Dose-dependent pharmacokinetics of delavirdine in combination with amprenavir in healthy volunteers

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Objectives: To investigate different dose combinations of amprenavir and delavirdine in order to assess an optimal dose suitable for clinical use.

Methods: This was a prospective, open-label, controlled, three-period, multiple-dose study with nine healthy volunteers. The volunteers received three different dose combinations of amprenavir and delavirdine twice a day for 10 days with a subsequent 12 h pharmacokinetic evaluation. Combination 1: amprenavir 600 mg and delavirdine 600 mg; combination 2: amprenavir 600 mg and delavirdine 800 mg; combination 3: amprenavir 450 mg and delavirdine 1000 mg. The combinations were taken at least 2 weeks apart.

Results: Differences in median delavirdine Cmax, C12 and AUC0–12 were seen when comparing the three combinations (3 > 2 > 1) (P < 0.04). A considerable and clinically important higher median C12 was seen with combination 3 compared to combination 1 (835 to 3944 ng/mL) (P = 0.0039). Only small differences in the amprenavir pharmacokinetic parameters were seen between the three dose combinations, with a median C12 of 412, 434 and 536 ng/mL, respectively.

Conclusions: In this study, an increase of 472% in median delavirdine C12 was seen with a delavirdine dose increase of only 67% (600 to 1000 mg). Saturation of the CYP3A4 enzymes and/or possibly also P-glycoprotein could be involved. Combination 3 was considered most suitable for clinical use, but because of the large inter-individual variation in steady-state concentrations, the use of the combination should be supported by therapeutic drug monitoring and restricted to certain patients.

Keywords: interactions, protease inhibitors, reverse transcriptase inhibitors

Introduction

The use of antiretroviral combination therapy has resulted in long-term suppression of HIV replication, which has been correlated to a decrease in morbidity and mortality for HIV-infected patients receiving treatment.1–3 There is, however, a need for the continuing development of new antiretroviral regimens that are more effective, have fewer side effects and are easier to administer, e.g. reduced pill burden and dose intervals.

Amprenavir is a protease inhibitor used in the treatment of HIV-infected patients. The recommended dose in adults, when not co-administered with ritonavir, is 1200 mg twice a day with or without food.4 Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds directly to the HIV-1 reverse transcriptase, thereby inhibiting viral RNA transcription to proviral DNA. The recommended dose for delavirdine is 400 mg three times a day with or without food.5 Both drugs are primarily metabolized by cytochrome P450 (CYP) 3A4, in the wall of the upper intestine and in the liver.5,6 In vitro data and experiments in rats indicate that delavirdine is an inhibitor and that amprenavir is an inducer of CYP3A4 and the drug transporter P-glycoprotein.7–10

In a steady-state interaction study in healthy volunteers, we have previously shown that the combination of amprenavir 600 mg and delavirdine 600 mg twice a day for 10 days resulted in an increase in the median C12 of amprenavir of 125% (112 to 252 ng/mL), but an 88% decrease in median delavirdine C12 (7916 to 933 ng/mL) compared with the drugs given alone.11 The results have been confirmed by Tran et al.12 The mutual interactions were probably caused by inhibition of intestinal
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CYP3A4 by delavirdine together with induction of hepatic CYP3A4 by amprenavir. The possible involvement of P-glycoprotein is uncertain, as data are limited. The investigated dose combination must be considered unsuitable for clinical use if an effect of delavirdine is required.

Studies have shown that HIV isolates from protease inhibitor-experienced patients are still susceptible to amprenavir, making amprenavir a possible candidate as part of salvage therapy in patients failing another protease inhibitor-containing regimen.11,14 A twice a day regimen with 600 mg of amprenavir combined with 100 mg of ritonavir, a strong inhibitor of CYP3A4, has become widely used because of the favourable pharmacokinetics, resulting in a more than six-fold increase in amprenavir Cmin from 300 to 1920 ng/mL, compared with 1200 mg of amprenavir twice a day without ritonavir.4,16 A 1.32 log10 drop in plasma HIV RNA was achieved in protease inhibitor-experienced patients after 3 months of treatment with this regimen.15 Unfortunately, the use of ritonavir as a pharmacokinetic enhancer is associated with an increase of side effects in some patients, e.g. nausea, diarrhoea and lipid abnormalities. A small study has indicated that treatment with delavirdine can increase high-density lipoprotein cholesterol concentrations, which could make it an alternative to ritonavir in patients with lipid abnormalities.17,19

It is not known whether it is possible, through a change in the dose of delavirdine and/or amprenavir, to achieve antiretroviral effect of both drugs when administered as a combination. The amprenavir/delavirdine combination could be an option for salvage therapy in protease inhibitor-experienced patients, in particular if they are NNRTI-naive, or it might prove useful as a salvage therapy in protease inhibitor-experienced patients. The purpose of this study was to investigate the pharmacokinetics of different dose combinations of amprenavir and delavirdine in order to assess an optimal dose suitable for clinical use. A combination with a delavirdine C12 of ~3700 ng/mL (8.1 mM) and an amprenavir C12 well above 228 ng/mL in protease inhibitor-naive patients, and a amprenavir C12 above 1250 ng/mL in protease inhibitor-experienced patients was assessed to be suitable for clinical use.3,13,20 A safety evaluation of the different combinations was also performed, as doses above 600 mg of delavirdine have not been studied before.

Materials and methods

Study population

Eighteen healthy male volunteers were investigated in the previously reported steady-state interaction study.11 They were included in the study if they matched the following criteria: age 18–50 years; standard medical examination, including electrocardiogram and laboratory tests, without signs of medical illness; seronegative for HIV; haemoglobin, creatinine and alanine aminotransferase within the reference interval; body mass index 19–29 kg/m2. No concomitant medication, herbal medicine (phytomedicine) or grapefruit juice were allowed during the study. Individuals with alcohol abuse, a history of unsuspected allergic or other serious reactions to drugs, psychiatric disease or diseases that could interfere with drug metabolism (gastroenterological, hepatic or renal diseases) were to be excluded from the study. Blood donors were not included if they had given blood, 500 mL within 3 months or 1000 mL within 12 months. All participants gave written informed consent.

Of the 18 participants, nine were randomly selected to participate in the changing dose study, which was complete in immediate connection with the steady-state interaction study.11 All of the nine selected volunteers gave written informed consent. The protocol for the study was approved by the local Ethics Committee (County of Funen and Vejle, case no. 20000007) and the Danish Medicines Agency (Laegemiddelstyrelsen).

Study design

A prospective, open-label, controlled, three-period multiple-dose study with nine healthy volunteers was conducted at a single clinical pharmacology research facility.

The nine healthy volunteers received three different dose combinations of amprenavir and delavirdine (Combinations 1–3). The combinations were taken at least 2 weeks apart (washout period), starting with combination 1, then 2 and finally 3. Combination 1, which was part of the previously reported steady-state interaction study11, involved dosing for 9 days with amprenavir 600 mg (Agenerase, 150 mg capsule) and delavirdine 600 mg (Rescriptor, 200 mg tablet) twice a day, with a 12 h pharmacokinetic evaluation on day 10 after a single dose of amprenavir 600 mg and delavirdine 600 mg in the morning. Combinations 2 and 3 were studied in the same way. Combination 2 was amprenavir 600 mg and delavirdine 800 mg twice a day and combination 3 was amprenavir 450 mg and delavirdine 1000 mg twice a day. The reduced 450 mg dose of amprenavir with combination 3 was chosen to avoid a possible excessive increase in amprenavir concentrations, caused by an expected increase in CYP3A4 inhibition by the 1000 mg dose of delavirdine. The participants were instructed to take the assigned medication with a light meal, apart from the days of the pharmacokinetic evaluation.

The participants reported to the research facility at 07.30 h on the days of the pharmacokinetic evaluations after fasting overnight, which included non-smoking. They were allowed to drink water. The last dose had been taken at ~20.00 h on the evening before. At 08.00 h, the first blood sample was taken from a venous catheter, referred to as blood sample 0 h, and the assigned medication was taken with 200 mL of water. Blood samples were then collected in 10 mL lithium-heparin tubes at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h post-dosing. Samples were centrifuged immediately after collection for 20 min at 800 g to separate the plasma, which was then frozen at ~80°C until analysis. A standardized breakfast of ~500 kcal (25% fat, 20% proteins and 55% carbohydrates) was served after the 1 h blood sample, and the participants had lunch and dinner after the 4 and 10 h blood samples, respectively.

Safety assessment and adverse events

All participants completed a physical examination, including a medical history, electrocardiogram and laboratory tests (haemoglobin, leucocyte count, platelet count, sodium, potassium, creatinine, coagulation factors II, VII, X, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, total bilirubin and HIV antibody) before entering the study. Adverse events were recorded on the days of the pharmacokinetic evaluation. Adverse events were graded 1–4 according to the National Institute of Allergy and Infectious Diseases, Division of AIDS, Table for grading severity of adult adverse experiences, 1992. The duration and number of the events was also noted. The participants were instructed to contact the physician in charge of the study in case of cutaneous pruritus, any rash, fever, conjunctivitis, oral mucosal lesions or if they in any way felt the need to discuss their condition.
Determination of amprenavir and delavirdine concentrations

Plasma concentrations of amprenavir and delavirdine were determined by a validated assay using liquid–liquid extraction followed by high-performance liquid chromatography, with UV detection at a wavelength of 210 nm. Ritonavir from Abbott Laboratories (Abbott Park, IL, USA) was used as an internal standard. Calibrator concentrations were in the range 25–5000 ng/mL for amprenavir and delavirdine, and the calibration curves showed linearity in this concentration range. Accordingly, the lower limit of quantification was defined as 25 ng/mL. If the concentrations of amprenavir or delavirdine from study samples were above the range of the calibrators, the samples were diluted. In each run, quality control samples of 75 and 2500 ng/mL were included. To establish precision and accuracy for the assay, the quality control samples were analysed four times in each of four different series. Accuracy, expressed as percentage bias (%bias), ranged from −4.6 to −0.6 and 3.8 to 8.9 for amprenavir and delavirdine, respectively. Total variation, the sum of within- and between-assay variations, for amprenavir expressed as a percentage coefficient of variation (%CV), was 6.9 and 2.3 at 75 and 2500 ng/mL, respectively. The corresponding values for delavirdine were 4.4 and 2.2, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated from concentration–time data, obtained on the days of the pharmacokinetic evaluation, using the non-compartmental pharmacokinetic method supplied with WinNonlin Standard Edition 3.1 (Pharsight Corporation, Mountain View, California, USA). The maximum plasma concentration at steady-state, \( C_{\text{max}} \), and the time to reach \( C_{\text{max}} \), \( T_{\text{max}} \), were obtained by examination of the concentration–time data, together with steady-state plasma concentrations at 12 h, \( C_{12} \). AUC\(_{0–12}\) was calculated using the linear trapezoidal method. The terminal elimination half-life, \( t_{\text{1/2}} \), was calculated from the final slope of the log-linear concentration–time curve with at least three data sets (\( n \geq 3 \) points).

Statistical analysis

Nine evaluable participants were estimated to be sufficient to detect a difference of >30% in the \( C_{12} \) for amprenavir and delavirdine, with a 0.8 power at the 0.05 level and an intra-individual CV of 20% for the \( C_{12} \). The study would continue until nine participants had finished all three combination periods. Data are presented as medians and interquartile ranges. Results were compared with the Wilcoxon signed rank test, and a \( P \) value of 0.05 or less was considered statistically significant. Hodges–Lehmann estimates of median differences with exact 95% confidence intervals (CI) are presented and differences were considered statistically significant when the 95% CI excluded zero. The statistical analyses were performed using StatXact-3 (Cytel Software Corporation, Cambridge, Massachusetts, USA).

Results

Study population

All nine participants completed the three combination periods. None of the participants was a smoker. Data on the study population as medians and ranges: age 26 years (23–29), weight 77 kg (61–85), height 1.80 m (1.65–1.83) and body mass index 24.7 kg/m\(^2\) (20.1–25.7). All participants were Caucasians.
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Table 1. Amprenavir and delavirdine pharmacokinetic parameters, with the median difference between combinations 1 and 3

<table>
<thead>
<tr>
<th>Amprenavir parameters (n = 9)</th>
<th>Amprenavir/delavirdine 600/600 mg [median (IQR)]</th>
<th>Amprenavir/delavirdine 600/800 mg [median (IQR)]</th>
<th>Amprenavir/delavirdine 450/1000 mg [median (IQR)]</th>
<th>Median difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>5798 (5462–7153)</td>
<td>7377 (6892–8572)</td>
<td>6231 (5985–6593)</td>
<td>ND</td>
</tr>
<tr>
<td>C12 (ng/mL)</td>
<td>412 (252–441)</td>
<td>434 (411–542)</td>
<td>536 (383–596)</td>
<td>139 (4–275)</td>
</tr>
<tr>
<td>AUC0–12 (ng.h/mL)</td>
<td>12156 (11128–15871)</td>
<td>17111 (13651–17749)</td>
<td>14654 (13575–14861)</td>
<td>ND</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.75 (0.75–1.0)</td>
<td>0.75 (0.75–0.75)</td>
<td>1.0 (0.75–1.0)</td>
<td>ND</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>2.4 (2.2–4.5)</td>
<td>3.2 (2.8–3.5)</td>
<td>3.2 (3.0–3.6)</td>
<td>ND</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delavirdine parameters (n = 9)</th>
<th>Amprenavir/delavirdine 600/600 mg [median (IQR)]</th>
<th>Amprenavir/delavirdine 600/800 mg [median (IQR)]</th>
<th>Amprenavir/delavirdine 450/1000 mg [median (IQR)]</th>
<th>Median difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>13110 (9834–14028)</td>
<td>20929 (13400–23371)</td>
<td>28132 (17423–31684)</td>
<td>14890 (7589–24840)</td>
</tr>
<tr>
<td>C12 (ng/mL)</td>
<td>835 (586–1799)</td>
<td>2253 (1594–3207)</td>
<td>3944 (3189–7071)</td>
<td>3645 (2182–7863)</td>
</tr>
<tr>
<td>AUC0–12 (ng.h/mL)</td>
<td>37629 (27325–47145)</td>
<td>57828 (44210–71075)</td>
<td>85160 (70583–112426)</td>
<td>54390 (34240–84120)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.0 (1.0–1.5)</td>
<td>1.0 (1.0–1.5)</td>
<td>1.0 (1.0–1.0)</td>
<td>ND</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>2.6 (2.2–3.1)</td>
<td>3.4 (3.2–4.0)</td>
<td>4.3 (3.9–6.1)</td>
<td>2.1 (0.6–4.0)</td>
</tr>
</tbody>
</table>

*Statistically significant difference at the 0.05 level between: amprenavir/delavirdine 600/600 and 450/1000 mg.
*Statistically significant difference at the 0.05 level between: amprenavir/delavirdine 600/800 and 450/1000 mg.
*Statistically significant difference at the 0.05 level between: amprenavir/delavirdine 600/600 and 450/1000 mg.

There were only minor changes in the amprenavir pharmacokinetic parameters. No decrease in median amprenavir C12, but small decreases in median amprenavir Cmax and AUC0–12 were seen with combination 3, despite the 25% reduction of amprenavir dose. This could have been caused by increased inhibition of intestinal CYP3A4 (and possibly P-glycoprotein) by 1000 mg dose of delavirdine. This would result in increased absorption of amprenavir, culminating in almost the same concentrations as with the 600 mg dose of amprenavir. These findings also indicate that the increased concentrations of delavirdine with combination 3 are caused by the dose increase of delavirdine and not by reduced induction of amprenavir, as amprenavir exposure is almost unchanged.

There was a considerable inter-individual variation in steady-state concentrations of both amprenavir and delavirdine with all the three dose combinations. This makes it very difficult to make firm recommendations concerning the doses that should be used in a heterogeneous patient population. The amprenavir C12 seen with all three combinations makes the regimen unsuitable in protease inhibitor-experienced patients, although extrapolation from healthy volunteers to HIV-infected patients should be made with caution. Most patients will achieve sufficient drug concentrations with dose combination 3, an amprenavir C12>228 ng/mL and a delavirdine C12 of ~3700 ng/mL. The combination could be an option in patients with nucleoside reverse transcriptase-inhibitor intolerance and where more established therapies—combining a protease inhibitor and an NNRTI—are not a possibility, e.g. lopinavir/ritonavir and efavirenz. However, because of the large inter-individual variation in steady-state concentrations, the use of the combination should be supported by therapeutic drug monitoring. Delavirdine appears significantly to increase amprenavir concentrations, but with combinations 1 and 2 the role of delavirdine would only be as a pharmacokinetic enhancer. This could be relevant as second-line therapy in patients with ritonavir intolerance and known NNRTI-resistant virus, where antiretroviral effect of delavirdine is not required.

Delavirdine may prove more useful as a pharmacokinetic enhancer in combination with protease inhibitors without
CYP3A4-inducing capacity. However, because interactions often seem to be unpredictable, this needs to be confirmed through clinical investigations before such combinations are used in clinical practice.

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References