Gd-EOB-DTPA as a Correlate for Chronic Liver Disease Through Contrast Uptake, Uptake Rate, and Bile Excretion

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INTRODUCTION

Chronic liver disease is the cause of 112,000 inpatient services and 27,555 deaths (9.2 per 100,000) per year, of which 14,505 (4.8 per 100,000) are attributed to non-alcoholic liver disease. Although liver disease can be detected in biopsies and less reliably in liver enzymes, magnetic resonance imaging (MRI) has demonstrated significant potential as a non-invasive, quantitative methodology to measure the degree of hepatic fibrosis.

Of particular interest are the gadolinium-based contrast agents because of their pharmacodynamic uptake and associated MRI signal response in the liver. One agent that holds significant promise is gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) because of a lipophilic moiety that allows an increased degree of liver excretion as compared to other clinical contrast agents.

Advances in 3D T1-weighted (T1W) gradient echo (GRE) MRI have made it possible to visualize the uptake response of Gd-EOB-DTPA in the liver, as well as the excretion kinetics in the biliary tract. Here, a method to quantify Gd-EOB-DTPA uptake is discussed and demonstrated in control subjects and chronic liver disease patients, showing differences in hepatic function between patients and controls as well as in comparison with an independently collected fibrosis score.

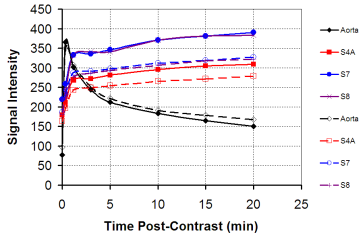
METHODS

All studies were performed with Institutional Review Board (IRB) approval and informed patient consent. Control subjects (n = 7) received Gd-EOB-DTPA (Eovist (gadoxetate disodium)/Primovist (gadoxetic acid), Bayer AG, Leverkusen, Germany). Patients with known chronic liver disease without bile duct obstruction or stricture (n = 30) were enrolledfor a liver examination with Gd-EOB-DTPA administration. A number of the patients also had undergone a previous gadolinium benzyloxypropionictetro-acetate (Gd-BOPTA) (MultiHance (gadobenate dimeglumine), Bracco, San Donato Milanese (MI), Italy) examination, where the severity of chronic liver disease was categorized according to a fibrosis score from 1-3 (8 mild, 4 moderate, and 2 severe). All subjects were scanned on a Siemens Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a 6-channel body matrix coil and a 24-channel spine matrix coil. A 3D T1W GRE volumetric interpolated breath-held examination (VIBE) sequence was acquired pre-contrast and at 20 s, 70 s, 3 min, 5 min, 10 min, 15 min, and 20 min post-contrast with parameters as follows: TR/TE = 3.6/1.96 ms, slice thickness/gap = 3/0.3 mm, slices = 88, FOV = 380 x 356 mm, matrix = 256 x 179, acquisitions = 1, FA = 10 degrees, and acquisition time = 0:17.

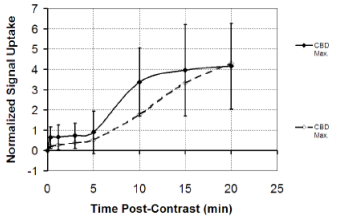
Regions of interest (ROIs) were placed on the aorta and Couinaud Segments 4A, 7, and 8 of the liver to obtain a mean signal intensity (I(t)) over each time point. An additional ROI was placed on the common bile duct (CBD) to obtain a maximum signal intensity (I(t)) to detect bile excretion. Analyze (Mayo Clinic, Rochester, MN) was used for ROI placement with particular care to avoid hepatic vasculature in measurements. By subtracting the pre-contrast signal (I(0)), signal intensities were converted to a signal uptake ($I_{uptake}(t)$) by further dividing by the pre-contrast signal, a normalized signal uptake ($I_{uptake}(t)$) was computed. A signal uptake rate ($I'_{uptake}(t)$), and a normalized signal uptake rate ($I'_{uptake}(t)$) were also computed by dividing by the change in time from the previous measurement.

RESULTS

1. Mean Signal: The left figure shows the mean signal intensity over time post-contrast in the aorta and Segments 4A/7/8 averaged over all patients (dotted line) and controls (solid line).
2. Normalized Signal Uptake Rate: The statistical significance of normalized signal uptake rate in Segments 4A/7/8 based on p values from t tests comparing controls and mild fibrosis patients to moderate fibrosis patients at 70 s post-contrast is listed in the table.
3. CBD Excretion: The right figure shows the normalized signal uptake over time post-contrast in the CBD averaged over all patients (dotted line) and controls (solid line).



Group	Segment 4A Normalized Signal Uptake Rate (s^{-1})	Segment 7 Normalized Signal Uptake Rate (s^{-1})	Segment 8 Normalized Signal Uptake Rate (s^{-1})	Liver Mean Normalized Signal Uptake Rate (s^{-1})
Controls	0.07	0.04	0.02	0.02
Mild	0.07	< 0.01	0.01	0.01



DISCUSSION

The control subjects demonstrate a higher mean signal in all liver segments as compared to patients. The decreased overall uptake is correlated to the presence of liver fibrosis. Normalized signal uptake rate can be used to further discriminate between patients with moderate chronic liver disease and those with mild fibrosis or healthy liver subjects. This finding is statistically significant.

The time of bile excretion into the CBD can be also used as a marker for chronic liver disease. It can be shown that a normalized signal shows a statistically significant difference in CBD excretion at 10 min post-contrast. Subjects with bile excretion before 10 min are correlated with having healthy livers and those with delayed excretion past 10 min may demonstrate chronic liver disease.

CONCLUSION

Gd-EOB-DTPA has unique liver excretion properties that make it favorable for screening of liver fibrosis. Mean signal uptake, uptake rate, and CBD excretion delay are reliable markers for chronic liver disease.