Purrfect fit: Validation of PK-Sim cat model for iv administration

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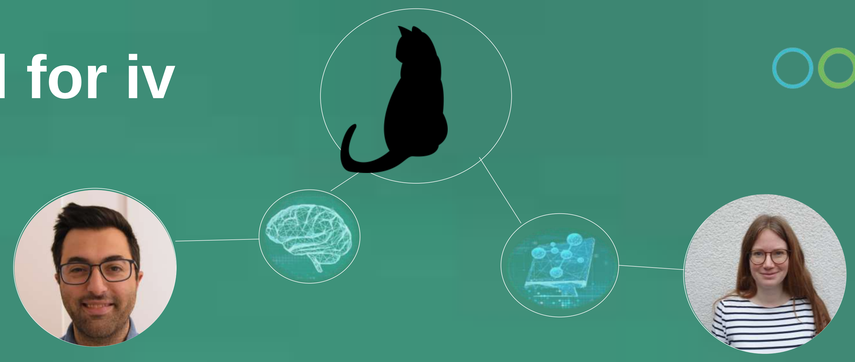

Introduction

Domestic cats, together with dogs, are among the most popular pets in the world. Given the growth in pet populations and increased life spans, the need for developing new treatment options tailored to cats' needs is increasing.

Physiologically-based pharmacokinetic (PBPK) models mathematically describe and simulate concentration-time course of chemicals in tissues of organisms using species-specific physiological parameters and chemical specific parameters. These models can play an essential role in drug developmental processes.

Our aim: Developing and applying a cat PBPK model integrated in PK-Sim

How?

Cat PBPK model was structurally based on the beagle dog model available in PK-Sim. Physiological data for the cat was added.

Model was applied to two chemicals.

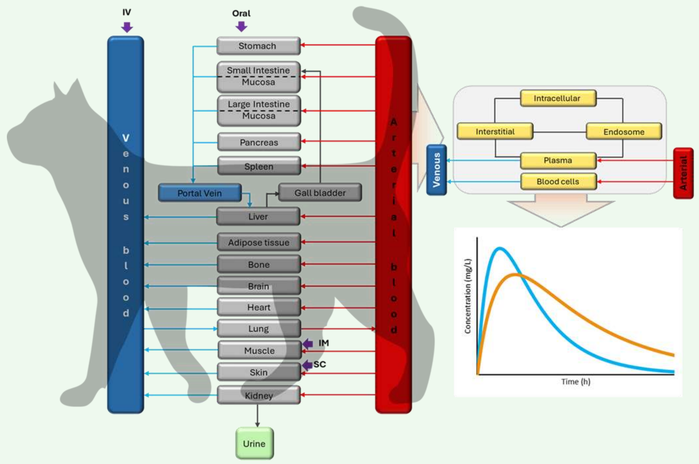

Fig 1: Schematic structure of the PBPK PK-Sim model for cats. Chemical uptake/administration can be modelled via oral, intravenous, intramuscular and subcutaneous routes

Material and Methods

Data collection

→ Organ volumes

→ Blood flows

→ Hematocrit values

→ Pharmacokinetic data on lotilaner and furosemide

Model development

→ Generic PBPK model (Figure 1)

→ Model input parameters obtained from literature

Model application

→ Model performance was illustrated for lotilaner and furosemide in cats and dogs

→ The validated model in PK-Sim for the beagle dog was primarily used for parameter identification and setting the partition coefficient method before it was applied to the cat

→ Model was validated by comparisons of measured concentrations in plasma with the PBPK model predictions [1-4]

Results

→ Time-concentration curves matches with the measured data

→ Model predictions were within a 2-fold change for both chemicals and species

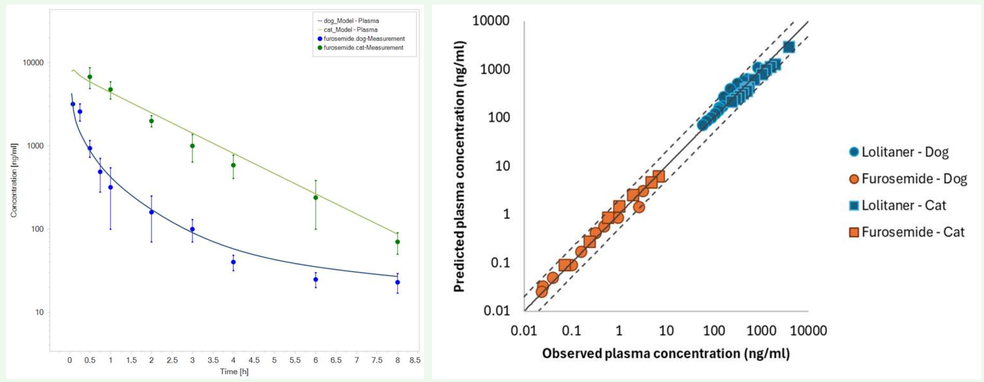

Figure 2: A) Predicted time-concentration curves in plasma for lotilaner in dogs and cats compared to measured plasma data. B) Comparison between observed and predicted plasma concentrations in cats and dogs for lotilaner and furosemide. Dotted lines represent a 2-fold change.

Discussion/Conclusion

→ Integration of physiological data to develop a cat PBPK model in PK-Sim

→ Validation of the cat model for intravenous administration

→ The validated cat model applies to “normal” lean cats. Specific conditions, such as obesity, kidney insufficiency, and others, were not considered

→ PBPK models can be helpful in the veterinary drug developmental process

Next steps…

→ Application to 10 other chemicals, covering a broader range in logP and pKa values

→ Extend and validate the model for oral drug applications

1) Toutain 2018. https://doi.org/10.1186/s13071-018-2966-6
2) Toutain 2017. https://doi.org/10.1186/s13071-017-2475-z
3) Sleeper 2019. https://doi.org/10.1177/1098612X18805879
4) Koh 2021. https://doi.org/10.1186/s12917-021-02998-4

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