Prediction of Cardiac Contractility and Hemodynamics in Conscious Dogs using Mechanism Based Platform

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Objectives: Cardiovascular safety is one of the most frequent causes of safety related attrition both pre-clinically and clinically. The objective was to develop a mechanism based platform to assess drug induced changes in contractility along with hemodynamic end-points routinely measured in dog telemetry studies.

Methods: Data from contractility (dPdT\(_{\text{max}}\)), heart rate (HR) and blood pressure (MAP) were available from dog telemetry studies for atenolol (n=27), albuterol (n=5), L-NG-Nitroarginine methyl ester (L-NAME; n=4), and milrinone (n=4). The model developed by Snelder et al. [1,2] was used as a starting point and was adapted to include dPdT\(_{\text{max}}\). Separate drug effects for all drugs included in this analysis were evaluated using linear and (sigmoid) E\(_{\text{max}}\) relations on dPdT\(_{\text{max}}\), HR and/or TPR. Nonparametric bootstrap (n=500) was performed to assess model robustness. Model was further evaluated using Sobol Sensitivity analysis to identify the most influential parameters.

Results: Population PK models for dogs were developed for atenolol and milrinone using available and literature data, while for albuterol and LNAME, literature PK models were utilized. Drug effects of atenolol, albuterol, LNAME and milrinone were included on either dPdT\(_{\text{max}}\), HR and/or TPR capturing the drug effects adequately well for all studies. Bootstrap analysis demonstrated adequate model robustness with comparable mean values of parameter estimates to the final model. Preliminary results from sensitivity analysis suggest that baseline, diurnal rhythm and feedback related parameters were more important than first order rate constants (k\(_{\text{out}}\)).

Conclusions: The developed mechanism based platform can be used to simultaneously capture drug induced changes in dPdT\(_{\text{max}}\) along with other hemodynamic end-points, HR and MAP, for multiple drugs in order to assess the hemodynamic safety profiles.

References