

Doxorubicin cardiotoxicity in the rat detected with cardiac function MRI and late gadolinium enhancement

Neil Woodhouse¹, Howard Mellor², Jose Ulloa¹, Guy Healing², Jason Kirk², and Paul Hockings³

¹PHB Imaging, AstraZeneca, Alderley Edge, Cheshire, United Kingdom, ²GSA, AstraZeneca, Alderley Edge, Cheshire, United Kingdom, ³PHB Imaging, AstraZeneca, Molndal, Gothenburg, Sweden

Introduction

Chemotherapy induced cardiotoxicity is a significant issue in the treatment of cancers. Here we examine the effect of the best known cardiotoxicity inducing chemotherapy, doxorubicin, on myocardial function and late gadolinium enhancement in the rat. The development of doxorubicin cardiotoxicity is associated with an impairment of mitochondrial metabolism and has recently been shown to impair mitochondrial respiration in permeabilised myocardial fibres (1).

Methods

Animal experiments were conducted under licences issued under the UK Animals (Scientific Procedures) Act 1986, following local ethical committee review. Two groups of male Han-Wistar rats (n = 6/group), Vehicle (0.9 % saline) and Dox (doxorubicin 1.25 mg/kg), were dosed intravenously into the tail vein once per week for 8 weeks followed by a 4 week recovery period, after which imaging was performed. Rats were imaged on a Bruker BioSpec 4.7T system under isoflurane anaesthesia using a retrospectively gated IntraGate FLASH multi-slice cine sequence. Scans were acquired in the short axis orientation covering the whole left ventricle to measure left ventricular mass (LVM), end diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and fractional shortening (FS): TR/TE 120/1.4 (ms), Flip Angle 30°, Matrix 192/256, FOV 45mm, Slices 14-16, Slice Thickness 1mm, Repetitions 150. Three rats per group received 0.3mM/kg gadopentetate i.v. after a five minute baseline IntraGate FLASH DCE acquisition followed by a further 25 minutes image acquisition to determine late gadolinium enhancement (LGE). Images were processed using Segment (Medviso, Sweden) to calculate indices of cardiac function.

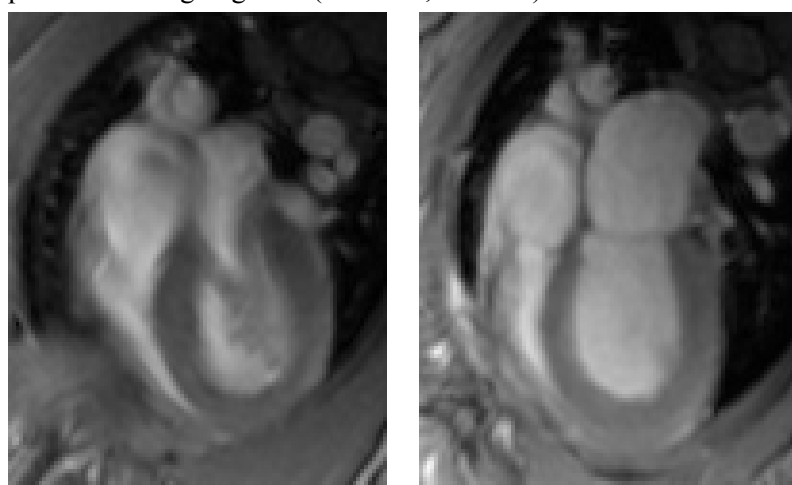


Figure 1: Vehicle

Dox

Results:

Figure 1 shows typical long axis images from Vehicle and Dox treated animals indicating dilated left atrium. Indices of cardiac function derived from the IntraGate cine images showed significant differences between the Vehicle and Dox groups (Table 1). Gadopentetate infusion also demonstrated statistically significant (p=0.001) differences in LGE.

Discussion/Conclusions:

The changes in ESV, SV, EF, and FS are consistent with doxorubicin induced cardiomyopathy. Peak enhancement of the myocardium immediately following a bolus of gadopentetate is also sensitive to myocardial damage caused by doxorubicin and consistent with histology findings

(1). Results are concordant with the findings of Lightfoot et al (2) but add the additional parameters of ESV, SV and FS.

		Animal Weight[g]	LVM [g]	EDV [ml]	ESV [ml]	SV [ml]	EF [%]	FS [%]	LGE [%]
Vehicle	Mean	409	0.66	0.34	0.06	0.28	82	65	59
	95% C.I.	24	0.07	0.03	0.01	0.03	3	12	7
Dox (1.25 mg/kg)	Mean	344	0.70	0.33	0.17	0.16	50	43	91
	95% C.I.	14	0.04	0.04	0.05	0.03	13	13	7
	t-test	0.001	0.33	0.85	0.003	0.0002	0.001	0.04	0.001

References: (1) Montaigne *et al* Toxicology and Applied Pharmacology **244**, 300 (2010); (2) Lightfoot *et al* Circulation: Cardiovascular Imaging **3**, 550 (2010)