Contractility Assessment in Rats and Guinea Pigs: Comparison From Isolated Heart to Whole Animal

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1 INTRODUCTION

When thinking of cardiotoxicity in drug development, most think of the effect the compound has on the hERG cardiac ion channel or the QT interval of the ECG and not myocardial dysfunction. The ICH S7 A and B guidance focuses on new chemical entities for IKr block and delays in ventricular repolarization. In fact, since ICH S7B, no drugs have been removed from the market for the polymorphic ventricular arrhythmia Torsades de Pointes. However, the limited assessment of hemodynamics, beyond heart rate and blood pressure, may present a gap in preclinical drug development for the continued high rate of drug attrition due to cardiotoxicity.

Early in the drug development lifecycle, the process of evaluating compounds for left ventricular dysfunction does not follow a regulated guidance, but more of an investigational method. The ability to assess new chemical entities, for changes in myocardial contractility requires models that are translatable to the clinical outcome. An added consideration should be on the amount of test material available at this early stage to conduct investigative in-vivo experiments. The rat is a go to species for toxicology studies, however, lacks the cardiac ion channel responsible for delays in human ventricular repolarization. The guinea pig is studied much less in toxicology programs, maybe due to a lower mean arterial blood pressure and prothrombin time. The guinea pig heart possess the IKr cardiac ion channel and although mean arterial blood pressure is lower, contractility indicators are more similar to human values.

The objective of the study was to evaluate the effects of a positive and negative inotropic agent in both conscious rats and guinea pigs instrumented with a telemetry device to measure ECG, arterial blood pressure and left ventricular pressure. Additionally, to assess these same test compounds in the isolated, perfused, guinea pig heart for comparison with the in-vivo experiments.

2 METHODS

In-vivo – Rats (n=6/group, male; Crl:CD(SD), 400 – 550 g) and guinea pigs (n=5/group, males; Hartley, 600 -800 g) were surgically implanted with a Data Sciences International (DSI) HD-S21 radiotelemetry transmitters. The implanted devices collected left ventricular pressure waveforms, arterial blood pressure waveforms, ECGs, and body temperature. Rats were also instrumented with vascular access ports to allow for intravenous bolus administration via a tether system, to avoid induced stress from any potential handling procedures for dosing. Dosing was as follows: rat (0.1 µg/kg) IV bolus and guinea pig (10 µg/kg) SC isoproterenol and rat (6 mg/kg) and guinea pig (50 mg/kg) oral gavage atenolol.

The telemetry system (DSI, St. Paul, MN) consisted of the hardware connected to the Dataquest™ OpenART™ Acquisition Interface which provided direct digital signals to the DSI PONEMAH software. The left ventricular and arterial waveforms and body temperature data were recorded and analyzed by the DSI PONEMAH data acquisition software, version 5.0 or higher. Left ventricular and arterial waveforms were sampled at 500 Hz. Data acquired continuously was logged every 10 seconds.

Ex-vivo – Guinea pigs (n=5/group) were anesthetized to a surgical plane with isoflurane, hearts removed and perfused with modified Kreb's solution (MKH). Guinea pig hearts were perfused with MKH w/0.1% DMSO for a minimum of 20 minutes followed by a 20 minute baseline collection. Hearts were then perfused with escalating concentrations (at 20 minutes per concentration) of either isoproterenol (0.1, 0.3, and 1.0 µM) or atenolol (1.88, 18.8 and 188 µM). Control hearts were perfused with MKH w/0.1% DMSO. All pressure and electrocardiogram data were collected continuously using IOX Data Acquisition System and post processing analysis was conducted using ECGAuto (Emka Technologies; Paris, France).

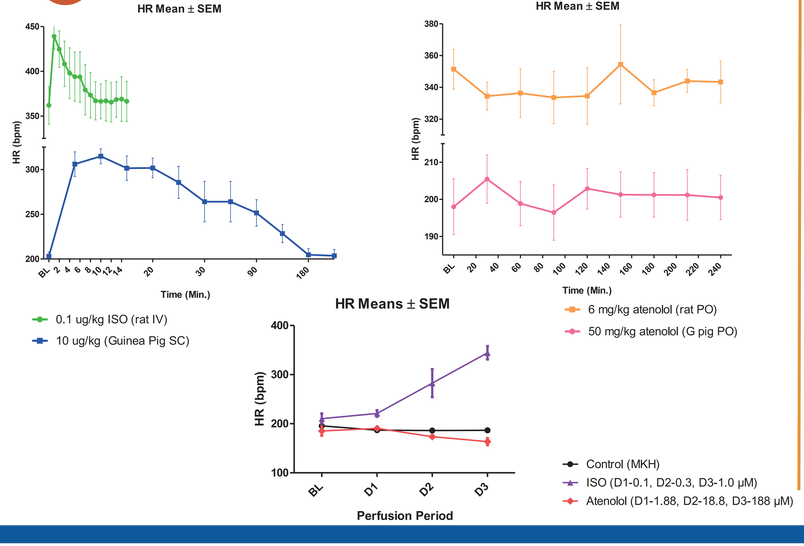
4 DISCUSSION

The subcutaneous dose of isoproterenol was 10x for the guinea pigs, so the expectation was that the effects would be slightly delayed with regard to onset and prolonged compared to the intravenous dose administered to rats. The magnitude of increase for heart rate and dP/dt_{max} were similar between the two species. Heart rate (max) increased ~ 100 bpm for both rats and guinea pigs and dP/dt_{max} and dP/dt_{min} had a more robust response in guinea pigs. Whereas the rats had a larger absolute increase in dP/dt_{max}. The isolated perfused guinea pig hearts increased heart rate similarly to the in-vivo guinea pig model, as well as, with a similar doubling of dP/dt_{max}.

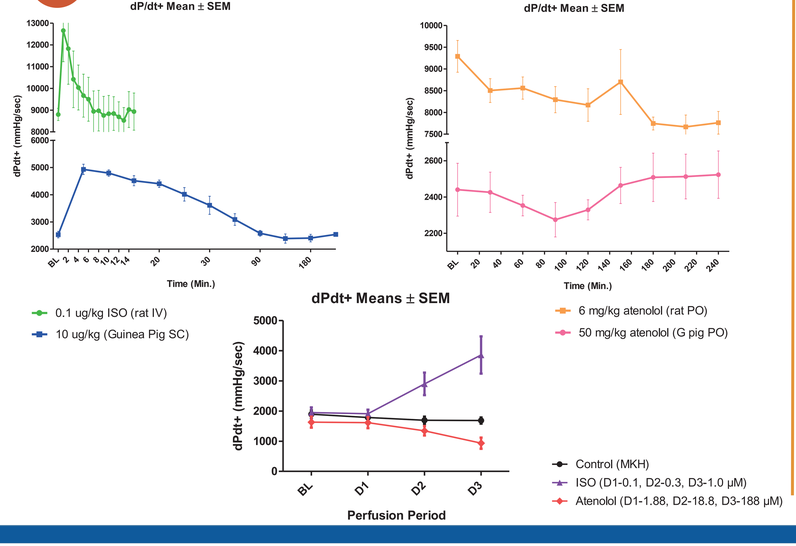
An oral dose of atenolol to rats (6 mg/kg) and guinea pigs (50 mg/kg) had minimal effects on heart rate for either species. Decreased dP/dt_{max} over 240 minutes for rats and decreased, minimally and transiently, for guinea pigs. The time course of change was different between rats and guinea pigs. The isolated perfused guinea pig hearts had no change or a minimal decrease in heart rate and a decrease in dP/dt_{max} and dP/dt_{min} similar to the in-vivo experiment.

The guinea pig in-vivo model, utilizing the dual pressure telemetry unit (HD-S21), demonstrated a range of responses that were similar to or robust for both isoproterenol and atenolol as compared to rats. The small animal telemetry model is a nice alternative to anesthetized preparations in both small and large animals at the earlier stages of drug development. Additionally, the model has demonstrated stability of the functional endpoints over months, leading to the reuse of these animals (3Rs). The isolated perfused guinea pig hearts displayed similar functional changes as those from the in-vivo experiments.

3 RESULTS- Heart Rate



3 RESULTS- dP/dt_{max}



3 RESULTS- dP/dt_{min}