Superparamagnetic Iron Oxide (SPIO) MRI Contrast Agent for Bone Marrow Imaging: Differentiating Bone Metastasis and Osteomyelitis

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Purpose: We explored appropriate scan timing for bone marrow imaging enhanced using superparamagnetic iron oxide (SPIO) and evaluated the usefulness of SPIO in differentiating metastasis and osteomyelitis in patients.

Methods: To determine the adequate scan timing after administration of SPIO, 5 healthy subjects were examined using a 1.5T magnetic resonance (MR) imaging scanner. Sagittal images of their lumbar spines were obtained using short-T1 inversion recovery (STIR) sequence before and 3, 6, 9, 24, and 48 hours after intravenous injection of 8 µmol Fe/kg SPIO (ferucarbotran). MR signal intensities (SIs) were evaluated. Based on the results, 12 patients, five with bone metastasis and seven with vertebral osteomyelitis, were examined using the same procedure before and 3 hours after intravenous injection of ferucarbotran at the same dose. SIs of the bone metastases, osteomyelitis, and surrounding normal bone marrow were measured, and relative enhancement (RE) was calculated for each lesion.

Results: In the healthy volunteers, maximum reduction in signal was observed 3 to 24 hours (P<0.05) after administration of SPIO; thereafter and up to 48 hours, the SI gradually recovered. In the patients, the RE of the bone metastases was −12.2%, which was significantly higher than that in the osteomyelitis (−35.0%, P<.001) and normal bone marrow (−46.6%, P<.0005).

Conclusion: Maximum suppression of signal intensity in bone marrow was seen 3 hours after injection of ferucarbotran, the point at which ferucarbotran allows differentiation of bone metastasis from osteomyelitis.

Keywords: MR imaging, SPIO, bone metastasis, osteomyelitis, STIR

Introduction

Superparamagnetic iron oxide (SPIO) particles have been used as a liver-specific negative contrast agent for magnetic resonance (MR) imaging. SPIO particles, which are phagocytosed by the reticuloendothelial system (RES, i.e. Kupffer cells, macrophages) after intravenous injection, are mostly taken up into the liver (~80%) and conspicuously reduce MR signal in normal tissue by the shortening of tissue T2 and T2* by bulk susceptibility effects.1–4

The particle size of most SPIOs vary, and particles smaller than approximately 20 nm have less affinity for the RES in the liver and have a longer blood half-life. Thus, some of the SPIOs are taken up into the lymph nodes and bone marrow,5 thereby acting as a negative contrast agent in bone marrow.6 Several studies using animal models report that SPIO particles were taken up in the bone marrow and significantly decreased relaxation time of tissue to improve diagnostic ability for focal lesions occurring within 1 to 24 hours or 2 hours.7–8

We recently reported the potential of SPIO in differentiating between metastasis and osteomyelitis at 24 hours post administration in a rabbit model; we used ferucarbotran, an SPIO particle used clinically as a liver-specific contrast agent.9
Table. Change in relative enhancement (mean ± standard deviation [SD], %) in bone marrow in normal healthy volunteers at precontrast and 3, 6, 9, 24, and 48 hours after intravenous injection of ferucarbotran at a dose of 8 μmol Fe/kg on short-T1 inversion recovery (STIR) imaging

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<th>3 hours</th>
<th>6 hours</th>
<th>9 hours</th>
<th>24 hours</th>
<th>48 hours</th>
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<tr>
<td>STIR</td>
<td>−39.3 ± 9.7</td>
<td>−33.7 ± 21.6</td>
<td>−28.1 ± 20.0</td>
<td>−24.6 ± 18.4</td>
<td>−6.6 ± 15.7</td>
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The values show mean ± SD (n = 5).
Pre-values of each group are 0.0 ± 0.0%.
The Friedman test showed a signal reduction between these 6 points (P < 0.0001), and there was significant difference between the 3-hour and 24-hour and between the 3-hour and 48-hour time points (P < 0.05).

In this study, we first investigated the change in signal intensity of bone marrow in the vertebral bodies after intravenous injection of ferucarbotran in healthy human volunteers. This exploratory experiment provided appropriate scan timing for the subsequent study to evaluate the potential of SPIO in the differential diagnosis in patients with bone metastasis or osteomyelitis.

Materials and Methods

The ethics committee of our institution approved this study, and all patients gave informed consent. All MR studies were performed on a 1.5T imaging system (Gyroscan Intera™, Philips Medical, Best and Heeren, Netherlands) using a spine coil and short-T1 inversion recovery (STIR) sequence. The imaging parameters were: repetition time/echo time/flip angle: 3000 ms/60 ms/180°; section thickness: 4 mm; field of view: 300 mm; and matrix size: 400 × 512, affording a total scan time of approximately 3 min.

Volunteers

To determine an appropriate scan timing for SPIO-enhanced bone marrow imaging, the lumbar spines of 5 healthy volunteers (4 men and 1 woman; aged 27 to 41 years, mean age, 29 years) were examined. SPIO-enhanced images were obtained before and 3, 6, 9, 24, and 48 hours after intravenous administration of 8 μmol Fe/kg ferucarbotran (Resovist®, Schering AG, Berlin, Germany).

Patients

To investigate whether ferucarbotran could differentiate bone metastasis from osteomyelitis, 12 patients (8 men and 4 women; aged 44 to 79 years, mean age, 61.5 years) with back pain were enrolled. All patients had been diagnosed by clinical data and MR imaging. Five of the 12 were diagnosed with metastatic bone tumor from hepatocellular carcinoma (n = 4) or non-small cell lung cancer (n = 1), and the remaining 7 patients were diagnosed with vertebral osteomyelitis. All metastatic bone tumors analyzed were osteolytic, and the patients with osteomyelitis were examined either during or after antibiotic therapy.

Data Analysis

In volunteers, signal intensity (SI) of bone marrow and background noise were measured in circular regions of interest (ROI) measuring 3 cm in diameter and placed in the bone marrow region (SIbone marrow) of each vertebral body through L1 to L5 and in the background (SIbackground). The signal-to-noise ratio (SNR) of vertebral bone marrow was calculated by the following equation: SNR = SIbone marrow/SIbackground.

Relative enhancement (RE), which indicates the change in SNR after injection of SPIO relative to the baseline, was calculated in the vertebral bone marrow at each time point by the following equation: RE (%) = [(SIpost − SIpre)/(SIpre)] × 100, where SIpre and SIpost are the signal intensities of bone marrow before and after administration of SPIO. The mean REs were obtained from L1 to L5 vertebral bodies for each volunteer at each time point.

In patients, the RE of bone metastasis, osteomyelitis, and neighboring bone marrow were calculated in patients using the same procedure.

Statistical Analysis

All values were expressed as mean ± standard deviation (SD), and the Friedman test was used to compare the RE at each time point against the baseline (before injection) in volunteers. For patients, the relationships between the RE among the regions, bone metastasis, osteomyelitis, and normal bone marrow were tested with ANOVA followed by Tukey multi-comparison test. In all tests, statistical significance was considered P < 0.05.
Fig. 1. Relative enhancement (%) of bone metastasis (n = 5), osteomyelitis (n = 7), and normal regions (n = 12) in the bone marrow at 3 hours after intravenous injection of 8 μmol Fe/kg ferucarbotran on short-TI inversion recovery (STIR) imaging. The figure indicates the quantile and mean ± standard deviation of the data in each region. Probability (P) was determined by Tukey multiple comparison test.

Fig. 2. Short-TI inversion recovery (STIR) images of osteomyelitis from a 75-year-old man. (a) Unenhanced STIR and (b) 3 hours after ferucarbotran injection. The end plate of osteomyelitis lesion of L1 and L2 (arrow) showed relatively higher intensity than muscle (a), and the neighboring bone marrow (arrow head) showed low intensity. The margin of disc space appeared clearly after injection of ferucarbotran (b).

Fig. 3. Short-TI inversion recovery (STIR) images of bone metastasis from a 54-year-old man with hepatocellular carcinoma (HCC) unenhanced STIR (a) and 3 hours after injection of ferucarbotran (b). The images of Th12 vertebral bone metastasis with HCC. The change in magnetic resonance (MR) signal intensity was not conspicuous in the bone metastasis before and after injection of ferucarbotran.

**Results**

Table 1 shows the RE values on the STIR images of volunteers after administration of ferucarbotran at a dose of 8 μmol Fe/kg. Upon administration of ferucarbotran, signal was reduced among the precontrast and 3 hours, 6 hours, 9 hours, 24 hours and 48 hours of 6 points (P < 0.001). Thereafter, the SI gradually recovered and returned to the baseline level at 48 hours. The RE at 3 hours was smaller than those at 6, 9, 24, and 48 hours, but there was a significant difference between 3- and 24-hour and between 3- and 48-hour time points (P < 0.05).

Figure 1 demonstrates the REs of the patients 3 hours after injection of ferucarbotran at a dose of 8 μmol Fe/kg. In the quantitative analysis, the SI of the bone metastasis, osteomyelitis, and neighboring normal bone marrow decreased by −12.2 %, −35.0 %, and −46.6 % on the STIR images. The RE of bone metastasis was significantly higher than that of the neighboring normal region and of osteomyelitis (P < 0.05; Figs. 2, 3).
Discussion

The difficulty in differentiating between inflammatory change and bone metastasis is common in clinical diagnosis. Even using dynamic contrast with gadolinium-complex, it is difficult to differentiate bone metastasis from osteomyelitis. Our current study showed that the signal change in the osteomyelitis and neighboring normal bone marrow was completely different from that of bone metastasis. It showed the potential of SPIO-enhanced MR imaging in detecting bone marrow lesions and differentiating bone metastasis and osteomyelitis. Although osteomyelitis and neighboring normal bone marrow were not significantly different, hypointense signal on T1-weighted images may reliably indicate spinal infection.

MR imaging of bone marrow using SPIO particles has been expected for over a decade, and many studies have proved its ability. However, studies in human subjects are still sparse. Currently, 2 types of SPIO particles can be used clinically ([AMI-25 (ferumoxides), mean diameter 80–150 nm] and [SHU 555A (ferucarubotran), mean diameter 60 nm]). Their mean diameters and distribution of particle size are somewhat different, and they require different dosing applications; specifically, ferumoxides are administered by slow infusion and ferucarbotran by single shot. In the present study, we used ferucarbotran because of its single-shot administration.

We first monitored MR signal behavior in vertebral bone marrow on STIR images after healthy volunteers were injected with ferucarbotran at a dose of 8 μmol Fe/kg. The resultant SIs in the vertebral bone marrow apparently reduced and then gradually recovered in a time-dependent manner. The maximum signal reduction (~39.3%) was observed at 3 hours after injection and returned to baseline level at 48 hours.

In the patients, when we compared SIs before and after SPIO injection, we found the signal reduction in bone metastasis (~12.2%) significantly less than that in the region of osteomyelitis (35%, P<0.001) or in the normal bone marrow (~46.6%, P<0.0005) at 3 hours after injection, implying a potential usefulness of SPIO in differentiating these conditions.

Our previous study in a tumor model in rabbits indicated that the difference in the SI profiles of the tumor and inflammation in bone marrow reflected the difference in the quantity of ferucarbotran taken up by macrophage cells. It was difficult to detect normal hematopoietic cells, including macrophages, in the histological findings of the rabbit model of bone tumor, whereas pseudoeosinocytes acting as macrophages were seen in inflammatory models. Although tumor cells occupied the bone marrow in bone metastasis, and thus, SPIO was not taken up by neoplastic bone marrow in clinical cases, in general, macrophages are generated in bone marrow with inflammation. As a result, the signal intensity of bone marrow decreased in the osteomyelitis.

When USPIO was used for MR imaging, animal studies have shown a steep decrease of marrow relaxation times in T2-weighted images within 1- and 12-hour time points before slowly returning to normal over the next 7 days. Other studies in patients suggested that on T2-weighted fast spin-echo sequence, the SNR value in bone marrow showed maximal decrease at between 1 and 3 hours. Based upon these literature findings and considering realistic human studies, we decided to set the scan timing before and 3 to 48 hours after the SPIO injection to monitor the SIs in our study. However, the maximum signal reduction in our study was observed at 3 hours, which was the first time point for the post injection of MR imaging. We speculated that a somewhat earlier time point (1 to 2 hours) might also be acceptable to achieve a similar signal reduction.

MR signal reduction by SPIO particles is caused by its susceptibility effect, which perturbs the local magnetic field, thereby reducing T1*/T2 values in the tissue. The effect of this signal reduction on MR images is determined by several factors, such as tissue concentration and intrinsic ability of SPIO particles as well as the magnetic field strength and imaging parameters.

For uptake into bone marrow by the reticuloendothelial system (RES), 2 types of cells, lining cells and parenchymal macrophages, are mainly associated. The lining cells directly access intravascular particles, and extravascular macrophages access particles crossing the vascular barrier, where iron particles smaller than 4 to 5 nm can accumulate through vascular transcytosis. Therefore, the total amount of particles accumulating in bone marrow depends upon particle size. In addition, the fraction of the particles distributing into bone marrow comprises smaller particles than that distributing into the liver.

This difference in particle size causes different T1 and T2 shortening effects (T1 relaxivity: R1 and T2 relaxivity: R2, respectively) between imaging of liver and bone marrow. R1 is known to increase and R2 to decrease as the size of SPIO particles become smaller. Indeed, SPIO injection increased the SI in the bone marrow on T1 weighted
images (T1WI), whereas it decreased the SI in the liver in the same patients. The consequence of the size difference is that the sequence/imaging parameters for bone marrow may need to be more T2*/T1 weighted when we expect signal reduction by SPIO particles.

In our study, we selected STIR sequence because of its sensitivity to bone marrow and its use as one of the most common sequences for bone marrow imaging in clinical routine. Using a similar SPIO particle, Daldrup-Link and associates demonstrated signal reduction at a rate of 34.2% in bone marrow on STIR images, which was more prominent than that observed on the T1 or T2 turbo spin-echo (TSE) sequences. This result seems to be consistent with our result, although there are several differences in scan timing and imaging parameters between the studies.

Hundt and colleagues used T, FLASH, T2 TSE, and T2* FLASH to compare the change in SI between the liver and bone marrow and suggested that T2*WI helps differentiate higher and lower iron uptake of the reticuloendothelial cells. This may be true in cases of the liver and the long bones. In our preliminary study, however, the signal in the vertebral bone marrow reduced substantially before SPIO injection on T2*WI (gradient sequence), and we could see fewer signal changes in T2*WI than STIR images after SPIO injection. This was presumably because of the presence of trabecular bones in the vertebral bodies, which also cause susceptibility effect (data not shown) and may be different in long bones. Moreover, this effect may be exacerbated at higher magnetic fields (3T) in that susceptibility effect increases in proportion to magnetic field strength. Finally, marrow composition, including hematopoietic and yellow marrow, varies with age so that initial marrow signal and signal reduction by SPIO particles can change. Therefore, the selection of imaging sequences/parameters should be carefully considered to suit the individual purpose.

Our study has several limitations. Although there are 3 types of metastatic bone tumors, osteolytic, osteoblastic, and mixed types, we studied only the osteolytic type, as characterized by MR imaging, and we did not perform the traditional gold standard of biopsy or histopathology. The patients need to be examined twice, and SPIO needs to be administered 3 hours prior to MR imaging with our method so that the examination can be completed in the same day as bone scintigraphy. Using SPIO, it is difficult to appreciate the decrease in signal intensity at a glance by our method. We need to calculate the RE of MR imaging signals to differentiate bone metastasis from osteomyelitis. MR imaging sequences more sensitive to this signal change are desirable to detect the lesions.

Conclusion

In summary, the most prominent signal reduction of normal bone marrow is seen 3 hours after intravenous injection of ferucarbotran at a dose of 8 µmol Fe/kg. Comparison of signal intensity using STIR images obtained before and after ferucarbotran injection is thought to be useful in differentiating bone metastasis and osteomyelitis.

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References


