

The Effect of Atazanavir and Atazanavir/Ritonavir on UGT1A4 Using Lamotrigine as a Phenotypic Probe

David M. Burger
864 Department of Clinical Pharmacy
Radboud University Nijmegen Medical Center
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel: +31-24-3616405
Fax: +31 24 3668755
e-mail: D.Burger@akf.umcn.nl

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D.M. Burger¹, A. Huisman¹, N. van Ewijk¹, H. Neisingh¹, G. Rongen¹, P. Koopmans¹, R. Bertz²
¹Radboud University Nijmegen Medical Center, The Netherlands; ²Bristol-Myers Squibb, USA

Abstract

Background: Antiretroviral agents are well-known for their effects on cytochrome P450 enzymes leading to various drug-drug interactions. Some agents also influence other metabolizing enzymes such as UDP-Glucuronosyl-Transferases (UGT). We have recently shown that lopinavir/ritonavir induces glucuronidation using lamotrigine (LTG) as phenotypic probe for UGT1A4 (reduction in AUC of 55%; Van der Lee et al. Clin Pharmacol Ther 2006). Atazanavir (ATV) is known to inhibit glucuronidation through UGT1A1, leading to asymptomatic hyperbilirubinemia. The objective of this study was to evaluate the effect of ATV and ATV/r on UGT1A4 using LTG as phenotypic probe.

Methods: Twenty-one healthy male volunteers received a single dose of 100mg of LTG on three occasions (Days 1, 13, and 27); on each occasion blood was sampled predose and through 120h post ingestion (13 samples). From Day 8-17 subjects took ATV 400mg QD. From Day 18-30 subjects took ATV 300mg plus ritonavir 100mg QD. Pharmacokinetic parameters were calculated using WinNonlin software version 4.1. Geometric Mean Ratios (GMRs) + 90% confidence interval (CI) of LTG AUC and C_{max} in the two test periods (ATV or ATV/r) vs. in the reference period (LTG alone) were calculated. The absence of an interaction corresponds to the 90% CI of the GMR falling completely within 0.80-1.25.

Results: Seventeen subjects completed the trial. Four subjects were withdrawn from the study (protocol violation: 1; personal reasons: 1; nonadherence: 1; rash and neurological symptoms: 1). GMRs (+ 90% CI) of LTG AUC_{0-inf} and C_{max} when taken with ATV vs. LTG alone were 0.88 (0.86-0.91) and 0.99 (0.95-1.02), respectively, indicating no relevant interaction between ATV and LTG occurred. GMRs (+ 90% CI) of LTG AUC_{0-inf} and C_{max} when taken with ATV/r vs. LTG alone were 0.68 (0.65-0.70) and 0.94 (0.90-0.97), indicating an interaction between ATV/r and LTG was observed. In agreement with these observations, the mean (+SD) ratio of LTG-2N-glucuronide and LTG AUC_{0-inf} increased from 0.45 (0.09) when LTG was taken alone to 0.52 (0.13) when LTG was taken with ATV, and to 0.71 (0.11) when LTG was taken with ATV/r (both p<0.001; paired-samples T-test). ATV and RTV plasma concentrations were comparable to historical controls (Burger et al. AAC 2006).

Conclusions: ATV alone does not significantly influence glucuronidation of single dose LTG. In contrast, ATV/r resulted in moderately decreased exposure (32% decrease in AUC_{0-inf}) to LTG.

1. Introduction

- Antiretroviral agents are well-known for their effects on CYP₄₅₀ enzymes; some agents also influence other metabolizing enzymes such as UDP-Glucuronosyl-Transferases (UGT).
- We have recently shown that lopinavir/ritonavir induces glucuronidation using lamotrigine (LTG) as phenotypic probe for UGT1A4 (Van der Lee et al. Clin Pharmacol Ther 2006).
- Atazanavir (ATV) is known to inhibit glucuronidation through UGT1A1, leading to asymptomatic hyperbilirubinemia.
- The objective of this study was to evaluate the effect of ATV and ATV/r on UGT1A4 using LTG as phenotypic probe.

2. Methods

- Twenty-one healthy male volunteers received a single dose of 100mg of LTG on three occasions (Days 1, 13, and 27)
- On each occasion blood was sampled predose and through 120h post ingestion (13 samples).
- From Day 8-17 subjects took ATV 400mg QD.
- From Day 18-30 subjects took ATV 300mg plus ritonavir 100mg QD.

2. Methods (continued)

- Pharmacokinetic parameters were calculated using WinNonlin software version 4.1.
- Geometric Mean Ratios (GMRs) + 90% confidence interval (CI) of LTG AUC and C_{max} in the two test periods (ATV or ATV/r) vs. in the reference period (LTG alone) were calculated.
- The absence of an interaction corresponds to the 90% CI of the GMR falling completely within 0.80-1.25.

3. Results

- Four subjects were withdrawn from the study (protocol violation: 1; personal reasons: 1; nonadherence: 1; rash and neurological symptoms: 1).
- Seventeen subjects completed the trial (15 Caucasians; 1 Black; 1 other).
- Mean (+SD) age, body weight, BMI and length of the 17 subjects was 35 (13) years, 77 (7) kg, 24 (2) kg/m² and 1.79 (0.05) m, respectively.
- GMRs (+ 90% CI) of LTG AUC_{0-inf} and C_{max} are listed in **Table 1** LTG plasma concentration vs. time curves are presented in **Figure 1**.
- Mean (+SD) ratios of LTG-2N-glucuronide and LTG AUC_{0-inf} were 0.45 (0.09), 0.52 (0.13) and 0.71 (0.11) when LTG was taken alone, with ATV, or with ATV/r, respectively (paired samples T-test: both p < 0.001 for LTG+ATV vs. LTG alone and LTG+ATV/r vs. LTG alone).
- ATV and RTV plasma concentration vs. time curves are presented in **Figure 2** ATV and RTV PK parameters were comparable to historical controls (Burger et al. AAC 2006)

Table 1. Geometric Mean Ratios and 90%CI of LTG PK parameters for the LTG/ATV (test 1) and LTG/ATV/r (test 2) relative to LTG alone (reference)

Pharmacokinetic parameter	Geometric Means		Ratios of GMs Point Estimate (90% CI)
	LTG/ATV Day 13 (n=17)	LTG Day 1 (n=17)	
AUC(INF), (mg/L.h)	41.36	46.76	0.88 (0.86-0.91)
Cmax (mg/L)	1.07	1.09	0.99 (0.95-1.02)
	LTG/ATV/RTV		
	Day 27 (n=17)	LTG Day 1 (n=17)	
AUC(INF), (mg/L.h)	31.61	46.76	0.68 (0.65-0.70)
Cmax (mg/L)	1.02	1.09	0.94 (0.90-0.97)

Figure 1. LTG plasma concentration vs. time curves

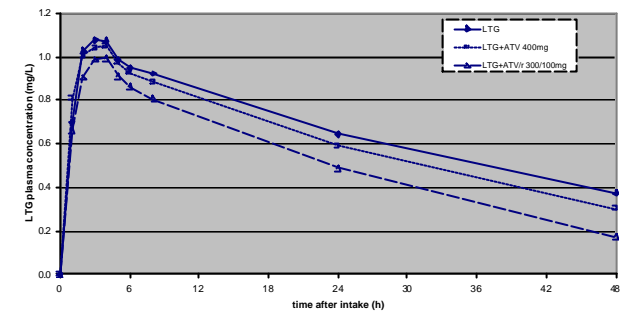
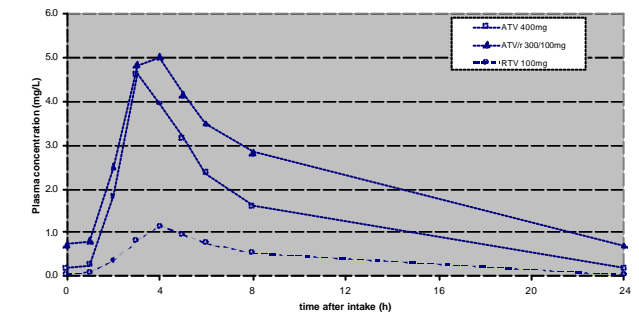


Figure 2. ATV and RTV plasma concentration vs. time curves



4. Conclusions

- ATV alone does not significantly influence glucuronidation of single dose LTG.
- In contrast, ATV/r resulted in moderately decreased exposure (32% decrease in AUC_{0-inf}) to LTG.
- This effect of ATV/r is smaller than the effect of LPV/r of LTG AUC: -55% (Van der Lee et al. Clin Pharmacol Ther 2006)
- Single dose LTG appears an attractive metabolic probe to phenotype the activity of UGT1A4.