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Effect of Rilpivirine on the Pharmacokinetics of Methadone in HIV-Infected Chinese Patients

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Abstract

Background: The combination of rilpivirine with methadone may result in complex interactions secondary to the induction of oxidative metabolism by rilpivirine.

Research design and methods: TMC278IFD4007 was a single-center, prospective, open-label, multiple-dose study with 12 HIV-infected Chinese participants. The objective was to evaluate the potential effect of rilpivirine on the pharmacokinetics of methadone. The participants received a daily dose of 25 mg rilpivirine for 11 days with individualized methadone ranging from 25 to 100 mg. Pharmacokinetic studies of methadone were conducted on day 1 and 11. Opiate withdrawal symptoms were evaluated.

Results: A large inter-subject variability was noted in methadone pharmacokinetics. Rilpivirine increased methadone minimum and maximum plasma concentrations (C_{min}; C_{max}) and area under the plasma concentration-time curve versus methadone alone (least-square mean ratio; 90% confidence interval) by 5% (1.05; 0.46, 2.39), 5% (1.05; 0.73, 1.52), and 6% (0.75; 0.74, 1.50) as measured in S-methadone, and 5% (1.05; 0.50, 2.22), 5% (1.05; 0.74, 1.50), and 5% (1.05; 0.76, 1.46) as measured in R-methadone, respectively. No opioid withdrawal symptoms or methadone dose adjustments were reported. Co-administration was well tolerated without serious adverse effects or discontinuations.

Conclusion: Concomitant administration of rilpivirine was unlikely to have significant effects on the pharmacokinetics of methadone.

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SL, LH, CY, QM and HL were involved in the conception and design. SL, LH, QM and HL mainly contributed to analysis and interpretation of the data. SL, LH, CY, SZ, YZ, SH, RX and XL conducted the study. SL, QM and HL drafted the paper and all authors approved this submission. All authors agreed to be accountable for all aspects of the work.

Reviewer Disclosures

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Keywords

methadone; rilpivirine; HIV; drug interactions

1. Introduction

The combination of rilpivirine (TMC278, Edurant®) with opioid maintenance therapy methadone may result in complex pharmacokinetic interactions secondary to the induction of oxidative metabolism by rilpivirine [1]. Methadone is converted to inactive metabolites by the cytochrome P450 enzymes, primarily CYP3A4, –2B6 and to a lesser extent –2D6 [2, 3]. Since rilpivirine is a substrate and inducer of CYP3A4, a modest change in the pharmacokinetics of methadone was reported when co-administered with rilpivirine among healthy volunteers [4]. While rilpivirine pharmacokinetics remained within normal range in the presence of methadone, the exposure of R- and S-methadone decreased by 16%. In addition, significant differences in pharmacokinetics and metabolic profiles of methadone in Asians have been suggested in genetic studies indicating lower clearance of methadone [5]. No data were available on the administration of methadone with rilpivirine in HIV-infected Chinese participants or the pharmacokinetic interactions that result at steady-state.

TMC278IFD4007 was developed to examine these interactions, in which rilpivirine was introduced after a prior period of methadone maintenance therapy in HIV-seropositive Chinese participants. Previous studies on efavirenz and nevirapine have reported clinically significant drug interactions when taken together methadone resulting with withdrawal symptoms and increases in methadone doses [6, 7]. As a new non-nucleoside reverse transcriptase inhibitor, rilpivirine has recently become available in China. The primary goal of TMC278IFD4007 was to investigate drug interactions of rilpivirine-containing regimens when combined with methadone and obtain data to examine influence of rilpivirine on methadone pharmacokinetics in HIV-infected Chinese participants.

2. Patients and methods

2.1. Study population

HIV-infected Chinese participants, males or females, were included in the study according to the following criteria: age between 18 and 65 years; standard medical examination, including electrocardiogram and laboratory tests; seropositive for HIV and on stable methadone maintenance treatment for at least 2 months. Participants with a history of alcohol use, suspected allergic or other serious reactions to drugs, psychiatric disease or diseases that could interfere with drug metabolism, in the methadone initiation phase or requiring dosage adjustments were excluded. All participants gave written informed consent and the protocol was approved by the Institutional Review Board of the participating institution.

2.2. Study design

This was a prospective, open-label, controlled, multiple dose study with 12 HIV-infected Chinese participants. All participants on stable methadone maintenance treatment were

instructed to undertake the first 24-hour pharmacokinetic evaluation prior to an initiation of rilpivirine/tenofovir/lamivudine dosing (25/300/300 mg, once daily) on day 1 in the morning and to continue on morning administration of both treatments until day 11. On day 11, participants were instructed to complete the second 24-h pharmacokinetic evaluation after the morning dose of methadone and rilpivirine.

2.3. Blood sampling

Participants reported to the research facility early in the morning on day 1 and day 11 after fasting overnight, and abstained from drinking alcohol or from performing high-impact exercise. They were allowed to drink water throughout the study. The first blood sample (0 h) was taken from a venous catheter, and a standardized breakfast was served to limit variations as administration of rilpivirine under fasting conditions or with only a protein-rich nutritional drink substantially lowered the oral bioavailability when compared to administration with a normal-fat breakfast [8]. After the assigned medications were taken, blood samples were then collected in 2 ml K2-EDTA tubes at 1.5, 3, 4, 6, 9, 12 and 24 h post-dose. Samples were centrifuged within 60 min after collection for 10 min at 1300 g to separate the plasma, which was then frozen at -20°C until analysis.

2.4. Safety assessment and adverse events

All participants underwent clinical and laboratory evaluations at all pharmacokinetic study visits and at the final safety visit. Adverse events with a severity of grade 1 or above, as defined by the National Institute of Allergy and Infectious Diseases, Division of AIDS Toxicity Tables, were monitored by the study team. For all participants prior to and after rilpivirine initiation, the number of severe reactions were counted and recorded. Additional assessment included measures of opioid withdrawal symptoms utilizing the Withdrawal Symptom Rating Scale [Liu, 2009 #29], which was administered at the baseline and the end of the study by trained nursing staff.

2.5. Determination of methadone concentrations and pharmacokinetic analysis

Plasma concentrations of methadone, both R- and S-methadone, were determined by a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method (SHBTM-1118-R0) performed at the Frontage Laboratory (Shanghai, China) [9]. Briefly, a 50- μl aliquot of plasma samples was fortified with an (R, S)-methadone-d3 internal standard followed by liquid extraction. The final extract was analyzed on a chromatographic system with a chiral- α 1-acid glycoprotein (AGP) analytical column (5 cm $\times$ 2.0 mm; 5 μm pore size), and MS/MS detection using API 4000 detector. MRM transitions were: for (R, S)-methadone, Q1 mass was 310.2 and Q3 mass was 265.0; and for (R, S)-methadone-d3, Q1 mass was 313.2 and Q3 mass was 268.0. The calibration range was 5 to 1,000 ng/ml for both R- and S-methadone. The average correlation coefficient from standard curves was >0.999 for both analytes. For R-methadone, the between-runs accuracy (percent bias) for the assay ranged from -3.0% to 2.8% , the within-run precision (%CV) was less than or equal to 4.5% , and the between-runs precision (%CV) was less than or equal to 10.4% for quality control. For S-methadone, the between-runs accuracy (percent bias) for the assay ranged from -3.3% to 4.0% , the within-run precision (%CV) was less than or equal to 7.2% , and the between-runs precision (%CV) was less than or equal to 11.4% for quality control. The

pharmacokinetics of R- and S-methadone were evaluated based on concentration-time data obtained on days 1 and 11, using non-compartmental method (WinNonlin V7.0, Certara, Princeton, NJ). Plasma concentration-time curves were used to derive pharmacokinetic parameters for methadone (R- and S-isomers), including maximal (C_{max}) and minimal concentrations (C_{min}), time to C_{max} (T_{max}), and the area under the concentration-time curve (AUC_{last}). AUC_{last} was calculated by linear trapezoidal summation. These parameters were descriptively summarized and compared.

2.6. Statistical analysis

Sample size calculations were based on a previous drug interaction study {Bruce, 2013 #28}. A sample size of 8 participants could provide 94% power to conclude no significant alterations in R- or S-methadone in terms of AUC_{last} or C_{max} within 70% to 143%. For more reliable assessments of safety and opioid withdrawal symptoms, a total of 12 participants were enrolled. Only participants who were able to provide pharmacokinetic data on both study days were included in the statistical analysis of pharmacokinetic parameters. Within-subject differences between parameters on day 1 and 11 were evaluated using non-parametric Wilcoxon signed rank test, and a p value of 0.05 or less was considered statistically significant. Comparisons between day 1 and 11 were also performed using least square means (LSmeans) and 90% confidence interval (90% CI).

3. Results

3.1. Study population

A total of 12 Chinese participants completed both pharmacokinetic assessments. Data on the study population were summarized as medians and ranges: age 41 years (36–50), weight 61 kg (44–80) and height 168 cm (162–172). Six participants were females (6/12, 50%).

3.2. Pharmacokinetics

The pharmacokinetic parameters of R- and S-methadone, as estimated by the non-compartmental analysis, are summarized in Table 2. Figure 1 provides the mean plasma concentration-time profiles for R- and S-methadone. Large inter-subject variabilities were noted in methadone pharmacokinetics. Co-administration of rilpivirine for 11 days affected methadone disposition only moderately. The mean C_{max} and AUC_{last} of R- and S-methadone decreased an average of 4% on day 11 relative to methadone alone (no rilpivirine, day 1). The exposure ratios between S- and R-methadone were ~95% and remained unchanged after rilpivirine co-administration (Table 1). The geometric means of AUC, C_{max} and C_{min} of methadone slightly increased after 11 days of rilpivirine dosing without statistical significance and all least square means ratios were within 80–125% (Table 2). No significant changes were observed that addition of rilpivirine into methadone regimen slightly raised geometric means of C_{max} and AUC_{last} in R-methadone by 5% (90% CI 74–150%, p = 0.8009 for C_{max}, 76–146%, p = 0.8032 for AUC_{last}), and resulted similar changes with S-methadone.

3.3. Adverse events and clinical outcomes

No serious clinical adverse events were reported. In general, these combinations were very well tolerated and adverse events were only mild (grade 1). The reported adverse events after the study were gastrointestinal adverse reaction and liver abnormal function test. Among the subjects who completed the study on day 11, one experienced grade 1 nausea and vomiting. Abnormal liver function test occurred in one subject. Both events were observed outside the study period and resolved without treatment discontinuation (Table 3).

The Withdrawal Symptom Rating Scale (WSRS) was employed to assess acute withdrawal symptoms in order to monitor the clinical effects of co-administration of methadone with rilpivirine. This instrument was utilized before and throughout co-administration. No significant signs of withdrawal occurred during the course of this study, and no dosage adjustments for methadone were required [mean doses (SD): 58 (25) mg; median doses (range): 53 (25–100) mg]. Mean scores at the baseline and the end of the study (day 1 vs. day 11) were listed as follows with their respective standard deviations: WSRS, 11 (1) vs. 11 (1). No relationship was observed between methadone dosage and the magnitude of pharmacokinetic variations.

4. Discussion

This work reports the lack of pharmacokinetic interaction between methadone and co-administered rilpivirine in TMC278IFD4007 study among HIV-infected Chinese participants. The rationales for our investigation related to known characteristics of methadone including ~85% bioavailability [10], large inter-subject variability [11] and oxidative metabolism via CYP3A4, –2B6 and –2D6 to inactive demethylated metabolites, with subsequent urinary excretion [12]. In previous investigations, nevirapine or efavirenz, inducers of CYP3A4 and –2B6, significantly decreased the plasma concentrations of methadone, indicating that either CYP3A4 or CYP2B6 or both contribute to the biotransformation of methadone. In genetic association studies, the *CYP2B6 516TT* genotype was associated with a decreased clearance and increased plasma concentrations of methadone, supporting a significant role for CYP2B6 in its biotransformation [13].

Previous studies have examined methadone with rilpivirine in healthy volunteers and found that while rilpivirine had inductive effects on CYP3A4, –2C19, –1A2 and 2B6, there was little influence on methadone disposition [4]. Unlike nevirapine or efavirenz, potent inducers of CYP3A4 and –2B6, rilpivirine exhibited weak induction of CYP3A4 at higher doses (150–300 mg) in healthy volunteers, and its inductive effects on CYP2B6 demonstrated *in vitro* [14]. Thus, at a dose of 25 mg once daily, rilpivirine was unlikely to have a clinically relevant effect on the exposure of drugs including methadone metabolized by CYP enzymes [15]. A multiple dose study on rilpivirine and CYP3A substrate tadalafil in combination in healthy volunteers found rilpivirine did not change tadalafil exposure or CYP3A activity measured by the oral midazolam microdose test confirming the negligible effect of rilpivirine (25 mg daily dose) on CYP3A-dependent drug metabolism [16].

Rilpivirine has been recently approved by the State Food and Drug Administration in China as a new-generation non-nucleoside reverse transcriptase inhibitor. One of the main

rationales for our study focusing on potential drug interactions between rilpivirine and methadone was the fact that methadone maintenance treatment is recommended to HIV-infected Chinese with injection drug use due to its beneficial effect to reduce mortality in this population [17]. Currently, efavirenz and nevirapine remain the first-line antiretroviral therapy in China, but their use have been a challenge among HIV+ injection drug users due to significant interactions with methadone. It is likely that rilpivirine would be a better option because of its similar efficacy and negligible drug interaction with methadone as suggested from the previous observations in healthy volunteers [4].

The findings from our study in HIV+ Chinese participants confirmed minimal effects of rilpivirine on the pharmacokinetics of methadone. Thus, the pharmacokinetic parameters of methadone obtained in TMC278IFD4007 on day 11 in the presence of rilpivirine were comparable to published values for methadone monotherapy. The estimated average maximal concentrations of R-methadone (3.749 ng/ml/mg, ranging 1.480–5.920 ng/ml/mg) in the present study was almost identical to that previously reported in Taiwanese subjects receiving methadone only (3.871 ng/ml/mg) [18]. For other parameters including trough concentrations and total exposures of R- and S-methadone at steady state, estimates were also consistent with literature [18, 19, 20]. These data along with previous observations indicate that rilpivirine does not substantially alter methadone pharmacokinetics.

There was a remarkable inter-individual variability in the methadone pharmacokinetic parameters prior to and after addition of rilpivirine consistent to that reported on methadone monotherapy [12, 21]. Although rilpivirine had no significant effect on the exposure or concentrations of methadone, clinical monitoring for withdrawal symptoms was still recommended for concurrent use of rilpivirine and methadone as dosage adjustment of methadone might be required due to the large inter-individual variability [4]. In our study, significantly lower exposures of R- and S-methadone in one participant were observed without withdrawal symptoms or methadone dosage adjustment (Figure 2), suggesting the importance of withdrawal monitoring in HIV+ individuals receiving rilpivirine and concomitant methadone.

The lack of pharmacokinetic interactions between rilpivirine and methadone may be due to not only the weak effects of rilpivirine on CYP3A, but also that methadone is primarily metabolized by CYP2B6 whereas CYP3A only plays a minor role. According to a number of drug interaction clinical studies [22, 23, 24], there was no correlation between methadone systemic exposure and inhibition of CYP3A4 activity. Mounting evidence indicated the methadone is primarily metabolized by CYP2B6 that genetic mutations of *CYP2B6* were associated with methadone dosage and effectiveness of maintenance treatment [25, 26]. Unlike efavirenz or nevirapine, both potent CYP2B6 inducers, rilpivirine significantly inhibited CYP2B6 *in vitro* with an IC₅₀ of 4.2 µmol/L [27], which might be the underlying mechanism of their differential effects on methadone metabolism.

Several limitations of our present study should be outlined. First of all, the number of participants for this pharmacokinetic interaction investigation, namely methadone together with rilpivirine seemed to be somewhat small considering the large inter-individual variability. This was mainly because the design of TMC278IFD4007 was based on the

bioequivalence study requirement of 12 participants. Nevertheless, the pharmacokinetic parameters of methadone obtained in our present study in the presence of rilpivirine (on day 11) were comparable with published values for methadone monotherapy. This observation reinforces the indication that rilpivirine does not substantially alter methadone pharmacokinetics. While no dose adjustment might be needed for methadone with concurrent use of rilpivirine in general, clinical monitoring of withdrawal symptoms is recommended mainly due to the large inter-individual variability of methadone. Secondly, there were no measures of rilpivirine concentrations. Previous studies in health volunteers have explored the effects of methadone on rilpivirine pharmacokinetics showing minimal effects on its concentrations [4].

5. Conclusions

Co-administration of rilpivirine had only a limited effect on the methadone pharmacokinetics in HIV-infected Chinese participants suggesting no dose adjustment needed for methadone with concurrent use of dual rilpivirine.

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The study was registered with Chinese Clinical Trial Registry (www.chictr.org.cn) and the trial registration number was ChiCTR-TRC-14004908.

Declaration of Interest

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Key issues:

- Methadone maintenance treatment for opioid addiction is common among HIV-infected Chinese patients.
- Rilpivirine has been recently introduced for the management of HIV infection in China.
- Evidence on drug interactions between methadone and rilpivirine is sparse and none in Chinese.
- No significant changes in methadone pharmacokinetics suggested concurrent use of rilpivirine safe in HIV-infected Chinese patients.

Compound= (R) - Methadone

1A: R-methadone

Compound= (S) - Methadone

1B: S-methadone

Fig 1. Plasma R- and S-methadone concentrations/sample time when methadone was co-administered with rilpivirine (Day 1 vs. Day 11).

Mean R- or S-methadone concentrations were plotted against scheduled sample times when participants had taken methadone only (Day 1) and when participants had taken methadone and rilpivirine (Day 11). Error bars indicate the standard derivation of R- or S-methadone concentrations. (1A: R-methadone, 1B: S-methadone)

2A: R-methadone

2B: S-methadone

Fig 2. Changes in plasma R- and S-methadone exposure when methadone was co-administered with rilpivirine (Day 1 vs. Day 11).

Individual S-methadone exposure as indicated by area under concentration-time curve (AUClast) were plotted when participants had taken methadone only (Day 1) and when participants had taken methadone and rilpivirine (Day 11). Participant 19 (P19) had remarkable decreases in AUClast. (2A: R-methadone, 2B: S-methadone)

Table 1.

Pharmacokinetic data for R- and S-methadone before and after co-administration of rilpivirine

R-Methadone	Methadone Only (Day 1)	Methadone + Rilpivirine (Day 11)
N	12	12
T _{max} (hr)	4.00 [1.5~9]	3.00 [0~6]
C _{max} (ng/ml)	210.3 ± 156.0	198.9 ± 74.84
C _{min} (ng/ml)	115.1 ± 76.35	107.7 ± 47.02
AUC _{last} (hr*ng/ml)	3590 ± 2224	3418 ± 1031
S-Methadone		
N	12	12
T _{max} (hr)	3.00 [1.5~9]	3.00 [0~4]
C _{max} (ng/ml)	217.8 ± 155.0	210.9 ± 92.87
C _{min} (ng/ml)	90.15 ± 68.87	86.83 ± 54.98
AUC _{last} (hr*ng/ml)	3297 ± 2062	3221 ± 1237
AUC _{last} S-Methadone/AUC _{last} R-Methadone (%)	94±26	96±27

Data presented as mean±SD, except T_{max}: median [range]

Table 2.

Statistical comparisons of R- and S-methadone pharmacokinetic data before (day 1) and after co-administration of rilpivirine (day 11)

GeoMean					
Parameter	Day 1 (reference)	Day11 (test)	LSmeans ratio, %	90% CI	Pr> t
R-Methadone					
AUClast (hr*ng/ml)	3100	3254	105	76, 146	0.8032
Cmax (ng/ml)	176	186	105	74, 150	0.8009
Cmin (ng/ml)	82	87	105	50, 222	0.9037
S-Methadone					
AUClast (hr*ng/ml)	2827	2999	106	75, 150	0.7727
Cmax (ng/ml)	183	192	105	73, 152	0.8142
Cmin (ng/ml)	59	62	105	46, 239	0.9187

GeoMean: geometric means; LSmeans ratio: least square means ratio; 5 ng/mL used for Cmin if below lower limit of quantification (LLQ, 10 ng/mL)

Table 3.

Summary of adverse events (n=12)

Adverse Event	N (%)	Note
Nausea/vomiting (grade 1)	1 (8)	No dosage change or treatment discontinuation, resolved
AST/ALT increase (grade 1)	1 (8)	No dosage change or treatment discontinuation, resolved

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase