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Contrast-enhanced MR cholangiography with Gd-BOPTA and Gd-EOB-DTPA in healthy subjects

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Abstract

Purpose: To evaluate the biliary enhancement dynamics of the two gadolinium chelates Gd-BOPTA (MultiHance®) and Gd-EOB-DTPA (Primovist®) in normal healthy subjects.

Material and Methods: Ten healthy volunteers were evaluated with both agents by magnetic resonance imaging at 1.5 T using a breath-hold gradient-echo T1-weighted VIBE sequence. The relative signal intensity (SI) differences between the common hepatic duct (CHD) and liver parenchyma were measured before and 10, 20, 30, 40, 130, 240 and 300 minutes after contrast medium injection.

Results: Biliary enhancement was obvious 10 minutes post injection for Gd-EOB-DTPA and was noted at 20 minutes for Gd-BOPTA. At 40 minutes delay, Gd-BOPTA reached its peak biliary enhancement, but neither at 30 nor 40 minutes delay was there any significant difference compared with that of Gd-EOB-DTPA. At later delays, the contrast between CHD and liver continued to increase for Gd-EOB-DTPA, whereas it decreased for Gd-BOPTA.

Conclusion: The earlier onset and longer duration of a high contrast between CHD and liver for Gd-EOB-DTPA facilitates examination of hepatobiliary excretion. Therefore, Gd-EOB-DTPA may provide adequate hepatobiliary imaging within a shorter time span than Gd-BOPTA and facilitate scheduling at the MR unit. Further studies in patients are required to compare the imaging advantages of Gd-EOB-DTPA and Gd-BOPTA in clinical practice.

Keywords: Biliary, Liver, MR Imaging, Bile Ducts, Intravenous Contrast Agents, Comparative studies

Several imaging techniques can be applied in the investigation of biliary anatomic variants and of abnormalities in the anatomy and function of the biliary system. In patients with signs of biliary obstruction, examination of the morphology is primarily performed non-invasively, using sonography and magnetic resonance cholangiography (MRC).

Magnetic resonance cholangiography gives accurate diagnostic and anatomic information about the biliary system (20) and has therefore become a routine examination before endoscopic retrograde cholangiopancreatography (ERCP) (1, 5, 10, 22). ERCP is associated with a complication rate of around 10%, most of the complications being due to pancreatitis and sepsis (6, 21). Functional abnormalities can be explored by hepatobiliary scintigraphy, whereby a radioactive tracer, $^{99}\text{Tc}^{\text{m}}$ -HIDA, is taken up by hepatocytes and excreted into the biliary system. The same principle can be utilized in biliary-specific contrast-enhanced computed tomography (CT cholangiography) (13, 25) and biliary-specific contrast-enhanced MR. The advantages of MRC over CT cholangiography are that no radiation is used and there is greater experience of MRC in the literature.

In routine MRC, T2-weighted sequences in multiple planes depict the water content of bile in the biliary ducts and in the gallbladder. It is a non-invasive method requiring no contrast agent. However, MRC is not always conclusive, due to limited spatial resolution. MRC is also sensitive to motion artifacts and does not provide any information on hepatobiliary function.

In recent years, several new liver-specific MR imaging contrast media have been introduced. Some of the agents are targeted to hepatocytes: gadobenate dimeglumine, Gd-BOPTA (MultiHance[®]; Bracco Imaging, Milan, Italy), gadoxetic acid, Gd-EOB-DTPA (Primovist[®], Schering, Berlin, Germany), and mangafodipir trisodium, Mn-DPDP (Teslascan[®]; GE Healthcare, Chalfont St. Giles, United Kingdom). All these substances are to some extent eliminated by biliary excretion and may therefore be useful for investigating hepatobiliary function.

Mn-DPDP is a manganese-fodipir chelate that, after intravenous injection, releases manganese, which is taken up mainly by hepatocytes and later excreted into the biliary system. It is given as a slow infusion and therefore cannot be used for dynamic hepatic imaging. Both Gd-BOPTA and Gd-EOB-DTPA offer imaging properties of conventional

extracellular MR contrast agents, as well as of liver-specific agents. They differ both in the proportion of biliary elimination (50% for Gd-EOB-DTPA vs. 3-5% for Gd-BOPTA) and in their in vitro T1 relaxation rate, which is higher for Gd-BOPTA (11, 19, 24). Their side effects are in the same range as other liver-specific contrast agents (8). It has not previously been shown in a comparative study which of Gd-BOPTA or Gd-EOB-DTPA has the greatest influence on biliary T1 signal intensity in vivo.

This study aimed to evaluate the time course of biliary enhancement and the effect on T1 signal intensity of the two gadolinium chelates Gd-BOPTA (MultiHance®) and Gd-EOB-DTPA (Primovist®) in normal healthy subjects.

Material and Methods

Subjects

After approval from the local ethics committee and written informed consent, ten healthy volunteers were evaluated with each agent. Of these, four were men with an age range of 19–46 years (mean age, 30 years) and six were women with an age range of 20–45 years (mean age, 30 years). In order to exclude unknown liver and renal dysfunction, serum bilirubin and creatinine were evaluated prior to MRI.

Contrast Media

Gd-BOPTA (gadolinium benzyloxypionictetraacetate) behaves both as an extracellular and as a hepatocyte-specific contrast agent, allowing extracellular space enhancement in early acquisitions and prolonged hepatocyte enhancement in delayed acquisitions. It is injected as a bolus at a dosage between 0.05 and 0.1 mmol/kg. Although only a small fraction of Gd-BOPTA (3 - 5% of the injected dose) (11) is excreted in the human biliary system, enhancement of the biliary ducts is achieved, due to the high relaxivity of this compound. The major portion is excreted by the kidneys (15).

Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid) is a recently approved liver-specific contrast agent that combines hepatocellular specificity with T1-relaxivity and extracellular behavior (19, 23). After intravenous injection, Gd-EOB-DTPA is first distributed into the extracellular space and then taken up by the hepatocytes. It is excreted unmetabolized via two pathways: 50% via the kidneys and 50% by active transport

in the hepatocytes to the biliary system (18). Renal excretion can be substituted by the hepatobiliary excretion and vice versa. After bolus injection of 0.025 mmol/kg (the recommended dose), the peak liver enhancement is reached after about 20 minutes, followed by a plateau phase. The agent is cleared from the serum to reach a concentration below the limit of quantification 24 hours after injection (7).

The amounts of contrast media used in this study were 0.025 mmol/kg for Gd-EOB-DTPA (Primovist[®] 0.25 mmol/ml, Schering, Berlin, Germany), and 0.1 mmol/kg for Gd-BOPTA (MultiHance[®] 0.5 mmol/ml; Bracco Imaging, Milan, Italy). The contrast bolus was injected by power injector at 2 ml/s and immediately followed by an equal amount of physiologic saline. One ml of contrast was delivered as a test bolus followed by saline to enable accurate timing of the imaging sequences.

MR imaging technique

The examinations were performed on a 1.5-T magnetic resonance system (Magnetom Vision, Siemens, Erlangen, Germany) combining the spine coil and the flexible phased-array body coil.

Examinations were performed in the early morning after more than seven hours of fasting. After one hour of scanning, a light meal containing less than 2 g of fat was allowed. Each examination lasted about six hours, and the two examinations for each subject were performed at least six days apart.

The study protocol was designed by extending a standard protocol for contrast-enhanced examination of the liver by adding several late phases, resulting in a total of nine post-contrast axial breath-hold gradient-echo T1-weighted VIBE (TE 1.9 ms, TR 4.5 ms, FOV 40 cm, 120 slices of 1.7 mm thickness) sequence acquisitions at arterial and portal venous phases and 10, 20, 30, 40, 130, 240 and 300 minutes after injection.

Image and signal intensity analysis

Three reviewers (N.D., T.B. and N.A.) performed all measurements independently, using diagnostic workstations (PACS IDS5 v10.1, Sectra Imtec AB, Linköping, Sweden). To measure the signal intensity (SI) of the biliary duct lumen, the reviewers placed a single measuring point in the central voxel in an axial or near-axial view of the common hepatic duct

(CHD). Mean SI of liver parenchyma was measured in operator-placed regions of interest (ROI) of 0.7 cm² in the same slice. The ROI was placed at the same anteroposterior level as the measurement of the duct SI, avoiding large vessels (Fig. 1).

The bile duct-to-liver contrast, $C_{\text{Duct-Liver}}$, was calculated as $(SI_{\text{Duct}} - SI_{\text{Liver}}) / SI_{\text{Liver}}$.

Statistical analysis was performed in JMP 6.0 (SAS Institute Inc, Cary, NC, USA) using an ANOVA model with the subject and the reviewer defined as random effects, testing for each time point the null hypothesis of no difference in $C_{\text{Duct-Liver}}$ between Gd-BOPTA and Gd-EOB-DTPA within subjects. To evaluate the possible difference in late enhancement behavior, a similar linear model was applied on the $C_{\text{Duct-Liver}}$ values between 40 and 240 minutes post injection, using time, subject (random effect) and reviewer (random effect) as model effects.

Results

The total set of examinations was completed in a time span of 49 days, resulting in 600 measurements (3 reviewers, 2 contrast media, 10 volunteers and 10 image series per examination). Due to technical problems, one of the examinations did not include the acquisition at 20 minutes post injection. Thus, at that time point 27 instead of 30 measurements were available for analysis. All subjects underwent both their examinations without adverse reactions or subjective symptoms.

The biliary SI rose earlier, at 10 minutes post injection, for Gd-EOB-DTPA than for Gd-BOPTA ($p < 0.001$) and decreased after 40 minutes, although somewhat less than Gd-BOPTA (Fig. 2). With Gd-BOPTA, the SI of liver parenchyma stayed elevated for a longer time than with Gd-EOB-DTPA.

In the image series acquired before contrast administration, there was no significant difference in $C_{\text{Duct-Liver}}$ between Gd-BOPTA and Gd-EOB-DTPA. At 10 minutes post injection, biliary enhancement was evident for Gd-EOB-DTPA ($p < 0.0001$), whereas there was none for Gd-BOPTA. At 20 minutes delay, biliary enhancement was recognized also for Gd-BOPTA (Fig. 3), but bile duct-to-liver contrast values were significantly higher for Gd-EOB-DTPA ($p < 0.02$). During the interval 20 to 40 minutes, $C_{\text{Duct-Liver}}$ increased for both contrast media, with no significant difference between them at any time point. Later than 40 minutes post

injection (i.e. at 130-300 minutes delay), the values of $C_{\text{Duct-Liver}}$ were significantly higher for Gd-EOB-DTPA than for Gd-BOPTA ($p < 0.002$, Table).

The mean $C_{\text{Duct-Liver}}$ began to decrease after 40 minutes post injection when using Gd-BOPTA ($p < 0.0001$), but when using Gd-EOB-DTPA the $C_{\text{Duct-Liver}}$ continued to increase until 240 min post contrast injection ($p < 0.0001$, Fig. 4).

Discussion

When applying contrast media for functional biliary imaging, the time course of biliary contrast enhancement is important. Despite the lack of prominent differences in the peak SI or maximal bile duct-to-liver contrast, the contrast media compared in this study demonstrate very different biliary enhancement dynamics.

In clinical practice, the limited time frame of routinely performed MR examinations has to be taken into account. When using Gd-BOPTA to evaluate hepatobiliary function, imaging is usually repeated 1-2 hours post injection to obtain high SI in liver parenchyma and biliary enhancement (12, 14). The delay necessary to achieve a high level of parenchymal enhancement is less with Gd-EOB-DTPA, which has been pointed out as an opportunity to investigate focal liver lesions in a single examination (8, 16).

This study analyzes tissue enhancement based on absolute signal intensity values to negotiate differences in bile duct-to-liver contrast for Gd-BOPTA and Gd-EOB-DTPA. Due to the paired nature of the study design, the focus is on a per-time-point within-subjects analysis. The time course of contrast enhancement can be divided in two parts:

- up to 40 minutes after contrast administration related to the limited time frame that applies to a single clinical MR examination, and
- after 40 minutes, concerning e.g. the potential for extended or repeated examinations.

In the phase I clinical evaluation of Gd-EOB-DTPA, Hamm et al. reported bile duct enhancement within 10 minutes after injection (7), Carlos et al. describe in a technical report good biliary enhancement 20 minutes after injection in sixteen patients with hepatic masses but without known biliary disease (3). In another study with ten patients, the contrast medium

was visible in all cases at 20 minutes post injection (4) The two latter studies, however, did not include additional measurement time points, so the onset of visible biliary enhancement was not determined. Research on Gd-BOPTA has focused on lesion detection and characterization in dynamic and delayed (hepatobiliary) phases, and on vascular visualization. Thus, biliary enhancement dynamics have not been reported in detail. However, biliary imaging performed at the same time as the hepatobiliary phase has been described (12).

To our knowledge, no previous comparisons of biliary enhancement dynamics in healthy human subjects for Gd-EOB-DTPA and Gd-BOPTA have been reported. The enhancement properties of liver parenchyma have been studied and compared more thoroughly.

In keeping with previous studies (7), the present study showed excretion of Gd-EOB-DTPA into the biliary system, where it was readily visualized at 10 minutes post injection. The first biliary enhancement for Gd-BOPTA was noted at 20 minutes. At that time, however, the duct-to-liver contrast, $C_{\text{Duct-Liver}}$ was still significantly higher for Gd-EOB-DTPA. No significant difference between the two contrast media in their $C_{\text{Duct-Liver}}$ was noted at either 30 or 40 minutes delay. Thus, although the shape of contrast curves (Fig. 4) may give the impression that the $C_{\text{Duct-Liver}}$ of Gd-BOPTA exceeds that of Gd-EOB-DTPA at 30-40 minutes delay, the statistical analysis does not support this.

In the later phases, i.e. at 130-300 minutes post injection, the duct-to-liver contrast values of the contrast media were significantly different. Their trend over time during this time interval also differed; the bile duct-to-liver contrast of Gd-EOB-DTPA showed a slight increase whereas that of Gd-BOPTA decreased. There was a decrease in the mean $C_{\text{Duct-Liver}}$ for Gd-EOB-DTPA from delay 240 minutes to 300 minutes (Fig. 4), but the data is not sufficient to evaluate this more closely.

The choice of 300 minutes as the latest phase was made for practical reasons to limit the total study time per subject. In this way, however, we could emulate an extended or repeated examination more than twice the duration of extended examinations used in clinical practice.

The functional information from the assessment of the biliary enhancement dynamics gives added value to conventional MRC. The findings of this study contribute to the knowledge of normal enhancement behavior, especially for Gd-EOB-DTPA. It has recently been found that

Gd-EOB-DTPA-enhanced MRC gives added morphological information to conventional T2-weighted imaging (4). In a study on rabbits, Ryeom et al. described a method for measuring the hepatic extraction fraction and reported a significant correlation with the plasma indocyanine green (ICG) retention rate 15 minutes after an intravenous injection of ICG (ICG R15), which is an important clinical test for evaluating liver function (17). The authors discuss the potential of Gd-EOB-DTPA-enhanced liver examinations as “a direct, non-invasive technique for the quantitative evaluation of liver function.” Scintigraphic methods can also be employed to non-invasively evaluate liver function, even regional liver function, although the resolution is low (9). To our knowledge, no comparative studies have been made between scintigraphic methods and functional biliary MRI.

Several sources of error must be taken into consideration. First of all, the lack of an absolute signal intensity scale that is inherent to MR imaging leads to difficulties when comparing signal intensity variations between studies of different subjects and between studies within the same subject. We have addressed this by comparing relative contrast rather than absolute SI and by designing the experiment with each subject undergoing examination with both contrast agents. This makes it possible to focus the analysis on the effect the type of contrast agent has on the time course of biliary enhancement.

Care was taken to start each image series acquisition as near as possible to the intended time point. The mean difference between the intended time and the actual time from injection to acquisition was 10%.

To accurately time the arterial phase acquisition, a test bolus was used. This means that by the time of acquisition at 10 minutes post injection a small portion of the contrast medium had progressed further in its elimination than had the main bolus. Due to a delay of a few minutes between the test bolus and the main bolus, a very small amount of contrast may have been present in the biliary system. As no contrast enhancement of the bile duct was, however, noted in either arterial or portovenous phase images, the potential influence of the test bolus was negligible. Whereas the common hepatic duct and the central parts of the right and left hepatic bile ducts were clearly visible in all subjects regardless of the type of contrast medium, the more peripheral intrahepatic ducts were not discernible. This corresponds well with findings reported by Bollow et al. (2) that the delineation of intrahepatic ducts was possible only at the lowest dose, 0.01 mmol/kg Gd-EOB-DTPA. In 2002, Carlos et al (4)

reported an improved visualization of biliary ducts when combining contrast-enhanced T1-weighted MRC with standard T2-weighted MRC, but the visualization scores of second-order intrahepatic ducts were still low. The dose of contrast administered was not stated. In a recent study of 88 healthy liver donor candidates, Lim et al noted that Gd-BOPTA-enhanced MRC compared favorably with Mn-DPDP-enhanced MRC, with average visualization grades for second-order bile ducts (12). Further studies are needed to evaluate the potential for intrahepatic bile duct visualization with Gd-EOB-DTPA in a clinical setting, and whether a lower dose would be more suitable.

The earlier onset and longer duration of a high contrast between CHD and liver parenchyma for Gd-EOB-DTPA is useful for examination of hepatobiliary excretion. In clinical practice, hepatobiliary imaging can be performed in a shorter time when using Gd-EOB-DTPA, enabling combined vascular, hepatocellular and biliary imaging in a single exam. Gd-EOB-DTPA also provides a more flexible time window, facilitating scheduling at the MR unit. Further studies in patients are required to assess these potentials and to compare the imaging advantages of Gd-EOB-DTPA and Gd-BOPTA in clinical practice.

In conclusion, in healthy subjects the biliary enhancement dynamics of Gd-BOPTA (MultiHance®) and Gd-EOB-DTPA (Primovist®) differed significantly, with the latter yielding an earlier onset and a longer duration of biliary duct-to-liver contrast.

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Table. Mean and standard deviation of $C_{\text{Duct-Liver}}$ for Gd-BOPTA and Gd-EOB-DTPA.

	Gd-BOPTA		Gd-EOB-DTPA			
Delay (min)	Mean $C_{\text{Duct-Liver}}$	Std Dev $C_{\text{Duct-Liver}}$	Mean $C_{\text{Duct-Liver}}$	Std Dev $C_{\text{Duct-Liver}}$	n	p
0	-0.57	0.14	-0.56	0.12	30	0.84
0.25	-0.46	0.24	-0.48	0.22	30	0.76
0.8	-0.56	0.15	-0.53	0.19	30	0.46
10	-0.30	0.18	0.29	0.26	30	<0.0001
20	0.19	0.27	0.36	0.37	27	0.016
30	0.42	0.26	0.35	0.47	30	0.34
40	0.50	0.34	0.41	0.43	30	0.076
130	0.25	0.35	0.49	0.48	30	0.0002
240	0.22	0.39	0.68	0.57	30	<0.0001
300	0.24	0.39	0.52	0.44	30	<0.0001

P-values demonstrate significant ($p < 0.05$) $C_{\text{Duct-Liver}}$ differences between the contrast media at time points (delays) 10, 20, 130, 240 and 300 minutes.

Fig. 1. Typical Gd-BOPTA-enhanced common hepatic duct (CHD) and parenchymal enhancement at 130 minutes post injection. A circular ROI is placed in liver parenchyma and a point of measurement placed centrally in the CHD (arrow).

Fig. 2. Mean absolute SI values of CHD and liver for Gd-BOPTA and Gd-EOB-DTPA. The SI of liver remains at a high level for a longer time when Gd-BOPTA is used, whereas the corresponding values for Gd-EOB-DTPA decrease after a shorter plateau 10-40 minutes post injection. The biliary SI rises earlier, at 10 minutes post injection, for Gd-EOB-DTPA, and shows decreasing values after 40 minutes. From the same time point, biliary SI of Gd-BOPTA appears to decrease somewhat more.

Fig. 3. Axial T1W images of the same volunteer before and 10, 20, 130 and 300 minutes after injection. Note that the first enhancement of the CHD is seen at 10 minutes for Gd-EOB-DTPA and at 20 minutes for Gd-BOPTA (arrows).

Fig. 4. Mean contrast ($C_{\text{Duct-Liver}}$) between the common hepatic duct (CHD) and liver parenchyma at 0, 10, 20, 30, 40, 130, 240 and 300 minutes after injection of contrast medium. (Please refer to Table for further details). From 40 to 240 minutes post injection, there is an increase of $C_{\text{Duct-Liver}}$ when using Gd-EOB-DTPA vs. a decrease when using Gd-BOPTA ($p < 0.0001$, both).