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ORIGINAL ARTICLE

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Pharmacokinetics of imatinib mesylate in end stage renal disease. A case study

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Abstract *Aim*: To evaluate the pharmacokinetics of imatinib mesylate (Glivec) and its main metabolite (CGP74588) in a patient with end stage renal disease on hemodialysis and compare it with published data from subjects with normal renal function. *Patients and Methods*: Serial blood samples were collected over a 2-weeks period in a patient who was receiving daily 400 mg oral imatinib mesylate for the treatment of a gastrointestinal stromal tumor metastatic to the liver while on hemodialysis. Plasma levels of imatinib and CGP74588 were determined by a liquid chromatography-tandem mass spectrometry assay. *Results*: The pharmacokinetic values for imatinib and CGP74588, respectively, were: maximum concentration (3,340 and 781 ng/ml), time to maximum concentration (2 h), half-life (18.2 and 34.0 h), area under the curve (53.9 and 14.8 μg.h/ml), and trough concentration (1,540 and 508 ng/ml) for at least 24 h. All obtained values fell within the range of values of imatinib and its metabolite obtained in patients with normal renal function. Dialysis courses were not found to intervene with plasma kinetics of the study drug. *Conclusions*: Our results indicate that the pharmacokinetics of imatinib and its metabolite CGP74588 do not change in patients with end stage renal disease on hemodialysis. Thus, the standard dose of imatinib can be safely administered to patients on hemodialysis, and probably with renal failure, at any stage.

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Introduction

Imatinib mesylate (GLIVEC, STI571) is a breakthrough targeted therapeutic with a well-established activity in CML, GIST and chronic myeloproliferative disorders and three well-characterized molecular targets: BCR–ABL, c-KIT and PDGFR. Impressive early clinical results have fast propelled this agent into regulatory approval and clinical practice. Today, imatinib represents a prototype targeted therapeutic that is characterized by target specificity and an optimal therapeutic index. Due to the major clinical importance of this drug, any information that can be obtained regarding its pharmacokinetics, dosage and safety in different clinical settings is warranted [1, 2].

Imatinib is predominantly metabolized in the liver and is eliminated through the billiary route. However, no data exist in patients with an impaired renal function to guide the dosage in such cases [3–5].

The present PK study case was conducted to safeguard a safe and active dose of imatinib in a patient with end stage renal impairment. The secondary endpoint of this study was to investigate if hemodialysis affected pharmacokinetic of imatinib or/and its major (and active) metabolite.

Methods

Patient history and treatment

The patient in this study was a 44-year-old female, who 7 years ago underwent abdominoperineal resection for a malignant gastrointestinal stromal tumor of the rectum. Two years later, the patient was diagnosed with an evolving failure of her renal function. Renal biopsy at

that time failed to designate the exact cause of the renal disease. The patient eventually reached end stage renal disease and 3 years later started on hemodialysis.

One year later, while on hemodialysis, she was diagnosed with liver metastases. A liver biopsy proved that liver lesions were metastases of the resected rectal GIST that expressed CD 117 surface antigen (c-kit).

Staging CT scan of the thorax and abdomen did not reveal any other metastases. The patient started treatment with oral imatinib 400 mg daily. However, due to lack of data capable of supporting an efficient and safe dosage of drug in this situation, a blood sampling at two consecutive weeks was arranged following a written informed consent obtained from the patient. One year later, the patient remains in good shape on hemodialysis and is receiving 400 mg oral imatinib on a daily basis. Her liver metastases remain in partial remission.

Sampling

Heparinised blood (5-ml samples) was collected from the patient at the following time points: 0 h, +0.25 h, +1 h, +2 h, +19 h (pre-dialysis), +23 h (0 h post-hemodialysis) and 24 h (1 h post-dialysis). The same blood sampling procedure was repeated 1 week later (day 8).

Drug determination analysis

Plasma concentrations for imatinib and its main metabolite (CGP74588) were determined by a previously reported liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay [6].

Pharmacokinetics

All the steady-state pharmacokinetic parameters were evaluated by non-compartmental analysis (WinNonlin standard version 2.1, Pharsight Corp., Palo Alto, CA, USA). The following parameters were calculated from the plasma concentration–time profiles of both imatinib and its metabolite: sampling time of maximum observed plasma concentration (t_{max}), plasma concentration corresponding to t_{max} (C_{max}), terminal elimination phase constant (λ_z), terminal half-life ($t_{1/2}$ or $t_{1/2\_Lambda\_z}$), area under the concentration–time curve from the time of dosing to the time of the last observation (AUC_{all}), area under the concentration–time curve from the time of dosing extrapolated to infinity (AUC_{inf}), volume of distribution based on the terminal phase (V_z/F), and total body clearance (Cl/F). In addition, the trough concentration (plasma concentration at the end of dose interval) as well as the total time above 1.0 μM were calculated based on the concentration–time curve of imatinib and/or CGP74588 (Table 1).

Table 1 Pharmacokinetics of imatinib (STI571) and its major metabolite (CGP74588), at steady-state

	Imatinib	CGP74588
t_{max}(h)	2	2
C_{max}(ng/ml)	3,340	781
Lamda_z (/h)	0.038	0.020
$t_{1/2\_Lamda\_z}$(h)	18.2	34.0
AUC_{all} (μg h/ml)	53.9	14.8
AUC_{inf} (observed) (μg h/ml)	94.4	39.7
V_z/F (observed) (l)	111.4	494.2
Cl/F (observed) (L/h)	4.2	10.1
Trough Concentration (ng/ml)	1,540	508
Time above 1 μM (h)	>24	>24

Results

Hematologic and non-hematologic toxicity

The patient has to date received a 1-year non-stop treatment with 400 mg/day imatinib uneventfully and without any clinically relevant toxicity.

Pharmacokinetic results

The pharmacokinetic parameters of imatinib and CGP74588 determined by non-compartmental analysis are listed in Table 1. Pharmacokinetic data in this study compared with steady-state pharmacokinetic values assessed in a number of patients with normal renal function [4, 7]. Figure 1 illustrates the determined plasma levels of both imatinib and CGP74588 assessed twice with a week's interval (day1 and day8).

After multiple-dose oral administration of imatinib, sampling t_{max} for both compounds (imatinib and CGP74588) was 2 h and the C_{max} was 3,340 and 781 ng/ml, respectively (Table 1). The $t_{1/2}$ was 18.2 h for the parent drug and 34.0 h for its main metabolite. The

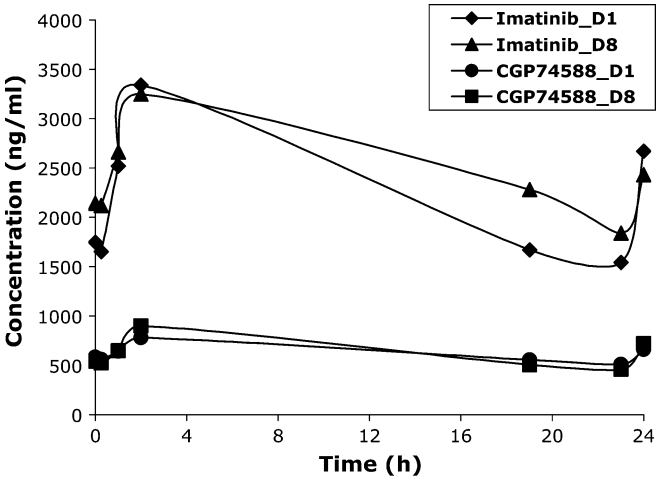

Fig. 1 Concentration–time curve for imatinib and its main metabolite (CGP74588), on a typical day of hemodialysis (D1) and a week later (D8), at steady-state

pharmacokinetics of imatinib were characterized by an AUC_{all} value of 53.9 μg h/ml, and an AUC_{inf} of 94.4 μg h/ml. The same parameters for the CGP74588 metabolite were 14.8 and 39.7 μg h/ml (Table 1). The observed volume of distribution (V_z/F) and total body clearance (Cl/F) of imatinib were 111.4 l and 4.2 l/h, and for the metabolite 494.2 l and 10.1 l/h. The trough concentration for imatinib and CGP74588 was 1,540 and 508 ng/ml, respectively, during the 24-h interval between consecutive administrations (Table 1).

All the determined pharmacokinetic values (C_{max}, $t_{1/2}$, AUC_{0-24}, AUC_{inf}, V_z/F, Cl/F) for both the parent drug and its metabolite were similar a week later (Fig. 1).

Discussion

The present study demonstrated comparable pharmacokinetics of imatinib in our end-stage renal disease patient as in subjects with normal renal function. Our results showed that the pharmacokinetics of imatinib and its main metabolite (CGP74588) do not change by hemodialysis and fall within the range of PK values expected from patients with a normal renal function [4, 7]

Parameters regarding drug levels and exposure to (C_{max}, AUC_{all} and AUC_{inf}) were higher for the parent drug compared to the metabolite (Table 1), as other published data have also revealed, either in steady-state conditions [7] or in its absence [2, 6].

For the main metabolite of imatinib, the *N*-desmethyl derivative of the parent compound (CGP74588), which is also pharmacologically active, terminal elimination was found to be longer than in the parent drug ($t_{1/2}$: 34.0 vs 18.2), which is in keeping with published data [6–9]. It has been shown that the discontinuation of imatinib produces a faster decline of imatinib plasma levels compared with CGP74588 [7]. Additionally, the same is denoted by the fact that the observed volume of distribution and clearance for the metabolite is greater than for imatinib (V_z/F: 494.2 vs 111.4; Cl/F: 10.1 vs 4.2).

The present CGP74588/imatinib ratio for AUC_{all} and AUC_{inf} (0.27 and 0.42, respectively) indicate a significant contribution of metabolite exposure to the drug activity. Given that the accumulation of the metabolite at steady-state (4–7 fold) is greater than that of the parent drug (1.5–3 fold), a convincing reason for the above ratios to be higher than those reported by other researchers (AUC_{all}: 0.13–0.17, AUC_{inf}: 0.18–0.21) is that none of them presents steady-state conditions [2, 6, 10]. The same ratio for the maximum concentration (0.23) is comparable to those reported by Coutre et al. [7] (0.17); the fact that the same ratio for trough concentration is greater (0.33) than for C_{max} (0.23) strengthens the previous comment on the faster decrease of imatinib plasma levels compared with CGP74588.

The trough concentration for the parent compound was above 1,540 ng/ml (relative concentration of 2.61 μM) for the 24-h interval between two oral administrations of imatinib. This amount exceeded the concentration required for the inhibition of cellular phosphorylation (IC_{50}: 0.25 μM) and the death of cell lines positive for BCR-ABL in vitro [11, 12]. Also above the nominal and effective concentration of imatinib (~100 ng/ml) was the trough concentration of *N*-desmethyl-imatinib (CGP74588; 508 ng/ml).

We conclude that imatinib and its metabolite CGP74588 pharmacokinetics do not change in patients with end-stage renal disease on hemodialysis. Therefore, the same dosage of imatinib can safely be administered to patients in hemodialysis, and probably with renal failure, at any stage.

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