Hepatobiliary contrast enhancement using gadofosveset trisodium

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Gadofosveset trisodium (Ablavar®, Lantheus, Billerica, MA) is an intravascular gadolinium based contrast agent (GBCA) that has recently gained FDA-approval in the US for MR angiography (MRA) in aorto-iliac and suspected peripheral vascular disease. It is a promising gadolinium-based agent that made its clinical debut in Europe in 2006 (Vasovist® (discontinued), Bayer-Schering, Berlin, Germany). Gadofosveset trisodium holds promise as a high relaxivity agent with prolonged blood pool persistence as a result of transient, non-covalent binding with serum albumin. Administration is performed at a relatively lose dose (0.03mmol/kg vs. 0.1mmol/kg for typical extracellular GBCA's).

According to the package insert, gadofosveset trisodium is primarily excreted through renal (94% within the first 72 hours) and fecal (4.7%) pathways [1]. Interestingly, early reports in monkeys have demonstrated up to 22% biliary excretion [1,2] which could potentially be clinically exploited.

Other so-called "hepatobiliary" contrast agents such as gadobenate dimeglumine (Multihance®, Bracco Pharmaceuticals, Princeton, NJ) show renal and hepatic uptake and excretion, with up to 3-5% biliary excretion in humans, but upwards of 50% in rodents [3]. In 2008, gadoxetic acid (Eovist®, Bayer Pharmaceuticals, Wayne, NJ, Europe: Primovist®) was FDA-approved for characterization of liver lesions, with approximately 50% biliary excretion. Both gadoxetic acid and gadobenate dimeglumine are highly effective GBCA's that have exploited the hepatic uptake and biliary excretion for detection and characterization of liver lesions, as well as high resolution T1 weighted (T1w) biliary imaging [4-14].

It is therefore interesting to speculate whether gadofosveset trisodium could play a role in hepatobiliary imaging in addition to its established role as an intravascular contrast agent. It was therefore the propose of this proof-of-concept work to report preliminary observations on delayed phase hepatobiliary magnetic resonance imaging (MRI) using gadofosveset trisodium.
Methods and Materials

We report on findings in nine volunteers and eleven pigs examined with different MR imaging protocols. In human subjects, studies were HIPAA compliant and were performed after obtaining institutional review board (IRB) approval and written informed consent. Swine were imaged after obtaining approval from our institution's research animal resource center (RARC) following IACUC (The Institutional Animal Care and Use Committee) guidelines.

Exams on a 3T MR scanner (Discovery MR 750, GE Healthcare, Waukesha, WI) with a 32-channel phased-array receive-only coil (NeoCoil, Pewaukee, WI) consisted of various gradient echo T1w imaging sequences. Sequences were applied prior to and at multiple time points after injection of Gadofosveset trisodium at 0.03mmol/kg body weight. In human volunteers, injections were performed with a power injector (MedRad Spectris Solaris) at 0.6ml/min via a 20G antecubital intravenous line and were followed by a 30ml saline chaser.

Either a 3D-SPGR MR angiography acquisition (n=9) using ARC for parallel imaging [15] or a 3D SPGR sequence with spectrally selective partial inversion fat suppression [(LAVA) [16] (n=42)] were used, with scan parameters (FOV, number of slices) individually adapted to each individual's anatomy.

Image evaluation consisted of the detection and location of contrast in the biliary system (0 = no contrast in the biliary system, 1 = gallbladder only, 2 = gallbladder and intrahepatic bile ducts, 3 = gallbladder, intra- and extrahepatic bile ducts). Further, a grading of the enhancement strength (1 = weak contrast enhancement, 2 = moderate contrast enhancement, 3 = strong contrast enhancement) was performed.
Results

8/9 volunteers and 11/11 pigs demonstrated hepatobiliary enhancement.

Swine showed more pronounced enhancement (3 = strong [n=10], 2 = moderate [n=1]) of gallbladder, intra- and extrahepatic biliary structures than human volunteers (3 = strong [n=1], 2 = moderate [n=2], 1 = weak [n=5]).

In 7/9 humans, enhancement was seen in bile ducts and gallbladder or confined to the gallbladder in 2/9 humans, even after considerable delay of 80±15min (range 60-100min). Enhancement appeared to start earlier in swine, the majority of swine demonstrating enhancement after 25-30 minutes.

Figures 1-3 depict examples of hepatobiliary contrast enhancement in human subjects and in swine.
Fig. 1: Hepatobiliary imaging 65 minute after injection of gadofosveset trisodium in a 43-year-old female. In the axial T1w scan (A), gallbladder enhancement is seen anterior to the indicated orientation of the maximum intensity projection (MIP) displayed in B. The MIP (B) demonstrates the identification of right and left main biliary duct (RMD, LMD, respectively), and the common hepatic duct (CHD) draining into the duodenum. Scores for the exam were 2 (moderate enhancement) and 3 (depiction of gallbladder, extra- and intrahepatic bile ducts).

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Fig. 2: Hepatobiliary excretion of gadofosveset trisodium in a 32-year-old woman. (B) -(D) shows unformatted axial SPGR images 60 minutes after injection of 0.03mmol/kg gadofosveset trisodium. White arrowheads delineate the left and right hepatic duct (LHD< RHD, respectively). In (A), a coronal maximum intensity display (MIP) also shows
common hepatic duct (CHD) and gallbladder (GB). Scores for the exam were 2 (moderate enhancement) and 3 (depiction of gallbladder, extra- and intrahepatic bile ducts).

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**Fig. 3:** Hepatobiliary imaging 65 minute after injection of gadofosveset trisodium in a 43-year-old female. In the axial T1w scan (A), gallbladder enhancement is seen anterior to the indicated orientation of the maximum intensity projection (MIP) displayed in B. The MIP (B) demonstrates the identification of right and left main biliary duct (RMD, LMD, respectively), and the common hepatic duct (CHD) draining into the duodenum. Scores for the exam were 2 (moderate enhancement) and 3 (depiction of gallbladder, extra- and intrahepatic bile ducts).

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Conclusion

This preliminary observational study demonstrates that gadofosveset trisodium shows species-dependent hepatobiliary enhancement.

Our data suggest earlier and more pronounced enhancement in swine as compared to human subjects. These differences may be attributable to the well-established lower albumin binding of gadofosveset trisodium in swine plasma compared to human plasma [17]. Reduced albumin binding potentially leads to higher availability of unbound gadofosveset trisodium for uptake into hepatocytes and excretion into bile. This naturally leads to the speculation of whether reduced serum albumin, or drugs interfering with the binding of gadofosveset trisodium with albumin, could result in higher hepatobiliary enhancement.

The presented results further indicate that gadofosveset trisodium may be used as a hepatobiliary agent for swine, and holds potential for combined intravascular and hepatobiliary imaging in humans as a third alternative in gadolinium-based hepatobiliary MRI.

However, further studies on time course, dose-dependence, and degree of hepatobiliary enhancement in humans are warranted before the hepatobiliary contrast enhancement can be exploited for clinical purposes, e.g. in comprehensive imaging protocols for liver transplantation.
References


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