Multiple-dose pharmacokinetics of peginterferon alfa-2b in patients with renal insufficiency

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What is already known about this subject?

- Current therapy for hepatitis C typically consists of pegylated interferon (PEG-IFN) alfa in combination with ribavirin.
- Pegylation of IFN alfa-2b confers a 10-fold increase in elimination half-life and a 30% reduction in volume of distribution compared with non-PEG-IFN alfa-2b.
- A single-dose pharmacokinetic study conducted in patients with chronic renal dysfunction has shown that renal elimination accounts for 30% of total PEG-IFN alfa-2b clearance and that PEG-IFN alfa-2b exposure increases with severity of renal insufficiency.

What this study adds

- Because the primary mechanism of IFN clearance is catabolism in the kidney, appropriate dosing of IFN-based therapies in patients with renal insufficiency is an important issue.
- This multiple-dose pharmacokinetic study shows that exposure to PEG-IFN alfa-2b is increased in patients with renal insufficiency, suggesting that doses of the drug should be reduced by 50% in patients with severe renal insufficiency and by 25% in those with moderate insufficiency.
- PEG-IFN alfa-2b was well tolerated in all patient groups during the 4-week treatment period, with similar adverse events occurring in patients with renal insufficiency and in those with normal renal function.

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Aim

To evaluate the safety, tolerability and multiple-dose pharmacokinetics of pegylated interferon (PEG-IFN) alfa-2b in patients with moderate or severe renal insufficiency and in those with normal renal function.

Methods

In an open-label study, subjects with normal renal function (creatinine clearance >80 ml min⁻¹ per 1.73 m²) and patients with moderate (30–50 ml min⁻¹ per 1.73 m²) or severe (10–29 ml min⁻¹ per 1.73 m²) renal impairment received weekly injections of PEG-IFN alfa-2b (1.0 µg kg⁻¹) for 4 weeks. Safety assessments were made before each injection and blood samples were taken up to 168 h after the final dose.

Results

Renal insufficiency increased PEG-IFN alfa-2b exposure. Area under the curve for 0–τ (dosing interval of 168 h), AUC_τ, was increased 30% and 120% in patients with moderate or severe renal insufficiency, respectively. Mean maximum serum concentration was almost doubled in patients with severe insufficiency [1305.8 pg ml⁻¹; 95% confidence interval (CI) 825, 1786] compared with subjects with normal renal function (731.4 pg ml⁻¹; 95% CI 407, 1056), whereas the apparent volume of distribution was reduced (0.80 l kg⁻¹ vs. 1.28 l kg⁻¹, respectively). Elimination half-life was extended in patients with moderate and severe renal insufficiency (65.6 h and 64.9 h, respectively) compared with subjects with normal renal function (51.5 h). Significant differences were observed in the AUC and C_{max} values of patients with severe renal dysfunction, compared with those who had normal renal function (*P* < 0.05; Kruskal–Wallis test). PEG-IFN alfa-2b was well tolerated and adverse events were similar in both treatment groups.

Conclusions

Exposure to PEG-IFN alfa-2b is increased in patients with renal insufficiency, suggesting that doses of the drug should be reduced by 50% in patients with severe renal insufficiency and by 25% in those with moderate insufficiency.

Introduction

Hepatitis C virus (HCV) infection is a common and important cause of liver disease. Today, infection with HCV occurs primarily through sharing of needles. In the past, HCV infection was also frequently contracted during hospital or clinic visits as a consequence of contaminated dialysis membranes or through receipt of blood products [1]. Current therapy for hepatitis C typically consists of pegylated interferon (PEG-IFN) alfa in combination with ribavirin. Because the primary mechanism of IFN clearance is catabolism in the kidney [2], appropriate dosing of IFN-based therapies in patients with end-stage renal disease is an important issue.

Previous pharmacokinetic studies with PEG-IFN have not clarified whether dose adjustments are required in patients with renal insufficiency. In its pegylated form, the IFN molecule is attached to a polyethylene glycol moiety, which confers a 10-fold increase in the elimination half-life of IFN alfa-2b and a 30% reduction in its volume of distribution [3]. Additionally, clearance of PEG-IFN alfa-2b is approximately 10 times slower than that of the unmodified drug ($22 \text{ ml h}^{-1} \text{ kg}^{-1}$ vs. $231 \text{ ml h}^{-1} \text{ kg}^{-1}$, respectively) [3]. A single-dose pharmacokinetic study in patients with renal dysfunction has suggested that renal clearance of PEG-IFN alfa-2b (PegIntron®; Schering-Plough Corp., Kenilworth, NJ, USA) accounts for only 30% of the total clearance of the drug [4], possibly indicating that other, more dominant routes of elimination exist. The relatively low proportion of the drug cleared through the kidney may be attributed to the large size of the PEG-IFN molecule. However, in the same study, exposure to PEG-IFN alfa-2b increased with the severity of renal insufficiency, conversely suggesting that the kidney is an important route for the elimination of this drug [4]. Because this study evaluated only the single-dose pharmacokinetic characteristics of PEG-IFN alfa-2b, the multiple-dose properties remain uncharacterized.

It is unclear whether PEG-IFN alfa-2b dose reductions are needed in patients with renal impairment. We therefore evaluated the safety, tolerability and pharmacokinetics of multiple doses of PEG-IFN alfa-2b in patients with moderate and severe renal insufficiency.

Methods

This open-label trial of the safety, tolerability and multiple-dose pharmacokinetics of PEG-IFN alfa-2b in patients with moderate or severe renal insufficiency, compared with patients with normal renal function, was conducted in accordance with Good Clinical Practice, and the investigators agreed to comply with the guidelines set forth by the World Medical Association Decla-

ration of Helsinki concerning written informed consent and the rights of human subjects. Written informed consent was obtained from all participants. Before study initiation, the study protocol, the written informed consent form and all applicable amendments were reviewed and approved at each site by an institutional review board.

Study participants included adults aged 18–75 years with moderate and severe chronic renal insufficiency and included age- and weight-matched volunteers with normal renal function. Body weights of participants were required to be between 50 kg and 115 kg and clinical laboratory test findings (other than those expected to be outside the normal range for subjects with moderate and severe renal insufficiency) had to be within normal limits or be clinically acceptable to the investigator, including white blood cell count $\geq 4000 \text{ cells mm}^{-3}$, neutrophil count $\geq 2000 \text{ cells mm}^{-3}$, platelet count $\geq 100\,000 \text{ cells mm}^{-3}$ and thyroid-stimulating hormone (TSH) within normal limits (patients requiring medication to maintain TSH levels in the normal range were eligible if all other inclusion and exclusion criteria were met). In addition, participants were required to have antinuclear antibody counts $\leq 1:160$ and to have negative screens for drugs with a high potential for abuse. Physical examination and 12-lead electrocardiography were to be within normal limits or be clinically acceptable to the investigator. Women of childbearing potential were required to have negative results of pregnancy testing and to be practising adequate contraception. Women who were nursing were also excluded from the study. Major exclusion criteria included previous organ transplantation; any known pre-existing medical condition that could have interfered with participation in and completion of the study; clinically significant retinal abnormalities; donation of blood within the preceding 60 days; history of clinically significant local or systemic infectious disease within 4 weeks before initial treatment administration; and positive test findings for HIV antibody or hepatitis B surface antigen.

After determination of eligibility and creatinine clearance, participants were stratified into three groups based on renal function. Group 1 consisted of the subjects with normal renal function (creatinine clearance $>80 \text{ ml min}^{-1}$ per 1.73 m^2). Group 2 included patients with moderate renal insufficiency (creatinine clearance $30\text{--}50 \text{ ml min}^{-1}$ per 1.73 m^2). Group 3 consisted of patients with severe insufficiency (creatinine clearance $10\text{--}29 \text{ ml min}^{-1}$ per 1.73 m^2). Patients in group 1 were not to take other medication, with the exception of paracetamol, within 14 days of treatment or during the study. After screening, PEG-IFN alfa-2b ($1 \mu\text{g kg}^{-1}$

subcutaneous injection) was given once weekly in the morning for 4 weeks (days 1, 8, 15, 22). Doses on days 1, 8 and 15 were based on the patient's day 1 weight, whereas the day 22 injection was based on the patient's weight on that day. Participants were confined for approximately 12 h before the final injection and for 48 h afterwards. The dose of PEG-IFN alfa-2b used in the study is within the range that has shown antiviral efficacy in patients with compensated chronic hepatitis C and HIV-1 (Schering-Plough Research Institute; data on file).

Blood samples (5 ml) for pharmacokinetic analysis were drawn immediately before PEG-IFN alfa-2b injection (0 h) on all dosing days and at 2, 6, 10, 12, 24, 36, 48, 72, 96, 120, 144 and 168 h after the final dose (day 22). Blood samples were collected in additive-free tubes, were allowed to clot at room temperature for 30 min and were centrifuged for 15 min at 4°C and 1500 g. Serum was frozen until analysed. PEG-IFN alfa-2b concentrations were determined as previously described with the use of a validated electrochemiluminescence assay with a lower limit of quantification of 50 pg ml⁻¹, a range of 50–2000 pg ml⁻¹, a variability of 12% at 50 pg ml⁻¹ and <3% at 2000 pg ml⁻¹ [5]. The observed pharmacokinetic parameters were trough concentration ($C_{\min}$), maximum concentration ($C_{\max}$), time to maximum concentration ($T_{\max}$) and the final quantifiable sampling time (last). Calculated parameters included the terminal-phase rate constant (K), calculated as the negative of the slope of the log-linear terminal portion of the serum concentration–time curve using linear regression, and the terminal-phase half-life ($t_{1/2}$), calculated as $0.693/K$. The area under the serum concentration–time curve from time 0 to dosing interval (0–168 h), AUC_{τ} , was calculated with the use of the linear trapezoidal method, and apparent clearance at steady state (CL_{ss}/F) was calculated from the ratio of dose to AUC_{τ} . It was assumed that steady state was achieved on day 22. The apparent volume of distribution at steady state (Vd_{ss}/F) was calculated as the ratio of CL_{ss}/F to K .

Tolerability was assessed during the study by recording adverse events. Laboratory safety tests, physical examination and measurement of vital signs were carried out at screening and before each PEG-IFN alfa-2b injection.

To evaluate the influence of renal dysfunction on the pharmacokinetics of PEG-IFN alfa-2b, $C_{\max}$ and AUC_{τ} values from patients with moderate and severe renal dysfunction were compared with those patients who had normal renal function using the Kruskal–Wallis test. SAS software version 8.0 (SAS Institute, Cary, NC, USA) was used for statistical analysis. $C_{\max}$ and AUC_{τ}

were analysed using an analysis of variance (ANOVA) model, extracting the effects caused by group. Pooled residual error and associated degrees of freedom from the ANOVA 90% confidence intervals (CIs) for the mean difference between the two treatments and the power to detect a 50% difference at $P = 0.05$ were calculated. The 90% CIs were calculated based on log-transformed data. Summary statistics, including mean, SD and 95% CIs, were calculated for the derived parameters.

Results

Baseline characteristics for the 21 study participants are shown in Table 1. Of these, 17 completed the study (Figure 1). Two participants (one subject with normal renal function and one patient in the moderate insufficiency group) withdrew for reasons unrelated to treatment, and two (one patient each in the moderate and severe insufficiency groups) withdrew because of adverse events. One patient in the moderate insufficiency group withdrew because of mild neutropenia, although the patient's neutrophil count (1.8×10^9 cells l⁻¹) did not reach the protocol-specified threshold

Table 1
Baseline characteristics

	Normal renal function <i>n</i> = 6	Moderate renal insufficiency <i>n</i> = 8	Severe renal insufficiency <i>n</i> = 7
Age (years)			
Mean ± SD	54.8 ± 13.3	59.1 ± 14.0	65.1 ± 9.0
Median	50.5	63.5	65.0
Sex, <i>n</i> (%)			
Female	2 (33)	4 (50)	2 (29)
Male	4 (67)	4 (50)	5 (71)
Race, <i>n</i> (%)			
Black	1 (17)	4 (50)	2 (29)
White	5 (83)	4 (50)	2 (29)
Hispanic	0	0	3 (43)
Weight (kg)			
Mean ± SD	83.7 ± 14.6	93.7 ± 21.0	95.9 ± 21.4
Median	85.7	97.1	103.0
Height (cm)			
Mean ± SD	168.4 ± 6.3	172.1 ± 7.3	170.2 ± 11.8
Median	168.5	172.9	170.5

Subjects with normal renal function had creatinine clearance >80 ml min⁻¹ per 1.73 m². Moderate renal insufficiency and severe renal insufficiency were defined as creatinine clearance 30–50 ml min⁻¹ per 1.73 m² and 10–29 ml min⁻¹ per 1.73 m², respectively.

Figure 1
Patient flow

for withdrawal (0.75×10^9 cells l^{-1}) and one patient in the severe insufficiency group withdrew as a result of headache, myalgia and nausea.

Mean pharmacokinetic parameters with 95% CIs for PEG-IFN alfa-2b are shown in Table 2. After subcutaneous injection, PEG-IFN alfa-2b was slowly absorbed, with T_{max} occurring 28–40 h after the fourth dose. Serum concentrations of PEG-IFN alfa-2b were above the lower limit of quantification in all participants at the 168-h time point, and variability in AUC_t was low to moderate.

Patients with severe renal dysfunction had significantly higher C_{max} and AUC values than patients with normal renal function ($P < 0.05$ for both comparisons; Kruskal–Wallis test) (Table 2). Renal insufficiency resulted in increased PEG-IFN alfa-2b exposure (Figure 2). Compared with subjects with normal renal function, patients with moderate renal insufficiency experienced a 30% increase in AUC_t , whereas patients with severe renal insufficiency experienced a 120% increase in AUC_t . In addition, mean C_{max} in patients with severe renal insufficiency was almost double that in subjects with normal renal function, although C_{max} in patients with moderate insufficiency was similar to that in subjects with normal renal function (Figure 2). V_{dss}/F was lower only in patients with severe renal insufficiency, compared with subjects with normal renal function and those with moderate insufficiency, whereas $t_{1/2}$ was extended in both renal insufficiency groups, compared with subjects with normal renal function. Results of the ANOVA based on log-transformed C_{max} and AUC_t are shown in Table 3. Exposure to PEG-IFN alfa-2b was approximately doubled in patients with severe renal dys-

Figure 2
Mean serum concentrations of peginterferon alfa-2b on day 22. (●) Group I = Normal renal function ($n = 5$); (○) Group II = Moderate renal insufficiency ($n = 6$); (▽) Group III = Severe renal insufficiency ($n = 6$)

function and increased by approximately 30% in those with moderate insufficiency.

Overall, 16 (76%) participants reported at least one adverse event during the study. Of these, six (100%) were subjects with normal renal function, six (75%) were in the moderate insufficiency group and four (57%) were in the severe insufficiency group. The most commonly reported adverse events during the study were musculoskeletal pain, fever, inflammation of the injection site, headache, rigors and nausea, and most events were rated as mild or moderate according to the Common Toxicity Criteria.

Severe adverse events (headache, hypertriglyceridaemia and musculoskeletal pain) were reported in three subjects with normal renal function and in one patient (hyperuricaemia) in the severe insufficiency group. No serious adverse events were reported during the study. Decreases in platelet and leucocyte levels were observed in all groups and were consistent with the known effects of IFN therapy. In general, patients with renal insufficiency experienced greater decreases in leucocyte count than subjects with normal renal function. As would be expected of patients with renal insufficiency and diabetes, several participants had low values for haemoglobin and haematocrit and high values for blood urea nitrogen, creatinine, uric acid, blood glucose and potassium. There were no consistent trends in the safety data to indicate that the severity or frequency of adverse events increased with worsening renal dysfunction.

Table 2

Mean (95% CI) pharmacokinetic parameters for peginterferon alfa-2b

	Normal renal function <i>n</i> = 5	Mean (95% CI) Moderate renal insufficiency <i>n</i> = 6	Severe renal insufficiency <i>n</i> = 6
C_{max} (pg ml ⁻¹)	731.4 (407, 1056)	751.5 (577, 926)	1305.8* (825, 1786)
T_{max} (h)	28.4 (5.21, 51.6)	40.0 (27.0, 53.0)	28.0 (9.04, 47.0)
AUC_{τ} (pg h ⁻¹ ml ⁻¹)	60 360 (42 845, 77 874)	77 368 (64 013, 90 724)	131 980* (69 336, 194 625)
$t_{1/2}$ (h)	51.5 (31.6, 71.4)	65.6 (47.7, 83.4)	64.9 (40.0, 89.3)
CL_{ss}/F (ml min ⁻¹)	25.3 (17.7, 32.8)	20.8 (15.4, 26.3)	14.1 (8.72, 19.4)
Vd_{ss}/F (l kg ⁻¹)	1.28 (0.73, 1.83)	1.27 (0.81, 1.72)	0.80 (0.30, 1.31)
Creatinine clearance (ml min ⁻¹)	129.7 (65.7, 194)	38.6 (31.0, 46.2)	18.9 (15.0, 22.8)
C_{min} (pg ml ⁻¹)			
Day 22	93.8 (10.3, 177)	189.3 (139, 239)	389.0 (134, 645)
Day 15	76.2 (7.2, 145)	165.5 (140, 191)	331.2 (105, 558)
Day 8	34.6 (-27.2, 96.4)	142.2 (100, 184)	279.6 (36.9, 522)
Day 1	146† (-259, 551)	0 (-)	0 (-)

* $P < 0.05$, Kruskal–Wallis test. †Only one patient had a measurable C_{min} value on day 1. Subjects with normal renal function had creatinine clearance >80 ml min⁻¹ per 1.73 m². Moderate renal insufficiency and severe renal insufficiency were defined as creatinine clearance 30–50 ml min⁻¹ per 1.73 m² and 10–29 ml min⁻¹ per 1.73 m², respectively.

Table 3

Estimates with 90% (and 95%) CIs of the pharmacokinetic parameters for peginterferon alfa-2b in patients with moderate or severe renal insufficiency, compared with subjects with normal renal function, based on log-transformed data from day 22

Parameter	Moderate renal insufficiency*		Severe renal insufficiency†	
	Ratio estimate (%)	90% CI	Point estimate	90% CI
AUC_{τ} (pg h ⁻¹ ml ⁻¹)	129.7	95, 176	208.3	153, 283
C_{max} (pg ml ⁻¹)	106.4	75, 151	178.7	126, 254

Moderate renal insufficiency and severe renal insufficiency were defined as creatinine clearance 30–50 ml min⁻¹ per 1.73 m² and 10–29 ml min⁻¹ per 1.73 m², respectively. Non-log-transformed mean ratio percentage (95% CI; lower–upper).

* $C_{max} = 114\%$ (68, 160); $AUC_{\tau} = 135$ (84, 186). † $C_{max} = 197\%$ (117, 280); $AUC_{\tau} = 236$ (131, 342).

One patient with severe renal insufficiency secondary to diabetes and hypertension experienced a decrease in serum creatinine clearance that was considered medically significant. After treatment, creatinine clearance improved but did not return to baseline values. Otherwise, changes in laboratory values were not generally considered clinically significant, and evaluations of vital signs and physical examinations showed no consistent changes in clinical relevance. Overall, any adverse events possibly or probably related to PEG-IFN alfa-2b

resolved without treatment, and no study participant developed anti-IFN antibodies after receiving PEG-IFN alfa-2b.

Discussion

This study confirms that the pharmacokinetics of subcutaneously administered PEG-IFN alfa-2b are influenced by renal function, as previously shown in a single-dose pharmacokinetic study [4]. Overall, exposure to PEG-IFN alfa-2b in the present study was doubled in patients

with severely impaired renal function and increased by approximately 30% in those with a moderate level of renal impairment. These results are consistent with the recent single-dose study, in which exposure to PEG-IFN alfa-2b after a single injection was increased by 77% and 107% in patients with moderate and severe renal insufficiency, respectively [4]. Findings of these studies also confirm a role for the kidneys in the elimination of IFN, as previously shown in animals [2], although the kidneys are probably less involved in the clearance of PEG-IFN alfa-2b than in the clearance of non-PEG-IFN molecules [4].

A multiple-dose pharmacokinetic study in patients with hepatitis C and normal renal function has shown that PEG-IFN alfa-2b $C_{\max}$ and AUC values increase in a dose-related manner over the dose range of 0.035–1.4 $\mu\text{g kg}^{-1}$ [5]. This observation, combined with the mean exposure data from the present study, indicates that patients with renal insufficiency would benefit from a reduction in the standard dose of PEG-IFN alfa-2b. Thus, patients with moderate renal insufficiency (creatinine clearance 30–50 ml min^{-1} per 1.73 m^2) should receive a 25% reduction in PEG-IFN alfa-2b dose and those with severe insufficiency (creatinine clearance 10–29 ml min^{-1} per 1.73 m^2) should receive a dose reduction of 50%. Reduction in dose or dosing regimen of various therapeutic and prophylactic agents, including antibiotics, anticoagulants, myeloma therapies and oral contraceptives, is not uncommon in patients with renal insufficiency [6–9]. Studies of hepatitis C therapies have shown that dose reductions of ribavirin, which has been used in combination with PEG-IFN alfa-2a and alfa-2b, may be beneficial in this patient population, particularly with regard to the incidence of dose-dependent haemolysis [10, 11]. The pharmacokinetics of PEG-IFN alfa-2a, however, are not thought to be affected by renal insufficiency [12].

In the present study, as in previous trials in several patient populations [4, 13–16], PEG-IFN alfa-2b was associated with influenza-like symptoms, such as nausea, fatigue and headache. Decreases in leucocyte and platelet counts were observed in all groups, with numerically greater decreases in leucocyte counts in patients with renal insufficiency than in subjects with normal renal function. Based on the available data from the study, it is unclear whether this decrease was secondary to increased PEG-IFN alfa-2b exposure or was related to the higher baseline leucocyte counts observed in these patients with renal insufficiency.

In previous studies, observations of renal insufficiency or renal failure during IFN therapy were rare [17]; in the present study, decreased creatinine clearance

was reported in one patient with end-stage renal disease. Moreover, patients with renal dysfunction may also have concomitant disorders such as diabetes and dyslipidaemia, which can be exacerbated by IFN treatment [18]. Therefore, the risk : benefit ratio of hepatitis C treatment should be considered before PEG-IFN alfa-2b therapy is initiated in patients with renal insufficiency. Monitoring of renal function during treatment is also recommended in this patient population.

This study indicates that exposure to PEG-IFN alfa-2b is increased in patients with renal insufficiency. These observations, combined with data from previous pharmacokinetic studies [3–5], suggest that doses of PEG-IFN alfa-2b should be reduced by 50% in patients with severe insufficiency and by 25% in those with moderate insufficiency. Consistent with previous studies, PEG-IFN alfa-2b was well tolerated in all patient groups, with similar adverse events occurring in patients with renal insufficiency and in subjects with normal renal function. Careful patient selection and monitoring of renal function are recommended in patients with renal insufficiency receiving PEG-IFN alfa-2b therapy.

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