Diffusion- and $T_2$-weighted MR Imaging of the Liver: Effect of Intravenous Administration of Gadoxetic Acid Disodium

Ali MUHI, Tomoaki ICHIKAWA*, Utaro MOTOSUGI, Hironobu SOU, Katsuhiro SANO, and Tsutomu ARAKI

Department of Radiology, University of Yamanashi
1110 Shimokato, Chu-o-shi, Yamanashi 409-3898, Japan
(Received January 5, 2012; Accepted April 4, 2012)

Purpose: We evaluated the effect of intravenous administration of gadoxetic acid disodium to hepatic lesions and liver parenchyma on $T_2$-weighted ($T_2$WI) and diffusion-weighted imaging (DWI).

Materials and Methods: One hundred and one consecutive patients with 259 hepatic lesions underwent $T_2$WI and DWI (b-values of 500 and 1000 s/mm$^2$) before and after gadoxetic acid administration. We compared the ratio of signal intensity (SIR) of the liver parenchyma and hepatic lesions, the ratio of contrast intensity of the lesion to the liver (CIR), the apparent diffusion coefficients (ADCs) of the liver and lesions, and lesion detectability between pre- and post-contrast images.

Results: SIRs, CIRs, and ADC of focal hepatic lesions were comparable on pre- and post-contrast images, and lesion detectability did not differ significantly between pre- and post-contrast $T_2$WI and DWI. The SIRs of the liver parenchyma were significantly lower on post-contrast DWI ($1.4 \pm 0.68$ [b = 500 s/mm$^2$] and $1.71 \pm 0.67$ [b = 1000 s/mm$^2$]) than pre-contrast images ($1.89 \pm 0.68$ [b = 500 s/mm$^2$] and $2.26 \pm 0.78$ [b = 1000 s/mm$^2$]) ($P < 0.001$). ADCs of the liver parenchyma were also significantly decreased on post-contrast DWI ($0.77 \pm 0.32$ mm$^2$/s) than pre-contrast images ($0.64 \pm 0.33$ mm$^2$/s) ($P = 0.001$).

Conclusion: $T_2$WI and DWI after administration of gadoxetic acid are feasible and do not compromise the SIR, CIR, and ADC of focal hepatic lesions. However, the signal intensity of DWI and ADC value of the liver parenchyma were decreased on gadoxetic acid-enhanced hepatocyte phase images.

Keywords: diffusion-weighted MR imaging, gadoxetic acid, $T_2$-weighted MR imaging

Introduction

Gadoxetic acid disodium (Primovist, Bayer Schering Pharma, Berlin, Germany) is a recently introduced liver-specific magnetic resonance (MR) contrast agent with both dynamic and hepatocyte-specific properties.\textsuperscript{1-5} Uptake by hepatocytes of approximately half the injected dose of gadoxetic acid improves detection of liver malignancies on hepatocyte-phase imaging.\textsuperscript{6-8}

When gadoxetic acid is used, hepatocyte-phase imaging can be acquired 10 to 20 min after injection of the contrast material.\textsuperscript{9} Performing $T_2$-weighted ($T_2$WI) and diffusion-weighted imaging (DWI) during the interval between the early dynamic and hepatocyte phases is reasonable and can shorten examination time in the busy clinical practice. This would be feasible if the diagnostic capability of post-contrast $T_2$WI and DWI was comparable to that of pre-contrast $T_2$WI and DWI in terms of detection and characterization of focal liver lesions. Gadoxetic acid increases magnetic susceptibility and shortens $T_2$-relaxation time and may thus alter signal intensities on $T_2$WI and DWI and apparent diffusion coefficient (ADC) values.

We evaluated the effect of intravenous administration of gadoxetic acid disodium to hepatic lesions and liver parenchyma on $T_2$WI and DWI.

Materials and Methods

Patients

This study followed the principles of the Declara-
tion of Helsinki. Our hospital’s institutional review board approved the study; informed consent was waived. From January to April 2008, 101 consecutive patients (62 men, 39 women; aged 37 to 84 years; mean age, 65.4 years) who underwent magnetic resonance (MR) imaging for the evaluation of focal hepatic lesions were included in this study. All patients underwent DWI and T₂WI before and after gadoxetic acid administration, and we retrospectively evaluated pre- and post-contrast images.

In the 101 consecutive patients, we assessed 259 focal hepatic lesions—145 hepatocellular carcinomas (HCCs) in 62 patients, 35 metastases in 10 patients, 2 cholangiocarcinomas (CCCs) in 2 patients, 15 hemangiomas in 11 patients, and 59 cysts in 26 patients.

Liver metastases originated from the following primary malignancies: colorectal carcinoma (26 lesions in 5 patients), breast carcinoma (3 lesions in 2 patients), pancreatic carcinoma (2 lesions in 1 patient), and gastric carcinoma (4 lesions in 2 patients). Lesion diameters ranged from 0.7 to 9.4 cm (mean, 1.7 cm). Specifically, diameters ranged from 0.8 to 9.4 cm (mean, 1.8 cm) for HCCs; 0.8 to 8.4 cm (mean, 2.8 cm) for metastases; 0.9 to 3.8 cm (mean, 1.6 cm) for hemangiomas; and 0.7 to 4.5 cm (mean, 1.4 cm) for cysts; diameters of the 2 CCCs were 4.8 and 3.4 cm.

The diagnosis of HCC was confirmed by pathological examination (37 lesions in 21 patients) or on the basis of typical radiological findings described in the literature using multi-imaging modalities. These included MR imaging, contrast-enhanced computed tomography (CT), CT during arteriography (CTA), and CT during arterial portography (CTAP) with intense enhancement in the arterial phase, contrast medium washout in the delayed phase, coronal enhancement, and progression of the disease presented on follow-up CT or MR images (108 lesions in 41 patients).

The diagnosis of metastases was confirmed by pathological examination (9 lesions in 5 patients) or on the basis of the histological findings of the primary tumor and observation of increased (21 lesions in 3 patients) or decreased (5 lesions in 2 patients) size after chemotherapy on follow-up dynamic contrast-enhanced CT and abdominal ultrasonography.

The diagnosis of hepatic hemangiomas was based on typical findings that include nodular or globular enhancement with a gradual filling-in pattern on dynamic CT, very high signal intensity on both moderately and heavily T₂-weighted images (T₂WI), and lack of growth on CT or MR images during a follow-up period of at least 6 months.

Cysts were diagnosed on the basis of their typical appearance on nonenhanced T₁WI (markedly low signal intensity) and T₂WI (very high signal intensity on heavily T₂WI and absence of contrast enhancement) and the lack of growth on CT or MR images during a follow-up period of at least 6 months.

**MR imaging technique**

All patients underwent MR imaging using a superconducting magnet operating at 1.5 tesla (Signa EXCITE HD; GE Medical Systems, Milwaukee, WI, USA) and an 8-channel phased-array coil. After pre-contrast T₁W fast spoiled gradient-echo imaging, T₁W first-spin echo images and diffusion-weighted single-shot spin-echo echo-planar images were obtained. Dynamic images were obtained using fat-suppressed T₁W gradient-echo imaging with a 3-dimensional (3D) acquisition sequence (liver acquisition with volume acceleration [LAVA]) before (pre-contrast) and 20 and 60 s and 2, 5, 10, and 20 min after intravenous administration of gadoxetic acid (0.025 mmol/kg body weight) followed by 20-mL saline flush using a power injector (Sonic Shot 50; Nemoto, Tokyo, Japan). Pre- and post-contrast T₁W fast spin-echo images were acquired using fat saturation (FS) and respiratory triggering. The post-contrast FS T₁W images were obtained 13 min after the administration of gadoxetic acid. Parameters were: repetition time (TR)/echo time (TE), 3200 to 8000 ms/65 to 67 ms; flip angle (FA), 90°; number of signals acquired (NSA), one; matrix, 256×192; and acquisition time, 3 min.

DWI with motion-probing gradients in 3 directions was performed before and after administration of the contrast agent using the respiratory-triggered technique. Post-contrast DWI was performed after 20 min of hepatocyte-phase imaging under the following conditions: sequence, single-shot spin-echo echo-planar with parallel imaging technique (factor = 2); fat-suppression technique; spatially selective radiofrequency; scan direction, axial; b-value, 500 and 1000 s/mm²; directions of diffusion gradients, 3 orthogonal directions; TR/TE/time of inversion (TI) = 8000 to 10000 ms/73.2 to 73.4 ms/70 ms; matrix, 128×128; slice number, 60; slice thickness, 4 to 6 mm; field of view (FOV), 40 cm; number of signal averages (NSA), 4; and acquisition time, approximately 5 to 6 min.

**Image analysis**

We performed quantitative image analysis by measuring the signal intensity of the liver parenchyma, focal hepatic lesions, and skeletal muscles using operator-defined regions of interest (ROIs) for...
DWI and T2WI after Gadoxetic Acid

Statistical analysis

We classified all hepatic lesions into 2 groups as either malignant (including HCCs, metastases, and CCCs) or benign (including hemangiomas and cysts); used paired sample t test to compare SIR, CIR, and ADC between the pre- and post-contrast images; used Pearson correlation to assess the bivariate correlation between the pre- and post-contrast T2WI and DWI; and used Mann-Whitney test to compare the ADC values of the 2 groups (malignant and benign lesions). We used chi-square test to assess the statistical difference in lesion detectability between the pre- and post-contrast T2W and DW images. For all the tests, P<0.05 was considered significant difference. Statistical analyses were performed using version 16 of Statistical Package for Social Science (SPSS for Windows; SPSS Japan, Tokyo, Japan).

Results

T2WI

The SIRs of the liver parenchyma, malignant tumors, and benign lesions were comparable between pre- and post-contrast T2WI (pre- vs. post-contrast T2WI: liver, 2.1±0.54 vs. 2.09±0.57; HCC, 3.6±1.29 vs. 3.71±1.40; metastasis, 3.67±0.62 vs. 3.66±0.77; CCC, 4.65±0.92 vs. 5.2±0.18; hemangioma, 6.12±1.64 vs. 6.38±1.73; and cyst, 8.54±2.27 vs. 8.45±2.11) (Table 1).

The CIRs of malignant and benign hepatic lesions were comparable between pre- and post-contrast T2/WI (pre- vs. post-contrast T2/WI: HCC, 1.49±0.85 vs. 1.54±0.89; metastasis, 1.98±0.72 vs. 2.09±0.75; CCC, 2.49±0.83 vs. 2.44±0.16; hemangioma; 4.02±1.55 vs. 4.38±1.68; and cyst, 6.77±2.59 vs. 6.66±2.41) (Table 1).

One more malignant lesion was detected by pre-(46.7%, 85/182) than post-contrast T2/WI (46.1%, 84/182), but detectability of malignant and benign lesions did not differ significantly between pre- and post-contrast T2/WI (Figs. 1, 2).

Bivariate correlation analysis revealed a strong correlation between SIR and CIR of pre- and post-contrast T2/WI (correlation coefficient range, 0.735 to 0.917) (Table 1).

DWI

The mean SIR of the liver parenchyma was significantly decreased on post-contrast DWI (1.4±0.68, 1.71±0.67) compared to pre-contrast DWI (1.89±0.68, 2.26±0.78) at b-values of 500 and 1000 s/mm² (P<0.001). The mean ADC value of the liver parenchyma was significantly higher on pre-contrast (0.77±0.32 mm²/s) than post-contrast...
Lesion detectability with pre- and post-contrast T2-weighted imaging (T2WI).
1. Lesion detected with post-contrast images only; 2. more conspicuous with post-contrast images; 3. comparable; 4. more conspicuous with pre-contrast images; 5. detected with pre-contrast images only.

Fig. 2. A 46-year-old man with liver metastasis in the lateral segment of the liver. The metastasis is clearly detected with both pre- (a) and post-contrast (b) T2-weighted imaging (T2WI). The metastasis shows comparable high signal intensity with both pre- (c) and post-contrast (d) DWI at \( b = 500 \) s/mm\(^2\). Note the drop in signal intensity of the liver parenchyma with post-contrast DWI.

The SIRs, CIRs, and ADCs of malignant lesions and hemangiomas were comparable on pre- and post-contrast DWI (Table 2). ADC values were lower for malignant lesions (pre-, 0.94 ± 0.41 mm\(^2\)/s; post-, 0.92 ± 0.41 mm\(^2\)/s) than hemangiomas (pre-, 1.41 ± 0.29 mm\(^2\)/s; post-, 1.33 ± 0.34 mm\(^2\)/s) on both pre- and post-contrast DWI (\( P < 0.0001 \)) (Table 2).

Lesion detectability did not differ significantly between pre- and post-contrast DWI (Figs. 2, 3). However, 14 focal hepatic lesions showed discrepancies between pre- and post-contrast images. Lesions visible only on post-contrast images included 4 HCC, 3 metastases, and one hemangioma, and those visible only on precontrast images included 4 HCC, one case of metastasis, and one cyst. Bivariate correlation analysis revealed fair-to-strong correlation between the SIR, CIR, and ADC of the pre- and post-contrast DW images (correlation coefficient range, 0.227 to 0.793).
Table 1. Signal intensity ratio (SIR) and contrast intensity ratio (CIR) of liver and focal liver lesions on T2-weighted imaging (T2WI)

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>No. of lesions (patients)</th>
<th>Pre-contrast</th>
<th>Post-contrast</th>
<th>P</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>—(97)</td>
<td>2.1 ± 0.54</td>
<td>2.09 ± 0.57</td>
<td>.73</td>
<td>.917</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>85(40)</td>
<td>3.64 ± 1.15</td>
<td>3.73 ± 1.26</td>
<td>.19</td>
<td>.916</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>74(37)</td>
<td>7.97 ± 2.36</td>
<td>7.96 ± 2.2</td>
<td>.97</td>
<td>.735</td>
</tr>
<tr>
<td>CIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>85(40)</td>
<td>1.74 ± 1.56</td>
<td>1.73 ± 1.56</td>
<td>.93</td>
<td>.784</td>
</tr>
<tr>
<td>Benign lesions</td>
<td>74(37)</td>
<td>6.52 ± 3.57</td>
<td>6.13 ± 2.43</td>
<td>.14</td>
<td>.774</td>
</tr>
</tbody>
</table>

Data represent means ± standard deviation (SD).

Table 2. Signal intensity ratio (SIR), contrast intensity ratio (CIR), and apparent diffusion coefficient (ADC) of liver and focal liver lesions on diffusion-weighted imaging (DWI)

<table>
<thead>
<tr>
<th>No. of lesions (patients)</th>
<th>b-value (s/mm²)</th>
<th>Pre-contrast</th>
<th>Post-contrast</th>
<th>P</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>—(97)</td>
<td>500</td>
<td>1.89 ± 0.68</td>
<td>1.4 ± 0.68</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>2.26 ± 0.78</td>
<td>1.71 ± 0.67</td>
<td>.059</td>
<td>.734</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>87(42)</td>
<td>500</td>
<td>4.52 ± 1.93</td>
<td>4.18 ± 2.25</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>4.54 ± 2.07</td>
<td>4.41 ± 1.8</td>
<td>.482</td>
<td>.649</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>15(11)</td>
<td>500</td>
<td>4.62 ± 1.91</td>
<td>3.73 ± 1.41</td>
<td>.063</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>3.95 ± 1.33</td>
<td>3.24 ± 1.16</td>
<td>.071</td>
<td>0.375</td>
</tr>
<tr>
<td>CIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>87(42)</td>
<td>500</td>
<td>2.66 ± 1.87</td>
<td>2.84 ± 2.07</td>
<td>.317</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>2.41 ± 1.89</td>
<td>2.71 ± 1.72</td>
<td>.085</td>
<td>0.644</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>15(11)</td>
<td>500</td>
<td>2.89 ± 1.81</td>
<td>2.5 ± 1.32</td>
<td>.404</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>1.91 ± 1.22</td>
<td>1.58 ± 1.14</td>
<td>.345</td>
<td>0.403</td>
</tr>
<tr>
<td>ADC (×10⁻³ mm²/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>—(97)</td>
<td>500</td>
<td>.77 ± .32</td>
<td>.64 ± .33</td>
<td>.001*</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td>87(42)</td>
<td>500</td>
<td>.94 ± .41</td>
<td>.92 ± .41</td>
<td>.72</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>15(11)</td>
<td>500</td>
<td>1.41 ± .29</td>
<td>1.33 ± .34</td>
<td>.33</td>
</tr>
</tbody>
</table>

Data represent means ± standard deviation (SD).

Discussion

In our study, the SIRs and CIRs of the liver and focal hepatic lesions were comparable on pre- and post-contrast T2WI. However, the SIR and ADC of the liver on DWI were decreased after gadoxetic acid administration, perhaps because of the relative T2*-shortening effect of gadoxetic acid.

Though the ADC of the liver was significantly lower on post-contrast images, ADC values of the focal hepatic lesions were comparable on pre- and post-contrast images. Our result indicates that administration of gadoxetic acid does not affect the signal intensity with DWI or ADC values of the focal liver lesions that usually show no or minimal uptake of the contrast agent.

To evaluate the effect of gadoxetic acid on lesion characterization, we compared the ADC values of malignant and benign lesions on pre- and post-contrast DWI. Our results indicate comparable lesion characterization between DWI obtained after gadoxetic acid administration and pre-contrast images, possibly as a result of elimination of most of the contrast agent, even in hypervascular lesions, after the 20-min delay for hepatocyte phase image.

With regard to lesion detectability, 4 HCCs were detected using pre-contrast DWI only, and the 4 other HCCs were detected using post-contrast DWI.
Fig. 3. Lesion detectability with pre- and post-contrast diffusion-weighted imaging (DWI). 1. Lesion detected with post-contrast images only; 2. more conspicuous with post-contrast images; 3. comparable; 4. more conspicuous with pre-contrast images; 5. detected with pre-contrast images only.

only. None of the 4 HCCs that is not detected on post-contrast DWI showed significant signal increase after gadoxetic acid administration. That suggests that the signal change in the liver parenchyma did not affect the conspicuity of HCC lesions. Two additional metastases were detected using post-contrast DWI only, but the reason for this discrepancy is unclear. Because hepatocyte-phase imaging can be acquired 10 to 20 min after injection of the gadoxetic acid, T2WI and DWI can be obtained between the dynamic (5 min) and hepatocyte (20 min) phases to shorten examination time.

Choi’s group reported similar results using a 3T MR system. They reported that DWI after gadoxetic acid administration can be substituted for pre-contrast DWI without compromising contrast-to-noise ratio and ADC of the focal hepatic lesions. In another study, Kim and associates reported comparable diagnostic capability for T2WI after gadoxetic acid administration and pre-contrast T2WI for the detection and characterization of hepatic tumors. On the other hand, the teams of Tamada and Saito reported that late acquisition of T2WI and DWI after gadoxetic acid administration can affect signal drop of the liver parenchyma. Considering those previous results, however, most researchers concluded that DWI and T2WI after gadoxetic acid administration can be substituted for those before contrast.

We applied 2 non-zero or high b-values (b = 500 and 1000 s/mm²) to obtain ADC values. The choice of 2 high b-values over conventional b-values, e.g., b = 0 and 1000 s/mm², has some advantage. First, the ADC value calculated using 2 high b-values can be considered unaffected by microcirculation or regarded as reflecting pure diffusion. Second, DWI with b = 500 is clinically useful to find a lesion together with b = 1000 s/mm² images, whereas b = 0 s/mm² image usually has no clinical use. On the other hand, we should be aware that our results for ADC values cannot be compared with those in the other study using b = 0 s/mm² as the lower b-value because of the influence of microcirculation on results.

Our study was limited by our small number of patients, the absence of histopathological confirmation for some lesions, and our inability to calculate interreader agreement because we evaluated focal hepatic lesions and measured ADC by consensus reading.

In conclusion, our results suggest that acquisition of T2WI and DW images during the hepatocyte phase can be feasible and does not compromise the SIR, CIR, and ADC values of focal hepatic lesions. However, the signal intensity of DWI and ADC value of the liver parenchyma were decreased on gadoxetic acid-enhanced hepatocyte phase images.

References