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Population pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia: results of a phase III study

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Aims
This study was designed to investigate the biochemical and physiological covariates or comedications that affect the pharmacokinetics of imatinib mesylate in patients with chronic-phase chronic myeloid leukaemia (CP CML).

Methods
Pharmacokinetic data were analyzed in 371 patients receiving 400 mg imatinib once daily during a phase III trial of imatinib *vs* interferon-alfa plus cytarabine for the treatment of newly diagnosed CP CML. Covariates included age, weight, sex, ethnicity, haemoglobin (Hb) concentration, white blood cell (WBC) count, liver function, and creatinine concentration. Blood samples for imatinib analysis were taken on treatment days 1 and 29. Nonlinear mixed effects modelling was used for the population pharmacokinetic analysis.

Results
Population mean estimates (95% confidence interval) at day 1 for apparent clearance (CL) and apparent volume of distribution (V) of imatinib were 14 (13-15) l h^{-1} and 252 (237-267) l, respectively. Modelling suggested that CL decreased by 4 (3-5) l h^{-1} from day 1 to day 29, whereas V remained unchanged. Interindividual variability in CL and V was 32% and 31%, respectively. Weight, Hb, and WBC count demonstrated small effects on CL and V. Doubling body weight or Hb or halving the WBC count was associated with a 12%, 86% and 8% increase in CL, respectively, and a 32%, 60% and 5% increase in V, respectively. Comedications showed no clear effects on imatinib CL.

Conclusions
Population covariates and coadministered drugs minimally affected imatinib pharmacokinetics in newly diagnosed CP CML patients.

Introduction

Imatinib mesylate (Gleevec®, Glivec®, formerly STI571; Novartis Pharma AG, Basel, Switzerland) is an orally bioavailable, potent, and selective inhibitor of Bcr-Abl tyrosine kinase, which is central to the pathogenesis of chronic myeloid leukaemia (CML) [1, 2]. Imatinib therapy for newly diagnosed chronic phase (CP) CML has produced complete haematological and cytogenetic responses in 95% and 74% of patients, respectively [3].

A noncompartmental pharmacokinetic (PK) and pharmacodynamic (PD) analysis of imatinib performed

during a phase I trial in CML patients showed rapid absorption and dose-proportional area under the concentration-time curve (AUC) after oral administration. The results also showed there was a 1.5- to 3-fold accumulation of drug after repeated once daily dosing. The analysis of the relationship between the haematological response and PK parameters at steady-state indicated that a dose of 400 mg or greater is required for maximal PD effect [4]. The orally administered capsule is completely absorbed and almost totally bioavailable (>97%) [5]. CYP3A4 is the major enzyme responsible for the metabolism of imatinib whereas other enzymes, such as CYP2D6, play a minor role [4].

The present analysis [6] was performed to determine whether population covariates or comedication affect the PK of imatinib. The population consisted of newly diagnosed Philadelphia chromosome–positive CP CML patients from a phase III, prospective, multicentre, open-label, randomized trial designed to compare the efficacy of imatinib *vs* interferon-alfa plus cytarabine (IFN + Ara-C) in the treatment of CML [3].

Methods

Patient characteristics and clinical study design

The study design and the patient characteristics and outcomes have been described in detail previously [3]. Patients in the International Randomized Study of Interferon and STI571 (IRIS) were randomized (1 : 1) to receive imatinib or IFN + Ara-C. Crossover to the alternative arm was permitted using stringently defined criteria concerning treatment failure or intolerance. Pharmacokinetic analysis was planned to include all patients who received imatinib as initial therapy. The drug was supplied as 100 mg capsules and patients were randomized to receive a 400 mg dose by mouth once daily.

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed by the ethics committees or institutional review boards of all participating centres. All patients gave written informed consent according to institutional regulations.

Blood sampling for pharmacokinetic analysis

A sparse PK sampling method was used for patients randomized to imatinib treatment. Sampling was typically performed on day 1 (early treatment) and day 29 (later treatment) of therapy. Three samples were usually drawn between 1 and 3 h following imatinib administration (sample 1), between 6 and 9 h following imatinib administration (sample 2), and prior to administration of the capsules on the next day (sample 3).

Laboratory analyses and demographic covariates

Patient demographic data were recorded at screening with respect to age, sex, weight, and ethnicity (Caucasian, Black, Asian, Other). Samples for laboratory analysis were taken at screening and at regular intervals according to the protocol evaluation and visit schedule. Laboratory analyses included haemoglobin (Hb), white blood cell (WBC) count, total bilirubin, albumin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and creatinine. Creatinine clearance for individual patients was calculated based on creatinine concentration, weight, and sex according to the formula of Cockcroft & Gault [7].

Drug analysis

Imatinib plasma levels were analyzed by liquid chromatography/tandem mass spectronomy (LC/MS/MS). The limit of quantification was 0.025 mg l^{-1} and the assay was fully validated. The accuracy and precision were 104% ± 6% at the lower limit of quantification and 99% ± 5% to 108% ± 5% over the entire concentration range of 4–10 000 ng ml^{-1} [8].

Pharmacokinetic and statistical analysis

NONMEM nonlinear mixed effect modelling software (version V, level 1.1, double precision; University of California, San Francisco, CA, and GloboMax, Hanover, MD, USA) was used for the population PK analysis of imatinib. The first-order (FO) estimation method was used, since no difference to the first-order conditional estimation (FOCE) was expected due to the sparse sampling approach. The final model was also estimated using FOCE.

Pharmacokinetic data on imatinib were previously collected in 491 CML patients in three phase II studies. Population analyses of these data suggested that the PK of imatinib are adequately described by a one-compartment model with zero-order absorption and linear elimination (not published). This type of model is described in more detail by Gibaldi & Perrier [9]. The same basic PK model was also used in this phase III study. It was assumed that for a single dose of imatinib, the concentration $C(t)$ at time t after dose administration is given by:

$$C(t) = (F \times \text{dose})/(\text{D1} \times \text{CL}) \times \{1 - \exp[-(\text{CL}/V) \times t]\} \quad \text{for time } t \le \text{D1}$$

$$C(t) = (F \times \text{dose})/(\text{D1} \times \text{CL}) \times \{\exp[-(\text{CL}/V) \times (t\text{-D1})] - \exp[-(\text{CL}/V) \times t]\} \quad \text{for } t > \text{D1}$$

where D1 is the duration of absorption, CL the clearance, V the volume of distribution and F the fraction

absorbed. Only apparent clearance CL/*F* and apparent volume *V*/*F* can be estimated, but the fraction absorbed *F* is very close to one [5]. The superposition principle was used for calculating the concentration-time profile after multiple doses. To evaluate the sensitivity of the results to the assumptions made, the final model was also analyzed using a one-compartment model with first-order absorption.

Apparent CL and *V* were modelled as random effects with exponential interindividual error and with unstructured (block) covariance. Duration of absorption was fixed to 1.5 h, a value taken from phase II study data, since the sampling schedule did not allow individual estimation of this parameter. To investigate the consistency of this value, the absorption time (θ_3) was also estimated based on the final model, which allowed for a change in the population means of CL and *V* from day 1 to day 29. The effect on CL was modelled as $CL = \theta_1 + \theta_4 \times OCC$, with $OCC = 0$ for day 1 and $OCC = 1$ for day 29. The parameter θ_1 corresponds to the population mean of CL on day 1, and θ_4 to the change in CL from day 1 to day 29. Similarly, the effect on *V* was modelled as $V = \theta_2 + \theta_5 \times OCC$. Since samples were taken on two occasions only (day 1 and day 29) and only sparse PK data were available for each individual, reliable estimation of interoccasion variability appeared to be difficult. An attempt was made to estimate interoccasion variability on CL by expanding the final model. The residual-error model contained both a proportional and additive component.

As a first univariate assessment of the effect of covariates on PK, each covariate was added separately to the base model. The effects on CL and *V* of indicator variables, such as sex, were modelled additively ($\theta \times$ Covariate, with parameter θ to be estimated), whereas numerical variables were included as power models (Covariate$^{\theta}$, with parameter θ to be estimated). Laboratory values were included as time-varying covariates. Effects on both apparent clearance and volume were assessed simultaneously because of correlations between CL and *V*. Covariates were considered potentially relevant when the parameter estimate was at least twice the standard error (SE) of the parameter estimate. This corresponds to a two-sided Wald test for the statistical significance of the parameter estimate with a significance level of 5% [10]. The NONMEM objective function corresponding to −2 log-likelihood was also calculated.

As a next step, all covariates identified as potentially relevant by the univariate assessment were included in a full multivariate model with parameters estimated by NONMEM. The final model was then obtained by dropping all covariates with nonsignificant parameter estimates (Wald test, 5% significance level), and estimating parameters for the remaining covariates with NONMEM. Graphical diagnostic plots were used to assess the fit of the final model.

For each of five comedication classes of interest (CYP2D6 substrates, CYP2D6 inhibitors, CYP3A4 substrates, CYP3A4 inducers, and CYP3A4 inhibitors), the effect on CL was investigated separately for the 2 days of PK sampling (nominal day 1 and nominal day 29). Only comedications taken on the days of PK sampling were considered. For each drug class, the average residual CL was calculated for patients with and without comedication on the day of PK sampling, as well as a 95% confidence interval on the difference. Large differences in mean residual CL would then indicate an effect of comedication on the PK of imatinib.

After the completion of the initial population analysis, additional PK data from patients in the same phase III study became available. These data were used to validate the final population PK model, by predicting the imatinib concentrations for the additional patients, using only covariate information of these patients (population prediction). Observed and model-predicted concentrations were then compared graphically, and residuals were plotted against covariates [11].

Results

One thousand nine hundred and thirty evaluable imatinib measurements were obtained from 371 patients randomized to imatinib in the phase III study. The demographic characteristics and baseline laboratory values of patients included in the population PK analysis (Table 1) did not differ significantly from the 553 patients of the imatinib-treated patients in the overall study population [3] (data not shown). Median patient

Table 1
Patient demographic characteristics (*n* = 371)

Sex (*n*)	
Male	235
Female	136
Age (years)	
Mean (range)	47.7 (18–70)
Race (*n*)	
Caucasian	326
Black	23
Asian	9
Other	13
Weight (kg)	
Mean (range)	81.8 (40–169.5)

laboratory values did not change appreciably from day 1 to day 29, with the exception of WBC count, which decreased from 16×10^9/l to 4.6×10^9/l (Table 2). This decrease reflects the efficacy of imatinib for the treatment of CML.

A base population PK model was developed employing a one-compartment model with zero-order absorption and linear elimination, which included no covariates, but allowed a change in CL and *V* from day 1 to day 29. The estimated values for CL and *V* on day 1 were 13.3 l h^{-1} and 246 l. These values were consistent with those obtained for CL and *V* in patients receiving imatinib, 400 mg daily, in a phase I trial [4]. Modelling of the changes from day 1 to day 29 suggested that CL decreased by approximately 3 l h^{-1} (95% confidence interval 2, 4 l h^{-1}), whereas *V* remained essentially unchanged. The effect of this change in CL on the PK of imatinib in a typical CML patient is illustrated in Figure 1.

The model building process for covariates is summarized in Table 3. The univariate analyses showed no statistically significant effects (Wald test) on CL or *V* for SGOT, SGPT or total bilirubin. Other covariates were included simultaneously in the full PK model. Only weight, Hb and WBC count had statistically significant effects (Wald test) on CL or *V* in this full PK model. These three covariates were therefore included in the final model (Table 4). Only minimal differences between the FO and FOCE estimation methods were found for the final model.

CL and *V* were found to correlate with weight. Parameter estimates (Table 4) indicated that doubling the weight of a patient increased CL by 23% and *V* by 32%. However, interindividual variability was considerable such that the CL values for the patient with the lowest (40 kg) and the highest weight (170 kg) fell within the range for patients with a weight of 80 kg (Figure 2).

Doubling the Hb concentration was associated with an increase in CL of 44% and in *V* of 32% (Figure 3). Since Hb was modelled as a time-varying covariate, the same increase in CL or *V* is also expected if a patient has a Hb concentration on a specific day that is 50% higher than on a previous day. A patient with a WBC count that is three times lower than that of another patient is expected to have an increased CL of 12% and an increased *V* of 8% (Figure 4). WBC count was also modelled as a time-varying covariate, and hence within-patient changes in this variable are also expected to have an effect on CL and *V*. In this phase III study, the median

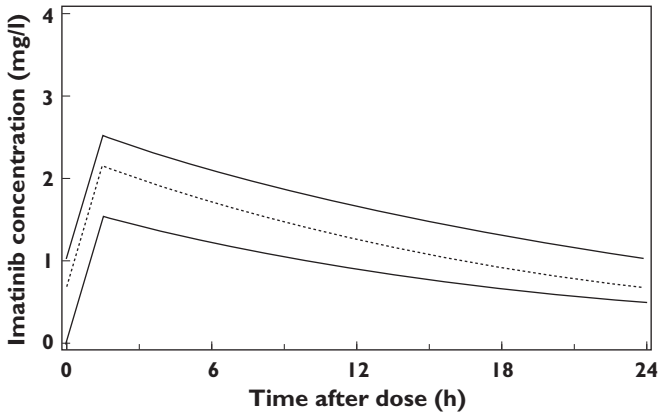

Figure 1
Predicted pharmacokinetic profile for imatinib at day 1 (lower solid line) and at steady-state (upper solid line) for a CML patient with *V* = 250 l, CL = 13 l h^{-1} at day 1 and CL = 10 l h^{-1} at steady state. Also shown is the pharmacokinetic profile at steady state for a CML patient with CL = 13 l h^{-1} at steady state (dotted line).

Table 2
Laboratory values at day 1 and day 29

Parameter	Day 1 median (range)	Day 29 median (range)
Creatinine clearance (ml min^{-1})	103.6 (48.2–270.0)	98.6 (45.2–300.4)
Albumin (g l^{-1})	42.0 (30.0–55.0)	40.0 (25.0–52.6)
SGOT (U l^{-1})	22.0 (5.0–65.0)	21.0 (7.0–100.0)
SGPT (U l^{-1})	21.0 (3.0–105.0)	19.2 (3.0–166.0)
Total bilirubin (μmol l^{-1})	8.6 (1.7–49.6)	8.6 (1.7–39.3)
Haemoglobin (g dl^{-1})	13.2 (8.2–16.9)	12.3 (8.4–16.1)
WBC count (10^9/l)	16.0 (1.5–222.6)	4.6 (1.3–75.0)

SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell.

Table 3
Summary of model building steps

Model step	Objective function	Objective function difference to base model	Wald-test results (5% significance level)
1	–503.945	NA	Base NONMEM model without covariates
Covariate screening			Separate inclusion of covariates
2	–542.584	–38.639	Significant effect of black race on CL
3	–539.762	–35.817	Significant effect of sex on CL and *V*
4	–511.342	–7.397	No significant effect of age on CL or *V*
5	–547.415	–43.470	Significant effect of weight on CL and *V*
6	–531.659	–27.714	Significant effect of creatinine clearance on CL and *V*
7	–525.187	–21.242	Significant effect of albumin on CL and *V*
8	–516.076	–12.131	No significant effect of SGOT on CL or *V*
9	–508.140	–4.195	No significant effect of SGPT on CL or *V*
10	–508.559	–4.614	No significant effect of total bilirubin on CL or *V*
11	–583.325	–79.380	Significant effect of haemoglobin on CL and *V*
12	–520.194	–16.249	Significant effect of white blood cell count on CL and *V*
Full model			Simultaneous inclusion of black race, sex, weight, creatinine clearance, albumin, haemoglobin and white blood cell count
13	–667.536	–163.591	No significant effect of black race, sex, creatinine clearance and albumin on CL or *V*
Final model			Simultaneous inclusion of weight, haemoglobin and white blood cell count
14	–641.298	–137.353	Significant effect of all included covariates on both CL and *V*

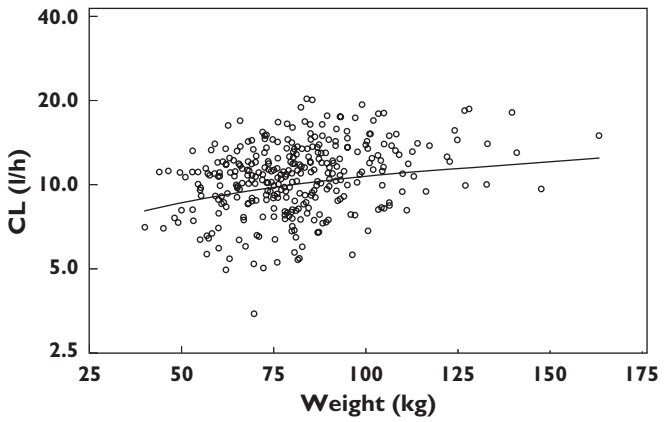

Figure 2
Individual predicted imatinib apparent clearance at steady-state (day 29) against patient weight (solid line: population predicted imatinib CL)

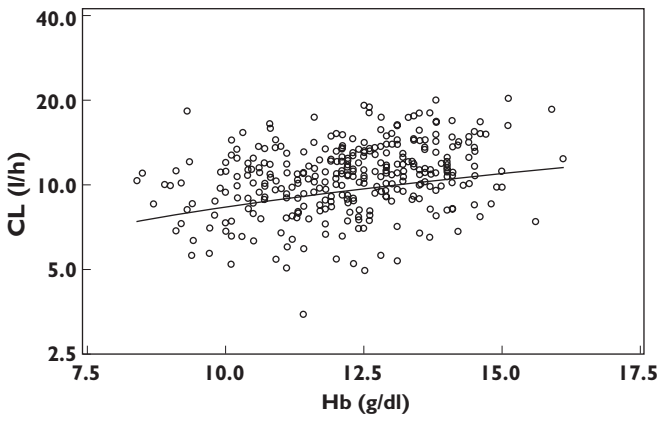

Figure 3
Individual predicted imatinib apparent clearance at steady-state (day 29) against patient haemoglobin (solid line: population predicted imatinib CL)

WBC count decreased by a factor of approximately 3, from 16×10^9/l on day 1 to 4.6×10^9/l on day 29. This would imply an increase in CL with time. However, since overall CL was reduced by approximately 25% from day 1 to day 29 (Figure 5), factors other than WBC count were likely to have been responsible for this effect on CL.

In the final model, the interpatient coefficient of variation (CV), after adjusting for covariates, was 32% for

Table 4
Final model population pharmacokinetic parameters

Parameter		Estimate	Standard error (SE)	95% confidence interval
Fixed effects				
Apparent clearance model				
$CL = (\theta_1 + \theta_4 \times OCC) \times (WEIGHT/80)^{\theta 6} \times (Hb/13)^{\theta 8} \times (WBC/16)^{\theta 10}$				
θ_1	CL intercept (l h^{-1})	13.8	0.478	[12.8-14.8]
θ_4	OCC on CL (l h^{-1})	–3.81	0.436	[–4.68 to –2.94]
θ_6	WEIGHT on CL	0.301	0.096	[0.109-0.493]
θ_8	Hb on CL	0.897	0.187	[0.523-1.271]
θ_{10}	WBC on CL	–0.105	0.035	[–0.175 to –0.035]
Apparent volume model				
$V = (\theta_2 + \theta_5 \times OCC) \times (WEIGHT/80)^{\theta 7} \times (Hb/13)^{\theta 9} \times (WBC/16)^{\theta 11}$				
θ_2	*V* intercept (l)	252	7.62	[237-267]
θ_5	OCC on *V* (l)	–7.82	11.6	[–31.0-15.4]
θ_7	WEIGHT on *V*	0.405	0.118	[0.169-0.641]
θ_9	Hb on *V*	0.676	0.151	[0.374-0.978]
θ_{11}	WBC on *V*	–0.070	0.029	[–0.127 to –0.013]
Duration of zero-order absorption				
θ_3	D1 (h) (fixed)	1.50		
Random effects				
Interindividual variability/Exponential model				
ω^2_1	IIV on CL	0.102 (CV = 31.9%)	0.0142	
ω^2_2	IIV on *V*	0.099 (CV = 31.4%)	0.0157	
ω^2_{12}	cov (CL, *V*)	0.071	0.0104	
Residual error/Combined model				
σ^2_1	proportional part	0.068 (CV = 26.0%)	0.012	
σ^2_2	additive part	0.062	0.022	

OCC = dichotomous covariate for time; OCC = 0 for day 1; OCC = 1 for day 29; CV = Coefficient of variation.

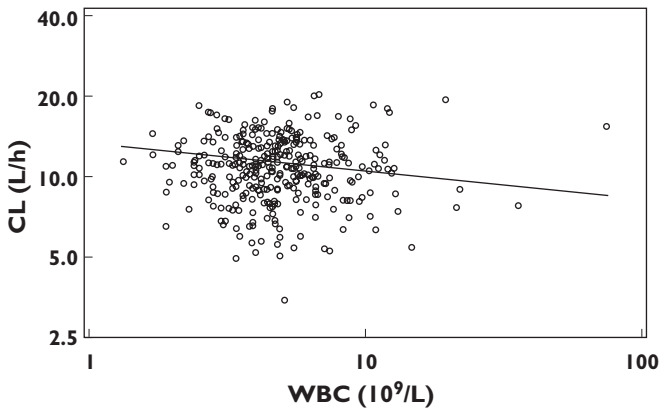

Figure 4
Individual-predicted imatinib apparent clearance at steady-state (day 29) against patient white blood cell (solid line: population-predicted imatinib CL)

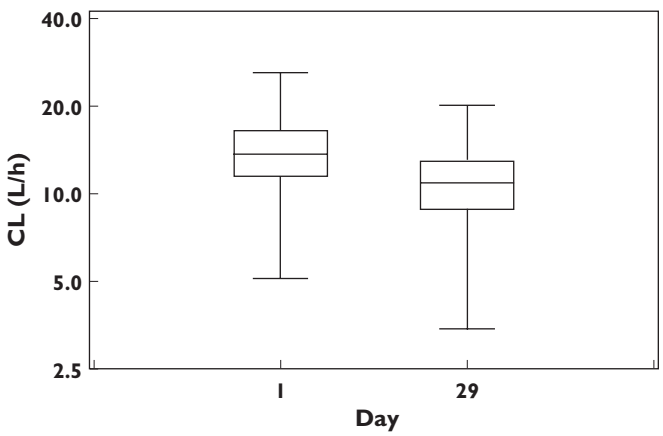

Figure 5
Individual-predicted imatinib apparent clearance day 1 and day 29 (box plots show minimum, lower quartile, median, upper quartile, maximum)

CL and 31% for *V*. In the base model without adjustment for covariates, the CV was 34% for both CL and *V*.

The predicted individual and population plasma imatinib concentrations, based on the final model, were comparable with the experimental values (Figures 6 and 7). The correlation between individual predicted and observed imatinib concentration was 0.89, and that between population predicted and observed imatinib concentration was 0.68.

A substantial number of patients received comedications that could potentially interact with imatinib (Table 5). No clinically relevant differences were

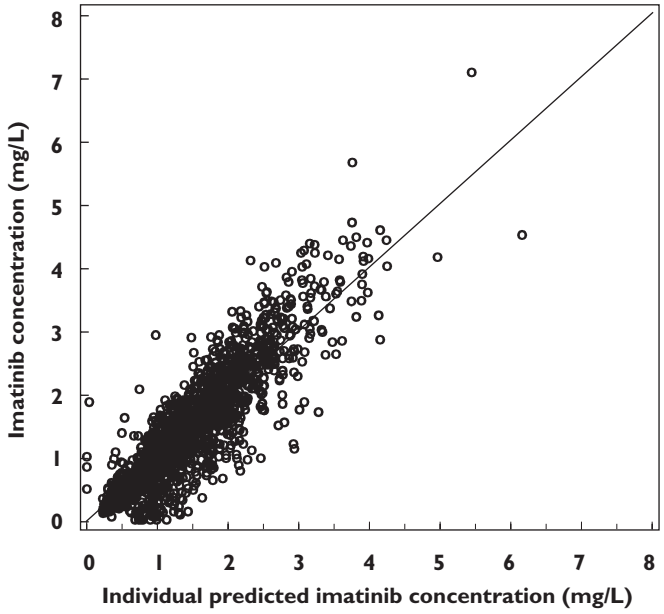

Figure 6
Plasma imatinib concentration: individual predicted *vs* observed (with line of unity)

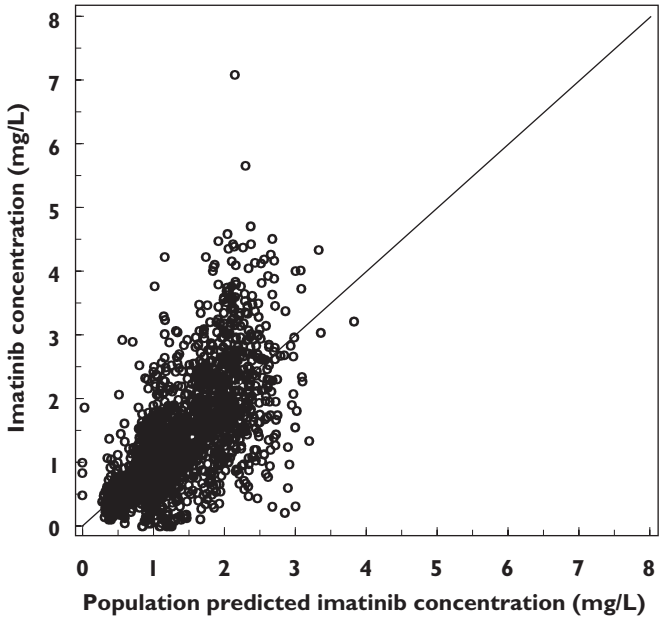

Figure 7
Plasma imatinib concentration: population predicted *vs* observed (with line of unity)

Table 5
Comedications taken on day of blood sampling grouped by drug class

Comedication class	Comedications taken on day of PK sampling
CYP2D6 substrates	Amitriptyline, bupropion, captopril, carvedilol, chlorpheniramine, cinnarizine, codeine, cyclobenzaprine, diphenhydramine, doxepin, hydrocodone, hydrocortisone, hydroxyamphetamine, loratadine, methadone, metoclopramide, metoprolol, mirtazapine, morphine, nortriptyline, ondansetron, orphenadrine, oxycodone, paroxetine, promethazine, propranolol, timolol, tramadol, trazodone, venlafaxine
CYP2D6 inhibitors	Amiodarone, celecoxib, cimetidine, codeine, dextropropoxyphene, fluoxetine, methadone, paroxetine, ranitidine, sertraline, valproic acid, venlafaxine
CYP3A4/5 substrates	Alprazolam, amiodarone, amitriptyline, amlodipine, atorvastatin, bromazepam, budesonide, bupropion, buspirone, carbamazepine, cimetidine, cisapride, clarithromycin, clonazepam, codeine, cortisone, cyclobenzaprine, diazepam, digitoxin, diltiazem, enalapril, estradiol, felodipine, fentanyl, fexofenadine, fluoxetine, hydrocortisone hydroxyarginine, lansoprazole, lidocaine, loratadine, losartan, lovastatin, methadone, miconazole, midazolam, mirtazapine, nifedipine, nisoldipine, omeprazole, ondansetron, oral orphenadrine, pioglitazone, pravastatin, prednisone, progesterone, quinine, repaglinide, salmeterol, sertraline, sildenafil citrate, simvastatin, temazepam, theophylline, trazodone, venlafaxine, verapamil, warfarin, zolpidem
CYP3A4/5 inducers	Carbamazepine, hypericum, progesterone, rofecoxib
CYP3A4/5 inhibitors	Amiodarone, azithromycin, cimetidine, clarithromycin, clotrimazole, diltiazem, fluconazole, fluoxetine, metronidazole, miconazole, norfloxacin, omeprazole, paroxetine, propoxyphene, quinine, ranitidine, sertraline, valproic acid, verapamil

Table 6
The number of patients who received particular comedications (*n*) and the difference in mean residual apparent clearance (CL) between patients not taking and taking comedication

Comedication class	Day 1 *n*	Day 1 Difference in CL (95% CI) (l h^{-1})	Day 29 *n*	Day 29 Difference in CL (95% CI) (l h^{-1})
CYP3A4 inhibitors	27	–0.137 (–0.239 to –0.034)	55	–0.50-0.007 (–0.084-0.0702)
CYP3A4 inducers	5	0.0379 (–0.195-0.2704)	7	–0.50-0.078 (–0.278-0.122)
CYP3A4 substrates	73	–0.01 (–0.079-0.0581)	126	–0.50-0.02 (–0.079-0.0394)
CYP2D6 substrates	46	–0.002 (–0.084-0.08)	73	–0.50-0.021 (–0.091-0.048)
CYP2D6 inhibitors	22	–0.112 (–0.225-0.0016)	40	0.0202 (–0.068-0.1085)

observed in average residual apparent clearance between patients taking and not taking comedication for each drug class and day (Table 6).

To evaluate the sensitivity of the final model results to the assumptions made, alternative models were used. Instead of fixing the absorption time to 1.5 h, this parameter was estimated in the final model, resulting in an absorption time (95% confidence interval) of 1.6 (1.4-1.7) h. The estimates of other parameters changed slightly (less than 2% corresponding to covariate effects and less than 4% change in their SEs). As an alternative to the zero-order absorption one-compartment PK model, the final model was fitted using a one-compartment model with first-order absorption. The estimate (95% confidence interval) of the absorption parameter k_a was 1.1 (1.0-1.3) h^{-1}. Very similar estimates were obtained for the other parameters (less than 6% change corresponding to covariate effects and less than 2% change in their SEs). The final model was expanded to assess the effect of interoccasion variability on CL. Parameter estimates were very similar (less than 1% change corresponding to covariate effects and less than 2% change in their SEs). Interoccasion variability in CL had a CV of 2%. The decrease in CL from day 1 to day 29 was estimated as 3.8 l h^{-1} (95% confidence interval 2.9-4.7 l h^{-1}).

Pharmacokinetic data from an additional 33 imatinib-treated patients in the phase III trial of imatinib *vs* IFN + Ara-C became available after the completion of the population PK analysis. To validate the final model (based on data from 371 patients), predicted and observed imatinib concentrations were compared for the 33 patients using graphical methods. The plots of residuals against covariates did not reveal any systematic unexplained covariate effect. The correlation between observed and predicted imatinib concentrations was $r = 0.62$ for the 33 patients, which was only slightly lower than that between population predicted and observed imatinib concentration for the 371 patients used for model building ($r = 0.68$). If covariate information was not used for prediction and no change in CL and *V* from day 1 to day 29 was considered, then the correlation between observed and predicted imatinib concentrations decreased to $r = 0.57$ for the 33 patients. An updated population PK model for all 404 (371 plus 33) patients gave very similar results compared with the model based on 371 patients only. Parameter estimates corresponding to covariate effects changed less than 12% and their SEs by less than 6%.

Discussion

The results of this population PK analysis complement recently published PK and PD data from a phase I trial of imatinib in patients with CML [4]. In the phase I study, a noncompartmental approach in 64 patients was used to evaluate the basic PK characteristics and PK/PD properties. The analysis of PK/PD relationships indicated that the initial haematological response depends on the administered dose for patients with CML [4]. In contrast to traditional PK studies, which require many samples per patient, the population approach allows the use of sparse sampling, so PK information on many patients in the target population can be obtained. Because of the diversity and large number of patients, factors affecting PK can be identified and the need for dose adjustment can be assessed. The correlation between predicted and observed plasma imatinib concentrations indicated a good fit of the final population PK model to the data. This was further confirmed by a validation step involving additional patients.

The effect of population covariates and comedications on the CL and *V* of imatinib appeared to be small in this population of patients. No effect was sufficiently pronounced to warrant dose adjustment. In the final model, only weight, Hb and WBC count demonstrated apparent

effects. However, these were small compared with the PK variability. For example, the CL in patients with the lowest and highest weight (40 kg and 170 kg) was within the range of apparent clearance for median weight patients (80 kg). Clearance decreased by 25% from day 1 to day 29, which seems to be larger than the interoccasion variability on CL (CV = 2%). However, interoccasion variability is difficult to estimate reliably from PK data available from two occasions only. The reason for this change in CL is not yet understood. Another study in patients with a gastrointestinal stromal tumour (GIST) found that there was a trend towards increased imatinib clearance after chronic exposure over 12 months [12], which might be due to a change of health status or other factors affecting intrapatient variability.

No important effects of comedications were observed. Based on the results of this study, imatinib can be administered at the standard recommended doses without adjustment for age, weight, ethnicity or sex.

The increased *V* and CL associated with higher weight are consistent with increased body mass and adipose tissue. These observations are consistent with those observed in the population PK study conducted in patients with GIST and sarcomas, showing that low CL was associated with low body weight and high granulocyte count, whereas low Hb was associated with low *V* [12]. The basis of the relationships between CL and *V,* and Hb concentration and WBC count are not clearly understood. These two biochemical parameters may reflect the health of the patients, causing CL to increase with improvement in health status. In addition, it was found recently that the blood cell distribution of imatinib was 10–25% in humans [13] such that Hb and WBC count might have a direct effect on the PK of imatinib. Imatinib also displayed high binding to human α_1-acid glycoprotein. Acute myeloid leukaemia patients have a decreased haematocrit and show substantial variability in their blood binding parameters [13]. Thus, the variation in protein binding might also contribute to the changes in CL and *V* and to variation in PK between and within patient populations.

CYP3A4 is the major enzyme responsible for the metabolism of imatinib and its activity varies significantly between individuals [14]. Increased imatinib CL and decreased plasma concentrations can occur in patients treated concomitantly with CYP3A4 inducers such as rifampicin [15]. Conversely, increased plasma imatinib concentrations can arise from coadministration of CYP3A4 inhibitors such as ketoconazole [16]. Since imatinib is a potent inhibitor of CYP3A4, coadministration of imatinib with CYP3A4 substrates such as simvastatin would increase exposure to these agents [17].

Other CYP isoenzymes, such as CYP2D6, play a minor role in imatinib metabolism. However, imatinib is a potent competitive inhibitor of CYP2D6, and drug–drug interactions can occur when imatinib is coadministered with drugs that are substrates of CYP2D6 [18]. In the present population PK study, a substantial number of patients received comedications that could interact with imatinib, but no clear effect on imatinib CL was observed. However, this study was not designed to investigate the effect of other drugs on the PK of imatinib.

The effect of population covariates and co-medications on the CL and *V* of imatinib appeared to be minimal in this phase III study of CPCML patients. The results of a prospective evaluation of the final model indicated a modest contribution of covariates and change in PK parameters for improving the correlation between predicted and observed imatinib concentrations. In patients where rifampicin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered prior to initiating imatinib treatment. Only patient weight, Hb and WBC count had an effect on imatinib CL and *V*. The population PK analysis yielded a good correlation between predicted and observed plasma imatinib concentrations.

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