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Hemodynamic systems model to characterize cardiovascular drug effects

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The cardiovascular system (CVS) is complex and highly regulated. Early prediction and quantification of cardiovascular drug effects is crucially important to support decision making during drug development. Previously a hemodynamic CVS model was developed using rat data by Snelder et al. ("Snelder model") [1,2]. System-specific parameters were distinguished from drug-specific parameters by challenging the system with eight compounds with different mechanism of action (MoA). The current study aims to 1) further evaluate if the mode of action of new drugs can be identified while keeping the system-specific parameters fixed; 2) identify the minimal required data to translate the model to other species by evaluating if the system-specific parameters can be identified using data from only one compound with known MoA. We performed a structural identifiability analysis using the Matlab toolbox GenSSI 2.0 with different combinations of observations, including heart rate (HR), cardiac output (CO) and mean atrial pressure (MAP) [3]. Practical identifiability was evaluated using stochastic simulation and estimation (SSE) using Perl-speaks-NONMEM to determine if the model can be used to identify and quantify drug mode of action. Using the SSE analysis, we quantified the number of models that correctly identified drug mode of action, and we evaluated bias and precision of drug effect parameters. The cardiovascular-hemodynamic model proposed by Snelder is structurally locally identifiable based on observations of HR, MAP and CO. The SSE analyses indicated that mode-of-action of drug effect could be identified for different EC_{50} and Emax values and statistical significance of $p < .05$ (power 100%). Both system-specific parameters and drug-specific parameters can be estimated precisely with a minimal bias. Models including observations for CO showed increased percentages of successful minimization compared to models without CO. Our analysis supports the use of the Snelder model to identify and quantify drug mode of action in preclinical cardiovascular experiments. MAP, HR and CO measurements following administration of one compound with known MoA provide a good starting point for translating this model to other species and guide study design.

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Hemodynamic simulator: A Shiny web application for predicting drug effect on hemodynamics

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Characterization of hemodynamic drug effects and mode of action is a crucial part of cardiovascular translational safety assessment. Mathematical modelling of the hemodynamic system can be helpful to quantitatively assess mode of action and to study the effect of different dose schedules on hemodynamic endpoints. Previously, Snelder et al. [1,2] developed a hemodynamic systems model consisting of five biomarkers and their interactions, including heart rate (HR), stroke volume (SV), total peripheral resistance (TPR), cardiac output (CO) and mean atrial pressure (MAP). This modelling framework can be of relevance to support preclinical safety pharmacologists, but cannot be easily used by non-modelling safety pharmacology scientists. We aimed to develop a user-friendly web application to perform model-based predictions of drug effect on hemodynamic endpoints based on the Snelder model. A web application was implemented using the R package Shiny. The RxODE R package was used to perform the simulations. Typical values of species-specific parameters in rat and drug-specific parameters for seven reference drugs are available according to estimates in Snelder model [1,2]. The shiny app can be accessed at http://hemodynamic-simulator.eu/.The source code is posted to Github available through this website. Model-based prediction can be obtained following these steps:

1. select species (rat or dog) for simulation;
2. select reference drug and define dosage for simulation (optional);
3. simulate investigational drug by define drug-specific PK and PD parameters;
4. input data file for plotting following pre-set dataset template (optional)
5. generate a PDF report (optional).

This application with user-friendly interface can help safety evaluation and decision making in drug development and clinical practice. We plan to expand this app with additional reference drugs and species in the future.

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2. Snelder, N.et al.*Br J Pharmacol***171**, 5076–5092, doi:https://doi.org/10.1111/bph.12824 (2014).

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Simultaneous measurement of Ca-transient and contractility in isolated canine ventricular myocytes using IonOptix: Assay development and validation

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For therapeutic evaluation and safety assessment in drug development, the simultaneous measurement of contractility and calcium fluctuations in primary isolated cardiac myocytes can provide valuable understanding on mechanism of drug action. The current study was designed to develop and validate an assay for measuring Ca-transients (CT) and myocyte contractility in isolated canine ventricular myocytes. Left ventricular myocytes were isolated from one-year old male beagle dogs and loaded with Fura2-AM. Contractility (sarcomere shortening) and CT were measured with a