

Contrast-enhanced MR cholangiography: comparison of Gd-EOB-DTPA and Mn-DPDP in healthy volunteers

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Objective: The purpose of this study was to compare the biliary enhancement dynamics of gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic-acid (Gd-EOB-DTPA) and mangafodipir trisodium (Mn-DPDP) for contrast-enhanced MR cholangiography (MRC) in healthy subjects.

Methods: 15 healthy volunteers underwent MRI at 1.5 T with volumetric interpolated breath-hold examination sequence. Each volunteer was scanned once for each contrast agent. The signal-to-noise ratio (SNR) of the liver parenchyma and common hepatic duct (CHD) and the contrast-to-noise ratio (CNR) of CHD to liver parenchyma were evaluated and compared before and at several time points (5, 15, 30, 45, 60, 90, and 120 min) after injection of each agent.

Results: SNR was significantly higher for Gd-EOB-DTPA than for Mn-DPDP in liver parenchyma after 5 min and in CHD after 15 min ($p < 0.05$). CNR of CHD to liver parenchyma using Gd-EOB-DTPA showed an initial decrease at 5 min post-injection followed by a steep increase to a peak at 15 min post-injection. CNR using Mn-DPDP showed a steady increase to a peak at 15 min post-injection without an initial decrease. At 15 min, the value of CNR was significantly higher for Gd-EOB-DTPA than for Mn-DPDP ($p < 0.05$).

Conclusion: For both contrast agents, CNR reached a peak at 15 min after contrast injection. At this time point, CNR of Gd-EOB-DTPA was significantly higher than that of Mn-DPDP. Therefore, Gd-EOB-DTPA may provide better contrast-enhanced MRC than Mn-DPDP at 15 min after contrast administration.

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The bile ducts are generally studied using fast spin echo T_2 weighted sequences with half-Fourier reconstruction. This conventional MR cholangiography (MRC) examination is highly accurate in detecting biliary tree disease [1, 2]. However, the conventional MRC has diagnostic limitations, which include poor visualisation of the intrahepatic biliary tree compared with the extrahepatic biliary tree [3], limited spatial resolution and not being able to provide functional information of the biliary tree.

Contrast-enhanced MRC has created interest in the field of MRC because of its potential to provide functional assessment and to improve the visualisation of the intrahepatic biliary trees [4–6]. The specific indications include pre-operative anatomical assessment of the biliary tree in preventing inadvertent complications in common laparoscopic cholecystectomy, and also in complex biliary surgical procedures such as biliary–enteric anastomosis and liver transplantation; post-operative assessment of the biliary tree after surgery when complications such as bile leak or inadvertent biliary tree stricture or ligation are suspected; and functional assessment of bile secretion and excretion [7–9].

Contrast-enhanced MRC is performed with hepatobiliary MR contrast agents such as mangafodipir trisodium (Mn-DPDP), gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic-acid (Gd-EOB-DTPA) or gadobenate dimeglumine (Gd-BOPTA), which are administered intravenously, taken up by the hepatocytes, and then excreted via the biliary system.

Only a small fraction of Gd-BOPTA (3–5% of the injected dose) is excreted into the biliary system [10]. On the other hand, 50–60% of Mn-DPDP and 50% of Gd-EOB-DTPA is eliminated via the biliary system [11–13]. To the best of our knowledge, no comparative study has investigated which of Mn-DPDP or Gd-EOB-DTPA has a greater influence on biliary signal intensity (SI) on T_1 weighted MRI.

The purpose of this study was to evaluate and compare the time course of biliary enhancement of Gd-EOB-DTPA and Mn-DPDP for contrast-enhanced MRC in normal healthy volunteers.

Methods and materials

Subjects

After we obtained written informed consent, 15 healthy volunteers with an age range of 22–33 years (mean age 27

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years) were included in this study under a protocol approved for human investigation by our institutional review board. Of these, 10 were male and 5 were female. To exclude unknown liver and renal dysfunction, serum bilirubin and creatinine were evaluated prior to MRI scanning.

MRI

Contrast-enhanced MRC was performed with a 1.5T imaging system (MAGNETOM Sonata®; Siemens, Erlangen, Germany) using a torso phased array coil. Three-dimensional volumetric interpolated breath-hold examinations (VIBEs) were obtained at baseline and then sequentially at 5, 15, 30, 45, 60, 90 and 120 min after administration of contrast agent. The parameters were follows: repetition time (TR), 4.8 ms; echo time (TE), 2.26 ms; flip angle, 10°; field of view (FOV), 34 cm; matrix size, 256×134 or 256×140; slice thickness, 4 mm; reconstruction interval, 2 mm.

Contrast agents

Mn-DPDP MRC was obtained following an intravenous injection of Mn-DPDP (Teslascan®; Nycomed Amersham, Princeton, NJ) at the standard dose of 5 µmol kg⁻¹ administered via a slow injection for 1–2 min followed by a 10-ml saline flush. In the case of Gd-EOB-DTPA MRC, Gd-EOB-DTPA (Primovist®, Schering, Germany) was infused at the standard dose of 25 µmol kg⁻¹ of body weight using an automated injection at a rate of 2 ml s⁻¹ followed by a 10-ml saline flush. The two examinations for each subject were performed at least 7 days apart.

Image analysis

One reviewer performed operator-defined region-of-interest (ROI) measurements of the SI of CHD, liver parenchyma and background noise using a picture archiving and communication system (PACS) monitor and digital imaging and communications in medicine (DICOM) imaging viewing software (PiView™ v. 4; Infinitt, Seoul, Republic of Korea). Three ROIs were drawn on the most proximal portion of the CHD on each image, to include as much CHD as possible. The mean value of the SIs in the three ROIs was defined as the SI of the CHD. The SI of the liver parenchyma was similarly calculated, with the ROIs placed at the same anteroposterior level used in measuring the CHD, and avoiding inclusion of imaging artefacts and major vascular structures in the same slice. Background noise was measured on the same image using ROIs positioned lateral to the abdominal wall. The same set of ROIs was applied to pre- and post-contrast images obtained with each contrast agent, for each subject.

Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were calculated using the following standard equations:

$$\text{SNR}_{\text{CHD}}(t) = \frac{\text{SI}_{\text{CHD}}(t)}{\text{SD}_{\text{background noise}}(t)}$$

$$\text{SNR}_{\text{liver}}(t) = \frac{\text{SI}_{\text{liver}}(t)}{\text{SD}_{\text{background noise}}(t)}$$

$$\text{CNR}(t) = \frac{\text{SI}_{\text{CHD}}(t) - \text{SI}_{\text{liver}}(t)}{\text{SD}_{\text{background noise}}(t)}$$

SNR(*t*) and CNR(*t*) are the SNR and CNR, respectively, at the time point *t* (min) after injection of contrast agent; SI_{CHD}(*t*) is the SI of the CHD; SI_{Liver}(*t*) is the SI of the liver parenchyma; and SD_{background noise}(*t*) is the standard deviation (SD) of background noise at this time.

Statistical analysis

At each time point, we performed a statistical analysis to compare the SNR of liver and CHD, and the CNR of CHD to liver between the two contrast media using a Wilcoxon signed-rank test. A *p*-value ≤0.05 was considered to indicate significant difference.

Results

All subjects underwent both examinations without any adverse reactions or subjective symptoms. Representative MR images of both contrast agents are shown in Figure 1. Figure 2 and Table 1 show the time courses of the mean SNRs of liver parenchyma and CHD for both contrast media. SNR of liver parenchyma reached a peak at 15 min after injection of Mn-DPDP and 30 min after Gd-EOB-DTPA, before reaching a plateau. SNR of liver parenchyma began to decrease after 90 min for both contrast agents. Between 5 and 120 min, SNR in liver parenchyma was significantly higher for Gd-EOB-DTPA than for Mn-DPDP (*p*<0.05).

For both contrast agents, SNR of CHD reached a peak at 15 min after injection, after which time SNR of CHD showed a gradual decrease for both contrast agents. Between 15 and 120 min, SNR in CHD was significantly higher for Gd-EOB-DTPA than for Mn-DPDP (*p*<0.05).

Figure 3 and Table 2 show the time courses of mean CNR of CHD to liver parenchyma for both contrast groups. CNR of Gd-EOB-DTPA showed an initial decrease in the 5 min after injection, a steep increase to a peak at 15 min, followed by a steep decrease. CNR using Mn-DPDP showed a steady increase to a peak at 15 min after injection, without an initial decrease, followed by a gradual decline. At 15 min, the value of CNR was significantly higher for Gd-EOB-DTPA than for Mn-DPDP (*p*<0.05).

Discussion

During the past decade, MRC has proven to be an accurate imaging tool for evaluation of the extrahepatic biliary system [14]. Conventional MRC relies on the use of a heavily *T*₂ weighted sequence to produce high SI in stationary tissues such as water and bile that have long *T*₂ relaxation times. Tissues with short *T*₂ relaxation times, such as liver and pancreas, and flowing blood, have low SI, allowing for optimal contrast between the hyperintense bile and hypointense background. The

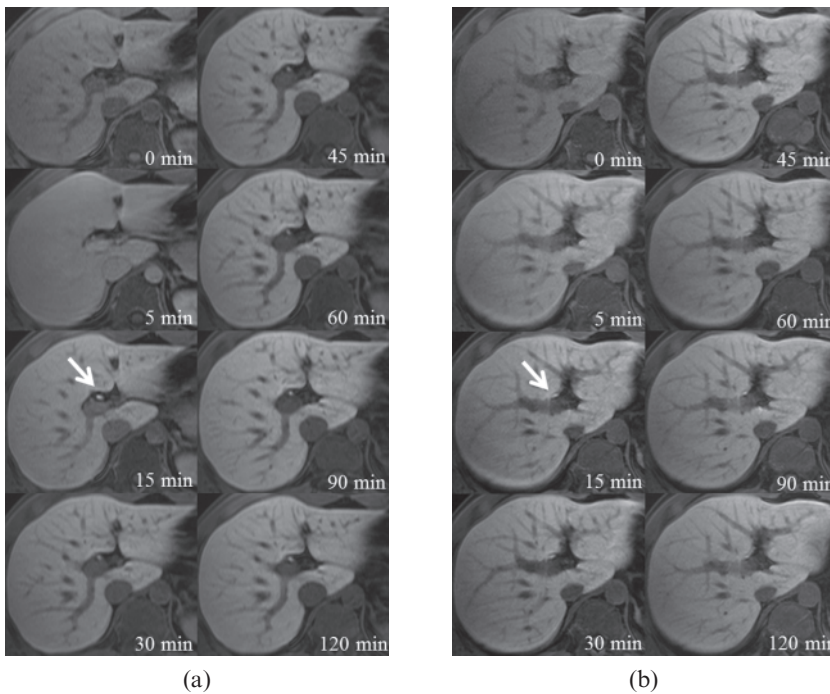


Figure 1. Axial T_1 weighted images with (a) Gd-EOB-DTPA and (b) Mn-DPDP of a 28-year-old male volunteer before and at 5, 15, 30, 45, 60, 90 and 120 min after contrast injection. Arrows indicate the proximal common hepatic duct. Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; Mn-DPDP, mangafodipir trisodium.

sensitivity and specificity of MRC for detection of choledocholithiasis are 90% and 100%, respectively [15]. Despite the impressive clinical performance reported in the literature, MRC has diagnostic limitations that include poor visualisation of the intrahepatic biliary tree compared with the extrahepatic biliary tree [3], variation in T_2 weighting causing depiction of slow-flow vascular structures (such as the portal vein and hepatic vein) that may obscure adjacent biliary structures [16], and limited spatial resolution. However, detailed anatomical depiction of the non-distended intrahepatic biliary ductal system is occasionally required (*e.g.* in pre-operative evaluation of potential living liver donors) because biliary variants are seen in up to 45% of the population [17].

To overcome the above limitations, radiologists have developed new imaging strategies in recent years by

using contrast agents that are excreted by the bile ducts for T_1 weighted MRI [9]. In addition to functional assessment of the biliary tree, hepatobiliary contrast agents enable definition of intrahepatic ductal anatomy because it acts as a positive biliary contrast by differentiating hepatic vessels from bile ducts, which can be difficult on conventional MRC because of slow flow [5]. Traditional two-dimensional imaging using turbo spin-echo sequences to generate conventional T_2 MRC source data results in low spatial resolution [1], whereas three-dimensional T_1 weighted imaging using hepatobiliary contrast agents has improved resolution [5, 6].

To the best of our knowledge, no studies have directly compared the time course of biliary enhancement of Gd-EOB-DTPA and Mn-DPDP for contrast-enhanced MRC in normal healthy volunteers.

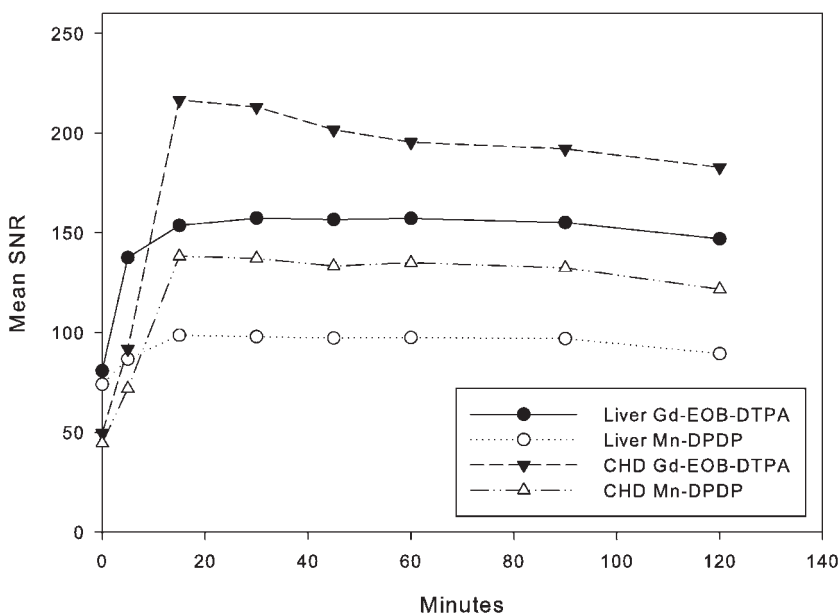


Figure 2. Mean signal-to-noise ratios (SNRs) of the common hepatic duct (CHD) and liver parenchyma. The SNRs are significantly higher for Gd-EOB-DTPA than for Mn-DPDP in liver parenchyma after 5 min and in CHD after 15 min ($p < 0.05$). Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; Mn-DPDP, mangafodipir trisodium.

Table 1. Signal-to-noise ratios for Gd-EOB-DTPA and Mn-DPDP at liver and common hepatic duct

Time	Liver		Common hepatic duct	
	Gd-EOB-DTPA	Mn-DPDP	Gd-EOB-DTPA	Mn-DPDP
Baseline	80.8 ± 14.6	74.1 ± 15.4	49.6 ± 15.7	44.5 ± 9.4
5 min	137.6 ± 19.8 ^a	86.7 ± 21.4 ^a	91.8 ± 31.2	71.9 ± 35.1
15 min	153.7 ± 26.0 ^a	98.7 ± 18.9 ^a	216.6 ± 37.0 ^a	138.2 ± 27.8 ^a
30 min	157.4 ± 32.2 ^a	97.9 ± 18.0 ^a	213.1 ± 40.2 ^a	137.2 ± 24.8 ^a
45 min	156.7 ± 29.1 ^a	97.3 ± 20.6 ^a	201.7 ± 36.6 ^a	133.3 ± 22.3 ^a
60 min	157.2 ± 28.1 ^a	97.5 ± 18.1 ^a	195.4 ± 35.9 ^a	135.0 ± 23.2 ^a
90 min	155.2 ± 30.0 ^a	97.0 ± 19.8 ^a	192.1 ± 41.3 ^a	132.4 ± 21.5 ^a
120 min	147.0 ± 30.5 ^a	89.4 ± 16.4 ^a	182.8 ± 33.8 ^a	121.7 ± 13.7 ^a

Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; Mn-DPDP, mangafodipir trisodium.

Data are mean ± standard deviation.

^a $p < 0.05$ (Wilcoxon signed rank test was used).

Mn-DPDP is a manganese chelate developed as an MR contrast agent for the hepatobiliary system. The DPDP complex is chemically related to pyridoxal phosphate, a vitamin B₆ analogue; therefore, uptake of Mn-DPDP into the hepatocytes via the vitamin B₆ pathway was expected [18]. Gd-EOB-DTPA is a paramagnetic hepatobiliary contrast agent with hepatocellular uptake via the anionic transporter protein [19, 20].

In the present study, the SNR curves of liver parenchyma and CHD showed a similar pattern between two contrast agents. But the SNRs were significantly higher for Gd-EOB-DTPA than for Mn-DPDP in liver parenchyma after 5 min and in CHD after 15 min. The shape of the CNR curve may give the impression that the CNR of Gd-EOB-DTPA exceeds that of Mn-DPDP at 15–45 min delay, but the statistical difference was noted only at 15 min.

Our results indicate that contrast-enhanced MRC using Gd-EOB-DTPA could be superior to that using Mn-DPDP at 1.5 T. This is an intriguing result, because the proportion of Gd-EOB-DTPA excreted into the biliary system is comparable to that of Mn-DPDP. Previous studies have shown that 50–60% of Mn-DPDP and 50% of Gd-EOB-DTPA were eliminated via the biliary system [11–13]; however, the T_1 relaxivity of Mn-DPDP in aqueous solution is less pronounced than that of Gd-EOB-DTPA. The value of T_1 relaxivity of Gd-EOB-DTPA

is reported as 5.301 mmol⁻¹s⁻¹ in water, and that of Mn-DPDP as 2.81 mmol⁻¹s⁻¹ in water [20, 21]. Another possible cause of the higher SNRs and CNRs observed with Gd-EOB-DTPA may be the injected dose difference between the two contrast agents at the standard dose. The administered dose of Gd-EOB-DTPA (25 µmol kg⁻¹) was five times higher than that of Mn-DPDP (5 µmol kg⁻¹).

A major limitation of the present study is the small number of volunteers. In addition, depiction of the biliary tree on contrast-enhanced MRC may show different results according to liver function, regardless of the administered contrast agents; however, only healthy volunteers with normally functioning livers were included in this study. We obtained serial images using both contrast agents, but no images were obtained more than 2 h after contrast administration. However, it has been reported that the optimal window for evaluating liver parenchyma and bile duct after injection is 15–20 min for Mn-DPDP contrast-enhanced MRC [4, 5, 22] and 20–30 min for Gd-EOB-DTPA contrast-enhanced MRC [12, 23–25]. We did not perform a qualitative analysis, and we did not evaluate whether differences in the SNRs and CNRs between the two contrast agents would affect clinical practice.

In conclusion, the biliary enhancement dynamics to liver parenchyma of Gd-EOB-DTPA differed from that of

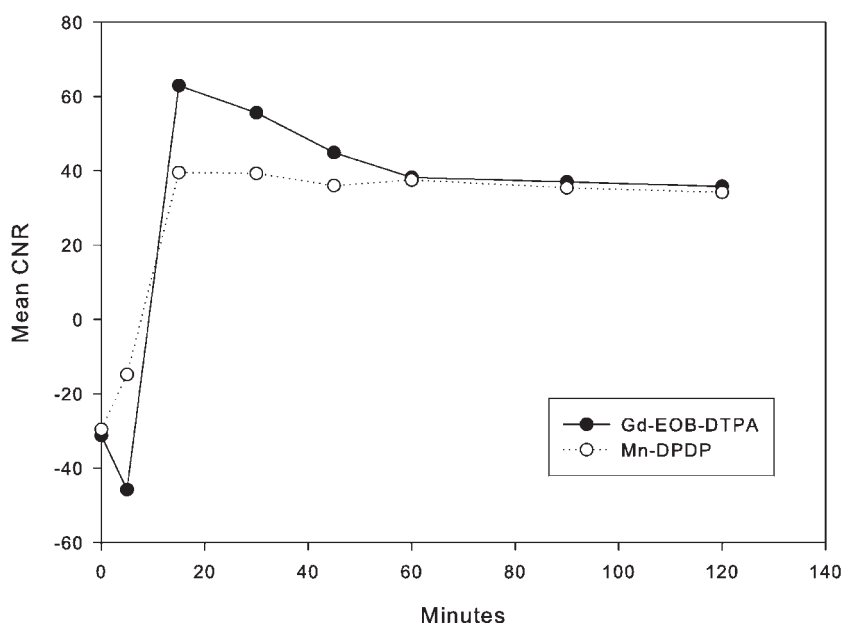


Figure 3. Mean contrast-to-noise ratios (CNRs) of common hepatic duct to liver parenchyma. The CNR of Gd-EOB-DTPA shows an initial decline and then steep increase to a peak at 15 min, whereas the CNR of Mn-DPDP shows a steady increase to a peak at 15 min. At a peak (15 min) the CNR of the Gd-EOB-DTPA is significantly higher than that of Mn-DPDP ($p < 0.05$). Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; Mn-DPDP, mangafodipir trisodium.

Table 2. Contrast-to-noise ratios for Gd-EOB-DTPA and Mn-DPDP

Time	Contrast agent	
	Gd-EOB-DTPA	Mn-DPDP
Baseline	-31.2 ± 16.4	-29.6 ± 13.2
5 min	-45.8 ± 22.8	-14.8 ± 30.7
15 min	62.9 ± 20.3 ^a	39.5 ± 15.6 ^a
30 min	55.6 ± 23.2	39.3 ± 21.0
45 min	44.9 ± 20.1	36.0 ± 16.6
60 min	38.2 ± 19.1	37.5 ± 19.3
90 min	37.0 ± 19.1	35.4 ± 17.3
120 min	35.8 ± 22.0	34.2 ± 15.0

Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid; Mn-DPDP, mangafodipir trisodium.

Data are mean ± standard deviation.

^a*p* < 0.05 (Wilcoxon signed rank test was used).

Mn-DPDP in healthy volunteers. CNR of Gd-EOB-DTPA showed an initial decline and then a steep increase to a peak at 15 min. However, CNR of Mn-DPDP showed a steady increase to a peak at 15 min. At 15 min, the value of CNR was significantly higher for Gd-EOB-DTPA than for Mn-DPDP. Therefore, contrast-enhanced MRC using Gd-EOB-DTPA may provide more adequate images than that of Mn-DPDP at 15 min after contrast administration.

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