Modeling of pharmacokinetic data using nonlinear mixed effects: a paradigm shift in veterinary pharmacology
A case study with the NSAID robenacoxib in cats

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Research Rationale

- **Background:** Very often in veterinary medicine characterization of drugs pharmacokinetics is performed using a so-called 2 stages approach, thereby limiting most of the analyses to rich data.

- **Objectives:** Model the disposition kinetics of robenacoxib in cats by pooling data from diverse sources in order to leverage the richness of the intensively sampled individuals to inform parameter estimates of the more sparsely sampled patients.

Methods

- **Data:** From 83 cats were pooled from 7 preclinical (laboratory cats) and 1 field (client-owned cats, peroperative sampling) **robenacoxib** PK studies.

- **Cats:** Received **robenacoxib subcutaneously** (SC) and/or **intravenously** (IV). Sampling was rich for 47 laboratory cats and sparse for 36 clinical cats.

- **Data:** Both routes were modeled simultaneously with NLMEs in Monolix 4.3.2.

Results

A 2-compartment mamillary model with 1st-order absorption and elimination best described the kinetics of robenacoxib in blood. The precision of the final models parameters was considered satisfactory (RSE<20% for most parameters).

The total body clearance was estimated to be moderate (0.50 L/kg/h) and the global extraction ratio E was small (0.06). The SC bioavailability was high (79%) and the steady state volume of distribution was 0.27 L/kg.

The absorption constant (Ka: 0.86 h-1) was lower than the elimination constant of the combined model (K10: 2.17 h-1), thus confirming flip-flop kinetics with the SC route.

None of the population characteristics was found to explain the between-subject variability observed in the present studies.

Conclusions and Perspectives

- The population approach allows pooling of data from different individuals, even from different studies with different application routes and dosing regimens.

- Simultaneous modeling of the IV and SC routes unveiled the flip-flop kinetics of robenacoxib in cats.

- Estimates of robenacoxib exposures from peroperative (sparse) and conscious (rich) cats did not differ substantially.

- Using population modeling to estimate the pharmacokinetics of anaesthetized cats is new to veterinary pharmacology.

References:

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