Phospholipidosis affects Hepatobiliary Function as assessed by Gadoxetate DCE-MRI

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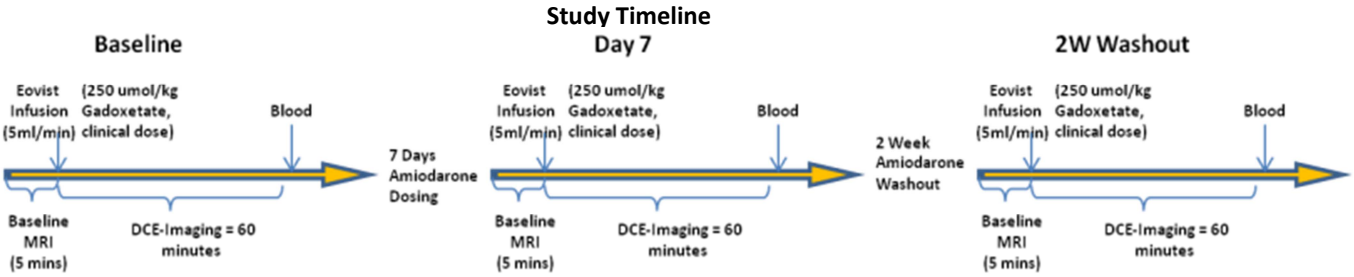
Purpose- Phospholipidosis (PLD) induced by drugs with a cationic amphiphilic structure (CAD) is a generalized condition in humans and animals characterized by an intracellular accumulation of phospholipids and the concurrent development of concentric lamellar bodies. While the biochemical and ultrastructural features of the condition have been well characterized, much less effort has been directed toward understanding whether the condition has any adverse effects on hepatobiliary function. Amiodarone is a well characterized CAD drug known to induce hepatic PLD. Using a clinically available liver specific MRI contrast agent (Eovist™;Gadoxetate), hepatobiliary Dynamic Contrast Enhanced MRI (DCE-MRI) was performed to determine if Gadoxetate kinetic changes could be detected with a compound known to induce hepatic PLD in order to determine the utility of Gadoxetate DCE-MRI in assessing PLD's potential liability on hepatobiliary function.

Methods – All procedures were approved by GlaxoSmithKline IACUC. Male Han Wistar rats (~12 weeks of age) with a mean body weight of 300g (270-320) were used. DCE-MRI was performed at 4.7T using a 72mm Volume Coil. IG-FLASH Sequence (TR/TE/FA= 7.12/1.8 ms/30 deg) was used: FOV= 6x6cm, slice thickness= 2mm, spatial resolution= ~ 468 um, matrix 128x128, TA=1h5m. Retrospective reconstruction (1 minute temporal resolution) was performed. Data analysis was a manual tracing of entire liver to obtain mean signal intensity of the liver. Amiodarone was dosed orally (300 mg/kg or vehicle) for 7 days. DCE-MRI was performed at baseline, Day 7, and 2 weeks post-washout time points. An empirical mathematical model (EMM) was used to calculate the Gadoxetate uptake and washout kinetics.[1]



Results- Amiodarone induced a significant decrease in Gadoxetate washout rate from baseline at Day 7 which significantly improved after the 2W washout of Amiodarone (Fig.1). All Amiodarone treated rats showed a consistent pattern of decreased washout at Day 7 which subsequently improved after 2 week washout (Fig.2). The black points in figure 2 represent animals in Amiodarone treated group sacrificed for histological verification of hepatic PLD, while red points represent animals allowed to recover during the 2 week post washout of Amiodarone.

Figure 1

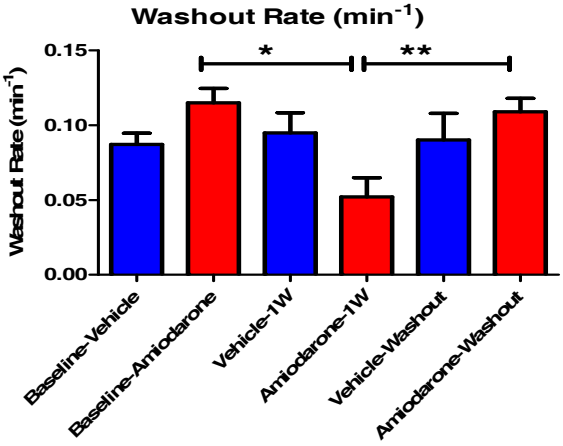
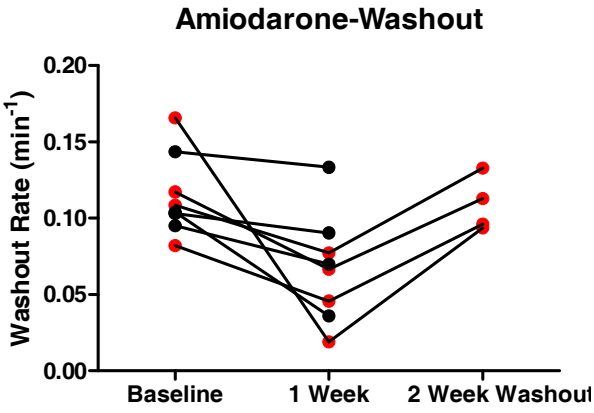


Figure 2



Discussion- Amiodarone induced a significant decrease in the Gadoxetate washout rate at Day 7 which significantly improved at 2 weeks post-washout of Amiodarone. No significant changes were seen in biomarkers of liver injury (ALT/AST/ALP), total bilirubin, or bile acids (data ns). Electron microscopy revealed that all the Amiodarone treated rats showed histological evidence (concentric lamellar bodies) of PLD at Day 7 while the 2 week post-washout group showed no histological evidence of PLD after washout (data ns). In summary, hepatic PLD induced by Amiodarone significantly altered the Gadoxetate washout rate and correlated highly to histological presence of PLD. This is the first study to show the application of Gadoxetate DCE-MRI to detect hepatobiliary functional changes induced by PLD**.** The novel results of this study suggest Gadoxetate DCE MRI of liver function may be a useful technique to assess hepatic functional consequences of PLD.

Reference - [1] Saito et al, JMRI, 36:1483-89