Gadoxetate contrast kinetics are altered in rat liver by a peptide deformylase inhibitor known to induce phospholipidosis

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Purpose- Phospholipidosis (PLD) induced by drugs with a cationic amphiphilic structure is a generalized condition in humans and animals that is characterized by an intracellular accumulation of phospholipids and the concurrent development of concentric lamellar bodies. The primary mechanism responsible for the development of PLD is an inhibition of lysosomal phospholipase activity by the drugs. 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 adverse effects on the organism. GS503A is a peptide deformylase inhibitor which has a known cationic amphiphilic structure and was shown to produce pre-clinical evidence of PLD in a 7 day rat toxicology study. 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 PLD in order to determine the utility of Gadoxetate DCE-MRI in assessing PLD’s potential hepatobiliary function liability in pre-clinical drug development.

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. GS503A was dosed orally (1000 mg/kg or vehicle) one hour prior to DCE-MRI. 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. DCE-MRI was performed at baseline, Day 1, Day 3, Day 8, and 2 weeks washout timepoints. An empirical mathematical model (EMM) was used to calculate the Gadoxetate uptake and washout kinetics. 1

Results- Gadoxetate signal intensity is increased in the liver with signal peaking at ~5 min post-injection(Fig.1). GS503A induced a significant elevation in liver enzymes (ALT) by Day 3 (Fig.2). Mean RE(t) curves at Day 3 for Vehicle and GS503A groups is shown in Fig.3. Significant changes in Gadoxetate kinetics were detected at Day 3 (uptake, p<0.01) and the washout rate reduced (p=0.052) and maintained at Day 8 (uptake, p=0.07 and washout, p<0.01) (Fig.4). The correlations between Gadoxetate kinetics and ALT elevation in liver enzymes (ALT) by Day 3 (Fig.2). Mean RE(t) curves at Day 3 for Vehicle and GS503A groups is shown in Fig.3. Significant changes in Gadoxetate kinetics were detected at Day 3 (uptake, p<0.01) and the washout rate reduced (p=0.052) and maintained at Day 8 (uptake, p=0.07 and washout, p<0.01) (Fig.4). The correlations between Gadoxetate kinetics and ALT elevation in liver enzymes (ALT) by Day 3 (Fig.2). Mean RE(t) curves at Day 3 for Vehicle and GS503A groups is shown in Fig.3. Significant changes in Gadoxetate kinetics were detected at Day 3 (uptake, p<0.01) and the washout rate reduced (p=0.052) and maintained at Day 8 (uptake, p=0.07 and washout, p<0.01) (Fig.4).

Discussion- Gadoxetate kinetic changes were observed despite GS503A not inhibiting either the uptake (OATPB1) or washout (MRP2) transporters in the rat liver at the dose used in this study (Transporter IC50 data not shown). After the 2 week washout of GS503A, the return of uptake kinetics to baseline levels (and washout kinetics to ~70% baseline levels) suggests liver function may return to normal after the cessation of PLD inducing compounds. Future studies to address the mechanisms by which PLD may affect Gadoxetate transport need to be performed to better understand how PLD affects Gadoxetate transport in the hepatocyte. In addition, hepatocellular necrosis independent of PLD may also play a role in reducing Gadoxetate transport within the liver. In summary, Gadoxetate DCE MRI of liver function may be a useful pre-clinical technique to assess hepatic functional consequences of PLD in vivo to support drug development decisions for compounds found to induce PLD.