

Model-based comparison of modified-release metoprolol formulations in beagle dogs and rabbits

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INTRODUCTION

The selective adrenergic β 1-receptor antagonist, metoprolol (MTP) is commonly prescribed for a variety of cardiovascular conditions. This drug is available in different salt forms as well as different modified-release formulations. Beagle dogs and rabbits are used interchangeably, in our institution, to study preclinical PK of in-house developed pharmaceutical dosage forms.

OBJECTIVES

Absorption kinetics were investigated of three different MTP (model compound Biopharmaceutics Classification System (BCS) class I) modified-release formulations in beagle dogs and rabbits, using compartmental models.

METHODS

Drug formulations

- iv formulation based on MTP tartrate
- Prills and Slow-lopresor[®] (matrix formulations) based on MTP tartrate
- ZOK-ZID[®] (reservoir formulation) based on MTP succinate and hydrochlorothiazide

Data

- Single doses of 50-200 mg MTP tartrate were intravenously or orally administered
- 258 and 205 plasma concentrations were measured above the LoD (Limit of Detection, 10.1 ng/ml) in 30 Beagles and 24 rabbits, respectively

PK model development procedure

- Nonlinear mixed effect modeling was performed using NONMEM 7.3.0
- M3 method (with F_FLAG) was applied to handle data below LoD (BLoD)
- The LAPLACIAN numerical estimation method was used for parameter estimation
- Percentages of BLoD (BLoQ) data: 6.2% (9.5%) in Beagles and 6% (16.5%) in rabbits

Model evaluation

- The final PK model was evaluated using log likelihood profiling (LLP) and prediction-corrected visual predictive checks (pcVPC)

RESULTS

Final PK model

A two-compartment model with sequential zero and first order absorption was selected to describe the PK of MTP in Beagles. The PK of MTP in rabbits was best described by using a two-compartment model with first order absorption. In both models, residual variability was described with an additive error in the log domain. Prior to the analysis, the pharmacokinetic observations were ln-transformed. No covariates were included in the final PK model.

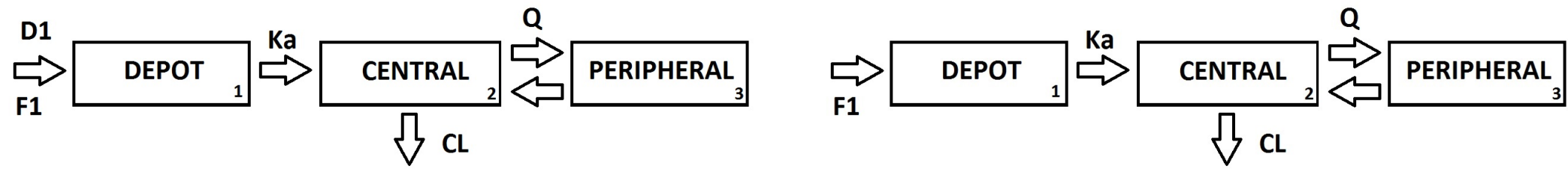


Figure 1: Schematic representation of the PK model for MTP in Beagles (left) and rabbits (right)

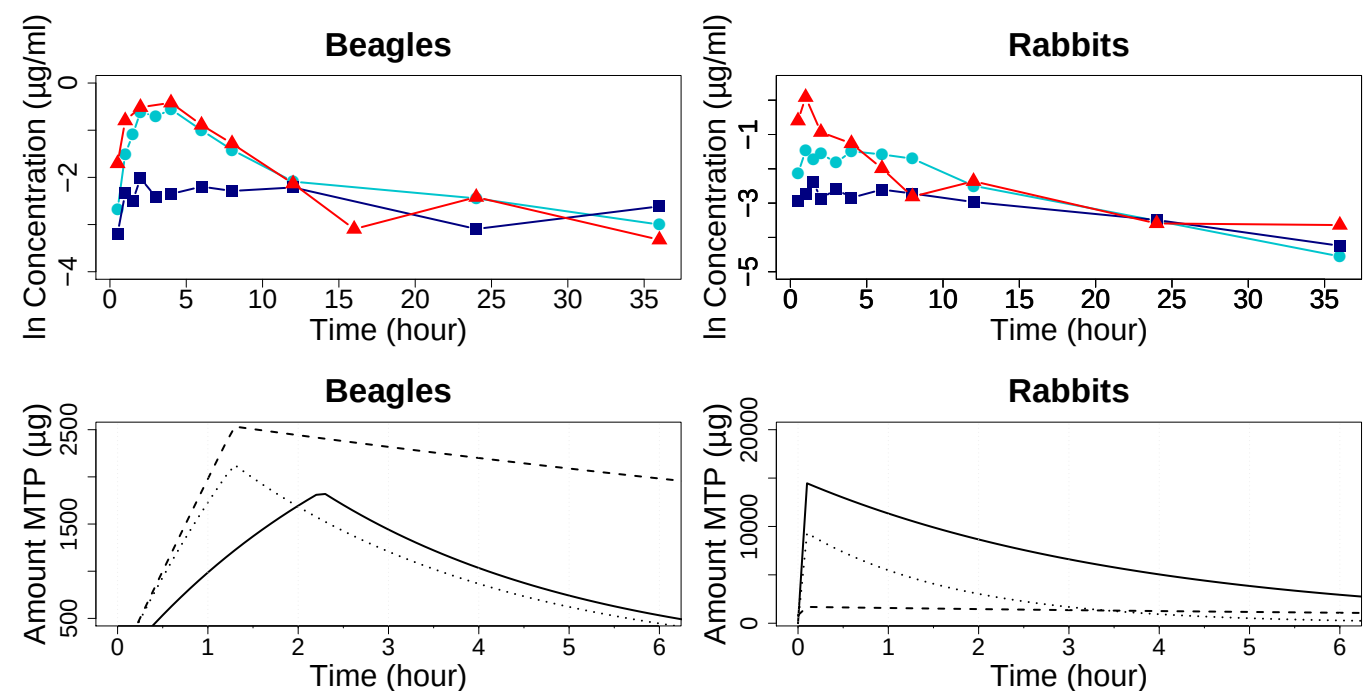


Figure 2: Top: mean plasma concentration-time curves in Beagles and rabbits, bottom: amount MTP over time in depot compartment for Beagles and rabbits
Dots/Solid line: prills, squares/dashed line: ZOK-ZID[®] and triangles/dotted line: Slow-lopresor[®]

Model evaluation

Model evaluation using LLP and pcVPC demonstrated that the model is performing relatively well. However, the dog model is not correctly capturing the fraction of BLoD data at early and later time points.

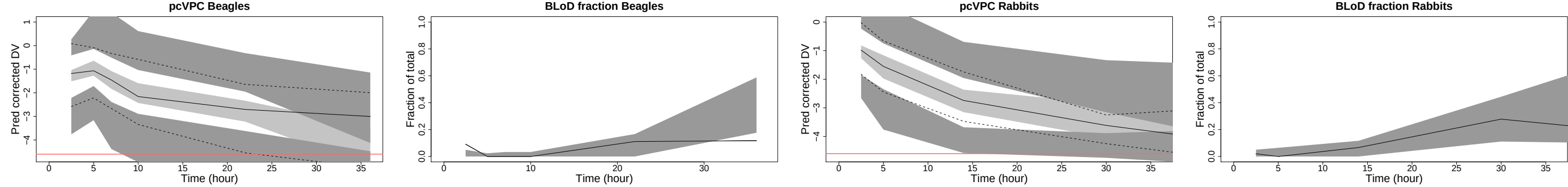


Figure 3: pcVPC and fraction BLoD data over time for Beagles and rabbits
Red lines in pcVPC refer to LoD. Grey areas are 95% confidence intervals based on 500 simulated data sets, solid black line: observed 50th percentile, dashed lines refer to the observed 5th and 95th percentile

Table 1: Final population parameter estimates in Beagles

MLE*=Maximum likelihood estimate, ω^2 : Interindividual variability, σ^2 : Residual unexplained variability

Parameter [units]	Final model Estimate	LLP MLE* (95% CI)
CL [ml/h]	776	776 (471-1 242)
V2 [ml]	631	631 (339-934)
V3 [ml]	1 490	1488 (729-8 559)
Q [ml/h]	116	116 (62.5-170)
Ka prills/Slow-lopresor [®] [/h]	0.332	0.332 (0.277-0.406)
Ka ZOK-ZID [®] [/h]	0.0521	0.052 (0.037-0.070)
F1	0.0131	0.013 (0.008-0.021)
D1 prills [h]	2.26	2.255 (1.701-2.932)
D1 ZOK-ZID [®] /Slow-lopresor [®] [h]	1.29	1.294 (0.978-1.879)
ω^2 CL	0.445	0.445 (0.252-0.821)
ω^2 V2	0.71	0.710 (0.377-1.793)
ω^2 V3	0.699	0.699 (0.155-2.696)
ω^2 Q	0.349	0.349 (0.146-1.280)
σ^2 add	0.457	0.457 (0.426-0.503)

Table 2: Final population parameter estimates in rabbits

MLE*=Maximum likelihood estimate, ω^2 : Interindividual variability, σ^2 : Residual unexplained variability

Parameter [units]	Final model Estimate	LLP MLE* (95% CI)
CL [ml/h]	3 390	3 390 (2 340-4 978)
V2 [ml]	7 350	7 349 (5 843-9 197)
V3 [ml]	29 800	29 825 (15 866-93 091)
Q [ml/h]	2 180	2 177 (1 424-3 236)
Ka prills [/h]	0.27	0.270 (0.197-0.376)
Ka ZOK-ZID [®] [/h]	0.075	0.075 (0.042-0.127)
Ka Slow-lopresor [®] [/h]	0.59	0.590 (0.358-1.029)
F1 prills/Slow-lopresor [®]	0.0871	0.087 (0.051-0.151)
F1 ZOK-ZID [®]	0.0588	0.059 (0.026-0.156)
ω^2 CL	0.266	0.266 (0.083-0.802)
ω^2 F1	0.414	0.414 (0.162-1.043)
σ^2 add	0.569	0.569 (0.509-0.641)

CONCLUSION AND PERSPECTIVES

Different absorption models were selected to describe the PK of MTP in both species. Across species, large PK variability was observed with a faster absorption phase in rabbits. For both animals, the best slow-release profile (lowest peak-to-trough ratio) was obtained with ZOK-ZID[®]. Flip-flop kinetics were not observed for Slow-lopresor[®] in rabbits. Further model improvement is needed to capture the BLoD fraction in Beagles more correctly and to better describe the double peak phenomenon.

CONTACT INFORMATION

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