Saquinavir exposure in HIV-infected patients with chronic viral hepatitis

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Objectives: The aim of this study was to assess the influence of hepatitis B virus or hepatitis C virus co-infection and the extent of liver fibrosis on saquinavir and ritonavir pharmacokinetics in HIV-infected subjects without liver function impairment.

Methods: A cross-sectional, comparative study enrolling HIV-infected adults receiving saquinavir/ritonavir 1000/100 mg twice daily or 1500/100 mg once daily was conducted. Patients with chronic viral hepatitis (HEP) were grouped as having advanced liver fibrosis (HEP/FIB) or not (HEP/FIB) based on the FIB-4 index. Saquinavir and ritonavir trough concentrations (Ctrough) in plasma were determined by HPLC. The geometric mean ratio (GMR) was used to compare saquinavir and ritonavir Ctrough between HEP− and HEP+ patients, and the influence of the extent of liver fibrosis on saquinavir and ritonavir pharmacokinetics was explored using analysis of variance.

Results: One hundred and thirty-eight patients on twice-daily saquinavir/ritonavir (67 HEP−, 71 HEP+) and 36 patients on once-daily saquinavir/ritonavir (12 HEP−, 24 HEP+) were included. Saquinavir Ctrough was comparable between HEP− and HEP+ patients receiving either saquinavir/ritonavir 1000/100 mg twice daily [GMR 0.91, 95% confidence interval (CI) 0.60–1.37; P = 0.655] or 1500/100 mg once daily (GMR 0.88, 95% CI 0.39–1.97; P = 0.752). Similarly, ritonavir Ctrough was also comparable between HEP− and HEP+ patients. The extent of liver fibrosis was not significantly related to saquinavir or ritonavir Ctrough in patients receiving either of the two studied doses.

Conclusions: Saquinavir Ctrough was not increased in HIV-infected patients with chronic viral hepatitis in the absence of liver function impairment. These results confirm that no specific dose modification of saquinavir/ritonavir should be recommended in this setting.

Keywords: saquinavir/ritonavir, clinical pharmacokinetics, HIV/HBV-HCV co-infection, liver fibrosis

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SQV pharmacokinetics in HIV-infected patients with chronic viral hepatitis

Introduction
As HIV management has improved, the impact of other diseases such as hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection on morbidity and mortality has become more evident.1–3 Because of shared routes of transmission, co-infection with HBV or HCV and HIV is common. Globally, estimates of the rate of HCV co-infection among HIV-positive patients range from 15% to 30% to as much as 50% to 80% in individuals who acquired HIV through parenteral exposure.4,6 Chronic viral hepatitis progresses differently in co-infected patients. Liver cirrhosis and liver function impairment have been described as developing earlier in these patients,2 with a significant proportion of deaths among persons with HIV infection being caused by end-stage liver disease.8,9

Reductions in liver function, changes in blood flow and modifications in the cytochrome P450 (CYP) system are likely to occur in liver disease,10 potentially modifying the pharmacokinetics of many antiretrovirals.11,12 depending on whether the drug has a low or a high hepatic extraction ratio. Drugs with a low ratio are expected to show increased plasma concentrations when there is a reduction in liver function and/or a reduction in albumin or alpha-1-acid glycoprotein concentrations in plasma. On the other hand, a high hepatic extraction ratio would lead us to expect a high plasma concentration of the drug if blood flow is reduced as a consequence of liver disease. Even in patients with no clinical evidence of liver disease, a relationship between the extent of liver fibrosis and changes in the pharmacokinetic parameters of protease inhibitors such as saquinavir or tipranavir has been described.13–15

Saquinavir is a protease inhibitor of HIV that is extensively metabolized by the hepatic cytochrome P450, essentially by the isoenzyme CYP3A4. At the recommended dose, saquinavir is co-administered with low doses of ritonavir, which inhibits the metabolism of saquinavir. Plasma concentrations of saquinavir are thereby increased enough to suppress replication of wild-type viral strains of HIV.16 International guidelines for therapeutic drug monitoring for antiretroviral agents have proposed 100 ng/mL as a threshold value,17 thereby increased enough to suppress replication of wild-type viral strains of HIV.16

Patients and methods
Participants in this multicentre, cross-sectional, comparative study were prospectively included from 28 different hospitals in Spain. Eligible patients were HIV-infected individuals aged 18 years or older who were receiving stable antiretroviral therapy with oral saquinavir (Invirase® 500 mg tablets) and ritonavir (Norvir® 100 mg capsules) at dosages of 1000/100 mg twice daily or 1500/100 mg once daily for at least 4 weeks. The Child–Pugh score was used to assess hepatic insufficiency,18 and patients with liver function impairment (Child–Pugh score >5) were excluded. Other exclusion criteria were self-reported treatment adherence of <90% in the previous 2 weeks, prior or current therapy with interferon or ribavirin, active alcohol consumption (>50 g/day) and concomitant administration of other drugs known to affect saquinavir pharmacokinetics. The protocol was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol and by the equivalent review boards at each additional site. All participants signed written informed consent statements before enrolment.

Demographic and clinical variables, including age, sex, body mass index (BMI), time since HIV diagnosis, HBV surface antigen, HCV antibodies and concomitant medications (including over-the-counter medications), were recorded for each participant. In addition, a complete blood count, prothrombin time, analysis of serum chemistry [including creatinine, total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase and alkaline phosphatase], CD4 T cell count and HIV-1 RNA load were determined. Chronic viral hepatitis (HEP++) was diagnosed in the presence of HBV surface antigen or HCV antibodies.

In order to assess the influence of liver damage on exposure to saquinavir and ritonavir, the extent of liver fibrosis in HEP+ patients was estimated through the FIB-4 index.20 This index was calculated by the equation:

\[
\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\text{platelets} \times \text{ALT}}
\]

where age is expressed in years, AST and ALT concentrations in U/L and platelets as the cell count ×10¹²/L.

Based on their FIB-4 score, HEP+ patients were grouped into three categories. Patients with a FIB-4 score ≤1.45 were regarded as not having advanced liver fibrosis (HEP+/FIB−); subjects with a FIB-4 score >1.45 and ≤3.25 were classified as having advanced liver fibrosis (HEP+/FIB+). Since FIB-4 scores ranging from >1.45 to <3.25 are less predictive of the extent of liver fibrosis,20 patients having these values were excluded from the data analysis for the purpose of assessing the influence of liver damage on exposure to saquinavir.

Patients were asked to record the time they had last taken a saquinavir/ritonavir dose on the day before the visit, and saquinavir and ritonavir trough concentrations (C₉₀₉) in plasma were determined 10–14 h after the last dose in patients receiving saquinavir/ritonavir 1000/100 mg twice daily or 20–26 h after the last dose in those receiving 1500/100 mg once daily.

Blood samples for the determination of saquinavir and ritonavir concentrations were collected in potassium and ethylenediaminetetraacetic acid-containing 10 mL tubes. Plasma was isolated by centrifugation (15,000 g for 15 min) and stored at −20°C until analysis. Samples were heat inactivated, and saquinavir and ritonavir concentrations in plasma were simultaneously determined by HPLC with photodiode array (HPLC-PDA 2996, Waters, Barcelona, Spain), according to a validated method. The analytical column was a NovaPak C18 3.9×150 mm with a NovaPak C18 guard column (Waters). The method involved liquid–liquid extraction of the two drugs from plasma with tert-butyl methyl ether after basification and a second wash with hexane. The mobile phase consisted of a gradient elution with phosphate buffer acetoni trile (pH 6.70) and was linear over a range of 40–8800 ng/mL for saquinavir and 50–20000 ng/mL for ritonavir. The intra-day and inter-day coefficients of variation were lower than 10%. Our pharmacokinetics laboratory participates in an international quality control and quality assessment program.
assessment programme, and therefore has cross-validation with other international pharmacokinetic laboratories.21

Statistical analysis

The statistical analysis was performed considering each of the two saquinavir/ritonavir doses separately, by means of SPSS version 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Variables with normal distribution were described as mean (SD) and compared by an unpaired t-test. Median and interquartile range were employed to describe variables that did not follow a normal distribution and these were compared with the Mann–Whitney non-parametric test. Percentages were compared with the χ² test or Fisher’s exact test, as appropriate. Saquinavir and ritonavir $C_{\text{trough}}$ were described as the geometric mean, and inter-individual variability in drug concentrations was expressed as the coefficient of variation (CV%), which was calculated by dividing the SD by the mean. Saquinavir and ritonavir concentrations were calculated by dividing the SD by the mean. Saquinavir and ritonavir $C_{\text{trough}}$ were compared between HEP− and HEP+ patients using the geometric mean ratio (GMR) and the 95% confidence interval (CI). In addition, analysis of variance was used to evaluate using the geometric mean, and inter-individual variability in drug concentrations was expressed as the coefficient of variation (CV%), which was calculated by dividing the SD by the mean. Saquinavir and ritonavir $C_{\text{trough}}$ were compared between HEP− and HEP+ patients using the geometric mean ratio (GMR) and the 95% confidence interval (CI). In addition, analysis of variance was used to evaluate the influence of the extent of liver fibrosis on saquinavir and ritonavir $C_{\text{trough}}$. In order to account for the potential influence of sex, BMI or albumin concentrations in plasma on drug exposure, multiple regression models including these variables were tested.

The minimum sample size in each study group to detect a difference of 30% or greater in saquinavir $C_{\text{trough}}$ was calculated by dividing the SD by the mean. Saquinavir and ritonavir $C_{\text{trough}}$ were compared between HEP− and HEP+ patients was 62, when accepting an α risk of 0.05 and a β risk of 0.20.22,23

Results

A total of 174 patients (79 HEP− and 95 HEP+) were enrolled in the study. The saquinavir/ritonavir dose was 1000/100 mg twice daily for 138 patients (106 males and 32 females) and 1500/100 mg once daily for 36 patients (25 males and 11 females). Patients had been diagnosed with HIV infection for a mean of 11.7 (5.7) years, and they had received saquinavir/ritonavir for a median of 32 (9–56) weeks before the pharmacokinetic assessments. At enrolment, the mean CD4+ T cell count was 467 (293) cells/mm³, HIV-1 RNA load was <50 copies/mL in 112 (64.4%) patients and 62 patients had detectable HIV-1 RNA in plasma (median 785 copies/mL, interquartile range 111–12 250 copies/mL).

Demographic characteristics and total protein concentration in plasma were similar between HEP− and HEP+ patients (Table 1). However, AST and ALT concentrations in plasma were higher in HEP− than in HEP+ patients, while albumin concentrations in plasma were lower in HEP+/FIB+ compared with HEP+/FIB− patients (Table 1).

Overall, the geometric mean saquinavir $C_{\text{trough}}$ was 433 ng/mL (114%) in patients taking saquinavir/ritonavir 1000/100 mg twice daily and 183 ng/mL (189%) in patients taking saquinavir/ritonavir 1500/100 mg once daily (GMR 2.38, 95% CI 1.52–3.69, $P<0.001$). Mean saquinavir and ritonavir $C_{\text{trough}}$ and CV% are shown in Table 2, stratified by patient HBV and HCV status and FIB-4 score; none of the differences was statistically significant. The GMR of saquinavir concentrations between HEP− and HEP+ patients was 0.91 (95% CI 0.60–1.37; $P=0.655$) in those receiving saquinavir/ritonavir 1000/100 mg twice daily and 0.88 (95% CI 0.39–1.97; $P=0.752$) in those receiving 1500/100 mg once daily. No significant relationship between saquinavir $C_{\text{trough}}$ and sex, BMI or albumin concentrations in plasma was observed.

Geometric mean (CV%) ritonavir $C_{\text{trough}}$ was 413 ng/mL (81%) in patients taking saquinavir/ritonavir 1000/100 mg twice daily and 114 ng/mL (119%) in those taking saquinavir/ritonavir

Table 1. Demographic characteristics of the enrolled patients

<table>
<thead>
<tr>
<th>HEP− n = 79</th>
<th>HEP+ n = 95</th>
<th>FIB− (n = 37)</th>
<th>FIB+ (n = 29)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir/ritonavir dose</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1000/100 mg twice daily</td>
<td>67 (84.8)</td>
<td>71 (74.7)</td>
<td>28 (75.7)</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>1500/100 mg once daily</td>
<td>12 (15.2)</td>
<td>24 (25.3)</td>
<td>9 (24.3)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>55 (69.6)</td>
<td>76 (80.0)</td>
<td>29 (74.8)</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.7 (8.4)</td>
<td>43.2 (7.0)</td>
<td>41.6 (7.2)</td>
<td>43.5 (5.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 (3.8)</td>
<td>22.6 (3.0)</td>
<td>22.8 (3.1)</td>
<td>22.3 (3.0)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>24 (18–29)</td>
<td>57 (32–98)</td>
<td>36 (26–43)</td>
<td>99 (63–138)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>23 (17–30)</td>
<td>64 (38–106)</td>
<td>40 (27–70)</td>
<td>83 (51–143)</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>7.7 (0.7)</td>
<td>7.7 (0.8)</td>
<td>7.8 (0.7)</td>
<td>7.7 (0.9)</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>4.4 (0.4)</td>
<td>4.2 (0.5)</td>
<td>4.3 (0.4)</td>
<td>3.9 (0.5)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL</td>
<td>49 (62.0)</td>
<td>63 (66.3)</td>
<td>24 (64.9)</td>
<td>16 (55.2)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB, fibrosis; HEP, hepatitis; NS, not significant.

Data are expressed as mean (SD), except saquinavir/ritonavir dose, sex and HIV-1 RNA <50 copies/mL [expressed as n (%)] and AST and ALT concentrations [expressed as median (interquartile range)].

aComparisons were performed by analysis of variance or by the χ² test as appropriate.

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Table 2. Saquinavir and ritonavir trough concentrations in plasma, by patient HBV/HCV status and FIB-4 score

<table>
<thead>
<tr>
<th></th>
<th>HEP− n=79</th>
<th>all (n=95)</th>
<th>FIB− (n=37)</th>
<th>FIB+ (n=29)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saquinavir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{trough} (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000/100 mg twice daily</td>
<td>454 (102%)</td>
<td>414 (125%)</td>
<td>288 (125%)</td>
<td>458 (131%)</td>
<td>0.154</td>
</tr>
<tr>
<td>1500/100 mg once daily</td>
<td>199 (181%)</td>
<td>175 (159%)</td>
<td>230 (163%)</td>
<td>169 (78%)</td>
<td>0.609</td>
</tr>
<tr>
<td><strong>Ritonavir</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{trough} (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000/100 mg twice daily</td>
<td>419 (78%)</td>
<td>406 (84%)</td>
<td>321 (84%)</td>
<td>512 (88%)</td>
<td>0.131</td>
</tr>
<tr>
<td>1500/100 mg once daily</td>
<td>130 (119%)</td>
<td>106 (119%)</td>
<td>125 (129%)</td>
<td>83 (124%)</td>
<td>0.705</td>
</tr>
</tbody>
</table>

FIB, fibrosis; HEP, hepatitis.
Data are expressed as geometric mean (coefficient of variation %).
*Comparisons were performed by analysis of variance.

Discussion

Our results show that, despite great inter-individual variability, saquinavir and ritonavir C_{trough} in plasma are comparable between HIV-infected patients with and without chronic viral hepatitis in the absence of liver function impairment.

Because of the extensive hepatic metabolism of protease inhibitors and their high plasma protein binding, dose adjustments of some protease inhibitors, such as fosamprenavir, atazanavir or indinavir, are currently recommended in patients with different degrees of liver function impairment. Although no specific dose adjustment for saquinavir is recommended for HIV-infected patients with liver disease, the pharmacokinetics of this drug can also be considered likely to change in this setting. Elevated exposure to saquinavir was reported in a small series of four HIV/HCV-co-infected patients with severe hepatic disease. In this larger study in HIV-infected patients without evidence of hepatic insufficiency, however, neither the presence of chronic viral hepatitis nor the extent of liver fibrosis had a significant influence on saquinavir exposure, probably due to the high inter-individual variability in drug concentrations. These results confirm that no dose adjustment for saquinavir is needed in this scenario. However, it has to be considered that the statistical analysis of the present study was powered only for the twice-daily dosing regimen.

Ritonavir pharmacokinetics were reported to be affected by the extent of liver fibrosis in a previous pharmacokinetics study in HIV/HCV-co-infected patients without liver cirrhosis receiving lopinavir/ritonavir. In that study, ritonavir clearance was reduced by half and C_{trough} increased 2-fold in co-infected patients with advanced liver fibrosis compared with non-co-infected patients or co-infected patients without liver fibrosis. We have not been able to reproduce these findings in the present study, however, probably due to the wide inter-individual variability observed in ritonavir concentrations as well as because of a difference in the effects of lopinavir and saquinavir on cytochrome P450 activity.

The decrease in the use of saquinavir for the treatment of HIV-infected patients in developed countries since the approval of newer antiretroviral agents may limit the relevance of the present study. However, saquinavir is considerably cheaper than new antiretroviral drugs, making it a suitable therapeutic option in poor resource settings. In addition, it is worth pointing out that saquinavir/ritonavir is still considered one of the preferred options for the initial treatment of HIV-infected patients according to the Guidelines for Clinical Management and Treatment of HIV Infected Adults in Europe. The extent of liver fibrosis in HEP+ patients included in the present study was evaluated through the FIB-4 index. We did not perform liver biopsy since this is an invasive procedure that cannot be routinely performed in every co-infected patient. On the other hand, although liver stiffness measured by transient elastography might have been a candidate method, as it has good correlation with the fibrosis stage observed in the liver biopsy in HIV/HCV-co-infected patients, it is not available for its routine use in many clinical units. The FIB-4 index, in contrast, is a simple non-invasive scoring system that has the advantage that it may be calculated along with routine laboratory tests, so it can be easily implemented in clinical practice and it correlates reasonably well with histology.

Although the approved dosage of saquinavir/ritonavir is 1000/100 mg twice daily, dosing of 1600/100 mg once daily has been shown to be a viable option for the treatment of HIV-infected patients naive to antiretroviral agents. Nevertheless, there is concern that 1600/100 mg once daily may be too low a dose for maintaining viral suppression. Studies in a Thai population showed high saquinavir exposure in patients receiving saquinavir/ritonavir 1600/100 mg once daily.
However, these results have not been confirmed in a Caucasian population.\textsuperscript{22, 34, 35} Boffito et al.\textsuperscript{22} found that as many as half the Caucasian patients treated with this regimen of saquinavir/ritonavir may have subtherapeutic saquinavir plasma concentrations. In line with these results, in our study, saquinavir C_{\text{trough}} in patients receiving saquinavir/ritonavir 1500/100 mg once daily was half that observed in patients receiving the standard twice-daily dose, and the likelihood of having a saquinavir C_{\text{trough}} <100 ng/mL was 3-fold higher in patients on once-daily dosing. Despite these caveats, we did not observe differences in the proportion of patients with HIV-1 RNA load <50 copies/mL between patients treated with once- or twice-daily saquinavir/ritonavir. However, the cross-sectional design of the present study does not allow us to draw firm conclusions in this regard. In our opinion, these data indicate that once-daily saquinavir/ritonavir at a dose of 1500/100 mg may not be as robust a treatment as the twice-daily regimen for the treatment of Caucasian HIV-infected patients. Moreover, we feel that the monitoring of saquinavir C_{\text{trough}} may be useful in this setting.

In conclusion, saquinavir exposure was not increased in HIV-infected patients with chronic viral hepatitis in the absence of liver function impairment. Based on these results, no specific dose modification of saquinavir/ritonavir can be recommended in this setting. The wide variability and the high prevalence of suboptimal saquinavir C_{\text{trough}} in patients receiving once-daily saquinavir/ritonavir mean that it would be reasonable to monitor saquinavir concentrations in this setting.

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Transparency declarations

J. M. has received honoraria for speaking and participation in advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Roche and Janssen-Cilag. J. M. L. has received research funding, consultancy fees or lecture sponsorships from, or served on advisory boards for, Abbott, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Merck Sharp&Dohme, Pfizer, Roche and Janssen-Cilag. E. R. has received investigational grants and/or honoraria for lectures or advisory boards from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Roche Farma and Schering Plough. C. Mínguez has received research funding, consultancy fees or lecture sponsorships from, or served on advisory boards for, Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Roche and Schering Plough. J. S. del R. has no conflicts to declare during the course of this study. E. P. has received honoraria for speaking and participation in advisory boards from Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, MSD, Pfizer and Roche. G. V. has received honoraria for speaking and participation in advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences, GlaxoSmithKline, Roche and Janssen-Cilag. S. C. has no conflicts to declare during the course of this study. M. V. has no conflicts to declare during the course of this study. C. Miranda has no conflicts to declare during the course of this study. E. N. has received honoraria for speaking and participation in advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences and GlaxoSmithKline. B. C. has received honoraria for speaking and participation in advisory boards from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead Sciences and GlaxoSmithKline.
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References


