

T-021 Development of a Physiologically Based Pharmacokinetic Model for Losartan and Its Active Metabolite E3174 - Ethnic Differences in Pharmacokinetics between Caucasian and Asian Populations

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OBJECTIVE

Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) antagonist for hypertension treatment. Although losartan itself is pharmacologically active, its primary metabolite, E3174, produced by CYP2C9 and CYP3A4 enzymes, has 10- to 40-fold higher potency and a longer half-life.

Ethnic differences in E3174 exposure have been observed between Caucasian and Asian subjects, which cannot be explained by genetic polymorphism of CYP2C9 alone. A validated losartan and E3174 model was developed to investigate the sources of ethnic differences in E3174 pharmacokinetics.

METHODS

A physiologically-based pharmacokinetic (PBPK) model for losartan and E3174 was previously developed by another group based on the *in vitro* data [1]. In this study, the published model [1] was extended by

- ❖ Adding gut P-glycoprotein (P-gp)
 - ❖ Adding kidney transporter
 - ❖ Assigning two different sets of hepatic transporters to losartan and its metabolite E3174 as suggested by Soldner et al. [2] that the primary transporters modulating losartan and E3174 active transport could be different (Figure 1)
 - ❖ Optimizing Hepatic transport kinetics
- The extended final model was validated using plasma and urinary excretion data after IV and PO administration from several studies in Caucasian subjects.

Table 1: Transporter parameters of the Final Extended PBPK Model

Substrate	Transporter	Location	Expression (mg-trans/g-tissue)	V _{max} (mg/s or mg/s/mg-trans)	K _m (mg/L)
Losartan	Lumped	Kidney-AP Efflux	1.00	0.01	4.23
	P-gp	Gut-AP Efflux	G+	3.93E-4	0.42
	P-gp	Liver-AP Efflux	CAU: 1.00 JPN: 1.37	8.46E-7	0.42
	OATP2B1	Liver-BL Influx	1.00	2.39E-4	0.42
	Lumped1	Liver-BL Efflux	1.00	3.64E-7	0.42
E3174	Lumped	Kidney-AP Efflux	1.00	0.01	4.37
	Lumped2	Liver-BL Influx	CAU: 1.00 JPN: 0.40	8.37E-4	4.37
	Lumped3	Liver-BL Efflux	CAU: 1.00 JPN: 20.00	8.87E-5	4.37
	Lumped4	Liver-AP Efflux	CAU: 1.00 JPN: 5.00	1.00E-4	4.37

where AP = apical; BL = basolateral; CAU, Caucasian; JPN, Japanese; G+ = default value in GastroPlus™ 9.5

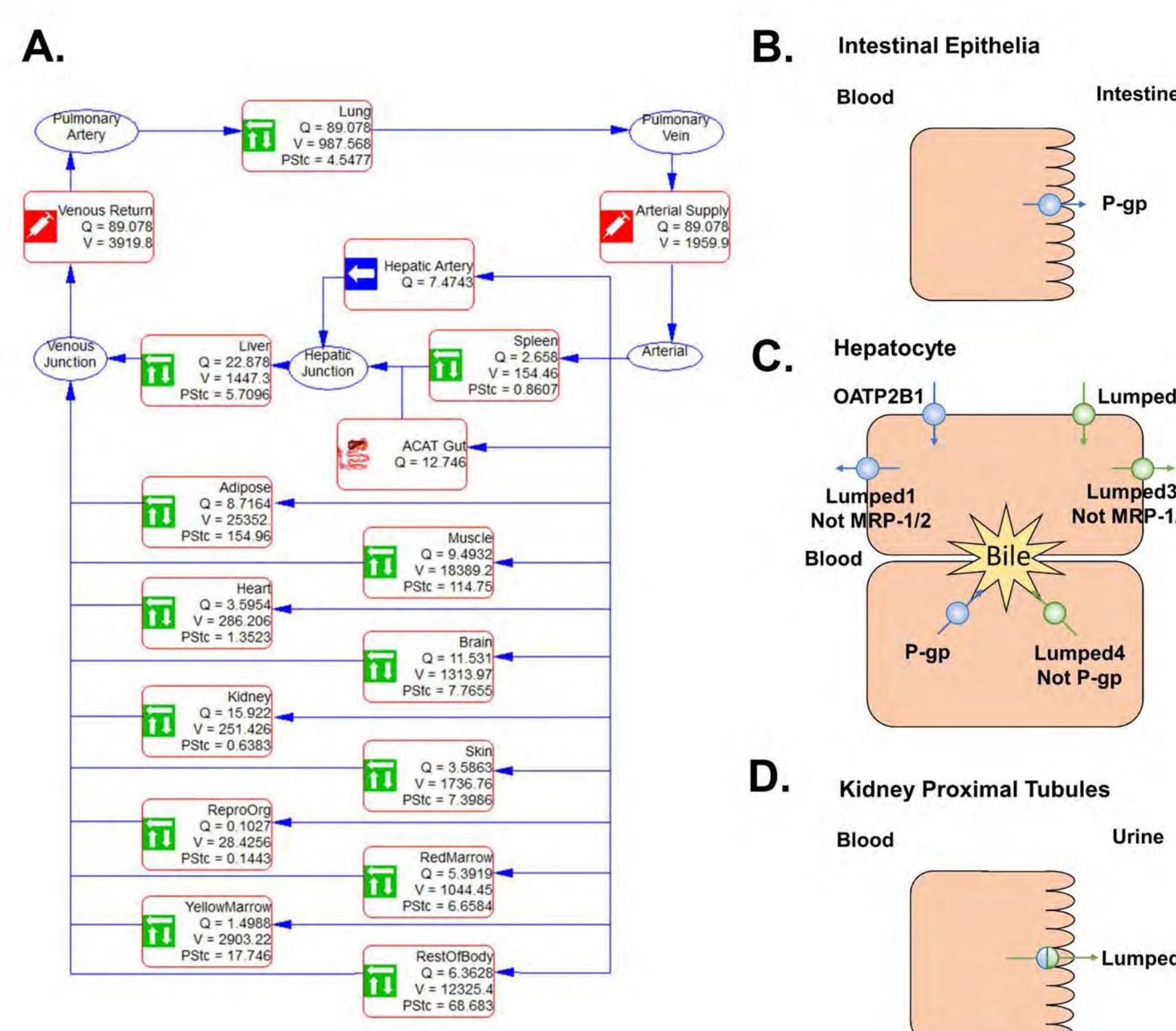


Figure 1: Schematic diagram of the losartan and E3174 PBPK model (A) with summary of transporters added to the gut (B), liver (C), and kidney (D) compartments of the final extended PBPK model.

RESULTS

The extended final model well described pharmacokinetic profiles of losartan and its metabolite E3174 after both IV and PO administrations in Caucasians (Figures 2A and B). However, the model significantly underpredicted E3174 plasma concentration-time profile in Japanese subjects (Figure 2C).

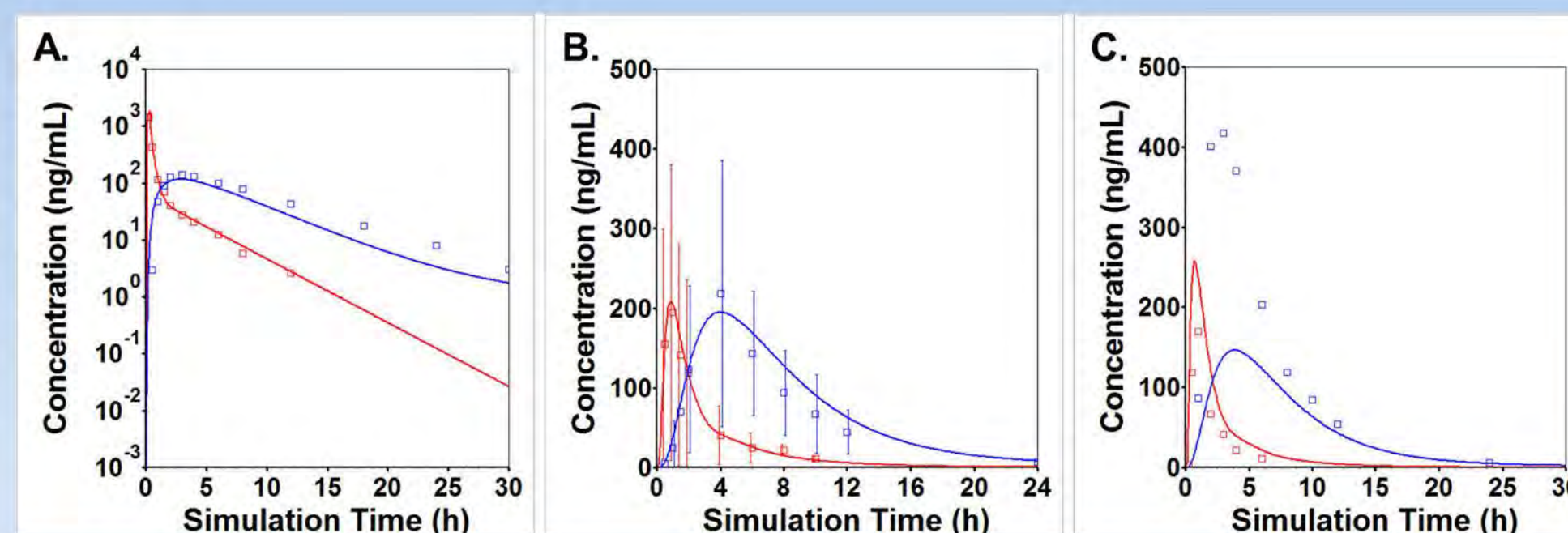


Figure 2: Observed (points) and simulated (lines) plasma concentration-time profiles of losartan (red) and E3174 (blue) after 30 mg IV infusion of losartan in 20 min in Caucasians (A), 50 mg PO administration of losartan in Caucasians (B) and in Japanese (C). Experimental data were obtained from literature [3-5].

The extended final model also successfully simulated the cumulative amount of E3174 secreted in urine after IV administration of E3174 in Caucasians (Figure 3). The observed cumulative amount of E3174 secreted in urine as percent of dose was reported to be 55.1% [3].

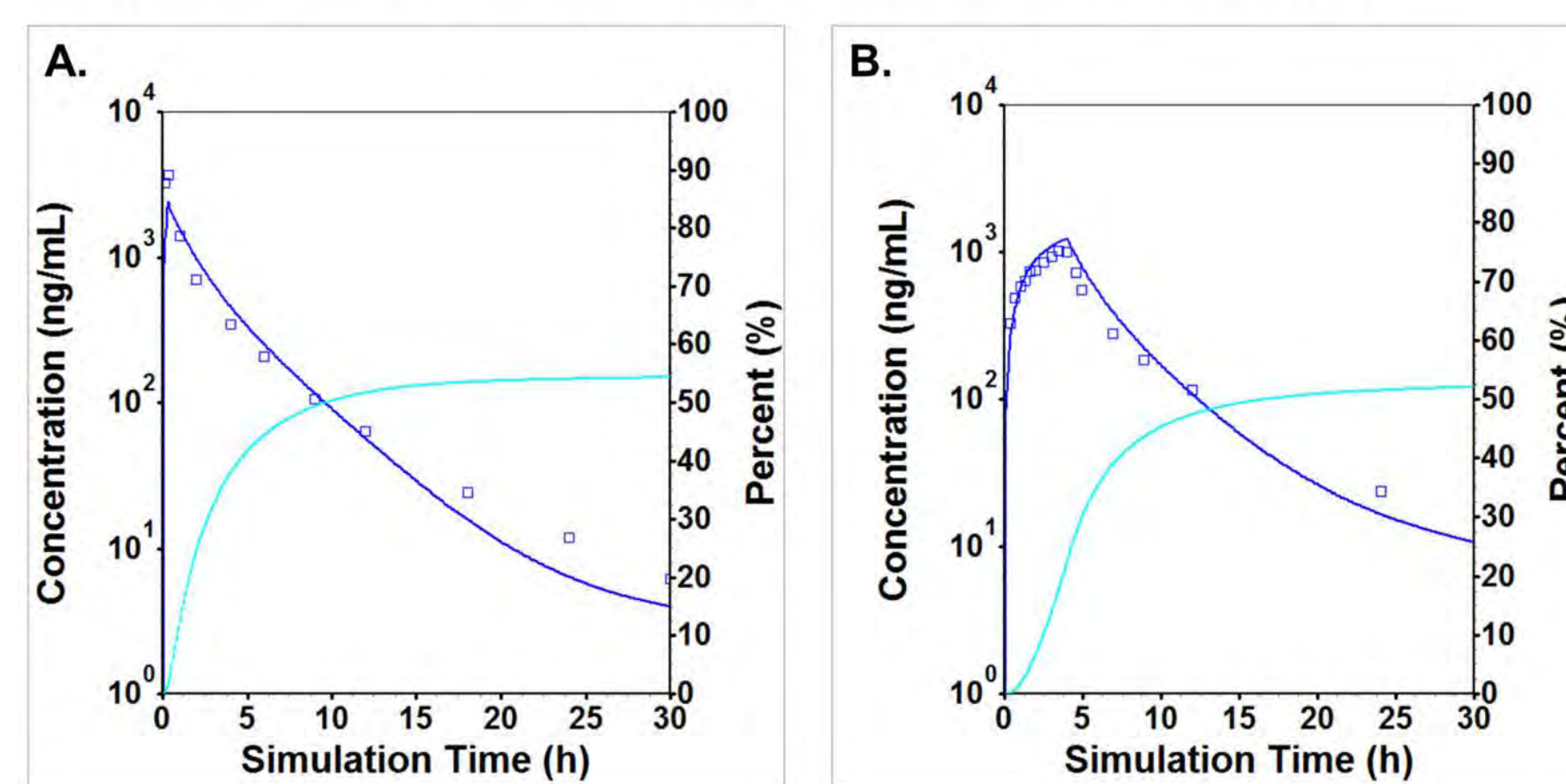


Figure 3: Observed (points) and predicted (lines) E3174 PK profiles after E3174 IV administration of 20 mg over 20 min (A) and 20 mg in 4 h in Caucasians. E3174 plasma concentration (blue) and cumulative amount secreted in urine (cyan). Experimental data were obtained from the literature [3,6].

The extended final model adequately described dose proportional pharmacokinetics of losartan and its metabolite E3174 in Japanese after PO administration over the dose range of 25 to 200 mg by adjusting expression levels of hepatic transporters modulating E3174 hepatic disposition (Figure 4).

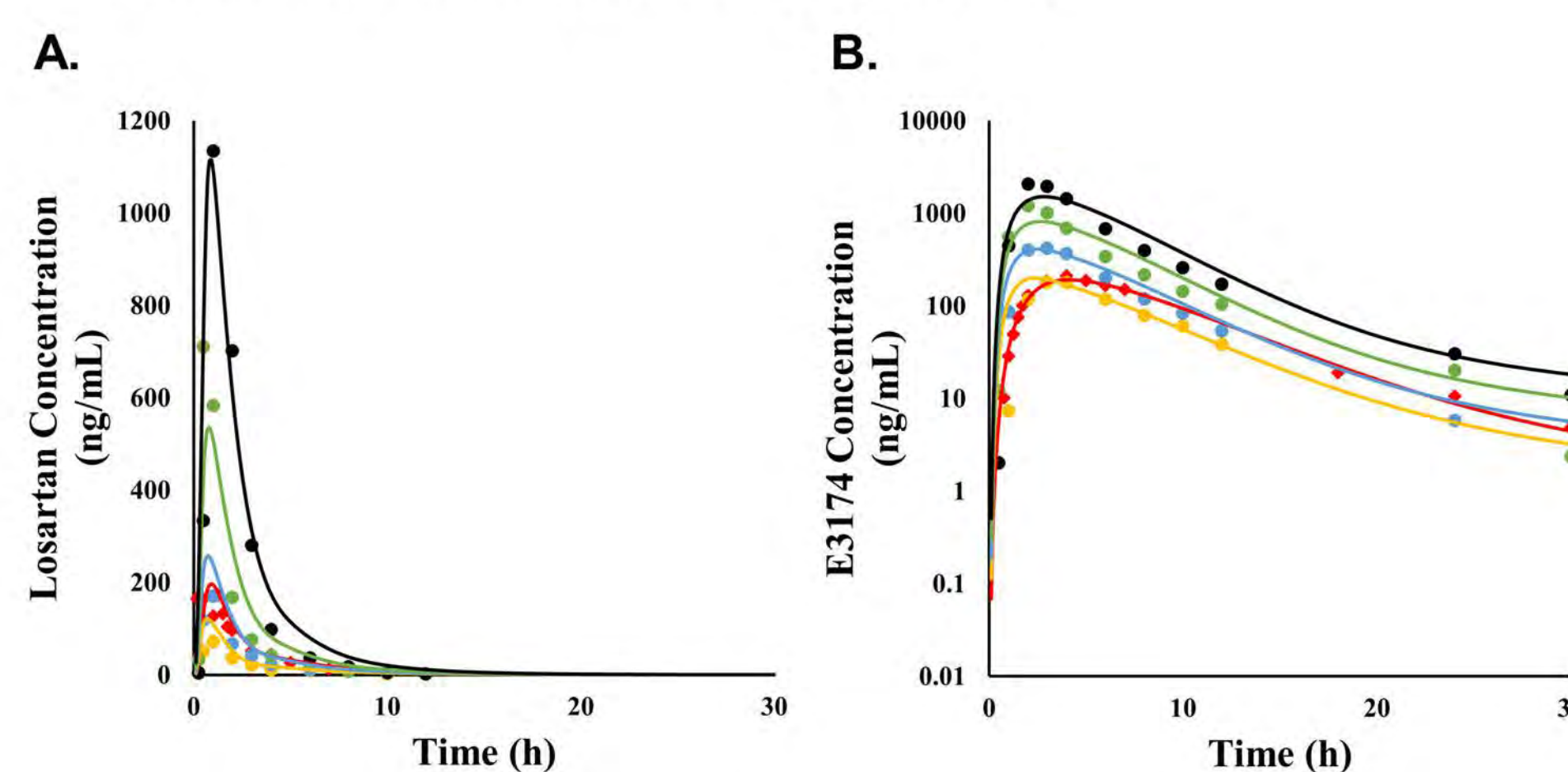


Figure 4: Observed (points) and simulated (lines) plasma concentration-time profiles of losartan (A) and E3174 (B) after 25 (yellow), 50 (blue), 100 (green), and 200 (black) mg PO administration of losartan in Japanese and 50 mg (red) PO administration of losartan in Caucasians. Experimental data were obtained from literature [3,5].

Table 2: Influence of complete inhibition of P-gp mediated active transport on losartan and its metabolite E3174 disposition.

	Baseline		Complete Inhibition of P-gp		Ratio	
	Losartan	E3174	Losartan	E3174	Losartan	E3174
C _{max} (ng/mL)	196.28	192.83	216.47	240.04	1.10	1.24
AUC _{inf} (ng-h/mL)	565.66	1892.60	602.58	2134.60	1.07	1.13
AUC ₀₋₃₀ (ng-h/mL)	564.41	1846.30	602.46	2091.10	1.07	1.13

- Simulation results of complete inhibition of P-gp (Table 2) suggest that P-gp mediated transport kinetics does not have significant influence on losartan and its metabolite E3174 disposition. This is consistent with the clinical evidence reported by Yasar et al. [7].
- Parameter sensitivity analysis (PSA) results (Figure 5) indicate that hepatic efflux transporters have higher impact on E3174 disposition than hepatic influx transporters.
- E3174 has a shorter half-life of elimination ($t_{1/2,\beta}$) in Japanese than in Caucasians while its renal clearances in these two populations are the same [8]. This suggests the biliary clearance of E3174 is higher in Japanese. For this reason, higher activities of apical hepatic efflux transporters in Japanese are expected.
- Given that the clearance of E3174 is higher in Japanese, most likely, the activities of basolateral hepatic efflux transporters must be higher in Japanese as the observed E3174 plasma exposure is higher in Japanese.

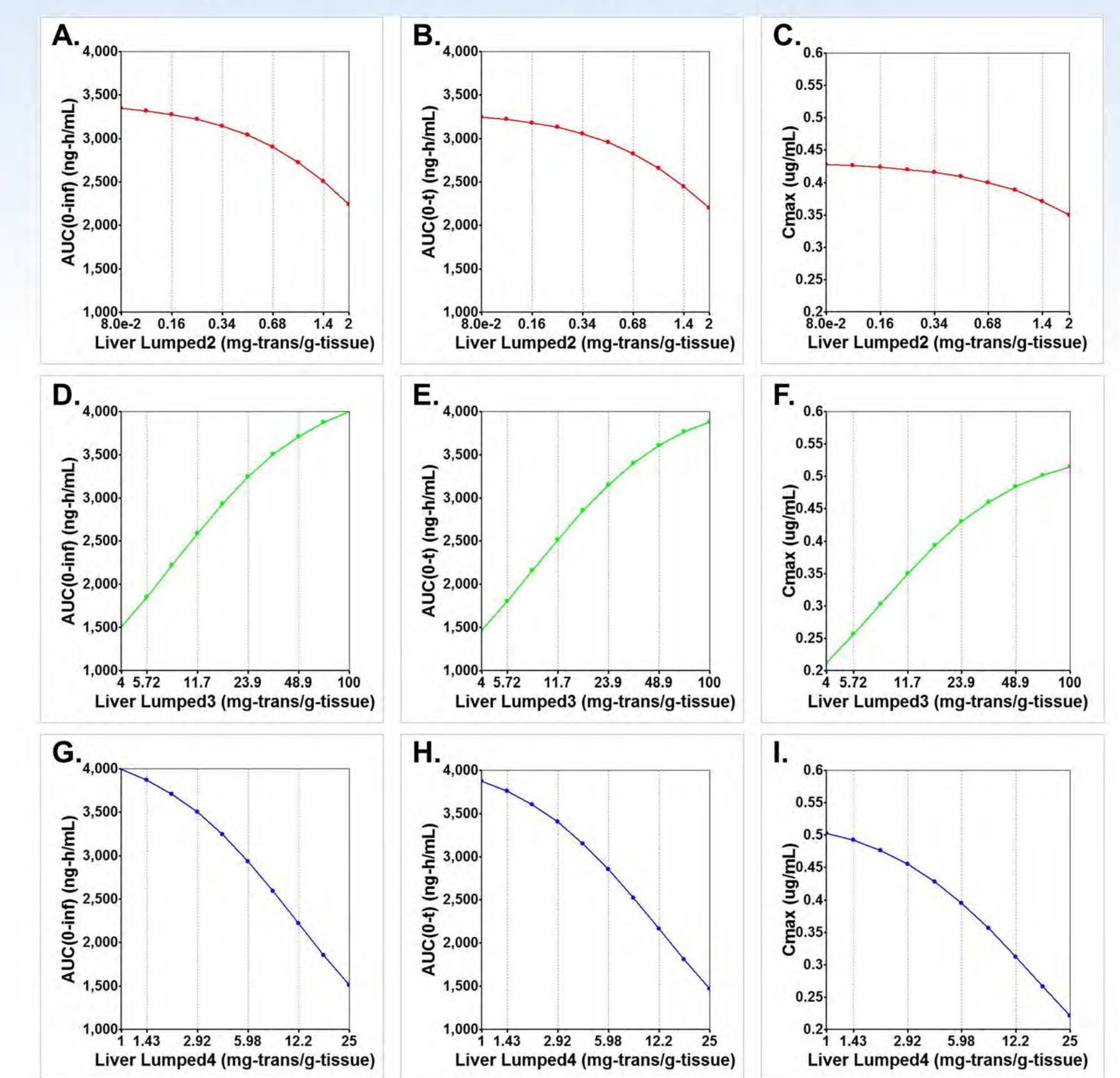


Figure 5: Influence of transporter Lumped2 expression level on PK of E3174 after 50 mg PO administration of losartan (A, AUC_{0-inf}; B, AUC₀₋₃₀; C, C_{max}); Influence of transporter Lumped3 expression level on PK of E3174 after 50 mg PO administration of losartan (D, AUC_{0-inf}; E, AUC₀₋₃₀; F, C_{max}); Influence of transporter Lumped4 expression level on PK of E3174 after 50 mg PO administration of losartan (G, AUC_{0-inf}; H, AUC₀₋₃₀; I, C_{max}).

CONCLUSIONS

- Losartan itself doesn't display significant ethnic differences in pharmacokinetics. However, there are differences observed for the metabolite E3174.
- CYP2C9 polymorphism is unlikely to be the reason for the observed ethnic difference in E3174 pharmacokinetics.
- The ethnic differences in the pharmacokinetics of E3174 could be driven by differences in transporter kinetics, and not metabolism, between Caucasian and Japanese populations.

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