Pharmacokinetic interaction between amprenavir and delavirdine after multiple-dose administration in healthy volunteers

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Aims To evaluate the safety and the pharmacokinetic interaction between amprenavir and delavirdine after multiple dose administration in healthy volunteers.

Methods This was a prospective, open-label, randomized, controlled, two-sequence, two-period multiple dose study with 18 healthy subjects. Volunteers were randomly assigned to amprenavir, 600 mg twice a day, or delavirdine, 600 mg twice a day, for 10 days, followed by both drugs for another 10 days with pharmacokinetic evaluation on day 10 and day 20. Adverse events were recorded throughout the study.

Results Amprenavir decreased all the delavirdine pharmacokinetic parameters apart from $t_{\max}$. Delavirdine C_{12h} dropped from 7916 to 933 ng mL⁻¹ (median decrease 5930 ng mL⁻¹, 95% CI 3013, 8955 ng mL⁻¹). A decrease in amprenavir $t_{1/2}$ was also seen leading to almost identical median amprenavir C_{24h} values. No serious clinical adverse events were observed during the study. The most frequently reported effects were gastrointestinal symptoms, headache, fatigue and rash.

Conclusions Amprenavir is an effective inducer of delavirdine metabolism, probably through its effect on hepatic CYP3A4. This could have consequences in other drug-drug interaction situations. Delavirdine is an inhibitor of amprenavir metabolism. The regimen of amprenavir 600 mg and delavirdine 600 mg twice a day is not recommended when an antiretroviral effect from delavirdine is required.

Keywords: amprenavir, antiretroviral therapy, combination therapy, delavirdine, pharmacokinetic interaction, protease inhibitors, reverse transcriptase inhibitors

Introduction

The use of combination therapy with antiretroviral drugs against HIV has improved the prognosis of HIV-infected patients considerably [1, 2]. However, there is still a need for the development of new antiretroviral regimens that are more potent, easier to administer, with fewer side-effects and lower pill burden.

Amprenavir (APV) is a protease inhibitor (PI) used in the treatment of HIV-infected patients. The recommended dosage in adults, when not coadministered with ritonavir, is 1200 mg twice a day with or without food [3, 4]. Delavirdine (DLV) 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 dosage 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 [6, 7].

A number of studies have shown that HIV isolates from protease inhibitor-experienced patients are still susceptible to amprenavir, making the latter a possible component of salvage therapy in patients failing other protease inhibitor-containing regimens [8–10]. However, the pill burden of the 1200 mg twice a day dose of amprenavir is considerable (16 large capsule).

In vitro data indicate that delavirdine is a potent inhibitor of CYP3A and would inhibit the metabolism of amprenavir [11]. It has been shown, for example, that delavirdine inhibits the metabolism of the protease inhibitor indinavir [12]. The combination with delavirdine might reduce the pill burden of amprenavir without reducing the antiretroviral effect. Furthermore, amprenavir combined with delavirdine could be an option for salvage therapy in protease inhibitor-experienced patients, especially if they are NNRTI-naïve.

Studies on the interaction between amprenavir and delavirdine are scarce. In a small study of HIV-infected children ($n = 6$) treated with amprenavir and delavirdine, there was a five- to ten-fold higher trough concentration

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of amprenavir than observed in adults [13–15]. The plasma concentration of delavirdine was not determined. However, pharmacokinetic studies in adults and children should be compared with caution. A study investigating the effect of a single dose of amprenavir (1200 mg) on the plasma concentration of delavirdine (600 mg twice a day) and the effect of delavirdine (600 mg twice a day) on a single dose of amprenavir (1200 mg) showed a significant increase in the C_{12h} of amprenavir, from 310 ng mL⁻¹ to 1800 ng mL⁻¹ and no clinically significant effect on delavirdine plasma concentrations [16]. Data on steady-state pharmacokinetics of the drugs when given in combination or on their long-term effect on drug metabolism are not available. The purpose of this study was to evaluate the safety and the pharmacokinetic interaction between amprenavir and delavirdine after multiple dose administration in healthy volunteers.

Methods

Study population

Healthy male individuals were included in the study according to the following criteria: age between 18 and 50 years; standard medical examination, including electrocardiogram and laboratory tests, without signs of medical illness; seronegative for HIV; haemoglobin, creatinine and ALT within the reference interval; body mass index between 19 and 29 kg m⁻². No concomitant medication, herbal medicine (phytomedicine) or grapefruit juice were allowed during the study. Individuals with a history of alcohol abuse, unsuspected allergic or other serious reactions to drugs, psychiatric disease or diseases that could interfere with drug metabolism were excluded. Subjects were excluded if they had donated 500 ml blood within 3 months, or 1000 ml within 12 months. All participants 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, randomized, controlled, two-sequence, two-period multiple dose study with 18 healthy volunteers was conducted at a single clinical pharmacology research facility. The volunteers were randomly assigned to either regimen A ($n = 9$) or regimen B ($n = 9$). Regimen A involved dosing for 9 days with amprenavir, 600 mg (Agenerase, 150-mg capsule) twice a day, followed by a 24-h pharmacokinetic evaluation on day 10 after a single dose of amprenavir 600 mg in the morning. Regimen B involved dosing for 9 days with delavirdine, 600 mg (Rescriptor, 200-mg tablet) twice a day, followed by a 24-h pharmacokinetic evaluation on

day 10 after a single dose of delavirdine 600 mg in the morning. Both regimens were followed by regimen C, on day 11, which was amprenavir 600 mg and delavirdine 600 mg twice a day for another 9 days and a 24-h pharmacokinetic evaluation on day 20 after single doses of amprenavir 600 mg and delavirdine 600 mg in the morning. The participants were instructed to take the assigned medication with a light meal, apart from the days of the pharmacokinetic evaluation. The dosage of 600 mg of amprenavir was chosen to reduce the pill burden, but still achieve a C_{12h} well above the estimated EC_{90} of 228 ng mL⁻¹ for amprenavir [17].

Blood sampling

Participants reported to the research facility at 07.30 h on day 10 and day 20 after fasting overnight, and refraining from smoking. They were allowed to drink water throughout the study. The last dose of drug had been taken at approximately 20.00 h on the evening before. At 08.00 h, the first blood sample (0 h) was taken from a venous catheter, 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, 12 and 24 h postdosing. 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 was served after the 1 h blood sample and the participants had lunch and dinner after the 4 h and 10 h blood samples, respectively.

Safety assessment and adverse events

All participants underwent 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, LDH, ALT, total bilirubin and HIV antibody) before entering the study. Adverse events were recorded on the day of the pharmacokinetic evaluation, days 10 and 20. 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 [18]. The duration and number of the events were also noted. The participants were instructed to contact the physician in charge of the study if they developed cutaneous pruritus, 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 simultaneously by high-performance

liquid chromatography (HPLC) using 500 µl of plasma. To the plasma sample, calibrator or control were added 50 µl of aqueous ammonium acetate (1 mol l^{-1}), and 50 µl of an internal standard solution, 8000 ng ml $^{-1}$ of ritonavir (Abbott Laboratories, Abbott Park, IL, USA). The drugs were isolated by liquid-liquid extraction with 5 ml of heptane-ethyl acetate, 1:1. Organic phase (4.2 ml) was transferred to a conical glass tube and evaporated to dryness at 37°C under a gentle stream of nitrogen. The residue was redissolved in 300 µl of phosphate buffer (5 mmol l^{-1} and pH 3.5) containing 20% methanol and 20% acetonitrile. The solution was washed with 3 ml of heptane and 50 µl of the buffer layer were injected. Chromatography was performed on a LiChrospher column 100 CN ($250 \times 4 \text{ mm}$, 5 µm particle size) (Merck, Darmstadt, Germany) with u.v. detection at a wavelength of 210 nm. The mobile phase consisted of 59 ml of potassium dihydrogen phosphate (0.04 mol l^{-1} and pH 4.5), 25.5 ml of methanol and 15.5 ml of acetonitrile. Concentrations of standards ranged from 25 ng ml $^{-1}$ to 5000 ng ml $^{-1}$ for both drugs, and the calibration curves showed linearity over this concentration range. In each run, quality control samples of 75 ng ml $^{-1}$ and 2500 ng ml $^{-1}$ 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, 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 percentage coefficient of variance (%CV), was 6.9% and 2.3% at 75 ng ml $^{-1}$ and 2500 ng ml $^{-1}$, respectively. The corresponding values for delavirdine were 4.4% and 2.2%, respectively. The limit of determination was 15.6 ng ml $^{-1}$ for amprenavir and 9.9 ng ml $^{-1}$ for delavirdine.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated from concentration-time data obtained on day 10 and day 20, using noncompartmental methods (WinNonlin Standard Edition 3.1; Pharsight Corp., Mountain View, CA, USA). The maximum plasma concentration at steady state, $C_{\text{max,ss}}$, and the time to reach $C_{\text{max,ss}}$, $t_{\text{max,ss}}$, were obtained directly from the concentration-time data, as were steady-state plasma concentrations at 12 h and 24 h ($C_{12\text{h,ss}}$ and $C_{24\text{h,ss}}$). $AUC_{(0-12\text{h})}$ was calculated using the linear trapezoidal method. The elimination half-life, $t_{1/2}$, was calculated from the final slope of the log-linear concentration-time curve with at least three data sets ($n \geq 3$ points). To improve the precision of the estimate of $t_{1/2}$, the $C_{24\text{h,ss}}$ sample was analysed in duplicate.

Statistical analysis

It was estimated that nine evaluable participants per treatment regimen were needed to detect a difference of >30% in $AUC_{(0-12\text{h})}$ for amprenavir and delavirdine with a power of 0.8 at the 0.05 significance level and an intraindividual CV of 20% for the $AUC_{(0-12\text{h})}$. The study continued until nine participants in each group had completed the protocol. Data are presented as medians and ranges. Results were compared with the Wilcoxon signed rank test. The statistical test values presented are Hodges-Lehmann estimates of median differences with exact 95% confidence intervals (CI). Differences were considered statistically significant when the 95% CI excluded zero. The statistical analyses were performed using StatXact-3 (Cytel Software Corp., Cambridge, MA, USA).

Results

Study population

Twenty participants were screened. One participant withdrew consent because he was unable to participate on the given dates. A second participant was excluded because of an ALT value above the reference interval. None of the remaining 18 participants was a smoker. Data on the study population are given in Table 1.

Effect of amprenavir on the pharmacokinetics of delavirdine

A considerable decrease of 88% in the median delavirdine $C_{12\text{h}}$ from 7916 to 933 ng ml $^{-1}$ was seen (Table 2). The median delavirdine $AUC_{(0-12\text{h})}$ and C_{max} also decreased by 61% and 47%, respectively, when coadministered with amprenavir.

Effect of delavirdine on the pharmacokinetics of amprenavir

Delavirdine caused an increase in the median $C_{12\text{h}}$ (125%), C_{max} (40%) and $AUC_{(0-12\text{h})}$ (130%) values for amprenavir (Table 2). A decrease in the amprenavir $t_{1/2}$ was also seen, leading to almost identical median amprenavir $C_{24\text{h}}$ values ($P = 0.31$). The median plasma amprenavir and delavirdine concentration-time curves alone and in combination are shown in Figures 1 and 2. No differences in t_{max} were observed. All other differences were significantly different from zero with a P -value <0.02.

The two subject groups had similar pharmacokinetic parameters when the two drugs were coadministered. Median delavirdine C_{max} , $C_{12\text{h}}$ and $AUC_{(0-12\text{h})}$ values were 13110 ng ml $^{-1}$ h (12 684), 1493 ng ml $^{-1}$ h (933) and 62 824 ng ml $^{-1}$ h (62 715), respectively, for the participants starting on amprenavir, and 7121 ng ml $^{-1}$ h

Table 1 Baseline characteristics of the study populations.

	APV 600 mg $\times$ 2 (n = 9)	DLV 600 mg $\times$ 2 (n = 9)	Total (n = 18)
Age (years)	27 (24–30)*	25 (23–27)	25.5 (23–30)
Weight (kg)	81 (67–85)	73 (61–93)	77 (61–93)
Height (m)	1.81 (1.78–1.90)	1.80 (1.65–1.81)	1.805 (1.65–1.90)
BMI (kg m ⁻²)	23.8 (20.5–25.4)	23.8 (20.1–28.7)	23.8 (20.1–28.7)
Race			
White	9	7	16
Other	0	2	2

APV, Amprenavir; DLV, delavirdine; BMI, body mass index. *Values are given as medians and ranges.

Table 2 Amprenavir (APV) and delavirdine (DLV) pharmacokinetic parameters.

Parameter	APV 600 mg $\times$ 2 (n = 9) Median and range	APV 600 mg $\times$ 2 ⁺ DLV 600 mg $\times$ 2 (n = 9) Median and range	Median difference and 95% CI
APV			
$C_{\max}$ (ng ml ⁻¹)	4737 (2798–9602)	6643 (4285–10 237)	1468 (553; 2527)
C_{12h} (ng ml ⁻¹)	112 (53–287)	252 (76–604)	150 (50; 259)
C_{24h} (ng ml ⁻¹)	36 (13–139)	42 (16–210)	14 (–12; 40)
$AUC_{(0-12h)}$ (ng ml ⁻¹ h)	8737 (5829–17 538)	20059 (11 391–34 143)	10 230 (7262; 13 490)
$t_{\max}$ (h)	0.75 (0.5–1.5)	0.75 (0.5–1.5)	No difference
$t_{1/2}$ (h)	7.0 (4.4–11.9)	4.8 (2.9–7.4)	–1.8 (–0.7; –3.0)
DLV			
$C_{\max}$ (ng ml ⁻¹)	24 085 (10 292–29 632)	12 684 (7650–18 019)	–7757 (–13 340; –1943)
C_{12h} (ng ml ⁻¹)	7916 (1721–11 562)	933 (516–2547)	–5930 (–8955; –3013)
C_{24h} (ng ml ⁻¹)	1920 (89–4697)	42 (13–255)	–1039 (–2561; –192)
$AUC_{(0-12h)}$ (ng ml ⁻¹ h)	160 609 (60 884–223 183)	62 715 (40 307–87 298)	–79 250 (–133 500; –34 340)
$t_{\max}$ (h)	1.5 (0.75–1.5)	1.5 (0.75–1.5)	No difference
$t_{1/2}$ (h)	5.7 (2.7–9.6)	2.5 (2.2–3.8)	–3.2 (–5.3; –1.4)

Figure 1 Median plasma amprenavir (APV) concentration-time curves after the last dose of the two regimens used. DLV, Delavirdine.

(6643), 412 ng ml⁻¹ h (252) and 25 943 ng ml⁻¹ h (20 059), respectively, for the participants starting on delavirdine (Table 2). These findings indicate that the order of administration of amprenavir and delavirdine

did not have an effect on the magnitude of the interaction.

Adverse events

No serious clinical adverse events were reported (Table 3). The most frequently reported effects were gastrointestinal symptoms, headache, fatigue and rash. Of these, only the rashes and one event with nausea were assessed as grade 2. Rashes were most often maculopapular and started on day 8 or day 9 during either the amprenavir or delavirdine regimen with a similar incidence. They lasted for 3–4 days, with no other symptoms. Rashes were limited to the extremities and sometimes the torso or neck, and disappeared without stopping drug exposure. There were no major differences in the occurrence of adverse events between the amprenavir and delavirdine regimens. They were generally more frequent during regimen C, but this did not apply to any particular adverse event. One participant presented on day 17, during regimen C, with a mucosal

erythema under the tongue. At the time of the pharmacokinetic evaluation (day 20) it had almost disappeared, but a small mucosal plaque very similar to an aphthae was present. He did not contact the physician in charge of the study at the time. The event was not considered related to either amprenavir or delavirdine exposure. In general, the regimens were very well tolerated and all participants completed the study

Discussion

Our data show a drug-drug interaction between amprenavir and delavirdine. A favourable increase in

Figure 2 Median plasma delavirdine (DLV) concentration-time curves after the last dose of the two regimens used. APV, Amprenavir.

amprenavir C_{12h} but a dramatic decrease in delavirdine C_{12h} was seen. The coadministration of amprenavir 600 mg and delavirdine 600 mg resulted in a amprenavir C_{12h} of 252 ng ml⁻¹, which is comparable to the trough value of 280 ng ml⁻¹ obtained at steady state in HIV-infected patients treated with amprenavir, 1200 mg twice a day [17]. A C_{12h} value of 7916 ng ml⁻¹, when delavirdine was given alone, is somewhat higher than the C_{min} value of 5479 ng ml⁻¹ from a similar study in healthy volunteers ($n = 12$) receiving 600 mg delavirdine twice a day [16].

The decrease in $t_{1/2}$ for both amprenavir and delavirdine suggests that the systemic clearance of both drugs is increased because of induction of hepatic CYP3A4. A study in rats has shown that plasma concentrations of amprenavir are reduced after dosing for 14 days, and this was accompanied by an increase in hepatic CYP3A protein levels [19]. An increase in the $t_{1/2}$ of amprenavir was expected during concomitant intake of delavirdine. However, a small but statistically significant decrease was observed (Table 2). This could be due to delavirdine lowering the volume of distribution of amprenavir more than it decreases its clearance. The increase in C_{max} for amprenavir and decrease in this parameter for delavirdine could be caused by interaction in the intestine. One mechanism might be induction of intestinal CYP3A4, leading to greater first pass metabolism of delavirdine and a decrease in C_{max} . Delavirdine has been shown to bind irreversibly to CYP3A, thereby serving as a CYP3A inhibitor, and this could explain the simultaneous increase in amprenavir C_{max} [20]. These changes could be mediated by intestinal P-glycoprotein. The above-

Table 3 Adverse events by drug regimen.

Adverse event	APV 600 mg × 2 (n = 9)	DLV 600 mg × 2 (n = 9)	APV 600 mg × 2 + DLV 600 mg × 2 (n = 18)
No. of participants experiencing any adverse event	7 (78%)	6 (67%)	15 (83%)
Headache	1 (11%)	3 (33%)	2 (11%)
Fatigue	3 (33%)	1 (11%)	6 (33%)
Fever	0	0	1 (6%)
Oral/perioral parasthesia	1 (11%)	0	1 (6%)
Nausea/vomiting	0	1 (11%)	3 (17%)
Gaseous symptoms	2 (22%)	0	2 (11%)
Loose stools	2 (22%)	1 (11%)	2 (11%)
Abdominal pain	0	1 (11%)	0
Rash	4 (44%)	5 (56%)	9 (50%)
Mucosal erythema/plaque	0	0	1 (6%)★
Cutaneous pruritus	1 (11%)	0	0
Respiratory infection or general malaise	1 (11%)	1 (11%)	2 (11%)
Miscellaneous	3 (33%)†	3 (33%)‡	0

APV, Amprenavir; DLV, delavirdine. ★Grade 3, probably not related to drugs. †Conjunctivitis, metallic taste (taste disorder) and one event of difficulties falling asleep (sleep disorder). ‡More thirsty than normal, urine darker than normal and feeling hot.

mentioned study with amprenavir in rats also showed induction of intestinal P-glycoprotein. It is possible that delavirdine could act as an inhibitor of P-glycoprotein, and this could also explain the increase in amprenavir $C_{\max}$. The combination of effects on $t_{1/2}$ and $C_{\max}$ suggests that amprenavir has an inducing effect on hepatic CYP3A4, which cannot be overcome by the inhibitory effect of delavirdine. *In vitro* data have shown that delavirdine is also an inhibitor of CYP2C9 and CYP2C19 activity, which have been reported to be involved in amprenavir metabolism, although to a lesser extent [4, 11]. Thus it is unlikely that effects on CYP2C9 or CYP2C19 would have a major influence on the pharmacokinetics of these drugs.

Considerable interindividual variation in steady-state concentrations of both amprenavir and delavirdine was observed. Four of the participants had a C_{12h} value $<252 \text{ ng mL}^{-1}$. This means that in a clinical setting some patients could have subtherapeutic concentrations of both amprenavir and delavirdine, based on estimated amprenavir EC_{90} of 228 ng mL^{-1} [17]. Furthermore, patients failing on another protease inhibitor-containing regimen might harbour virus with reduced drug susceptibility and would have to achieve even higher concentrations of drug to obtain a virological response. When a new regimen with PIs or NNRTIs is initiated, the measurement of plasma drug concentrations gives the opportunity of making dose changes early on, before virological failure develops.

The adverse events observed during this study were as expected and comparable to other studies with amprenavir and delavirdine both in HIV-infected patients and in healthy volunteers [12, 21–24].

On the basis of the results of the present study, the regimen amprenavir 600 mg and delavirdine 600 mg twice a day, is not recommended when an antiretroviral effect from delavirdine is required. The very low delavirdine plasma concentrations would probably result in rapid development of resistance towards this drug, thereby eliminating any potential benefit of treatment. Future use of another NNRTI, such as efavirenz or nevirapine, would also be affected because of cross-resistance. The increase in amprenavir C_{12h} could also have been achieved with ritonavir [24]. However, a regimen of amprenavir and ritonavir would not provide antiretroviral effect against reverse transcriptase. Ongoing studies will elucidate whether increasing doses of delavirdine could circumvent the inducing effect of amprenavir, thus making the combination suitable for clinical use.

In conclusion, amprenavir is an effective inducer of delavirdine metabolism, probably through its effect on hepatic CYP3A4. Given the magnitude of the reduction in delavirdine concentrations induced by amprenavir, it may be difficult to achieve effective antiretroviral con-

centrations of delavirdine when coadministered with amprenavir. The extent of this interaction suggests that amprenavir may reduce plasma concentrations of other drugs metabolized by CYP3A4. Additionally, although it might not be possible to achieve effective antiretroviral concentrations of delavirdine when amprenavir and delavirdine are coadministered, delavirdine appears to boost amprenavir concentrations, and may prove to be useful for this purpose, particularly in patients who are intolerant of ritonavir.

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