Bilirubin - a potential marker of drug exposure in atazanavir based antiretroviral therapy

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Conclusions

A model describing atazanavir induced hyperbilirubinemia has been developed. Based on the model a nomogram has been constructed to predict suboptimal exposure in patients. Although this nomogram needs external validation before full scale clinical implementation, it could facilitate the use of bilirubin as a more readily available and cost efficient marker of sufficient atazanavir exposure

Purpose

This work aimed at examine the bilirubin-atazanavir relationship using a population-based approach and to investigate possible application of bilirubin as cost efficient and more readily available marker of atazanavir exposure.

Background

Atazanavir is widely used in antiretroviral therapy. Elevated bilirubin levels are commonly observed in patients on an atazanavir based treatment. Atazanavir increases bilirubin plasma levels by inhibition of UGT1A1 and possibly OATP1B1 (Figure 1A).

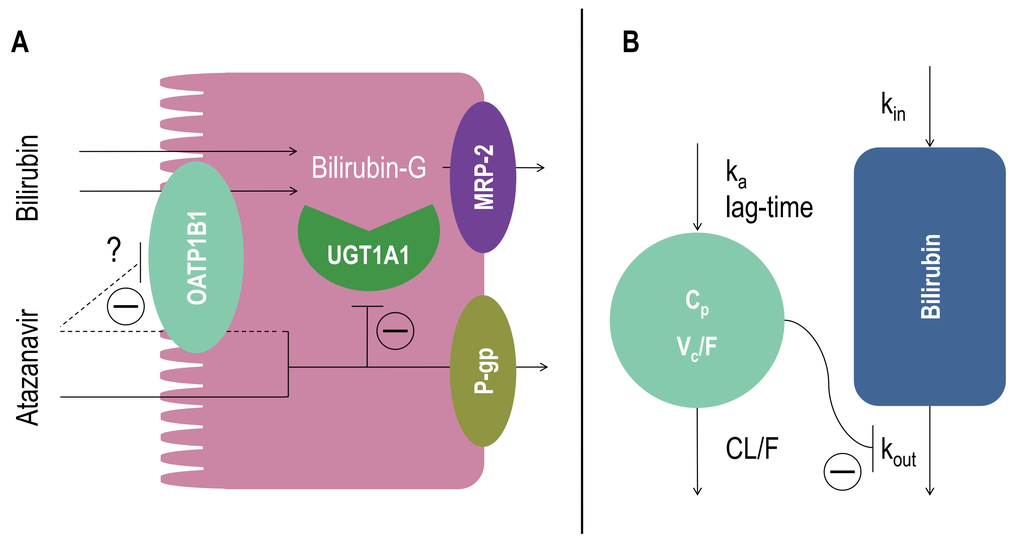

Figure 1. (A) Bilirubin can enter the hepatocytes passively (diffusion) and actively trough the organic anion-transporting polypeptide (OATP) 1B1. Bilirubin glucuronidation is mediated by glucuronosyltransferase (UGT) 1A1. Atazanavir inhibits UGT1A1 and possibly OATP1B1 **(B)** Schematic illustration of the final mathematical model describing the physiological process in panel A.

Method

The NORTHIV trial was a randomized open-label multicentre trial conducted in Sweden and Norway [1]. One third of the patients were administered 300 mg atazanavir and 100 mg ritonavir for once a day oral dosing. The current data included observations from 82 antiretroviral naïve HIV serum positive patients. Plasma atazanavir concentrations were measured at week 4, 12, 48, 96 and 144. Bilirubin concentrations were available at baseline and at time points matching atazanavir concentration measurements. In total 361 bilirubin observations, and 200 atazanavir steady state plasma samples were available. Concentration time profiles were modelled by nonlinear mixed effects modelling using NONMEM VI (ICON Developmental Solutions, Ellicot City, MD, USA) with first-order conditional estimation method with interaction.

Table 1. Parameter estimates of the final pharmacokinetic and pharmacodynamic models describing atazanavir and its influence on bilirubin in HIV/AIDS patients.

	Parameter	Estimate (95% CI)	IIV, %CV (RSE%)
PK model	Lag-time (h)	0.96*	
	k_a (h^{-1})	3.4*	
	V/F (L)	93.6 (62.4-125)	53 .1(43.6)
	CL/F (L/h)	6.47 (5.39-7.55)	43.8 (19.5)
	Correlation		
	p(CL/F, V/F)	0.29	
	Residual error		
	σ_{prop} (%)	51.0 (42.7-59.3)	
PD model	Baseline (µmol/L)	7.69 (6.99-8.39)	32.6 (20.2)
	K_{out} (h^{-1})	0.42 (0.36-0.48)	
	I_{max}	0.91 (0.87-0.94)	
	IC_{50} (µmol/l)	0.30 (0.24-0.37)	
	Residual error		
	σ_{prop} (%)	39.4 (35.5-43.3)	
	σ_{add} (µmol/l)	2.39 (1.96-2.82)	

k_a; absorption rate constant, V/F; volume of distribution, CL/F; Clearance, p; correlation coefficient, σ_{prop}; proportional residual variability, K_{out}; fractional turnover rate, I_{max}; maximum inhibition constant, IC_{50}; concentration resulting in 50% of Imax, σ_{add}; additive residual error. * fixed according to [2].

Results

Due to few samples obtained during the absorption phase, lag-time (0.96 h) and absorption rate (3.4 h^{-1}) were fixed to published values [2]. The data was adequately described with a one-compartment model. Parameter estimates of the final pharmacokinetic model are found in Table 1. Visual predictive checks of observed and predicted atazanavir /bilirubin concentrations as well as basic goodness of fit plots can be seen in Figure 2. The effect of atazanavir on bilirubin elevation was described by an indirect response model, where atazanavir inhibits the bilirubin elimination (Figure 1B). A 300 mg dose of ATZ(r) resulting in an average steady state concentration of 2.75µmol/L reduced bilirubin k_{out} by 82.0% and increased bilirubin's half-life 5 fold. Steady state bilirubin concentrations were predicted at the minimal effective concentration of atazanavir (MEC=0.2 µmol/L) for patients with various baseline bilirubin concentrations as shown in Figure 3. The borders of the green area represent how peak and trough steady state bilirubin concentrations vary with bilirubin baseline concentrations. The pink area represents results from individuals with atazanavir exposure below MEC.

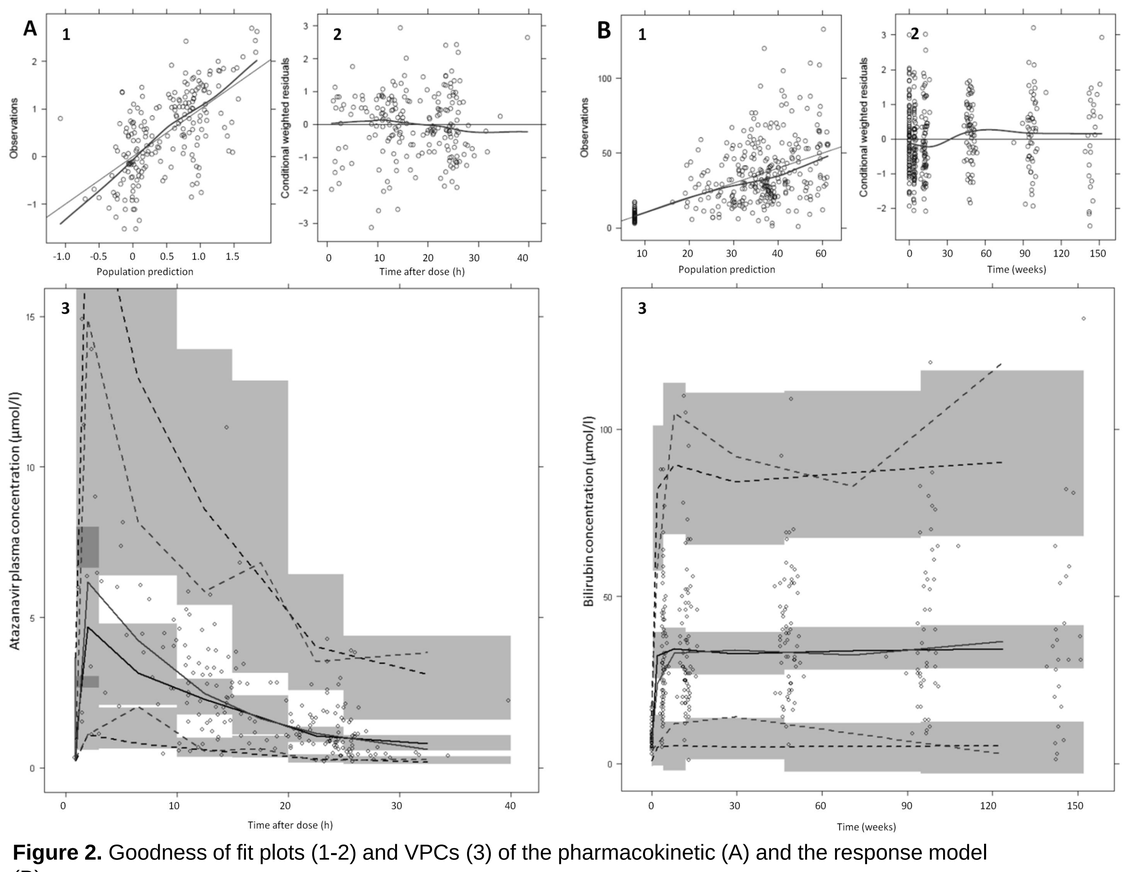

Figure 2. Goodness of fit plots (1-2) and VPCs (3) of the pharmacokinetic (A) and the response model (B).

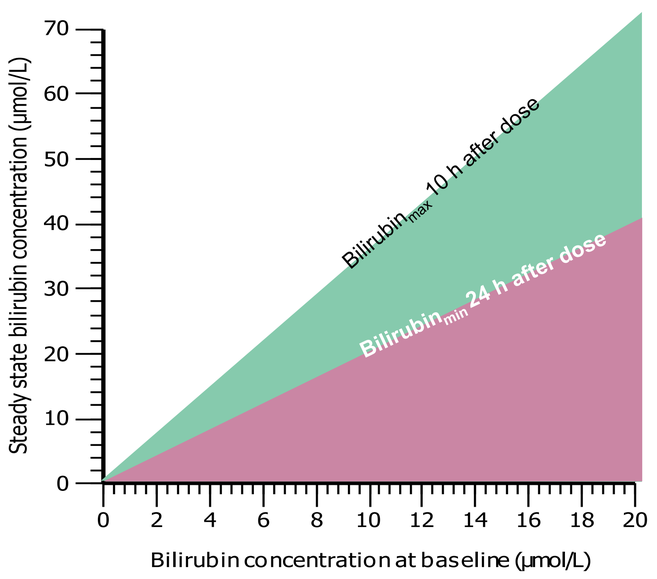

Figure 3. The pink area represents bilirubin steady state levels associated with atazanavir exposure below (MEC). The borders of the green area represent maximal (10 h after atazanavir dose) and the minimal (24 h after atazanavir dose) bilirubin steady state concentrations associated with atazanavir exposure at MEC

[1] Josephson, F. *et al. European journal of clinical pharmacology* **66**, 349-57 (2010)
[2] Dickinson, L. *et al. Journal of Antimicrobial Chemotherapy*, **3 (6)**,1233-1243 (2009).

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