q3 mass was 322.3; and for telaprevir-d_{11}, Q1 mass was 691.5 and Q3 mass was 322.2.

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 levels. Telaprevir was separated chromatographically from its epimer. The calibration ranges for telaprevir were 2 to 1,000 ng/ml and up to 8,000 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 curve. 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 (percent coefficient of variation [%CV]) was less than or equal to 10.3%.

(ii) Total *R*- and *S*-methadone concentrations. Plasma concentrations of total (bound plus unbound) *R*- and *S*-methadone in human K_2EDTA plasma samples were determined using a validated LC-MS/MS method.

A 50-μl aliquot of human plasma containing *R*- and *S*-methadone was fortified with an (*R*, *S*)-methadone-d_9 internal standard, extracted by liquid extraction using an Isolute 200-mg SLE+ plate, and eluted with dichloromethane. After evaporation under nitrogen, the residue was reconstituted with 1,000 μl of 12% isopropyl alcohol–10 mM ammonium acetate. The final extract was analyzed on a chiral chromatographic system with a chiral-α1-acid glycoprotein (AGP) analytical column (50 by 2.0 mm; 5 μm pore size), an isocratic elution mixture of 12% isopropyl alcohol–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 as follows: for (*R*, *S*)-methadone, Q1 mass was 310.3 and Q3 mass was 265.4; and for (*R*, *S*)-methadone-d_9, Q1 mass was 319.3 and Q3 mass was 268.2.

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 1,000 ng/ml for both *R*- and *S*-methadone. The ability to dilute samples that were originally above the upper limit of the calibration range was validated by analyzing six replicate 4,000 ng/ml quality controls as 20-fold dilutions. A linear, 1/concentration squared-weighted, least-squares (LS) 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-runs accuracy (percent 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-runs precision (%CV) was less than or equal to 4.39%.

For *S*-methadone, the between-runs accuracy (percent 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-runs 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 predose plasma samples before coadministration of telaprevir (predose samples were pooled from days −4, −3, −2, and −1 per subject) and in the presence of coadministered telaprevir (predose samples were pooled from days 2, 3, 4, 5, 6, and 7 per subject). The pooled plasma samples were fortified with [^{3}H]*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 h in a Dianorm system with identical macro-1 Teflon cells and Diachema 10.17 dialysis membranes (M_r cutoff, 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, CA). Noncompartmental analysis model 200 (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 plus telaprevir]) to day −1 (reference [methadone alone]). The primary PK parameters for *R*- and *S*-methadone were the minimum plasma concentration in the dosing interval (C_{min}), the maximum plasma concentration (C_{max}), and the area under the plasma concentration-time curve from h 0 (time of administration) to 24 h postdose (AUC_{0-24}) on the logarithmic scale. Additionally, statistical analysis was performed on the ratios of the individual AUC_{0-24} value of *S*-methadone over the value of *R*-methadone (ratio AUC_{0-24}, *S*-methadone/*R*-methadone), comparing day 7 (test [methadone plus telaprevir]) to 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 that corresponded to the difference between the LS means of test and reference data. Both the differences between the LS means and the 90% CIs were transformed to the original scale.

The unbound fraction of *R*-methadone (f_u) was calculated as the ratio of the unbound concentrations (C_u) in the buffer compartment to the total concentrations (C_{ED}) in the plasma compartment of the dialysis cell (according to the formula $f_u = C_u/C_{ED}$). The f_u was multiplied by the C_{min} on day −1 and day 7, based on total concentration, to derive the absolute unbound C_{min} or multiplied by 100 to derive the unbound percentage of *R*-methadone.

With an intrasubject variability of 0.22 for the AUC_{0-24}, C_{max}, and C_{min} 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 coadministration 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 coadministration of telaprevir with methadone), and one on day 4 of the coadministration 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%). The median age was 33 years (range, 23 to 45 years), the median weight was 78.5 kg (range, 65 to 96 kg), and the median BMI was 25.25 kg/m^2 (range, 20.7 to 30.0 kg/m^2). The median methadone dose was 85 mg q.d. (range, 40 to 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 coadministered with methadone versus administration of methadone alone (Fig. 1). Based on the LS mean ratios, the *R*-methadone C_{min}, C_{max}, and AUC_{0-24} were reduced by 31%, 29%, and 29%, respectively, and the *S*-methadone C_{min}, C_{max}, and AUC_{0-24} were reduced by 40%, 35%, and 36%, respectively, in the presence of telaprevir versus methadone alone (Table 1). Although the decrease in AUC_{0-24} in the presence of telaprevir versus methadone alone was numerically slightly greater for *S*-methadone than for *R*-methadone, the *S*-methadone/*R*-methadone geometric mean ratio for AUC_{0-24} did not show a relevant difference (0.90 [90% CI, 0.86 to 0.94]), suggesting no stereospecific effect of telaprevir on methadone (Table 1). The mean predose *R*-methadone concentrations were stable prior to day −1, which confirms that steady-state conditions were achieved, while after 1 day of telaprevir coadministration, a decrease was observed which remained stable throughout the remainder of the coadministration period (Fig. 2).

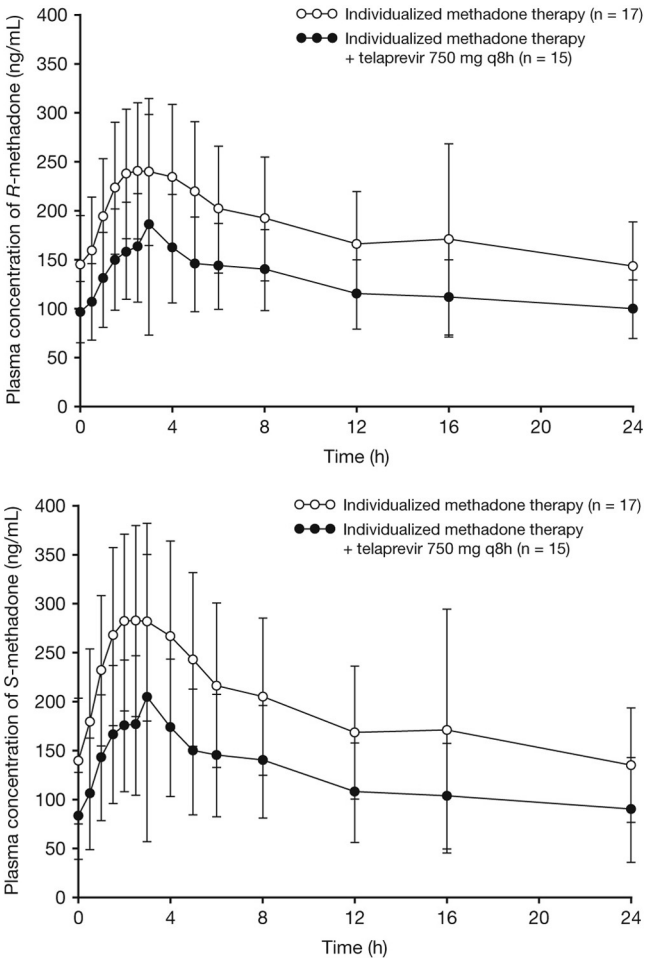

FIG 1 Mean (standard deviation) plasma concentration-time profiles of *R*-methadone and *S*-methadone.

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 coadministration and 91.6 (±24.7) mg/dl and 4.66 (±0.12) g/dl, respectively, in the samples collected during coadministration of telaprevir. The median unbound percentage of *R*-methadone in the predose samples was 7.92% (range, 5.27 to 9.94%) before coadministration of telaprevir and increased to 9.98% (range, 8.17 to 13.20%) after coadministration of telaprevir. An analysis of covariance was applied to the unbound percentage of *R*-methadone, controlling for AGP concentration and administration of telapre-

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

Pharmacokinetic parameter[a]	Value(s)[b]		
	Individualized methadone therapy (reference [day −1])	Individualized methadone therapy + telaprevir (750 mg q8h) (test [day 7])	LS mean ratio (90% CI) for methadone + telaprevir vs methadone only
R-Methadone			
n	17	15	
t_{max} (h)	2.5 (1.5, 16.0)	3.0 (1.5, 4.0)	
C_{min} (ng/ml)	139.2 ± 45.31	93.47 ± 28.63	0.69 (0.64, 0.75)
C_{max} (ng/ml)	257.7 ± 92.69	189.8 ± 113.8	0.71 (0.66, 0.76)
AUC_{0-24} (ng · h/ml)	4,334 ± 1,542	2,991 ± 959.6	0.71 (0.66, 0.76)
S-Methadone			
n	17	15	
t_{max} (h)	2.5 (1.5, 16.0)	2.5 (1.0–4.0)	
C_{min} (ng/ml)	132.8 ± 57.12	81.97 ± 42.79	0.60 (0.54, 0.67)
C_{max} (ng/ml)	301.8 ± 114.4	211.9 ± 145.3	0.65 (0.60, 0.71)
AUC_{0-24} (ng · h/ml)	4,562 ± 1,982	2,941 ± 1,378	0.64 (0.58, 0.70)
S-Methadone vs *R*-methadone AUC_{0-24}			0.90 (0.86, 0.94)

[a] *n*, number of subjects.
[b] t_{max} data are shown as median (range); all other parameters are shown as mean ± standard deviation.

vir. A negative relationship was observed between the percentage of the free fraction of *R*-methadone and the AGP (slope, $\beta = -0.04329$; $P = 0.0006$), while the concomitant administration of telepravir increased the percentage of the 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 coadministration of telaprevir, the unbound minimum concentrations of *R*-methadone before (median, 10.63 ng/ml; range, 5.63 to 15.04 ng/ml) and after (median 10.45 ng/ml; range, 5.97 to 13.56 ng/ml) coadministration of telaprevir were comparable.

PK of telaprevir. The mean plasma concentration-time profile for 8 h after coadministration of methadone and telaprevir on day 7 is presented in Fig. 4. The median time to reach the maximum plasma concentration was 4 h (range, 2.5 to 8 h) postdose. The mean (±SD) AUC_{0-8} of telaprevir was 20,480 (±7,628) ng · h/ml, with a C_{min} of 1,894 (±905) ng/ml and a C_{max} of 3,376 (±1,260) ng/ml.

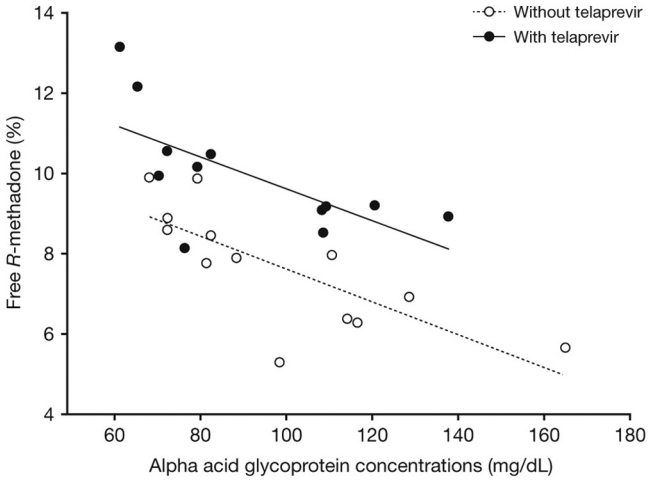

FIG 3 Relationship between α_1-acid glycoprotein concentrations and unbound *R*-methadone in predose samples collected before and during coadministration of methadone plus telaprevir.

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 coadministered, 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 period of coadministration of methadone plus telaprevir, 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 (i.e., feeling sick) on day 2 of methadone and telaprevir coadministration that was considered severe. This may

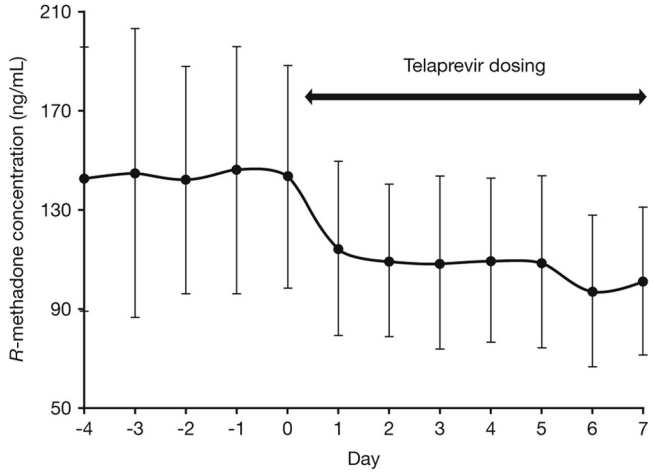

FIG 2 Mean (standard deviation) of predose concentrations of R-methadone over time.

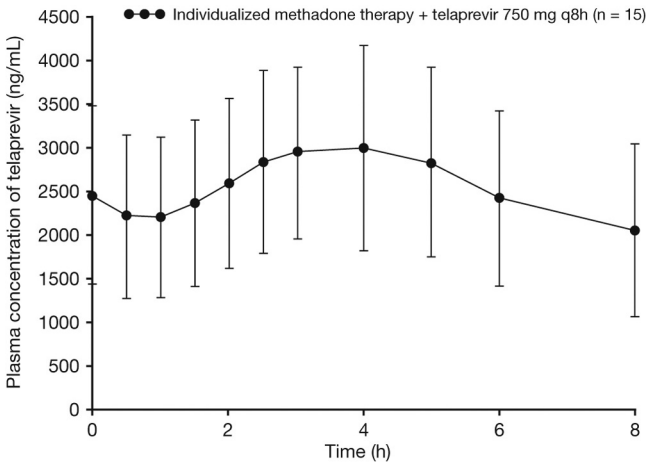

FIG 4 Mean (standard deviation) plasma concentration-time profile of telaprevir (750 mg q8h).

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 coadministration. 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 coadministration of methadone and telaprevir at all time points compared to that measured on 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) and +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 period of administration of methadone plus telaprevir was similar to the incidence in the run-in period (4 [25.0%] subjects). Nausea, euphoric mood, and pruritus were reported only during the period of coadministration of methadone plus telaprevir. No clinically relevant trends or changes over time in laboratory values were observed. No clinically relevant changes in vital signs and ECG parameters during the period of coadministration of methadone plus telaprevir were seen. None of the subjects had a Fridericia's correction (QTcF) value above 450 ms or a QTcF increase compared to the reference value of more than 60 ms during the period of coadministration of methadone plus telaprevir. No abnormal vital signs or ECG parameters were reported as AEs.

DISCUSSION

The results of this study showed that the *R*- and *S*-methadone total plasma concentrations after coadministration of telaprevir were reduced to similar extents. The *R*- and *S*-methadone AUC_{0-24} values were reduced by 29% and 36%, respectively, indicating a lack of a stereospecific effect. The results of exposure to telaprevir coadministered with methadone in the current study were 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 coadministered 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 coadministered methadone increased by approximately 2-fold via induction of alternative metabolic pathways and renal clearance.

Evaluation of the individual predose concentrations of *R*-methadone in the current study indicated a rapid onset of the effect of telaprevir on methadone exposure (first observation at 24 h after initiating telaprevir coadministration) without a further reduction upon continued coadministration (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 predose 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 coadministration 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, mainly to AGP and human serum albumin, at concentrations ranging from 0.1 μM to 20 μM (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 coadministration of the ritonavir-boosted HIV protease inhibitors saquinavir and fosamprenavir, which both bind primarily to AGP (19). Coadministration of saquinavir and ritonavir and of 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 concentrations 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 effects of telaprevir on the percentage of unbound *R*-methadone were similar across the range of AGP concentrations.

The median unbound percentage of *R*-methadone increased by 26% during coadministration 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 is distributed throughout the body and eliminated more rapidly; hence, a new equilibrium is achieved where the unbound drug concentrations returns to the predisplacement level (20, 21). Consistent with this theory, the median absolute unbound (active) concentrations of *R*-methadone with (10.45 ng/ml) and without (10.63 ng/ml) coadministration of telaprevir in the current study were indeed similar, which may explain why the approximately 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 period of coadministration of methadone plus telaprevir. 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 coadministration 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

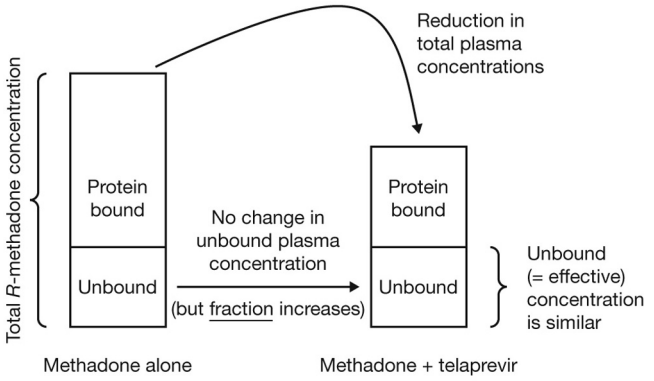

FIG 5 The effect of telaprevir coadministration on total and unbound concentrations of *R*-methadone.

(active) concentrations of *R*-methadone were not affected by coadministration 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, coadministration 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 or permanent discontinuations of treatment. The results of this study suggest that no adjustment of the methadone dose is required during coadministration of telaprevir.

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