MR Urography: Improved Visualization of the Urinary Collecting System Using a Negative Oral Contrast Agent

Masaaki KAWAHARA and Takehiko GOKAN

Abstract: To evaluate the image quality of the urinary tract using oral administration of a combination of both water and a negative gastrointestinal contrast agent, Bothdel. The study was divided into two parts: the phantom study and the healthy volunteers study. The imaging sequences used were the rapid acquisition with relaxation enhancement (RARE) and the half-Fourier acquisition single-shot turbo spin-echo (HASTE) techniques. Magnetic resonance Urography (MRU) was performed in 13 healthy volunteers using the RARE imaging sequences. After collection of the pre-contrast images, post-contrast MRU was obtained 30 min and 60 min after the oral administration of the contrast agent. Image assessment was based on the contrast effect, the image effect, and the opacification score. Statistical analysis was performed using the Wilcoxon signed-rank test. The signal intensity using 100%–12.5% Bothdel was no different to the background noise using the RARE sequence. At concentrations below 12.5%, there were statistically significant improvements in the contrast, the image effect, and the opacification score between pre-and post-contrast images. No significant difference was observed between the 30 min and 60 min post-contrast images. In contrast, the effect and pre-contrast images were graded as poor in seven cases, whereas no post-contrast images were graded as poor. There was a particularly significant improvement in the opacification score with the distal ureter being the most difficult segment to opacify. Oral administration of both water and Bothdel effectively removed the bowel signal and improved visualization of the urinary tract.

Key words: magnetic resonance (MR), urography, contrast agent

Introduction

Magnetic resonance urography (MRU) is a valuable diagnostic technique used to evaluate the urinary collecting system without the use of ionizing radiation and contrast medium. MRU can be performed using two different imaging strategies\(^1\). The first is based on heavily T2-weighted turbo spin-echo sequences (heavily T2-weight MRU) employed for obtaining unenhanced static-fluid MRU, the second on T1-weighted pulse sequence following intravenous gadolinium administration. There are two principle ways of obtaining urographic views using heavily T2-weighted MRU: (1) by acquiring a single-slice projection MR image...
with a section thickness of up to 80 mm or, (2) by acquiring multiple, overlapping thin
sections of the urinary collecting system. Heavily T2-weighted MRU is especially suited for
imaging the dilated urinary tract, where a large amount of water generates a good signal-
to-noise ratio. However, heavily T2-weighted MRU has several limitations, including the
relatively low resolution of sequences used, superimposition of hyperintense extraurinary fluid
collections on thick slice MR urography, and the inability to visualize non-dilated ureters.
Fasting prior to examination is insufficient to eliminate signals from the gastrointestinal tract.
Therefore, the use of a negative contrast agent is sometimes necessary for the superimposi-
tion of hyperintense extraluminally fluid. Takahara et al reported that FerriSeltz (Otsuka
Pharmaceutical, Tokushima, Japan), when used at a high concentration of 12 times the
normal dose, could reduce signals from the gastrointestinal tract(10). However, they found
that the total amount of usable solution was not more than 50 mL, which was insufficient
for eliminating signals from the small intestine. Bothdel (Meiji Dairies and Kyowa Hakko
Kogyo Corporation Tokushima, Japan) is a new, oral negative contrast medium for the gas-
троintestinal tract, with manganese chloride tetrahydrate as its active ingredient, and has been
used clinically in Japan since 2006.

To achieve sufficient visualization of the non-obstructed urinary tract on T2-weighted MR
urograms, substantial hydration is necessary for dilatation of the ureter. Oral administra-
tion of water is a simple and safe technique for the substantial hydration of the patient.
However, this can intensify signals from the gastrointestinal tract. We propose that the
combined oral administration of both water and Bothdel may improve visualization of the
urinary collecting system. To date, there have been no reports of combining oral negative
gastrointestinal contrast and oral administration of water for use in MRU. The purpose of
our study was to compare the image quality of heavily T2-weighted MRU obtained with
and without oral administration of water and Bothdel, and to determine the usefulness of
this technique in improving visualization of non-dilated urinary collecting systems.

Materials and Methods

Informed consent was obtained from all volunteers in the study.

Participants

The study was divided into two parts: the phantom study and the healthy volunteer
study. The contrast agent, Bothdel, is a safe, effective and reliable agent for MR imaging,
and contains 36 mg manganese chloride tetrahydrate (10 mg of manganese). The imaging
sequences used were as follows:

1. T2-weighted SSFSE localizer: TR: 1000, TE: 90, number of excitations [NEX] = 0.5,
   matrix 256×128, thickness 8 mm, coronal and axial plane.

2. Half Fourier segmented turbo spin echo (HASTE): TR: 1870, TE: 185, half-Fourier
   acquisition, echo spacing 6.18 millisecond, matrix 320×224, FOV 40×40 cm, received band-
   width 422 kHz, slice thickness 4 mm, Flip angle 120°, fat-saturation pulse, coronal plane.

3. Single-shot rapid acquisition with relaxation enhancement (RARE): TR: 10000, TE:
   801, half-Fourier acquisition, echo spacing 5.64 millisecond, matrix 768×512, FOV 40×40 cm,
   received bandwidth 407 kHz, slice thickness 80 mm, Flip angle 150°, fat-saturation pulse,
   coronal plane.
The phantom study

We conducted a phantom study to determine the effect of the concentration of Bothdel on the relaxation times in spin-echo (SE) MR imaging. The phantom study comprised of 12 plastic tubes (12 mL each). One tube was filled with 10 mL of Bothdel and the other 10 tubes were filled with diluted Bothdel of different concentrations (50%, 33%, 25%, 20%, 12.5%, 10%, 5%, 2.5%, and 1%). Distilled water was used as a control. All 12 tubes were scanned by a 3.0-T scanner (MAGNETOM Trio 3.0T: Siemens, Erlangen, Germany) using a head coil. The imaging sequences used were the rapid acquisition with relaxation enhancement (RARE) and the half-Fourier acquisition single-shot turbo spin-echo (HASTE) techniques. The relative signal intensities (signal-to-noise ratios) were calculated for each phantom by dividing the absolute signal intensity for each image by the signal of the control noise. The size of the region of interest was 20 mm$^2$. The relative signal intensities were measured by placing an elliptically defined region of interest over the image on a Fujifilm Workstation (Fujifilm Medical, Tokyo, Japan).

The healthy volunteer study

MRU was performed in 13 healthy volunteers (12 men and 1 woman, aged 26-41 years, mean age: 31.6 years). All 13 conventional MRU studies were performed on a 3.0-T scanner (MAGNETOM Trio 3.0T: Siemens, Erlangen, Germany) using two body array coils. The imaging sequence used was the RARE technique. The volunteers were not allowed to eat or drink for 3 hours before MRU. Pre-contrast images were obtained before the administration of oral negative gastrointestinal contrast and water. Post-contrast MRU was obtained 30 and 60 min after administration of 250 mL of Bothdel and 400 mL of water.

Two expert radiologists independently reviewed the MRU images. If the assessments were discordant, the final judgment was determined by consensus.

Image assessment was based on: (a) the extent to which the signals from gastrointestinal organs were eliminated (contrast effect); (b) the extent to which the image quality was improved (image effect); and (c) the extent to which the upper tracts were defined by the contrast (opacification score).

(a) The contrast effect was evaluated on pre- and post-contrast images and was based on the signal intensity in the stomach, duodenum, jejunum, and ileum. The images were assigned one of four grades:

4 = excellent (entirely no signal intensity)
3 = good (part of the gastrointestinal tract has a signal intensity that does not affect the reading)
2 = fair (part of the gastrointestinal tract has a signal intensity that adversely affects the reading)
1 = poor (part of the gastrointestinal tract has a signal intensity that makes reading difficult)

The total points gained were then compared between pre- and post-contrast images. Statistical analysis was performed using the Wilcoxon signed-rank test.

(b) The image effect was evaluated on pre- and post-contrast images. Operator defined circular regions of interest were placed in the center of the pelvic region, at the L5 level of spinal fluid on the thick slab TSE sequence. The region of interest was 25 mm$^2$ in size. The mean pixel values in these regions were used to calculate the following signal intensity
ratios (SR): $SR = \frac{SI \text{ (pelvic)}}{SI \text{ (spinal fluid)}}$. The signal intensity ratios were expressed as mean values ± standard deviation. The image effect data were compared using the Wilcoxon signed-rank test for paired samples.

(c) The opacification score was evaluated on pre- and post-contrast images of each collecting system and ureter. Each collecting system and ureter was divided into six segments: the upper and lower intrarenal collecting systems, renal pelvis, proximal (above the iliac crest), lower (level with the sciatic notch) and distal ureter (below the sciatic notch). The scoring system used assigned a score of 0 or 1 to each segment: 0, unopacified segment and 1, completely opacified segment. The quality of the signal was not addressed. The total points assigned were compared between the pre- and post-contrast images.

Statistical analysis was performed using the Wilcoxon signed-rank test. Statistical significance was assumed at $p < 0.05$ in all cases. All side effects were recorded.

Results

The phantom study

The relative signal intensities (signal-to-noise ratio) using the RARE and HASTE sequences are presented in Fig. 1. The signal intensity of the tubes with 100% Bothdel down to 12.5% Bothdel appeared equal to background noise. The other tubes showed increased signal intensity as the concentration of Bothdel was reduced (Fig. 2).

The healthy volunteer study

All volunteer participants tolerated and completed the study and all images were of diagnostic quality. For all volunteers, no significant effect was diagnosed on image interpretation at either field strength, such as a chemical shift or a susceptibility artifact.

(a) The mean contrast effect score was $1.62 \pm 0.77$ for pre-contrast images, $3.46 \pm 0.66$ for post-contrast images (30 min) ($P < .001$), and $3.69 \pm 0.63$ for post-contrast images (60 min) ($P < .001$; Table 1). Pre-contrast images were graded as poor in seven cases. For post-
a: When Bothdel level exceeds 50%, signal intensity of the tube becomes the same level as background noise on the HASTE sequence.
b: Signal intensity of the tube with 100%–10% Bothdel appears equal to background noise on the RARE sequence.

Table 1. Significance (p) values for the comparison of contrast effect scores, image effect scores and opacification scores between pre and post images

<table>
<thead>
<tr>
<th></th>
<th>Contrast effect</th>
<th>Image effect</th>
<th>Opacification</th>
</tr>
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<tbody>
<tr>
<td>Pre-contrast images</td>
<td>1.62 ± 0.77</td>
<td>0.12 ± 0.10</td>
<td>1.30 ± 1.19</td>
</tr>
<tr>
<td>pre vs. post (30 min)</td>
<td>3.46 ± 0.66 (P = .00049)</td>
<td>0.35 ± 0.16 (P = .00024)</td>
<td>4.31 ± 1.09 (P ≤ 0.0001)</td>
</tr>
<tr>
<td>pre vs. post (60 min)</td>
<td>3.69 ± 0.63 (P = .00024)</td>
<td>0.51 ± 0.25 (P = .00024)</td>
<td>4.31 ± 1.38 (P ≤ 0.0001)</td>
</tr>
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contrast images, none were graded as poor.

(b) The mean image effect score was 0.12 ± 0.10 for pre-contrast images, 0.35 ± 0.16 for post-contrast images (30 min) (P < .001), and 0.51 ± 0.25 for post-contrast images (60 min) (P < .001; Table 1).

(c) The mean opacification score was 1.30 ± 1.19 for pre-contrast images, 4.31 ± 1.09 for post-contrast images (30 min) (P < .001), and 4.31 ± 1.38 for post-contrast images (60 min) (P < .001; Table 1). The distal ureter was the most difficult segment to opacify. No significant differences were observed between 30 and 60 min post-contrast images concerning the contrast effect, image effect, and opacification scores.

All volunteers consumed the entire dose, and no side effects were observed during the examination. They were interviewed the next day and their stool condition checked. One subject (8%) was reported to have mild diarrhea, but recovered quickly without any medication.

Discussion

MRU permits evaluation of the urinary tract without exposure of the patient to ionizing radiation or an iodinated contrast medium. Therefore, it can be performed in patients with impaired renal function who are unable to tolerate iodinated contrast medium normally used for intravenous urography or computed tomography urography (CTU) studies. We performed MRU using two different imaging strategies. Heavily T2-weighted turbo spin-echo sequences were employed for obtaining unenhanced static-fluid MRU. In addition, the T1-weighted MR urographic technique was used to imitate conventional intravenous pyelography and was referred to as excretory MR urography. There are two principles of obtaining urographic views using heavily T2-weighted turbo spin-echo sequences. One
Fig. 3. 25-year-old man with healthy urinary collecting system

a : Pre-contrast MRU shows suboptimal visualization of renal collecting system because of signals from overlying bowel.
b, c : Oral administration of both water and Bothdel may remove the bowel signal and improve the urinary tract visualization.

approach is to acquire a single-slice projection MR image with a thick section during a short breath-hold\textsuperscript{4,6,11-13}. It can provide a quick coronal or sagittal urographic overview without any post-processing. The second approach is based on the acquisition of multiple, overlapping, thin sections of the urinary tract obtained mostly in the coronal or paracoronal plane\textsuperscript{1-3,11,13,14}. In static-fluid MR urography, heavily T2-weighted turbo spin-echo pulse sequences are used to obtain water images of the urinary tract.

The usefulness of projection images obtained with fast SE techniques using magnetic resonance cholangio-pancreatography (MRCP) and MRU has been increasingly recognized. Such techniques include the single-shot RARE sequence\textsuperscript{4,6,15}, which allows rapid performance imaging. Since the effective echo time is long in the single-shot RARE sequence, images of fluids (cerebrospinal fluid, gastrointestinal fluid, urine, bile, and pancreatic fluid) can be obtained. With a single-slice projection MR image, intensified signals from the gastrointestinal tract can sometimes disturb a diagnosis of the urinary tract. Therefore, elimination of intensified signals from the gastrointestinal tract is important. In our study the pre-contrast images were graded as poor \((n = 7)\), thus fasting prior to examination was insufficient to eliminate signals from the gastrointestinal tract (Fig. 3a).

A number of negative oral contrast agents are available for MR imaging of the abdomen and pelvis. Examples include perfluorocetyl bromide\textsuperscript{16}, superparamagnetic iron oxide\textsuperscript{10,17}, Kaopectate\textsuperscript{18}, gadopentate dimeglumine\textsuperscript{19}, ferric ammonium citrate\textsuperscript{20}, Kaolinite, antacid, and barium sulfate. Many of these are relatively unpalatable and become extremely diluted in the gastrointestinal tract. However, naturally available agents can be used, including air\textsuperscript{21}.
blueberry juice\textsuperscript{22), pineapple juice\textsuperscript{23), and roselle [Hibicus sabdariffa Linn.] flower tea\textsuperscript{24). However, it is difficult to use large quantities of air, and many of these other agents are only available commercially in Japan in limited amounts. The negative contrast agent, FerriSeltz (Otsuka Pharmaceutical, Tokushima, Japan), has been reported to reduce signals from the gastrointestinal tract when used at a high concentration of 12 times the normal dose\textsuperscript{10). However, the total amount of usable solution was only 50 mL, which is an insufficient amount for eliminating signals from the small intestine. Normally, 600 mL of a mixture is required to be effectively distributed as far as the small intestine\textsuperscript{25). Bothdel (Meiji Dairies and Kyowa Hakko Kogyo Corporation Tokushima, Japan) is an oral negative contrast medium for the gastrointestinal tract, with manganese chloride tetrahydrate as its active ingredient, and has been used clinically in Japan since 2006.

Visualization of the urinary tract was poor due to pre-examination fasting (Fig. 3a). Substantial hydration is necessary to ensure sufficient visualization of the unobstructed urinary tract on T2-weighted MR urograms. Such hydration necessitates the supplementation of intravenous furosemide at relatively high doses (eg, 0.3 mg of furosemide per kilogram of body weight)\textsuperscript{14,26). Even an injection of 20 mg of furosemide could not safely achieve a complete and detailed depiction of the non-dilated pelvicalices and ureters\textsuperscript{26). Rothpearl et al suggested combining a furosemide injection with an external ureteral compression to induce urinary stasis and improve the distention of the collecting system\textsuperscript{13). However, the application of furosemide at intravenous doses larger than 10 mg and using an inconvenient compression device can impede the patient’s cooperation during the examination, which may lead to interruption or termination of the procedure\textsuperscript{27). Furthermore, anaphylaxis to furosemide is infrequent, but may cause life-threatening reactions\textsuperscript{28). Intravenous administration of saline is a common method of hydration. However, oral administration of water is easier and safer in CTU\textsuperscript{29) and has been used for hydration and gadolinium-enhanced excretory MR urography\textsuperscript{30}. A previous study demonstrated that intravenous administration of normal saline and oral administration of water equally improved opacification of the ureter in CTU\textsuperscript{30). Therefore, we assumed that a sufficient oral administration of water could remove the bowel signal effectively to ultimately improve the urinary tract visualization of MRU. This study revealed significantly better opacification using a combination of an oral negative gastrointestinal contrast (250 mL) with the oral administration of water (400 mL). We were concerned that the Bothdel would become too dilute with the oral administration of water, but the mixture was sufficient to eliminate signals from the small intestine (Fig. 3b, 3c). The distal ureter was the most difficult segment to opacify, thus it is important to develop different techniques to overcome this difficulty. Oral administration of 650 mL of fluid would be acceptable to patients with the exception of those required to limit their fluid intake.

Recently, static-fluid MR urography has been shown to be suitable for the imaging of the dilated urinary tract [ref needed]. Due to the difficulties associated with imaging the non-dilated urinary tract, we propose that our protocol could be used to determine the level of obstruction in dilated systems for the evaluation of urinary tract anomalies, and to assess tumor morphology.

We have identified several limitations with this study. For example, although there is a significant difference in MR images before and after oral administration of water and negative contrast, our sample size is relatively small. Further studies may need to be conducted
in a larger population. In addition, the appropriate concentration of Bothdel and the correct volume of water has yet to be determined. Also, we did not evaluate the effect of the oral intake of water or Bothdel alone. The variable hydration status and renal function in patients may have had an impact on the amount of urine excreted by the kidneys, which in turn affects the resultant image. Motility of the gastrointestinal tract may also affect the elimination of the signal from the gastrointestinal tract. Although the administration of 250 mL of Bothdel and 400 mL of water are preliminary amounts, we believe the resultant volume to be reasonable, as at least 600 mL of liquid is necessary to fill the entire small intestine. We noted the oral administration of 250 mL of Bothdel with 400 mL of water was well tolerated by the volunteer participants. According to the results of the phantom study, we may be able to reduce the concentration of Bothdel and increase the volume of water. More studies need to be performed to investigate these findings in more detail.

In conclusion, we found MR urography, with the oral administration of both water and the negative oral contrast (Bothdel), could improve the elimination of the fluid signal from the gastrointestinal tract and enhance the visualization of the upper collecting system.

References

MRU: Improved Visualization Using Bothdel


[Received February 1, 2008; Accepted February 8, 2008]