BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03810.x

Effects of imatinib mesylate on the pharmacokinetics of paracetamol (acetaminophen) in Korean patients with chronic myelogenous leukaemia

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Keywords
acetaminophen, CML, imatinib, Korean, paracetamol, pharmacokinetics

Received
19 May 2010

Accepted
26 August 2010

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Imatinib mesylate, a tyrosine kinase inhibitor, exhibits a weak competitive inhibition on paracetamol (acetaminophen) *O*-glucuronidation with an inhibition constant (K_i) value of 59 μM. However, the clinical significance of the inhibition has not been evaluated. The pharmacokinetics of imatinib have been studied in white patients with chronic myelogenous leukaemia (CML), but not in Korean patients with CML.

WHAT THIS STUDY ADDS

- Imatinib (400 mg once daily) had no clinically relevant effect on the plasma exposure and the pharmacokinetics of paracetamol (1000 mg once daily) in patients with CML.
- The pharmacokinetic profile of imatinib in Korean patients with CML was similar to that in whites.

AIMS

The major objective of the present study was to investigate the effect of imatinib on the pharmacokinetics of paracetamol in patients with chronic myelogenous leukaemia (CML).

METHODS

Patients ($n = 12$) received a single oral dose of acetaminophen 1000 mg on day 1 (control). On days 2–8, imatinib 400 mg was administered daily. On day 8 (treatment), another 1000 mg dose of paracetamol was administered 1 h after the morning dose of imatinib 400 mg. Blood and urine samples were collected for bioanalytical analyses.

RESULTS

The area under the plasma concentration–time curve (AUC) for paracetamol, paracetamol glucuronide and paracetamol sulphate under control conditions was similar to that after treatment with imatinib; the 90% confidence interval of the log AUC ratio was within 0.8 to 1.25. Urinary excretion of paracetamol, paracetamol glucuronide and paracetamol sulphate was also unaffected by imatinib. The pharmacokinetics of paracetamol and imatinib in Korean patients with CML were similar to previous pharmacokinetic results in white patients with CML. Co-administration of a single dose of paracetamol and multiple doses of imatinib was well tolerated and safety profiles were similar to those of either drug alone.

CONCLUSIONS

The pharmacokinetics of paracetamol and its major metabolites in the presence of imatinib were similar to those of the control conditions and the combination was well tolerated. These findings suggest that imatinib can be safely administered with paracetamol without dose adjustment of either drug.

Introduction

Imatinib mesylate (Gleevec/Glivec®, formerly STI571, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a protein tyrosine kinase inhibitor which has proven efficacy in the treatment of chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GIST) [1, 2]. Following oral administration, imatinib is rapidly absorbed into the body with high oral bioavailability and has a plasma terminal half-life of ~20 h [3, 4]. Despite a favourable pharmacokinetic profile for daily dosing, drug–drug interactions may occur because imatinib has been shown to interact with several metabolizing enzymes. Imatinib is primarily metabolized by CYP3A4 and is metabolized to a lesser extent by CYP1A2, CYP2D6, CYP2C9 and CYP2C19 [3]. CGP74588 is a major metabolite of imatinib, and its biological activity is similar to that of imatinib; CGP74588 represents ~20% of the parent drug exposure in patients. Co-administration of imatinib with a CYP3A4 inhibitor or inducer has been shown to alter imatinib pharmacokinetic exposure [5–9]. *In vitro* studies have shown that imatinib is a competitive inhibitor of CYP3A4/5 and CYP2D6 isozymes with inhibition constant (K_i) values of 8 and 7.5 μM, respectively [3]. In patients with CML, co-administration of imatinib 400 mg once daily increased the plasma exposure of simvastatin, a CYP3A4 substrate, by approximately 3-fold [10]. However, no significant drug–drug interactions were observed following co-administration of imatinib and metoprolol, a CYP2D6 substrate, in Chinese patients with CML with known CYP2D6 phenotypes [11]. *In vitro,* imatinib competitively inhibits paracetamol (acetaminophen) *O*-glucuronidation with a K_i value of 59 μM, but imatinib has no effect on the formation of intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) from paracetamol. The potential for drug–drug interactions between imatinib and paracetamol has not been studied.

Paracetamol is an analgesic and antipyretic agent that is widely available without prescription and is frequently used in routine clinical practice in imatinib-treated patients. Adverse events associated with paracetamol use include headache, myalgia and arthralgia. The absorption of low therapeutic doses of paracetamol is usually rapid, and the systemic bioavailability and plasma terminal half-life are 75% and 1.5–2.5 h, respectively [12]. The major metabolic pathways of paracetamol are conjugation with glucuronide (~60% of dose) or sulphate (~30% of dose) [13, 14] and the minor metabolic pathway involves CYP2E1 with CYP1A2 and CYP3A4 as additional minor contributors [15, 16] (Figure 1). Paracetamol is biotransformed by CYP2E1 to the intermediate metabolite, NAPQI, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates (~8% of dose) [14, 17]. Overdoses of paracetamol in humans can saturate the sulphate conjugation pathway and result in an increased amount of NAPQI, which can lead to glutathione depletion and eventually to hepatic necrosis. Metabolism

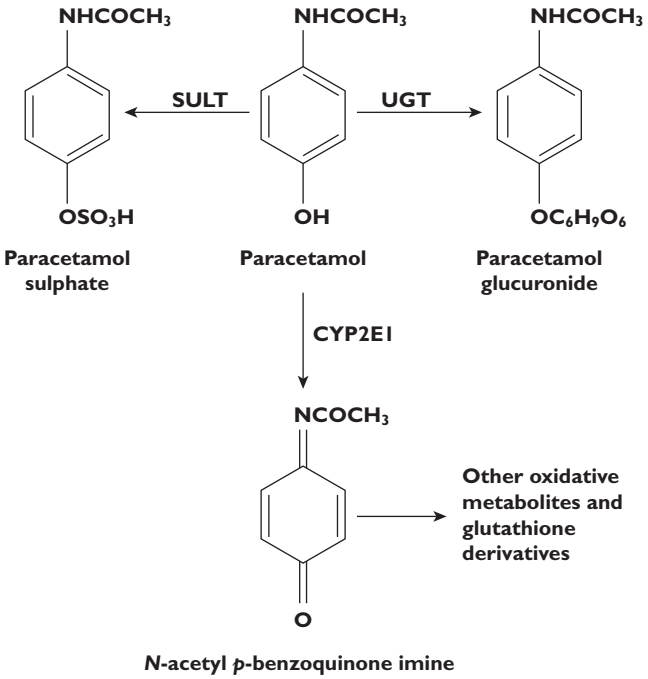

Figure 1

Metabolism of paracetamol glucuronidation by UDP-glucuronosyltransferase (UGT) and sulphation by sulphotransferase (SULT) are major metabolic pathways, and oxidation by cytochrome P450-2E1 (CYP2E1) is a minor metabolic pathway

can shift from one pathway to another, for example, after saturation of sulphation by a paracetamol overdose or by inhibition of a particular pathway by concomitant medications [12].

It is known that the glucuronidation pathway represents ~60% of paracetamol metabolism [14] and imatinib competitively inhibits paracetamol *O*-glucuronidation with a K_i value of 59 μM. Inhibition of paracetamol glucuronidation by imatinib can result in shunt metabolism of paracetamol to other pathways. Thus, the present study was designed to examine the effect of imatinib on the plasma exposure of paracetamol and its major metabolites, paracetamol glucuronide and paracetamol sulphate. In addition, the present study also investigated the pharmacokinetic characteristics of imatinib (400 mg once daily) at steady state when co-administered with paracetamol at a dose of 1000 mg (once daily) in Korean patients with CML.

Methods

Patients

Korean patients (≥18 and ≤75 years of age) with newly diagnosed, cytogenetically confirmed chronic phase Philadelphia chromosome positive (Ph+) CML, who were imatinib naïve, were eligible for this study. Patients were

required to have an Eastern Cooperative Oncology Group Performance status ≤3. Patients with significant hepatic, renal, respiratory or cardiac abnormalities were excluded.

Study design

This was an open-label, one-sequence study of 12 male and female patients with Ph+ early chronic phase CML. Patients received a single oral dose of paracetamol (1000 mg) on study day 1. On days 2–7, patients received an oral dose of imatinib (400 mg). Based on previous imatinib pharmacokinetic data [3, 4], the accumulation half-life of imatinib is ~17 h. Thus, imatinib reached steady state at day 7 of the study. On day 8, patients received imatinib (400 mg) together with paracetamol (1000 mg). The pharmacokinetics of imatinib have been widely studied in large CML populations. Race does not affect the pharmacokinetics of imatinib [3, 4] and we have adequate data to support the pharmacokinetics of imatinib in the absence of paracetamol. Thus, imatinib concentrations were not measured in the absence of paracetamol. The study was conducted according to the ethical principles of the Declaration of Helsinki and the study protocol was approved by the Independent Ethics Committee of Seoul St. Mary's Hospital. Informed consent was obtained from each patient prior to study enrolment.

Safety assessment and monitoring

The safety assessment included the recording of pregnancies and all adverse events (AEs), serious adverse events (SAEs), including their severity and relation to the study drug. Regular monitoring consisted of haematologic and blood chemistry testing, urinalysis, electrocardiography, recording of concomitant medication use, and any significant non-drug therapies. Vital signs, physical condition, and body weight were also assessed. After study completion, all patients continued imatinib therapy either outside of or as part of another clinical study.

Pharmacokinetic sample collection and analysis

Blood samples for determination of plasma paracetamol, paracetamol glucuronide, paracetamol sulphate, imatinib, and imatinib metabolite (CGP74588) concentrations were collected predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after paracetamol administration on study days 1 and 8. Plasma concentrations of imatinib and CGP74588 were determined by liquid chromatography and tandem mass spectrometry. The limit of quantification was 20 ng ml^{-1} for both imatinib and CGP74588, and the assay was fully validated [18]. The bias and precision of quality control samples for imatinib ranged from 1.1 ± 17 to 3.5 ± 9.5% over the entire concentration range of 20 to 10 000 ng ml^{-1}. The bias and precision for CGP74588 ranged from 0.8 ± 19.5 to 3.3 ± 3.9% over the entire concentration range of 20 to 10 000 ng ml^{-1}.

Plasma samples were analyzed for paracetamol, paracetamol glucuronide, and paracetamol sulphate by PPD, Inc. (Middleton, WI, USA). The limit of quantification for paracetamol, paracetamol sulphate and paracetamol glucuronide in plasma was 0.1, 0.1 and 0.5 μg ml^{-1}, respectively, using 0.050 ml of plasma. The bias and precision of quality control samples ranged from –0.96 ± 3.35 to 1.28 ± 2.25% over the range of 0.1 to 50 μg ml^{-1} for paracetamol, from –0.13 ± 3.70 to 2.48 ± 3.35% over the range of 0.1 to 50 μg ml^{-1} for paracetamol sulphate and from 0.032 ± 4.32 to 2.00 ± 3.49% over the range of 0.5 to 100 μg ml^{-1} for paracetamol glucuronide.

Urine samples were also analyzed for paracetamol, paracetamol sulphate and paracetamol glucuronide by PPD, Inc. For determinations in urine, the limit of quantification for paracetamol, paracetamol glucuronide and paracetamol sulphate were 0.2, 0.5 and 1.0 μg ml^{-1}, respectively, using 0.025 ml of urine. The bias and precision of quality control samples ranged from –3.08 ± 5.78 to 1.47 ± 2.47% over the range of 0.2 to 200 μg ml^{-1} for paracetamol, from –6.01 ± 6.25 to 4.78 ± 4.64% over the range of 0.5 to 500 μg ml^{-1} for paracetamol sulphate and from –6.25 ± 6.39 to 4.12 ± 4.63% over the range of 1.0 to 1000 μg ml^{-1} for paracetamol glucuronide.

Noncompartmental methods (WinNolin Pro, Version 5.2, Pharsight Corp, Mountain View, CA) were used to estimate the following pharmacokinetic parameters for paracetamol, paracetamol glucuronide, paracetamol sulphate, imatinib, and CGP74588: maximum plasma concentration after administration (C_{max}), time to reach maximum plasma drug concentration (t_{max}) and area under the plasma concentration *vs.* time curve from time 0 to infinity ($AUC_{0-\infty}$) or from time 0 to τ ($AUC_{0-\tau}$), where τ is the dosing interval (24 h). In addition, the trough (24 h) plasma concentrations (C_{min}) were determined for imatinib and CGP74588. The apparent total body clearance (or, oral clearance; CL/*F*) and volume of distribution (V_z/F) of paracetamol were calculated as (dose/$AUC_{0-\infty}$) and (dose/$AUC_{0-\infty}/k$), respectively, where *k* is the elimination rate constant. The terminal half-life ($t_{1/2}$) was calculated as 0.693/*k*. The CL/*F* and V_z/F of imatinib were calculated as (dose/$AUC_{0-\tau}$) and (dose/$AUC_{0-\tau}/k$), respectively. The metabolic ratio (MR) was calculated as the ratio of pharmacokinetic parameters of the metabolite over the parent drug adjusted by the molecular weight of the molecules. The percentage of dose excreted in urine (F_{ren}) was calculated for paracetamol, paracetamol glucuronide and paracetamol sulphate, and the renal clearance (CL_{ren}) was calculated as the ratio of total amount excreted in urine for 24 h over the $AUC_{0-\tau}$.

Statistical analysis

On the basis of intrapatient coefficient of variation of 20% for paracetamol AUC, it was expected that a sample size of 12 patients would provide at least 80% power in claiming no effect of imatinib on paracetamol pharmacokinetic parameters (AUC and C_{max}) using the default no-effect

region (90% confidence interval [CI] of log parameter ratio within 0.8 to 1.25). Descriptive statistics of paracetamol pharmacokinetic parameters included geometric and arithmetic means, standard deviation (SD), and coefficient of variation (CV). Median values and ranges were provided for t_{max}. Imatinib pharmacokinetic parameters obtained on day 8 were summarized similarly.

The effect of imatinib on the pharmacokinetics of a single paracetamol dose was assessed using a linear mixed-effects model approach. Log-transformed C_{max}, AUC and CL/*F* of paracetamol were analyzed using the model, with treatment as a fixed factor and subject as a random factor. A point estimate and its 90% CI for the difference between least squares means with (test treatment) and without co-administration of imatinib (reference treatment) were calculated. This estimate and its 90% CI were anti-logged to obtain the point estimate and the 90% CI for the ratio of geometric means on the untransformed scale. Lack of a drug–drug interaction is claimed if the 90% CI of the ratio of the geometric means was completely contained (0.8, 1.25).

All statistical analyses (including the selection of the linear mixed effects model) followed the suggestion from FDA and EMEA guidance documents for Bioavailability and Bioequivalence trials [19, 20].

Results

Twelve patients (eight males and four females) were enrolled and completed the study. All patients were native Korean with a mean age of 44 ± 12 years (range 27–68 years) and a mean bodyweight of 70 ± 15 kg (range 51–105 kg).

Pharmacokinetics of paracetamol

The plasma concentration–time profiles for paracetamol and its metabolites are shown in Figures 2 and 3, respectively. The pharmacokinetic parameters and a summary of the statistical analyses for paracetamol and its metabolites are shown in Tables 1 and 2, respectively. The 90% CI of the geometric mean ratios of AUC for paracetamol, paracetamol glucuronide and paracetamol sulphate were within the equivalence limits of 0.8 to 1.25. The 90% CI of the geometric mean ratio of C_{max} for paracetamol was not within the equivalence limits of 0.8 to 1.25 because of large variability in the C_{max} (14 ± 6.3 μg ml^{-1} for paracetamol monotherapy). The mean CL/*F* and $t_{1/2,z}$ of paracetamol were similar in the presence and absence of imatinib (Table 1). The 90% CI of the geometric mean ratios of C_{max} for paracetamol glucuronide and paracetamol sulphate was within the equivalence limits of 0.8 to 1.25. The renal clearance of paracetamol glucuronide or paracetamol sulphate was similar in the presence and absence of imatinib (Table 1). In addition, the 90% CI of the geometric mean ratios of the metabolite-to-parent drug AUC ratio (MR-AUC) for paracetamol glucuronide and paracetamol sulphate were within the bioequivalence limits of 0.8 to 1.25. Paracetamol was extensively metabolized, and its major metabolites, paracetamol glucuronide and paracetamol sulphate, were excreted predominantly in urine. The average urinary excretion of the parent compound, paracetamol glucuronide and paracetamol sulphate was ~4, ~60, and ~31% of the dose, respectively, either in the absence or presence of imatinib.

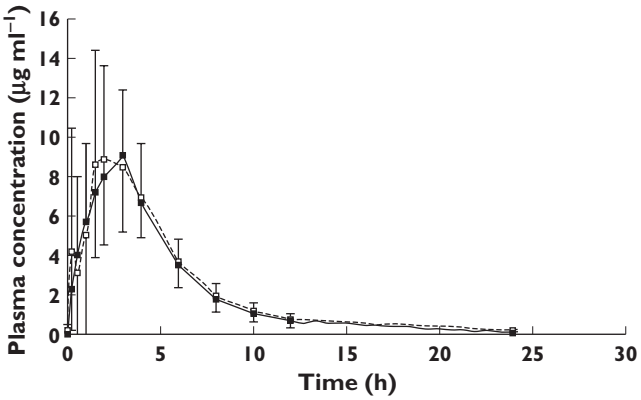

Figure 2

Mean plasma paracetamol concentration–time profiles on day 1 (control; -SD) and day 8 (after treatment with imatinib; +SD) in patients with CML (n = 12). Control (--□--); Treatment (—■—)

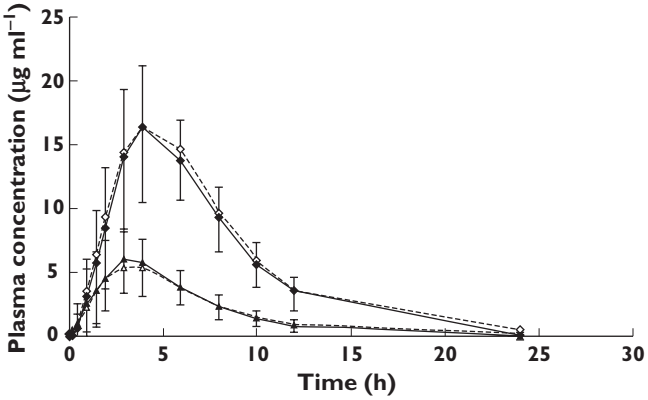

Figure 3

Mean paracetamol glucuronide (PG) and paracetamol sulphate (PS) plasma concentration–time profiles on day 1 (control; -SD) and day 8 (treatment with imatinib; +SD) in patients with CML (n = 12). PG-Control (--◇--); PG-Treatment (—◆—); PS-Control (—△—); PS-Treatment (—▲—)

Based on the $t_{1/2,z}$ of imatinib (~20 h) and previous clinical studies [4], imatinib (400 mg once daily) reached steady state after day 7. Plasma concentration–time profiles of imatinib and CGP74588 on day 8 are shown in Figure 4. The mean plasma C_{max}, C_{min} and AUC(0,24 h) of imatinib were 2.2 μg ml^{-1}, 0.91 μg ml^{-1} and 33 μg ml^{-1}h, respectively, and are shown in Table 3. The $t_{1/2,z}$, CL/*F*, and V_z/*F* of imatinib, estimated on the basis of one dosing interval on day 8,

Table 1

Mean (±SD) pharmacokinetic parameters of paracetamol and its metabolites (paracetamol glucuronide and paracetamol sulphate) in patients with CML (n = 12) after a single 1000 mg dose of paracetamol alone (day 1) and in combination with imatinib (day 8)

Analyte	Day	$AUC_{0-\tau}$ (μg ml^{-1} h)	C_{max} (μg ml^{-1})	t_{max} (h)*	V_2/F (l)	CL/F (l h^{-1})	$t_{1/2,z}$ (h)	F_{ren}	CL_{ren} (l h^{-1})	MR-AUC
Paracetamol	1	54 ± 20 (55 ± 21)†	14 ± 6.3	2 (0.3, 4)	115 ± 42	21 ± 8.5	4.1 ± 1.5	0.043 ± 0.028	0.79 ± 0.19	NA
	8	50 ± 18 (51 ± 18)†	11 ± 4.0	2 (0.3, 4)	94 ± 31	22 ± 8.4	3.1 ± 1.2	0.040 ± 0.019	0.84 ± 0.39	NA
Paracetamol glucuronide	1	136 ± 37	18 ± 3.4	4 (3, 6)	NA	NA	3.6 ± 1.2	0.63 ± 0.16	9.3 ± 2.0	1.3 ± 0.55
	8	127 ± 29	17 ± 4.5	4 (3, 6)	NA	NA	3.2 ± 0.8	0.58 ± 0.22	9.2 ± 2.9	1.3 ± 0.53
Paracetamol sulphate	1	42 ± 17	6.3 ± 1.6	3 (1, 4)	NA	NA	4.2 ± 1.2	0.32 ± 0.14	11 ± 2.0	0.54 ± 0.12
	8	43 ± 17	6.3 ± 2.1	3 (2, 4)	NA	NA	3.4 ± 1.0	0.30 ± 0.12	11 ± 4.0	0.59 ± 0.14

*Values are expressed as median (range). †Values in parentheses are expressed as area under the plasma concentration–time curve from time 0 to infinity. $AUC_{0-\tau}$, area under the plasma concentration–time curve from time 0 to 24 h; C_{max}, maximum plasma concentration after administration; t_{max}, time to reach C_{max}; V_2/F, oral volume of distribution; CL/F, oral clearance; $t_{1/2,z}$, terminal half–life; F_{ren}, fraction of the acetaminophen dose excreted in urine as metabolite; CL_{ren}, renal clearance; MR–AUC, metabolic ratio calculated as the $AUC_{0-\tau}$ ratio of the metabolite to acetaminophen adjusted for the molecular weight of the molecules; NA, not available.

Table 2

Summary of statistical analysis of primary pharmacokinetic parameters for paracetamol and its metabolites (paracetamol glucuronide and paracetamol sulphate) in patients with CML (n = 12) after a single 1000 mg dose paracetamol alone (day 1) compared with paracetamol in combination with imatinib (day 8)

	$AUC_{0-\tau}$ (μg ml^{-1} h)			C_{max} (μg ml^{-1})			MR-AUC		
Analyte	Geometric mean ratio	Lower 90% CI	Upper 90% CI	Geometric mean ratio	Lower 90% CI	Upper 90% CI	Geometric mean ratio	Lower 90% CI	Upper 90% CI
Paracetamol	0.95	0.91	0.99	0.85	0.69	1.04	NA	NA	NA
Paracetamol glucuronide	0.94	0.89	1.00	0.91	0.85	0.97	0.99	0.93	1.06
Paracetamol sulphate	1.02	0.98	1.07	1.00	0.93	1.07	1.07	1.01	1.15

$AUC_{0-\tau}$, area under the plasma concentration–time curve from time 0 to 24 h; C_{max}, maximum plasma concentration after administration; MR-AUC, metabolic ratio calculated as the $AUC_{0-\tau}$ ratio of the metabolite to paracetamol adjusted for the molecular weight of the molecules; geometric mean ratio, the ratio of treatment (combination of paracetamol and imatinib) to control (paracetamol monotherapy); CI: confidence interval; NA: not available.

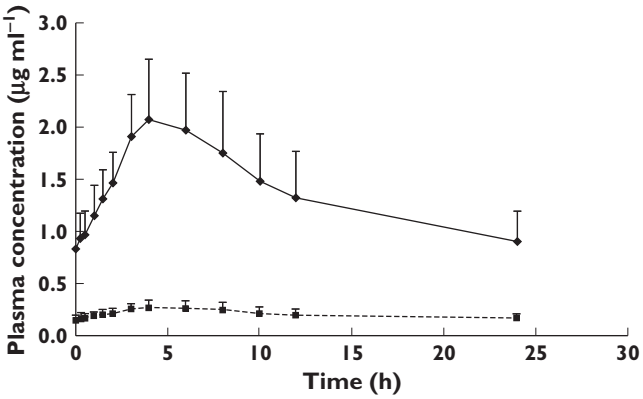

Figure 4

Mean (+SD) plasma concentration–time profiles of imatinib and its metabolite (CGP74588) on day 8 in patients with CML (n = 12). Imatinib (–◆–); CGP74588 (–■–)

were 16 h, 13 l h^{-1} and 306 l, respectively. The ratios of metabolite (CGP74588) to imatinib C_{max}, C_{min} and AUC(0,24 h) were 0.14, 0.21 and 0.16, respectively.

Safety and tolerability

Co-administration of imatinib 400 mg once daily for 8 days and a single dose of paracetamol 1000 mg on day 8 was well tolerated, and no clinically significant changes in laboratory parameters, vital signs or electrocardiogram (ECG) were observed. The safety profiles on day 8 were similar to those on day 1 when only a single 1000 mg dose of paracetamol was administered.

Discussion

The purpose of the present drug–drug interaction study was to examine the effect of imatinib on the pharmacokinetics of paracetamol in Korean patients with CML. The similar plasma AUC values of paracetamol, paracetamol glucuronide and paracetamol sulphate in the presence and absence of imatinib suggest that imatinib has no clinically significant effects on the metabolism of paracetamol. In addition, the similar urinary F_{ren} values of paracetamol, paracetamol glucuronide and paracetamol sulphate in the presence and absence of imatinib further support a lack of effect on the pharmacokinetics of paracetamol by imatinib. These F_{ren} values are similar to those found by Haderslev *et al.* [14]. The geometric mean ratio of C_{max} for paracetamol was not within the equivalence limits because of the large variability in C_{max} values (~45% coefficient of variation) in these patients. However, the 90% CI

Table 3

Mean (±SD) pharmacokinetic parameters of imatinib and its metabolite (CGP74588) on day 8 in patients with CML ($n = 12$) after once daily dose of 400 mg

Analyte	$AUC_{0-\tau}$ (μg ml^{-1} h)	C_{max} (μg ml^{-1})	t_{max} (h)*	C_{min} (μg ml^{-1})	V_z/F (l)	CL/F (l h^{-1})	$t_{1/2,z}$ (h)
Imatinib	33 ± 9.2	2.2 ± 0.55	4 (1, 6)	0.91 ± 0.29	306 ± 93	13 ± 3.8	16 ± 3.8
CGP74588	5.0 ± 1.5	0.29 ± 0.081	4 (0.5, 8)	0.17 ± 0.046	NA	NA	NA
MR	0.16 ± 0.028	0.14 ± 0.020	NA	0.21 ± 0.046	NA	NA	NA

*Values are expressed as medians (ranges). $AUC_{0-\tau}$, area under the plasma concentration–time curve from time 0 to 24 h; C_{max}, maximum plasma concentration after administration; t_{max}, time to reach C_{max}; C_{min}, minimum plasma concentration after administration; V_z/F, oral volume of distribution; CL/F, oral clearance; $t_{1/2,z}$, terminal half-life; MR, metabolite ratio of CGP74588 to imatinib adjusted for the molecular weight of the molecules; NA, not available.

for the geometric mean ratio of C_{max} included 1, suggesting a similarity in C_{max} between the two treatment groups. Co-administration of a single dose of paracetamol 1000 mg and imatinib 400 mg once daily was well tolerated, with no changes in laboratory and safety profiles, suggesting no relevant clinical effect on the safety of paracetamol by imatinib. Moreover, the management of CML in the patients in this clinical trial was unaffected by paracetamol administration.

Previous population pharmacokinetic data of imatinib supported that race does not appreciably impact on the pharmacokinetics of imatinib [3]. The mean (±SD) plasma C_{max} and AUC values of imatinib in Korean patients with CML in this study (2.2 ± 0.6 μg ml^{-1} and 33 ± 9.2 μg ml^{-1} h, respectively) were comparable with those reported in white patients with CML at the same dose level (400 mg once daily) from the phase 1 study [4] (2.6 ± 0.8 μg ml^{-1} and 40 ± 16 μg ml^{-1} h, respectively) considering the variability of the data. Similarly, the mean $t_{1/2,z}$, CL/F and V_z/F values of imatinib in Korean patients with CML (16 ± 4 h, 13 ± 4 l h^{-1} and 306 ± 93 l, respectively) were similar to those in white patients with CML [4] at steady state (19 ± 4 h, 11 ± 4 l h^{-1} and 295 ± 63 l, respectively). The ratios of metabolite to parent drug for $AUC_{0-\tau}$, C_{max} and C_{min} were 0.16, 0.14 and 0.21, respectively, which were similar to those of previous imatinib studies [21, 22]. Taken together, these data suggest that the pharmacokinetics of imatinib are similar between Korean and white patients with CML. There was no evidence of an effect on the pharmacokinetics of imatinib by a single dose of paracetamol.

The pharmacokinetics of paracetamol have been well studied in different countries and ethnic populations. The CL/F of paracetamol (21 l h^{-1} or 0.29 l h^{-1} kg^{-1} for a 73 kg adult) in Korean patients in the present study was similar to that in Chinese populations in Asia, which ranged from 0.27 l h^{-1} kg^{-1} to 0.32 l h^{-1} kg^{-1} [23, 24]. It is also close to that of some white populations in the United States, Australia, Denmark and the United Kingdom, which ranged from 0.28 to 0.37 l h^{-1} kg^{-1} [14, 25–27]. Although the plasma clearance of paracetamol can be affected by environmental factors [28] and age [29], Osborne *et al*. [26] found no difference in the pharmacokinetics of paracetamol between Australian Chinese and Australian whites. Thus, the lack of an effect on the pharmacokinetics of paracetamol by imatinib observed in Korean patients with CML may serve as indirect guidance for other racial CML populations.

The present study showed that imatinib 400 mg once daily had no effect on paracetamol plasma exposure and its disposition. This finding is consistent with what is expected on the basis of peak plasma concentrations of imatinib achieved (2.2 μg ml^{-1} or 4.5 μM) and the reported *in vitro* K_i value (59 μM). Based on the equation below [30] with a fraction metabolized (f_m) value of 0.6 for paracetamol glucuronidation, the predicted AUC with inhibitor (AUC_i) : AUC ratio for paracetamol will be 1.04, or a minimal 4% increase, which is well within the variability of the study results.

$$\frac{AUC_i}{AUC} = \frac{1}{\frac{f_m}{1+[I]/K_i} + (1-f_m)} \quad (1)$$

Even at the higher recommended dose level of 800 mg daily, the predicted extent of interaction between imatinib and paracetamol would be minimal. Assuming a linear dose–exposure relationship for imatinib [4] and a C_{max} of ~9 μM for imatinib, the estimated AUC_i : AUC ratio for paracetamol would only be 1.09 (9% increase) at a daily dose of 800 mg imatinib, which is unlikely to be clinically relevant and is well within the variability of the study results.

In conclusion, imatinib had no clinically relevant effect on the plasma exposure or pharmacokinetics of paracetamol in patients with CML. The pharmacokinetics of imatinib in Korean patients were similar to those observed in white patients. These data suggest that no dose adjustment for paracetamol or imatinib will be necessary if the two drugs are co-administered.

Competing Interests

DK is the principal investigator of the study, and SP is the Clinical Trial Manager of Seoul St. Mary's Hospital, Korea. ET, YW, HS, YJ, ED, and MH are employees of Novartis Pharmaceuticals Corporation.

Financial support for this study was provided by Novartis Pharmaceuticals Corporation. The authors would like to thank Camille Pierre Granvil, PhD and Beth Burke, PhD for their medical editorial assistance with this manuscript.

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