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Research article

The effects of housing conditions on baseline cardiovascular parameters and the sensitivity to detect changes in contractility in telemetry-implanted dogs

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ABSTRACT

Introduction: There is a growing weight of evidence to suggest that myocardial contractility is an important parameter to assess as part of IND enabling studies in addition to standard assessments as per the ICH S7A and S7B guidelines. Historically, assessments of contractility have been limited to snap-shot echocardiography or single housed telemetry assessments of left ventricular pressure. There is a growing number of studies showing that social housing conditions in large animals are beneficial, do not impact the integrity of the data collected and improve animal welfare. With current advances in cardiovascular technology it is now feasible to conduct cardiovascular assessments under group housing conditions. Therefore, the purpose of this study was to evaluate baseline hemodynamic parameters, within a group housed environment, and to demonstrate that the model retains the sensitivity of the traditional assessments.

Methods: Four animals were instrumented with DSI HD-L21 implants for continuous 24-hour assessment of systemic arterial pressures, left ventricular pressures, heart rate and electrocardiogram intervals in group housed conditions. The animals were administered either Atenolol (0.3, 1 and 3 mg/kg), a known negative inotrope, or Pimobendan (0.1, 0.3 and 1 mg/kg), a known positive inotrope.

Results: The results showed that group housing had no influence on baseline hemodynamic assessments as compared to historical data from single housed animals. The administration of Atenolol and Pimobendan induced the expected changes in cardiovascular parameters.

Discussion: The baseline hemodynamic parameters remained within physiological ranges and were not influenced by group housing conditions. The model retained sensitivity to detect the expected changes in contractility in line with known effects of Atenolol and Pimobendan in dogs. In conclusion, the use of social housing conditions in dogs provides an enriched environment, compliant with animal welfare recommendations, and is in line with the ICH S7A safety pharmacology guidelines, while retaining sensitivity to detect changes in myocardial contractility.

1. Introduction

As per ICH S7A and S7B guidelines, the potential effects of new pharmaceutical entities on vital organs or systems, such as the cardiovascular system, need to be assessed prior to the first-in-human studies. The core battery for those assessments includes blood pressure, heart rate and electrocardiogram evaluations. Effects on other cardiovascular parameters, such as myocardial contractility, are only required as follow-up studies when there is a suspected effect based upon the pharmacological or chemical class of the new pharmaceutical, or when safety concerns arise from other studies (ICH S7A, 2000; ICH S7B, 2005).

It is well known that cardiovascular toxicity, such as QT prolongation, is one of the main reasons for compound attrition or withdrawal (Cools et al., 2014). However, there is a growing weight of evidence to suggest that myocardial contractility is an important parameter to assess as part of IND (investigational new drug) enabling studies (Cools et al., 2014; Markert et al., 2007). Cardiac output depends largely on the intrinsic contractile properties of the heart and changes in those properties may lead to unwanted and harmful side effects, especially in a more vulnerable patient population with pre-existent cardiac pathologies (Guth et al., 2015). Moreover, although the majority of cardiac adverse events reported following drug approval are due to cardiac arrhythmias, the US Food and Drug Administration has reported just under 50,000 cardiac post-approval adverse events related to heart failure and myocardial disorders since 1969. The risk of heart failure and myocardial damage can be assessed by measuring the left ventricular function and myocardial contractility in preclinical studies (Laverty et al., 2011). Although evaluation of left ventricular pressure–volume loops is the gold standard, preclinical assessments of contractility

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mainly include echocardiography and measurements of the maximum rate of left ventricular contraction ($LVdP/dt_{max}$) (Cools et al., 2014; Markert et al., 2007; Guth et al., 2015). The $LVdP/dt_{max}$ assessments are generally conducted in a chronically instrumented conscious animal, the preferred model as per ICH S7A guidelines (Markert et al., 2007; ICH S7A, 2000). Indeed, it has been shown that $LVdP/dt_{max}$, measured in instrumented conscious dogs, accurately assesses changes in myocardial contractility consistent with clinical outcomes (Cools et al., 2014; Guth et al., 2015; Laverty et al., 2011).

These telemetry assessments have been traditionally conducted in single housed animals, mainly due to the limitations of data acquisition systems, as well as the general belief that those types of assessments should be conducted without any external stimuli, such as socialization (Hawkins et al., 2004). Moreover, there is concern over the study design, such as the standard latin-square design, commonly used in stand-alone safety pharmacology studies, that no longer applies in a group housed setting (Bottomley, Prior, & Cordes, 2015). There is no evidence that socialization during acquisition of physiological parameters leads to increased level of stress capable of disturbing the quality of the data (Hawkins et al., 2004). Dogs are a social species and many studies have shown the harmful effects of social isolation. Indeed, the benefits of social housing conditions have been supported by studies showing that vocalization and stereotypic behaviour was decreased, and sleeping time was increased in dogs housed in pairs (Hawkins et al., 2004; Klumpp, Trautmann, Markert, & Guth, 2006; Hetts, Clark, Calpin, Arnold, & Mateo, 1992). These studies demonstrate that social housing, when conducted under appropriate conditions, may decrease abnormal and stress-related behaviour and stimulate species-specific behaviour as well as cognitive development. Therefore, the social housing conditions have been strongly recommended for all types of studies conducted (Hawkins et al., 2004; National Research Council, 1996; Prescott et al., 2004).

Regarding the quality of data, it has been shown that baseline hemodynamic parameters are not altered by social housing conditions and are actually improved in animals that were pair-housed (Klumpp et al., 2006; Kaiser, Tichenor, Regalia, York, & Holzgrefe, 2015). The social housing environment during telemetry studies has been limited to pair housing in which one implanted dog is co-housed with a run mate who is not implanted or used during the study, due to the limitations of the acquisition systems. Inevitably, although this fulfills the requirement for social housing, this setting also requires the use of additional, unnecessary animals. With the current advancements in cardiovascular technology, it is now feasible to conduct these assessments under group housing conditions with animals in the same cages/pens being recorded simultaneously. This allows the group housing of animals throughout the monitoring period, as well as avoiding the use of additional animals. In order to consider the use of this new study design, the specificity and sensitivity of the recorded parameters need to be assessed, and this evaluation has not yet been documented. Therefore, the objective of this study was to evaluate baseline cardiovascular parameters, within a group housed environment and to demonstrate that the model retains the sensitivity of the traditional assessments.

2. Methods

2.1. Animals

The study was conducted in a facility (Charles River Laboratories, Senneville, Quebec, Canada) accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). The study design was reviewed and approved by the test facility's Institutional Animal Care and Use Committee (IACUC). Five male naïve Beagle dogs were ordered from Marshall BioResources USA, Inc., North Rose, NY, USA. The animals were 10 months old and weighed between 9.4 and 11.2 kg at the initiation of treatment.

2.2. Housing

Animals were socially housed in European pens with a pultruded fibreglass slatted floor and equipped with an automatic watering valve. An individual pen had the following dimension: 42″ width × 78″ length × 89″height. During telemetry acquisition periods, the animals were pair housed across two pens. During off monitoring periods, 5 pens were opened to form a single run.

2.3. Acclimation

A minimum acclimation period of 7 days was allowed between animal receipt and the surgeries (telemetry implantation) in order to accustom the animals to the laboratory environment. A 4-week period was allowed between the surgeries and the start of treatment.

2.4. Surgical implantation of telemetry devices

Five male Beagle dogs were instrumented with Data Sciences International (DSI) Physiotel™ Digital L21 Implants (Data Sciences International, St. Paul, MN, USA) for acquisition of blood pressure, left ventricular pressure, electrocardiogram and body temperature.

The animals were anesthetized using Thiopental sodium (10 mg/kg), and maintained under anesthesia with isoflurane (1.5 to 3%). A preoperative and postoperative analgesic (BuprenorphineSR®, 0.06 mg/kg), an anti-inflammatory (Carprofen, 4 mg/kg) and an antibiotic (Cefazolin, 20 mg/kg) were administered to all animals as per the facility's standard procedures.

The telemetry transmitter was placed in the abdominal muscle and the arterial blood pressure catheter was placed in a femoral artery. A right thoracotomy was performed and the ribs separated to visualize the heart. The electrocardiogram (ECG) leads and the left ventricular pressure catheter were tunneled inter-muscularly from the muscle pouch to the 7th inter-costal space and then tunneled into the thoracic cavity. Direct access to the heart was obtained by opening the pericardium. The tip of the left ventricular pressure catheter was inserted through the apex of the heart into the left ventricle. ECG leads were fixed in a Lead 2 configuration with the positive ECG electrode fixed on the apex of the heart and the negative ECG electrode attached to the right atrium.

2.5. Study design and drug administration

The traditional latin-square design, where each animal receives a different dose level, cannot be performed in a social housing setting. The risk of possible contamination needs to be avoided, therefore animals receiving different dose levels cannot be housed together. Hence, a partial latin-square or modified cross-over design was used in the study where two animals received the same dose level at a time.

For the first phase of the study, each animal received up to 4 oral doses of either vehicle (deionized water) or Atenolol, a selective β1-receptor antagonist and a known negative inotrope (Markert et al., 2007; Takahara, Dohmoto, Yoshimoto, Sugiyama, & Hashimoto, 2001, Guth et al., 2015) at 0.3, 1 and 3 mg/kg with a minimum of 3 days between each dose, based on the toxicokinetic properties of the test article.

For the second phase of the study, following a 6-day washout period, each animal received up to 4 oral doses of either vehicle (empty gelatin capsules) or target doses of 0.1, 0.3 and 1 mg/kg of Pimobendan, a selective phosphodiesterase III inhibitor and a known positive inotrope (Markert et al., 2007; Guth et al., 2015) with a minimum of 3 days between each dose, based on the toxicokinetic properties of the test article. The selected dose levels for each compound have been shown to induce the expected changes in left ventricular contractility in dogs (Guth et al., 2015). The study design is presented in Table 1.