PK and Cardiac Assessment in Rats Administered Doxorubicin

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ABSTRACT

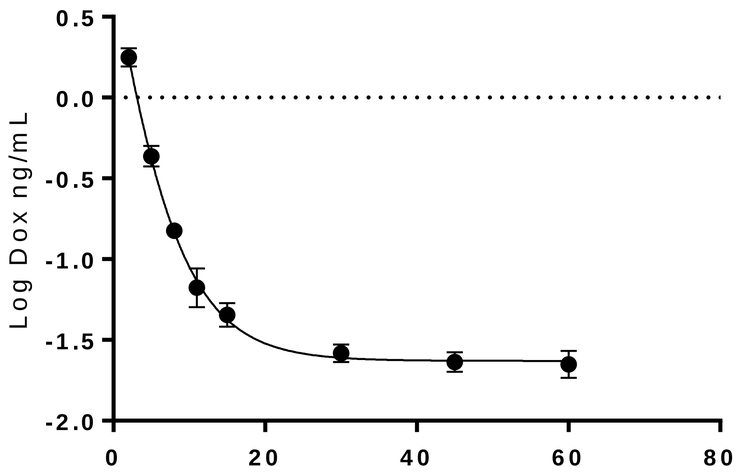
Doxorubicin (dox) is a widely used oncology drug with known cardiotoxicity. The purpose of this study was to determine systemic exposure of a clinically relevant dose of dox in Sprague Dawely rats and assess cardiac toxicity by ex-vivo assessment. Rats were given one IV dose (2 mg/kg) of dox (n=6) or saline (n=6). Blood samples were taken using an automated Culex instrument (n=5) at 8 time points over 60 minutes for PK analysis. The C_{max} was 1560±230 ng/mL, $t_{1/2}$ was 35.6±4.2minutes, V_d was 9370±1310mL/kg, and AUC∞ was 10,900±1500min*ng/mL. 21 days following dose administration rats were anesthetized, hearts removed and arrested in cold cardioplegic solution and perfused via the aorta with Modified Henseliet Krebs solution at constant pressure of 60 mmHg. A balloon was inserted into the left ventricle to assess ±dP/dt, developed pressure (DP), and EDP. Heart rate, perfusion flow rate, and ECG signals were also analyzed. Contractility, lusitropy, and EDP were similar in the dox and vehicle groups. DP (78.5±6.2 vs 87.0±12.9 mmHg) was slightly reduced and heart rate (273±11.6 vs 293.4±16.0beats/min) and perfusion flow rate (14.1±0.6 vs 15.9±1.0mL/min) were significantly ($p<0.05$) reduced in the dox versus vehicle group. There were no differences in ECG intervals between groups. We found that mild effects on heart function from one doxorubicin exposure can be seen 21 days later.

METHODS

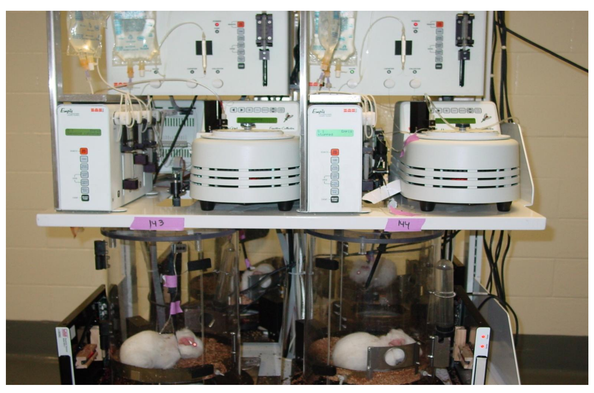
- **Dose Administration**
  - Rats were given one IV dose of dox (2mg/kg) n=6 or saline n=6
- ***Pharmacokinetics Assessment of Doxorubicin***
  - Blood was collected using an automated Culex instrument via an implanted venous access port at 2, 5, 8, 11, 15, 30, 45, and 60 minutes post dose. Plasma was isolated from each blood specimen.
  - Plasma doxorubicin concentrations were analyzed using the non-compartmental analysis component of WinNonlin (Version 6.3) to determine pharmacokinetic parameters including Cmax, t1/2, Vd, and AUC∞
  - ***Ex-vivo (Langendorff isolated heart)***
  - 21 days after dose administration rats were anesthetized with Na-Pentobarbital (80 mg/kg). Hearts were removed and placed in cardioplegic solution prior to perfusion with Modified Krebs-Henseliet Solution (118 NaCl, 1.18 KH_2PO_4, 25 $NaHCO_3$, 5 KCl, 1.17 $MgSO_4$, 11 glucose, 2 NaPyruvate, 1.8 $CaCl_2$ mM) in a Langendorff system (Emka, France), in constant pressure (60 mmHg) mode
  - A Water-filled balloon was inserted into the left ventricle to measure left ventricular pressure (LVP) parameters (dP/dt_{max} and dP/dt_{min}, developed pressure, end diastolic pressure), coronary flow rates, heart rate, and ECG waveforms were simultaneously measured

RESULTS

Blood Sampling Using an Automated Culex Instrument and Pharmacokinetics Assessment of Doxorubicin in Rats Administered a Single IV dose

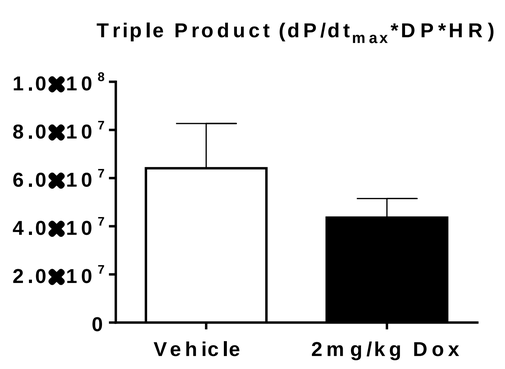


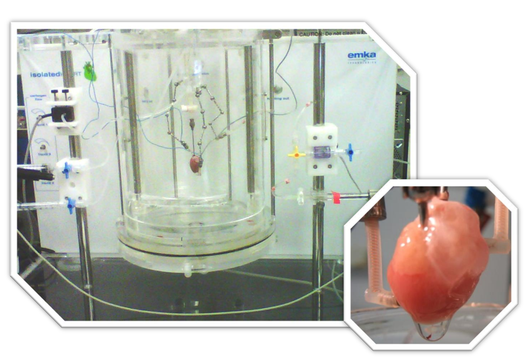
C_{max}	1560±230 ng/mL
$T_{1/2}$	35.6±4.2 Min
V_d	9370±1310 mL/kg
AUC∞	10900±1500 min*ng/mL

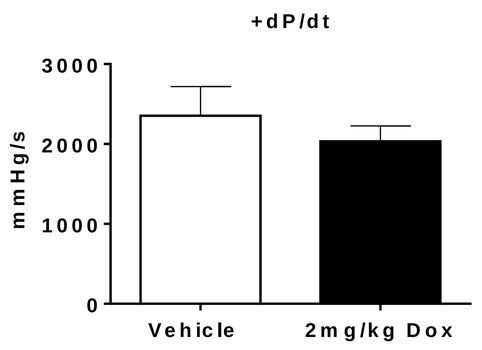


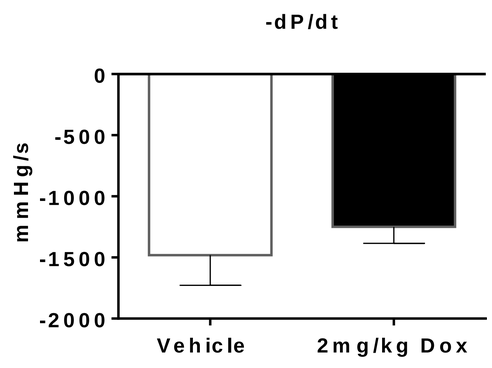
RESULTS CONTINUED

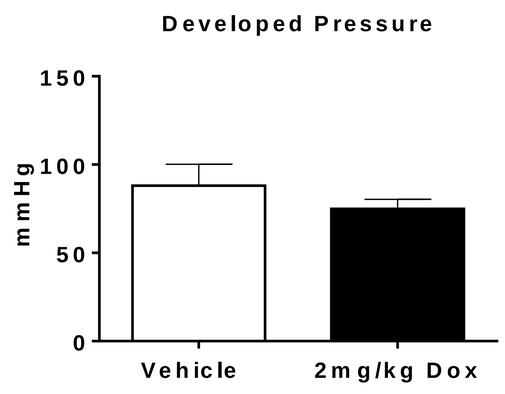
Single Dose Doxorubicin vs Saline Effects on Cardiac Function Following 21 Days After Dose

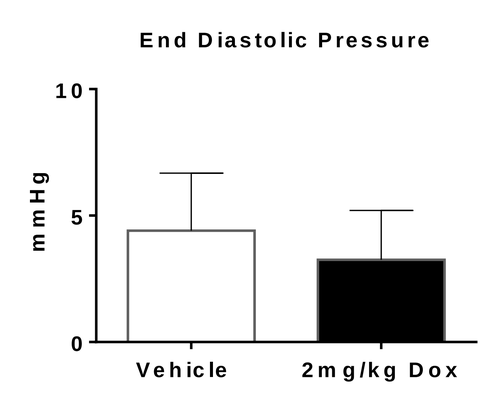


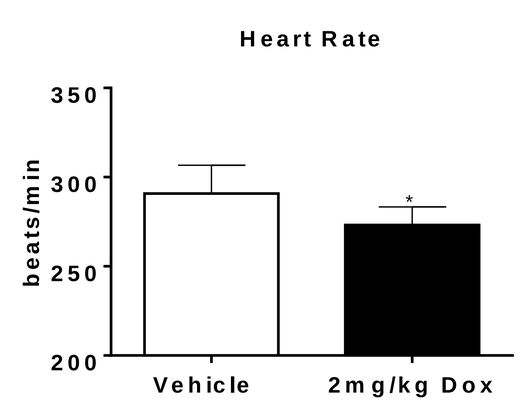


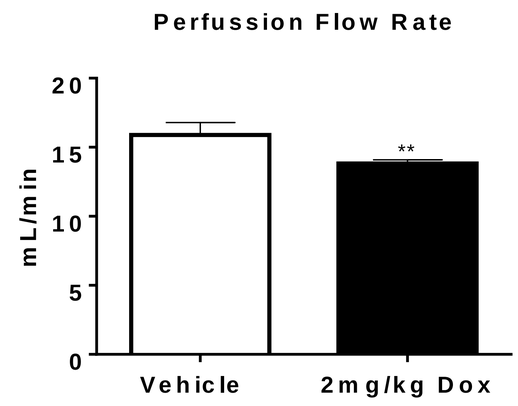












ECG Intervals (ms)

	PR	QRS	QTcF
Saline	34.2±3.4	26.4±1.6	132.2±3.9
Dox	33.8±2.0	29.2±2.1	139.8±8.1

Discussion

- **Pharmacokinetic Assessment**
  - The doxorubicin plasma concentration-time profile for rats had a biphasic decline. Elimination was rapid with a half-life of approximately 30 to 40 minutes
- **Cardiac Function Following 21 Days Post Dose**
  - DP (78.5±6.2 vs 87.0±12.9 mmHg) was slightly reduced
  - Heart rate (273±11.6 vs 293.4±16.0beats/min) and perfusion flow rate (14.1±0.6 vs 15.9±1.0mL/min) were significantly ($p<0.05$) reduced in the dox versus vehicle group.
  - There were no differences in ECG intervals between groups.
  - There were indications of SA node function impairment and increases in vascular resistance as well as mild negative inotropy that were present 21 days following a single dose of doxorubicin at 2 mg/kg.