



Neither MDR1 Genotypes (C3435T, G2677T/A, C1236T) nor Hepatic and Intestinal CYP 3A4 Activity Are Associated with Plasma and Intracellular Concentrations of Lopinavir and Ritonavir

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Background

Protease inhibitors (PIs) are substrates of Cytochrome P450 3A4 (CYP3A4) and of transporters such as P-glycoprotein (P-gp), a product of the multi-drug resistance (MDR1) gene. Previous studies demonstrated discordant results concerning associations between CYP3A4 activity, genetic variations in MDR1 and P-gp expression on peripheral blood mononuclear cells (PBMCs) on the one hand and plasma and intracellular concentrations (IC) of PIs on the other hand. The aim of this study was to comprehensively evaluate the influence and clinical relevance of MDR1 polymorphisms and of CYP3A4 activity on Lopinavir (LPV) and Ritonavir (RTV) drug concentrations in vivo.

METHODS

In a prospective study, 30 treatment-naïve HIV infected patients were phenotyped for hepatic and intestinal CYP3A4 activity as published earlier (Jabrane et al., *Eur J Clin Pharmacol* 2001; 57: A35) before and after start of an antiretroviral regimen (ART) containing LPV and RTV. MDR1 genotypes (C3435T, G2677T/A and C1236T) were determined by real-time PCR. 12-hours plasma concentrations of LPV and RTV were analysed using HPLC and pharmacokinetic (PK) parameters were calculated using noncompartmental methods. In 10 patients, 12-h monitoring of intracellular (IC) drug concentrations was performed, and expression of P-gp, MRP1 (multidrug resistance associated protein 1) and BCRP (breast cancer resistant protein) on PBMCs was investigated.

RESULTS

28 patients were eligible for analysis. Large interindividual variability in LPV and RTV pharmacokinetics in plasma and IC was observed. Hepatic and intestinal CYP3A4 activity measured before and under ART did not correlate with plasma PK (AUC_{0-12h} , $C_{through}$) of LPV and RTV. As to the effect of MDR1 genotypes C3435T, G2677T/A and C1236T on plasma concentrations, we found a trend towards lower plasma- AUC_{0-12} of RTV with TT genotype of G2677T/A (GG vs TT, $p=0.079$). LPV plasma concentrations were not associated with MDR1 genotype at all. Plasma-LPV exposure (AUC_{0-12h}) was significantly correlated with IC concentrations ($p=0.01$), but for RTV no relationship between plasma and IC exposure could be demonstrated. IC accumulation of both LPV and RTV was not associated with lymphocyte surface expression of P-gp, MRP1 and BCRP.

All patients (n;[%])	30	(100)
female	7	(23)
male	23	(77)
Mode of transmission (n;[%])		
Gay or bisexual man	19	(63)
Heterosexual	10	(33)
Injecting drug use	1	(3)
Median age (years, [range])	39.2	(25.2-60.2)
Ethnic groups (n;[%])		
African	5	(17)
Caucasian	25	(83)
CDC Status (n;[%])		
A	4	(13)
B	17	(57)
C	9	(30)
Median CD4 ⁺ count at baseline (cells/ μ L, [range])	155	(10-330)
HIV-RNA at baseline (copies/mL, [range])	114,000	(5,000-500,000)

Tab. 1: Baseline characteristics.

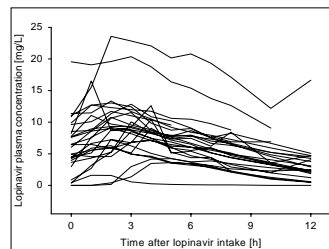


Fig. 1: LPV plasma concentration over the 12h dosage interval (n=28).

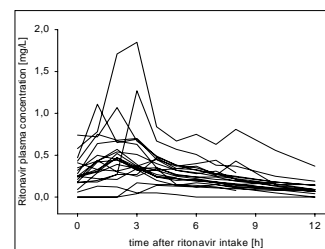


Fig. 2: RTV plasma concentration over the 12h dosage interval (n=28).

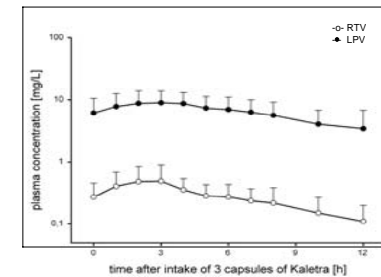


Fig. 3: 12- hours median plasma concentrations of LPV and RTV (n=28).

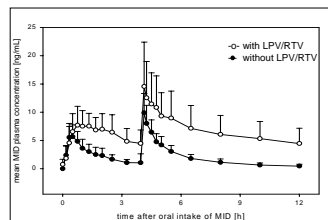


Fig. 4: Mean midazolam plasma concentration before and after at least 2 weeks of treatment with LPV and RTV (n=28).

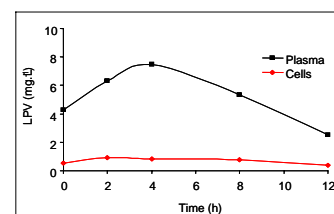


Fig. 5: Median LPV concentration within plasma and cellular compartments over the 12h dosage interval ($p = 0.01$; n=10).

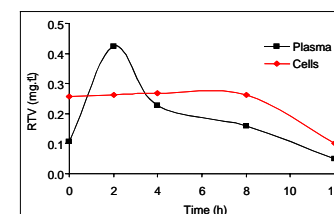


Fig. 6: RTV concentration within plasma and cellular compartments over the 12h dosage interval ($p = 0.6$; n=10).

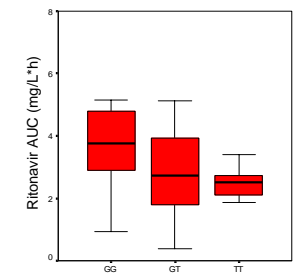


Fig.7: Plasma AUC of RTV and genotypes of G2677T/A (GG vs. TT, $p=0.079$; n=28)

CONCLUSION

Neither variations in hepatic and intestinal CYP3A4 activity nor genetic variations of MDR1 showed a correlation with LPV and RTV plasma concentrations. Furthermore, in a small cohort of patients, IC concentrations of LPV and RTV were not related to expression of different efflux transporters on lymphocytes. Further studies in larger populations are required to shed more light on the complex relationship between different genetic variables and plasma concentrations of PIs.