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CiToxLAB
Safety and Health Research Laboratories
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TOXICOLOGY SERVICES
• General toxicology:
  - Rodents
  - Non-rodents: dogs, NHPs and minipigs
• Infusion
• Inhalation
• Dermal
• Ocular
• Immunotoxicology
• Reproductive toxicology including minipigs and NHPs
• Carcinogenicity studies also in rasH2 and p53+/− mice
• Genetic toxicology: ICH compliant package
• In vitro toxicology: BCOP, MUSST, DPRA, Photo 3T3, EpiSkin™
• Agrochemical / Chemical / REACH
• QSAR
• Physical chemistry
• Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
• Early safety pharmacology
• Jacketed External Telemetry (JET) / ECG / BP
• CV implanted telemetry / ECG / BP / LVP
• Respiratory / JET telemetry / Plethysmography
• CNS / ECG / EMG

DMPK AND BIOMARKERS
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• Bioanalytical LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
• Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
• Immunology: 10-color flow cytometry, LumineX, Mesoscale

SPECIALIZED EXPERTISES
• Juvenile studies including minipigs
• Fertility studies in rodents and NHPs
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• Tissue Cross Reactivity: human and animal tissue banks
• Gene therapy vector biodistribution via qPCR
• ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
• Lead optimization and predictive toxicology services: LeadScreen™

CiToxLAB in France
Safety and Health Research Laboratories

Left Ventricular Pressure (LVP) and Contractility in Free-Moving Rats: The Application of Marginal Distribution Analysis
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**ABSTRACT**

Introduction: Chronotropic effects are the most frequent cardiovascular change in drug development. Interpretation of left ventricular contractility requires correction for heart rate and circadian cycle effects. Methodology: Left ventricular pressure (LVP) was measured in conscious rats by telemetry with a transmural catheter. Pharmacological agents known for their positive inotropic (Pimobendan, Morphine and Amrinone) or negative inotropic (Atenolol and Itraconazole) properties were administered to rats and cardiovascular function was monitored for at least 24 hours after each dosing. The results were analyzed by the application of a marginal distribution curve on the contractility index and heart rate. Results: In the rat model, Pimobendan (3 to 30 mg/kg, po), Morphine (2 to 20 mg/kg, sc) and Amrinone (10 to 100 mg/kg, capsule) induced dose dependent increases in the contractility index compared to control. Atenolol (1 to 100 mg/kg, po) had negative chronotropic effects. The negative inotropic effects of Itraconazole (10 to 100 mg/kg, po) on LVP were not observed in the rat telemetry model. The application of marginal distribution analysis to telemetry data at Tmax increased sensitivity compared to analysis for the entire 24 hour period. Discussion: We explored a new analysis strategy to dissociate true positive or negative inotropic pharmacological changes from physiological effect of heart rate on ventricular contractility. The application of the marginal distribution curve was considered a valuable tool in the overall interpretation of drug-induced changes in cardiac contractility.

**MATERIALS AND METHODS**

**Test System:**

Anesthesia induction was attained with injectables (ketamine, 100 mg/mL/xylazine, 20 mg/mL). Animals were intubated and placed in assisted ventilation to enable open chest surgery. Preparation of the Test System for contractility index recording: A mid-line laparotomy was performed and the liver carefully deflected to expose the diaphragm. An incision was made in the diaphragm over the apex of the heart. The apex of the heart was localized and a purse string suture was placed on the left part of the apex.

A needle (20 or 22 g) was inserted in the left ventricle through the center of the purse string suture. An LVP catheter (DSI HD-S21 telemetry device) was inserted in the left ventricle through the hole, then secured by tightening the purse string suture.

**Control and Reference Items:**

- **Pimobendan:** (3 to 30 mg/kg, po)
- **Morphine:** (2 to 20 mg/kg, sc)
- **Amrinone:** (10 to 100 mg/kg, PO)
- **Atenolol:** (1 to 100 mg/kg, po)
- **Itraconazole:** (10 to 100 mg/kg, po)

**Contractility Index data analysis:**

Data from all animals were continuously recorded via a computerized system (Dataquest ART, DSI). Data are presented as group means for a period of 0 to 24 hours post dosing or for a period of 2 to 4 hours post dosing. The Origin 2015® software was used to created marginal distribution graphs.

**RESULTS**

**DISCUSSION**

The effects of cardioactive agents on the contractility index were measured in conscious rats by telemetry. The analysis strategy presented herein was used to assess the effect relationship between the two cardiac variables but also their distribution. The analysis of the heart rate and contractility index at selected times (i.e. Tmax) increased the sensitivity of the assay. The marginal distribution curve analysis was considered a valuable method for the interpretation of cardiac telemetry data following pharmacological treatments.

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