The hepatic uptake of Gd-EOB-DTPA is strongly correlated with the uptake of Gd-BOPTA

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Introduction

There are at present two commercially available T1-enchancing liver-specific contrast agents, Gd-EOB-DTPA and Gd-BOPTA. They are excreted both via the kidneys and the liver; early reports have indicated 50% hepatobiliary excretion of Gd-EOB-DTPA and 5% of Gd-BOPTA. The hepatobiliary transport route have for both substances been described as passive across the basolateral membrane and ATP-dependent active transport across the canalicular membrane. Quantitative measurement of the hepatic uptake of a liver-specific contrast agent would provide functional information about this transport. However, today there is no such method capable of accurately describing the hepatocyte uptake and excretion of the agent, due to the non-linear response of signal intensity (SI) to contrast concentration, partial volume effects of blood and extracellular compartments in the liver, and variable renal excretion rates.

In the present study, the aim was to investigate whether the hepatic uptake of Gd-EOB-DTPA and that of Gd-BOPTA are correlated, and to develop a method capable of such comparisons despite the large variation in the dynamics of the two contrast media.

Method

Subjects: After approval of the local ethics committee, 10 healthy volunteers were examined twice, once using Gd-EOB-DTPA (0.025 mmol/kg), and once using Gd-BOPTA (0.05 mmol/kg) in randomized order. T1-weighted images (THRIVE, TR 5.2 ms, FA 10°, scan time 23 s) were acquired prior to, in the arterial and venous phase, 10, 20, 30, and 40 minutes after the bolus injection using a 1.5 T Philips Achieva MR scanner.

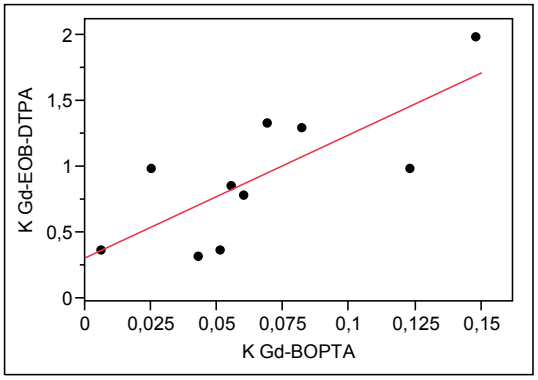
Image analysis: The image time series were analyzed using in-house developed software allowing co-registration of regions of interest (ROIs) compensating for patient movement during the time series, while carefully preserving the signal intensities. Seven ROIs were placed in homogenous liver tissue, and three ROIs were placed in splenic tissue, avoiding major vessels and bile ducts. The time series were recalculated to relaxivity values using the sequence-specific signal equation assuming a T1 of 586 ms in liver tissue and 1057 ms in splenic tissue prior to contrast injection. By this procedure, the non-linear response of the contrast concentration was compensated. Finally, the contrast concentration was estimated by

$C(t) = (R(t) - R(t{=}0))/R_{media}$ were R_{media} is the relaxivity of the contrast agent.

Pharmacokinetic modelling: A simple two-compartment model of the liver tissue was assumed, consisting of a passive compartment, including liver blood and the extracellular space, and a hepatobiliary compartment accessible to contrast media only after contrast transport into the hepatocyte and to the biliary ductules. In the spleen, the contrast agent was assumed to remain in the blood and extracellular compartment. Furthermore, the blood and extracellular compartment were assumed to have equal volume fractions (0.5 of the MR-visible water), in the liver and spleen. The relative uptake in the hepatocytes compartment was estimated using

$$Fraction(t) = (C_{liver}(t) - C_{spleen}(t))/C_{spleen}(t) = C_{liver}(t)/C_{spleen}(t) - 1$$

A slope, K, with unit [min^{-1}] was estimated from each examination by fitting a linear slope to the estimated fraction at the venous phase, 10 and 20 minutes after the contrast injection. The latter time points (30 and 40 minutes) were excluded from the analysis, since the splenic contrast concentration decreased under the detection level in some subjects.



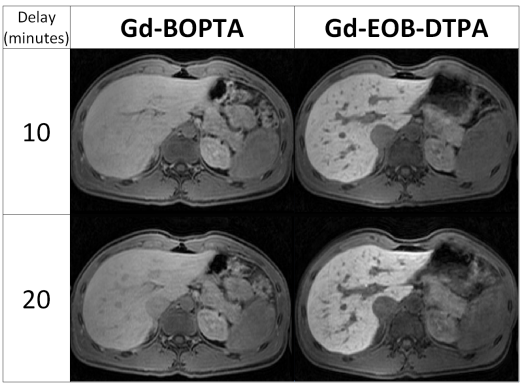


Figure
Left, Regression plot for the slopes K for Gd-EOB-DTPA and Gd-BOPTA.

Right, Images from one subject illustrating the hepatic and splenic enhancement 10 and 20 minutes after contrast injection.

Results

Comparisons of measured SI did not show any significant correlation between the contrast media. Pairwise comparison of K estimated using Gd-EOB-DTPA and Gd-BOPTA in each subject showed a statistical significant linear correlation of 0.76 (95% CI 0.20 to 0.95). The fitted linear regression line was $K_{EOB} = 0.32(\pm 0.22) + 9.32(\pm 2.79) \cdot K_{BOPTA}$ (see Figure).

Discussion and Conclusion

In the time segment of 10-20 minutes post-injection, hepatic enhancement with Gd-BOPTA largely reflects the blood concentration, whereas the higher enhancement seen with Gd-EOB-DTPA relates to the hepatocellular and biliary contrast concentration. Therefore, the correction of the influence of the blood contrast concentration estimated via the splenic enhancement is required to obtain a reliable estimate of the hepatocyte uptake. The observed correlation between measurements using Gd-EOB-DTPA and Gd-BOPTA suggests that both contrast media measure the same functional hepatic transport route. It also indicates that the suggested pharmacokinetic analysis is able to estimate the hepatocyte-specific uptake of the contrast over a large range of concentrations. By dividing the liver contrast concentration with the splenic contrast concentration not only the influence of different blood concentrations and injected dose is corrected; such an analysis is also insensitive to differences in relaxivity between contrast media, provided that the relaxivity of contrast medium in the liver vs. in the spleen are similar.

Finally, it can be noted that the estimated regression slope of 9.32±2.79 between the contrast agents is in agreement with the expected ratio of the hepatic uptake of Gd-EOB-DTPA (50 %) / Gd-EOB-BOPTA (5 %), even if large individual variations were observed.