

The Effect of Multiple Doses of Peginterferon alfa-2b on the Steady-State Pharmacokinetics of Methadone in Patients With Chronic Hepatitis C Undergoing Methadone Maintenance Therapy

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This multicenter, open-label study evaluated the effects of multiple doses of peginterferon alfa-2b on the steady-state pharmacokinetics of methadone in 20 adults with hepatitis C virus infection who were enrolled in a methadone maintenance program. All subjects received peginterferon alfa-2b 1.5 µg/kg/wk for 4 weeks and maintained their normal methadone regimen. Serial blood samples were collected immediately before the first and after the fourth peginterferon alfa-2b dose (day 23). At day 23, exposure to the active methadone R-enantiomer increased by approximately 15% following administration of peginterferon alfa-2b, with 90% confidence intervals just outside the bioequivalence criteria (range,

80%-125%). Similar increases in exposure (C_{max} , AUC_{0-24} , and AUC_{last}) were observed with S-methadone and total methadone. Peginterferon alfa-2b was well tolerated. Peginterferon alfa-2b is associated with minor increases in exposure to methadone in individuals with hepatitis C virus infection; however, these increases are unlikely to be clinically meaningful and are not associated with any safety concerns.

Keywords: Drug interactions; hepatitis C; methadone; peginterferon alfa-2b; pharmacokinetics
Journal of Clinical Pharmacology, xxxx;xx:x-x
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Illicit injection drug use is associated with a high risk of hepatitis C virus (HCV) infection: the prevalence of disease in injection drug users (IDUs) ranges from 50% to 95%.^{1,2} It is estimated that at least two thirds of cases of HCV infection in the United States are in IDUs.² Interestingly, preliminary evidence suggests that prolonged opioid use may enhance HCV replicon expression in human hepatic cells, which may further contribute to the development of HCV infection in IDUs.³

There are a number of barriers to the treatment of chronic hepatitis C in IDUs, including ongoing drug use, health care access (particularly because many IDUs are underinsured), treatment adherence, concurrent HIV infection, and comorbid psychiatric illnesses.^{1,4} Recent guidelines have highlighted the importance of appropriately treating such individuals, particularly those in health care settings such as methadone maintenance programs, because this allows for integrated care and consequent improved outcomes.^{5,6} The effective treatment of HCV-infected IDUs will help relieve the overall burden of this disease by addressing one of the groups in which HCV is underreported in North America.⁷⁻⁹

Pegylated forms of interferon alfa, alone or in combination with ribavirin, have become the standard of care for the treatment of individuals with chronic hepatitis C. In clinical trials, sustained virologic response rates between 42% and 46% have been achieved in subjects with HCV genotype 1 and

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 DOI: 10.1177/0091270007299760

between 78% and 82% in subjects with HCV genotype 2 or 3.¹⁰⁻¹⁴ However, data regarding sustained virologic response rates among IDUs receiving antiviral therapy are lacking, perhaps because of concerns about treating IDUs with peginterferon alfa, including those IDUs participating in methadone maintenance programs.⁴ These concerns include the increased risk for neuropsychiatric events with therapy, which may predispose IDUs to return to using injected drugs, as well as other issues. Last, the effects of peginterferons on the catabolism of methadone have not been clearly established.

Methadone is a racemic mixture, with analgesic properties residing predominantly in the R-enantiomer.¹⁵ The drug is primarily metabolized by N-demethylation via the cytochrome P450 (CYP450) 3A4 system, secondarily by CYP2D6, and, to a lesser extent, by CYP1A2 and CYP2B6. Stereoselectivity in the metabolism of R- and S-methadone may exist.^{16,17} Although interferon alfa has been shown to inhibit various CYP450 enzymes, several studies using therapeutic doses (3 million units [MU] 3 times weekly) for HCV have not revealed any clinically important effects on enzymatic activity.^{18,19} However, 1 study (using high-dose interferon alfa in patients with high-risk melanoma) showed that interferon alfa has no effect on some CYP enzymes (eg, CYP2E1) but notably inhibits others (eg, CYP1A2).²⁰ Conversely, a single-dose study showed that peginterferon alfa-2b did not have any effect on the activity of CYP1A2.²¹ The effects of multiple doses of peginterferon alfa-2b on CYP450 enzyme activity and the pharmacokinetics of methadone have not been established.

The most commonly observed symptoms in patients with chronic hepatitis C are intermittent fatigue, with right upper quadrant pain (or liver ache), nausea, and poor appetite also occurring in some patients.²² Serum alanine aminotransferase (ALT) levels are usually continuously or intermittently elevated.²² Adverse effects associated with peginterferon therapy include flulike symptoms, marrow suppression (leucopenia and thrombocytopenia), emotional effects (eg, irritability and depression), and autoimmune reactions such as autoimmune thyroiditis.²³ Conversely, the most common toxicities associated with methadone include respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention, and hypotension.²⁴

Given the high prevalence of HCV infection in IDUs, it is important to evaluate the impact of antiviral therapy on the pharmacokinetics of methadone to ensure that the treatment of chronic hepatitis C

will not have an unfavorable risk-benefit profile in this population. This study evaluated the effects of multiple-dose peginterferon alfa-2b on the steady-state pharmacokinetics of R-methadone, S-methadone, and total methadone in individuals with chronic hepatitis C who were otherwise healthy.

METHODS

Subjects

Subjects 18 to 57 years of age who were HIV negative and HCV positive at screening (confirmed by quantitative polymerase chain reaction), had compensated liver disease, and were enrolled in a methadone maintenance program were eligible for entry into this study if otherwise healthy. All subjects were to have been adherent with a methadone maintenance program for 3 months or more, were to have received a stable dose of methadone for 4 weeks or more, and were to be receiving methadone 40 mg/d or more at screening. Screening for drugs with a high potential for abuse (other than methadone) was carried out at the screening visit and at day -1; results must have been negative. Sexually active women of childbearing potential were required to use an appropriate form of contraception. Subjects were excluded from study participation if they had cause of liver disease other than HCV infection, had evidence of advanced liver disease (including history or presence of ascites, bleeding varices, or spontaneous encephalopathy) or hemoglobinopathy, or had undergone organ transplantation. Continuing substance abuse (including alcohol consumption ≥ 20 g/d, intravenous drug use, and inhaled drug use) was also grounds for exclusion, as was the presence of any known preexisting medical condition that could have interfered with participation in and completion of the study or would have required the care of a physician, including preexisting or a history of psychiatric disorders such as severe depression, central nervous system trauma, or active seizure disorders; significant cardiovascular dysfunction; poorly controlled diabetes mellitus; chronic pulmonary disease; or immunologically mediated disease.

Additional exclusion criteria included a history of clinically significant local or systemic infectious disease in the 4 weeks before the initial administration of study drug, use of medications known to alter CYP450 activities (eg, phenytoin, carbamazepine, barbiturates, rifampin, rifabutin, and cimetidine), consumption of alcohol within 72 hours before study drug administration, clinically significant retinal abnormalities, pregnancy or lactation, donation of

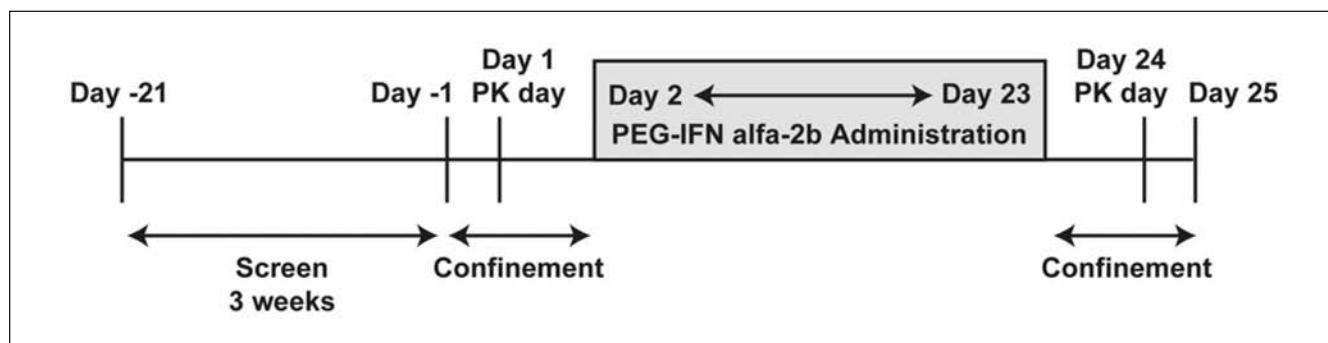


Figure 1. Study design.
PEG-IFN, peginterferon; PK, pharmacokinetics.

blood within the 60 days before study entry, and participation in other clinical trials or use of any investigational drug within 30 days before study entry.

Study Design

This was an open-label, multiple-dose, fixed-sequence pharmacokinetics study (Figure 1) carried out at Sunnybrook and Women's College Health Sciences Centre, Toronto, Canada; University of Cincinnati Medical Center, Cincinnati, Ohio; and Shawnee Mission, Kansas. The study design is shown in Figure 1. Subjects (N = 20) who met eligibility criteria at the screening visit were administered peginterferon alfa-2b (PegIntron, Schering Corp, Kenilworth, NJ) 1.5 µg/kg/wk on the mornings of days 2, 9, 16, and 23. The drug was injected subcutaneously (SC) in the anterior abdominal wall by the principal investigator or an appropriately qualified designee at approximately the same time each week (08:00-10:00). Injection site was rotated as necessary. The dose was calculated using the subject's body weight at day 1, and the drug was administered within 24 hours of preparation. Therapy was to be interrupted in subjects who experienced a decrease in neutrophil count to less than 750 cells/µL, in platelet count to less than 50 000 cells/µL, or in hemoglobin level to less than 9 g/dL.

Subjects continued their normal methadone maintenance program, and efforts were made to ensure that they continued the same dose of methadone throughout the study (approximately 40 mg/d). On the mornings of days 1 and 24 (after a 10-hour fast), subjects were given their usual dose of methadone with approximately 240 mL of noncarbonated, room-temperature water. On other days, methadone could be given on an outpatient basis under supervised conditions. Treatment adherence was ensured by supervised administration of study medications; after inpatient methadone

dosing, the mouth was examined to ensure the tablets had been swallowed. Adherence with study-related procedures was ensured by confinement of the subjects at the study site for at least 12 hours before and approximately 24 hours after the day 1 and day 24 methadone doses.

Subjects were to be confined for 2 periods of approximately 36 hours each between days -1 and 2 (period 1) and days 23 to 25 (period 2) for assessment of pharmacokinetic variables.

All concomitant medications were to be reviewed by the investigator before enrollment. Acetaminophen (paracetamol) was permitted within 14 days of study participation and also permitted before and after administration of peginterferon alfa-2b for the symptomatic treatment of interferon-induced flulike symptoms. Use of medications known to alter CYP450 activity was not permitted during the course of the study without prior approval from the principal investigator or sponsor, and alcohol, caffeine, or xanthine-containing substances were not permitted within 72 hours before drug administration or during inpatient confinement periods. Furthermore, quinine or tonic water, grapefruit, and grapefruit juice were not permitted during the confinement periods. Tobacco use was not allowed during the confinement periods until 4 hours after dose; subjects who were smokers were permitted to use nicotine patches during the confinement periods. If it was considered safe, subjects were to discontinue concomitant medication during the pharmacokinetic assessment days. If it was medically unfeasible to do this, subjects were to take their medications at the same time and at the same dose on each pharmacokinetic sampling day.

The study was carried out in accordance with the Declaration of Helsinki and guidelines on good clinical practice. The institutional review boards and independent ethics committees at each center (Institutional

Review Board Services, Aurora, Ontario; Institutional Review Board, University of Cincinnati Medical Center, Cincinnati, Ohio; and the Ethical Review Committee, Inc, Kansas City, Mo) reviewed and approved the study protocol. Written, informed consent was obtained from each subject before commencing any study-related procedures.

Pharmacokinetic Assessments

The following pharmacokinetic parameters were evaluated using model-independent methods²⁵: maximum concentration (C_{\max}), time to C_{\max} (t_{\max}), and final quantifiable sampling time (t_{last}). The area under the plasma concentration-time curve from time 0 to t_{last} ($AUC_{0-\text{last}}$) and from time 0 to 24 hours after dosing (AUC_{0-24}) was calculated using the linear trapezoidal method. Dose-normalized (to 1 mg) C_{\max} and AUC values were also calculated.

Peginterferon alfa-2b Assay Method

For the purpose of quantifying serum peginterferon alfa-2b concentrations, serial blood samples (5 mL each) were collected on day 23 at 0 hours (immediately before peginterferon alfa-2b administration) and at 12, 24, and 48 hours after peginterferon alfa-2b dosing. Blood samples were collected in additive-free tubes and allowed to clot for 30 minutes before being centrifuged for 15 minutes at approximately 4°C and 1500g. The serum was split into 2 equal aliquots and immediately frozen at or below -20°C until analysis. Serum peginterferon alfa-2b concentrations were determined using a validated electrochemiluminescence assay with a lower limit of quantification (LLOQ) of 50 pg/mL and with a calibration range of 50 to 2000 pg/mL.²⁶ Precision (coefficient of variation [%CV]) and accuracy (mean % difference) results for calibration standards were within 12% (12% at 50 pg/mL), whereas interassay variability was less than or equal to 10%.

Methadone Assay Method

For the purpose of quantifying plasma R-methadone, S-methadone, and total methadone concentrations, serial blood samples (7 mL) were collected on days 1 and 24 at 0 hours (immediately before methadone administration) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours after methadone dosing. Blood samples were collected in heparinized tubes and centrifuged for 15 minutes at approximately 4°C and 1500g. The plasma was split into 2 equal aliquots and immediately frozen at or below -20°C until analysis. Plasma R-methadone, S-methadone, and total methadone

concentrations were determined using a validated chiral liquid chromatography (LC) tandem mass spectrometry (MS) assay at CEDRA Corporation (Austin, Tex). Samples were kept frozen until analyzed. A 250- μ L sample of heparinized human plasma was analyzed for methadone enantiomers.²⁷ Human plasma was diluted with acid and extracted via solid-phase extraction. An aliquot of the dried reconstituted extract was injected onto an LC/MS/MS system equipped with a chiral column. This assay had an LLOQ of 5 ng/mL for both analytes and a calibration range of 5 to 500 ng/mL. Precision (%CV) and accuracy (mean % difference) results for calibration standards for R- and S-methadone were within 15% (20% at the LLOQ; 5 ng/mL). The interday %CV for the assay ranged from 0.86% to 6.2%.

Safety Assessments

Details of all reported adverse events were recorded throughout the study, with severity graded as *mild*, *moderate*, *severe*, or *life threatening* (according to Common Toxicity Criteria), and a relationship to treatment was assigned. Clinical laboratory testing was carried out at the screening visit and at days -1, 9, 16, 23, and 30. Electrocardiography and a physical examination were performed at screening and at the end of the study. Vital signs were measured at screening and on days -1, 1, 2, 9, 16, 23, 24, 25, and 30.

Statistical Methods

C_{\max} , $AUC_{0-\text{last}}$, and AUC_{0-24} for R-methadone, S-methadone, and total methadone were statistically analyzed using an analysis of variance (ANOVA) model. The effects caused by treatment and subject were extracted. Ninety percent confidence intervals (90% CI) for the mean difference between the 2 treatments and the power to detect a 20% difference at a *P* value of .05 were calculated using the pooled residual error and associated degrees of freedom from the ANOVA. C_{\max} , $AUC_{0-\text{last}}$, and AUC_{0-48} for peginterferon alfa-2b were also statistically analyzed using ANOVA. Summary statistics, including means, standard deviations, and %CV, were provided for the derived parameters for methadone and peginterferon alfa-2b.

An interim analysis of pharmacokinetic parameters was planned to assess the variability in R-methadone, S-methadone, and total methadone when 18 subjects had completed study participation without adjustments in methadone dose. If the power

of the study, based on the variability estimate and current sample size, were to become at least 80% or the variability were to become too high to achieve adequate power with a sample size of 36, enrollment was to stop. Otherwise, enrollment was to continue until at least 36 subjects completed study participation without adjustments in methadone dose. Assuming no difference in the pharmacokinetics of methadone between measurements made before and measurements made after peginterferon alfa-2b treatment, sample size was based on the power required for the 90% CI of the mean difference in pharmacokinetic parameters, expressed as a ratio, to fall in the range of 80% to 125%.²⁸

RESULTS

An interim pharmacokinetic analysis was carried out when 20 subjects had been enrolled in the study and was then presented to the US Food and Drug Administration. This led to the determination that the study had sufficient statistical power to close enrollment at 20 subjects. Of those enrolled, 19 subjects completed the study and were included in the pharmacokinetic analysis. One patient withdrew from the study after 3 doses of peginterferon alfa-2b on day 16 because of an occurrence of hot flushes (the event resolved within 2 days). All 20 subjects were included in the safety analysis. Baseline patient demographics are summarized in Table I.

For the subjects who completed the study, no doses of peginterferon alfa-2b or inpatient doses of methadone were missed. Outpatient doses of methadone were administered under supervised conditions, and drug administration records were used to record compliance. The methadone dose remained stable for all subjects during the study.

Influence of Peginterferon alfa-2b on the Pharmacokinetics of Methadone

R-Methadone

The mean pharmacokinetic parameters of R-methadone before injection of peginterferon alfa-2b (period 1) and after 4 weekly injections of peginterferon alfa-2b are summarized in Table II. Paired R-methadone AUC₀₋₂₄ values for each patient are presented in Figure 2. The plasma concentration-time profile for R-methadone followed a similar curve in period 1 and period 2, peaking at approximately 2 to 3 hours after administration and gradually returning to steady-state levels over 24 hours;

Table I Baseline Characteristics of the 20 Subjects Enrolled in the Study

Characteristic	Subjects (N = 20)
Median age, y (range)	46.0 (36-57)
Sex, n (%)	
Male	13 (65)
Female	7 (35)
Race, n (%)	
Caucasian	16 (80)
Black	3 (15)
American Indian	1 (5)
Median bodyweight, kg (range)	90.55 (64.7-133.2)
Median body mass index, kg/m ² (range)	28.57 (23.5-38.2)

Table II Mean (SD) Pharmacokinetic Parameters of R-Methadone Before Injection of Peginterferon alfa-2b (Period 1) and After 4 Weekly Injections of Peginterferon alfa-2b (Period 2)

	Period 1			Period 2		
	n	Mean	SD	n	Mean	SD
AUC _{last} , ng·h/mL	19	53.37	17.7	18 ^a	18.5	31
AUC ₀₋₂₄ , ng·h/mL	19	53.37	17.7	16 ^{a,b}	18.5	30
C _{max} , ng/mL	19	3.13	1.06	18 ^a	0.90	26
t _{max} , h	19	2.18	1.07	18 ^a	1.27	45

Concentration parameters were dose normalized to 1 mg.

a. No data available for 1 subject for period 2.

b. Twenty-four-hour data missing for 2 subjects (1 due to a missing sample and 1 due to assay difficulties).

however, R-methadone concentrations were consistently higher during period 2 (Figure 3).

R-methadone exposure increased by approximately 15% after 4 weekly doses of peginterferon alfa-2b based on log-transformed data. When point estimates (based on the ratios of each log-transformed pharmacokinetic parameter for period 2/period 1) were determined, an increase of approximately 15% was seen for C_{max} (115.5%; 90% CI: 102-130; *P* = .054), AUC₀₋₂₄ (115.0%; 90% CI: 103-128; *P* = .038), and AUC_{last} (114.5%; 90% CI: 104-126; *P* = .028). The upper limit of the 90% CI for each parameter was outside the upper limit of the bioequivalence criteria (125%), and the lower limit did not encompass 100%.

S-Methadone

The mean pharmacokinetic parameters of S-methadone before injection of peginterferon alfa-2b

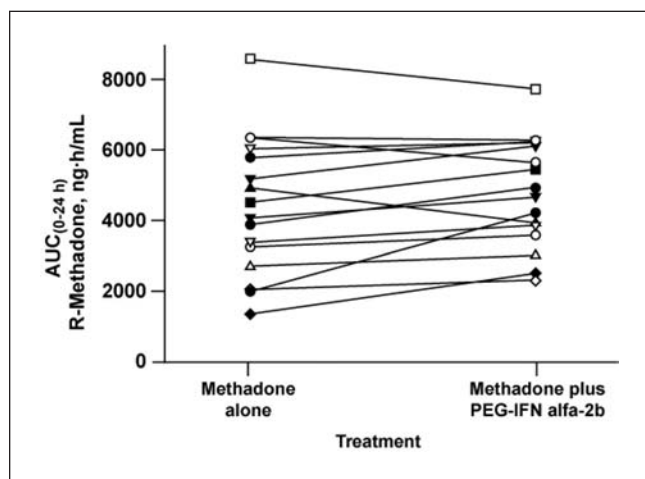


Figure 2. Individual AUC_{0-24} values for R-methadone after administration of methadone alone or in combination with peginterferon alfa-2b (PEG-IFN alfa-2b).

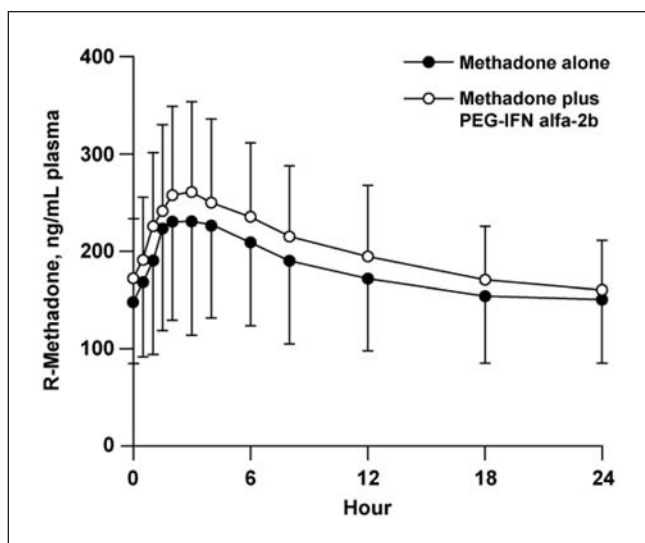


Figure 3. Mean \pm SD serum R-methadone concentration-time profiles after administration of racemic methadone alone or in combination with peginterferon alfa-2b (PEG-IFN alfa-2b).

(period 1) and after 4 weekly injections of peginterferon alfa-2b are summarized in Table III. As with R-methadone, the plasma concentration-time profile for S-methadone followed a similar curve in period 1 and period 2, with S-methadone concentrations consistently higher during period 2 (data not shown).

For S-methadone, an increase in point estimates of approximately 17% to 19% was observed for log-transformed C_{max} (116.6%; 90% CI: 102-134;

Table III Mean (SD) Pharmacokinetic Parameters of S-Methadone Before Injection of Peginterferon alfa-2b (Period 1) and After 4 Weekly Injections of Peginterferon alfa-2b (Period 2)

	Period 1			Period 2		
	n	Mean	SD	n	Mean	SD
AUC_{last} , ng-h/mL	19	53.12	21.4	18 ^a	61.31	23.3
AUC_{0-24} , ng-h/mL	19	53.12	21.4	17 ^{a,b}	62.77	23.2
C_{max} , ng/mL	19	3.67	1.33	18 ^a	4.15	1.25
t_{max} , h	19	1.82	2.0	18 ^a	2.36	1.16

Concentration parameters were dose normalized to 1 mg.

a. No data available for 1 subject for period 2.

b. Twenty-four-hour data missing for 1 subject.

Table IV Mean (SD) Pharmacokinetic Parameters of Total Methadone Before Injection of Peginterferon alfa-2b (Period 1) and After 4 Weekly Injections of Peginterferon alfa-2b (Period 2)

	Period 1			Period 2		
	n	Mean	SD	n	Mean	SD
AUC_{last} , ng-h/mL	19	106.05	37.6	18 ^a	119.89	40.8
AUC_{0-24} , ng-h/mL	19	106.05	37.6	16 ^{a,b}	123.29	40.8
C_{max} , ng/mL	19	6.71	2.3	18 ^a	7.55	2.09
t_{max} , h	19	2.00	2.0	18 ^a	2.39	1.12

Concentration parameters were dose normalized to 1 mg.

a. No data available for 1 subject for period 2.

b. Twenty-four-hour data missing for 2 subjects (1 due to a missing sample and 1 due to assay difficulties).

$P = .066$), AUC_{0-24} (119.1%; 90% CI: 104-136; $P = .039$), and AUC_{last} (117.2%; 90% CI: 103-134; $P = .05$) following administration of peginterferon alfa-2b. The upper limit of the 90% CI for each parameter was outside the upper limit of the bioequivalence criteria (125%), and the lower limit did not encompass 100%.

Total Methadone

The mean pharmacokinetic parameters of total methadone before injection of peginterferon alfa-2b (period 1) and after 4 weekly injections of peginterferon alfa-2b are summarized in Table IV. Increases in total methadone exposure of 15% to 16% were observed after 4 weekly injections of peginterferon alfa-2b: log-transformed C_{max} (116.3%; 90% CI: 102-132; $P = .059$), AUC_{0-24} (115.1%; 90%

Table V Mean (SD) Pharmacokinetic Parameters of Peginterferon alfa-2b on Day 23 (Period 2)

	n	Mean	SD
AUC _{last} , ng·h/mL	18 ^a	47.55	30
AUC ₀₋₄₈ , ng·h/mL	17 ^a	47.65	30.1
C _{max} , ng/mL	18 ^a	1.49	1.17
t _{max} , h	18 ^a	20.67	14.1

a. No data available for 1 subject for period 2.

CI: 103-129; $P = .044$), and AUC_{last} (115.5%; 90% CI: 104-128; $P = .03$).

Pharmacokinetics of Peginterferon alfa-2b (Day 23)

The mean pharmacokinetic parameters of peginterferon alfa-2b are summarized in Table V. Other studies have reported similar values of mean pharmacokinetic parameters of peginterferon alfa-2b.²⁹

Safety

All 20 subjects reported at least 1 adverse event during the study. Headache, nausea, fever, fatigue, and increased sweating were the most frequently reported adverse events (consistent with adverse events previously reported with peginterferon therapy²⁹), most of which were rated as mild or moderate. The most common treatment-related adverse events were headache and nausea, each occurring in half the subjects (Table VI). No deaths or serious adverse events were reported. Ten severe adverse events were reported in 7 subjects: hot flushes (1), headache (4), nausea (1), toothache (1), hypertriglyceridemia (1), musculoskeletal pain (1), and increased sweating (1).

No clinically significant changes in electrocardiogram or vital signs were seen. Although high or low values for hematology and blood chemistry were reported in a number of subjects, laboratory values in only 2 individuals were sufficiently clinically significant to be classified as adverse events (elevated triglycerides). Decreases in the number of white blood cells (especially neutrophils) and platelets, which are typically seen in subjects receiving interferon therapy,³⁰ were observed in several subjects during the study. Typical of patients with HCV infection, several subjects had elevated hepatic enzymes. Other abnormalities in laboratory variables were sporadic. No subject required a reduction in the dose of peginterferon alfa-2b as a result of laboratory abnormalities.

Table VI Treatment-Related Adverse Events

Adverse Event	Subjects, n (%)
Headache	10 (50)
Nausea	10 (50)
Fatigue	6 (30)
Fever	6 (30)
Sweating increased	5 (25)
Injection site inflammation	4 (20)
Musculoskeletal pain	4 (20)
Asthenia	3 (15)
Rigors	3 (15)
Weakness	3 (15)
Vomiting	3 (15)
Anorexia	2 (10)
Confusion	2 (10)
Feeling cold	2 (10)
Hot flushes	2 (10)
Hypertriglyceridemia	2 (10)
Injection site reaction	2 (10)
Rash	2 (10)
Somnolence	2 (10)
Abdominal pain	1 (5)
Anxiety	1 (5)
Depression	1 (5)
Feeling hot and cold	1 (5)
Herpes simplex	1 (5)
Hypoesthesia	1 (5)
Injection site bruising	1 (5)
Insomnia	1 (5)
Irritability	1 (5)
Retching	1 (5)
Rhinorrhea	1 (5)
Therapeutic response decrease	1 (5)
Tremor	1 (5)
Withdrawal syndrome	1 (5)
Vision blurred	1 (5)

DISCUSSION

Screening of donated blood products has resulted in negligible transmission of HCV via transfusion. Elimination of transmission of HCV by this route has switched focus to other means of infection—in particular, HCV transmitted between IDUs. Indeed, treatment of chronic hepatitis C in IDUs is becoming recognized as an important public health goal.⁵

Several small studies have shown that interferon alfa therapy is effective in IDUs with chronic hepatitis C.³¹⁻³⁴ Approximately 40% to 60% of patients enrolled in the key peginterferon alfa-2a and 2b trials contracted HCV infection via injection drug use¹⁰⁻¹⁴; however, their status with respect to drug dependency has not been reported, and the effects of

interferon alfa therapy in this subset of patients have not been separately analyzed.

This is the first study to evaluate the effects of multiple doses of a pegylated interferon on the steady-state pharmacokinetics of the active R-methadone enantiomer. An interim pharmacokinetics analysis showed that the power of the study was sufficiently high to close enrollment at 20 patients. This study showed that SC administration of peginterferon alfa-2b in subjects with chronic hepatitis C involved in a methadone maintenance program is associated with a 15% and 19% increase in exposure to R-methadone and S-methadone, respectively, and a 15% to 16% increase in total methadone, with the upper limit of the 90% CI for the pharmacokinetic parameters outside the upper limit of the bioequivalence criteria (125%).

The absence of symptoms and signs of methadone overdose indicates that the increase in methadone exposure observed after pegylated interferon alfa-2b therapy (15%) was not clinically significant. This lack of effect is probably the result of the wide range in interpatient variability in methadone elimination and clearance,²⁴ varying degrees of tolerance,³⁵ and the poor correlation between methadone concentration and clinical efficacy.³⁶ However, given the potential range of interpatient variability, patients stabilized via methadone should be monitored for an increase in narcotic effect when receiving peginterferon alfa-2b therapy.

Increased exposure to R-methadone and S-methadone in the presence of peginterferon alfa-2b may be the result of an inhibitory effect of peginterferon alfa-2b on CYP450 enzymes, thereby reducing the metabolism and elimination of methadone. However, it should also be noted that, because of the design of the study (fixed-sequence crossover), the effect of peginterferon alfa-2b on methadone pharmacokinetics was confounded by a period effect. Therefore, it is possible that some of the observed increase in pharmacokinetic parameters may be attributed to adherence to methadone, which was a requirement for study inclusion.

Although the design of this trial did not permit direct evaluation of the effects of methadone on the pharmacokinetics of peginterferon alfa-2b, comparison with previous reports of pharmacokinetic data indicates that any clinically significant changes are unlikely (data on file).

Peginterferon alfa-2b was well tolerated in individuals receiving concomitant methadone, with adverse events consistent with those reported in previous clinical trials with peginterferon alfa.¹⁰⁻¹⁴

In conclusion, this study found that, although SC administration of peginterferon alfa-2b in patients with chronic hepatitis C participating in a methadone maintenance program increases systemic exposure to methadone, this increase is not clinically meaningful. Therefore, involvement in a methadone maintenance program need not preclude an individual from treatment with peginterferon alfa-2b. Further work should evaluate whether ribavirin, a common adjunct to interferon treatment for chronic hepatitis C, has any influence on the pharmacokinetics of methadone. Potential interactions between buprenorphine, another common opioid maintenance therapy, and treatments for hepatitis C should also be evaluated.

This study was sponsored by Schering-Plough Corporation. The authors acknowledge Lynn Brown, PhD, and Maribeth Bogush, PhD, of ApotheCom Associates LLC for editorial assistance in the preparation of this manuscript.

Financial disclosure: Drs Gupta, Cutler, and Kolz are employees of Schering-Plough Research Institute.

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