

Effects of Pegylated Interferon Alfa-2b on the Pharmacokinetic and Pharmacodynamic Properties of Methadone: A Prospective, Nonrandomized, Crossover Study in Patients Coinfected with Hepatitis C and HIV Receiving Methadone Maintenance Treatment

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is common among methadone-maintained HIV-positive individuals. Pegylated interferon (pegIFN) used in combination with ribavirin is conventional treatment for HCV. However, pegIFN has been associated with adverse effects (AEs) that may simulate opioid withdrawal and be confused with insufficient methadone dosage.

Objective: The aim of this study was to determine, using methadone pharmacokinetic properties, whether methadone dosage adjustments are needed on initiation of treatment with pegIFN alfa-2b for HCV in methadone-maintained HIV-positive patients.

Methods: This prospective, nonrandomized, crossover study was conducted at the Albert Einstein College of Medicine and Montefiore Medical Center (Bronx, New York). Patients who were aged ≥ 18 years, coinfecting with chronic HCV and HIV, and had been receiving methadone maintenance treatment (dosage, 40–200 mg/d PO) for at least 8 weeks prior to enrollment were eligible. We determined mean methadone C_{max} , T_{max} , C_{min} , AUC, and oral clearance (CL/F) values over a 24-hour period before (baseline) and after the administration of pegIFN alfa-2b 1.5 $\mu\text{g}/\text{kg}$ SC (2 doses given 1 week apart). To determine differences in opiate withdrawal symptoms, one of the primary investigators administered the Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS) at baseline and 7, 14, and

21 days after the administration of the first dose. Study participants underwent weekly clinical evaluation for signs and symptoms of methadone withdrawal and for AEs of pegIFN.

Results: Nine patients were included in the study (7 men, 2 women; 7 Hispanic, 2 black; mean [SD] age, 41 [8.3] years; mean [SD] weight, 75.0 [12.3] kg). We did not observe any significant changes from baseline in mean C_{max} , T_{max} , C_{min} , AUC, and CL/F values despite 80% power to detect a 30% change in either direction. Changes from baseline in SOWS and OOWS scores were not statistically significant. The only AEs reported were mild and consistent with those expected after pegIFN alfa-2b administration, such as inflammation at the injection site and mild, brief, flulike symptoms.

Conclusion: Based on the results of this small, prospective, nonrandomized study, pegIFN alfa-2b did not appear to precipitate opioid withdrawal in this sample of methadone-maintained persons with HIV and chronic HCV coinfection; methadone dosage adjustments were unlikely to be needed. (*Clin Ther.* 2007;29:131–138) Copyright © 2007 Excerpta Medica, Inc.

Key terms: hepatitis C, HIV, pegylated interferon, methadone.

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INTRODUCTION

Hepatitis C virus (HCV) infection is common among users of injectable illicit drugs, with a reported prevalence of 66% to 95% in some US samples.¹⁻³ Concurrent infection with HIV is also common among these users, with a reported prevalence ranging from 26% to 72%.^{3,4} The progression of HCV infection is accelerated in the presence of HIV coinfection, making HCV treatment an important goal in dually infected persons,^{5,6} particularly because HIV-infected persons now live long enough to be at risk for HCV-related hepatic disease. HIV-infected users may receive maintenance treatment with methadone, which has been found to improve HIV- and HCV-related treatment outcomes.^{7,8}

Conventional treatment of HCV infection is combination therapy with pegylated interferon (pegIFN) 1.5 µg/kg · wk⁻¹ and ribavirin 800 mg/d, which has been found to yield a sustained virologic response (undetectable HCV RNA 24 weeks after treatment cessation) rate of ~54% in treatment-naive adults with HCV.⁹ The presence of HIV coinfection and recent or ongoing illicit drug use may complicate, but does not contravene, the decision to treat HCV infection.^{10,11}

In the authors' clinical experience, the constitutional adverse effects (AEs) of interferon (IFN) (eg, myalgias, arthralgias, chills, nausea, insomnia, irritability) in opioid-dependent persons can be difficult to distinguish from those of narcotic withdrawal. There have been anecdotal reports⁸ of methadone-maintained patients attributing such symptoms to withdrawal. In 1 prospective clinical trial,¹² 45% of 76 HCV-infected patients receiving treatment with methadone 79 to 160 mg required methadone dose increases (by a median of 15 mg) after initiation of combination IFN 3 MU TIW and ribavirin 800 to 1200 mg/d. Thus, clinicians face the following question: Should constitutional symptoms in a methadone-maintained patient soon after initiation of combination treatment with IFN and ribavirin prompt concern of a medication interaction with methadone, or should it simply trigger a standard AE management approach (eg, use of acetaminophen or NSAIDs, increased fluid intake, and/or nighttime administration of IFN)?

Medication interactions with methadone can be clinically significant and have received increasing attention, as found in a review of interactions with HIV-related medications.¹³ A major route of metabolism of methadone is *N*-dealkylation by the cytochrome P450

(CYP) 3A4 isozyme, with lesser involvement of CYP2D6 and CYP2C8.¹⁴⁻¹⁶ Medications that induce expression of CYP3A4 (eg, nevirapine, efavirenz, rifampin) may enhance methadone metabolism. Rifampin has been found to be associated with withdrawal symptoms in up to 70% of methadone-maintained patients.¹⁷ In contrast, medications such as ketoconazole (a CYP3A4 inhibitor) or paroxetine and fluvoxamine (inhibitors of multiple CYP isozymes) have been reported to inhibit methadone metabolism,¹⁶ with ≥1 case report of opioid toxicity.¹⁸

IFN has been reported to affect various CYP isozymes and therefore has the potential to cause drug-drug interactions. The results of 7 studies¹⁹⁻²⁵ have suggested an inhibitory effect of IFN on CYP-mediated drug metabolism, with the predominant effect on CYP1A2 and, to a lesser extent, CYP2C19 and CYP2D6. IFN has been associated with significant decreases in the clearance of theophylline (decreases, 15%–26%; *P* < 0.05 vs control), a drug known to be metabolized by the CYP1A2 isozyme.^{21,22,24} Clearance of antipyrine (metabolized by ≥6 CYP isozymes)²⁶ was found to be decreased with the use of IFN in 1 study²⁰ but not others,²⁷⁻²⁹ and to increase in patients with chronic active hepatitis B or C infection who responded favorably to IFN treatment.^{29,30} PegIFN has been found to have a 10- to 20-fold increased *t*_{1/2} compared with IFN.³¹ Additionally, a review³¹ has found that the 2 types of commercially available pegIFN, pegIFN alfa-2a and pegIFN alfa-2b, have been found to have differing pharmacokinetic properties. For these reasons, pegIFN may have effects on CYP isozymes that differ from those of IFN.

Therefore, the effects of IFN, and pegIFN in particular, on CYP-mediated medication metabolism may be variable and cannot be predicted a priori. One multicenter, nonrandomized, open-label study³² of the possible impact of pegIFN alfa-2a on methadone concentrations found no evidence of a significant interaction in 22 HIV-negative persons with HCV infection.³² Because of the high prevalence of HIV coinfection among HCV-infected users of injectable illicit drugs and the potential for increased rates of drug-drug interactions in persons with HIV infection, it is important to determine whether there is a risk for interaction between pegIFN and methadone in HIV-positive persons. Ribavirin, the other component of conventional HCV treatment, is not metabolized by the CYP system. A search of the MEDLINE (key terms:

methadone, ribavirin, and drug interactions; dates: 1966–August 2006) and the Micromedex and Lexi-Interact online drug-interaction databases revealed no documented effects of ribavirin on the metabolism of methadone. Therefore, the aims of the present study were to assess the potential interaction of pegIFN alfa-2b with methadone in patients co-infected with HCV and HIV receiving maintenance treatment with methadone, and to determine whether dose adjustments need to be made.

PATIENTS AND METHODS

This study was conducted at the Albert Einstein College of Medicine (AECOM) and Montefiore Medical Center, Bronx, New York. The study was approved by the institutional review boards at AECOM and Montefiore Medical Center. The study was conducted in accordance with the Good Clinical Practice guidelines³³ and the Declaration of Helsinki and its amendments.³⁴

Participant Characteristics

Participants were male and female outpatients recruited from the methadone maintenance treatment program of the Division of Substance Abuse at AECOM. All participants were aged ≥ 18 years and HIV-antibody positive with chronic HCV infection confirmed by detectable HCV RNA (≥ 615 IU/mL). All participants had been receiving a stable, directly observed oral methadone dose of 40 to 200 mg/d for at least 8 weeks prior to enrollment. All women capable of becoming pregnant were required to have a negative result on pregnancy testing within 1 week prior to study entry.

Patients were excluded if they had evidence of decompensated liver disease, uncontrolled hypertension (blood pressure, $>140/>90$ mm Hg) or diabetes (glycosylated hemoglobin, $>8.0\%$), thyroid or cardiovascular disease, renal insufficiency (estimated creatinine clearance, <50 mL/min), acute infection, and/or hemoglobin <10 g/dL. Participants were to be free of acute psychiatric illness and suicidality as assessed ~ 1 week before study initiation using the Mini-International Neuropsychiatric Interview.³⁵ None of the participants could receive medications known to alter methadone metabolism (eg, efavirenz, fluconazole, fluvoxamine, nevirapine, rifampin, ritonavir). Written informed consent was obtained from all participants on enrollment.

Pharmacokinetic Study Design

Participants were instructed to self-administer methadone at ~ 8 AM each morning starting 1 week prior to and for 2 weeks after the first methadone blood-sampling study (day 1). Compliance was ensured by direct observation of study drug administration by clinic staff or by return of empty methadone containers by patients to clinic staff. Before study drug administration on the morning of study day 1, participants reported to the General Clinical Research Center (GCRC) at AECOM. An alcohol breathalyzer test was administered, with a negative result required for participation. Immediately following phlebotomy for baseline serum methadone concentration measurement, patients ingested the morning oral dose of methadone. Methadone serum concentrations were determined at the ensuing 1, 2, 4, 6, 8, 12, and 24 hours. After the final sample was drawn on study day 2, participants received the initial subcutaneous injection of pegIFN alfa-2b* at a dose of 1.5 $\mu\text{g}/\text{kg}$ (per the manufacturer's prescribing recommendations³⁶). The second dose of pegIFN alfa-2b was administered 1 week later (day 9) in a similar fashion. Participants returned to the GCRC 1 week later (day 16) for the second 24-hour methadone blood-sampling study, with the same sampling sequence as the first. All blood samples were ~ 5 mL, collected in plain glass³⁷ red-top serum tubes (Vacutainer, Becton, Dickinson and Company, Franklin Lakes, New Jersey) and allowed to clot prior to centrifugation at 3000 rpm at 4°C for 10 minutes. Serum was collected and stored at -100°C (Ultima II freezer, Revco, Asheville, North Carolina) until assayed.

Methadone concentrations were determined using reversed-phase high-performance liquid chromatography as described previously.³⁸ Briefly, following alkalization and the addition of an internal standard (propoxyphene 1 mg/mL acetonitrile, provided by Cerrilant Corporation, Round Rock, Texas), serum was extracted with hexane containing 2% isobutanol. Following micro-back-extraction into dilute phosphoric acid, the aqueous phase underwent chromatography on a reversed-phase column (5- μm ID Spherisorb ODS-2, Alltech, Deerfield, Illinois) with UV detection at 210 nm. The lowest limit of detection was 25 ng/mL. Between-day coefficients of variation were 7.8%, 5.7%, and 9.5% at 400, 200, and 40 ng/mL, respectively.

*Trademark: Peg-Intron® (Schering-Plough Corporation, Kenilworth, New Jersey).

Pharmacodynamic Study Design

Study participants underwent weekly clinical evaluation for signs and symptoms of methadone withdrawal and for AEs of pegIFN. In addition, the Subjective Opiate Withdrawal Scale (SOWS) and the Objective Opiate Withdrawal Scale (OOWS) (29 self- and observer-rated questions about opiate withdrawal and AEs in the prior week),³⁹ as well as the Beck Depression Inventory (BDI),⁴⁰ were administered by 1 of the first 2 authors to all participants at baseline and on study days 7, 14, and 21. Urine toxicology (Abuscreen Online, Roche Diagnostics, Inc., Somerville, New Jersey) was also obtained on these days. Toxicity was assessed by clinical excess sedation noted by 1 of the first 2 researchers in the GCRC or by the methadone clinic staff. Withdrawal symptoms were assessed by the SOWS and OOWS instruments.

Statistical Analysis

A sample size of 9 participants was calculated as necessary to achieve 80% power at a 0.05 significance level to detect a 30% change in methadone AUC_{0-24} following pegIFN alfa-2b administration, when the expected difference was zero and the CV of the difference was 30%.

Methadone pharmacokinetic parameters were determined using standard noncompartmental methods (WinNonlin version 4.0 [Pharsight Corporation, Mountain View, California]), and included C_{max} , T_{max} , C_{min} , oral clearance (CL/F), and AUC_{0-24} .

Mean values for parameters before and after pegIFN alfa-2b administration were compared using the paired 2-tailed *t* test. Scores on the SOWS, OOWS, and BDI at baseline were compared with each of the post-pegIFN alfa-2b 7, 14, and 21 days values using the Wilcoxon signed rank test. $P < 0.05$ was considered significant for all statistical evaluations.

RESULTS

Study Participants

Of 10 participants who were enrolled in the study, 1 withdrew before completing the blood draws following pegIFN alfa-2b administration. The 9 participants who completed the protocol were included in the analyses (7 men, 2 women; 7 Hispanic, 2 black; mean [SD] age, 41 [8.3] years [range, 29–52 years]; mean [SD] weight, 75.0 [12.3] kg). The mean (SD) daily methadone dose was 104 (54) mg (range, 40–190 mg). CD4+ lymphocyte counts ranged from 200 to 1170 cells/ μ L (median, 437 cells/ μ L), and HIV RNA levels ranged

from undetectable to 318,740 copies/mL (median, 50,359 copies/mL). One patient was receiving anti-retroviral medications (abacavir, zidovudine, lamivudine, and atazanavir) under steady-state conditions prior to and during the study. Two patients were receiving various psychiatric medications (olanzapine, sertraline, bupropion, and trazodone) under steady-state conditions prior to and during the study. Urine toxicology results were positive for opiates at baseline in 1 participant who was using prescribed narcotic medication for analgesia, and in 1 participant who used intranasal heroin after negative baseline toxicology testing.

Pharmacokinetic Properties

Mean concentration–time profiles for methadone before and after 2 weeks of pegIFN alfa-2b administration are shown in the figure. Overall, there was a 16.5% increase in mean methadone AUC_{0-24} and a 23.9% increase in mean methadone C_{min} following pegIFN alfa-2b administration (both, $P = NS$). Use of pegIFN alfa-2b was not associated with statistically significant changes in any other pharmacokinetic parameters tested (Table).

Pharmacodynamic Properties

Differences versus baseline in objective or subjective opiate withdrawal, as measured using mean SOWS and OOWS scores at 7, 14, and 21 days after the first dose of pegIFN alfa-2b, were not statistically significant. The difference versus baseline in symptoms of depression, as measured using mean BDI score, at 21 days was also not statistically significant.

No serious AEs related to methadone or IFN were observed. Specifically, there was no evidence of methadone toxicity or withdrawal symptoms. There were no clinically significant changes in serum electrolytes, renal function, hepatic aminotransferases, or complete blood counts. The only AEs reported were mild and consistent with those expected after pegIFN alfa-2b administration, such as inflammation at the injection site and mild, brief, flulike symptoms (patient-reported fever, chills, headache, myalgias, and arthralgias for 1 to 2 days after pegIFN alfa-2b administration).

DISCUSSION

We found no evidence of a pharmacologic or pharmacodynamic interaction between pegIFN alfa-2b and methadone in our small, selected population. If simi-

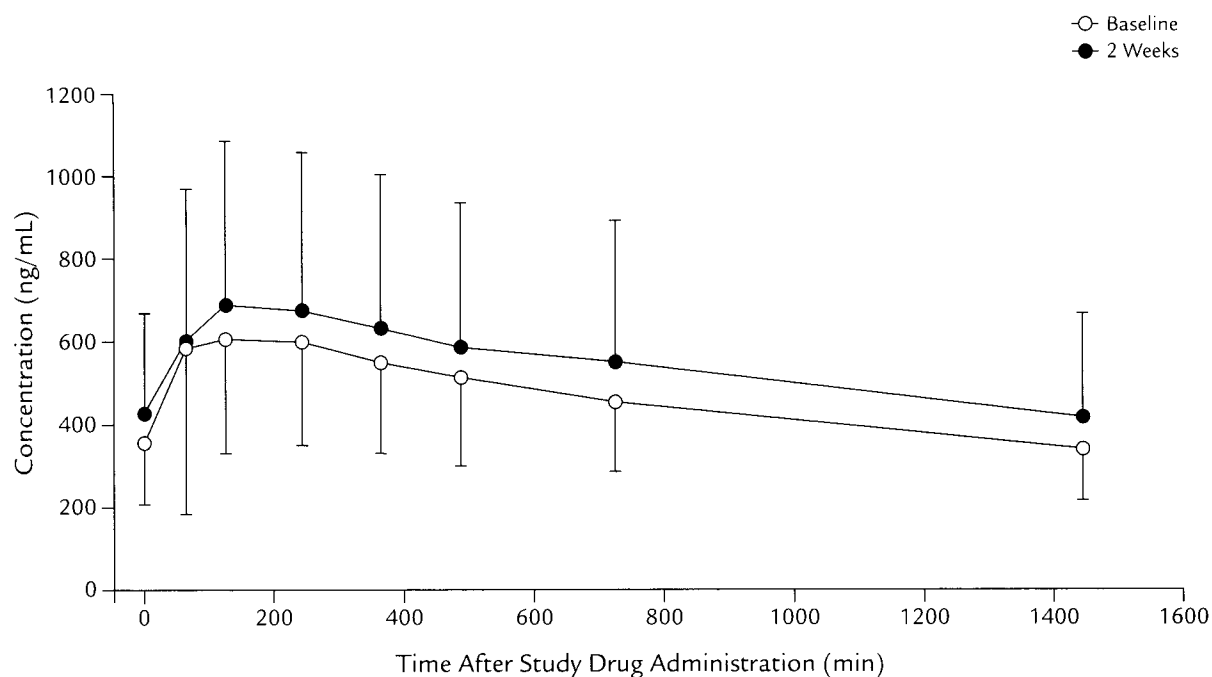


Figure. Twenty-four-hour mean (SD) methadone concentrations before (baseline) and after 2 weeks of pegylated interferon α_{2b} administration in patients coinfecting with hepatitis C virus and HIV (N = 9).

Table. Steady-state pharmacokinetic properties of methadone before (baseline) and after 2 weeks of pegylated interferon α_{2b} administration in patients coinfecting with hepatitis C virus and HIV (N = 9). Values are mean (SD).

Property	Before	After	<i>p</i> *
C_{max} , ng/mL	690 (380)	696 (390)	0.9
T_{max} , ng/mL	2.7 (1.1)	2.7 (1.0)	1.0
C_{min} , ng/mL	343 (128)	425 (246)	0.1
AUC_{0-24} , ng/mL · h ⁻¹	11,169 (4440)	13,009 (7622)	0.2
CL/F, L/h	9.6 (3.2)	8.9 (3.4)	0.4

CL/F = oral clearance.

*Paired 2-tailed *t* test.

lar patients are concerned that treatment with pegIFN alfa-2b may interfere with the effectiveness of methadone treatment, clinicians can provide reassurance to the contrary. If symptoms resembling those of opioid withdrawal are experienced by a methadone-maintained patient during treatment with pegIFN, it is unlikely that the symptoms reflect any effect of IFN on methadone metabolism.

The findings of the present study are similar to those from Sulkowski et al,³² who studied the effect of pegIFN alfa-2a on methadone pharmacokinetic prop-

erties in 22 HCV-infected but HIV-negative patients. They reported an 18.9% increase in methadone AUC_{0-24} after 4 weeks of pegIFN alfa-2a treatment, and no evidence of methadone withdrawal or toxicity or other serious AEs. Our study extends these findings to HIV-positive patients infected with HCV, a group at higher risk for HCV-induced liver disease and drug-drug interactions.

The findings of the present study are further supported by the results of 2 prospective clinical trials^{41,42} of HCV-infected, methadone-maintained patients

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treated with IFN-based therapy, in which methadone dosage adjustments were not required. In 1 study in 21 patients,⁴¹ the mean methadone dose was not statistically different from baseline after 6 to 12 months of IFN-based therapy (57 vs 59 mg/d). In another study in 25 patients,⁴² the median methadone dose at baseline was not significantly different from that at the end of 24 to 48 weeks of IFN-based therapy (55 vs 50 mg/d).

The present study had several limitations. The small sample size was designed to detect a 30% change in methadone AUC_{0-24} , a magnitude we considered likely to engender clinically significant symptoms of opioid withdrawal. In fact, we found a somewhat greater methadone AUC_{0-24} following pegIFN alfa-2b administration, but this difference was not statistically significant. Although our study was not powered to confirm this minor elevation in serum methadone levels, in this sample, pegIFN alfa-2b administration was not associated with significantly lower serum methadone concentrations.

Two patients received concurrent medications that may have affected methadone metabolism. Abacavir has been reported to increase methadone clearance in a modest and clinically nonsignificant manner.¹³ In addition, in 1 study,⁴³ sertraline was reported to cause a transient (6–12 week) and clinically nonsignificant increase in methadone levels. Although the patients in the present study were receiving these medications under steady-state conditions prior to and during the study period, it is conceivable that the pharmacokinetic properties of methadone were influenced by these medications.

We assessed the impact of pegIFN alfa-2b on methadone levels after a relatively short (2-week) duration of pegIFN alfa-2b administration. In previous reports,^{38,44} similar durations of treatment with lopinavir or fluconazole were considered sufficient to show significant reductions or increases in methadone concentrations, respectively. In 1 study,³⁸ 7 days of lopinavir/ritonavir administration was associated with significant reductions in methadone AUC (by 26%) and C_{max} and C_{min} (both, by 28%), and a significant increase in CL/F (by 42%) (all, $P < 0.001$). In another study,⁴⁴ 14 days of fluconazole administration was associated with significant increases in serum methadone AUC (by 35%), C_{max} (by 27%), and C_{min} (by 48%) and a significant decrease in CL/F (by 24%) (all, $P < 0.001$). We chose to measure the pharmaco-

kinetic properties of methadone at the end of the second week of pegIFN alfa-2b treatment to maximize duration of exposure of hepatic enzymes to pegIFN α_{2b} . A larger effect may have been found at an earlier time (coinciding with T_{max}). In addition, because pegIFN α_{2b} accumulates during long-term treatment, with mean C_{min} levels 3-fold higher after 48 weeks of therapy compared with week 4,³⁶ our findings may have differed had we studied this interaction after a greater duration of pegIFN alfa-2b treatment.

Finally, we did not assess the effect of pegIFN alfa-2b on the pharmacokinetic properties of the separate methadone enantiomers (the *R*-enantiomer being more active) or on changes in protein binding of methadone to the acute phase reactant, α_1 acid glycoprotein. However, because we did not observe any clinically significant impact of pegIFN on opioid-related symptoms, further investigation of these variables does not appear to be indicated.

How should the clinician manage methadone-maintained patients who report symptoms mimicking those of narcotic withdrawal during the course of treatment with pegIFN alfa-2b for hepatitis C infection? First, data suggest that these symptoms are most likely due to common AEs of the pegIFN and not to methadone withdrawal. Patients should be encouraged not to use illicit opioids to treat the symptoms they may be experiencing. Other potential causes of opioid withdrawal should be ruled out, including other medication interactions and illicit narcotic use. Finally, acetaminophen or NSAIDs may be used to treat pegIFN-related AEs, as indicated clinically.

The effects of long-term (24–48 weeks) treatment with pegIFN on the pharmacokinetic and pharmacodynamic properties of methadone warrant additional investigation.

CONCLUSION

Based on the results of this small, prospective, non-randomized study, pegIFN alfa-2b did not appear to precipitate opioid withdrawal in this sample of methadone-maintained persons with HIV and chronic HCV coinfection; methadone dosage adjustments were unlikely to be needed.

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