Intraindividual Crossover Comparison of Gadoxetic Acid Dose for Liver MRI in Normal Volunteers

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Purpose: We performed a quantitative intraindividual comparison of the performance of 0.025- and 0.05-mmol/kg doses for gadoxetic acid-enhanced liver magnetic resonance (MR) imaging.

Materials and Methods: Eleven healthy volunteers underwent liver MR imaging twice, once with a 0.025- and once with a 0.05-mmol/kg dose of gadoxetic acid. MR spectroscopy and 3-dimensional gradient-echo T1-weighted images (3D-GRE) were obtained before and 3, 10, and 20 min after injection of the contrast medium to measure T1 and T2 values and signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) performance. During the dynamic phase, highly time-resolved 3D-GRE was used to estimate the relative CNR (CNRrel) of the hepatic artery and portal vein (PV) to the liver. We used paired t-tests to compare the results of different doses.

Results: During the hepatobiliary phase, we observed shorter T1 values and higher SNRs of the liver ($P < 0.001$) and higher liver-to-PV and liver-to-muscle CNRs ($P < 0.002$) using 0.05 mmol/kg compared to 0.025 mmol/kg. Increasing the dose to 0.05 mmol/kg yielded a greater T1-shortening effect at 10 min delay even compared with 0.025 mmol/kg at 20 min ($P < 0.001$). During the dynamic phase, the peak CNRrel for the hepatic artery and portal vein were higher using 0.05 mmol/kg ($P = 0.007$ to 0.035).

Conclusion: Use of gadoxetic acid at a dose of 0.05 mmol/kg leads to significantly higher SNR and CNR performance than with 0.025 mmol/kg. Quantitatively, a 10-min delay may be feasible for hepatobiliary-phase imaging when using 0.05 mmol/kg of gadoxetic acid.

Keywords: gadoxetic acid, liver, magnetic resonance imaging, relaxometry, spectroscopy

Introduction

Gadoxetic acid is a gadolinium-based contrast agent used primarily for hepatobiliary imaging applications, and it is now widely accepted as a primary contrast agent in magnetic resonance (MR) imaging of the liver.1,2 Its pharmacokinetics is similar to that of extracellular contrast agents immediately after bolus injection; it is taken up rapidly into hepatocytes and subsequently excreted into bile. Recent studies have demonstrated important advantages of gadoxetic acid-enhanced MR imaging over other methods for imaging liver disease.3–6

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Typically, maximum liver-to-lesion contrast is obtained in the hepatobiliary phase, approximately 20 min after injection, and good liver-to-lesion contrast persists about 2 to 3 hours. In the hepatobiliary phase, normal liver and bile appear hyperintense from the presence of gadolinium, whereas blood vessels and focal liver lesions appear hypointense. This contrast enables detection of even very small hepatic metastases or hepatocellular carcinoma as hypointense lesions in bright liver tissue. The use of hepatobiliary-phase images for the evaluation of hepatic function has also been suggested.

The approved package insert dose of gadoxetic acid, 0.025 mmol/kg, yields a quarter of the dose of gadolinium of traditional formulation agents, including gadopentetate dimeglumine, gadoteridol, gadomiamide, gadoversetamide, and gadobenate dimeglumine. This dose was determined based on preclinical studies that demonstrated comparable early enhancement of hypervascular tumors between MRI with a 0.025 mmol/kg dose showed comparable early enhancement of hypervascular tumors to gadopentetate dimeglumine. A dose of 0.025 mmol/kg was also found to be the minimum effective dose during the hepatobiliary phase for the detection and characterization of lesions. However, the imaging sequences used in these studies (both published in 1996) are no longer routinely used in clinical MR imaging. In fact, many institutions have adopted the use of higher doses, such as a fixed dose of 10 mL rather than a dose based on patient weight, as a standard in clinical MR imaging. For patients weighing 50 to 100 kg, this results in effective doses of 0.025 to 0.05 mmol/kg. Considering that a dose of 0.025 mmol/kg of gadolinium is only a quarter of the conventional MR contrast agent dose, the expected risk of toxicity from dose escalation is likely to be minimal.

The growing use of doses that exceed the package insert dose motivated a systematic re-evaluation of higher dosing of gadoxetic acid when used with state-of-the-art MR imaging sequences. Greater arterial and tumor enhancement in the early dynamic phase is expected using a higher dose of 0.05 mmol/kg than the 0.025 mmol/kg, and this may improve the detection and characterization of small enhancing liver lesions. Moreover, a recent study demonstrated improved clinical performance of gadoxetic acid at a dose of 0.05 mmol/kg compared to 0.025 mmol/kg for both dynamic- and hepatobiliary-phase imaging in patients with cirrhosis.

The purpose of this crossover study was to perform a systematic and objective comparison of doses of 0.025 mmol/kg and 0.05 mmol/kg of gadoxetic acid in healthy volunteers. We compared the doses in both the dynamic and hepatobiliary phases using state-of-the-art pulse sequences and included measurements of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). Further, we used MR spectroscopy-based relaxometry to measure the fundamental relaxation parameters of the liver after the administration of the contrast medium to facilitate optimization of future acquisition strategies.

Materials and Methods

Subjects

This prospective crossover study complied with Health Insurance Portability and Accountability Act (HIPAA) requirements and was approved by our institutional review board (IRB). We recruited 11 healthy subjects (4 men, 7 women; aged 23 to 64 years, mean, 38 ± 15 years; weight 54 to 91 kg, mean 70 ± 13 kg) from a local IRB-approved database of healthy volunteers and obtained their written informed consent prior to scans. We screened all volunteers to confirm they had no liver or renal disease.

The SNR and CNR measurements performed for hepatobiliary-phase images at 20 min after injection of 0.025 mmol/kg of gadoxetic acid in this study (see below) have also been used in a separate unrelated study. However, the comparison between 2 doses of gadoxetic acid has not been previously investigated in these subjects.

Study protocol and contrast agent

This crossover study comprised 2 visits separated by more than 4 weeks (28 to 76 days, mean 57 days). At the first visit, gadoxetic acid-enhanced liver MR imaging was performed using 0.025 mmol/kg (0.1 mL/kg) of gadoxetic acid (Eovist®, Bayer Healthcare). At the second visit, the same imaging protocol was repeated using a dose of 0.05 mmol/kg (0.2 mL/kg). The 0.025 mmol/kg dose was diluted 1:1 with saline (0.9% NaCl) to ensure injection of the same volume as for the 0.05 mmol/kg dose (off-label use for the study). Injections were performed using a power injector (Spectris Solaris®, MedRad®, Inc., Warrendale, PA, USA) at 2 mL/s by means of a 20-gauge antecubital intravenous catheter followed by a 20-mL saline chaser at the same injection rate. The volume and injection rate for each protocol were the same to ensure accurate comparisons of the time to peak enhancement as well as enhancement during the dynamic phase.
**MR scanner**

All imaging was performed on a clinical 3-tesla MR system (MR750, v23, GE Healthcare, Waukesha, WI, USA) using a 32-channel phased-array abdominal coil (Neocoil, Pewaukee, WI, USA).

**MR spectroscopy-based relaxometry**

MRS was performed before and 3, 10, and 20 min after the injection of gadobenate dimeglumine to measure liver T1 and T2 values. A single-voxel stimulated echo acquisition mode (STEAM) MRS sequence was acquired in a single 21-s breath-hold. This STEAM sequence used varying repetition times (TRs; 150 to 1000 ms) to enable calculation of the T1 value of the object. Multiple echo times (TEs; 10 to 110 ms) were also acquired to measure T2 values of the object. These multiple acquisitions (multi TR and multi TE) were completed within a single breath-hold to enable independent measurement of the T1 and T2 of water and fat (if present). The MRS voxel was 20 × 20 × 20 mm³ and was placed in the right lobe (segments 6 or 7) of each subject, avoiding large blood vessels or bile ducts. Other acquisition parameters included: receiver bandwidth, ± 2500 Hz; number of acquired points, 256; total number of spectra acquired, 32 (including 4 prepulse excitations to reach steady state).

**MR imaging**

A 3-dimensional (3D) T1-weighted MR sequence was used before and 3, 10, and 20 min after contrast injection using parameters: breath-hold T1-weighted 3D spoiled gradient-echo (SPGR) sequence with dual-echo chemical shift-encoded water-fat separation, TR, 5.5 ms; TE1, 1.15 ms; TE2, 2.3 ms; bandwidth, ± 63 kHz; slab volume, 40 cm (right to left [R/L]) × 32 cm (anterior to posterior [A/P]) × 24 cm (superior to inferior [S/I]); matrix, 224 × 140 × 48; 15° flip angle; and partial k_z (0.75) acquisition for true spatial resolution of 1.8 × 2.9 × 5.0 mm³ (interpolated to 1.1 × 1.8 × 2.5 mm³ through zero-filling). Scan time was 23 s. No parallel imaging or B0 sensitivity correction was performed to avoid spatially heterogeneous noise distributions and allow for absolute SNR measurements.

After the above-mentioned scans were performed using a fixed flip angle of 15°, the acquisition was repeated with flip angles from 10° to 50° at 5° increments to determine the optimal flip angle to maximize contrast between liver and muscle and between liver and the PV. To ensure that any observed signal differences were due to flip angle rather than slowly varying changes of the gadolinium concentration in the liver, we reversed the flip angle order in 6 of the 11 volunteers.

To determine the effects of dose on enhancement during the dynamic phase, we used a highly time-resolved T1-weighted 3D SPGR sequence. High spatial and temporal resolution were achieved using interleaved variable density (IVD) undersampling, k-space corner-cutting, and data-driven parallel imaging. Autocalibration signal (ACS) lines were acquired at the center of the k-space only in the first time frame and then used for all 10 subsequent time frames acquired in the same breath-hold. Fat suppression was achieved using a dual-echo chemical shift-encoded water-fat separation.

Imaging parameters for the dynamic IVD sequence included: TR, 3.9 ms; TE1, 1.2 ms; TE2, 2.3 ms; bandwidth, ± 166.7 kHz; slab volume, 38 cm (R/L) × 34 cm (A/P) × 26 cm (S/I) matrix, 320 × 202 × 100, 15° flip angle; and partial k_z (0.75) acquisition, R = 2 × 2 data-driven parallel imaging acceleration (autocalibrating reconstruction for Cartesian imaging [ARC], GE Healthcare), for true spatial resolution of 1.2 × 1.7 × 2.6 mm³ (interpolated to 0.74 × 0.74 × 1.3 mm³ through zero-filling). Scan time was 24 s for 11 time frames with a temporal resolution of ~2 s.

After obtaining the precontrast scan, dynamic-phase imaging was performed with the same prescan values to facilitate relative CNR calculations. The scan delay was fixed at 13 s after the beginning of the gadobenate dimeglumine injection.

**Data processing and analysis**

Quantification of the STEAM datasets was performed using a custom script developed in Matlab (The Mathworks, Inc., Natick, MA, USA). The processing script performed joint fitting of all 28 spectra acquired with different TRs and TEs by accounting for T2 decay and T1 recovery. Each spectrum was fitted using Voigt line shapes and assuming a single peak for water signals and 6 peaks for fat signals. This processing resulted in estimates of water and fat T1 and T2 values as well as proton-density fat-fraction (PDFF) of the liver.

In addition, we calculated the estimated concentration of gadobenate dimeglumine in the liver

\[
\frac{1}{T1_{Post}} = C \cdot r_1 + \frac{1}{T1_{Pre}},
\]

in which c (mM) is the estimated concentration of gadobenate dimeglumine in the liver; T1_{Pre} and T1_{Post} are the measured T1 values of the liver before and after contrast injection; and r1 is the relaxivity of gadobenate dimeglumine. The longitudinal relaxivity, r1, is dependent on field strength and tissue type. However, no available reports describe the r1 of the human liver at 3T. Previous studies reported \( r_1 = 16.6 \)
identical positions in images obtained at different time points or with different flip angles, and placed all ROIs equidistant to the anterior and posterior coils to account for the higher coil sensitivity for tissue closer to the coils. We placed ROI sw ered to minimize the effect of signal variations, and started all subjects with the liver parenchyma (liver-to-portal vein and liver-to-muscle CNR). The CNR was calculated as the difference in SNR between the liver and the tissue of interest:

\[ CNR = SNR_{liver} - SNR_{tissue}. \]

We measured signals of MR images offline using open-source DICOM viewer software (OsiriX v. 5.8, Pixmeo, Geneva, Switzerland). A board-certified radiologist with fellowship training in abdominal MR imaging and 6 years of experience in diagnostic imaging drew regions of interest (ROI) in specific tissues of interest, copying the ROIs to identical positions in images obtained at different time points or with different flip angles. Slight manual corrections were made to ensure proper alignment with the relevant anatomy in the cases in which misregistration occurred from variability in breath-hold position. ROIs were placed in the liver (2 ROIs), muscle, and portal vein and in an artifact-free area outside the body. We used muscle as a surrogate for weakly enhancing liver lesions such as hypovascular metastasis. 

We used the following equations to calculate the SNR of the liver, portal vein, and muscle:

\[ SNR = \frac{SI_{tissue}}{SD_{air}} \times 0.7049, \]

in which \( SI_{tissue} \) is the average of signal intensity in tissues of interest and \( SD_{air} \) is the standard deviation of the signal of air measured in areas outside the body not compromised by artifacts. We used a correction factor of 0.7049 to account for differences in the behavior of the noise variance in the background region in magnitude images acquired with multi-channel coils. We calculated the CNR to compare the contrast between the portal vein and muscle with the liver parenchyma (liver-to-portal vein and liver-to-muscle CNR). The CNR was calculated as the difference in SNR between the liver and the tissue of interest:

\[ CNR = SNR_{liver} - SNR_{tissue}. \]

We placed ROIs in the hepatic artery, portal vein, and liver (2 ROIs) to evaluate the performance of the time-resolved IVD scan during the dynamic phase, used the average signal of the 2 liver ROIs in all subjects to minimize the effect of signal variations, and placed all ROIs equidistant to the anterior and posterior coils to account for the higher coil sensitivity for tissue closer to the coils. We measured the performance of the relative CNR (CNR_{rel}) in the dynamic phase of gadoxetic acid to determine the impact of contrast dose during the dynamic phase using:

\[ CNR_{rel} = \frac{SI_{vessels} - SI_{liver}}{SI_{Precontrast \, liver}}, \]

in which \( SI_{vessels} \) is the signal intensity of the portal vein and hepatic artery and \( SI_{liver} \) is that of the liver during the dynamic phase. \( SI_{Precontrast \, liver} \) is the signal intensity of the liver before contrast injection. Relative CNR was used to evaluate the performance of the time-resolved acquisition because accurate absolute SNR and CNR measurements are not possible when using parallel imaging. 

\textbf{Statistical analysis}

All data are presented as the mean with 95% confidence intervals (95%CI) in all plots. We used paired t-test with Bonferroni correction to compare post-contrast (3, 10, and 20 min) T1 and T2 values of the liver with those values prior to contrast administration and paired t-tests to compare T1 values of the liver, estimated contrast agent concentration in the liver, and SNR, CNR, and CNR_{rel} of 0.025- and 0.05-mmol/kg doses at each time point. We also used paired t-test to compare measurements with a dose of a 0.05 mmol/kg at a 10-min delay to measurements with a dose of 0.025 mmol/kg at a 20-min delay to explore the potential advantage of a higher dose for shortening the total scan time. A 2-sided t-test with \( P \) value less than 0.05 was considered statistically significant. All statistical tests were performed using Microsoft Excel 2010.

\textbf{Results}

\( T_1 \) and \( T_2 \) value and signal alteration at 3-, 10-, and 20-min delays

After injection of gadoxetic acid, the \( T_1 \) values decreased significantly (\( P < 0.001 \)) from \( \approx1000 \text{ ms} \) before contrast administration to 284 ms with 0.025 mmol/kg and 220 ms with 0.05 mmol/kg. We observed significant changes in the \( T_1 \) value of the liver even 3 min after injection. The mean (95% CI) \( T_1 \) values were significantly lower for 0.05 mmol/kg than for 0.025 mmol/kg at all time points after injection of gadoxetic acid (all \( P < 0.001 \)) (Fig. 1a). The mean (95% CI) \( T_1 \) values of the 0.05-mmol/kg dose compared to the 0.025-mmol/kg dose were: 293 ms (263–323 ms) versus 376 ms (344–408 ms) at 3 min; 248 ms (223–272 ms) versus 326 ms (297–356 ms) at 10 min; and 220 ms (199–241 ms) versus 284 ms (258–311 ms) at 20 min. Figure 1b shows the corresponding estimated concentrations of gadoxetic acid in the liver.

The average of the precontrast \( T_1 \) values over all subjects was slightly lower, although not significantly, between the first and second scans (1063 ±
171 ms versus 997 ± 159 ms, \( P = 0.08 \)). This initially suggested that a very small amount of contrast may have remained in the liver in some subjects. For this reason, we plotted the precontrast T1 values in Fig. 2. As the figure shows, precontrast T1 values were lower for the first scan in half \((n = 5)\) of the subjects and for the second scan in the other half \((n = 6)\). However, we observed a relatively large difference in 2 subjects with lower T1 values at the second scan that led to an overall decrease in the average of the precontrast T1 values between the 2 scans. The intervals of the 2 examinations in the 2 subjects were 28 and 69 days.

Interestingly, the T1 measured in enhanced liver tissue using 0.05 mmol/kg at 10 min was significantly shorter than that for 0.025 mmol/kg at 20 min \(( P < 0.01)\). The estimated concentration of gadoxetic acid in the liver was also significantly higher using 0.05 mmol/kg at all time points. The estimated concentration of the contrast agent was calculated using the measured T1 values of the liver and known \( r_1 \) value in the liver of rats at 0.47T (16.6 mM–1·s−1). The graphs show mean values with 95% confidence intervals.

**SNR performance in the hepatobiliary phase**

The SNR of the liver during the hepatobiliary phase was significantly higher using 0.05 mmol/kg compared to 0.025 mmol/kg at all time points \(( P < 0.001; \text{Figs. 3, 4})\). The SNR in the portal vein was also significantly higher using a 0.05-mmol/kg dose at 3 and 10 min \(( P < 0.001)\) and at 20 min \(( P = 0.006)\). There was no significant difference between the 2 doses for the SNR of muscle \(( P = 0.581 \text{ to } 0.761)\). The CNR of the liver relative to the portal vein was significantly higher using 0.05 mmol/kg than 0.025 mmol/kg \(( P = 0.002 \text{ at } 3 \text{ min}; P < 0.001 \text{ at } 10 \text{ and } 20 \text{ min})\), and the CNR of the liver relative to muscle was significantly higher for 0.05 mmol/kg than 0.025 mmol/kg at all time points \(( P < 0.001)\).

As observed with the T1 measurements, the SNR of the liver \(( P = 0.002, \text{Fig. 4})\) and CNR of the liver relative to muscle \(( P = 0.006, \text{Fig. 4b})\) were also significantly higher at 10 min using 0.05 mmol/kg than at 20 min using 0.025 mmol/kg, whereas no significant difference was observed in the CNR of

![Fig. 1. T2 values measured from magnetic resonance (MR) spectroscopy were slightly, though significantly \(( P < 0.001)\), shorter after than before contrast administration for both doses. After contrast administration, T1 values were significantly shorter with 0.05 mmol/kg than 0.025 mmol/kg at all time points \((3, 10, \text{and } 20 \text{ min}, P < 0.01)\), but T2 values were not \(( P = 0.112 \text{ to } 0.183)\). Estimated concentrations of the contrast agent in the liver were also significantly higher using 0.05 mmol/kg at all time points. The estimated concentration of the contrast agent was calculated using the measured T1 values of the liver and known \( r_1 \) value in the liver of rats at 0.47T (16.6 mM–1·s−1). The graphs show mean values with 95% confidence intervals.](image-url)
We observed a small but insignificant difference between the average of precontrast T1 values (1063 ± 171 ms versus 997 ± 159 ms, \( P = 0.08 \)) between the first and second scans despite a relatively long washout period between scans (28 to 76 days, average 57 days). This initially suggested that a very small amount of contrast medium may have remained in the liver of some subjects. However, the change between precontrast T1 values in the subjects was highly variable and not related to the number of days between 2 scans. The relatively larger apparent change in T1 values of 2 subjects may have skewed the average.

Representative 3-dimensional (3D) gradient-echo T1-weighted images of the liver in a 32-year-old woman obtained 3, 10, and 20 min after injection of gadoxetic acid at 0.05 mmol/kg (bottom) and 0.025 mmol/kg (top). All images are shown with the same window width and window level. Images with a dose of 0.05 mmol/kg show higher signal-to-noise (SNR) and contrast-to-noise (CNR) ratios than those with 0.025 mmol/kg at every time point. Note: The CNR at 10 min using 0.05 mmol/kg was higher than that at 20 min with 0.025 mmol/kg. The CNR of the liver to portal vein (Liver-PV) and liver to muscle (Liver-muscle) are shown in the right bottom of each image.
the liver relative to the portal vein ($P = 0.751$, Fig. 4a).

**Flip angle optimization in the hepatobiliary phase**

The SNRs in the portal vein and muscle were highest with the lowest flip angle (10$^\circ$) for both doses, whereas the SNR in the liver was highest at 15$^\circ$ for the 0.025-mmol/kg dose and at 20$^\circ$ for the 0.05-mmol/kg dose (Figs. 5, 6). The CNR of the liver to the portal vein was highest at a flip angle of 20$^\circ$ for both doses, 0.025 mmol/kg (mean [SD], 168 ± 32) and 0.05 mmol/kg (232 ± 31). The CNR of the liver to muscle was also the highest at 20$^\circ$ for both doses, 0.025 mmol/kg (174 ± 25) and 0.05 mmol/kg (262 ± 25) (Fig. 6).

Comparing the 2 doses, the CNRs of both the liver to the portal vein and the liver to muscle were significantly higher using the 0.05-mmol/kg dose.
Our results indicate that increasing the dose of gadoxetic acid significantly reduces the T1 value of the liver and increases the SNR of the liver and CNR of the liver relative to the portal vein and muscle during the hepatobiliary phase. During the dynamic phase, enhancement was significantly higher in both the hepatic artery and portal vein with the 0.05-mmol/kg dose than with 0.025 mmol/kg. Further, we determined 20° as the optimal flip angle to maximize the CNR of the liver versus the portal vein/muscle for either dose protocol.

We also demonstrated that using the 0.05-mmol/kg dose of gadoxetic acid, the T1 value of the liver at 10 min was shorter than that using 0.025 mmol/kg at 20 min. The CNR between the liver and muscle using 0.05 mmol/kg at 10 min was also higher than that using 0.025 mmol/kg at 20 min. Interestingly, the T2 values of the liver during the hepatobiliary phase were only minimally (albeit statistically significantly) affected by gadoxetic acid in general and not affected by increasing the gadolinium dose. Several researchers have suggested that T2-weighted imaging can be performed after gadoxetic acid injection, before the 20-min hepatobiliary as a means to shorten the overall protocol time.36–39 Our T2 measurements confirm that T2-weighted imaging after the injection of gadoxetic acid at either 0.025 or 0.05 mmol/kg should have minimal impact on T2 contrast and can be used to shorten the overall protocol time.

Contrast enhancement of the vessels in the dynamic phase

During the dynamic phase, the CNRrel of the hepatic artery to the liver was significantly higher using 0.05 mmol/kg compared to 0.025 mmol/kg at a 17- to 25-s delay, whereas the CNRrel of the portal vein to the liver was highest at a 27- to 35-s delay (Fig. 7). These data show the significant increase of peak enhancement in both the hepatic artery and portal vein with 0.05 mmol/kg ($P < 0.035$) (Fig. 8).

Discussion

In this work, we have performed a systematic and objective comparison of 0.025-mmol/kg and 0.05-mmol/kg doses of gadoxetic acid as part of an intra-individual crossover study. Specifically, we performed MR relaxometry to measure both T1 and T2 values in the liver after the injection of the different doses of gadoxetic acid. Further, we quantified a significant improvement in SNR and CNR performance during both the dynamic and hepatobiliary phases by increasing the dose from 0.025 mmol/kg to 0.05 mmol/kg. We also performed flip angle optimization to determine the T1 weighting that maximizes SNR and CNR performance in the hepatobiliary phase for both contrast doses.
Enhancement of the vessels during the dynamic phase typically depends upon the concentration of the contrast agent in the vessels, which is affected by both dose and injection speed.\textsuperscript{40,41} The recommended dose of gadoxetic acid, 0.025 mmol/kg, and injection speed, $\bar{2}$ mL/s,\textsuperscript{42} would result in lower intravascular gadolinium concentration during the dynamic phase than that obtained with conventional gadolinium-based contrast agents, which are typically administered with a dose of 0.1 mmol/kg at $\sim$2 mL/s.\textsuperscript{43} Even considering the higher $r_1$ value effect with gadoxetic acid, the contrast effect is less with 0.025 mmol/kg of gadoxetic acid than that obtained with conventional gadolinium-based
contrast agents. Emerging evidence also demonstrates that 0.025 mmol/kg may be an insufficient dose for dynamic-phase imaging. Therefore, some radiologists prefer to use an undiluted fixed dose of 10 mL of gadoxetic acid independent of the patient’s weight and thereby often exceed the recommended package insert dose. As expected, we observed significantly greater arterial and portal enhancement in the early dynamic phase using a higher dose, which may support the use of doses exceeding 0.025 mmol/kg in clinical practice.

During the hepatobiliary phase, however, the impact of higher doses for liver-to-vessel and liver-to-lesion contrast have been controversial. A recent intraindividual comparison of 0.025 and 0.05 mmol/kg in patients with cirrhosis suggested significant improvement of liver-to-lesion (hepatocellular carcinoma) contrast in patients with decreased hepatic function (Child-Pugh class B disease) but not in patients with preserved hepatic function (Child-Pugh class A disease). A study performed in the early stages of gadoxetic acid development also showed that liver-to-lesion contrast during the hepatobiliary phase was not necessarily higher using 0.05 compared with 0.025 mmol/kg, although the degree of enhancement compared to precontrast images was consistently higher using 0.05 mmol/kg.

Our estimates of gadoxetic acid concentration in the liver during the hepatobiliary phase (Fig. 1b) demonstrated that using 0.05 mmol/kg significantly increased but did not double the intrahepatic concentration. This can be explained by the ability of the hepatocytes to take up gadoxetic acid; according to Michaelis-Menten kinetics, a higher concentration of contrast agents results in their slower uptake ratio due to the limitation of receptor ability. This speculation is complicated by the increased renal excretion that would be expected with higher contrast doses, but it is supported by the higher SNR of the portal vein with a higher dose. Additionally, we have demonstrated that the use of greater flip angles can improve SNR and CNR performance. It is possible that the previous study could not demonstrate a difference in lesion-to-liver CNRs between 0.025- and 0.05-mmol/kg doses because we used a suboptimal flip angle (12°). Further, the difference in results between the previous and current studies can be explained by the homogeneity of the study subjects; in this study, we assessed volunteers and not patients with cirrhosis and muscle rather than liver lesions as the object.

Acquisition of reliable hepatobiliary-phase images by gadoxetic acid-enhanced MR imaging requires a delay of approximately 20 min after the administration of the contrast medium. To shorten the total protocol time, some researchers have suggested the equivalent diagnostic ability for the detection of liver lesions of hepatobiliary-phase images obtained after 10 min. Despite the comparable results of visual assessment, quantitative results have shown lower contrast between the liver and lesion at 10 than 20 min. Our results suggest that the use of 0.05 mmol/kg resulted in higher SNR and CNR at 10 min than did 0.025 mmol/kg at 20 min. Considering these results, the use of a 10-min delay with an increased dose of gadoxetic acid can be justified both quantitatively and qualitatively. Shortening the overall protocol time may at least partially mitigate the increased cost of using a higher contrast dose.

This study had several limitations. First, our subjects were all healthy volunteers without liver disease. Because the pharmacokinetics of gadoxetic acid could be different in patients, especially those with cirrhosis, the clinical utility of 0.05 mmol/kg compared to 0.025 mmol/kg should be further evaluated in patients with focal liver lesions and/or diffuse liver disease. However, before studying patients with disease, it is important to optimize acquisition parameters and measure the range of normal relaxometry values in normal subjects.

An additional limitation is that we used the signal intensity of muscle as a surrogate for that of hypovascular intrahepatic lesions like metastases from colorectal carcinoma. According to this assumption, the advantage of a 0.05-mmol/kg over 0.025-mmol/kg dose was quantitatively obvious. However, we cannot conclude a definitive advantage of the 0.05-mmol/kg dose of gadoxetic acid until the diagnostic ability of the 2 doses is compared in patients with focal liver lesions.

Further, during the dynamic phase, we employed high temporal resolution (2 s) to show the time-to-intensity curve of each vessel. This sequence was well validated in previous studies. However, the view-sharing technique used in this sequence can introduce temporal blurring that can affect signal measurement. Nevertheless, we believe that the relative signal intensity among the phases within a single scan offers a reasonable comparison.

Estimation of the concentration in the liver has important limitations. The longitudinal relaxivity \( r_1 \) of a contrast agent may vary between different field strengths, solvents, or tissues. The resulting concentration estimates in our study were calculated assuming the known \( r_1 \) in the liver of rats at 0.47T, which may lead to inaccurate estimates of concentration in the human liver at 3T. In any case, the relative estimates of concentration remain meaningful because the \( r_1 \) value is a simple scaling co-
Finally, the order of injection of the 2 different doses of gadoxetic acid was the same in all subjects, 0.025 mmol/kg followed by 0.05 mmol/kg a month or more later. Although precontrast T₁ values did not differ significantly between the 2 doses of gadoxetic acid, that of the second scan (0.05 mmol/kg) was slightly lower than that of the first (Fig. 1). If we assume that the precontrast liver at the first scan had 0 mM of gadoxetic acid, the estimated residual concentration of gadoxetic acid in the liver at the second scan would be approximately 0.004 ± 0.007 mM, assuming \( T₁ = 16.6 \text{mM}^{-1}\text{s}^{-1} \). Considering the estimated concentration of gadoxetic acid in the liver between the 2 doses at 3 min (0.025 and 0.05 mmol/kg, 0.10 and 0.14 mM), 10 min (0.13 and 0.19 mM), and 20 min (0.16 and 0.22 mM), the effect of the precontrast T₁ value is probably not very important. Furthermore, previous research suggests that residual gadoxetic acid in the liver 7 days after administration was ~0.17% of the total dose for rats and 0.28 to 0.52% of the total dose for monkeys.³³ Those findings indicate that the effect of residual contrast in the liver at 4 weeks should be minimal compared to the further T₁ shortening effect achieved by doubling (200%) the dose.

In conclusion, our study has demonstrated that 0.05 mmol/kg of gadoxetic acid for hepatobiliary-phase MR imaging yields shorter T₁ values, higher SNR of the liver, and higher CNR of the liver relative to the portal vein and muscle than those with 0.025 mmol/kg. The higher dose also results in higher arterial and portal venous enhancement during the dynamic phase. These quantitative results also support the use of gadoxetic acid-enhanced hepatobiliary-phase images at 10 min instead of 20 min when using a 0.05-mmol/kg dose. Further work is needed to confirm these results in patients with diffuse liver disease and focal liver lesions.

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References

1. Okigawa T, Utsunomiya D, Tajiri S, et al. Incidence and severity of acute adverse reactions to four different gadolinium-based MR contrast agents. Magn Reson Med Sci 2014; 13:1–6.
2. Frydrychowicz A, Lubner MG, Brown JJ, et al. Hepatobiliary MR imaging with gadolinium-based contrast agents. J Magn Reson Imaging 2012; 35:492–511.
3. Zech CJ, Bartolozzi C, Bioulac-Sage P, et al. Consensus report of the Fifth International Forum for Liver MRI. AJR Am J Roentgenol 2013; 201:97–107.
4. Park MJ, Kim YK, Lee MW, et al. Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. Radiology 2012; 264:761–770.
5. Kim YK, Lee MW, Lee WJ, et al. Diagnostic accuracy and sensitivity of diffusion-weighted and of gadoxetic acid-enhanced 3-T MR imaging alone or in combination in the detection of small liver metastasis (≤1.5 cm in diameter). Invest Radiol 2012; 47:159–166.
6. Grazioli L, Bondioni MP, Haradome H, et al. Hepatocellular adenoma and focal nodular hyperplasia: value of gadoxetic acid-enhanced MR imaging in differential diagnosis. Radiology 2012; 262:520–529.
7. Nagle SK, Busse RF, Brau AC, et al. High resolution navigated three-dimensional T₁-weighted hepatobiliary MRI using gadoxetic acid optimized for 1.5 Tesla. J Magn Reson Imaging 2012; 36:890–899.
8. Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: what to expect? J Hepatol 2012; 57:421–429.
9. Motosugi U, Ichikawa T, Araki T. Rules, roles, and room for discussion in gadoxetic acid-enhanced magnetic resonance liver imaging: current knowledge and future challenges. Magn Reson Med Sci 2013; 12:161–175.
10. Motosugi U, Bannas P, Sano K, Reeder SB. Hepatobiliary MR contrast agents in hypovascular hepatocellular carcinoma. J Magn Reson Imaging 2015; 41: 251–265.
11. Joishi D, Ueno A, Tanimoto A, et al. Natural course of hypovascular nodules detected on gadoxetic acid-enhanced MR imaging: presence of fat is a risk factor for hypervascularization. Magn Reson Med Sci 2013; 12:281–287.
12. Motosugi U, Ichikawa T, Morisaka H, et al. Detection of pancreatic carcinoma and liver metastases with gadoxetic acid-enhanced MR imaging: comparison with contrast-enhanced multi-detector row CT. Radiology 2011; 260:446–453.
13. Goshima S, Kanematsu M, Watanabe H, et al. Gd-EOB-DTPA-enhanced MR imaging: prediction of hepatic fibrosis stages using liver contrast enhancement index and liver-to-spleen volumetric ratio. J Magn Reson Imaging 2012; 36:1148–1153.
14. Yamada A, Hara T, Li F, et al. Quantitative evaluation of liver function with use of gadoxetate disodium-enhanced MR imaging. Radiology 2011; 260: 727–733.
15. Reeder SB. Gadolinium-based contrast agents: What
does “single-dose” mean anymore? J Magn Reson Imaging 2014; 39:1343–1345.

16. Vogl TJ, Kümmel S, Hammerstingl R, et al. Liver tumors: comparison of MR imaging with Gd-EOB-DTPA and Gd-DTPA. Radiology 1996; 200:59–67.

17. Reimer P, Rummeny EJ, Shamsi K, et al. Phase II clinical evaluation of Gd-EOB-DTPA: dose, safety aspects, and pulse sequence. Radiology 1996; 199:177–183.

18. Frydrychowicz A, Nagle SK, D’Souza SL, Vigen KK, Reeder SB. Optimized high-resolution contrast-enhanced hepatobiliary imaging at 3 tesla: a cross-over comparison of gadobenate dimeglumine and gadoxetic acid. J Magn Reson Imaging 2011; 34:585–594.

19. Choi JW, Lee JM, Kim SJ, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR Images and their value as an imaging biomarker. Radiology 2013; 267:776–786.

20. Pietryga JA, Burke LM, Marin D, Jaffe TA, Bashir MR. Respiratory motion artifact affecting hepatic arterial phase imaging with gadoxetate disodium: examination recovery with a multiple arterial phase acquisition. Radiol 2014; 271:426–434.

21. Motosugi U, Ichikawa T, Sano K, et al. Double-dose gadoxetic acid-enhanced magnetic resonance imaging in patients with chronic liver disease. Invest Radiol 2011; 46:141–145.

22. Bannas P, Motosugi U, Hernando D, Rahimi MS, Holmes JH, Reeder SB. Combined gadoxetic acid and gadofosveset enhanced liver MRI: a feasibility and parameter optimization study. Magn Reson Med 2015 Feb 3; doi:10.1002/mrm.25554. [Epub ahead of print]

23. Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. Radiology 2010; 256:32–61.

24. Hamilton G, Middleton M, Sirlin C. In vivo liver 1H MRS measurement of PDF and T1 and T2 of water and fat, in a single breath-hold with multiple TRs and TEs. Proceedings of the 21st Annual Meeting of ISMRM. Salt Lake City, 2013; 1517.

25. Hamilton G, Ma J, Cunha G, Sirlin C. Effect of galolinium-based contrast agent on the relaxation properties of water and fat in human liver as measured in vivo by 1H MRS. Proceedings of the 21st Annual Meeting of ISMRM. Salt Lake City, 2013; 1516.

26. Ma J. Breath-hold water and fat imaging using a dual-echo two-point Dixon technique with an efficient and robust phase-correction algorithm. Magn Reson Med 2004; 52:415–419.

27. Reeder SB, Wintersperger BJ, Dietrich O, et al. Practical approaches to the evaluation of signal-to-noise ratio performance with parallel imaging: application with cardiac imaging and a 32-channel cardiac coil. Magn Reson Med 2005; 54:748–754.

28. Wang K, Busse RF, Holmes JH, et al. Interleaved variable density sampling with a constrained parallel imaging reconstruction for dynamic contrast-enhanced MR angiography. Magn Reson Med 2011; 66:428–436.

29. Bernstein MA, Fain SB, Riederer SJ. Effect of windowing and zero-filled reconstruction of MRI data on spatial resolution and acquisition strategy. J Magn Reson Imaging 2001; 14:270–280.

30. Brau AC, Beatty PJ, Skare S, Bammer R. Comparison of reconstruction accuracy and efficiency among autocalibrating data-driven parallel imaging methods. Magn Reson Med 2008; 59:382–395.

31. Salmani Rahimi M, Korosec FR, Wang K, et al. Combined dynamic contrast-enhanced liver MRI and MRA using interleaved variable density sampling. Magn Reson Med 2015; 73:973–983.

32. Hernandez D, Artz NS, Hamilton G, Roldan-Alzate A, Reeder S. Fully automated processing of multiecho spectroscopy data for liver fat quantification. Proceedings of the 22nd Annual Meeting of ISMRM. Milan, Italy; 2014; 2884.

33. Schuhmann-Giampieri G, Schmitt-Willich H, Press WR, Negishi C, Weismann HJ, Speck U. Preclinical evaluation of Gd-EOB-DTPA as a contrast agent in MR imaging of the hepatobiliary system. Radiology 1992; 183:59–64.

34. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weismann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 2005; 40:715–724.

35. Dietrich O, Raya JG, Reeder SB, Ingrisch M, Reiser MF, Schoenberg SO. Influence of multichannel combination, parallel imaging and other reconstruction techniques on MRI noise characteristics. Magn Reson Imaging 2008; 26:754–762.

36. Muhi A, Ichikawa T, Motosugi U, Sou H, Sano K, Araki T. Diffusion- and T2-weighted MR imaging of the liver: effect of intravenous administration of gadoxetic acid disodium. Magn Reson Med Sci 2012; 11:185–191.

37. Tamada T, Ito K, Yoshida K, et al. T2-weighted magnetic resonance imaging of the liver: evaluation of the effect in signal intensity after Gd-EOB-DTPA enhancement. J Comput Assist Tomogr 2010; 34:182–186.

38. Saito K, Araki Y, Park J, et al. Effect of Gd-EOB-DTPA on T2-weighted and diffusion-weighted images for the diagnosis of hepatocellular carcinoma. J Magn Reson Imaging 2010; 32:229–234.

39. Choi JS, Kim MJ, Choi JY, Park MS, Lim JS, Kim KW. Diffusion-weighted MR imaging of liver on 3.0-Tesla system: effect of intravenous administration of gadoxetic acid disodium. Eur Radiol 2010; 20:1052–1060.

40. Heverhagen JT, Wright CL, Schmalbrock P, Knopp MV. Dose comparison of single versus double dose in contrast-enhanced magnetic resonance angiography of the renal arteries: intra-individual cross-over blinded trial using Gd-DTPA. Eur Radiol 2009; 19:67–72.
41. Froehlich JM, Unterweger M, Kubik-Huch RA. Single- vs. double-dose in contrast-enhanced magnetic resonance angiography of the carotid arteries. J Magn Reson Imaging 2007; 26:1173–1174, author reply 1174.

42. Tanimoto A, Lee JM, Murakami T, Huppertz A, Kudo M, Grazioli L. Consensus report of the 2nd International Forum for Liver MRI. Eur Radiol 2009; 19 Suppl 5:S975–S989.

43. Semelka RC, Helberger TK. Contrast agents for MR imaging of the liver. Radiology 2001; 218:27–38.

44. Brismar TB, Dahlstrom N, Edsborg N, Persson A, Smedby O, Albiin N. Liver vessel enhancement by Gd-BOPTA and Gd-EOB-DTPA: a comparison in healthy volunteers. Acta Radiol 2009; 50:709–715.

45. Runge VM. A comparison of two MR hepatobiliary gadolinium chelates: Gd-BOPTA and Gd-EOB-DTPA. J Comput Assist Tomogr 1998; 22:643–650.

46. Feuerlein S, Gupta RT, Boll DT, Merkle EM. Hepatocellular MR contrast agents: enhancement characteristics of liver parenchyma and portal vein after administration of gadoxetic acid in comparison to gadobenate dimeglumine. Eur J Radiol 2012; 81:2037–2041.

47. Ringe KI, Husarik DB, Sirlin CB, Merkle EM. Gadoxetate disodium-enhanced MRI of the liver: part 1, protocol optimization and lesion appearance in the noncirrhotic liver. AJR Am J Roentgenol 2010; 195:13–28.

48. Schuhmann-Giampieri G. Nonlinear pharmacokinetic modeling of a gadolinium chelate used as a liver-specific contrast agent for magnetic resonance imaging. Arzneimittelforschung 1993; 43:1020–1024.

49. Jeong HT, Kim MJ, Park MS, et al. Detection of liver metastases using gadoxetic-enhanced dynamic and 10- and 20-minute delayed phase MR imaging. J Magn Reson Imaging 2012; 35:635–643.

50. Motosugi U, Ichikawa T, Tominaga L, et al. Delay before the hepatocyte phase of Gd-EOB-DTPA-enhanced MR imaging: is it possible to shorten the examination time? Eur Radiol 2009; 19:2623–2629.

51. Sofue K, Tsurusaki M, Tokue H, Arai Y, Sugimura K. Gd-EOB-DTPA-enhanced 3.0 T MR imaging: quantitative and qualitative comparison of hepatocyte-phase images obtained 10 min and 20 min after injection for the detection of liver metastases from colorectal carcinoma. Eur Radiol 2011; 21:2336–2343.

52. Tsuda N, Matsui O. Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi–gadoxetic acid-enhanced MR imaging. Radiology 2010; 256:767–773.