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Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor

Charles E. Frost,[1] Wonkyung Byon,[2] Yan Song,[1] Jessie Wang,[1] Alan E. Schuster,[1] Rebecca A. Boyd,[3] Donglu Zhang,[1†] Zhigang Yu,[1] Clapton Dias,[1] Andrew Shenker[1*] & Frank LaCreta[1]

[1]Bristol-Myers Squibb, Princeton, New Jersey, [2]Pfizer Inc, Groton, Connecticut and [3]Pfizer Inc, New York, New York, USA

Correspondence
Dr Charles E. Frost PharmD, Discovery Medicine and Clinical Pharmacology, Bristol-Myers Squibb Company, Mail Stop E12-16, Route 206 and Province Line Road, Princeton, NJ 08543-4000, USA.
Tel.: +1 609 252 3552
Fax: +1 609 252 6313
E-mail: charles.frost@bms.com

*Currently employed at GlaxoSmithKline, King of Prussia, Pennsylvania, USA.
†Currently employed at Genentech, South San Francisco, California, USA.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Modulation of cytochrome P450 (CYP) metabolism or P-glycoprotein (P-gp)-mediated drug transport by co-administered drugs, herbal remedies or certain foods can cause clinically significant pharmacokinetic and pharmacodynamic effects.
- Apixaban biotransformation occurs predominantly through oxidative metabolism via CYP3A4, although apixaban itself is neither an inducer nor an inhibitor of CYP enzymes.

WHAT THIS STUDY ADDS

- Co-administration of ketoconazole, a strong inhibitor of CYP3A4 and P-gp, or diltiazem, a mechanism-based inhibitor of CYP3A4 and an inhibitor of P-gp, resulted in a ≤ 2-fold increase in apixaban exposure compared with apixaban alone.

AIM

Apixaban is an orally active inhibitor of coagulation factor Xa and is eliminated by multiple pathways, including renal and non-renal elimination. Non-renal elimination pathways consist of metabolism by cytochrome P450 (CYP) enzymes, primarily CYP3A4, as well as direct intestinal excretion. Two single sequence studies evaluated the effect of ketoconazole (a strong dual inhibitor of CYP3A4 and P-glycoprotein [P-gp]) and diltiazem (a moderate CYP3A4 inhibitor and a P-gp inhibitor) on apixaban pharmacokinetics in healthy subjects.

METHOD

In the ketoconazole study, 18 subjects received apixaban 10 mg on days 1 and 7, and ketoconazole 400 mg once daily on days 4–9. In the diltiazem study, 18 subjects received apixaban 10 mg on days 1 and 11 and diltiazem 360 mg once daily on days 4–13.

RESULTS

Apixaban maximum plasma concentration and area under the plasma concentration–time curve extrapolated to infinity increased by 62% (90% confidence interval [CI], 47, 78%) and 99% (90% CI, 81, 118%), respectively, with co-administration of ketoconazole, and by 31% (90% CI, 16, 49%) and 40% (90% CI, 23, 59%), respectively, with diltiazem.

CONCLUSION

A 2-fold and 1.4-fold increase in apixaban exposure was observed with co-administration of ketoconazole and diltiazem, respectively.

Introduction

The coagulation factor Xa plays a pivotal role in the clotting cascade by prompting the conversion of prothrombin to thrombin, making factor Xa an important potential drug target for anticoagulation [1]. Apixaban is an orally active, selective inhibitor of factor Xa [2, 3] that is approved in a number of countries to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation [4, 5], for thromboprophylaxis in patients who have undergone elective hip or knee replacement surgery [6–8] and for the treatment of venous thromboembolism, including deep vein thrombosis and pulmonary embolism [9, 10].

Anticoagulants, including vitamin K antagonists and low molecular weight heparins, are associated with a risk of bleeding and require careful monitoring for signs and symptoms of bleeding. For example, dosing of vitamin K antagonists, such as warfarin, requires ongoing monitoring of the international normalized ratio (INR) for dose adjustment [11, 12]. Warfarin is subject to clinically significant interactions with food and drugs and requires even more frequent INR monitoring when starting or stopping concomitant interacting drugs. While clinical trials have shown that apixaban can be safely and effectively administered as a fixed dose without routine pharmacologic monitoring [4–8, 10], apixaban also carries a potential increased risk of bleeding with increased exposure. Therefore, it is important to identify potential factors that could increase the exposure of apixaban.

Peak apixaban plasma concentration is reached approximately 3 h after oral administration in healthy subjects, with an average elimination half-life ($t_{1/2}$) of approximately 12 h [13, 14]. Apixaban has a bioavailability of approximately 50% [15, 16]. Based on *in vitro* findings using a bidirectional permeability assay of P-glycoprotein (P-gp)–mediated drug transport (MDR-1 transfected LLC-PK1 cell monolayers), apixaban is a substrate for P-gp [17]. Therefore, P-gp may play a role in limiting the oral bioavailability of apixaban through intestinal efflux [18].

Apixaban is eliminated by multiple pathways, including renal and non-renal elimination. Renal clearance approximates the glomerular filtration rate and accounts for approximately 27% of apixaban total systemic clearance [15, 16]. Non-renal elimination pathways consist of metabolism by cytochrome P450 (CYP) enzymes, with subsequent sulfation by sulfotransferases [19, 20], as well as biliary and possible direct intestinal excretion [21, 22]. Apixaban metabolites account for approximately 25% of recovered radioactivity [19, 23] and have no detectable pharmacological activity [24]. A series of experiments with human cDNA-expressed CYP enzymes and CYP chemical inhibitors demonstrated that the oxidative metabolism of apixaban is predominantly catalyzed by CYP3A4, with only minor contributions from other CYP enzymes including CYP1A2, 2C8, 2C9, 2C19 and 2J2 [20]. Sulfate conjugation is mediated primarily by SULT1A1 [24]. *In vitro* studies indicate that apixaban, at concentrations corresponding to those in human subjects, is neither an inducer nor an inhibitor of CYP3A4 or other P450 enzymes [24]. Thus, apixaban is unlikely to affect the CYP-mediated metabolism of other drugs. Furthermore, the multiple dose pharmacokinetics (PK) in human subjects is time independent, demonstrating that exposure to apixaban does not result in induction or inhibition of its own metabolism [13]. Thus, on the basis of these data, modulation of P-gp and/or CYP3A4 activity by other concomitant medication appears to present the greatest potential for drug interactions with apixaban.

CYP3A4 is the major CYP enzyme expressed in the human intestine [25] and liver [26, 27]. CYP3A4 is known to be involved in the metabolism of a wide variety of xenobiotic compounds, including many therapeutic drugs [28–31]. Drugs that are activated or eliminated by CYP3A4 metabolism can potentially have drug–drug interactions (DDI) with other therapies that may induce or inhibit CYP3A4, and these interactions may result in clinically significant PK effects. CYP3A4 modulators consist of prescription and non-prescription drugs as well as other xenobiotics found in certain herbal remedies and food products [32–34] and can also result in clinically significant effects on some substrates [35–38]. When evaluating the impact of CYP3A4 modulators, the functional association between the drug efflux transporter, P-gp, and CYP3A4 should also be considered, since some drugs modulate both systems as inhibitors or inducers [39], and the net effect of P-gp and CYP3A4 modulation could be greater than the impact of modulation of either pathway alone. For example, ketoconazole, widely used in DDI studies as a representative strong inhibitor of both CYP3A4 and P-gp, increases midazolam exposure by up to 16-fold [40, 41]. Diltiazem, a mechanism-based moderate inhibitor of CYP3A4 [42] and a P-gp inhibitor [41, 43, 44], increases midazolam exposure less than 5-fold [40].

Although a role for CYP3A4-mediated metabolism and P-gp-mediated transport has been shown for apixaban *in vitro*, clinical PK studies are necessary to determine the potential clinical impact of concomitant administration of CYP3A4 and P-gp modulators. This report presents data on the effect of CYP3A4 and P-gp inhibitors on apixaban PK. The first of the two studies described in this report (ketoconazole DDI study) investigated the interaction between ketoconazole 400 mg once daily dosed to steady-state and a single 10 mg dose of apixaban. To define further the potential for DDI between moderate CYP3A4 inhibitors and apixaban, effects of co-administered diltiazem (360 mg once daily) dosed to steady-state on the PK of a single 10 mg dose of apixaban were examined in the second study (diltiazem DDI study).

Methods

Patients and study design

These studies were open label, non-randomized, single sequence, crossover studies conducted in healthy subjects at the Bristol-Myers Squibb Clinical Research Center (Hamilton, New Jersey, USA). Non-smoking men and women, 18–45 years of age, with a body mass index of 18–30 kg m^{-2} were eligible for the studies. The main exclusion criteria included history of bleeding disorder, history of gastrointestinal disease or surgery that would interfere with absorption of study drug, use of any hormonal contraceptive within 3 months, use of any prescription drug or over-the-counter acid controller within 4 weeks and use of any other drug or dietary supplement known to increase the potential for bleeding within 2 weeks before dosing. Exclusion criteria in the diltiazem DDI study also included patients with a history of significant arrhythmia, sinus bradycardia, low blood pressure or orthostatic hypotension. The studies were conducted in accordance with the principles stated in the Declaration of Helsinki and were consistent with International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. The protocol and patient consent form for both studies were approved by the New England Institutional Review Board (Wellesley, Massachusetts, USA) prior to study start. All subjects provided informed, written consent prior to the initiation of any study specific procedures.

Treatments

Subjects in both studies were admitted to the study centre on the day before the first dose and remained there until study completion. A summary of the study design and treatment schedule for each study is shown in Figure 1.

Subjects in the ketoconazole DDI study received a single 10 mg tablet of apixaban on days 1 and 7. In addition, from days 4–9, subjects received 400 mg once daily of ketoconazole (Nizoral®, Sanofi-aventis, Bridgewater, New Jersey, USA). Subjects in the diltiazem DDI study received a single 10 mg tablet of apixaban on days 1 and 11. Once daily doses of diltiazem 360 mg (Cardizem® LA, Abbott Laboratories, North Chicago, Illinois, USA) were given on days 4–13. The 10 mg single dose of apixaban was chosen for both studies because it represented the high end of the dose range tested in phase III trials. Subjects in both studies were required to fast (except for water) from 10 h before until 4 h after apixaban administration. In addition, subjects fasted from 1 h before until 1 h after diltiazem dosing in the diltiazem DDI study. Subjects were not permitted to consume alcohol-containing beverages, grapefruit, grapefruit-containing products, citrus juices or other citrus-containing products, or caffeine-containing food or beverages from 3 days prior to the first dose until study discharge. After dosing a mouth check was performed to ensure that the subject had swallowed each dose.

Sample collection

Blood samples for PK analysis of apixaban were collected immediately pre-dose and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h after apixaban administration on days 1 and 7 in the ketoconazole DDI study, and on days 1 and 11 in the diltiazem DDI study. In the ketoconazole DDI study, blood samples for determining trough ketoconazole concentrations were collected immediately pre-dose on days 6–10, and in the diltiazem DDI study, pre-dose blood samples for determining trough diltiazem concentrations were collected on days 8–11. Blood and urine samples were collected over the course of both studies for routine clinical safety laboratory evaluations.

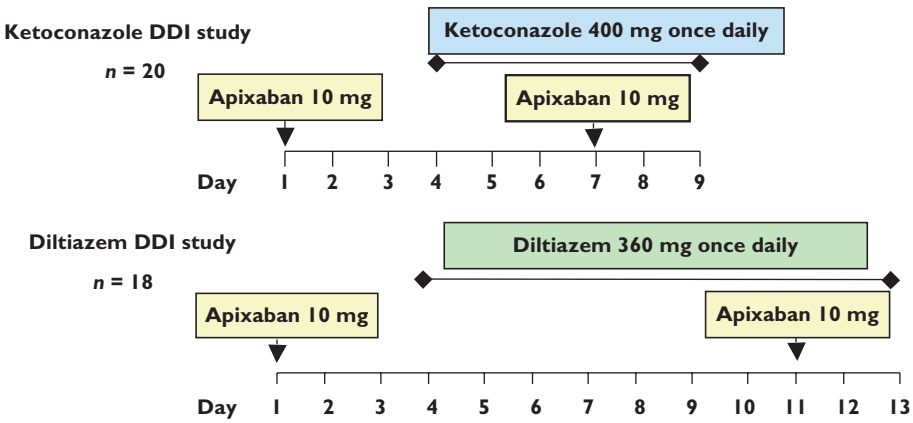

Figure 1

Study treatment schedules. Apixaban was administered as single doses on two occasions, ketoconazole and diltiazem as multiple daily doses for 6 and 10 days, respectively. DDI, drug–drug interaction

Sample analysis

Whole blood samples for apixaban PK analysis were collected into 4.5 ml sodium citrate tubes and centrifuged at 1000 *g* for 15 min to separate plasma. Samples of plasma were frozen at or below −20°C and shipped to the bioanalytical laboratory (Intertek Pharmaceutical Services [formerly known as Alta Analytical Laboratory], El Dorado Hills, California, USA). Apixaban concentrations were measured by a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LC-MS/MS) method using an acetonitrile protein precipitation extraction as the clean up step [45]. The standard curves were well fitted by a $1/\times^2$-weighted linear equation over the concentration range of 1 ng ml^{-1} to 1000 ng ml^{-1}. Values for the between-run and within-run precision for the analytical quality control samples of apixaban were ≤6.64% coefficient of variation (CV) and ≤5.55% CV, respectively, for the ketoconazole DDI study and ≤6.15% CV and ≤12.9% CV, respectively, for the diltiazem DDI study. The deviations from the nominal concentration were ± 7.50%.

Blood samples (6 ml) for ketoconazole analysis were collected in tubes with ethylenediaminetetra-acetic acid as anticoagulant, and centrifuged at 1000 *g* for 15 min to separate plasma. Plasma samples were frozen at or below −20°C and shipped to the bioanalytical laboratory (Tandem Labs, Inc., Salt Lake City, Utah, USA) for analysis by a validated LC-MS/MS method using a methanol protein precipitation extraction as the clean up step. Samples for diltiazem analysis were collected in a similar manner but with heparin as anticoagulant, and sent for analysis by a validated LC-MS/MS method (Vimta Labs, Andhra Pradesh, India) using Oasis HLB solid phase extraction as the clean up step. Values for the within-run precision for the analytical quality control samples were ≤4.5% CV for ketoconazole and ≤12.6% CV for diltiazem. The between-run precision for ketoconazole was not calculated because sample analysis was completed in one run. The between-run precision for the analytical quality control samples for diltiazem was ≤9.10% CV. The deviations from the nominal concentration were ± 5.3% and ± 4.2% for ketoconazole and diltiazem, respectively. Ketoconazole and diltiazem at concentrations of 950 ng ml^{-1} and 1 μg ml^{-1}, respectively, did not interfere with the analysis of apixaban.

Pharmacokinetic analysis

Single dose PK parameters were determined based on plasma concentrations over time. Maximum plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}) were recorded from experimental observations. Individual subject PK parameters were derived by non-compartmental methods using Kinetica version 4.2 (InnaPhase Corp., Philadelphia, Pennsylvania, USA). The area under the plasma concentration–time curve from time zero to the last quantifiable concentration [AUC(0,t_{last})] and extrapolated to infinity [AUC(0,∞)] were calculated using the log-linear trapezoidal method. The $t_{1/2}$ was estimated as $\ln 2/\lambda_z$, in which the slope of the terminal phase of the plasma concentration–time profile (λ_z) was determined by the least-squares method (log linear regression of at least three data points) with a weighting factor of 1.

Safety determinations

Adverse event (AE) data were obtained from information volunteered or solicited from subjects and from investigator review of vital signs, laboratory test results and electrocardiogram (ECG) data. All AEs were reviewed for severity, relation to study drugs and clinical importance. Any marked abnormalities in clinical laboratory test results were reviewed. Twelve-lead ECGs and physical examinations were performed at screening, baseline and before study discharge.

Statistical analyses

Statistical analyses were carried out using SAS/STAT® version 8.2 (SAS Institute, Cary, North Carolina, USA). Geometric means and CVs were presented for C_{max}, AUC(0,t_{last}) and AUC(0,∞), medians, minima and maxima were reported for t_{max} and means and SDs were reported for $t_{1/2}$. To assess the effect of concomitant administration of ketoconazole or diltiazem on the single dose PK parameters of apixaban, a general linear mixed model analysis was performed on ln(C_{max}), ln(AUC(0,t_{last})) and ln(AUC(0,∞)) to obtain point estimates and 90% confidence intervals (CIs) on ratios of apixaban C_{max}, AUC(0,t_{last}) and AUC(0,∞) geometric means with and without concomitant medication. A general linear mixed effects model was fitted to ln(C_{max}), ln(AUC(0,t_{last})) and ln(AUC(0,∞)). Factors in the model were treatment as fixed effect and measurements within subjects as repeated measures. Means and differences between means on a logarithmic scale were exponentiated to obtain point estimates and 90% CIs for the geometric ratios of apixaban C_{max}, AUC(0,t_{last}) and AUC(0,∞) with and without ketoconazole or diltiazem. No adjustments were made for multiplicity. Trough plasma concentrations of both ketoconazole and diltiazem were summarized by study day.

An absence of effect of ketoconazole or diltiazem on apixaban PK parameters would be concluded if the 90% CIs for the ratios of geometric means for apixaban C_{max} and AUC(0,∞) were contained within an 80–125% interval. On the basis of the observed variation between individual subjects in previous apixaban PK studies [14] and assuming log normal distributions of AUC(0,∞) and C_{max}, a sample size of 18 subjects was expected to provide greater than 90% power to conclude absence of an interaction. Twenty subjects were treated in the ketoconazole DDI study to allow for dropouts. Eighteen subjects were treated in the diltiazem study.

Results

Study populations

Eighteen of 20 subjects completed the ketoconazole DDI study. Two subjects discontinued the study prior to receiving all treatments. One subject discontinued the study due to an AE (rash) on day 1 after receiving a 10 mg dose of apixaban and one subject withdrew consent because of a family emergency. All 18 subjects in the diltiazem DDI study completed the study. Demographic characteristics of subjects are shown in Table 1.

Pharmacokinetic results

Mean plasma concentration–time profiles with and without co-administration of ketoconazole and diltiazem are shown in Figure 2A and B, respectively, and PK parameters are summarized in Table 2. Ketoconazole increased apixaban C_{max} by 62% and increased AUC(0,t_{last}) and AUC(0,∞) by 97% and 99%, respectively. The 90% CIs for C_{max} and AUC(0,∞) were not contained within the 80–125% interval and excluded the value of 100%, indicating the presence of a drug interaction. Although apixaban exposure increased with co-administration of ketoconazole, there was no change in median t_{max}. The mean $t_{1/2}$ of apixaban increased by 2.5 h (22%) following co-administration of ketoconazole. The geometric mean trough plasma concentrations of ketoconazole ranged from 173 ng ml^{-1} to 295 ng ml^{-1} on days 7–10.

Comparison of plasma concentration–time profiles and PK parameters showed that diltiazem also increased apixaban exposure (Figure 2B, Table 2). Concomitantly administered diltiazem increased apixaban C_{max} by 31% and AUC(0,t_{last}) and AUC(0,∞) by 39% and 40%, respectively, but had no effect on the t_{max} or $t_{1/2}$ of apixaban. The 90% CIs for C_{max} and AUC(0,∞) were not contained within the 80–125% interval and excluded the value of 100%, indicating the presence of a drug interaction. The geometric mean trough concentrations of diltiazem ranged from 125.0 ng ml^{-1} to 177.9 ng ml^{-1} on days 8–11.

Table 1

Subject demographics for the ketoconazole and diltiazem DDI studies

Characteristics		Ketoconazole (n = 20*)	Diltiazem (n = 18)
Gender, *n* (%)	Male	20 (100)	13 (72)
Age (years)	Mean (SD)	29 (6)	29 (7)
	Range	21–45	22–45
Race, *n* (%)	White	7 (35)	7 (39)
	Black	10 (50)	10 (56)
	Asian	3 (15)	1 (6)
Body weight (kg)	Mean (SD)	79 (11)	78 (16)
	Range	64–107	53–109
BMI (kg m^{-2})	Mean (SD)	25 (3)	26 (3)
	Range	20–30	21–30

*Eighteen subjects completed the study: one subject discontinued the study due to an adverse event (rash) and one subject withdrew consent because of a family emergency. BMI, body mass index; DDI, drug–drug interaction; SD, standard deviation.

Safety results

Adverse events reported in the studies were mild or moderate in intensity and all resolved without treatment. None was rated as serious. One subject discontinued the study due to an AE of a papular rash that lasted for 20 days beginning on day 8 in the ketoconazole DDI study. A total of 14 AEs occurred in six subjects during the ketoconazole DDI study and 34 AEs occurred in 10 subjects during the diltiazem DDI study. Headache was the most frequently reported AE in the ketoconazole DDI study (four subjects) and in the diltiazem DDI study (seven subjects). In addition, four subjects reported dizziness after taking diltiazem alone. Bleeding-related AEs occurred in one subject after receiving apixaban and ketoconazole (epistaxis) and in two subjects after receiving apixaban and diltiazem (subconjunctival haemorrhage and petechiae/contusions). All three events were considered mild and resolved without treatment.

Discussion

The data from these studies indicate that co-administration of apixaban with modulators of CYP3A4 and P-gp activity affect apixaban PK and that the extent of interaction is dependent on the strength of the modulator. Co-administration of apixaban with ketoconazole resulted in a 2-fold increase in apixaban AUC and a 1.6-fold increase in apixaban C_{max}. Diltiazem led to a 1.4- and 1.3-fold increase in apixaban AUC and C_{max}, respectively. Neither ketoconazole nor diltiazem impacted apixaban t_{max}. Apixaban $t_{1/2}$ was numerically longer by 2.5 h when administered in the presence of ketoconazole. This apparent small increase in apixaban $t_{1/2}$ is not expected to have a meaningful impact on the time to reach apixaban steady-state. Assuming that the volume of distribution of apixaban was not altered by ketoconazole or diltiazem, these data suggest that changes in systemic clearance are not solely responsible for the observed effects on apixaban exposure. The combination of increased C_{max} and AUC, and unchanged or slightly prolonged $t_{1/2}$, suggests that increased bioavailability also contributes to higher apixaban exposure, as would result from inhibition of intestinal/hepatic CYP3A4 metabolism and P-gp–mediated intestinal efflux.

Ketoconazole and diltiazem were administered to steady-state to ensure the maximum inhibition of CYP3A4 was achieved for each agent [46, 47]. The steady-state trough concentrations of ketoconazole and diltiazem observed in these studies were consistent with those previously reported in the literature [48, 49]. The effects of co-administered ketoconazole and diltiazem on the PK

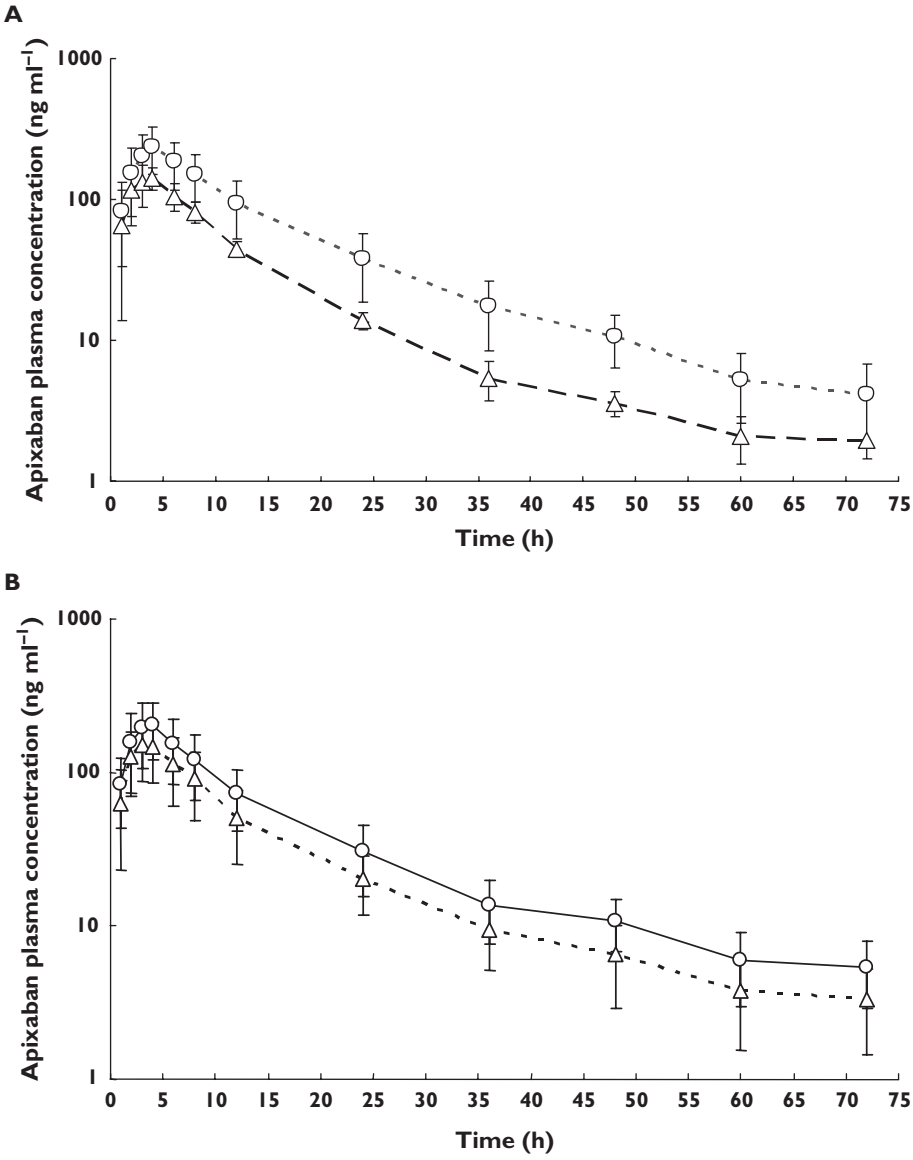

Figure 2

Mean plasma concentration–time profiles of apixaban (error bars show one standard deviation) in healthy subjects following a single 10 mg dose of apixaban alone or in the presence of multiple doses of (A) ketoconazole, -△-, apixaban 10 mg (n = 19); -○-, apixaban + ketoconazole 400 mg once daily (n = 18) and (B) diltiazem, -△-, apixaban 10 mg (n = 18); –○–, apixaban 10 mg + diltiazem 360 mg once daily (n = 18)

parameters of apixaban are likely to be representative of other drugs that inhibit CYP3A4 activity and/or P-gp [41]. The effect of ketoconazole on apixaban exposure in this study (a 2-fold increase in apixaban AUC) was much less than that reported in the literature for sensitive CYP3A4 substrates such as midazolam (15-fold increase) and simvastatin (12.5-fold increase) [48]. The results of the ketoconazole and diltiazem DDI studies demonstrate that moderate-to-strong CYP3A4/P-gp inhibitors increased apixaban exposure and they do not differentiate between the effects on CYP3A4 and P-gp. The doubling of apixaban exposure seen with concomitant ketoconazole likely represents the maximum potential for a DDI via combined inhibition of CYP3A4 metabolism and P-gp–mediated drug efflux (i.e. the increase in apixaban exposure with concomitant use of other strong inhibitors of CYP3A4 and/or P-gp is expected to be less than or generally comparable with that seen with ketoconazole) [50, 51].

The clinical relevance of an increase in apixaban exposure depends on the assessment of the benefit–risk profile within the patient population. Since apixaban is a direct reversible inhibitor of factor Xa, the primary concern with increases in exposure would be an increased risk of bleeding. The use of strong CYP3A4 inhibitors was prohibited in apixaban phase III clinical trials. Given the limited clinical experience with concomitant administration of apixaban

Table 2

Summary statistics for apixaban pharmacokinetics

Pharmacokinetic parameter*	Ketoconazole DDI study (n = 18) Apixaban	Apixaban + ketoconazole	Point estimate of RGM (90% CI)	Diltiazem DDI study (n = 18) Apixaban	Apixaban + diltiazem	Point estimate of RGM (90% CI)
C_{max} (ng ml^{-1})	139.5 (32) [80, 250]	225.3 (36) [103, 391]	1.62 (1.47, 1.78)	148.1 (38) [76, 304]	194.6 (41) [119, 463]	1.31 (1.16, 1.49)
AUC(0,t_{last}) (ng ml^{-1} h)	1490 (28) [818, 2165]	2939 (38) [1288, 5612]	1.97 (1.80, 2.16)	1779 (40) [892, 3574]	2475 (40) [1228, 5144]	1.39 (1.24, 1.56)
AUC(0,∞) (ng ml^{-1} h)	1523 (28) [846, 2229]	3027 (37) [1306, 5859]	1.99 (1.81, 2.18)	1897† (38) [941, 3589]	2606 (39) [1242, 5229]	1.40 (1.23, 1.59)
t_{max} (h)	4 (1, 4)	4 (3, 4)	–	3 (2, 8)	4 (2, 4)	–
$t_{1/2}$ (h)	11.3 (5.8) [4.6, 25]	13.8 (6.3) [5.6, 34]	–	17.2† (7.4) [8.6, 30]	16.3 (7.8) [5.6, 37]	–

*Geometric mean (%CV) [min, max] for C_{max}, AUC(0,t_{last}) and AUC(0,∞); median (min,max) for t_{max}; arithmetic mean (SD) [min, max] for $t_{1/2}$. †n = 17; in one subject AUC(0,∞) and $t_{1/2}$ could not be calculated. AUC(0,t_{last}), area under concentration–time curve from time zero to last quantifiable concentration; AUC(0,∞), area under concentration–time curve from time zero to infinity; CI, confidence interval; C_{max}, observed peak plasma concentration; CV, coefficient of variation; DDI, drug–drug interaction; RGM, ratio of geometric means estimated as concomitant treatment *vs.* apixaban alone; SD, standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time taken to reach C_{max}.

with strong inhibitors of CYP3A4 and P-gp, co-administration is generally not recommended [52, 53].

The use of moderate inhibitors of CYP3A4 and/or P-gp was allowed in phase III trials [4–8] and dose reduction is not necessary when apixaban is administered with moderate inhibitors of CYP3A4 and/or P-gp. However, caution is warranted in the presence of additional factors that increase apixaban exposure or that may pose an inherent risk of bleeding, such as significant renal impairment [52, 53].

In conclusion, a 2-fold and 1.4-fold increase in apixaban exposure was observed with co-administration of ketoconazole and diltiazem, respectively. The decision to administer apixaban in the presence of inhibitors of CYP3A4 and P-gp should follow apixaban approved product labelling.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: C.E. Frost, Y. Song, J. Wang, A.E. Schuster, D. Zhang, Z. Yu, C. Dias, A. Shenker and F. LaCreta were all employees of Bristol-Myers Squibb Company at time of the research and received salaries and benefits commensurate with employment; W. Byon and R.A. Boyd are employees of Pfizer Inc and receive salaries and benefits commensurate with employment.

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Contributors

C.E. Frost: Wrote manuscript, designed research, analyzed data; J. Wang: Designed research, analyzed data; A.E. Schuster: Analyzed data; Y. Song: Wrote manuscript; W. Byon: Wrote manuscript; R.A. Boyd: Wrote manuscript; D. Zhang: Performed research; Z. Yu: Wrote manuscript, designed research, analyzed data; C. Dias: Wrote manuscript, designed research, analyzed data; A. Shenker: Wrote manuscript, designed research, analyzed data; F. LaCreta: Wrote manuscript, designed research, analyzed data.

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