Pharmacokinetic interaction between rifampicin and the once-daily combination of saquinavir and low-dose ritonavir in HIV-infected patients with tuberculosis

Esteban Ribera1*, Carlos Azuaje1, Rosa M. Lopez2, Pere Domingo3, Adria Curran1, Maria Feijoo1, Leonor Pou4, Paquita Sánchez5, Maria Antonia Sambeat3, Joan Colomer6, Josep Lluís Lopez-Colomes5, Manuel Crespo1, Vicenç Falcó1, Imma Ocaña1 and Albert Pahissa1

1Infectious Diseases Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 2Pharmacy Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 3Infectious Diseases Unit, Hospital de Sant Pau, Barcelona, Spain; 4Clinical Biochemistry Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 5Internal Medicine Department, Hospital del Mar, Barcelona, Spain; 6Internal Medicine Department, Hospital Santa Caterina, Girona, Spain

Received 22 May 2006; returned 14 September 2006; revised 22 November 2006; accepted 20 December 2006

Objectives: To assess plasma steady-state pharmacokinetics (PK) of rifampicin, isoniazid, saquinavir and ritonavir in HIV and tuberculosis (TB) co-infected patients, and investigate potential interactions between TB drugs and protease inhibitors (PIs).

Methods: Open-label, single-arm, sequential PK study including 22 patients with HIV infection and TB. During the first 2 months, patients received rifampicin, isoniazid and pyrazinamide, with or without ethambutol (first PK study, n = 22). Then patients stopped pyrazinamide and ethambutol and started once-daily antiretroviral therapy (ART) with didanosine, lamivudine, ritonavir (200 mg) and saquinavir (1600 mg) (second PK study, n = 18). Patients stopped all TB drugs after 9 months continuing the same ART (third PK study, n = 15). Differences between TB drug parameters in the first and second PK studies, and between PI parameters in the second and third PK studies were used to assess interactions.

Results: Rifampicin and isoniazid pharmacokinetics did not change substantially with saquinavir and ritonavir. A significant 39.5%, 34.9% and 48.7% reduction in median saquinavir AUC0–24, Cmax andCtrough, respectively, was seen with rifampicin and isoniazid. Ritonavir AUC0–24, Cmax andCtrough decreased 42.5%, 49.6% and 64.3%, respectively, with rifampicin and isoniazid.

Conclusions: There was a significant interaction between saquinavir, ritonavir and rifampicin, with reduction in median plasma concentrations of saquinavir and ritonavir. Saquinavir should be given with caution in patients receiving rifampicin. Twice-daily dosing or higher saquinavir doses in once-daily administration should be tested to obtain more appropriate plasma levels.

Keywords: protease inhibitors, antiretroviral therapy, HIV infection, tuberculosis therapy

Introduction

Tuberculosis (TB) remains one of the most important infections in HIV-infected individuals and the decline in its incidence seems to be smaller than for other opportunistic infections. In patients with TB and HIV co-infection, optimal management of the two diseases concurrently has been a challenge for HIV care providers.1 Active TB must be treated immediately and rifampicin is an essential drug. Treatment for HIV infection can be postponed on the basis of CD4 cell counts and the viral load. However, when CD4 count is less than 200–350 cells/mm³, delaying initiation of antiretroviral therapy (ART) until TB treatment is completed can be dangerous, leading to higher mortality and the appearance of opportunistic diseases.2

The main problem in simultaneous treatment of these two infections is the pharmacokinetic (PK) interaction produced...
between rifampicin and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs).\textsuperscript{1,2} Rifampicin is a strong inducer of the drug-metabolizing enzyme cytochrome P450 3A4 (CYP3A4) and the drug transporter P-glycoprotein in the liver and intestinal wall, and produces a significant decrease in plasma concentrations of the NNRTIs and PIs. Available PK data indicate that rifampicin can be combined with efavirenz\textsuperscript{4,5} or nevirapine,\textsuperscript{6} although it is still not clear whether the doses should be increased. Non-boosted PIs cannot be administered with rifampicin because of considerable decreases in plasma PI concentrations, leading to subtherapeutic concentrations of all of them except ritonavir.\textsuperscript{7,8} Ritonavir is a strong inhibitor of CYP3A4 and P-glycoprotein, and when it is co-administered with other PIs, an important increase in their plasma concentrations is achieved. Based on these facts, one can hypothesize whether the inducing effect of rifampicin on these enzymes could be overcome by the inhibitory effect of ritonavir. However, substantial decreases in plasma concentrations of indinavir,\textsuperscript{8} lopinavir\textsuperscript{9} and atazanavir\textsuperscript{10} have been observed when co-administered with rifampicin, even when small doses of ritonavir are given. The boosting effect of ritonavir varies with different PIs and a small study involving two patients has shown that co-administration of saquinavir and rifampicin is possible if combined with ritonavir.\textsuperscript{11}

Directly observed therapy and other adherence-promoting strategies are especially important in patients with HIV-related TB. Antiretroviral regimens administered once-daily make this treatment strategy possible in care structures that support therapy supervision, such as methadone-dispensing centres and day care clinics.\textsuperscript{12} Several trials have shown than a once-daily dosing regimen of saquinavir is feasible, even when combined with the CYP3A4-inducer efavirenz.\textsuperscript{13–16}

The purpose of our study was to evaluate the PK interaction between rifampicin and a once-daily regimen with saquinavir/ritonavir in patients with HIV infection and TB.

**Materials and methods**

**Study population and design**

Patients with HIV and TB infection included in a study on the treatment of both infections (TBQD study)\textsuperscript{17} were asked to participate in an intensive PK study. Briefly, the TBQD study was a single-arm, prospective, open-label study that assessed the efficacy of ART and anti-TB therapies in HIV-infected antiretroviral-naive patients with TB. The TB drug therapy was a 9 month regimen consisting of a triple or quadruple combination of rifampicin (600 mg/day), isoniazid (300 mg/day) and pyrazinamide (30 mg/kg/day), with or without ethambutol (25 mg/kg/day) for 2 months, followed by the same doses of rifampicin and isoniazid for another 7 months. Rifampicin and isoniazid were administered in a single commercial preparation (Rifinah\textsuperscript{10}, tablets containing 300 mg of rifampicin and 150 mg of isoniazid). During the first 2 months after the diagnosis of TB, patients were treated only with TB drugs. Then pyrazinamide and ethambutol were stopped, and the patients started once-daily ART consisting of didanosine enteric-coated capsules (400 mg or 250 mg when body weight was <60 kg), lamivudine (300 mg), ritonavir soft gel capsules (200 mg) and saquinavir soft gel capsules (1600 mg). Exclusion criteria for the study included concomitant use of other drugs known to interfere with PI pharmacokinetics, particularly azoles or macrolides.

In this PK substudy, patients undertook extra sampling in three PK sessions: the first during TB treatment before initiating ART, the second during administration of both treatments, and the third after completing the TB treatment. Twenty-six patients accepted to be enrolled in the study. Four of them were excluded before the first PK study because of drug changes due to rifampicin intolerance, self-reported poor adherence to the study medications or withdrawal of consent. Twenty-two patients were enrolled in the study.

The study protocol was approved by the institutional review boards of all the participating centres and informed consent was obtained from all patients.

**Blood collection and drug concentration assays**

Blood samples for the measurement of drug concentrations were collected after at least 30 days of TB therapy (for rifampicin and isoniazid, without PIs) (mean ± SD, 39 ± 8 days) in the first PK study, after at least 30 days of ART (for saquinavir, ritonavir, rifampicin and isoniazid) (46 ± 11 days) in the second PK study, and after at least 30 days of stopping anti-TB therapy (for saquinavir and ritonavir, without TB drugs) (61 ± 9 days) in the third PK study.

All subjects were instructed to take rifampicin, isoniazid and didanosine at 8:00 a.m. before breakfast, and the other anti-TB drugs (pyrazinamide and/or ethambutol) or antiretroviral drugs (saquinavir, ritonavir and lamivudine) at 9:00 a.m. with a standard breakfast, during the week before the day of intensive PK assessment of drug concentrations. On that day, patients came to the hospital at 7:40 a.m. after an overnight fast. All study drugs were administered at the hospital at the hours indicated. Administration of all the study medications, including rifampicin, isoniazid, saquinavir and ritonavir, was observed by an investigator on the day of PK evaluation. At the first PK session, blood samples were drawn before rifampicin/isoniazid dosing and at 1, 1.5, 2, 3, 4, 6, 8 and 12 h after dosing. At the second PK session, blood samples were drawn at 8:00 (before rifampicin/isoniazid dosing), 9:00 (before saquinavir/ritonavir dosing), 9:30, 10:00, 11:00, 12:00, 13:00, 14:00, 16:00, 20:00 and 21:00 h. At the third PK session, blood samples were drawn before saquinavir/ritonavir dosing and at 1, 2, 3, 4, 5, 7, 11 and 12 h post-dosing. All samples were centrifuged at 1500×g for 20 min and serum was stored at −80°C in semi-transparent Eppendorf tubes until assay.

Serum concentration–time data were analysed by non-parametrical methods. The area under the serum concentration–time curve from 0 to 24 h (AUC\textsubscript{0–24}) was calculated by using the trapezoidal rule in the Abbottbase Pharmacokinetic System (Abbott Laboratories, Abbott Park, IL, USA). The highest concentration of drug in serum (C\textsubscript{max}), with the corresponding sampling time (T\textsubscript{max}) and the concentration of drug in serum before the morning dose (C\textsubscript{ trough}), were determined directly from the concentration–time data. Total oral clearance (CL\textsubscript{oral}) was calculated by dividing the dose by the AUC\textsubscript{0–24}.

Serum rifampicin concentrations were determined by high-performance liquid chromatography (HPLC) using a modification of the method reported by Le Guellec \textit{et al.}\textsuperscript{18} Chromatographic separation was achieved with a short column (30 mm × 4.6 mm ID) packed with Perkin-Elmer C18, particle size 3 μm. Retention time was 2.1 min. Batch-to-batch precision and lower limit of quantification of the assay were 7.5% and 0.1 μg/mL, respectively. Serum isoniazid concentrations were determined by HPLC using a modification of the method
reported by Gupta and Lew.\textsuperscript{19} Chromatographic separation was achieved with a short column (40 \times 4.6 mm) packed with Nucleosil 120 C18, particle size 3 \( \mu \)m. The day-to-day imprecision at 2.5 \( \mu \)g/mL and 10 \( \mu \)g/mL was 7.9% and 5.2%, respectively. Assay sensitivity was 0.25 \( \mu \)g/mL.

Serum concentrations of saquinavir and ritonavir were simultaneously measured by a validated method developed in our laboratory, consisting of linear gradient reverse-phase ion-paired HPLC and UV detection at 240 nm, as previously described.\textsuperscript{20} Assay correlation coefficients exceeded 0.995. Mean recovery and accuracy were 98.7% and 105.0%, respectively, for saquinavir, and 97% and 106.7%, respectively, for ritonavir. Within-day and between-day variations of quality control samples in serum were less than 3.9% and 5.2%, respectively, for saquinavir, and 4.9% and 5.8%, respectively, for ritonavir. The lower limit of quantification was 0.025 \( \mu \)g/mL for saquinavir and ritonavir. The assay was linear up to concentrations of at least 10 \( \mu \)g/mL.

Statistical analysis

SPSS software for Windows (version 12.0; SPSS, Chicago, IL, USA) was used to perform the statistical analyses. All analyses were performed by non-parametric tests. For quantitative variables, the medians and interquartile ranges (IQR, 25th to 75th percentiles) were used as measures of central tendency and dispersion. For qualitative variables, the number of patients in each category and the corresponding percentages are given. The between-group characteristics were compared by the Mann–Whitney \( U \) test (unpaired variables) or Wilcoxon signed-rank test (paired variables, pair-wise comparison on changes in variables and the serum drug concentrations and PK parameters) for quantitative variables and the \( \chi^2 \) test for qualitative variables, with the continuity correction for the \( \chi^2 \) when a subgroup included five or fewer subjects. Correlations were analysed by Spearman's rank test. All statistical tests were two-tailed and were performed at a level of statistical significance of 0.05.

Results

Study population

A total of 22 patients were included in the first PK study, 18 patients in the second PK study and 15 patients in the third PK study. Four of the 22 initial patients did not participate in the second PK study for the following reasons: rifampicin was discontinued in two because of toxicity, one did not start ART and in the last ART was discontinued before the second PK study. Three of the 18 patients who underwent the second PK study did not participate in the third because of PI changes due to virological failure in two cases and adverse events in one case. Demographic and baseline characteristics of the patients enrolled in the study were as follows: 18 (82%) were male, median age 37.5 years (30.3–41.5), 9 (41%) injection drug users, 4 (18%) homosexual, 8 (36%) heterosexual, 1 (5%) blood transfusions, 5 (23%) had CDC C events before onset of TB, 2 (9%) were co-infected with HBV and 12 (55%) with HCV. Median HIV RNA (log\textsubscript{10} copies/mL) was 5.19 (4.86–5.9) and median CD4 cell count 117 cells/mm\textsuperscript{3} (47–218). Median body weight was 59.8 kg (53.6–73) and body mass index (BMI) 21 (19.3–23.3). In the second and third periods (with 18 and 15 patients) baseline characteristics did not change significantly except HIV RNA level which went down to 3.23 and 1.40 log\textsubscript{10} copies/mL, CD4 cell count which rose to 234 and 292 cells/mm\textsuperscript{3} and body weight increased 2 and 3.25 kg, respectively.

Pharmacokinetics of rifampicin and isoniazid

The median steady-state plasma concentration–time profiles of rifampicin and isoniazid during saquinavir/ritonavir therapy were similar to the profiles for the same patients before starting ART (Figure 1 and Table 1). There was no significant effect of co-administration of saquinavir and ritonavir on rifampicin AUC\textsubscript{24} (42.1 versus 44.9 \( \mu \)g.h/mL, \( P = 0.62 \)) or \( C_{\text{max}} \) (8.9 versus 9.7 \( \mu \)g/mL, \( P = 0.91 \)), or on isoniazid AUC\textsubscript{0–24} (25.1 versus 32.4 \( \mu \)g.h/mL, \( P = 0.37 \)) or \( C_{\text{max}} \) (5.3 versus 6.4 \( \mu \)g/mL, \( P = 0.54 \)).

![Figure 1](https://example.com/figure1.png)

\textbf{Figure 1.} Median steady-state rifampicin (a) and isoniazid (b) plasma concentration–time profiles with and without saquinavir/ritonavir (\( n = 18 \)). Error bars indicate interquartile ranges (25th and 75th percentiles). Open circles indicate drug concentrations without saquinavir/ritonavir. Filled circles indicate drug concentrations with saquinavir/ritonavir.
Rifampicin and saquinavir/ritonavir interactions

Table 1. Steady-state pharmacokinetic parameters of rifampicin (600 mg once daily) and isoniazid (300 mg once daily) in the absence or presence of saquinavir boosted with ritonavir

<table>
<thead>
<tr>
<th>Drug, parameter</th>
<th>Without saquinavir/ritonavir</th>
<th>With saquinavir/ritonavir</th>
<th>Ratio for with/without saquinavir/ritonavir (95% CI)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–24h&lt;/sub&gt;, μg·h/mL</td>
<td>42.1 (27.1–81.3)</td>
<td>44.9 (33.7–76.5)</td>
<td>1.01 (0.83–1.58)</td>
<td>0.62</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, μg/mL</td>
<td>8.9 (5.8–17.8)</td>
<td>9.7 (6.5–16)</td>
<td>1.05 (0.61–1.64)</td>
<td>0.91</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt;, μg/mL</td>
<td>&lt;0.1 (&lt;0.1–&lt;0.1)</td>
<td>&lt;0.1 (&lt;0.1–&lt;0.1)</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>1.75 (1.5–2.5)</td>
<td>2 (1.5–3.0)</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;, L/h</td>
<td>14.3 (7.9–20.7)</td>
<td>13.4 (6.7–19.4)</td>
<td>1.09 (0.79–2.19)</td>
<td>0.40</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–24&lt;/sub&gt;, μg·h/mL</td>
<td>25.1 (18.1–39)</td>
<td>32.4 (23.0–41.9)</td>
<td>1.13 (0.77–1.81)</td>
<td>0.37</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, μg/mL</td>
<td>5.3 (3.9–7.8)</td>
<td>6.4 (4.1–8.2)</td>
<td>1.14 (0.82–1.39)</td>
<td>0.54</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt;, μg/mL</td>
<td>&lt;0.25 (&lt;0.25–&lt;0.25)</td>
<td>&lt;0.25 (&lt;0.25–&lt;0.25)</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>1.0 (1.0–1.5)</td>
<td>1.5 (1.0–1.75)</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>CL&lt;sub&gt;tot&lt;/sub&gt;, L/h</td>
<td>9.5 (7.3–13.2)</td>
<td>12.7 (7.2–16.6)</td>
<td>1.08 (0.6–1.4)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Given with rifampicin, saquinavir C<sub>trough</sub> was <0.05 μg/mL and <0.10 μg/mL in 6 of 18 and in 12 of 18 patients, respectively. None of 15 patients showed saquinavir C<sub>trough</sub> <0.05 μg/mL after completing TB treatment. Ritonavir C<sub>trough</sub> was below the limit of quantification in almost all patients during and after TB treatment.

A significant positive linear correlation was observed between saquinavir and ritonavir AUC<sub>0–24</sub> before (r = 0.72, P < 0.001, Spearman test) and during ART (r = 0.56, P = 0.03, Spearman test). There was no significant correlation between plasma saquinavir or ritonavir plasma concentrations and the patients’ body weight or BMI, either before or during ART.

Relationship between pharmacokinetic parameters and clinical evolution

TB resolved in 21 of 22 patients included in the study, without relapses 6 months after completing the treatment. Low plasma rifampicin or isoniazid levels were not associated with poor evolution or recurrence of TB. The remaining patient presented with cerebral TB 2 months after completing the 9 months of TB treatment, with *Mycobacterium tuberculosis* susceptible to all the anti-TB drugs isolated from brain biopsy. Plasma rifampicin and isoniazid concentrations during treatment in this patient were within the therapeutic range.

Among the 18 patients in whom plasma saquinavir and ritonavir levels were determined during anti-TB treatment, six presented virological failure. There was a tendency to present higher plasma saquinavir concentrations in patients with a good therapeutic response than in patients with virological failure (median AUC<sub>0–24</sub> 19.2 versus 8.2 μg·h/mL, P = 0.06, median C<sub>max</sub> 3.01 versus 1.42, P = 0.15 μg/mL, median C<sub>trough</sub> 0.07 versus 0.03 μg/mL, P = 0.21). Four of 6 patients with saquinavir C<sub>trough</sub> <0.05 μg/mL and 2 of 12 patients with saquinavir

---

<sup>a</sup> Determined by the Wilcoxon signed rank test.

Data are median values (interquartile ranges), unless otherwise indicated.

AUC<sub>0–24</sub>, area under the serum concentration–time curve over the administration interval of 24 h; C<sub>max</sub>, maximum serum concentration; C<sub>trough</sub>, trough serum concentration; T<sub>max</sub>, time to reach C<sub>max</sub>; CL<sub>tot</sub>, total oral clearance.

---

Pharmacokinetics of saquinavir and ritonavir

The median steady-state plasma concentration–time profiles of saquinavir and ritonavir in the presence or absence of rifampicin/isoniazid are shown in Figure 2, and saquinavir and ritonavir PK parameters are summarized in Table 2. When combined with rifampicin/isoniazid, saquinavir and ritonavir plasma concentrations showed significant decreases. The median saquinavir AUC<sub>0–24</sub>, C<sub>max</sub> and C<sub>trough</sub> with rifampicin/isoniazid was 39.5% (IQR, 9.4–72.9%), 34.9% (IQR, 12.3–74.3%) and 48.7% (IQR, 36.3–66.7%) lower than without rifampicin/isoniazid therapy. The median ritonavir AUC<sub>0–24</sub>, C<sub>max</sub> and C<sub>trough</sub> with rifampicin/isoniazid was 42.5% (IQR, 27.2–65.4%), 49.6% (IQR, 27.4–72.6%) and 64.3% (IQR, 28.3–81.1%) lower than without rifampicin/isoniazid therapy.
trough /C21 0.05 g/mL during TB therapy had virological failure (P = 0.11). Five of 12 patients with saquinavir trough, 0.1 mg/mL and 1 of 6 patients with saquinavir trough/C21 0.1 mg/mL during TB therapy had virological failure (P = 0.60).

Safety
Two of the 26 patients asked to participate in the study stopped rifampicin due to adverse events before the first PK (one laboratory grade 3 hepatotoxicity, and one methadone withdrawal syndrome). Another 2 of 22 patients included in the study discontinued rifampicin due to adverse events before starting ART (one laboratory grade 3 hepatotoxicity, and one fever, rash and laboratory grade 2 hepatotoxicity).

Two patients discontinued saquinavir and ritonavir owing to adverse events. One patient presented with moderate diarrhoea and did not want to continue treatment. In the second patient PIs were discontinued because of an asymptomatic increase in transaminase levels (grade 3).

Table 2. Steady-state pharmacokinetic parameters of saquinavir (1600 mg once daily) and ritonavir (200 mg once daily) in the absence or presence of rifampicin and isoniazid

<table>
<thead>
<tr>
<th>Drug, parameter</th>
<th>Without rifampicin/isoniazid</th>
<th>With rifampicin/isoniazid</th>
<th>Ratio for with/without rifampicin/isoniazid (95% CI)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0–24, μg·h/mL</td>
<td>22.9 (13.9–36.5)</td>
<td>13.6 (8.6–23.4)</td>
<td>0.57 (0.27–0.96)</td>
<td>0.031</td>
</tr>
<tr>
<td>Cmax, μg/mL</td>
<td>3.3 (2.3–4.7)</td>
<td>2.1 (1.3–3.3)</td>
<td>0.72 (0.26–0.88)</td>
<td>0.047</td>
</tr>
<tr>
<td>Ctrough, μg/mL</td>
<td>0.14 (0.09–0.21)</td>
<td>0.06 (&lt;0.05–0.11)</td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>3.6 (3.0–5.0)</td>
<td>3.0 (3.0–6.0)</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>CLtot, L/h</td>
<td>66 (44–128)</td>
<td>118 (68–187)</td>
<td>1.90 (1.06–3.75)</td>
<td>0.041</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0–24, μg·h/mL</td>
<td>14.8 (11–26.2)</td>
<td>9.9 (8.1–10.9)</td>
<td>0.58 (0.29–0.77)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cmax, μg/mL</td>
<td>2.0 (1.6–3.7)</td>
<td>1.2 (0.97–1.85)</td>
<td>0.50 (0.26–0.91)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ctrough, μg/mL</td>
<td>0.14 (0.05–0.19)</td>
<td>&lt;0.05 (&lt;0.05–0.07)</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>4.8 (3.8–6.0)</td>
<td>4.5 (3.0–5.0)</td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>CLtot, L/h</td>
<td>13.9 (8.2–19.7)</td>
<td>22.7 (18.9–44.4)</td>
<td>1.73 (1.35–2.61)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are median values (interquartile ranges), unless otherwise indicated.

AUC0–24, area under the serum concentration–time curve over the administration interval of 24 h; Cmax, maximum serum concentration; Ctrough, trough serum concentration; Tmax, time to reach Cmax; CLtot, total oral clearance.

a Determined by the Wilcoxon signed rank test.
Rifampicin and saquinavir/ritonavir interactions

Discussion

The results of this study indicate that rifampicin and isoniazid have an induction effect on saquinavir disposition despite co-administration of 200 mg of ritonavir. The AUC_{0–24}, C_{max} and C_{trough} of saquinavir were 40%, 35% and 49% lower, respectively, when saquinavir and rifampicin were administered with rifampicin and isoniazid, as compared with the concentrations reached without anti-TB treatment. Plasma levels of ritonavir were also significantly lower with co-administration of anti-TB treatment.

The complex drug interactions that occur with concurrent administration of rifampicin and ritonavir-boosted PIs can be unpredictable and changes in the PK parameters may vary from one PI to another. An 87% reduction in the median indinavir C_{trough} with only a minor change in the C_{max} was seen when rifampicin (600 mg) was added to a combination of indinavir and ritonavir (800/100 mg) in six patients with HIV infection.6 When lopinavir/ritonavir (400/100 mg) was combined with rifampicin (600 mg) in 22 healthy subjects, the lopinavir AUC, C_{max} and C_{trough} were reduced 75%, 45% and 99%, respectively. Lopinavir concentrations increase considerably when more elevated doses of lopinavir/ritonavir (800/200 mg and 400/400 mg) are used in combination with rifampicin.9 However, the lopinavir C_{trough} in that study was not equivalent to the standard lopinavir/ritonavir dosing without rifampicin, and both regimens resulted in numerous gastrointestinal and hepatic adverse events. In a study of 71 HIV-uninfected subjects, co-administration of rifampicin with atazanavir and ritonavir (300/100 mg) produced a marked reduction in atazanavir exposure, with the drop again not being offset by an increase in the atazanavir and ritonavir doses to 400/200 mg.10 Therefore, rifampicin combined with ritonavir-boosted indinavir, atazanavir or lopinavir in the standard-dose regimen is contraindicated.

The drop in saquinavir concentrations produced in the present study with co-administration of rifampicin seems smaller than with ritonavir-boosted indinavir, lopinavir or atazanavir. Based on the magnitude of this drug–drug interaction, it is likely that ritonavir-boosted saquinavir can be administered concurrently with rifampicin. However, in the present study, the C_{trough} of saquinavir was <0.10 µg/mL in 12 of 18 patients and <0.05 µg/mL in 6 of 18 patients. To obtain optimum efficacy, saquinavir concentrations need to be increased. In this study the saquinavir C_{trough} target of 0.05 µg/mL seems to be more related to clinical failure than the 0.10 µg/mL target. The majority of clinical and PK analyses with once-daily boosted saquinavir in adults with HIV infection have evaluated saquinavir 1600 mg plus ritonavir 100 mg. With these doses, from 0% to 20% of patients had saquinavir C_{trough}<0.05 mg/mL. Saquinavir/ritonavir when dosed as 2000/100 mg once-daily or 1000/100 mg twice-daily achieved higher saquinavir plasma levels as compared with saquinavir/ritonavir 1600/100 mg once-daily, with good tolerance, and the majority of patients achieved trough concentrations above target values.21,22 It is likely that the 2000 mg saquinavir dose is more suitable than the 1600 mg dose for patients with or without TB, particularly now that the recently available saquinavir formulation in 500 mg tablets will considerably lower the pill burden. The new saquinavir 500 mg film-coated capsules have demonstrated bioequivalence to saquinavir 200 mg hard capsules,23 and the latter achieves at least the same plasma levels as saquinavir soft capsules when boosted with ritonavir, apparently with better gastrointestinal tolerance.13,24

With regard to saquinavir concentration, the enhancing effects of different doses of ritonavir are similar in the absence of CYP3A4 and P-glycoprotein-inducing drugs.25 When co-administered with rifampicin, it is not known whether the 200 mg dose of ritonavir would be more effective than the 100 mg dose in overcoming the inducer effect of rifampicin.

In the present study administration of saquinavir and ritonavir did not modify plasma concentrations of rifampicin or isoniazid. Other studies have reported that plasma rifampicin does not change with the administration of various doses of lopinavir and ritonavir9 or atazanavir and ritonavir,10 or with the use of nevirapine8 or efavirenz.4 Rifampicin is a potent inducer of the majority of cytochrome P450 system isozymes and isoniazid inhibits several of the isozymes; nevertheless, neither of these drugs is significantly metabolized through this enzymatic system.3 Hence, it is not surprising that administration of CYP450 inhibitors or inducers does not modify the concentrations of these drugs.

After a communication by Grange et al.,26 this combination has to be used very cautiously: unexpected hepatotoxicity was seen in 11 of 28 healthy volunteers receiving rifampicin and saquinavir/ritonavir, the study was discontinued and the authors concluded that rifampicin should not be given to patients receiving saquinavir/ritonavir. Roche and the FDA issued a warning of drug-induced hepatotoxicity for this reason. Factors that might be involved in the high incidence of hepatotoxicity in this study are: (i) The participants were healthy volunteers, without TB or immunosuppression. Fifty cases of severe or fatal liver injury have been recently notified, mainly in non-HIV-infected patients taking rifampicin and pyrazinamide for latent TB infection in the USA.27 (ii) The highest incidence was seen in the group which started with rifampicin for 14 days and then saquinavir/ritonavir was added. Probably in a high number of patients hepatotoxicity was due to rifampicin, as this toxicity usually appears between the second and the eighth week of treatment. In our study and in a study by Losso et al.,28 the antiretroviral treatment was started after 2 months of TB therapy, when the risk of toxicity due to rifampicin is much lower, and only 1 of 18 patients and 1 of 14 patients, respectively, had to discontinue saquinavir treatment because of asymptomatic hepatotoxicity.

Detailed pharmacokinetic–pharmacodynamic data from human studies are lacking for TB drugs. The concentrations required for effective therapy and precise targets for therapeutic drug monitoring are poorly understood.29 Normal therapeutic ranges have been defined on the basis of concentrations achieved 2 h post-dose in healthy volunteers under controlled phase I study conditions (rifampicin 8–24 µg/mL, isoniazid 3–6 µg/mL).29 There are conflicting data on whether patients with HIV-related TB are more prone to malabsorption of anti-TB drugs than HIV-uninfected patients.30,31 In the present study plasma rifampicin and isoniazid concentrations were low in an elevated number of patients. However, the outcome of TB was favourable in all our patients except one, whose rifampicin and isoniazid levels were in the normal therapeutic range. Cases of delayed response, failure, and relapse have been reported in which serum concentrations of anti-TB drugs were lower than expected.32 On the basis of these findings, some groups have advocated routine therapeutic drug monitoring for the treatment of TB in HIV-infected patients.29 However, the clinical, radiological and microbiological responses to standard rifampicin-based regimens are similar regardless of HIV status.
and the cure rate averages 95% with directly observed therapy.33,34 These clinical results demonstrate that existing standards for serum concentrations of TB drugs cannot be taken as ‘therapeutic ranges’ and that monitoring of therapy in all patients is not necessary. Therapeutic drug monitoring should be recommended for patients who have an inadequate response to appropriate treatment that is not explained by non-adherence or drug resistance, whether or not they are HIV infected.32

In summary, saquinavir should be given with caution in patients receiving rifampicin. Decreases of 40%, 35% and 49% in the median saquinavir AUC\text{0–24}, C\text{max} and C\text{trough} respectively, were seen in this study. With regard to pharmacokinetics, the dose selected for saquinavir/ritonavir in this study does not seem to be appropriate. Twice-daily dosing might be preferable where at all possible, but for those patients in whom once-daily treatment is essential, studies with higher doses of saquinavir (e.g. 2000 mg/day) boosted with ritonavir to achieve a more favourable PK profile are warranted.

Acknowledgements

We thank Montse Llinas, Soﬁa Garcia, Dolors Palau, Teresa Garcia and the other members of the nursing staff for technical advice, and Celine L. Cavallo for English language editing. This study was supported in part with a grant from Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Red de SIDA (RIS).

Transparency declarations

We do not have any conﬂicts of interest, ﬁnancial or otherwise, regarding this manuscript.

References

Rifampicin and saquinavir/ritonavir interactions


32. Mehta JB, Shantaveerapa H, Byrd RP et al. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. Chest 2001; 120: 1520–4.
