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Calcium carbonate does not affect imatinib pharmacokinetics in healthy volunteers

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Abstract

Purpose—Imatinib mesylate (Gleevec®/Glivec®), has revolutionized the treatment of chronic myeloid leukemias (CML) and gastrointestinal stromal tumors (GIST), and there is evidence for an exposure response relationship. Calcium carbonate is increasingly used as a calcium supplement and in the setting of gastric upset associated with imatinib therapy. Calcium carbonate could conceivably elevate gastric pH and complex imatinib, thereby influencing imatinib absorption and exposure. We aimed to evaluate whether use of calcium carbonate has a significant effect on imatinib pharmacokinetics.

Methods—Eleven healthy subjects were enrolled in a 2-period, open-label, single-institution, randomized cross-over, fixed-schedule study. In one period, each subject received 400 mg of imatinib p.o.. In the other period, 4000 mg calcium carbonate (Tums Ultra®) was administered p.o. 15 min before 400 mg of imatinib. Plasma concentrations of imatinib and its active N-desmethyl metabolite CGP74588 were assayed by LC-MS; data were analyzed non-compartmentally, and compared after log transformation.

Results—Calcium carbonate administration did not significantly affect the imatinib area under the plasma concentration *versus* time curve (AUC) (41.2 µg/mL•h alone *versus* 40.8 µg/mL•h with calcium carbonate, *P*=0.99), maximum plasma concentration (*C*_{max}) (2.35 µg/mL alone *versus* 2.39 µg/mL with calcium carbonate, *P*=0.89).

Conclusions—Our results indicate that the use of calcium carbonate does not significantly affect imatinib pharmacokinetics.

Keywords

imatinib; calcium; CML; GIST; interaction

Introduction

Imatinib mesylate (Gleevec®, Glivec®) is widely used to treat chronic myeloid leukemias (CML) based on its inhibition of Bcr-Abl – the tyrosine kinase encoded by the Philadelphia Chromosome created by reciprocal translocation between chromosome 9 and 22 - and to treat gastrointestinal stromal tumors (GIST) based on its inhibition of c-KIT [3,5,6]. Common side-effects of imatinib therapy include dyspepsia (18%) and nausea (43%) [6], for which patients may self-administer over-the-counter remedies, including calcium carbonate. In addition, nearly a quarter of the population over age 20 has been reported to use calcium supplements, a number that is expected to continue to rise in parallel with the number of older adults at risk for osteoporosis [9,11]. Calcium carbonate may alter the pharmacokinetics (PK) of imatinib as it can: 1) increase the pH of the stomach content; 2) delay gastric emptying; and 3) supply calcium ions capable of forming non-absorbable complexes (e.g. as occurs with tetracycline antibiotics). Consequently, the absorption of imatinib may be decreased by calcium salts taken for either gastric upset or calcium supplementation, resulting in sub-therapeutic concentrations of imatinib, potentially leading to selection of resistant subclones and ultimately relapse.

Although prospective, confirmatory studies are lacking, there is evidence that imatinib trough levels are associated with clinical benefit in patients with advanced GIST and with response in patients with CML [8,4]. Therefore, it is important to document if coadministration compromises absorption and/or exposure in subjects, which likely would lead to a reduction in efficacy.

Methods

Subjects

This pharmacokinetic study aimed to enroll up to 20 subjects for a maximum of 12 evaluable healthy subjects (6 men, 6 women; 18 years of age; body mass index (BMI) < 31 kg/m²). Subjects signed an informed consent that had been approved by the University of Pittsburgh Institutional Review Board. This trial was listed on [ClinicalTrials.gov](https://clinicaltrials.gov) under identifier NCT00732784. Exclusion criteria were defined as follows and applied when considered clinically significant: abnormal bone marrow function (defined as leucocyte, neutrophil, or platelet counts outside the limits of the institution's normal ranges); renal dysfunction (proteinuria, estimated creatinine clearance < 60 mL/min/1.73 m²); impaired hepatic function (liver enzymes or bilirubin > the normal upper limit); pregnancy or breast-feeding; use of any medications (including over-the-counter products, herbal products or mineral supplements) within two weeks of start of the study, or an investigational new drug within 28 days of start of the study. Daily multivitamin preparations or oral contraceptives (for women) were allowed.

Study design

The study followed a 2-period, open-label, randomized cross-over, fixed-sequence design, and was powered at an effect size of 1.3 to detect a 13% difference in imatinib AUC with 80% power and a 5% type I error, assuming a within-subject variability of approximately 10%. In one period, each subject received 400 mg of imatinib (Gleevec®; Novartis Pharmaceuticals Corp, East Hanover, NJ) p.o. with 200 mL of water, while in the other period, 4000 mg of calcium carbonate (Tums Ultra 1000®) were administered p.o. 15 min prior to the imatinib dose. The two imatinib doses were separated by a wash-out of at least 14 days.

Pharmacokinetic sampling and bioanalysis

Subjects were asked to fast starting midnight before dosing and were given a normal diet on the first day of pharmacokinetic sampling. Venous blood samples (N=12 per subject, 6 mL each) were drawn into heparinized Vacutainer™ tubes before and at 0.5, 1, 2, 3, 4, 5, 6, 8, 24, 48, and 72 h after imatinib administration. Blood samples were centrifuged at 4 °C, 3000 × g for 10 min, and the resulting plasma was aspirated and stored at –20 °C or colder until quantitative analysis.

Plasma samples were analyzed for concentrations of imatinib and its active N-desmethyl metabolite (CGP74588) using a previously reported LC-MS method [10,7], which is linear over the range of 10 - 1,000 ng/mL, and exhibited acceptable performance (imatinib: accuracy 13.1-9.8%; precision <6.8% CV; CGP74588: accuracy 5.3-6.7%; precision <15.0% CV).

Pharm acokinetic data analysis

The pharmacokinetic parameters of imatinib and its equipotent metabolite CGP74588 were determined by standard non-compartmental methods, with PK Solutions 2.0 (Summit Research Services, Montrose, CO; www.summitPK.com). The maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (t_{max}) were determined by visual inspection of the plasma concentration *versus* time data. The imatinib elimination rate constant (k_e) was obtained using non-linear least-square regression of the terminal concentration *versus* time data. The imatinib area under the concentration *versus* time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity ($AUC_{0-\infty}$). The percentage of $AUC_{0-\infty}$ extrapolated beyond the last sample time (C_{last}) was calculated. Ideally, the percentage extrapolated is <20%.

Statistical analysis

Whether or not calcium carbonate had a significant effect on the pharmacokinetics of imatinib was determined with SPSS 21.0 for Windows (SPSS Inc., Chicago, IL). T_{max} was compared non-parametrically with the two-tailed exact Wilcoxon signed rank test (paired data). All other pharmacokinetic parameters were compared by paired t-test after log transformation. Data were considered significantly different when $p < 0.05$.

An analysis of bioequivalence was performed by calculating the 90% confidence intervals of the imatinib AUC ratio and the C_{max} ratio, based on log-transformed data. Equivalence limits were 80-125% as defined previously [2].

Results

Twenty subjects were enrolled to obtain 11 evaluable subjects with complete data sets. Reasons for subjects to fail screening included: elevated AST/ALT; BMI>31 kg/m²; symptomatic urinary tract infection, hypertension, and high urine glucose. Adverse events likely related to imatinib included dyspepsia (grade 2, N=1; grade 1, N=2), and nausea (grade 1, N=1).

The pharmacokinetic parameter estimates for imatinib are shown in Table 1. The percentage of the AUC extrapolated beyond C_{last} was <8.2% for imatinib, providing confidence in the AUC_{0-inf} values generated. Concentration *versus* time curves of imatinib and CGP74588 in the presence and absence of calcium carbonate, respectively, are shown in Fig. 1a.

Coadministration of calcium carbonate with imatinib did not result in statistically significant difference in imatinib plasma AUC_{0-inf} ($P = 0.99$) or C_{max} ($P = 0.89$). The 90% confidence

intervals of the imatinib AUC ratio (mean 1.00, 90% confidence interval 0.89-1.13) and the $C_{\max}$ ratio (mean 1.01, 90% confidence interval 0.90-1.13), both fall well within the limits set for bioequivalence [2]. None of the other pharmacokinetic parameters for imatinib or CGP74588 were significantly affected by calcium carbonate (Table 1 and Fig. 1).

Discussion

This healthy volunteer study demonstrates that the use of calcium carbonate is not associated with a significant change in the pharmacokinetics of imatinib or its metabolite. Our result of no interaction is similar to results when imatinib was coadministered with a Mg^{2+} - Al^{3+} -based antacid [10], or when nilotinib was co-administered with calcium carbonate (submitted). However, they are in contrast to data demonstrating that proton pump inhibitor use is associated with a nearly two-fold decrease in dasatinib AUC and $C_{\max}$ [1], a 27% decrease in nilotinib $C_{\max}$ and a 34% decrease in nilotinib AUC [12]. Based on our results, a transient elevation in gastric pH, such as occurs with calcium carbonate, and an abundance of calcium ions available for complexation, does not appear to limit imatinib absorption.

This study was not powered for bioequivalence, however, the 90% confidence interval of the log-transformed ratios of imatinib AUC and $C_{\max}$ fell within the bioequivalence limits, suggesting that the two modes of administration are equivalent.

Cancer patients are increasingly being treated with oral agents, often tyrosine kinase inhibitors (TKI) such as imatinib. The potential polypharmacy resulting from concomitant therapy with prescription or over-the-counter medications poses new challenges that need to be addressed. Novel oral anticancer agents such as TKI are generally not curative, are administered chronically, and there have been numerous reports of exposure response relationships. In particular for imatinib, there is evidence that trough plasma concentrations are associated with clinical benefit in patients with advanced GIST and with response in patients with CML [8,4]. . Therefore, drug-drug interactions are likely to significantly impact the outcomes of therapy, and systematic evaluations of such interactions are critical. Both underexposure resulting in therapeutic failure, and overexposure resulting in toxicity may be caused by seemingly harmless drug combinations.

In conclusion, our results show that concomitant administration of the calcium carbonate is not associated with alterations in imatinib pharmacokinetics.

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Fig. 1.

(a) Mean ($\pm$ standard deviation) concentration versus time profile of imatinib (circles) and CGP74588 (squares) after p.o. administration of 400 mg imatinib without calcium carbonate (solid) and with calcium carbonate (open) to eleven healthy volunteers; intra-individual changes of imatinib (b, d, f, and h) and CGP74588 (c, e, g, and i) AUC (b and c), C_{max} (d and e), T_{max} (f and g), and half-life (h and i) when p.o. imatinib was co-administered with calcium carbonate in eleven healthy volunteers

Table 1

Pharmacokinetic parameter estimates for imatinib and N-desmethyl-imatinib (CGP74588) after p.o. administration of imatinib alone and with co-administration of calcium carbonate (N = 11).

Analyte	Arm	AUC _{0-inf} (μg/mL·h)	C _{max} (μg/mL)	T _{max} (h)	t _{1/2} (h)	V _{ss/F} (L)	Cl/F (L/h)
Imatinib	Alone	41.2 (11.8)	2.35 (0.59)	2.5 (0.7)	14.3 (3.7)	179 (54)	10.5 (3.1)
	+ CaCO ₃	40.8 (9.4)	2.39 (0.62)	2.4 (1.1)	13.4 (2.0)	176 (55)	10.4 (2.9)
p-value		0.99	0.89	0.83	0.24	0.75	0.99
CGP74588	Alone	8.11 (2.98)	0.321 (0.078)	2.6 (1.0)	32.0 (11.9)	2219 (1007)	56.9 (26.5)
	+ CaCO ₃	8.47 (2.26)	0.349 (0.100)	2.4 (0.9)	31.2 (7.4)	2018 (831)	51.0 (16.4)
p-value		0.43	0.43	0.62	0.98	0.32	0.43

The data are expressed as mean (standard deviation).

The percentage of the AUC_{0-∞} extrapolated beyond C_{last} was <8.2% for imatinib and <42% for CGP74588.

p-values were obtained by non-parametric analysis of the pharmacokinetic parameters with the two-tailed exact Wilcoxon signed rank test (paired data).