Atazanavir and lopinavir with ritonavir alone or in combination: analysis of pharmacokinetic interaction and predictors of drug exposure

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Objectives

Studies on the pharmacokinetic interaction between atazanavir and lopinavir with ritonavir (lopinavir/ritonavir) report contradictory results. We aimed to establish the in vivo interaction between these two protease inhibitors as well as the variables influencing drug exposure.

Methods

Pharmacokinetic parameters were investigated in HIV-infected patients treated with atazanavir 300 mg with ritonavir 100 mg q24h (group A) or lopinavir/ritonavir 400/100 mg q12h (group B) or atazanavir 300 mg q24h with lopinavir/ritonavir 400/100 mg q12h (group C). Patients receiving other concomitant protease inhibitors or non-nucleoside reverse transcriptase inhibitors were excluded.

Results

In group A (n = 10), mean ± standard deviation atazanavir Cmin was 390 ± 460 ng/mL, Cmax 3051 ± 1996 ng/mL and AUC24 29 913 ± 17 686 ng/mL/h. In group B (n = 9), lopinavir Cmin was 7562 ± 4292 ng/mL, Cmax 12 944 ± 4838 ng/mL and AUC0–12 122 313 ± 38 225 ng/mL/h. In group C (n = 7), atazanavir Cmin was 876 ± 460 ng/mL (P = 0.039 vs. group A), Cmax 3421 ± 3399 ng/mL and AUC0–24 65 055 ± 49 843 ng/mL/h (two-sided P > 0.05 for each comparison with group A), lopinavir Cmin was 7471 ± 3745 ng/mL, Cmax 10 143 ± 5217 ng/mL and AUC0–12 104 501 ± 43 565 ng/mL/h (P > 0.05 for each comparison with group B). When analysing all the groups, including controls from routine clinical practice, higher body mass index was associated with lower atazanavir Cmin and with lower lopinavir Cmax. Atazanavir Cmin showed a correlation with total bilirubin levels.

Conclusions

Combination with lopinavir/ritonavir provides higher atazanavir Cmin than combination with ritonavir alone, possibly because of an effect of the additional ritonavir dose. Low BMI may be associated with higher drug exposure.

Keywords: atazanavir, lopinavir/ritonavir, therapeutic drug monitoring

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Introduction

In the treatment of HIV infection, the use of double-boosted protease inhibitors (PIs) has been proposed in selected patients in order to try to obtain an additive antiviral effect [1–3]. These associations are based on the use of low-dose ritonavir as a pharmacokinetic enhancer acting through the inhibition of liver cytochrome metabolism of the two other PIs used at therapeutic doses. This strategy could be particularly useful in heavily treatment-experienced patients with extensive resistance to other drug classes and few therapeutic options. It could also be useful in those intolerant to other drug classes: the combination of potent drugs with at least partially different resistance profiles could act against mixed viral strains, and the possible increase in plasma drug concentrations could overcome resistance by increasing drug exposure.

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Unfortunately, these hoped-for results are not always achievable in clinical practice. Indeed, double-boosting of PIs sometimes requires therapeutic drug monitoring (TDM) in order to handle dose adjustments resulting from complex drug–drug interactions [4–7]. In the AIDS Clinical Trials Group (ACTG) protocol A5413, the simultaneous use of fosamprenavir and lopinavir/ritonavir led to a significant reduction in the exposure to both drugs, increasing the risk of virological failure and leading to study discontinuation [8]. This result confirmed a previous observation obtained with amprenavir and lopinavir as deep salvage therapy [2]; an increase in ritonavir boosting dose can counterbalance this effect [9]. The co-administration of lopinavir and nelfinavir also led to negative drug–drug interactions [10], while the simultaneous administration of lopinavir/ritonavir with saquinavir [1,3,9] and that of lopinavir/ritonavir with indinavir [9] were found to be synergic.

The lopinavir/ritonavir fixed-dose formulation is a highly potent antiretroviral (ARV) drug with high genetic barrier, making it effective against viral strains resistant to older-generation PIs and allowing a low rate of selection of drug resistance mutations at failure. Because of these characteristics, all HIV treatment guidelines have considered it as a first-choice PI for many years [11]; moreover, the newer tablet formulation reduced the pill burden and avoided the need for refrigeration [12].

Atazanavir is a relatively new PI with convenient once-daily administration, low pill burden, better efficacy and higher genetic barrier when boosted with ritonavir, a distinct resistance profile with a signature mutation conferring hypersusceptibility to other PIs, generally good tolerability and less severe impact on glucidic and lipidic metabolism than the previously approved drugs in the same class [13–18]. Moreover, atazanavir inhibits the P-glycoprotein-mediated drug efflux from the cells; this effect has been related to this drug’s ability to increase exposure to other PIs (particularly saquinavir) [19,20].

Thus, lopinavir/ritonavir and atazanavir are potential candidates for a combined use but studies exploring drug concentrations to investigate potential drug–drug interactions have shown conflicting results. An in vitro evaluation of this combination showed additive antiviral effect [1]; a recent in vivo evaluation showed an increased exposure to both drugs [4]; another study showed no influence on atazanavir plasma levels after lopinavir was added and a significant decrease in lopinavir Cmin after the addition of atazanavir [5].

The aim of our study was to analyse the in vivo pharmacokinetic interactions between atazanavir and lopinavir, the tolerability of this association and the variables influencing the exposure to both drugs.

Patients and methods

Patients and design

This was a prospective, non-randomized pilot study in which the pharmacokinetics of atazanavir/ritonavir and lopinavir/ritonavir were analysed in HIV-infected patients receiving each drug alone or in combination. Before starting the pharmacokinetic assessment, patients had to be on an unmodified ARV regimen for at least 15 days. Patients started ARV therapy including a combination of atazanavir 300 mg with ritonavir 100 mg q24h plus other non-nucleoside reverse transcriptase inhibitors (NRTIs) (group A), or lopinavir/ritonavir 400/100 mg q12h with NRTIs (group B) or atazanavir 300 mg q24h with lopinavir/ritonavir 400/100 mg q12h and NRTIs (group C). We selected patients treated with atazanavir/ritonavir (group D) or lopinavir/ritonavir (group E) monitored for PI drug levels in clinical practice as further control groups. Inclusion criteria for group D and E patients were to have plasma drug levels determined at 24 ± 2 h from last drug intake for atazanavir and 12 ± 2 h from last drug intake for lopinavir. All lopinavir/ritonavir formulations used during the study were refrigerated capsules. Patients receiving other concomitant PIs or NNRTIs and (for the groups receiving atazanavir) those receiving proton pump inhibitors, antacids or H2-receptor antagonists were excluded. The protocol of the study required approval by the local institutional review board. All patients provided written informed consent before any study procedure was undertaken. Baseline data, including demographic data, prior AIDS-defining diseases (according to 1993 Centers for Disease Control classification) and concomitant medication, were collected. At each visit, complete blood cell counts and chemistry and a routine physical examination were performed. Patients’ clinical and laboratory data were retrieved at months 1, 3 and 6 after drug initiation.

Timing of blood collection and drug concentration assays

All patients from groups A–C were instructed to take lopinavir/ritonavir and atazanavir at 09:00 h and lopinavir/ritonavir at 21:00 h (with breakfast and dinner, respectively) during the week before the day of intensive pharmacokinetic assessment of drug concentrations. To ensure that the dose was taken exactly 24 h before the pre-dose analysis, patients were instructed to complete a form with the exact time they took the preceding doses of protease inhibitors. On that day, patients came to the hospital between 08:30 h and 09:00 h after fasting overnight. Both study drugs were administered at the hospital at 09:00 h with a standard breakfast. Blood samples were
drawn immediately before dosing and at 1, 2, 3, 4, 6 and 12 h post-dosing. For atazanavir, the 24 h concentration value was extrapolated by computing the pre-dose value.

Chemicals and equipment

Atazanavir pure form was a gift from Bristol-Meyers Squibb (Princeton, NJ, USA). Lopinavir and ritonavir were provided by Abbott (North Chicago, IL, USA). Internal standard was purchased from Sigma (Saint Quentin, France).

Solvents used were of high-performance liquid chromatography (HPLC) gradient grade, purchased from Merck (Nogent sur Marne, France).

The Empower chromatography data software (Waters Corporation, Milford, MA, USA) was used to control the HPLC system, consisting of a 600E pump equipped with a degasser, a 717 refrigerated autosampler and an ultraviolet spectrophotometer detector 2487, all from Waters (Milford, MA, USA).

Experimental procedures

Blood samples (5 mL) were drawn into ethylenediaminetetraacetic acid (EDTA) tubes and transported on ice to the laboratory, then immediately centrifuged for 10 min at 2000 × g at 4 °C. Plasma was decanted and stored at −20 °C until analysis. For quantitative determination of atazanavir, lopinavir and ritonavir, the compounds were separated on an analytic column X-TERRA RP18 (250 × 4.6 mm, particle size 5 μm) and precolumn X-TERRA RP18 (20 × 3.9 mm, 5 μm) (Waters). The column was maintained at 22 °C in a Peltier effect oven.

The mobile phase consisted of a mixture of 55% water (containing 0.1% H3PO4, pH 5.5) and 45% acetonitrile. Flow rate for the isocratic elution was 1 mL/min. Absorbance was monitored at 210 nm.

For standard curve, a 100 μg/mL stock solution was prepared by dissolving the pure equivalent of each ARV agent in a 50:50 water/acetonitrile mixture (vol/vol). This stock solution was further diluted in drug-free human plasma to give plasma concentrations of 50, 500, 1000, 5000, 7500 and 10 000 ng/mL; 250 μL of each standard and plasma sample were mixed with 500 μL of borate buffer (pH 9.6) and 50 μL internal standard working solution. We added 3 mL of tert-butyl methyl ether and vortex-mixed for 1 min, then centrifuged for 5 min. The organic phase was evaporated in a SpeedVac (Savant Instruments Inc., Holbrook, NY, USA) concentrator, and the residue was re-dissolved in 150 μL of mobile phase. The solution was washed with 500 μL hexane and centrifuged for 10 min at 2000 × g followed by aspiration to eliminate the hexane. The washed solution was then transferred to a glass insert, and 50 μL injected into the chromatograph.

Limit of accurate determination

The lower limit of quantification was set arbitrarily to the first calibration standard (50 ng/mL for all drugs), which is lower than the minimum target trough concentrations for naïve HIV-infected patients.

Internal quality control samples

For the preparation of internal quality controls used for the validation of the assay, independent stock and working solutions containing the compound of interest were created and further diluted in blank human plasma to achieve concentrations of 50, 500 and 5000 ng/mL.

Validation procedures

Least-squares weighted (weighting factor = 1/y where y = peak height ratio) linear regressions were used to calculate the equations relating the peak height ratio between the drug (50–10 000 ng/mL) and internal standard and the concentration of the drugs. The validation of the assay included six separate days. On the first day of validation, seven calibration standards containing all the drugs of interest were analysed together with seven replicates (six for the intra-day analysis and one for the inter-day assay) of each of the three quality control (QC) concentration levels (50, 500, 5000 ng/mL). On the other 5 days, one set of the three QC samples was assayed with a calibration curve processed the same day. The observed concentrations of the QC samples were calculated using the standard curve parameters; they were then compared to the expected plasma concentrations. The coefficient of variation (CV) was used to estimate the precision of the assay (inter-assay CV 2.4–8.1%; intra-assay CV 2.3–5.9%). Accuracy was defined as the percentage of the nominal concentration multiplied by 100 (average accuracy 97–106%).

The efficiency of the extraction procedure was determined by comparing the slopes of plasma calibration curves to that of the pure working standards injected directly the same day.

The accuracy of the present method was also estimated repeatedly from the analysis of four sets of two unknown samples of external quality controls from the INSTAND eV (Düsseldorf, Germany) (WHO Collaborating Centre for Quality Assurance and Standardization in Laboratory Medicine) quality control programme for ARV drugs.
Statistical analysis

Atazanavir and lopinavir $C_{\text{max}}$ were determined in each individual patient using the highest drug level achieved after the morning dose. Total drug exposure was expressed as the area under the concentration–time curve from 0 to 12 h ($AUC_{0–12}$) for lopinavir and from 0 to 24 h for atazanavir with or without lopinavir, using the non-compartmental method. The 24 h level of atazanavir was computed using the time 0 pre-dose value. The normality of variables distribution was tested using the Shapiro–Wilk $W$-test; an unpaired $t$-test or the Mann–Whitney $U$-test were used to analyse the difference between continuous variables, as appropriate. Correlations of variables with atazanavir and lopinavir exposure parameters were analysed by linear regression analysis. SPSS software for Windows (version 13.0; SPSS, Chicago, IL, USA) and STATISTICA workbook (version 6; Statsoft, Tulsa, OK, USA) were used for statistical analyses.

Results

Patient characteristics

Twenty-six HIV-infected patients were enrolled in the three full pharmacokinetics study groups: 10 in the atazanavir/ritonavir group (A), nine in the lopinavir/ritonavir group (B) and seven in the lopinavir/ritonavir with atazanavir group (C). Overall, median patient age was 42 years; 77% were male; the mode of HIV transmission was heterosexual contact for 31%, male homosexual contact for 46%, intravenous drug use for 23%; 27% of individuals had a history of previous AIDS-defining events. The median CD4 T-cell count was 432 cells/$\mu$L and the median plasma viral load 1.68 HIV-1 RNA copies/mL. Median body mass index (BMI) was 21.9 kg/m$^2$; 23% of patients were anti-hepatitis C virus (HCV) positive and 62% of patients received tenofovir concomitantly.

The characteristics of patients at baseline (divided by study group) are summarized in Table 1.

### Pharmacokinetic analysis

The pharmacokinetic profile of atazanavir when the drug was administered at 300 mg qd with ritonavir (100 mg qd) or with lopinavir/ritonavir (400/100 mg bid) and of the profile of lopinavir administered with ritonavir (400/100 mg bid) with or without atazanavir 300 mg qd are illustrated in Fig. 1. Comparison of the concentration–time profiles for when atazanavir was administered in combination with ritonavir (100 mg qd) (group A) or with lopinavir/ritonavir (400/100 mg bid) (group C) revealed that atazanavir $C_{\text{min}}$ levels were significantly higher in arm C (see Table 2). There were no significant differences in atazanavir $C_{\text{max}}$ and in atazanavir $AUC_{0–24}$ between groups A and C, although the mean overall exposure values were two times higher when atazanavir was co-administered with lopinavir/ritonavir (see Table 2). Given the available sample size and the resulting mean $AUC_{0–24}$ value and standard deviation in group A, to reach a statistically different $AUC_{0–24}$ in group C with a power of 80%, the mean value should have been at least equal to or higher than 75,000 ng*h/mL (i.e. at least 15% higher than the actually measured mean value). No significant differences in the pharmacokinetic parameters for lopinavir/ritonavir with or without atazanavir were observed (see Table 3).

In order to compare our findings to those from clinical practice, we then compared the $C_{\text{min}}$ of atazanavir and lopinavir of the study patients to those from patients undergoing routine TDM with available samples collected at or around the time of $C_{\text{min}}$ (see Patients and methods). Despite a trend towards higher drug levels with a wider variability in the untimed controls, there were no significant differences with the patients undergoing programmed pharmacokinetic analysis. In control group D ($n = 18$), untimed atazanavir $C_{\text{min}}$ was 652 ± 817 ng/mL.
while atazanavir $C_{\text{min}}$ was 390 ± 460 ng/mL in group A ($P = 0.054$); in control group E ($n = 30$), untimed lopinavir $C_{\text{min}}$ was 9106 ± 17 689 ng/mL, while lopinavir $C_{\text{min}}$ was 7562 ± 4292 ng/mL in group B ($P = 0.06$).

When analysing the whole population, higher patient BMI was associated with lower atazanavir $C_{\text{min}}$ ($n = 35$, $r = -0.31$, $P = 0.05$) and with lower lopinavir $C_{\text{max}}$ ($n = 16$, $r = -0.62$, $P = 0.008$). Atazanavir $C_{\text{min}}$ levels were directly associated with higher total bilirubin serum levels ($n = 35$, $r = +0.37$, $P = 0.029$). We could not detect any association between other patient-related or treatment-related variables – including sex, age, concomitant use of tenofovir and HCV serostatus – and pharmacokinetic parameters (not shown).

Safety of the atazanavir with lopinavir/ritonavir combination

At 6 months, no patients from the different study groups discontinued treatment because of adverse effects. In atazanavir-treated patients (groups A and D), 10 of 28 (35.7%) showed grade 3 or higher toxicity levels for total bilirubin; two (7.1%) patients showed grade 3 or higher toxicity levels for AST and one (3.6%) for ALT. The lipid profile changes were mild, with only one patient showing grade 3 toxicity levels for triglycerides and one for total cholesterol. No patient developed diabetes. No patient in this group showed grade 3 or higher clinical toxicity of any kind.

Among lopinavir/ritonavir-treated patients (groups B and E), one of 39 (2.6%) had a grade 3 or higher total bilirubin toxicity level; no other grades were observed. No other clinical toxicities were noted.

Table 2 Comparison of pharmacokinetic parameters of atazanavir 300 mg q24 h when administered with ritonavir 100 mg q24 h (group A) or with lopinavir/ritonavir 400/100 mg q12 h (group C)

<table>
<thead>
<tr>
<th>Group</th>
<th>$C_{\text{min}}$ (mean ± SD)</th>
<th>$C_{\text{max}}$ (mean ± SD)</th>
<th>AUC$_{0-24}$ (mean ± SD)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>390 ± 460 ng/mL</td>
<td>3051 ± 1996 ng/mL</td>
<td>29 913 ± 17 686 ng*h/mL</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>876 ± 460 ng/mL</td>
<td>3421 ± 3399 ng/mL</td>
<td>65 055 ± 49 843 ng*h/mL</td>
<td>0.039</td>
</tr>
</tbody>
</table>

AUC, area under curve; SD, standard deviation.

Table 3 Comparison of pharmacokinetic parameters of lopinavir when administered with ritonavir alone at 400/100 mg 12 h (group B) or combined with atazanavir 300 mg q24 h (group C)

<table>
<thead>
<tr>
<th>Group</th>
<th>$C_{\text{min}}$ (mean ± SD)</th>
<th>$C_{\text{max}}$ (mean ± SD)</th>
<th>AUC$_{0-12}$ (mean ± SD)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>7562 ± 4292 ng/mL</td>
<td>12 944 ± 4838 ng/mL</td>
<td>122 313 ± 38 225 ng*h/mL</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>7471 ± 3745 ng/mL</td>
<td>10 143 ± 5217 ng/mL</td>
<td>104 501 ± 43 565 ng*h/mL</td>
<td>0.96</td>
</tr>
</tbody>
</table>

AUC, area under curve; SD, standard deviation.
bilirubin increase, four (10.3%) patients had a grade 3 or higher AST and ALT increase, one (2.6%) patient showed a grade 3 or higher increase in triglycerides while no patient showed a grade 3 total cholesterol level. No patient developed diabetes. Twenty-four (61.5%) patients had grade 3 or higher diarrhoea.

In the atazanavir plus lopinavir/ritonavir group (C), one of seven patients (14.3%) showed a grade 3 or higher increase in total bilirubin and one patient had a grade 3 increase of ALT, while no patient showed grade 3 increases in AST, triglycerides and total cholesterol. No patient developed diabetes. Two patients from this group (28.6%) developed grade 3 diarrhoea.

When group C patients were compared to other groups in terms of mean changes from baseline laboratory values at months 1, 3 and 6 after drugs initiation, no significant differences were detected with the exception of total bilirubin levels, which were significantly more increased in group C patients compared to the lopinavir/ritonavir group (B and E) (P<0.05 at all time points).

Discussion

The combined use of atazanavir with lopinavir/ritonavir is an interesting therapeutic option for patients with prior heavy treatment exposure, multiple therapeutic failures and extensive resistance or intolerance to other ARV drug classes, but the pharmacokinetic characteristics of such a regimen remain to be understood more fully – previous studies have shown conflicting results [4,5].

In our study, this drug combination was not associated with increased clinical or laboratory toxicity compared to control groups using the drugs separately.

The combination of atazanavir with lopinavir/ritonavir resulted in an increase in atazanavir C_{min} while atazanavir C_{max} and AUC_{0-24} did not differ significantly compared to when atazanavir was administered with ritonavir alone. Atazanavir AUC_{0-24} showed not significantly higher levels, but it is possible that the small sample size of this study could have limited its ability to detect a statistical difference. The comparison of different individuals in the distinct study groups may have further limited the power to detect differences, given that inter-individual variability of protease inhibitors concentration is larger than intra-individual variability [21]. Indeed, the study was designed as an inter-individual comparison in order to prescribe individuals with the combination of atazanavir with lopinavir/ritonavir only when required by virus susceptibility testing or clinical history (including toxicity of or resistance to certain NRTIs) and to avoid the unnecessary potential toxicity of the combination. Despite these limitations, the effect of lopinavir/ritonavir co-administration on atazanavir C_{min} but not AUC_{0-24} confirms the data obtained by Ribera et al. [4] and by a recent report on HIV-negative volunteers [22]. The increased C_{min} is probably caused by the additional low-dose ritonavir at the 12th hour, administered in the co-formulation with lopinavir. The pharmacokinetic parameters of lopinavir were not influenced by the concomitant administration of atazanavir in our patients, whereas in previous studies an overall significant increase [4] or a global reduction with only the difference in C_{min} reaching statistical significance [5] was observed. On the other hand, results are in agreement with a study on healthy volunteers showing no effect of atazanavir co-administration on lopinavir concentrations [22].

At linear regression analysis, the only variable significantly related to the pharmacokinetic parameters of both atazanavir and lopinavir was BMI, which showed an inverse correlation with drug exposure. The effects of this finding on the development of drug intolerance and the severity of the side effects should be further investigated in order to reduce the toxicity of regimens containing these agents. The setting of patients with low BMI could represent an important application of TDM. Gender, age, HCV co-infection and simultaneous use of tenofovir were not associated with significant changes in the pharmacokinetic parameters of both atazanavir and lopinavir.

The atazanavir C_{min} was associated with higher serum total bilirubin levels. This was an expected finding, confirming a previous observation and justified by the dose-dependent competitive inhibition of uridine 5’-diphosphate (UDP)-glucuronidase determined by exposure to atazanavir [23]. Nonetheless, despite the increased atazanavir C_{min} in the patient group using the combination of atazanavir with lopinavir/ritonavir, this did not translate into significant differences in bilirubin levels in this specific patient group – probably because overall atazanavir exposure was not significantly increased in these patients. Furthermore, the relationship between atazanavir exposure and hyperbilirubinaemia is complex and regulated by at least two genetic polymorphisms that may influence drug exposure and bilirubin glucuronidation [24].

In conclusion, the simultaneous use of atazanavir and lopinavir/ritonavir produced an increase in the C_{min} of atazanavir, probably as a consequence of the increased boosting effect of the additional dose of ritonavir, with neither a significant change in the pharmacokinetic parameters of lopinavir nor an increase in drug toxicity. The inverse correlation observed between BMI and drug concentrations needs further investigation aimed at reducing the risk of toxicity-related drug discontinuation and optimizing treatment tolerability.

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Potential conflicts of interest
RC has received speakers’ honoraria or has been an advisor for GlaxoSmithKline, Bristol-Myers Squibb, Gilead, Abbott Virology, Boehringer Ingelheim, Merck Sharp and Dohme and Pfizer.

A.D.L. has received speakers’ honoraria or has been an advisor for GlaxoSmithKline, Bristol-Myers Squibb, Gilead, Abbott Virology and Boehringer Ingelheim.

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