

Population analysis of levofloxacin in plasma, lung and prostate measured by microdialysis in Wistar rats after intravenous and intratracheal administration



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OBJECTIVES

To evaluate levofloxacin (LEV) lung and prostate interstitial fluid (ISF) concentrations with and without tariquidar (TAR), a P-gp inhibitor, viewing to elucidate this fluoroquinolone tissue penetration mechanism and to develop a population pharmacokinetic (POPPK) model able to describe experimental data simultaneously.

METHODS

Wistar rats (300-400 g) were randomly distributed in eight groups ($n = 6$ /groups). For each dose/route of administration, one group was used for total plasma sampling and one for ISF concentrations sampling. Animals received LEV 7 mg/kg intravenously (i.v.) or intratracheally (i.t.) alone or 30 min after TAR 15 mg/kg i.v. dosing. Experiments approved by CEUA/UFRGS 21169. CMA/20 microdialysis probes (4 mm, cutoff 20 kDa), flushed with Ringer's solution 1.5 μ L/min, were used to collect ISF free concentrations in both tissues. Throughout the experiment, animals were kept anesthetized with urethane and under mechanical ventilation. Total LEV concentrations in plasma and free lung and prostate were investigated up to 12 h. A semi-mechanistic population pharmacokinetic model was developed using NONMEM version 7.2 to simultaneously characterize total plasma and free ISF tissues (lung and prostate) concentrations.

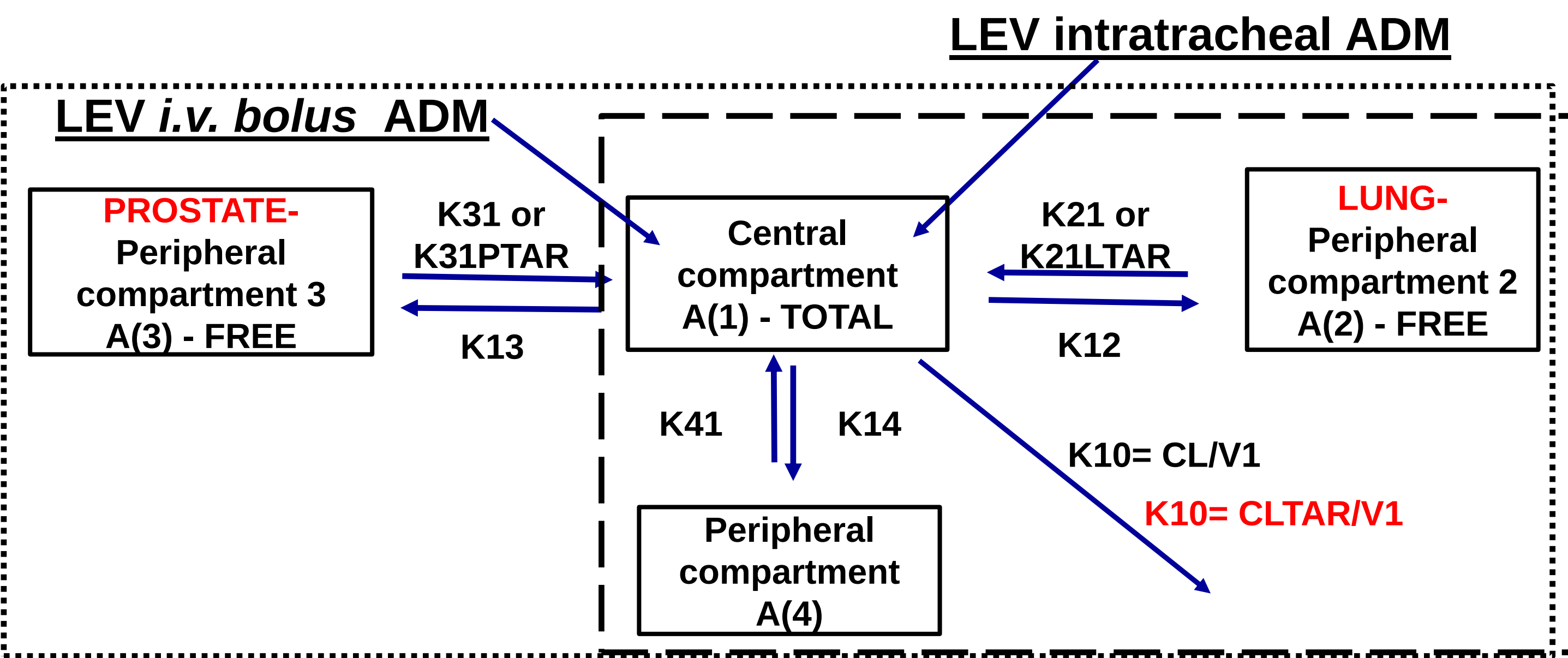


FIGURE 1. Schematic representation of the PK model used to describe LEV plasma and tissues concentration-time profiles after *i.v. bolus* and intratracheal dose of 7 mg/kg to Wistar rats in the presence and absence of the P-gp inhibitor TAR. A = amounts e V = volume with the number in the parenthesis indicating the respective compartment. Model after *i.v.* dosing (.....) and model after *i.t.* dosing (----)

TABLE 1: Parameter estimates of the final LEV population PK model from the original data set and from 100 bootstrap replicates.

4 Comp. Model		Bootstrap Results	
Objective Function Value		-4363	
Pharmacokinetic Parameters	Estimates (RSE%)	5 th percentile	95 th percentile
Clearance from central compartment [CL (L/h)]	0.2201 (5.86)	0.1976	0.2395
Volume of the central compartment [V1 (L)]	0.319 (8.21)	0.2778	0.3624
K12 (h-1)	8.991 (2.57)	8.582	9.3376
K21 (h-1)	7.194 (18.64)	5.397	9.812
K13 (h-1)	0.0454(31.98)	0.0293	0.0646
K31 (h-1)	8.598 (15.33)	6.779	10.927
K14 (h-1)	0.864 (15.52)	0.652	1.079
K41 (h-1)	0.479 (13.89)	0.388	0.581
K21LTAR (h-1)	8.467 (13.60)	6.914	10.527
K31PTAR (h-1)	4.861(16.75)	3.768	6.054
CLTAR (L/h)	0.176 (7.79)	0.154	0.197
F Control	0.4 (FIX)		
F Tariquidar	0.86 (FIX)		
Residual Unexplained Variability	Estimates (RSE%)		
Plasma proportional error (%)	33.07 (11.85)	29.69	35.96
Plasma additive error (mg/L)	0.0249 (30.92)	0.0179	0.0394
Lung proportional error (%)	37.69 (25.60)	33.05	47.93
Lung additive error (mg/L)	0.0146 (51.53)	0.0034	0.0285
Prostate proportional error (%)	42.11 (35.64)	29.22	51.09
Random Effects (Omega)	Estimates (RSE%)		
IIV CL (%)	23.84 (22.41)	19.45	27.86
IIV V1 (%)	31.74 (22.05)	26.61	37.88
IIV K21 (%)	25.91 (32.29)	19.09	33.83

RESULTS

- A four compartment model was adequate to simultaneously characterize and predict total plasma and in free prostate and lung ISF concentrations, target infections sites for this drug [1,2].
- Statistically significant differences were observed for three parameters in the TAR group compared to control group (*lung penetration, prostate penetration and kidney active secretion*).
- A significant difference in bioavailability (F) after *i.t.* dosing between control (F = 0.4) and TAR (F = 0.86) groups was determined by non-compartmental analysis (NCA). Because the estimation of F was not possible during modeling, F was fixed based on NCA values.
- The intratracheal model was initially designed with a depot compartment. However, the high value ($> 50 \text{ h}^{-1}$) obtained for absorption rate constant (K_a) indicated that the data did not support the estimation of this parameter.
- The intratracheal model with and without depot compartment were confronted. The model without depot compartment represented a significant improvement in term of curve fitting, OFV, precision of parameter estimates and model stability. The interindividual variabilities were reasonably small for the parameters in the model.

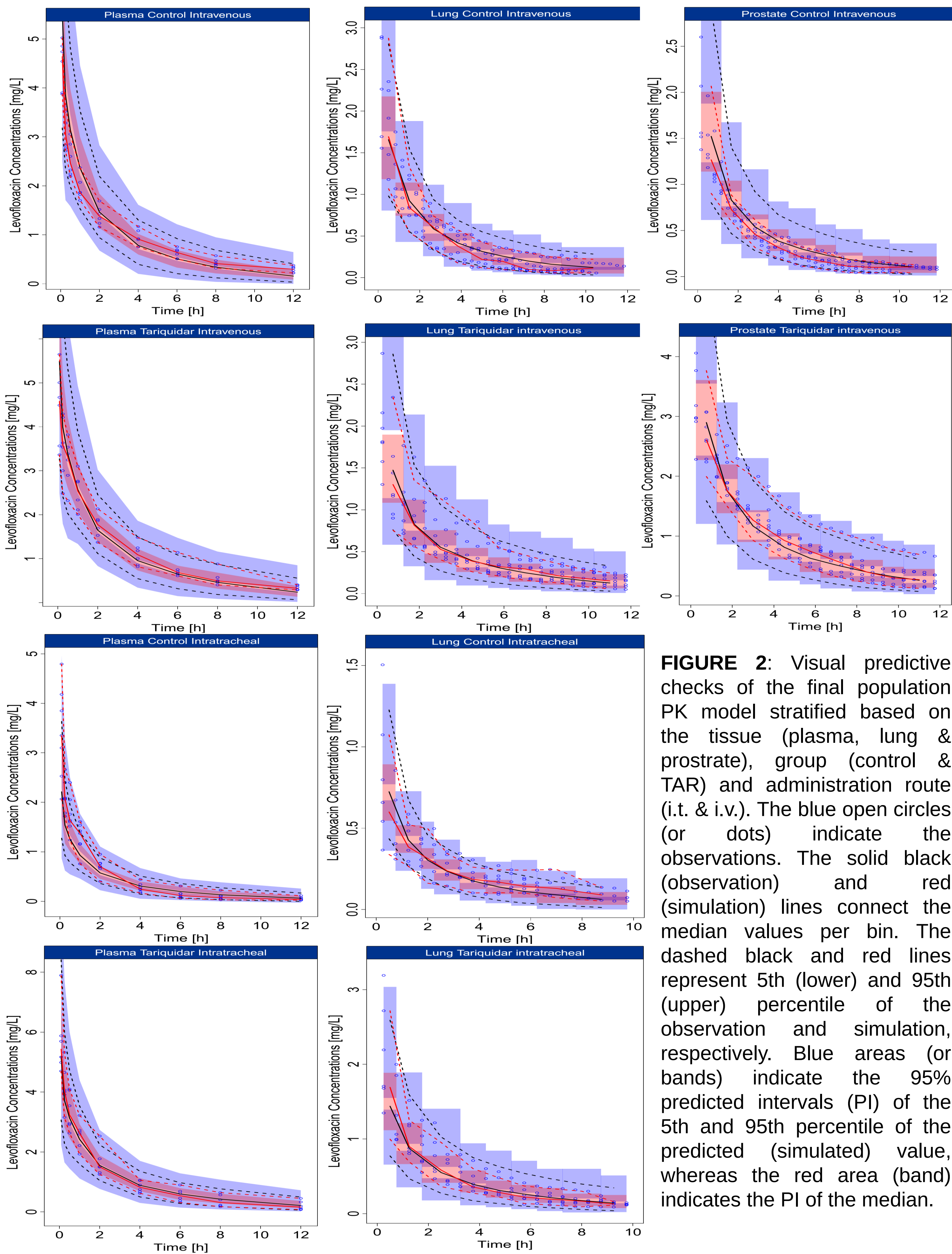


FIGURE 2: Visual predictive checks of the final population PK model stratified based on the tissue (plasma, lung & prostate), group (control & TAR) and administration route (*i.t.* & *i.v.*). The blue open circles (or dots) indicate the observations. The solid black (observation) and red (simulation) lines connect the median values per bin. The dashed black and red lines represent 5th (lower) and 95th (upper) percentile of the observation and simulation, respectively. Blue areas (or bands) indicate the 95% predicted intervals (PI) of the 5th and 95th percentile of the predicted (simulated) value, whereas the red area (band) indicates the PI of the median.

CONCLUSIONS

A semi-mechanistic POPPK model was successfully developed to describe LEV total plasma and free ISF concentrations in lung and prostate. The results indicate P-gp impact on LEV renal active secretion. Efflux transporters are relevant to pulmonary penetration only after intratracheal dosing. In the prostate, our findings strongly support the role of efflux transporters besides P-gp participating in LEV tissue penetration.

REFERENCES

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2. J. Mouton *et al.*, *J. Antimicrob. Chemother.* **61**, 2 (2008).

ACKNOWLEDGMENTS

