REVIEW ARTICLE

Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application

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ABSTRACT

Superparamagnetic iron oxide (SPIO) MR contrast agents are composed of nano-sized iron oxide crystals coated with dextran or carboxydextran. Two SPIO agents are clinically approved, namely: ferumoxides (Feridex in the USA, Endorem in Europe) with a particle size of 120 to 180 nm, and ferucarbotran (Resovist) with a particle size of about 60 nm. The principal effect of the SPIO particles is on T2* relaxation and thus MR imaging is usually performed using T2/T2*-weighted sequences in which the tissue signal loss is due to the susceptibility effects of the iron oxide core. Enhancement on T1-weighted images can also be seen with the smaller Resovist. Both Feridex and Resovist are approved specifically for MRI of the liver. The difference being that Resovist can be administered as a rapid bolus (and thus can be used with both dynamic and delayed imaging), whereas Feridex needs to be administered as a slow infusion and is used solely in delayed phase imaging. In the liver, these particles are sequestered by phagocytic Kupffer cells in normal reticuloendothelial system (RES), but are not retained in lesions lacking Kupffer cells. Consequently, there are significant differences in T2/T2* relaxation between normal tissue and lesions, resulting in increased lesion conspicuity and detectability. SPIO substantially increase the detectability of hepatic metastases. For focal hepatocellular lesions, SPIO-enhanced MR imaging exhibits slightly better diagnostic performance than dynamic CT. A combination of dynamic and static MR imaging technique using T1- and T2 imaging criteria appears to provide clinically more useful patterns of enhancement. Feridex and Resovist are also used for evaluating macrophage activities in some inflammatory lesions, but their clinical values remain to be further confirmed. The clinical development of Ferumoxtran (Combidex in the USA, Sinerem in Europe), designed for lymph node metastasis evaluation, is currently stopped.

KEY WORDS Liver; Contrast media; iron oxide; SPIO; MRI; Neoplasm; Hepatocellular carcinoma

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Introduction

Magnetic resonance imaging (MRI) contrast agents have made a significant impact in the use of MRI for various clinical indications. Since the introduction of the first MRI contrast agent Gd-DTPA (Magnevist, Schering AG) in 1988, there has been a tremendous increase in the number of contrast-enhanced examinations. MRI contrast agents contain paramagnetic or superparamagnetic metal ions that affect the MRI signal properties of surrounding tissue. These contrast agents are used primarily to increase the sensitivity of MRI for detecting various pathological processes and also for characterizing various pathologies. In addition, the contrast agents are used for depicting normal and abnormal vasculature, or flow-related abnormalities and pathophysiologic processes like perfusion. In this article, a brief review of superparamagnetic iron oxide (SPIO) based MRI contrast agents and their current clinical applications are presented.

No potential conflict of interest.

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SPIO contrast agents for MRI

A conglomerate of numerous nano-sized iron oxide crystals coated with dextran or carboxydextran forms SPIO contrast agents (1). Two SPIO particle formulations are now clinically available, namely ferumoxides and ferucarbotran. Both are approved specifically for MR imaging of the liver. After intravenous administration, clinical approved SPIO particles are cleared from the blood by phagocytosis accomplished by reticuloendothelial system (RES) so that uptake is observed in the normal liver, spleen, bone marrow, and lymph nodes. After the intracellular uptake, SPIOs are metabolized in the lysosomes into a soluble, nonsuperparamagnetic form of iron that becomes part of the normal iron pool (eg, ferritin, hemoglobin) (1).

Feridex: Ferumoxides (Feridex IV, Berlex Laboratories; and Endorem, Guerbet) are developed by AMAG Pharma (former Advanced Magnetics) and was referred to as AMI-25. The *r2* and *r1* relaxivites are 98.3 and 23.9 $mM^{-1}sec^{-1}$ respectively. Ferumoxides is available in USA, Europe, and Japan. Feridex is an SPIO colloid with low molecular weight dextran coating, with a particle size of 120-180 nm. To reduce the incidence of some side effects such as hypotension, Feridex is prepared as a dilution in 100 ml of 5% dextrose and administered as a drip infusion over about 30 min. At about 8 min following the intravenous injection, iron oxide particles are taken up by the reticululoendothelial cells in the liver and in the spleen with an approximate uptake of 80% and 6-10%, respectively (2). Maximum signal loss is obtained after 1 h with an imaging window ranging from 30 min to 6 h after the injection. The recommended dosage of Feridex IV (ferumoxides injectable solution) is 0.56 milligrams of iron (0.05 mL Feridex IV) per kilogram of body weight. Hypotension and lumbar pain/leg pain represent the most frequent symptoms associated with Feridex administration with an incidence ranging from 2 to 10%. Pain severe enough to cause interruption or discontinuation of the infusion was reported to occur in 2.5% patients.

Resovist: Ferucarbotran (Resovist, Bayer Healthcare) is developed by Schering AG, and was referred to as SH U 555A. Resovist is available in Europe and Japan. The active particles are carboxydextrane-coated SPIO, with a hydrodynamic diameter ranging between 45 and 60 nm. The *r2* and *r1* relaxivites are 151.0 and 25.4 $mM^{-1}sec^{-1}$ respectively. Unlike Feridex, Resovist can be safely injected rapidly in a bolus fashion, and the incidence of cardiovascular adverse events and back pain are significantly less. Resovist has an effect on the shortening of both T1 and T2 relaxation time. Resovist enables T1-weighted imaging ensuring a valuable although less pronounced positive T1 contrast effect. Dynamic T1-weighted GRE 3D sequences can be performed to acquire the perfusion properties of the lesion during the arterial and portal venous phases of the contrast agent. On dynamic MR imaging using T1-weighted GRE, enhancement was positive in the liver for at least 30 s after bolus injection of SPIO (3). However, positive enhancement of hypervascular hepatocellular carcinoma (HCC) in early phase of T1W-GRE has been reported to be weak to assess the tumor perfusion. Although this agent was found to cause significant T1 shortening of blood, its use for MR angiography was found to be suboptimal (4). Due to the high *r2* relaxivity, Resovist is more suited to T2/T2*-weighted imaging. On delayed images after 10 min, the T2/T2* effects are observed due to the reticuloendothelial uptake in the liver. Perfusion study using echo planar imaging (EPI) yields negative enhancement of hypervascular tumors (5), and one-stop shop diagnosis (involving both dynamic and RES-targeted MR imaging) for hypervascular HCC are feasible. Resovist come as 0.5 mmol Fe/ml solution in prefilled syringe. The recommended dose of Resovist is: for patients weighing less than 60 kg: 0.9 ml Resovist (equivalent to 0.45 mmol iron); for adults patients weighing 60 kg or more: 1.4 ml Resovist® (equivalent to 0.7 mmol iron). Resovist's overall incidence of adverse events was 7.1%, with vasodilatation and paraesthesia the most common event reported (<2%). Although considerably less post-marketing data is available on the safety of Resovist than on Feridex, the safety profile appears more favorable for Resovist.

Ferumoxtran-10 (AMI-227; Combidex, AMAG Pharma; Sinerem, Guerbet): The *r2* and *r1* relaxivites of Combidex/Sinerem are 60 and 10 $mM^{-1}sec^{-1}$ respectively. The small size and hydrophilic coating result in a longer circulation in the intravascular space, and the particles escape rapid accumulation in the RES. These particles are phagocytosed by macrophages and accumulate in the lymphatic system. Normal lymph nodes are characterized by a dramatic signal drop on T2*-weighted images, whereas malignant lymph nodes, being devoid of macrophages, do not accumulate iron oxide particles and maintain a high MRI signal intensity. It takes 24 to 36 h for Combidex/Sinerem to accumulate in the lymph nodes, thus, postcontrast imaging is usually obtained 24 h after administration of the contrast agent. Sinerem was used in some European countries (not available now) — but not in the USA. In 2003, a paper by Harisinghani *et al.* (6) offered extraordinary results of the way in which ferumoxtran-10 could demonstrate the presence of positive lymph nodes in patients with prostate cancer. However, a recent, multi-center study by Heesakkers *et al.* (7) evaluated the use of ferumoxtran-10 and MRI to detect and identify lymph node metastases occurring outside the normal area of pelvic lymph node dissection in 296 patients with prostate cancer. All patients had intermediate to high risk

for nodal metastases. There was a 24.1 % false positive rate in this study, leading to unnecessary surgical intervention. The clinical development for ferumoxtran-10 was stopped due to these results. Since ferumoxtran-10' safety profile has been good as an imaging agent, perhaps the most appropriate question that researchers need to ask is where it is possible to develop a "second generation" form of ferumoxtran-10 which will have a significantly lower rate of false positive findings.

Clariscan: Clariscan (PEG-fero; Feruglose; NC100150) was developed by former Nycomed Imaging (now part of GE healthcare). NC100150 is consisted of SPIO particles that are composed of single crystals (4 to 7nm diameter) and stabilized with a carbohydrate polyethylene glycol (PEG) coat. The iron oxide particles have to be suspended in an isotonic glucose solution. The final diameter of an NC100150 particle is approximately 20 nm. Blood pool half-life is more than two hours in humans. It can be used as a MR angiography agent, and has been tested clinically for characterization of tumor microvasculature. NC100150 particles are eventually taken up by the mononuclear phagocyte system and distributed mainly to the liver and spleen. The development of NC100150 was discontinued due to safety concern.

Iron oxide-based agents for gastrointestinal contrast: There have been a few oral iron oxide-based agents developed for gastoinetestine luminal contrast (filling of gastrointestinal lumen), including AMI-121 (Ferumoxsil, Lumirem for Guerbet and Gastromark for Advanced Magentics) and OMP (Abdoscan, Nycomed Imaging). Though those agents are effective and safe, there has been very little market take-up.

Clinical application of Feridex and Resovist for liver Imaging

Due to the high prevalence of benign liver lesions in the adult population, liver lesion characterization is an important objective during hepatic imaging. This is especially true for patients with known extra-hepatic malignancies, who are being evaluated for liver metastases, because benign and malignant lesions may coexist. Furthermore, due to advances in cross-sectional imaging, small sub-centimetre lesions are being detected with increasing frequency, making liver lesion characterization particularly challenging. It is for liver lesions these SPIO agents already found their useful application. SPIO particles are opsonized and sequestered by phagocytic Kupffer cells of normal RES. Phagocytosed SPIO particles in Kupffer cells produce strong T2/T2* relaxation effects in the liver parenchyma. Following the administration of this agent, the liver (because of a homogeneous distribution of reticuloendothelial cells) negatively enhances on T2- or T2*-weighted images (ie, it turns dark), resulting in increased conspicuity of pathologic lesions that do not contain reticuloendothelial cells. The degree of SPIO uptake and the consecutive extent of signal intensity drop are used to differentiate and characterize lesions. Pulse sequence optimization for SPIO-enhanced MR imaging has recently been discussed. Tanimoto *et al*. proposed long TE SPGR exhibited the best signal-to-noise ratio and detectability, and the flip angle was $45–60^0$ (8). SPIO agents provide a long imaging window after IV infusion, thus facilitating high-spatial-resolution thin-section imaging.

SPIO-enhanced MRI is more accurate than nonenhanced MRI for the detection of focal hepatic lesions, and combined analysis of non-enhanced and SPIO-enhanced images is more accurate in the characterization of focal hepatic lesions than review of SPIO-enhanced images alone (9). In one early multicenter trial, Feridex -enhanced T2-weighted images revealed additional lesions not seen on unenhanced images in 27% of cases and additional lesions not seen by conventional (non-spiral) computed tomography (CT) scans in 40%; the additional information would have changed therapy in 59% of cases (10). The detection of metastases is apparently improved with SPIO agent, as well as cholangiocellular carcinoma, due to the absence of Kupffer cells within these lesions. Undifferentiated HCC usually demonstrate no change in signal intensity when compared with T2/T2*-weighted images in unenhanced and SPIO-enhanced imaging. This leads to an improvement in the contrast-to-noise ratio of the lesion with subsequent improvement of demarcation as well as visualization and an increased detection rate for HCC. On the other hand, lesions that contain reticuloendothelial cells, such as focal nodular hyperplasia, may become isointense to normal liver because of a decreased lesion-to-liver contrast ratio (11). A questionable focal nodular hyperplasia may be confirmed on SPIO enhanced MR. However, because of the relative inconsistency in the amount of reticuloendothelial cells in focal nodular hyperplasia and hepatic adenoma, cares should be taken with such clinical use.

Differentiation between HCC and dysplastic nodules (DN) is of great importance for the early and precise treatment of HCC in cirrhotic liver. One study reported that the ratio of the intensity of tumorous lesion to that of nontumorous area on SPIO-enhanced MR images (SPIO intensity ratio) correlated inversely with Kupffer-cell-count ratio in HCCs and dysplastic nodules, and increased as the degree of differentiation of HCCs decreased, indicating that the uptake of SPIO in HCCs decreased as the degree of differentiation of HCCs declined (12). Phagocytic activity might overlap among some borderline lesions. One study found no significant difference in number of Kupffer cells between

well-differentiated HCC and surrounding liver tissue (13). Tanimoto *et al.* (8) reported that some well-differentiated HCC exhibited signal decrease similar to the surrounding liver on T2W-FSE images, but less signal decrease than surrounding liver on T2*W-GRE images. Conversely, DNs exhibited strong decrease in signal on both T2W and T2*W images. In well-differentiated HCC, Kupffer cell density would be maintained but Kupffer cell function could be reduced compared to surrounding liver. One criterion, of a threshold signal loss of 10% on SPIO enhanced MR images, had been proposed to distinguish benign from malignant lesions (sensitivity 88%, specificity 89%) by receiver operating characteristic analysis (14).

The decrease in signal intensity of cirrhotic liver with SPIO is reduced compared to that in normal liver. The percentage of signal-intensity loss and liver-lesion contrast-to-noise ratio on SPIO-enhanced images was significantly higher in patients with mild liver cirrhosis than in patients with severe liver cirrhosis. Inflammation, scarring, regeneration and shunting in cirrhotic liver reduces hepatic uptake of SPIO, shifts distribution to the spleen, and produces signal heterogeneity (8,11). Structural and functional inhomogeneity in cirrhosis may cause false-positive lesions after SPIO administration.

To clarify the clinical role of SPIO-enhanced MR imaging in multi-modality decision-making, numerous comparative studies have been conducted. However, results drawn from such comparative studies should be carefully weighed since imaging equipment and parameters were not uniform among institutions. Investigators' experiences and preferences might also play a role in the results. Final consensus has not been reached yet, or may not be reached due to consistent evolution of CT and MRI technologies.

SPIO-MRI versus dynamic CT: The combined approach of non-enhanced and SPIO enhanced T2-weighted MR images together resulted in a significantly higher sensitivity as well as in significantly more accurate differentiation of benign from malignant lesions as compared with results from spiral CT images, non-enhanced T2-weighted MR images or SPIO-enhanced T2-weighted images alone (9). For the depiction of small hypervascular HCC, Lee *et al.* showed that the mean sensitivity of SPIO-enhanced MR imaging was significantly higher (70.6%, $P<0.05$) than that of dual-phase spiral CT (58.1%) (15). Tanimoto *et al.* (8) compared three imaging modalities in the detection of 72 HCCs. Detection rates were 69% for triple-phase dynamic CT (single helical), 89% for triple-phase dynamic MR imaging, and 86% for SPIO-MR imaging. There was a significant difference among the three modalities in rate of detection of HCC ($P<0.01$), but not between dynamic MRI and SPIO-MRI. Kim *et al.* compared SPIO-enhanced MR imaging with triple-phase multi-detector CT (MDCT) for preoperative detection of HCC (16). In their study, the mean sensitivities of MR imaging and triple-phase MDCT were 90.2% and 91.3%, respectively, and their mean specificities were 97.0% and 95.3%, respectively. SPIO-enhanced MR imaging was as accurate as triple-phase MDCT in preoperative detection of HCC (16). In addition, SPIO-enhanced MR imaging provides information supplementary to that obtained with dynamic CT, particularly by excluding pseudolesions. SPIO-enhanced MR imaging may be preferable due to its lack of radiation.

SPIO-MRI versus Gd-based dynamic MRI: Several studies have shown that Gd-based dynamic MRI is slightly better than SPIO-enhanced MR imaging in the detection of small HCCs (17,18). In lesion conspicuity, Gd-enhanced MR imaging is better than SPIO-enhanced MRI. However, SPIO yields additional information when imaging findings on Gd-based dynamic MRI are questionable because of intrahepatic arterioportal shunt (AP shunt) and/or post-therapeutic liver damage (19). Ward *et al.* (20) reported the usefulness of double-contrast MR imaging, i.e. combined SPIO- and Gd-dynamic MR imaging, for diagnosis of HCC. SPIO-enhanced MR imaging (mean accuracy=0.76) was more accurate than non-enhanced MR imaging (mean accuracy=0.64, $P<0.04$), and double-contrast MR imaging (mean accuracy=0.86) was more accurate than SPIO-enhanced imaging ($P<0.05$). Combined Gd-enhanced dynamic and SPIO-enhanced MR imaging may obviate the need for more invasive combined arterial portography and CT hepatic arteriography for preoperative evaluation of patients with HCC (8).

SPIO-MRI versus paramagnetic hepatobiliary agents-enhanced MRI: Paramagnetic hepatobiliary compounds, such as Mangafodipir trisodium (Mn-DPDP, Teslascan, GE Healthcare), Gadoxetic acid (Gd-EOB-DTPA, Primovist, Schering AG), and Gadobenate dimeglumine (MultiHance, Gd-BOPTA, Bracco Diagnostics), are partially taken up by hepatocytes, yielding positive and sustained enhancement of the liver parenchyma on T1-weighted images. There are few reports regarding comparison of efficacy between SPIO and paramagnetic hepatobiliary agents. A recent report suggested that gadobenate dimeglumine-enhanced 3D dynamic imaging exhibited better diagnostic performance than SPIO-enhanced imaging in the detection of HCC (21). More studies are needed to confirm this finding.

Investigational clinical applications of SPIO

Following intravenous injection, SPIO is incorporated into macrophages via endocytosis. The uptake of SPIO by phagocytic monocytes and macrophages provides a valuable *in-vivo* tool by

which MRI can be used to monitor involvement of macrophages in inflammatory processes (22), such as multiple sclerosis, traumatic nerve injury, stroke, brain tumours, and vulnerable plaque in carotid artery. Saleh *et al.* (23) performed an MRI study with Sinerem in ischaemic stroke patients; macrophage activity was observed in all patients. For multiple sclerosis, Dousset *et al.* (24) used Sinerem to demonstrate visualisation of macrophage activity in patients with relapsing–remitting multiple sclerosis. Neuwelt *et al.* (25) conducted clinical studies with MRI monitoring of macrophages in brain tumours. The macrophage MRI detection with SPIO of tumour morphology might facilitate the surgical resection or biopsy of brain tumours. Trivedi *et al.* (26) reported that, 24-36 h after infusion, Sinerem particles accumulated in macrophages of carotid atheroma which was detectable *in vivo* by MRI. Recently, the therapeutic use of stem and progenitor cells as a substitute for malfunctioning endogenous cell populations has received considerable attention in tissue engineering. The development of stem cell–based therapies requires a quantitative and qualitative assessment of their distribution to target organs and their engraftment. To be visualized with MRI, these stem cells can be labelled with SPIO. However, SPIO stem cell labeling is not a FDA approved indication. How SPIO affect the function and fate of stem cells remains further clarification (27,28).

Conclusion

Until now, dynamic MRI after bolus injection of Gd-based extracellular agents is still the workhorse of liver imaging. SPIO-enhanced MR imaging is an effective means of pre-therapeutic evaluation and follow-up diagnosis of liver tumors, featuring improved detection of HCC and capacity to differentiate lesions. It improves the selection of patients who are candidates for curative liver surgery, since with it invasive surgery can be avoided if multiple lesions are present. The clinical application of new SPIO contrast agents must evolve into an integrated diagnostic scheme as a problem-solving tool in patients with atypical features of focal liver lesions and to supplement information provided by the use of non-specific extracellular Gd-based agents (or iodinated agent enhanced CT). For non-liver imaging, new applications of approved SPIO are being explored. Newer SPIOs with clinically relevant characteristics remain to be further developed.

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