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Introduction and Objectives

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is part of a multidisciplinary treatment proposed for patients suffering from peritoneal carcinomatosis. The evaluation of the efficacy and toxicity of HIPEC technique presents some difficulties, due in part to the lack of information about the pharmacokinetic (PK) behavior of the drugs administered in this procedure. The development of suitable animal models may contribute to separately evaluate the impact of different covariates related to HIPEC on the PK parameters and may give useful information for future clinical research.

The objective of this study was to characterize the population PK of Hyperthermic Intraoperative Peritoneal Oxaliplatin (HIPEO) in Wistar rats and to evaluate the effect of treatment-related covariates dose, instillation time and temperature on the PK parameters.

Materials and Methods

Experimental technique

42 male Wistar rats were randomly allocated in seven groups (G1-G7) and submitted to different experimental conditions of temperature, instillation time or dose (Table 1). As a common procedure, all of rats underwent a laparotomy followed by an intraperitoneal hyperthermic instillation (LIHI) with 100 mL of 5% dextrose solution². Out of them, 36 (G1-G6) were assigned to receive an HIPEO administration, carried by the heated 5% dextrose solution, as used in HIPEC procedure. In addition, to allow determination of the fraction of dose absorbed (F), six rats of one additional group (G7) were administered with one dose of intravenous (IV) oxaliplatin undergoing LIHI procedures, without adding oxaliplatin in the instillation solution. This procedure ensured that IV administrations were done at similar surgical conditions to the HIPEC groups³.

Plasma samples were taken immediately after the oxaliplatin administration at times 1, 10, 20, 30, 45, 60, 90, 150, 270 and 510 minutes. Samples were frozen after centrifugation until their analysis by graphite furnace atomic absorption spectrophotometry (LLQ of oxaliplatin = 0.06 mg/L).

Table 1. Experimental groups according to doses, instillation time and temperatures.

Oxaliplatin route of administration	Temperature (°C)	Instillation time (minutes)	Dose (mg)		
			10	20	1.5
Intraperitoneal	38 - 40	30'	G1 (n=6)		
		30'	G2 (n=6)	G6 (n=6)	
	40 - 42	45'	G3 (n=6)		
		60'	G4 (n=6)		
	42 - 43	30'	G5 (n=6)		
Intravenous	40 - 42	30'			G7 (n=6)

Pharmacokinetic model development and evaluation of surgical procedure on oxaliplatin parameters

The plasma concentrations profiles were analyzed together (NONMEM software v7.3). The impact of dose, temperature and instillation time on the PK parameters was explored. The graphs and statistical analysis were performed using the R software v3.3.2.

Bootstrap analysis was conducted to calculate 95% confidence interval for final model parameter estimates and relative standard errors of estimate (%RSE) after generating 1000 datasets by resampling with replacement method (Wings for NONMEM program). Model validation was performed by visual analysis of goodness of fit plots and prediction-corrected Visual Predictive Check (pcVPC).

Results

Oxaliplatin PK was described by an open two compartment distribution model with linear absorption from peritoneum, linear elimination and linear distribution from the central to peripheral compartment (Figure 1). This results agree with the results published elsewhere^{4,5}.

Preliminary graphical analysis showed a sharp inflection point in the course of the oxaliplatin plasma concentrations before the end of instillation (Figure 3). This fact was translated into the model including a decrease of the CL during the instillation, modelled through a step function on k_{el} (Equation 1 and 2).

$$STEP = \frac{TIME^{SIG}}{T_{50}^{SIG} + TIME^{SIG}} \quad (1)$$

$$k_{el} = \frac{CL_1}{V_2} + \left(\frac{CL_2}{V_2} - \frac{CL_1}{V_2} \right) * STEP \quad (2)$$

where T_{50} is the inflection time point at which CL_1 changed into CL_2 , and SIG is the sigmoidicity factor, fixed to the value of 20. T_{50} was estimated to be 31.4 minutes. This result agrees with the visual detection of this change in rats undergoing 45 or 60 minutes of instillation. Estimation of F after intraperitoneal administrations was not significantly different from 100%.

Conclusions

This study shows the deterioration of the drug elimination process due to the HIPEC procedure, and estimates the time at which this deterioration is most likely to occur. The covariates dose, instillation time and temperature had no influence on the PK parameters, in the studied range. This model may help to the understanding of how HIPEC procedure affects PK parameters and may contribute in the construction of solid hypothesis for future clinical trials.

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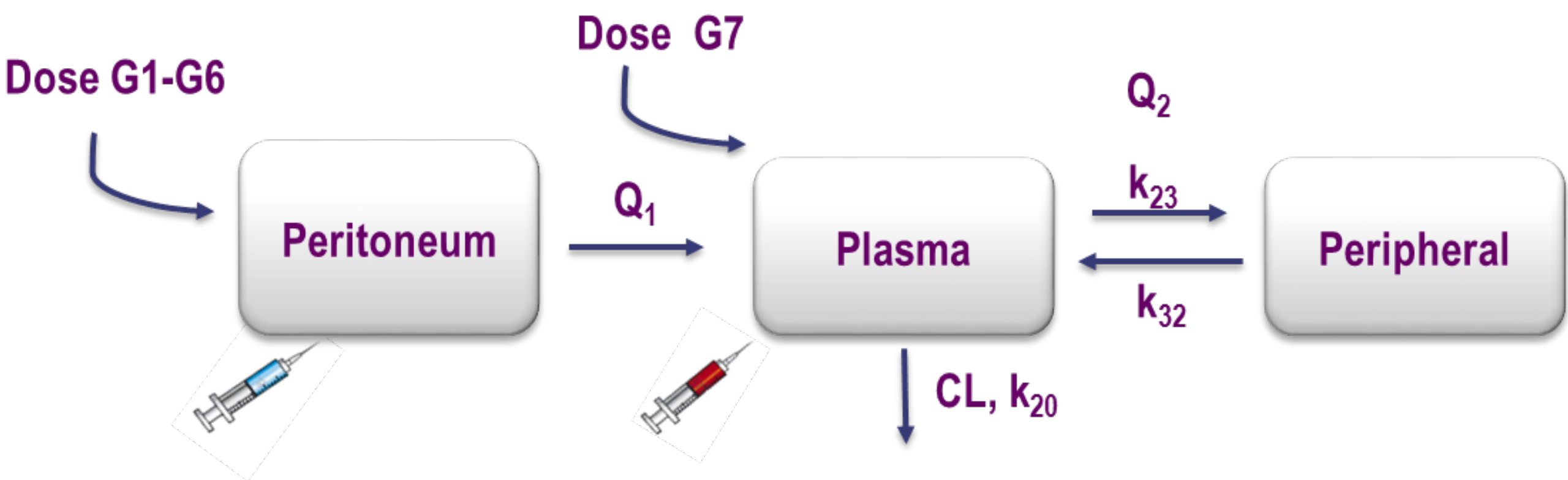


Figure 1. Pharmacokinetic model for oxaliplatin.

Table 2. Parameter estimates and bootstrap analysis of the oxaliplatin population PK model.

Model parameters	Original dataset Estimate ^a (RSE)	Nonparametric Bootstrap	
		Mean (RSE) ^a	95% CI
Fixed effect parameters			
CL ₁ (mL/min)	3.25 (16.3)	3.18 (17.2)	2.00 - 4.14
CL ₂ (mL/min)	0.151 (19.1)	0.154 (21.9)	0.0950 - 0.237
V ₁ (mL)	100 FIX	100 FIX	-
Q ₁ (mL/min)	0.864 (11.3)	0.866 (12.3)	0.660 - 1.09
V ₂ (mL)	53.6 (13.4)	54.0 (14.3)	39.9 - 69.4
Q ₂ (mL/min)	3.66 (28.4)	3.76 (34.0)	1.67 - 6.38
V ₃ (mL)	54.1 (35.3)	54.5 (35.9)	22.1 - 98.8
T ₅₀ (min)	31.4 (2.70)	32.3 (8.80)	30.3 - 43.1
Between subject variability (η) ^b			
η _{CL}	39.1 (21.8)	36.9 (29.5)	15.2 - 59.3
η _{V2}	37.8 (24.5)	34.9 (29.7)	14.2 - 53.2
η _{V3}	77.3 (21.8)	78.9 (25.2)	46.9 – 125
Residual variability ^b			
Peritoneal ^b	13.3 (9.64)	13.3 (9.64)	10.9 - 16.0
Plasma ^b	20.0 (7.92)	19.7 (8.36)	16.7 - 23.0

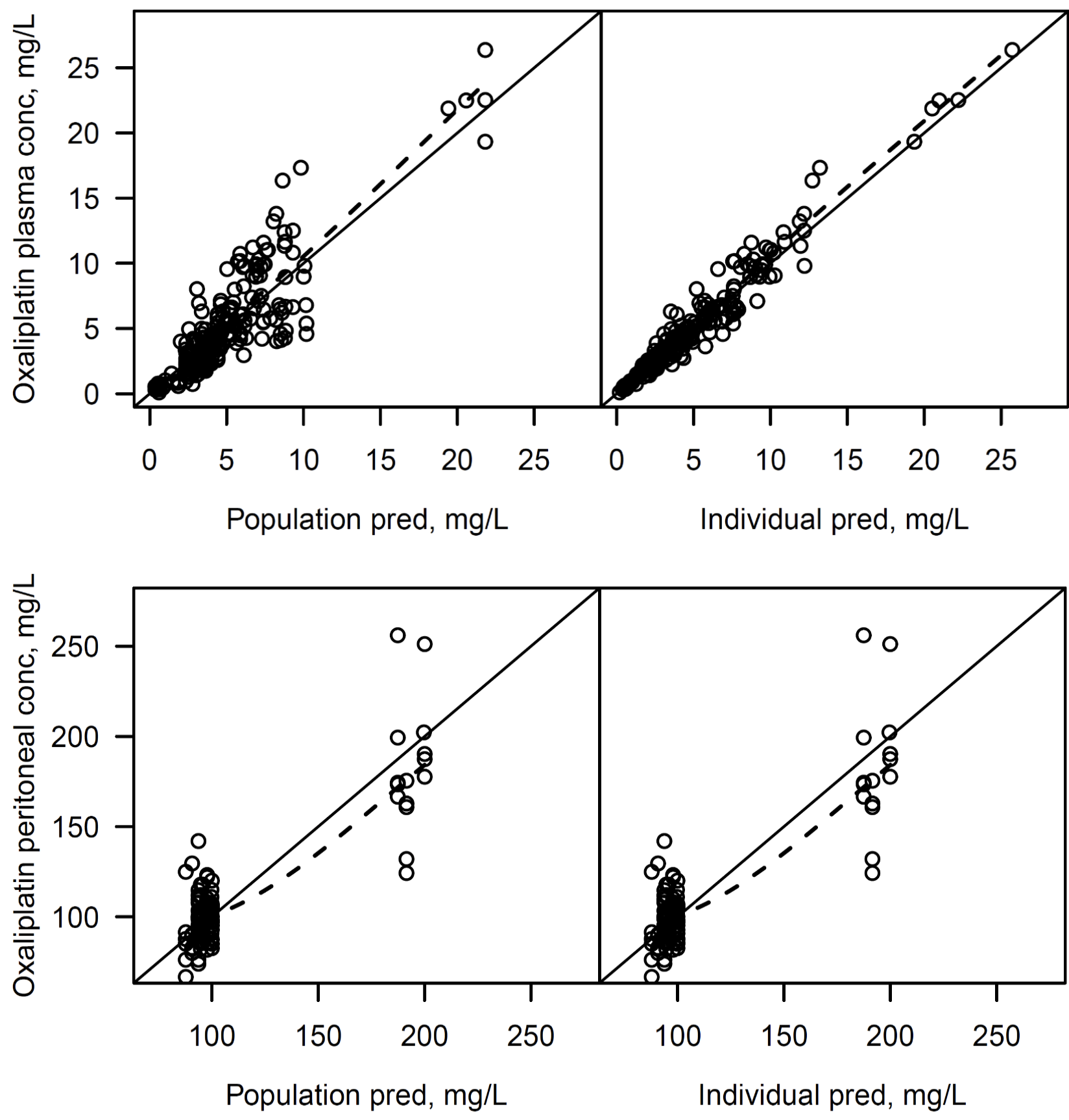


Figure 2. Upper panels, goodness of fit plots for plasma concentrations. Lower panels, goodness of fit plots for intra-peritoneal concentrations.

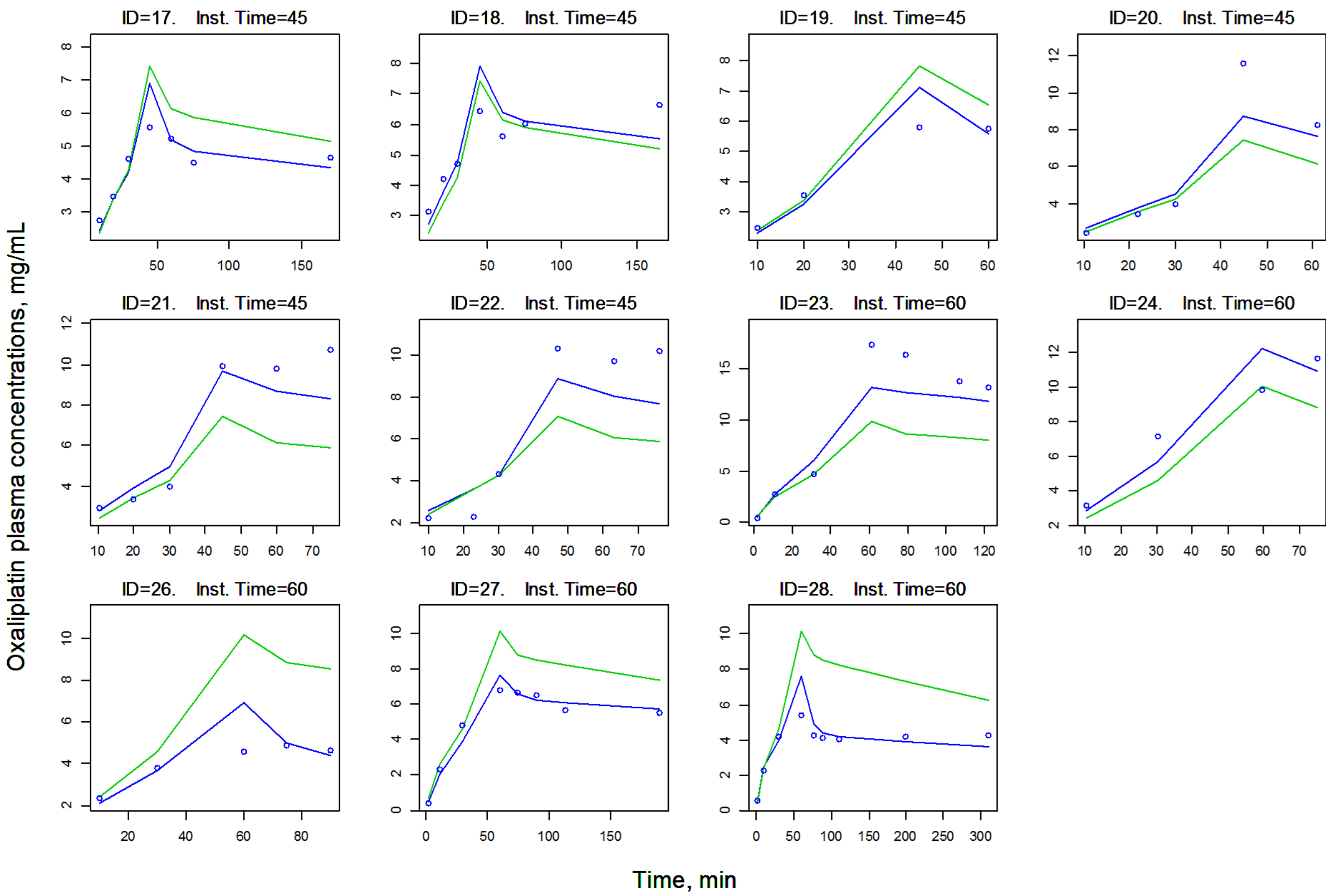


Figure 3. Individual and population predictions for the instillation times of 45' and 60'.