POPULATION PHARMACOKINETICS AND ANTIVIRAL EFFICACY IN NEONATAL LAMBS: EVIDENCE OF RAPID MATURATION AND AUTO-INDUCTION IN METABOLIC CLEARANCE

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OBJECTIVE

To develop a population pharmacokinetic (PK) model in neonatal lambs to describe plasma and lung concentrations of a new compound in development and determine its impact in viral replication inhibition.

PATIENTS AND METHODS

Study Design and Animal Data

Three groups of five lambs were inoculated with virus and doses of 2, 10 and 50 mg/kg of compound X were administered, respectively. Blood samples were collected just before the first dose, at 2 hours after the first and the last dose and at 24 hours following each dose until 6th day. A total of 112 plasma and 11 lung concentrations were obtained from the study.

Structural PK Model

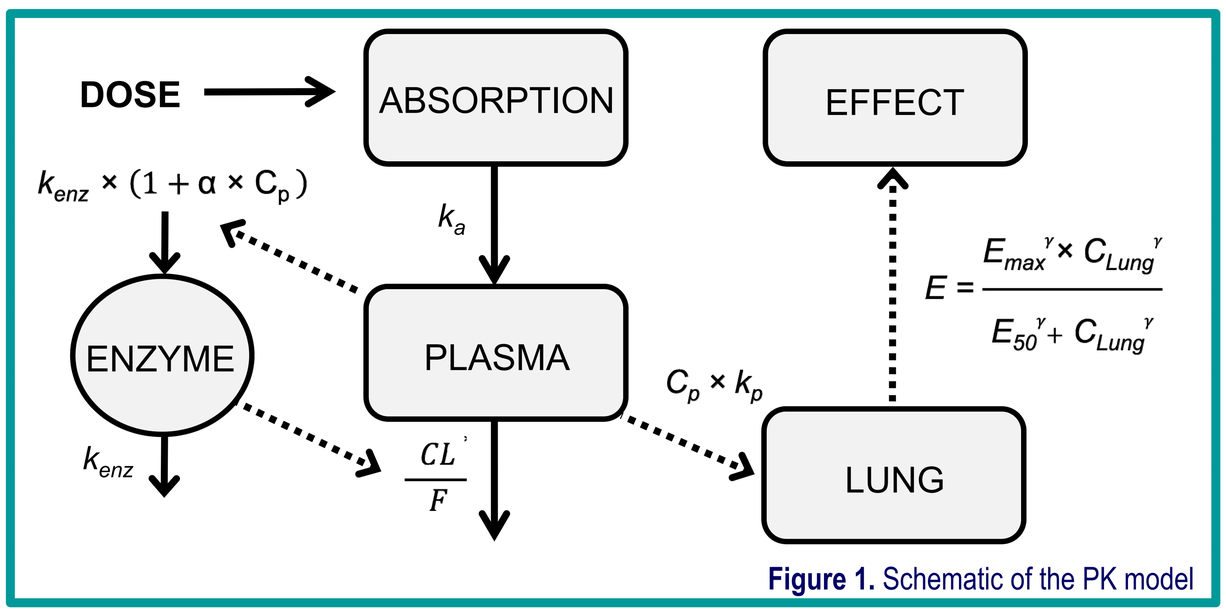

Figure 1. Schematic of the PK model

- PK data were analyzed with NONMEM® 7.3.
- The maturation and growth of the liver function was modeled as:

$$CL^*(time, W) = CL_{im} \times W^b \times e^{-kmat \times time} + CL_{ma} \times W^b \times (1 - e^{-kmat \times time})$$

where: W is body weight, k_{mat} is the maturation rate constant, b is the allometric body weight exponent (0.75), and CL_{im} and Cl_{ma} are immature and mature clearence at unit W respectively.[1]

- The auto-induction was described with an enzyme turn-over model where plasma concentration (C_p) increased the enzyme production rate (k_{enz}) in a linear fashion, and α was the linear relationship between the auto-induction effect and C_p.[2]
- Lung PK was described using a general linear distribution model [3] where the lamb physiological parameters were derived from the literature.[4,5]
- The drug-effect parameters on viral replication inhibition (EC50 and γ), where derived from *in vitro* experiments.

Model Qualification and Simulations

Non-parametric bootstrap, and VPC were used as validations tools. Deterministic simulations were conducted to evaluate the effect of dose in the concentration-time curve and its impact in viral replication inhibition.

RESULTS

Table 1. Parameter Estimates and Non-Parametric Bootstrap Analysis of the PK Model.

PK Model Parameters		Original Estimates (RSE, %)	Non-Parametric Bootstrap (n = 87 replicates out of 100)	
			Mean (RSE, %)	95% Confidence Interval
Drug related Parameters	CL_{im}/F (L/h/kg)	0.224 (20.6)	0.220 (19.4)	0.134 – 0.305
	CL_{ma}/F (L/h/kg)	0.402 (22.3)	0.389 (20.0)	0.237 – 0.541
	V/F (L)	3.74 (40.1)	3.88 (38.6)	0.944 – 6.82
	k_a (h^{-1})	0.143 (24.8)	0.151 (25.2)	0.076 – 0.226
Maturation related Parameter	k_{mat} (h^{-1}) × 10^{-3}	4.58 (20.3)	4.40 (19.3)	2.74 – 6.06
Auto-Induction related Parameter	k_{enz} (h^{-1}) × 10^{-3}	8.79 (35.4)	8.95 (33.2)	3.13 – 14.7
Drug-Effect On Auto-induction	α (L/mg)	0.094 (28.8)	0.088 (22.1)	0.011 – 0.126
Lung Distribution related Parameter	k_p	0.676 (18.8)	0.690 (18.2)	0.443 – 0.936
Interindividual variability (CV%)	ω CL_{im}/F	32.4 (42.7)	33.0 (44.2)	8.41 – 58.6
	ω CL_{ma}/F	32.4 (42.7)	32.7 (45.2)	8.73 – 61.7
	ω V/F	72.8 (36.5)	74.2 (39.5)	21.1 – 127
Residual variability (CV%)	σ_{plasma}	44.5 (8.90)	42.1 (8.50)	26.4 – 57.8
	σ_{Lung}	28.3 (13.1)	22.5 (12.7)	19.6 – 37.0

RESULTS

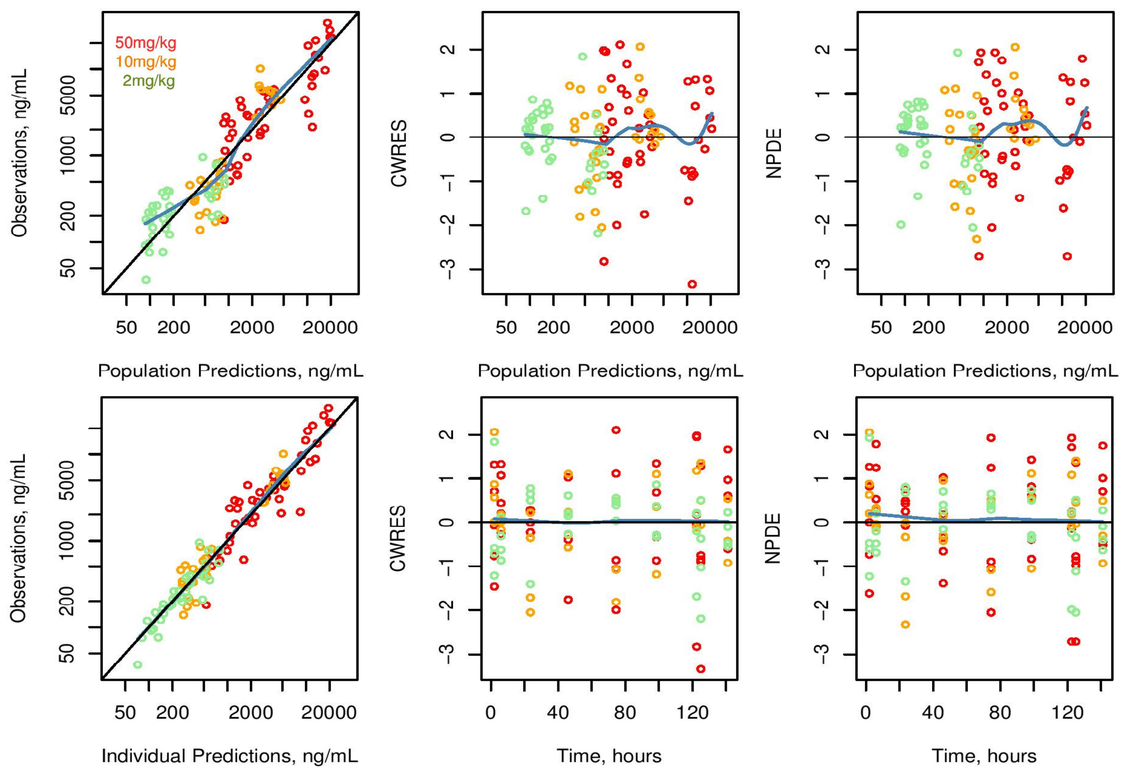

Figure 2. Goodness of fit plots of the PK model.

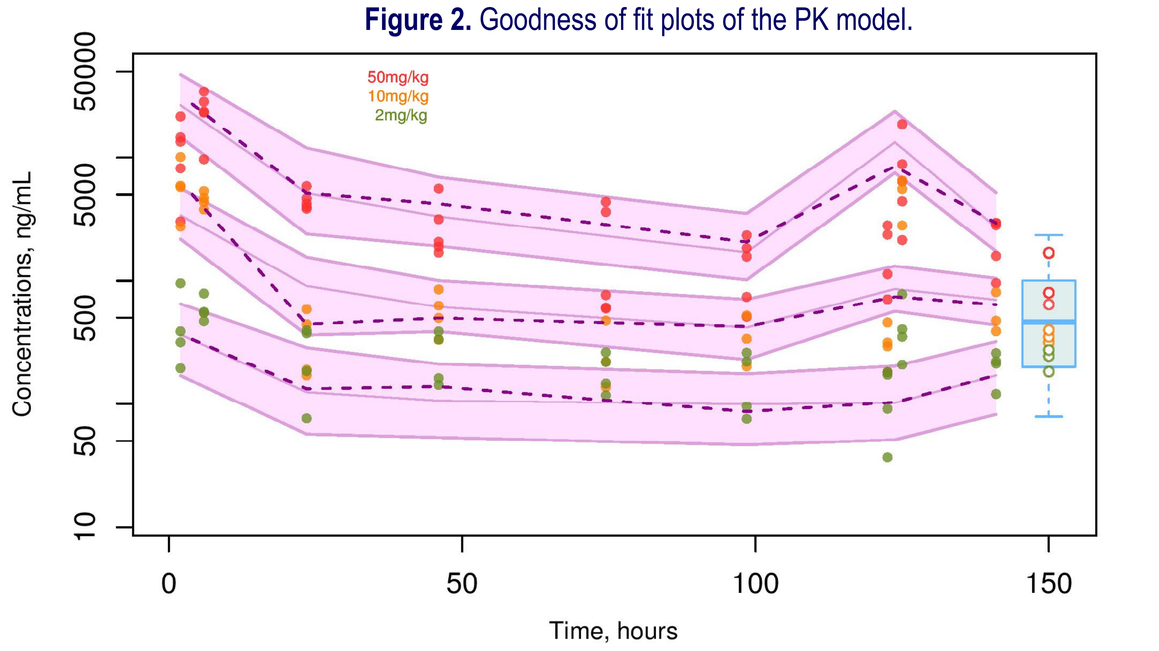

Figure 3. VPC which displays the 5th, 50th and 95th percentiles of the plasma concentrations, and the 95% confidence interval for the corresponding model-based predicted percentiles computed from 100 Monte Carlo replicates. All lung concentrations fell inside the prediction interval boxplot whiskers, which display the 5th and 95th percentiles of the model prediction interval.

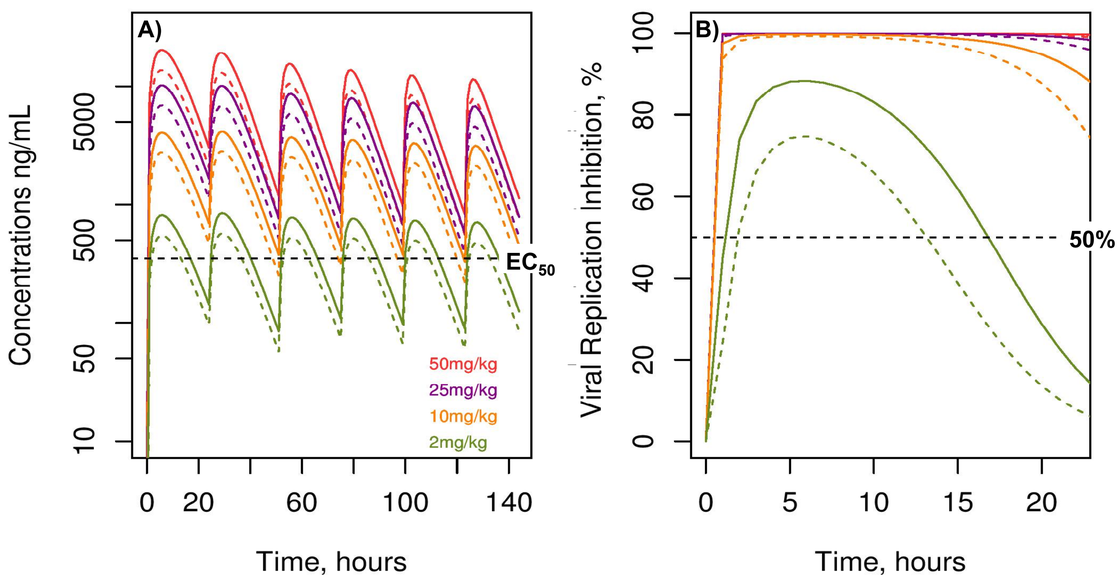

Figure 4. A) Deterministic simulations showing the time course of plasma (solid lines) and lung (dashed lines) concentrations for each dose level of compound X (2,10,25,50 mg/kg). B) Percentage inhibition of lung infection for the plasma (solid lines) and lung (dashed lines) concentrations achieved after 24 hours of compound X administration.

CONCLUSIONS

- **The PK model developed in neonatal lambs, properly describes the concentration time course in plasma and lungs, after accounting for clearance maturation and auto-induction.**
- **Model-based simulations suggest that a 25 mg/kg can produce a 95% mean inhibition of viral replication after 6 days post inoculation of the virus in lambs.**

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