2829 A Kinase Inhibitor (C377) Associated with Significantly Delayed QT Prolongation and Mortality in Dogs: *In Vivo* Characterization

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Kinase inhibitor (KI) C377 was precluded from consideration as a development candidate due to unexpected cardiovascular adverse events. In a 7-day dog toxicity study mortality occurred at ≥ 30 mg/kg on Days 4/5 in the absence of prodromal clinical signs or histopathology. During ECG collection on Day 5, a single animal given 100 mg/kg developed polymorphic ventricular tachycardia (probable Torsade de Pointe) and ventricular fibrillation, and expired. *In vitro* ion channel, receptor and kinase screens did not predict a cardiovascular signal for C377. IC50s for hERG and 11 other CV-related ion channels evaluated were >18µM. There was no effect on hERG trafficking. Subsequent single and 5-day repeat dose telemetry studies confirmed QT prolongation at doses ≥10 mg/kg. Single doses of 30 and 100 mg/kg produced persistent prolongation (up to 31 and 111 msec, respectively) of heart rate-corrected QT, beginning at 21 hr and peaking at 67 hr postdose, and persisting for the duration of data collection (4 days). At 100 mg/kg transient increases in heart rate, diastolic and mean arterial pressure occurred at 9-43 hr postdose; increased body temp (up to 2.2°C) occurred at 11-73 hr postdose. Daily administration of 10 mg/kg for 5 days produced mild but persistent prolongation of QT (9-19 msec) beginning Day 3 and continuing through Day 5. C377-related alterations in clinical pathology endpoints were confined to animals given 100 mg/kg. The onset of QT prolongation was not associated with Cmax. There was no evidence of a metabolite-mediated effect. These data indicate that the mortality noted in dogs resulted from a unique delayed and persistent QT prolongation; which occurred at projected AUC exposure margins of ≥ 2-fold. The mechanism of the observed QT prolongation is under further evaluation in several *in vitro* cardiovascular assays in order to identify an appropriate means to screen KIs against this type of cardiovascular toxicity.

2830 The Influence of Inhaled Multi-Walled Carbon Nanotubes on Autonomic Nervous System

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Heart rate and cardiovascular function are regulated by the autonomic nervous system. Heart rate variability (HRV) as a marker reflects the activity of autonomic nervous system. The prognostic significance of HRV in cardiovascular disease has been reported in clinical and epidemiological studies. The present study focused on the influence of inhaled multi-walled carbon nanotubes (MWCNTs) on autonomic nervous system by HRV analysis. Methods:Male Sprague-Dawley rats were pre-implanted with telemetry device and kept in the individual cages for recovery. At week four after device implantation, rats were exposed to MWCNTs for 5h at a concentration of 5 mg/m3. The real-time EKGs were recorded by a telemetry system at pre-exposure, during exposure, 1 day and 7 days post-exposure. HRV was measured by root mean square of successive differences (RMSSD); the standard deviation of RR interval (SDNN); the proportion of NN5 or NN10 divided by total number of NNs (pNN5 or pNN10); low frequency (LF) and high frequency (HF). Results: Exposure to MWCNTs significantly increased the percentage of differences between adjacent R-R intervals over 5 ms (pNN5) and 10 ms (pNN10) ($p<0.01$), the root mean square of the successive differences (RMSSD) ($p<0.01$), the power of low frequency (LF) ($P<0.05$) and high frequency (HF) ($p<0.01$). Conclusions: Inhalation of MWCNTs significantly altered the performance of autonomic nervous system dominated by an increased activity of the parasympathetic nervous system during the exposure. Such a transient alteration in autonomic nervous performance may raise the risk of cardiovascular events in people with pre-existing cardiovascular conditions.

2831 Subclinical Cardiovascular Effects of Short-Term Ergot Exposure in Beef Cows

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Ergot alkaloids are vasoactive compounds encountered in livestock feed. Prolonged exposure to ergot can produce clinical disease in cattle marked by reduced blood flow to peripheral vasculature leading to gangrene of hooves, tail tips, and ears. However, subclinical cardiovascular effects of ergot in cattle are poorly understood. This study was conducted to characterize hemodynamic changes in three arteries in response to increasing ergot concentrations in cattle feed that were at or below permissible levels of 2000ppb. Beef cows (n=16) were randomized into four groups: control (0ppb), low (125ppb), medium (500ppb), and high (2000ppb). Diets were fed daily for one week. Control diets were fed four days before and after the experimental period. The caudal, internal iliac, and median sacral arteries were imaged daily using color flow Doppler ultrasonography to assess the following hemodynamic parameters: arterial diameter, pulsatility index, resistivity index, blood velocity, blood flow per minute, and volume per heartbeat. Data were analyzed by repeated measures statistics (SAS; $P<0.05$). The caudal artery was most responsive to ergot. Internal iliac artery hemodynamics were unaffected at these levels of ergot feeding. Intermediate effects were observed in the median sacral artery. Caudal artery diameter was reduced at 2000 ppb ($P=0.02$), corresponding to a 19% decrease. Caudal artery hemodynamics also affected by ergot included flow per minute ($P=0.006$), volume per beat ($P=0.004$), pulsatility index ($P=0.01$), and resistivity index ($P=0.01$). Ambient temperature influenced arterial diameter (CA $P<0.0001$; MSA $P<0.0001$), mean blood velocity (CA $P=0.0001$), flow per minute (CA $P<0.0001$; MSA $P=0.001$), and volume per beat (CA $P<0.0001$; MSA $P=0.0006$). Recovery to pre-ergot caudal artery diameter occurred within one week of ergot removal (104% of pre-ergot diameter). Ergot action appears to depend on the anatomical location of the artery (i.e., peripheral or visceral). In conclusion, changes in caudal artery vascular parameters represent a reliable biomarker of ergot exposure. Short-term dietary ergot exposure in cattle feed alters peripheral artery hemodynamics however, results are strongly influenced by ambient temperature.

2832 Integrated Evaluation of Cardiac Inotropes Using Echocardiography, Telemetry, and Arrhythmia Detection Methods in the Beagle Dog

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Drug-induced effects on cardiovascular (CV) function, including changes in hemodynamics, cardiac contractility, and electrophysiology (proarrhythmic potential), are common causes of attrition in drug development. We conducted an integrated CV assessment of positive (milrinone and amrinone) and negative (itraconazole) inotropic agents at doses reported to match clinical exposures. Six female beagle dogs were dosed with the reference agents and corresponding controls on separate days, one day for continuous 24-hr telemetry monitoring (jacketed external telemetry with blood pressure [BP] implants [Data Sciences International- DSI]) and one day for echocardiography (echo) data collection (2 hr postdose). Echo indices of left ventricular (LV) size and function demonstrated expected changes (percent control) including LV internal systolic diameter (17% and 50% decreases and 17% increase) as well as ejection fraction (18% and 43% increases and 20% decrease) for amrinone, milrinone, and intraconazole, respectively. Expected ECG effects (% control) following the milrinone dose included increased heart rate (38%), decreased PR interval (26%), decreased QT and heart rate (HR)-corrected QT (QTca) intervals of approximately 13%, as well as decreased mean BP and pulse pressure of 27%. Similarly, there were decreased QT/QTca intervals (5% compared to control) following the amrinone dose with no HR or BP effects. Arrhythmia detection using Data Insights Software (DSI) showed no consistent compound-related changes in ECG waveform morphology or rhythm. QA interval (QAI) was shorter with milrinone and longer with itraconazole, consistent with positive and negative inotropy, respectively, supporting use of QAI as an indirect measure of cardiac contractility. Collectively, these novel integrated inotropic data demonstrate that a nonclinical model integrating both telemetry and echocardiography on separate dosing days in a repeat dose study design can provide robust assessments of CV function.

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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