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ORIGINAL ARTICLE

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Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects

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Abstract *Objective*: This study was carried out to investigate the influence of CYP3A induction with rifampicin on imatinib (Gleevec) exposure. *Methods*: The study employed a single center, single-sequence design. A group of 14 healthy male and female subjects received imatinib as a single 400 mg oral dose on two occasions: on study day 1 and on study day 15. Rifampicin treatment (600 mg once daily) for CYP4503A induction was initiated on study day 8 and maintained until day 18. Imatinib pharmacokinetics were determined up to 96 h after dosing on day 1 (no induction) and on days 15–18 (during concomitant rifampicin). Plasma concentrations of imatinib and its main metabolite CGP74588 were determined using a LC/MS/MS method. The ratio of 6β-hydroxycortisol to cortisol excreted in the urine was measured to monitor the induction of CYP3A. *Results*: During concomitant rifampicin administration, the mean imatinib C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ decreased by 54% (90% CI: 48–60%), 68% (64–70%) and 74% (71–76%), respectively. The increase in clearance (Cl/f) was 385% (348–426%) during rifampicin treatment. The mean C_{max} and AUC_{0-24} of the metabolite CGP74588 increased by 88.6% (68.3%–111.4%) and 23.9% (13.5%–35.2%) after rifampicin pretreatment. However, the $AUC_{0-\infty}$ decreased by 11.7% (3.3–19.4%). All subjects demonstrated a marked induction of hepatic microsomal CYP3A analyzed by the excretion ratio of 6β-hydroxycortisol to cortisol from a mean baseline concentration of 5.6 U to 50.5 U. *Conclusion*: Concomitant use of imatinib and rifampicin or other potent inducers of CYP4503A may result in subtherapeutic plasma concentrations of imatinib. In patients in whom rifampicin or other CYP3A inducers are prescribed, alternative therapeutic agents with less potential for enzyme induction should be selected.

Keywords Imatinib · Rifampicin · CYP3A · Drug interaction

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Introduction

Imatinib mesylate (Gleevec, formerly STI571) is a phenylaminopyrimidine derivative and is a member of a new class of drugs collectively known as signal transduction inhibitors. Specifically, it is an inhibitor of several protein-tyrosine kinases that are believed to play a role in the proliferation of tumor cells. These include the tyrosine kinases associated with Bcr-Abl, the platelet-derived growth factor receptor and c-kit of the receptor for stem cell factor [2]. Imatinib has been shown to be effective and well tolerated and is currently available for the treatment of chronic myeloid leukemia [3, 7, 10, 12, 13] and gastrointestinal stromal tumors [2, 6].

In vitro studies (human liver microsomes) have shown that imatinib is mainly metabolized by CYP3A

[9]. Therefore, there is the potential for clinically significant drug interactions, which could result in a decrease in exposure to imatinib with a possible loss of efficacy when imatinib is administered concomitantly with drugs known to be inducers of CYP3A.

Rifampicin is a semisynthetic antibiotic derivative of rifamycin SV [4]. It is a potent inducer of the cytochrome P-450 hepatic enzyme system [1]. Concomitant administration of rifampicin with drugs metabolized by cytochrome P-450 enzymes may lead to a clinically relevant acceleration of the clearance of these drugs. To maintain therapeutic blood concentrations, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitant therapy. The induction of hepatic CYP3A resulting from rifampicin treatment, monitored by measuring the ratio of 6β-hydroxycortisol to cortisol excreted in the urine, is reported to be reflected by an increase in the urinary ratio of 6β-hydroxycortisol to cortisol [5, 8, 11, 14].

Concomitant therapy with drugs that induce CYP3A could lead to a reduction in plasma concentrations of imatinib with a reduction in efficacy. This study was carried out to investigate the influence of CYP3A induction with rifampicin on imatinib exposure.

Materials and methods

Study design

The study employed a single-center, single-sequence design. A group of 14 healthy male and female subjects were enrolled into the study and any subjects who discontinued prematurely were required to be replaced. Local and regional Independent Review Boards approved the study protocol (Ethikkommission beider Basel and Interkantonale Kontrollstelle), and all experimental procedures performed in this study complied with current Swiss law.

As detailed in Table 1, each subject underwent a 21-day screening period followed by two treatment periods. Each period consisted of a baseline evaluation, the drug administration with a observation period for 48 h after dosing and a pharmacokinetic sampling phase. The study completion period 96 h after the last dosing was followed by a 4-week safety observation period. The ratio of 6β-hydroxycortisol to cortisol in the urine was measured on study days −1, 10, 14, and 18 to monitor the induction of hepatic CYP3A.

Subjects

A group of 14 healthy volunteers were enrolled in the study after giving written informed consent. The subjects were assessed as healthy following a screening including medical history, physical examination and routine blood tests. None of the subjects reported taking concomitant medication and all were screened and found negative for alcohol, cotinine, amphetamines, benzodiazepines, cannabinoids, cocaine and opiates.

Experimental procedures

Imatinib was supplied as 100 mg hard gelatin capsules and rifampicin was obtained commercially. On study days 1 and 15 imatinib 400 mg was administered with 250 ml tap water between 0900 and 1000 hours, 2 h after breakfast. On study days 8 to 18 subjects returned to the study center in the morning to receive daily doses of rifampicin 600 mg. Daily administration of rifampicin was maintained throughout the pharmacokinetic sampling period for imatinib when subjects were confined to the study site from study day 15 to day 18. On study day 19 subjects returned to the study center for the 96-h after-dosing sampling. Urine was collected on study days −1, 10, 14, and 18 from 0800 to 1200 hours.

Except for medication required for treating adverse events, no other medications were permitted from 14 days prior to the first dosing of study treatment until all end-of-study evaluations had

Table 1 Study schematic (*X* timing of clinical intervention—drug administration, and urine and blood sampling)

	Study phase (days)															
	Screen	Baseline	Treatment period I					Treatment period II								End study
	−21 to −2	−1	1	2	3	4	5	8	9	10	14	15	16	17	18	19	23
Administer imatinib			X									X					
Administer rifampicin								X	X	X	X	X	X	X	X		
6β-Hydrocortisol:cortisol		X								X	X				X		
Pharmacokinetic blood collection																	
Before dosing			X									X					
After dosing (h)																	
0.5			X									X					
1			X									X					
1.5			X									X					
2			X									X					
2.5			X									X					
4			X									X					
6			X									X					
8			X									X					
12			X									X					
24				X									X				
36				X									X				
48					X									X			
72						X									X		
96							X									X	

been completed. The subjects were confined to the study center for at least 12 to 14 h before administration of study drug until 48 h after. Safety assessments included the monitoring and recording of all adverse events, regular checks of blood chemistry, hematology and urine values, ECG recordings, measurements of vital signs and physical examinations.

Blood collection

On days 1 and 15 blood samples were collected before and at 30 min, and 1, 1.5, 2, 2.5, 4, 6, 8, 12, 24, 36, 48, 72 and 96 h after the patients received imatinib 400 mg orally.

Analytical methods

Parent drug and metabolite, *N*-desmethyl metabolite CGP74588, were analyzed by a validated LC/MS/MS method. Within-study assay validation was performed by analysis of calibration and quality control samples together with the study samples. The limit of quantification was 4 ng/ml for imatinib and CGP74588. The inter-day accuracies of quality control samples were 92.5%, 104%, 97.6% and 100% for imatinib and 102%, 100%, 94.4% and 95.3%, respectively, for CGP74588 for the concentrations 12, 600, 8000 and 15,000 ng/ml (1/2 diluted). The precision values were 14.8%, 6.0%, 6.8% and 7.2% for imatinib and 17.5%, 6.3%, 6.3% and 6.4% for CGP74588. Urinary 6β-hydroxycortisol and cortisol concentrations were measured by a competitive immunoassay.

Pharmacokinetic assessments

Data from all subjects who completed the trial were included in the pharmacokinetic analysis. Pharmacokinetic parameters were determined using noncompartmental methods using WinNonlin Pro (version 3.2). The following parameters were estimated: area under the concentration-time curve (AUC) from time zero to the 24-h sampling time point (AUC_{0-24}), AUC from time zero to time infinity ($AUC_{0-\infty}$) calculated as $AUC_{0-t} + C_t/\lambda_z$ where C_t is the concentration at the last measurable time t and λ_z is the terminal elimination rate constant; maximum concentration observed after dosing (C_{max}); time at which the C_{max} occurred (t_{max}); elimination half-life ($t_{1/2}$) determined as $0.693/\lambda_z$; apparent clearance (CL/f) (dose/AUC, where f is the bioavailability); and apparent volume of distribution ($V_{\lambda z}$/f) (dose/AUC* λ_z).

The pharmacokinetic parameters were log-transformed, and a linear model was fitted to each parameter. Due to the design of the study, the only effects that could be included in the model were the overall average, treatment (imatinib plus rifampicin, or imatinib alone), and error. The effect of coadministration of imatinib and rifampicin on the pharmacokinetic of imatinib and its main metabolite was assessed by 90% confidence intervals (CI) for the ratio g(imatinib + rifampicin)/g(imatinib), where, g stands for one of the following pharmacokinetic parameters: $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, CL/f and V/f for parent drug and $AUC_{0-\infty}$, AUC_{0-24} and C_{max} for the metabolite. The ratios and corresponding CIs were derived from the linear model as a treatment contrast, and back-transformed to the natural scale.

For the parameters t_{max} and $t_{1/2}$, nonparametric descriptive analyses were carried out. All statistical calculations were carried out using SAS version 8.2.

Results

Subjects

Table 2 provides details of the demographic and background characteristics of the patients recruited into the study.

Table 2 Demographic and background information

All subjects (*n*)	14
Age (years)	
Mean ± SD	49.8 ± 8.2
Range	40–64
Median	49.0
Height (cm)	
Mean ± SD	172 ± 6
Range	165–186
Median	171.0
Weight (kg)	
Mean ± SD	74.4 ± 8.1
Range	61.5–90.0
Median	73.20
Sex	
Male	13 (92.9%)
Female	1 (7.1%)
Race	
Caucasian	14 (100%)

Urinary ratio of 6β-hydroxycortisol to cortisol

After treatment with rifampicin at a dose of 600 mg once daily the urinary ratio of 6β-hydroxycortisol to cortisol had increased from a mean baseline concentration (mean ± SD) of 5.6 ± 2.4 to 19.9 ± 3.5, 41.8 ± 10.0 and 50.5 ± 15.7 after 3, 7 and 11 days treatment with rifampicin, respectively, indicating a marked induction of hepatic microsomal CYP3A in all patients.

Plasma profiles of imatinib and its metabolite CGP74588

The pharmacokinetic parameters of imatinib and its main metabolite CGP74588 for the 14 healthy subjects determined by noncompartmental analyses are listed in Table 3. The means and standard deviations for each parameter are given for the two treatment periods in which imatinib was administered. Figures 1 and 2 show the comparison of mean plasma concentrations and AUC_{0-24} of imatinib following oral administration either alone or in combination with rifampicin. During concomitant rifampicin administration, the mean imatinib C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ decreased by 54% (90% CI 48–60%), 68% (64–70%) and 74% (71–76%), respectively. The increase in clearance (Cl/F) was 385% (348–426%) after rifampicin pretreatment. The mean C_{max} and AUC_{0-24} of the principal metabolite CGP74588 increased by 88.6% (68.3–111.4%) and 23.9% (13.5–35.2%) after rifampicin pretreatment. However, the $AUC_{0-\infty}$ decreased by 11.7% (3.3–19.4%).

Subject safety

Few adverse events were reported during the course of the investigation. One subject experienced mild myalgia and loose stools. One subject experienced moderate

Table 3 Pharmacokinetic parameters of imatinib and its main metabolite CGP74588 following oral administration of 400 mg imatinib alone and during oral administration of 600 mg rifampicin. Values are means ± SD, except T_{max} median (range)

Parameter	Imatinib		CGP74588	
	Plus rifampicin	Alone	Plus rifampicin	Alone
T_{max} (h)	2.5 (1.0–2.5)	2.5 (2.0–4.0)	1.8 (1.0–2.5)	2.5 (1.5–4.0)
C_{max} (ng/ml)	727 ± 173	1563 ± 285	330 ± 76	174 ± 33
$t_{1/2}$	8.8 ± 0.7	16.7 ± 3.1	35.2 ± 9.9	38.8 ± 11.3
$AUC_{0–24}$ (ng·h/ml)	5331 ± 1369	16301 ± 3475	2285 ± 580	1820 ± 351
$AUC_{0–\infty}$ (ng·h/ml)	5996 ± 1631	22992 ± 5607	3669 ± 955	4115 ± 923
CL/f (l/h)	72.0 ± 21.5	18.7 ± 6.0		

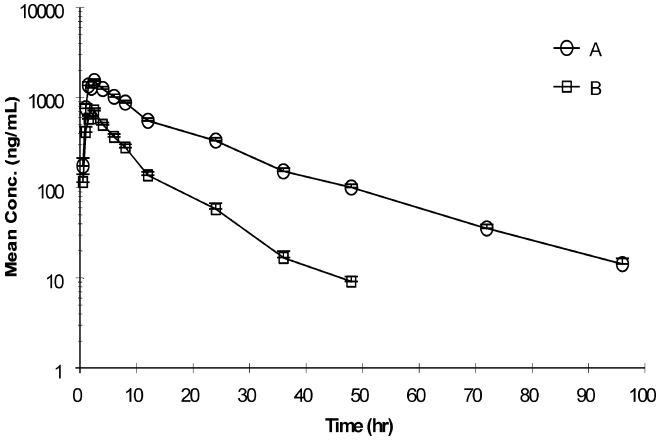

Fig. 1 Mean plasma concentrations of imatinib following oral administration of imatinib alone (*A*) and combined with rifampicin (*B*)

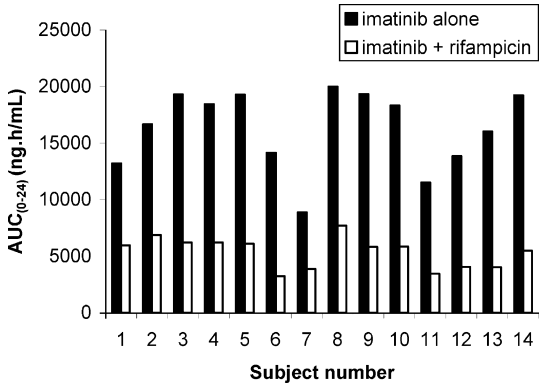

Fig. 2 Comparison of $AUC_{0–24}$ values of imatinib following oral administration of imatinib alone and combined with rifampicin

myalgia, headache and scrotal pain. One experienced severe myalgia and another severe migraine and moderate vomiting. None of these events was suspected to be related to study drug and all resolved within 1 to 2 days during the study period. None resulted in any deviation from the protocol assessment schedule or discontinuation of the study. In addition, one subject had a moderate elevation of SGPT (ALT) at study completion. However, this was not considered as clinically significant or related to study drug. No clinically significant abnormalities in other laboratory values, vital signs or ECG were reported.

Discussion

The results show that 7 days pretreatment with rifampicin decreased the plasma concentrations of imatinib with reductions in C_{max}, $AUC_{0–24}$, and $AUC_{0–\infty}$ compared to the values in the first phase during monotherapy with imatinib. Although there was a large variation in pharmacokinetics between subjects after oral administration of imatinib, an interaction was noted in each of the 14 subjects studied. The almost tenfold increase in the ratio of 6β-hydroxycortisol to cortisol in urine after pretreatment with rifampicin, which was observed in all patients, reveals that rifampicin is a potent inducer of CYP3A. This enzyme induction is probably the principal mechanism underlying the observed interaction between rifampicin and imatinib. This interaction may be the result of both induction of the hepatic metabolism of imatinib and prehepatic metabolism in the gut. The results are consistent with the in vitro finding that imatinib is the substrate of CYP3A.

However, the concentration of metabolite CGP74588 was increased only slightly. The pharmacokinetic parameters for the metabolite showed less consistency than those for the parent drug, imatinib. $AUC_{0–24}$ and C_{max} were increased while $AUC_{0–\infty}$ was decreased This is probably due to an increased rate of formation of other metabolites generated by CYP3A, which were not determined quantitatively in the present study. In addition, this metabolite is also a substrate of CYP3A according to in vitro experiments. The CYP3A enzyme induction may increase the elimination of the metabolite.

Since imatinib is relatively well tolerated, interaction with an inhibitor of CYP3A such as ketoconazole that could result in increased imatinib concentrations is unlikely to cause clinical problems [9]. However, the reduction in plasma concentrations of imatinib may result in subtherapeutic plasma concentrations of the drug. One patient with chronic myeloid leukemia in a phase I study treated at a dose of 350 mg daily failed to respond hematologically and was found to have inappropriately low plasma concentrations of imatinib [3].

The patient was receiving phenytoin, an anticonvulsant which is a potent inducer of CYP3A. The patient promptly responded when phenytoin administration was stopped, although simultaneous escalation of the imatinib dose to 500 mg was also performed. This observation suggests that plasma drug exposure is directly related to hematologic response in patients with leukemia and that concomitant administration of drugs inducing CYP3A could lead to low and ineffective plasma concentrations of imatinib.

Drugs that are potent inducers of CYP3A such as dexamethasone, phenytoin, carbamazepine, phenobarbital and St. John's Wort may increase imatinib metabolism and decrease imatinib plasma concentrations. This potential interaction should be taken into account when considering therapeutic alternatives, and drugs that do not induce CYP3A should be selected for the therapy of patients being treated with imatinib.

The study revealed an interaction between imatinib and rifampicin, with a clinically relevant reduction in exposure to imatinib in patients receiving concomitant treatment with rifampicin.

Concomitant use of imatinib with rifampicin or other potent inducers of CYP3A may result in subtherapeutic plasma concentrations of imatinib. In patients in whom rifampicin or other CYP3A inducers are indicated, alternative therapeutic agents with less potential for enzyme induction should be prescribed.

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