Pharmacokinetics of saquinavir co-administered with cimetidine

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The present study evaluated the effect of cimetidine, a histamine H2 receptor antagonist able to inhibit cytochrome P450 metabolism, on the steady-state pharmacokinetics of saquinavir soft gel. Twelve healthy volunteers (eight males and four females) participated in an open-label, double-phase pharmacokinetic study. Volunteers took saquinavir soft gel 1200 mg three times a day for 13 days and then saquinavir soft gel 1200 mg twice a day with cimetidine 400 mg twice a day from day 14 to 26. The pharmacokinetics of saquinavir on days 13 and 26 were compared. All 12 volunteers completed the study. The association of cimetidine with saquinavir soft gel 1200 mg twice a day resulted in a significant increase in saquinavir AUC0–24 (120%; P = 0.023) and Cmax (179%; P = 0.019), whereas Ctrough did not differ significantly (32% increase; P = 0.272). Increased exposure to saquinavir was observed in healthy volunteers after co-administration with cimetidine. The most significant increase involved Cmax. Further pharmacokinetic studies in HIV-infected subjects are warranted to confirm the boosting effect of cimetidine and to investigate any impact that the increase in saquinavir Cmax may have on intracellular accumulation of the drug.

Keywords: saquinavir, pharmacokinetics, cimetidine, protease inhibitors

Introduction

Combinations containing human immunodeficiency virus (HIV)-1 reverse transcriptase inhibitors and protease inhibitors have improved the therapeutic options for HIV disease and acquired immunodeficiency syndrome (AIDS), which has led to a significant decline in morbidity and mortality.1 In today’s clinical setting, protease inhibitor-containing regimens are typically administered as multiple oral doses throughout the day.

HIV-1 protease inhibitors undergo metabolism by cytochrome P450 (CYP450) in the gastrointestinal tract and liver and are subject to potentially significant drug–drug interactions.2 Co-administration with low dosages (100 or 200 mg) of ritonavir inhibits CYP450 3A4 metabolism and has been utilized as a strategy to enhance the pharmacological effects of concomitant protease inhibitors, which are primarily metabolized by this isoenzyme.2

In HIV clinical practice, enhanced protease inhibitor regimens have become the standard of care. Co-administration with low dosages of ritonavir is a pharmacokinetic strategy to increase the plasma concentration of concomitant protease inhibitors, which results in increased magnitude and durability of HIV suppression.3 For example, saquinavir boosted with ritonavir simplifies dosing schedules and increases saquinavir plasma concentrations.3

However, the use of ritonavir as a pharmacoenhancer has some drawbacks. First, the tolerability of ritonavir is still a problem in some HIV subjects, even when administered at very low dosages. The most common side effects are nausea and diarrhoea, observed in >40% of the patients on full-dosage ritonavir, and asthenia and circumoral paraesthesia, observed in >20% of the patients; long-term side effects such as body fat redistribution and metabolic abnormalities are also very common and serious.4 Secondly, no definitive data are available on the possible effect of low-dosage ritonavir in
terms of selective pressure on the HIV protease genome. Non-therapeutic plasma concentrations of ritonavir could be partly responsible for the development of resistance to protease inhibitors.

The histamine H₂ receptor antagonist cimetidine is a safe drug in clinical usage; severe adverse effects such as interstitial nephritis or granulocytopenia are extremely rare (1:100 000) and reversible, and milder side effects such as diarrhoea and dizziness seem to occur in 1% of the subjects on treatment. Cimetidine is rapidly absorbed after oral administration, and peak plasma concentrations are attained within 1 or 2 h. Cimetidine binds to the haem portion of the CYP450 complex, and this is responsible for several drug interactions, where inhibition of first pass metabolism and impairment of drug elimination occur. In humans, cimetidine inhibits CYP3A4, CYP2D6, CYP1A2 and probably other isoforms.

In view of the pharmacokinetic interactions that take place when saquinavir is co-administered with a CYP3A4 inhibitor, we conducted the present study to evaluate the pharmacokinetics of saquinavir soft gel (Fortovase) co-administered with cimetidine in order to explore whether other than ritonavir.

Materials and methods

Subjects

Twelve healthy volunteers who met the following criteria were enrolled in the study: aged 18 years or older; absence of any major medical illness during the month prior to enrolment; seronegativity for HIV, HBV or HCV; normal laboratory parameters; and absence of hypersusceptibility to the study drug. All subjects denied any other drug intake during the study period.

Study design and sample collection

This was an open-label, two-stage pharmacokinetic study carried out at a single site (Infectious Disease Department, University of Torino). Ethical approval was obtained from the local ethics committee, and all subjects signed a written informed consent at enrolment.

Subjects were initially administered saquinavir soft gel 1200 mg three times a day for 13 days. Intensive pharmacokinetic assessment of saquinavir plasma concentrations was carried out on day 13 before dosing and at 1, 2, 4, 8, 12 and 24 h after dosing. On day 13, subjects were administered saquinavir soft gel 1200 mg twice a day with cimetidine 400 mg twice a day. Saquinavir plasma concentrations were measured at the same times as before 13 days after switching (day 26). The study was conducted on an outpatient basis, and drug administration was carried out under staff supervision only on days 13 and 26. On these days, the sole morning drug dose was administered with a cup of whole milk and two butter croissants in order to facilitate the absorption of saquinavir.

Safety and tolerance were assessed by a written questionnaire.

Drug analysis

Blood (7 mL) was collected in heparinized tubes and centrifuged immediately (1851 g; 10 min). At each time-point, plasma was removed and stored at −20°C until analysis. Saquinavir plasma concentrations were measured using a fully validated HPLC/mass spectrometer system.

Data analysis

Saquinavir pharmacokinetic parameters were calculated with non-compartmental methods (TOPFIT computer software, version 2.0; Gustav Fischer Verlag, Stuttgart, Germany).

The highest observed plasma concentration was defined as $C_{\text{max}}$, with the corresponding sampling time as $T_{\text{max}}$. $C_{\text{trough}}$ was the concentration measured 8 h after saquinavir soft gel ingestion in the first study phase (days 1–13) and 12 h after saquinavir soft gel and cimetidine ingestion in the second study phase (days 14–26). AUC was calculated using the linear trapezoidal rule from 0 to 24 h. The study and associated analysis were designed to provide information suitable for possible therapeutic applications. $C_{\text{trough}}$ was measured after 8 h for saquinavir alone (administered three times a day) and after 12 h when the same dosage of saquinavir was co-administered with cimetidine. This provided an opportunity to compare the two regimens in their respective dosing schedules, as the latter are currently conceived in the absence and the presence, respectively, of a boosting agent.

Matched-pair analysis was carried out by the use of the Wilcoxon test. Two-sided $P$-values of $<0.05$ were considered to indicate statistical significance. Data were analysed using Statistica 4.5 software, version 6.0 (StatSoft, Tulsa, OK, USA). Results were summarized as median (range).

Results

Twelve subjects (eight males and four females; median age 31 years, range 24–42) were screened and enrolled in the study and all completed both study phases (saquinavir alone and saquinavir co-administered with cimetidine). The subjects’ weight ranged from 52 to 116 kg (median 63.5 kg). Saquinavir was well tolerated during both study phases. The most commonly reported side effects were mild and consisted of nausea (4/12), flatulence (5/12) and diarrhoea (5/12), which lasted only for the first few days of saquinavir intake.
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No substantial difference in side effects was observed between the two study phases.

Although marked inter-individual variability was observed in saquinavir AUC values (coefficients of variation were 102% for saquinavir alone and 76% for saquinavir co-administered with cimetidine; Figure 1), all but one subject showed an increase after co-administration with cimetidine. Median saquinavir AUC\(_{0-24}\) was increased by 120% after co-administration with cimetidine (\(P = 0.023\)). Median values on days 13 and 26 were 5.11 (0.56–25.96) and 11.23 (2.44–37.97) mg·h/L, respectively (Figure 2).

Median saquinavir \(C_{\text{max}}\) values were 0.69 (0.08–5.01) mg/L for saquinavir alone and 1.75 (0.85–6.79) mg/L for saquinavir co-administered with cimetidine, which resulted in a statistically significant increase in \(C_{\text{max}}\) of 179% (\(P = 0.019\); Figure 2). However, there was no statistical difference in median saquinavir \(C_{\text{trough}}\) values: 0.11 (0.02–0.78) mg/L for saquinavir alone and 0.14 (0.03–0.52) mg/L for saquinavir co-administered with cimetidine (increase of 32%; \(P = 0.272\)). No difference in the median elimination half-life was observed between the two study phases (4.2 versus 3.9 h).

Discussion

This study was designed to evaluate the impact of an alternative CYP3A4 inhibitor on saquinavir pharmacokinetics. The results show that co-administration with cimetidine resulted in higher exposure to saquinavir. However, although a large increase in saquinavir AUC was seen, there was only a small increase in \(C_{\text{trough}}\).

Cimetidine is a commonly prescribed \(H_2\) receptor antagonist able to bind to CYP450 and modify the metabolism of various drugs in humans through the inhibition of CYP3A4, CYP2D6 and CYP1A2.\(^6\)

Previously, median saquinavir AUC\(_{0-24}\) at steady state was shown to be 8.2 (3.8–45.1) mg·h/L after administration of saquinavir soft gel 1200 mg three times a day.\(^9\) In the present study, although adherence to saquinavir and cimetidine was high, food control was not carried out during the whole study but only on days 13 and 26, and this could be the reason for the wider range in saquinavir exposure: 8/12 subjects for saquinavir alone and 5/12 for saquinavir co-administered with cimetidine had a saquinavir \(C_{\text{trough}}\) lower than the suggested minimum effective concentration for HIV wild-type (0.13 mg/L).\(^7\)

Furthermore, when ritonavir was co-administered with saquinavir soft gel 800 mg twice a day, a 20-fold and a 9.6-fold increase in saquinavir AUC\(_{0-24}\) and \(C_{\text{max}}\), respectively, were observed.\(^9\) This shows that, compared with our
data, plasma concentrations of saquinavir are higher for co-administration with ritonavir than with cimetidine.

The lack of both a significant increase in saquinavir $C_{\text{trough}}$ after the addition of cimetidine and a difference in the elimination half-life between the two study phases suggests that the inhibitory effect is at the level of first pass metabolism rather than systemic elimination.

It should be noted, however, that target plasma concentrations of saquinavir have yet to be rigorously defined, and low plasma saquinavir $C_{\text{trough}}$ values were recently found to be associated with virological response. $^{10}$ Saquinavir $C_{\text{max}}$ values are significantly increased at steady state after co-administration with cimetidine, and this may favour higher intracellular accumulation, but interactions between cimetidine and saquinavir at the intracellular level remain unknown.

Today, the only agent employed for boosting protease inhibitors is ritonavir. However, its use is often associated with short- and long-term adverse effects, and the selection of ritonavir-resistant HIV strains due to prolonged exposure to low-dosage ritonavir cannot be excluded. Since no valid alternative protease inhibitor enhancer has been proposed so far, we deemed it important to investigate the effect of a drug without antiviral activity, such as cimetidine, on the pharmacokinetics of the protease inhibitor saquinavir. Since this study was carried out with healthy volunteers, the therapeutic relevance of the changes to saquinavir pharmacokinetics remains to be established. Therefore, the therapeutic impact of the higher $C_{\text{max}}$ and AUC achieved after saquinavir was co-administered with cimetidine should be verified in patients.

Acknowledgements

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References