Pharmacokinetic evidence for the induction of lopinavir metabolism by efavirenz

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Aims

The influence of efavirenz on lopinavir pharmacokinetics was investigated using a population approach.

Methods

Forty-five HIV patients treated with lopinavir/ritonavir plus efavirenz (A) and 24 patients treated with lopinavir/ritonavir plus nucleoside/nucleotide reverse transcriptase inhibitors (B) were studied.

Results

A relationship ($P < 0.01$) was established between the elimination rate constant of lopinavir (k_{10}) and treatment with efavirenz. Mean k_{10} was higher in group A than in group B (0.3838 vs 0.2810 h⁻¹) ($P < 0.001$, 95% confidence interval for difference between means 0.1004 , 0.1052).

Conclusions

These results suggest that lopinavir metabolism is induced by efavirenz.

Introduction

The combination of lopinavir/ritonavir, efavirenz and either two nucleoside reverse transcriptase inhibitors [1] or no antiretroviral drug [2] is a promising therapy in HIV-infected patients. However, several studies have shown that increased lopinavir/ritonavir dosage is necessary when this combination is administered with efavirenz to maintain an effective plasma concentration of lopinavir [3, 4]. This finding could be explained by the induction of lopinavir metabolism by efavirenz. The objective of the present study was to clarify the mechanism of the interaction between lopinavir and efavirenz using a population pharmacokinetic approach.

Methods

Patients

The population was composed of 53 male and 16 female patients infected with HIV (mean age of 39.2 years). Forty-five patients (group A) were treated with a regimen containing efavirenz (600 mg once daily), lopinavir/ritonavir (533.3/133.3 mg twice daily) and no other antiretroviral drug and 24 patients (group B) were treated with a regimen containing lopinavir/ritonavir (400/100 mg twice a day for 22 patients and 266.6/66.6 mg twice a day for two patients) and nucleoside/nucleotide reverse transcriptase inhibitors. Forty-three of the patients treated with the combination efavirenz

and lopinavir/ritonavir participated in the BIKS study, a multicentre open label controlled trial that assessed the efficacy/tolerability of this therapeutic combination [2]. Samples from the other patients were obtained in the context of routine therapeutic drug monitoring. Informed consent was obtained for the patients in the BIKS study, but was not required for the other patients since data were derived from a therapeutic drug monitoring programme and were reported anonymously in accordance with ethical guidelines. A total of 94 samples was collected at steady state. The mean number of samples per patient was 1.36 (range 1–5).

Analysis of lopinavir

Lopinavir plasma concentrations were determined according to a previously validated HPLC assay with UV detection [5]. The limit of quantification was 0.2 mg l^{-1} . The method was linear over the range $0.2\text{--}20 \text{ mg l}^{-1}$, was accurate (interday and intraday inaccuracy $\leq 10\%$) and showed good precision (interday and intraday imprecision $\leq 10.5\%$).

Population pharmacokinetic analysis

Basic pharmacokinetic model Data were analyzed by a nonlinear mixed effect modelling method using MP2 software (Micropharm Population, INSERM, Paris, France). A one-compartment model with first order input described the data adequately. The parameters of the basic pharmacokinetic model are V/F (volume of distribution), k_a (absorption rate constant) and k_{10} (elimination rate constant). F denotes bioavailability. Inter-patient and residual variability were best described by proportional error models.

Selection of covariates The influence of several covariates on V/F , k_a , k_{10} was assessed. These were age, gender (1 for male, 0 for female) and the combination of lopinavir with efavirenz (1 for the regimen with efavirenz, 0 for other regimens). The full and reduced models were compared using the chi-squared test. A decrease of at least 3.8 ($P < 0.05$, one degree of freedom) in the objective function value compared with that of the basic pharmacokinetic model was required for the addition of a single covariate in the model. An intermediate multivariate model was obtained including all significant covariates. During backward stepwise multiple regression analysis, a change of 6.63 ($P < 0.01$) in the objective function in the final multivariate model was required for the retention of a single covariate. Models were assessed by comparison of their respective objective function values and by visual examination of residual plots. The

predictive performance of the model was assessed also in terms of precision (the square root of the mean of square difference between C_{obs} (observed plasma concentration of lopinavir) and C_{pred} (model predicted concentration of lopinavir)) and bias (the mean difference between C_{obs} and C_{pred}).

Bayesian estimation From the final model, individual pharmacokinetic parameters were estimated by a Bayesian method and their mean values from groups A and B were compared by a Student's *t*-test. The individual trough plasma concentrations were calculated from these individual pharmacokinetics parameters. For the patients that did not have a recorded trough concentration, values were estimated from individual pharmacokinetic parameters.

Results

Plasma concentration vs time data after the last dose of lopinavir are presented in Figure 1. Efavirenz co-administration was the only covariate identified that significantly affected the pharmacokinetics of lopinavir. The effect of efavirenz on k_{10} was defined by the relationship $k_{10} = 0.1025 \times (\text{efavirenz in the antiretroviral treatment} = 1) + 0.2825$. The decrease in the objective function from 333 in the basic pharmacokinetic model to 326 in the final model exceeded the objective function cut-off value of 6.63. This improvement in fit is also evident from the relationship between the weighted residuals $[(C_{\text{obs}} - C_{\text{pred}})/C_{\text{pred}}]$ and C_{pred} . The equation derived by linear regression from the final model $[(C_{\text{obs}} - C_{\text{pred}})/C_{\text{pred}} = 0.077 - 0.014 \times C_{\text{pred}}]$ is closer to the theoretical equation $[(C_{\text{obs}} - C_{\text{pred}})/C_{\text{pred}} = 0]$ than that from the basic model $[(C_{\text{obs}} - C_{\text{pred}})/C_{\text{pred}} = 0.59]$

Figure 1

Plasma lopinavir concentrations in 69 HIV infected patients vs time after last dose. Forty-five patients were treated with lopinavir/ritonavir and efavirenz (◆) and 24 patients with lopinavir/ritonavir and nucleoside/nucleotide reverse transcriptase inhibitors (□)

Table 1

Comparison of lopinavir pharmacokinetic parameters for patients treated with lopinavir/ritonavir and efavirenz (group A) and patients treated with lopinavir/ritonavir and nucleoside/nucleotide reverse transcriptase inhibitors (group B)

	Group A	Group B	Student's <i>t</i> -test (<i>P</i>)	Difference in mean value between groups A and B
k_{10} (h^{-1})	0.3838 [0.3826, 0.3850]	0.2810 [0.2785, 0.2835]	<0.001	0.1028 [0.1004, 0.1052]
$t_{1/2}$ (h)	1.81 [1.804, 1.816]	2.47 [2.446, 2.494]	<0.001	-0.66 [-0.679, -0.641]
k_a (h^{-1})	0.0345 [0.03444, 0.03456]	0.0346 [0.03454, 0.03465]	NS	-0.0001 [-0.00014, -0.00005]
V/F (l)	25.31 [18.5, 32.27]	20.52 [14.87, 26.17]	NS	4.79 [-5.61, 15.19]

Results are expressed as means, 95% confidence intervals are shown in square brackets.

$-0.095 \times C_{\text{pred}}$. Bias was low in both models (basic = -0.069 , final = -0.052), but precision was decreased (from 4.20 to 4.08) in the final model, which indicates an improvement in fit. The convergence of these different elements showed the improvement in the model was due to the incorporation of the effect of efavirenz on the elimination rate constant. Thus k_{10} was significantly higher in group A than in group B ($P < 0.001$) (Table 1). The mean trough plasma concentration was not significantly different between the patients treated with lopinavir/ritonavir (533.3/133.3 mg twice a day) plus efavirenz ($6.1 \pm 2.6 \text{ mg l}^{-1}$) and the patients treated with lopinavir/ritonavir (400/100 mg twice a day) plus nucleoside/nucleotide reverse transcriptase inhibitors ($5.6 \pm 2.1 \text{ mg l}^{-1}$).

Discussion

Consistent with previous results [3, 4], no significant difference in the mean trough plasma concentration of lopinavir was found between patients treated with lopinavir/ritonavir (533.3/133.3 mg) plus efavirenz and patients receiving 400/100 mg of lopinavir/ritonavir without efavirenz but with nucleoside/nucleotide reverse transcriptase inhibitors. However, an increase in the elimination rate constant for lopinavir during administration with efavirenz was observed. Since no significant influence of the nucleoside/nucleotide reverse transcriptase inhibitors on lopinavir pharmacokinetics was expected [6] and a decrease in the plasma concentration of protease inhibitors following co-administration of efavirenz has been demonstrated [7], induction of lopinavir metabolism by efavirenz seems to be the most likely explanation for these findings.

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