A Comparison of Baseline Heart Rates, Left Ventricular and Systolic Pressures in Group versus Single Housed Dogs and the Effects of Housing on Sensitivity to Detect Changes in Contractility following Pimobendan administration

N Sadekova, G Boudreau and K Norton Charles River, Montreal, Quebec, Canada

Introduction

As per ICH S7A guidance, the effects on myocardial contractility are only required as follow-up studies when there is a suspected effect based upon the pharmacological properties or chemical class of the test substance, or when safety concerns arise from other studies. As such, there is a growing weight of evidence to suggest that these effects should be assessed as part of IND enabling studies. Typically, assessments of contractility are limited to echocardiography or single housed telemetry assessments of dP/dt max. With advancements in cardiovascular technology, it is now feasible to conduct these assessments under group housing conditions. The purpose of this study was to evaluate baseline cardiovascular parameters, within a group housed environment, compared to historical data from a single housed environment and to demonstrate that the model retains sensitivity of the traditional assessments.

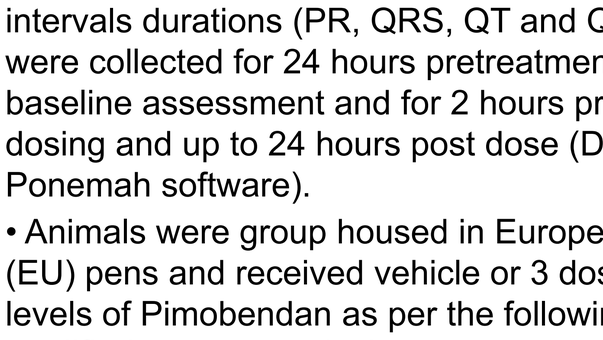
Methods

- 4 naïve male Beagle dogs were instrumented with Data Sciences International (DSI) Physiotel Digital L21 implants equipped with a blood pressure and LVP catheters and with ECG leads fixed in Lead 2 configuration.
- Heart Rate, LVP parameters (dP/dt max dP/dt min, LVEDP), systemic arterial pressures, QA interval duration and ECG intervals durations (PR, QRS, QT and QTc) were collected for 24 hours pretreatment for baseline assessment and for 2 hours prior to dosing and up to 24 hours post dose (DSI Ponemah software).
- Animals were group housed in European (EU) pens and received vehicle or 3 dose levels of Pimobendan as per the following modified cross-over design:

Animal No.	Dose 1 (mg/kg)	Dose 2 (mg/kg)	Dose 3 (mg/kg)	Dose 4 (mg/kg)
1001	0	0.1	0.3	1
1002	0	0.1	0.3	1
1003	1	0.3	0.1	0
1004	1	0.3	0.1	0

Results

Figure 1: Baseline Heart Rate in Group vs Single housed animals



Results

Figure 2: Baseline Systolic and Diastolic Blood Pressures in Group vs Single housed animals

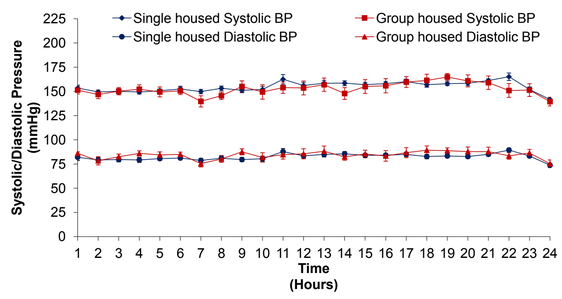


Figure 3: Effect of Pimobendan on maximum rate of left ventricular contraction (dP/dt max)

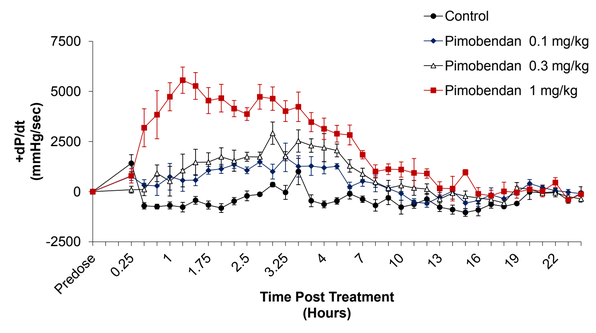


Figure 4: Effect of Pimobendan on LVEDP

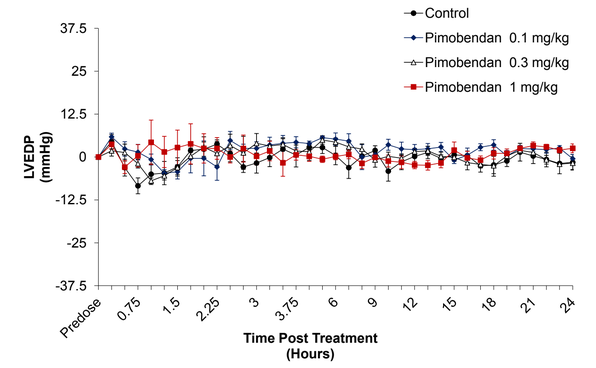


Figure 5: Effects of Pimobendan on QA interval

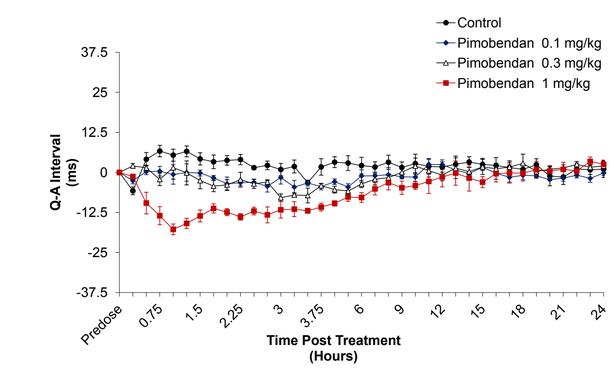


Figure 6: Effect of Pimobendan change in QA interval versus dP/dt max

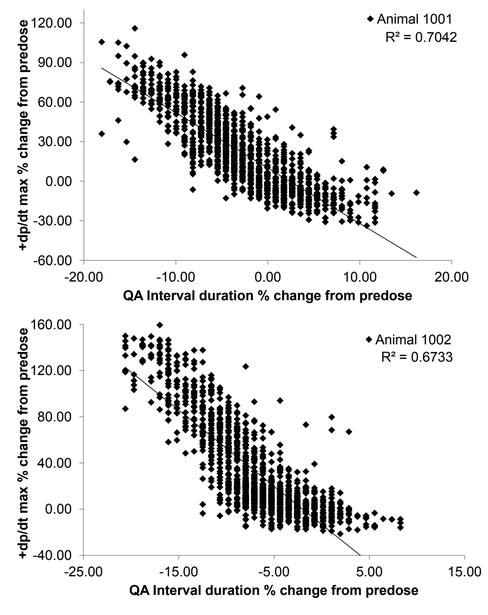
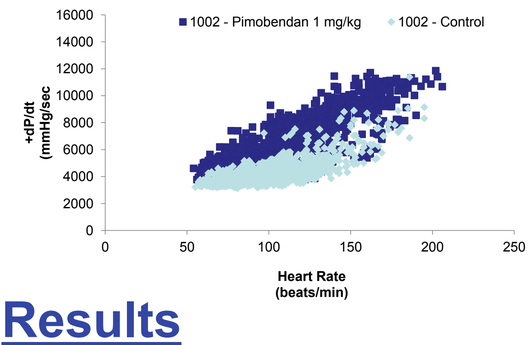


Figure 7: Effect of Pimobendan on dP/dt max versus heart rate



Results

- There was no apparent difference in pretreatment heart rates or diastolic or systolic blood pressures between group or single housed animals (Fig 1 and Fig 2).
- Administration of Pimobendan induced a dose-dependent increase in LVP dP/dt max up to ~ 5000 mmHg/sec at 1 mg/kg (Fig 3). The mean increase, relative to the predose values, was 83%, in line with previously published data (110% change, Markert et al., 2007) over a 7-hour period.
- Administration of Pimobendan induced a decrease in QA interval (Fig 5), especially at 1 mg/kg, showing a good correlation with the increase in dP/dt max (Fig 6).
- No changes noted in LVEDP (Fig 4) or in arterial pressures: no preload or afterload influence on the noted increase in contractility.
- Increase in heart rate was noted following administration of Pimobendan at 1 mg/kg. A plot of dP/dt max versus heart rate showed a clear separation between control and treated animals indicating that the increase in contractility was not solely attributable to increases in heart rate (Fig 7).

Conclusion

The collection of cardiovascular (CV) data in group housed male dogs, in EU caging, showed stable cardiovascular baseline data and was sensitive to detect expected changes in contractility. Therefore it is a suitable model to meet ICH-S7A requirements, while providing additional information on test substance safety and improved animal welfare.

Acknowledgments

The authors would like to acknowledge the contributions of the safety pharmacology technical and scientific staff at Charles River in the conduct of these projects.

References

Markert M et al., The value added by measuring myocardial contractility 'in vivo' in safety pharmacological profiling of drug candidates. J Pharmacol Toxicol Methods. 2007

ESPS, Prague, 2015
09/2015