Journal of Pharmacological and Toxicological Methods 87 (2017) 38–47

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Cardiac contractility: Correction strategies applied to telemetry data from a HESI-sponsored consortium

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ARTICLE INFO

Keywords:
Dog
Contractility
Inotropy
Heart rate
Correction formula
Left ventricular pressure
dP/dt_{max}

ABSTRACT

Introduction: QT has a long history of heart rate (HR) correction but limited investigations have been undertaken to assess the impact of cardiovascular parameters on left ventricular (LV) contractility in drug safety testing. Cardiac contractility is affected by preload (Cyon-Frank-Starling law), afterload (Anrep effect) and HR (Bowditch effect). We evaluated multi-parameter correction methods to help with dP/dt_{max} interpretation.

Methodology: Modeling was undertaken using data from dogs in single or double 4 × 4 Latin square studies. Correction models (16 fitting formulas × 2 modeling approaches (universal and individualized) × 2 correction approaches (linear or proportional)) were evaluated. 3D/2D cloud analysis of the beat-to-beat data for the control, pimobendan, and either itraconazole or atenolol groups were used to evaluate correlations between parameters and derive an optimal correction method.

Results: Cardiac contractility (i.e., dP/dt_{max}) was best correlated to HR and systolic LV pressure with a correlation coefficient of 0.8. In decreasing order, dP/dt_{min}, mean arterial blood pressure (BP), systolic BP, diastolic BP, arterial pulse pressure and LV end diastolic pressure (LVEDP) showed a reduced correlation to dP/dt_{max}. Subject-specific models improved the correction by up to 14% when compared to universal correction models. The non-linear correction model was superior to the linear model.

Discussion: Results suggest that the optimal correction formula for dP/dt_{max} would be subject-specific, non-linear and would include HR and LV systolic pressure. Correcting contractility for HR and systolic LV pressure may enhance data interpretation in non-clinical drug safety assessments. Similar correction methods could be evaluated for other species used in safety pharmacology.

1. Introduction

While the QT interval has a long history associated with multiple attempts to correct for changes due to heart rate (HR) (Bazett, 1920; Fridericia, 2003; Spence, Soper, Hoe, & Coleman, 1998; Van de Water, Verheyen, Xhonneux, & Reneman, 1989), limited investigation has been undertaken to assess the impact of changes in cardiovascular parameters on left ventricular (LV) contractility. The inclusion of contractility parameters in the standard cardiovascular evaluation of a new chemical entity (NCE) has become routine (Markert et al., 2012) for studies that traditionally employ the use of telemetry techniques to monitor drug-associated effects on blood pressure (BP), HR and the electrocardiogram (ECG) (Markert et al., 2012). However, no consensus exists regarding the degree of change to the measures of contractility necessary before there is concern regarding the safety profile of the NCE. An HESI-sponsored consortium assessed methodologies most commonly used to evaluate drug effects on contractility using drugs with positive and negative effects on myocardial contractility (Guth

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http://dx.doi.org/10.1016/j.vascn.2017.04.009
Received 28 November 2016; Received in revised form 3 April 2017; Accepted 19 April 2017
Available online 21 April 2017

et al., 2015). Cardiac contractility is influenced by multiple cardiac factors, such as the preload (as defined according to the Cyon-Frank-Starling law), afterload (or Anrep effect) and heart rate (or Bowditch effect) - all of which coordinate and modulate the force of contraction and cardiac stroke volume (Cingolani, Perez, Cingolani, & Ennis, 2013; Ker, 2009; Moss & Fitzsimons, 2002). However, cardiac contractility can also be greatly influenced by pharmacological agents that act either directly or indirectly on heart function as either positive or negative inotropes. For example, the antifungal drug itraconazole (a triazole) has been shown to cause significant reductions in cardiac contractility but no distinct mechanism of action has been defined for this effect (Qu et al., 2013). Similarly, the oncology drug, doxorubicin (an anthracycline), is known to induce severe depression of left ventricular systolic pressure (LV Sys), maximum rate of rise of left ventricular pressure (dP/dt_{max}) (an index of cardiac contractility), cardiac output and stroke work (Bátkai & Pacher, 2009).

Analysis of cardiac contractility parameters commonly rely upon statistical methods that evaluate changes by generating *P*-values. However, use of magnitudes of change in a specific parameter based solely upon *P*-values gives no indication of the clinical importance of an observed effect (Whitley & Ball, 2002) and it has been suggested that the common application of $\alpha = 0.05$ may entail inference limitations (Curtis et al., 2015). Cloud analysis can be a useful technique for cardiac contractility data evaluation and interpretation, especially the application of 2D cloud analysis which can be used to represent beat-by-beat data via marginal distribution curves which describe data density (Accardi et al., 2016) and detect outlier data (Buchanan et al., 2016). An extension of this involves 3D cloud analysis which can enhance the utility of the cloud analysis technique by comparing the relationships between three parameters (e.g., dP/dt_{max}, HR, and the LV Sys) which can be used to generate a qualitative 3D representation that can help visualize drug-induced effects. Chronotropic (direct or indirect) effects are amongst the most common in drug safety testing and non-clinical assay sensitivity is essential. We aimed to evaluate this novel methodology to characterize the pharmacodynamic response of cardiac contractility parameters measured in standard Beagle dogs instrumented with implantable telemetry systems administered drugs known to increase (pimobendan) or decrease (itraconazole and atenolol) the inotropic state of the heart (Guth et al., 2015). In doing so, we provide a potentially more sensitive approach to detect drug induced inotropic effects using a non-linear formula to correct dP/dt_{max} in order to assess drug-mediated effects on cardiac contractile function for use in non-clinical drug safety assessments.

2. Materials and methods

2.1. Test facility and experimental animals

The data used within this investigation were obtained from the HESI- sponsored Consortium, as outlined previously (Guth et al., 2015). The in-life phase of the study, from which the data were collected, was subjected to local guidelines in terms of the vivarium conditions, study conduct and animal use approval procedures. Male Beagle dogs were surgically instrumented with either the DSI Physiotel™ Digital L21 or D70-PCTP telemetry system (DSI, St. Paul, MN, USA) to monitor SABP, LV pressure, the electrocardiogram (EKG), body temperature and activity as previously described (Guth et al., 2015). After an appropriate recovery period following surgery or washout period after receiving a drug, animals were subjected to a standard clinical pathology examination to evaluate their health status according to local procedures.

2.2. Test drugs and study design

Animal placement and dosing regimens were based and analyzed on a double 4 × 4 Latin square design ($n = 8$) for the pimobendan and itraconzole data and a single 4 × 4 Latin square design ($n = 4$) for the atenolol. The dosing regimen was designed to ensure that all dose levels were represented on each dosing day and no animal received a dosage more than once. A double 4 × 4 Latin square, a combination of two identical 4 × 4 Latin squares, results in a study design consisting of 4 rows and 8 columns. An appropriate washout period (minimum of 72 h between treatment days which represented at least 6 half-lives for the drugs that were used) was observed. Food was withdrawn approximately 2 h before dosing in the morning and reintroduced in the afternoon, which was well after the anticipated time of maximal plasma concentration (T_{max}) of the tested drug.

Three drugs were reported within this investigation, each of which possesses a known positive or negative inotropic effect when given to humans in the clinical setting. All drugs were administered orally. Pimobendan and itraconazole were administered to the same animals ($n = 8$) after appropriate washout periods. Atenolol was administered to three independent animals ($n = 3$), which had not previously received pimobendan or itraconazole. Pimobendan is recognized as a calcium (Ca^{2+}) sensitizer and a selective inhibitor of phosphodiesterase-3 with positive inotropic and vasodilator effects, and was formulated using the PCCA Fixed Oil Suspension Vehicle™ to dose levels of 0.1, 0.3 and 1 mg/kg. Itraconazole, a negative inotropic agent, was formulated using 0.5% (*w*/w) methocel E50 in water containing 0.01% (*w*/w) polysorbate 80 and 10 mM phosphate buffer (pH 6.80–7.20) to dose levels of 3, 10, and 30 mg/kg. Atenolol is a selective beta-1 receptor antagonist, and as such, it decreases HR and workload. It was formulated using deionized water to dose levels of 0.3, 1 and 3 mg/kg. Each drug condition was tested with their respective vehicles (Table 1).

2.3. Data collection and analysis

LV pressure, BP and ECG signals were continuously acquired from at least 1 h prior to dosing through 24 h post-dose on each study day. Sampling rates were ≥ 500 Hz for LV pressure and ECG, ≥ 250 Hz for BP signals. A variety of derived parameters were calculated by the Ponemah (DSI, St. Paul, MN, USA) data analysis software which included: HR, diastolic, systolic and mean (aortic) BP, pulse pressure, end-diastolic and peak systolic LVP, dP/dt_{max}, dP/dt_{min}, dP/dt_{40}, Tau and the QA interval (Guth et al., 2015). Although a large number of parameters were available, this manuscript is limited to cardiac function and to hemodynamic parameters that are directly or indirectly relevant to the evaluation of cardiac contractility such as LV Sys, LV dP/dt_{max}, and HR. Data were analyzed and presented using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). 2D/3D cloud analysis was conducted using beat-to-beat contractility data and prepared using the Origin 2016 software (OriginLab, Northampton, MA, USA) for qualitative data interpretation.

Table 1
Drugs tested in conscious telemetered dogs for effects on left ventricular contractility.

Drug	Method of administration	Doses (mg/kg)	Formulation/vehicle
Pimobendan	PO	Vehicle, 0.1, 0.3, 1	PCCA Fixed Oil Suspension Vehicle™
Itraconazole	PO	Vehicle, 3, 10, 30	0.5% (*w*/w) Methocel E50 in water containing 0.01% (*w*/w) Polysorbate 80 and 10 mM phosphate buffer (pH 6.80–7.20)
Atenolol	PO	Vehicle, 0.3, 1, 3	Deionized water