Journal of Pharmacological and Toxicological Methods 69 (2014) 229–236

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

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

Original article

Evaluation of the sensitivity of a new fully implantable telemetry device and the importance of simultaneously measuring cardiac output and left ventricular pressure

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ARTICLE INFO

Article history:
Received 20 November 2013
Accepted 15 January 2014
Available online 24 January 2014

Keywords:
Blood flow
Cardiac output
Hydralazine
ICH S7A
Implants
Methods
Milrinone
Safety pharmacology
Sotalol
Telemetry

ABSTRACT

Introduction: The absence of drug-induced changes in heart rate (HR), aortic pressure (AOP) and ECG, the minimum endpoints suggested in ICH S7A, does not necessarily indicate the absence of cardiovascular (CV) pharmacodynamic activity. This potential pitfall can be avoided by prospectively incorporating "follow-up" endpoints in initial evaluations made possible by the advent of new telemetry implants capable of also measuring changes in cardiac output (CO) and left ventricular pressure (LVP). The purpose of this study was (1) to evaluate the sensitivity of a new, fully implantable telemetry device, and (2) to highlight the importance of the device to simultaneously measure cardiac output and left ventricular pressure in order to adequately evaluate the full potential for a drug to impact global cardiovascular function. ***Methods:*** 4 dogs were instrumented with Konigsberg Instruments, Inc. (KI) TU7/T27H series fully implantable telemetry device and recovered for >8 weeks. Sotalol (8 mg/kg), milrinone (0.2 mg/kg), hydralazine (0.2 mg/kg) and control were administered 1 week apart. Data were collected for 1 h pre- and 24 h post-treatment and time-averaged to fully characterize the a priori pharmacodynamic effects of interest for each drug. This included PR and QTci (sotalol); HR, AOP and LVP (milrinone); HR, AOP, CO and systemic vascular resistance (SVR) (hydralazine). ***Results:*** Expected changes in CV parameters were observed following all drugs with the following detection sensitivities: PR and QTci of 4 ms and 3 ms, respectively (sotalol); AOP and LVP $dP/dt+_{max}$ of 5 mm Hg and 232 mm Hg/s, respectively (milrinone); HR, CO and SVR of 11 bpm, 0.302 l/min and 5 mm Hg∗min/l, respectively (hydralazine). ***Discussion:*** KI TU7/T27H implant detects drug-induced CV changes with statistical significance using a standard, four-subject design. The ability of the TU7/T27H to also measure CO and LVP allowed for full characterization of the CV impact of hydralazine and milrinone, which could have been misinterpreted/missed altogether if these drugs were novel and the endpoints evaluated were prospectively limited to the minimum suggested in ICH S7A.

1. Introduction

As a safety pharmacologist, the onus is on us to adequately evaluate the potential for a new test substance to impact cardiovascular function prior to its administration to healthy volunteers. The key word in the preceding sentence is "adequately". The International Conference on Harmonization Harmonized Tripartite Guideline titled "Safety Pharmacology Studies for Human Pharmaceuticals S7A" (ICH S7A) states that the preclinical evaluation should, at a minimum, assess the potential for a new test substance to affect the ECG, heart rate and blood pressure. If these "core" cardiovascular endpoints indicate no cause for concern, assuming studies were appropriately designed and utilized the most sensitive technologies, is such an evaluation considered "adequate"? Perhaps, but given the pragmatic limitations on the sample sizes used in nonclinical studies and the limited information generated from the "core" cardiovascular endpoints, perhaps not.

The in vitro hERG and in vivo QT assays appear to be relatively adequate at predicting QT interval prolongation in man as evident by an approximately 86% success rate (Pollard, Valentin, & Hammond, 2008). However, this indicates that the hERG and QT assays still allow for the progression of false negatives into clinical development. This may be explained by the greater sensitivity of the thorough QT/QTc study which is capable of detecting a prolongation of the QT interval of 2.5% as compared with only 9–11% in dogs instrumented with non-invasive or implanted telemetry ($N = 4$; $\alpha = 0.05$; power = 0.8) (Guth et al., 2009). Compared with QT prolongation, the adequacy of our preclinical models to assess

Abbreviations: KI, Konigsberg Instruments; CO, cardiac output; LVP, left ventricular pressure; HR, heart rate; AOP, aortic pressure; SVR, systemic vascular resistance.

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http://dx.doi.org/10.1016/j.vascn.2014.01.003

potential cardiovascular liabilities based on changes in blood pressure is less clear. The sensitivity of our preclinical models to detect changes in blood pressure should strive to achieve detection of clinical changes in blood pressure that have resulted in regulatory action. The clinical development of torcetrapib was stopped because it raised systolic blood pressure by 3–5 mm Hg (Polakowski et al., 2009), and sibutramine was withdrawn from the European market and required a labeling change by the US FDA due to an increase in blood pressure of only 2–3 mm Hg (Scheen, 2010). The ability of our current preclinical models to detect changes in blood pressure of only 2–5 mm Hg is questionable. For example, to detect a 5 mm Hg change in blood pressure using a standard study design would require the within group standard deviation to be as low as 3 mm Hg ($N = 4$; 2-sided; $\alpha = 0.05$; power = 0.8). Similarly, the adequacy of our preclinical models to reliably detect clinically meaningful changes in heart rate is also questionable. An increase in heart rate of 10 bpm in hypertensive patients is associated with a 16% increased adjusted risk of cardiovascular mortality and a 25% greater risk of all-cause mortality (Okin et al., 2010). Similar findings have been reported in patients with chronic heart failure (Castagno et al., 2012). Contrast this to dogs equipped with non-invasive or implantable telemetry capable of detecting changes in heart rate of 30 bpm ($N = 4$; $\alpha = 0.05$; power = 0.8) (Guth et al., 2009). Others have reported that using a typical cross-over study using four dogs equipped with implantable telemetry can detect a change in heart rate as low as 10% (~6 bpm) with 90% statistical power (Klumpp, Trautmann, Markert, & Guth, 2006). The relatively large discrepancy in heart rate detection between these two examples is not known but is likely due to differences in experimental methodologies (Klumpp et al., 2006).

The minimum endpoints suggested by ICH S7A may not be adequate to fully appreciate the potential for a new test substance to affect cardiovascular function. For example, if hydralazine was a novel compound, increased heart rate with no detectable change in blood pressure may be interpreted to have a direct effect on pacemaker activity. However, given the known pharmacology of hydralazine, the correct interpretation is that the increase in heart rate is a baroreceptor-mediated response to hydralazine's ability to decrease vascular resistance. The inability to detect a corresponding decrease in blood pressure secondary to the decrease in vascular resistance is offset by an increase in cardiac output (Maekawa, Liang, Tsui, Chen, & Kawashima, 1984). Another example is milrinone, which at a dose of 0.2 mg/kg has been reported to cause no detectable changes in either heart rate or blood pressure in dogs (Mitchell et al., 2013). If milrinone were a novel compound one could conclude incorrectly that the compound is without pharmacodynamic effect based only on the minimum endpoints suggested by ICH S7A. If additional endpoints were interrogated it would become evident that this apparent "no effect" dose of milrinone actually causes a significant positive inotropic effect (Mitchell et al., 2013). In reality, these "undetected" changes in heart rate and blood pressure would likely be fleshed out during a dose–response evaluation of a novel compound, but let us assume that these "undetected" changes were only present at the high dose. This highlights the importance of having cardiac output and ventricular pressure when interpreting changes, or lack thereof, in blood pressure and heart rate. Furthermore, the hydralazine scenario would require the need for a follow-up study to determine the underlying cause of the increase in heart rate. Such a study would require the need for additional animals instrumented with more sophisticated implants, more drug, more time and more man-hours. This situation can be eliminated if follow-up endpoints (cardiac output, ventricular contractility, vascular resistance) are prospectively measured as part of the initial evaluation.

The purpose of this study was (1) to evaluate the sensitivity of a new, fully implantable telemetry device, and (2) to highlight the importance of the device to simultaneously measure cardiac output and left ventricular pressure in order to adequately evaluate the full potential for a drug to impact global cardiovascular function.

2. Methods

2.1. Regulatory compliance

All procedures in this study were approved by the Animal Care and Use Committee, were in compliance with the USDA Regulations, 9 CFR Parts 1, 2, and 3 (Code of Federal Regulations, 2010) and the Guide for the Care and Use of Laboratory Animals (National Research Council of the National Academies, 2011), and were conducted at a fully AAALAC accredited facility.

2.2. Animals

Four male purebred beagle dogs were obtained from Covance Research Products Inc. (Cumberland, Virginia). At initiation of dosing, dogs were 18 to 20 months old, and their body weights ranged from 12 to 14 kg. Dogs were single-housed in stainless steel runs and provided Canine Diet (Lab Diet Advance Protocol 5 L18) once daily. Dog runs were positioned adjacent to one another enabling visual contact. Water was provided ad libitum. Water is periodically analyzed for microbial and chemical contaminants, and there are no known contaminants in the water that would have interfered with this study. Environmental controls for the animal room were set to maintain 19 to 23 °C, a relative humidity of 30 to 70%, a minimum of 10 room air changes/h, and a 12-hour light/12-hour dark cycle. All dogs were given additional certified dietary supplements as a form of environmental enrichment and various cage-enrichment devices.

2.3. Reference drugs and formulation

Sotalol (D,L-sotalol; AvaChem Scientific) was formulated in 1% hydroxypropyl methylcellulose in distilled water. Sotalol is a nonselective, competitive β-adrenergic receptor antagonist that also exhibits Class III antiarrhythmic properties prolonging PR and QT intervals. Milrinone (AvaChem Scientific) was formulated in 0.5% methylcellulose and 0.1% polysorbate 80 in distilled water. Milrinone is a phosphodiesterase-3 inhibitor and enhances ventricular contractile force by increasing Ca^{2+}-ATPase activity. In addition to milrinone's positive inotropic actions, it also exhibits vasodilation and minimal chronotropic effect. Hydralazine HCL (Akorn, Inc.) was formulated in 0.9% Sodium Chloride Injection USP (Baxter, Deerfield, IL) to a final concentration of 1 mg/ml. Hydralazine is a direct-acting smooth muscle relaxant by increasing cyclic guanosine monophosphate levels and protein kinase G activity, thereby inhibiting myosin light-chain kinase. Hydralazine primarily affects arteries and arterioles decreasing systemic vascular resistance, thereby lowering blood pressure.

2.4. Dose justification and administration

All animals were acclimated to the dosing procedure prior to starting the study. Sotalol (8 mg/kg) was administered via oral gavage to manually restrained dogs at a dose volume of 5 ml/kg. The dose of sotalol was selected because it is the lowest dose reported to produce a statistically significant prolongation in the QT interval in telemeterized dogs (Batey & Doe, 2002; Mitchell et al., 2013). Milrinone (0.2 mg/kg) was administered via oral gavage to manually restrained dogs at a dose volume of 1 ml/kg. The dose of milrinone was selected because it has been shown not to affect heart rate or blood pressure in telemeterized dogs (Mitchell et al., 2013). If milrinone was a novel compound and only the minimum endpoints were evaluated per S7A, one would conclude incorrectly that milrinone is without cardiovascular effect. However, this dose of milrinone has been associated with a significant increase in left ventricular dP/dt_{max} through 3 h post-dosing (Mitchell et al., 2013). Hydralazine (0.2 mg/kg) was administered as an intravenous bolus to manually restrained dogs at a dose volume of 0.2 ml/kg. The dose of hydralazine was selected because it has been reported to