Poster 1244 Abstract 654

The Pharmacokinetic Interaction Between Methadone and the Investigational HCV Protease Inhibitor Telaprevir

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Introduction

- Telaprevir (TVR), in combination with pegylated interferon and ribavirin, is being investigated for the treatment of hepatitis C virus (HCV) infection.[1–3]
- Many HCV-infected patients are, or have been, injection drug users and a proportion receive methadone maintenance therapy.[4]
- Methadone is partly metabolized via the cytochrome P450 (CYP) enzyme system, in particular by the CYP 3A4 isozyme. TVR is a substrate and potent inhibitor of this enzyme:
  - Methadone is bound to plasma proteins. It has been estimated that about 85% of the drug is bound to α-1 acid glycoprotein (AAG) and, to a much lesser extent, to serum albumin.[5] TVR is approximately 59–76% bound to plasma proteins, mainly AAG and albumin.
- This study evaluated the potential interaction between methadone and TVR.

Methods

Study Design and Volunteers

- This was a single-sequence study in HCV-negative volunteers on a stable, individualized maintenance dose of methadone (commercially available solution). Volunteers were admitted to the testing facility on the morning of Day –2 and stayed in the testing facility until the morning of Day 8.
- The study design is shown in Figure 1.
- The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authority, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (clinical trials.gov identifier NCT00933283).
- Methadone (individualized dose) and TVR (750 mg every 8 hours [q8h]) were taken with food:
  - Methadone was administered as a mixture of the R- and S-isomer. The R-isomer is mainly responsible for the opioid effect.

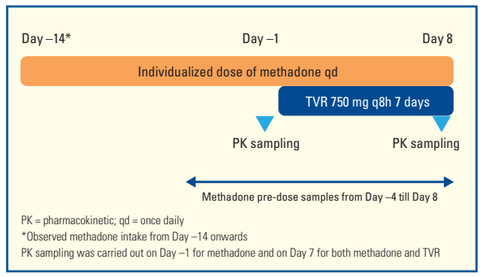

Figure 1. Study Design.

PK Evaluations

- A complete PK profile of TVR (8 hours) was obtained on Day 7.
- Pre-dose concentrations of R-methadone were measured from Day –4 until Day 7.
- Complete PK profiles for R-methadone and S-methadone (24 hours) were obtained on Day –1 and Day 7.
- Concentrations of R- and S-methadone and of TVR were determined by validated liquid chromatographic/tandem mass spectrometric methods.
- The free fraction of R-methadone in pre-dose samples was determined using equilibrium dialysis. Per volunteer, pre-dose samples before (Days –4 to –1) and after co-administration of TVR (Days 2 to 7) were pooled.
- PK parameters were calculated by standard non-compartmental methods.
- Symptoms of opioid withdrawal were monitored by Short Opiate Withdrawal Scale (SOWS), Desires for Drugs Questionnaire (DDQ) and pupillometry, performed 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.

Statistical Analyses

- Statistical analysis of log-transformed PK parameters of R- and S-methadone was performed using linear mixed effects modelling (least square means [LSM] ratio of test/reference and 90% confidence intervals [CIs]).

Results

Volunteer Disposition and Baseline Characteristics

- A total of 18 HCV-negative volunteers on a stable, individualized methadone dose were enrolled:
  - Two volunteers discontinued the study prior to start of TVR intake (both withdrew consent)
  - One volunteer discontinued the study during co-administration of TVR due to withdrawal of consent.
- Individual methadone doses ranged from 40 to 120 mg/day:
  - The median methadone dose was 85 mg.
- Two volunteers were female.
- The median age was 33 years (range 23 to 45 years) and median body weight was 78.5 kg (range 65 to 96 kg).

TVR Pharmacokinetics

- The TVR plasma concentration-time curve is shown in Figure 2. TVR PK parameters are shown in Table 1:
  - The PK parameters of TVR during co-administration of methadone were comparable with those observed in healthy volunteers receiving TVR 750 mg q8h in a previous study.[6]

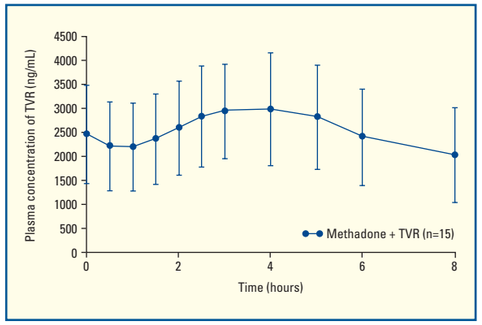

Figure 2. Mean (Standard Deviation [SD]) PK Profile of TVR During Co-administration with Methadone.

Table 1. TVR PK Parameters (n=15).

Parameter	Mean (SD)
C_{max} (ng/mL)	3376 ± 1260
C_{min} (ng/mL)	1894 ± 905
AUC_{8h} (ng•h/mL)	20480 ± 7628

AUC = area under the curve; C_{min} = minimum plasma concentration; C_{max} = maximum plasma concentration

R- and S-methadone Pharmacokinetics

- The plasma concentration-time curves for R- and S-methadone alone and in combination with TVR are shown in Figure 3.

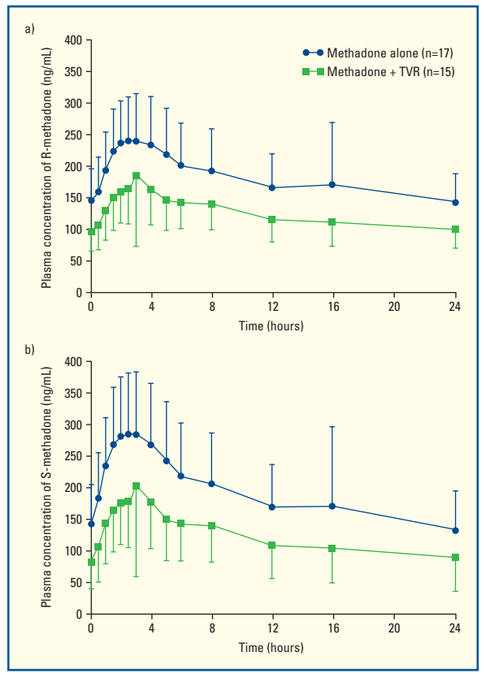

Figure 3. Mean (SD) PK Profiles of a) R-methadone and b) S-methadone Alone and During Co-administration with TVR.

- Co-administration with TVR led to a reduction in values of PK parameters of R- and S-methadone, relative to treatment in the absence of TVR (Table 2).
  - AUC_{24h} was reduced by 29% for R-methadone and by 36% for S-methadone.

Table 2. Mean (SD) PK Parameters and Statistics for R- and S-methadone.

Parameter, n (%)	Methadone alone (n=17)	Methadone + TVR (n=15)	LSM ratio (90% CI)
R-methadone			
C_{max} (ng/mL)	258 ± 93	190 ± 114	0.71 (0.66–0.76)
C_{min} (ng/mL)	139 ± 45	93 ± 29	0.69 (0.64–0.75)
AUC_{24h} (ng•h/mL)	4334 ± 1542	2991 ± 960	0.71 (0.66–0.76)
S-methadone			
C_{max} (ng/mL)	302 ± 114	212 ± 145	0.65 (0.60–0.71)
C_{min} (ng/mL)	133 ± 57	82 ± 43	0.60 (0.54–0.67)
AUC_{24h} (ng•h/mL)	4562 ± 1982	2941 ± 1378	0.64 (0.58–0.70)
Ratio AUC S-/R-methadone (%)	105 ± 21	98 ± 26	0.90 (0.86–0.94)

- In general, relative to administration of methadone alone, TVR co-administration led to a reduction in pre-dose R-methadone concentrations from Day 2 onwards (Figure 4).

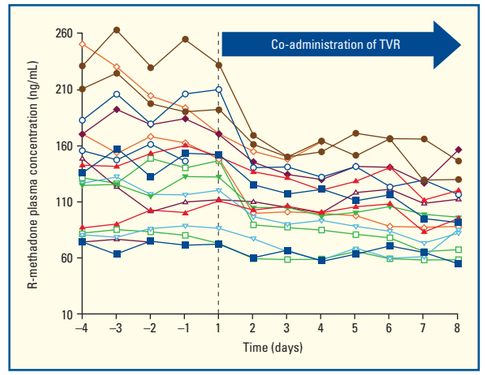

Figure 4. Individual Pre-dose R-methadone Concentrations Alone and During Co-administration with TVR.

- Co-administration of TVR reduced the total C_{min} for R-methadone by 31% (Figure 5a and Table 2).
- Although the free fraction of R-methadone was increased by 26% (Figure 5b), there was no change in the unbound (effective) concentration of R-methadone (Figure 5c) with or without co-administration of TVR.

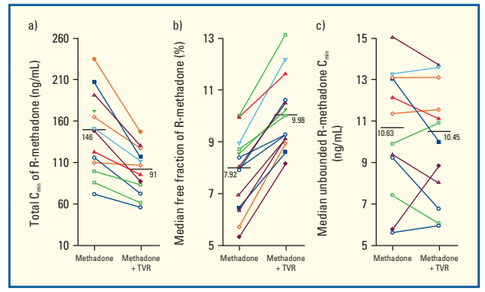

Figure 5. Effect of TVR Co-administration on a) C_{min}, b) Free Fraction and c) Unbound Concentration of R-methadone.

- The effects of protein displacement by TVR on methadone concentration (bound and unbound fractions) are shown in Figure 6:
  - The absolute unbound concentration of R-methadone was not affected by TVR co-administration.

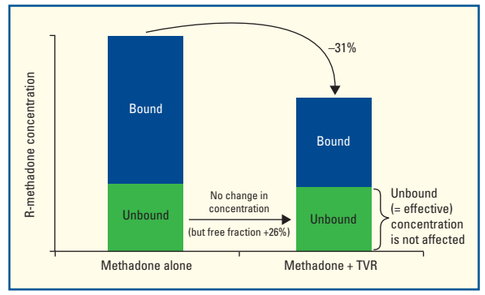

Figure 6. Representation of Effect of Protein Displacement by TVR on R-methadone Concentration (Bound and Unbound Fractions).

Symptoms of Opioid Withdrawal

- During co-administration of TVR and methadone, fewer volunteers experienced withdrawal symptoms than during treatment with methadone alone (SOWS).
- The desire for heroin was comparable with and without co-administration of TVR (DDQ).
- The median resting pupil diameter prior to methadone intake was 5.60 mm (range 3.6 to 6.5 mm). A median decrease versus reference was observed during methadone and TVR co-administration, at all timepoints (except pre-dose on Day 2), indicating that there were no signs of opiate withdrawal:
  - Larger decreases were observed when pupillometry was performed 2–4 hours after intake of methadone and TVR (ranging from –1.55 to –1.15 mm) than prior to intake (ranging from –0.85 to –0.10 mm).

Safety

- No volunteers discontinued the trial due to adverse events (AEs).
- The most frequently observed AEs during co-administration of TVR and methadone were headache (n=6), nausea (n=6), euphoric mood (n=5) and pruritus (n=3).
- All AEs were Grade 1 or 2 in severity, except for 1 case of Grade 3 aspartate transaminase increase during follow-up.
- No clinically relevant trends or changes over time in laboratory values were observed.

Conclusions

- Exposure to TVR was consistent with historic controls when combined with methadone, suggesting the absence of an effect of methadone on TVR pharmacokinetics.
- Exposure to R-methadone (AUC_{24h}) was decreased by 29% when combined with TVR.
- The observed interaction between TVR and methadone can be explained by protein-binding displacement:
  - Although the total R-methadone C_{min} was reduced, the median unbound concentration was not affected
  - Co-administration with TVR increased the median free fraction of R-methadone by 26%.
- As the unbound concentration of R-methadone was unchanged, the reduction in total R-methadone concentrations during TVR co-administration is not considered to be clinically relevant:
  - This is supported by the absence of withdrawal symptoms in this study.
- No dose adjustment of methadone is necessary when initiating co-administration of TVR:
  - Clinical monitoring is recommended as the dose of methadone may need to be adjusted in some patients.

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Acknowledgements

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Pharmacokinetic Interactions Between ARVs and Telaprevir

TVR Dose	ARV	TVR AUC	TVR C_{min}	ARV AUC	ARVC_{min}
TVR 750 mg tid	**ATV/r**	0.80 (0.76-0.98)	0.85 (0.75-0.98)	1.17 (0.97-1.43)	1.85 (1.40-2.44)
	DRV/r	0.65 (0.61-0.69)	0.68 (0.63-0.74)	0.60 (0.57-0.63)	0.58 (0.52-0.63)
	FPV/r	0.68 (0.63-0.72)	0.70 (0.64-0.77)	0.53 (0.49-0.58)	0.44 (0.40-0.50)
	LPV/r	0.46 (0.41-0.52)	0.48 (0.40-0.56)	1.06 (0.96-1.17)	1.14 (0.96-1.36)
TVR 1250 mg tid	**EFV**	0.82 (0.73-0.92)	0.75 (0.66-0.86)	0.82 (0.74-0.90)	0.90 (0.81-1.01)
	TDF			1.10 (1.03-1.18)	1.17 (1.06-1.28)
TVR 1500 mg bid	**EFV**	0.80 (0.73-0.88)	0.52 (0.42-0.64)	0.85 (0.79-0.91)	0.89 (0.82-0.96)
	TDF			1.10 (1.03-1.17)	1.06 (0.98-1.15)

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Boceprevir: Preclinical Metabolism

- Substrate of 1C2 and 1C3 isoforms of AKR → primary reduced metabolite, SCH 629144 (M+2)
- Substrate of CYP3A4/5
- Selective inhibitor of CYP3A4/5 isozymes:
  - Direct: CYP3A4 (IC_{50} = 11 μM) and 3A5 (IC_{50} = 0.97 μM)
- Substrate and inhibitor (IC_{50} ~25 μM) of P-gp

AKR - aldo-keto reductase
CYP3A4/5 - cytochrome P450 3A4/5
P-gp - P-glycoprotein.

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Efavirenz

N = 12 healthy volunteers

Days 1–5: BOC 800 mg TID
Day 6: BOC 800 mg single dose

Washout ≥7 days →

Days 1–10: EFV 600 mg QD

Days 11–15: BOC 800 mg TID
Day 16: BOC 800 mg single dose
Days 11–16: EFV 600 mg QD

	Treatment	LS Mean	Ratio Estimate,% (90% CI)
Effect of EFV (600 mg QD) on BOC (800 mg TID)			
C_{max} (ng/mL)	BOC BOC + EFV	2038 1871	92 (78–108)
$AUC_{(0\text{-}8h)}$ (ng·h/mL)	BOC BOC + EFV	6913 5630	81 (75–89)
C_{min} (ng/mL)	BOC BOC + EFV	94.4 52.5	56 (42–74)
Effect of BOC (800 mg TID) on EFV (600 mg QD)			
C_{max} (ng/mL)	EFV EFV + BOC	4573 5077	111 (102–120)
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	EFV EFV + BOC	78667 94655	120 (115–126)

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