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# Contrast agents for hepatic MRI

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**Abstract**

Liver specific contrast media (LSCM) can be subdivided according to different modalities of hepatic distribution: exclusive distribution to the hepatocellular compartment can be obtained using CM which accumulate within the hepatocytes after slow infusion; other CM demonstrate combined perfusion and hepatocyte-selective properties, with an initial distribution to the vascular-interstitial compartment (in an analogous manner to that of the conventional extracellular CM), thereafter, a fraction of the injected dose is taken up into the hepatocytes causing an increase in the signal intensity of the hepatic tissue. The use of the superparamagnetic effect of iron oxide particles is based on distribution in the reticuloendothelial system (RES), usually well represented in the normal parenchyma as well as in benign hepatocellular lesions, and absent in most malignant lesions. It is necessary to have an in-depth knowledge of either the biological and histological characteristics of focal liver lesions (FLL) or the enhancement mechanism of LSCM to gain significant accuracy in the differential diagnosis of FLL. Dynamic contrast-enhanced MRI is an important tool in the identification and characterization of FLL. With LSCM it is possible to differentiate benign from malignant lesions and hepatocellular lesions from non hepatocellular lesions with high accuracy. To understand the contrast behaviour after injection of LSCM it is necessary to correlate the contrast enhancement with both the biological and histological findings of FLL.

**Keywords:** *Liver; neoplasms; magnetic resonance; contrast media.*

## Introduction

MRI is an established imaging method for the evaluation of focal liver lesions; in order to adequately characterize focal hepatic lesions on magnetic resonance imaging (MRI), it is necessary to utilize contrast media (CM) which are able to modify the signal intensity of either the lesion or normal liver parenchyma and thus contribute towards the characterization of the lesion[1–4].

The sensitivity of MR to the variations of signal intensity induced by CM has led to the development of several different types of liver specific contrast media (LSCM), which utilize the paramagnetic properties of gadolinium or manganese or the superparamagnetic properties of iron. Non-specific gadolinium chelates such as gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) (Magnevist, Schering AG, Berlin, Germany) and Gd-DTPA-bismethylamide (BMA) (Amersham Health, Oslo, Norway)[5] which distribute in the extracellular fluid (ECF) space are currently the most widely employed CM. These CM are most effective during the dynamic phase of contrast enhancement when differential blood flow between tumour and normal liver parenchyma leads to characteristic lesion enhancement patterns[2,3]. Unfortunately, dynamic phase imaging alone can, at times, prove unsatisfactory for the accurate diagnosis of hepatic lesions[6].

## Classification of LSCM

The development of CM with liver-specific properties has increased the accuracy of MR for the identification and characterization of focal liver lesions[7–10]. The various CM can be distinguished on the basis of their distribution after intravenous injection.

Exclusive distribution to the hepatocellular compartment can be obtained using CM which – when injected by means of slow infusion – accumulate within the hepatocytes and cause an increase in the proton relaxation rate. In mangafodipir trisodium (Mn-DPDP, Teslascan, Nycomed, Oslo, Norway), the manganese ion

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is chelated with four molecules of meglumine. The molecule is isotonic with blood and has a low viscosity. It is infused slowly (2–3 ml/min over a 10–20 min period) at a concentration of 10 mmol/ml, and at a dose of 0.5 ml/kg. After administration, the $Mn^{2+}$ ion contained in the molecule is gradually released into the blood from the DPDP chelate, and is substituted by zinc. The latter has an affinity for the chelant that is hundreds of times greater than that of $Mn^{2+}$. The free $Mn^{2+}$ is then available for uptake into parenchymal cells, particularly those of the liver, pancreas, kidneys and adrenals in which metabolism of this metal takes place. Maximum tissue enhancement is observed at the end of the infusion after approximately 20 min and lasts for around 4 h[11]. Tumours of non-hepatocytic origin show little or no tumour enhancement resulting in increased lesion conspicuity. Several studies have shown improved lesion detection on images obtained after infusion of mangafodipir trisodium compared with pre-contrast images[12,13]. In a multicenter study, mangafodipir trisodium enhanced MRI in 77 patients with histologically confirmed lesions and had a sensitivity and specificity in differentiating lesions of 91% and 67% (malignant vs benign lesions) and 91% and 85% (hepatocellular vs non-hepatocellular lesions), respectively[14]. However, uptake of mangafodipir trisodium by both benign and malignant hepatic neoplasms limits the accurate differentiation between benign and malignant tumours of hepatocellular nature[15–17] and represents a major shortcoming of this agent. The significant biliary excretion may aid in the assessment of the patency of biliary-enteric anastomoses[18] and can be of value in the detection of complications of biliary surgery.

Other CM demonstrate combined perfusion and hepatocyte-selective properties. Such compounds distribute initially to the vascular-interstitial compartment in an analogous manner to that of conventional, extracellular CM. Thereafter, a fraction of the injected dose is taken up into the hepatocytes causing an increase in the signal intensity of the hepatic tissue. Agents of this type include gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco SpA, Milan, Italy), and gadolinium-ethoxybenzyl-DTPA (Gd-EOB-DTPA, Primovist, Bayer Schering Pharma SpA, Berlin, Germany).

### *Gadobenate dimeglumine*

Gadobenate dimeglumine is a chelate of the paramagnetic gadolinium ion, salified with two molecules of meglumine. Gd-BOPTA is a second generation gadolinium chelate which combines the properties of a conventional extracellular gadolinium agent with those of an agent targeted specifically for the liver[19]. Gd-BOPTA has an elimination profile that sees roughly 96% of the injected dose excreted renally via glomerular filtration; the remaining 2–4% taken up by functioning hepatocytes is eliminated in the bile via the hepatobiliary pathway[20], leading to a marked and long-lasting enhancement of the signal intensity of normal liver parenchyma beginning 40 min after Gd-BOPTA administration[21]. Gd-BOPTA behaves in an analogous way to conventional gadolinium agents during the dynamic phase of contrast enhancement[22], while in the delayed phase it not only improves the impact of MRI for the detection of focal liver lesions[1,23], but may also contribute to the improved characterization of detected lesions, particularly lesions demonstrating atypical enhancement on dynamic imaging[24,25]. For example, accurate characterization of focal nodular hyperplasia (FNH) is not always possible since atypical features can confound the interpretation. The Gd-BOPTA enhancement dynamics of FNH in the early phases parallel those seen with conventional extracellular agents. During the hepatobiliary phase (1–3 h after injection) on T1-weigted images substantial enhancement is noted within the parenchyma of FNH and the lesion appears iso- or hyperintense to the surrounding liver[25], whereas the central scar, which is the principal site of the biliary metaplasia, appears consistently hypointense. On the contrary, hepatic adenoma, which frequently affects women with a history of oral contraceptive use and needs to be differentiated by FNH, on delayed phase images after injection of Gd-BOPTA shows little evidence of uptake and appears hypointense[26,27].

### *Gadolinium ethoxybenzyldiethylenetriamine-pentaacetic acid*

Gadolinium ethoxybenzyldiethylenetriaminepentaacetic acid exploits the `carrier' used by hepatocytes for the uptake of bilirubin[28]. In an analogous manner to that of Gd-BOPTA, this CM distributes initially to the vascular-interstitial compartment after injection. With Gd-EOB-DTPA about 50% of the injected dose is taken up and eliminated via the hepatobiliary pathway. The maximum increase in liver parenchyma signal intensity is observed about 20 min after injection and lasts for approximately 2 h[29]. During the perfusion phase the dynamic enhancement patterns seen after injection of Gd-EOB-DTPA are similar to those seen with Gd-DTPA, while during the hepatobiliary phase Gd-EOB-DTPA-enhanced images have been shown to yield a statistically significant improvement in the detection rate of FLL compared with unenhanced and Gd-DTPA-enhanced images[10], with a modality of enhancement of the different FLL which is similar to that observed with Gd-BOPTA.

### *Superparamagnetic iron oxide*

The use of the superparamagnetic effect of iron oxide particles is based on distribution in the reticuloendothelial system (RES). The presence of superparamagnetic iron oxide locally augments the externally applied magnetic field, producing magnetic field heterogeneity which in turn, promotes dephasing, and results in signal loss from enhanced T2 relaxation. Superparamagnetic

iron oxide (SPIO) particles are cleared from the blood by phagocytosis accomplished by RES so that uptake is observed in the normal liver, spleen, bone marrow, and lymph nodes[30]. Inflammation, scarring, regeneration and shunting in cirrhotic liver reduces hepatic uptake of SPIO, shifts distribution to the spleen, and produces signal heterogeneity. Most focal liver lesions, mainly malignant ones, lack Kupffer's cells or the capacity to take up particles. After SPIO injection, the darkening of normal liver parenchyma which surrounds focal liver lesions increases the contrast/noise ratio (CNR) of these lesions, usually slightly hyperintense on precontrast T2-weighted images, which appear more hyperintense at T2-weighted images.

### *Ferumoxides*

Ferumoxides (Feridex IV, Berlex Laboratories Wayne, NY; and Endorem, Guerbet, Aulnay Sous Bois, France) were developed by Advanced Magnetics (Cambridge, MA) and referred to as AMI-25. Ferumoxides is an SPIO colloid with low molecular weight dextrane, with a particle size of 50–180 nm, according to the analytical system utilized (electron microscopy or photocorrelation spectroscopy)[31].

At about 8 min following an intravenous injection, iron oxide particles are taken up by the reticululoendothelial cells in the liver (Kupffer cells) and in the spleen with an approximate uptake of 80% and 6–10%, respectively[30]. Maximum signal loss is obtained after 1 h with an imaging window ranging from 30 min to 6 h after the injection[32,33]. The recommended dose is 15 mmol/kg. To reduce the incidence of some side effects such as hypotension, ferumoxides is prepared as a dilution in 100 ml of 5% dextrose and administered as a drip infusion over about 30 min. Hypotension and lumbar pain represent the most frequent symptoms associated with SPIO administration with an incidence ranging from 2 to 10%[31].

The clinical efficacy of Ferumoxides for detection of focal liver lesions on T2-weighted images has been investigated in several trials. In a multicenter trial, ferumoxides-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[33]. A comparison with spiral CT has demonstrated a better sensitivity of SPIO-enhanced MR images, but at the expense of reduced specificity with a higher number of false positive cases[34]. Other studies have compared the efficacy of SPIO-enhanced T2-weighted MR images to computed tomography during arterial portography (CTAP), and these have shown a higher sensitivity and specificity of MR images, especially with T2*-weighted breath-hold gradient echo (GRE) images. A study demonstrated a better sensitivity of CTAP, when performed with spiral CT[35].

### *SH U 555 A (Ferucarbotran)*

SH U 555 A (Ferucarbotran) is the code name of an SPIO contrast agent registered as Resovist® (Schering AG, Berlin, Germany) and commercially available since 2001. The active particles are carboxydextrane-coated super-paramagnetic iron oxide, with a hydrodynamic diameter ranging between 45 and 60 nm. The differing particle sizes determine the velocity of their uptake by cells of the RES, specially the Kupffer cells in the liver, as well as the relaxivity-related effects. It can be administered as a fast bolus. SH U 555 A has a strong effect on the shortening of both T1 and T2 relaxation time. Due to the high R2 relaxivity it is particularly suited to T2- and T2*-weighted imaging. Furthermore, SH U 555 A enables T1-weighted imaging with a tenth of the standard dose of extracellular contrast agents (Gd-DTPA) ensuring a valuable although less pronounced T1 effect. Fast bolus injection of SH U 555 A makes it possible to observe the early perfusion characteristics of the liver using T1- or T2*-weighted sequences. The accumulation phase imaging (RES phase) can be performed as early as 10 min post-injection utilising T1-, T2- and T2*-weighted sequences. The T2- and T2*-weighted accumulation phase imaging improves the visualisation, delineation and conspicuity of the lesions and hence improves detection[36]. However, 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[37].

## Conclusions

The utilization of ECF gadolinium-based contrast agents with dynamic acquisition is the predominant means of contrast-enhanced liver MRI. However, increased utilization of targeted CM can improve the sensitivity and specificity of the MR study in the identification and characterization of focal liver lesions. Expertise with all these agents will further reduce the need for tissue sampling and allow a better non-invasive means to triage patients with hepatic malignancies.

## References

[1] Petersein J, Spinazzi A, Giovagnoni A, *et al.* Focal liver lesions: evaluation of the efficacy of gadobenate dimeglumine in MR imaging – a multicenter phase III clinical study. Radiology 2000; 215: 727–36.

[2] Hamm B, Fischer E, Taupitz M. Differentiation of hepatic hemangiomas from metastases by dynamic contrast-enhanced MR imaging. J Comput Assist Tomogr 1990; 14: 205–16.

[3] Semelka RC, Shoenut JP, Kroeker MA, *et al.* Focal liver disease: comparison of dynamic contrast-enhanced CT and T2-weighted fat-suppressed, FLASH, and dynamic gadolinium-enhanced MR imaging at 1.5 T. Radiology 1992; 184: 687–94.

[4] Vogl TJ, Stupavsky A, Pegios W, *et al.* Hepatocellular carcinoma: evaluation with dynamic and static gadobenate dimeglumine-enhanced MR imaging and histopathologic correlation. Radiology 1997; 205: 721–8.

[5] Weinmann HJ, Laniado M, Mutzel W. Pharmacokinetics of GdDTPA/dimeglumine after intravenous injection into healthy volunteers. Physiol Chem Phys Med NMR 1984; 16: 167–72.

[6] Hamm B, Thoeni RF, Gould RG, *et al.* Focal liver lesions: characterization with nonenhanced and dynamic contrast material-enhanced MR imaging. Radiology 1994; 190: 417–23.

[7] Kuwatsuru R, Kadoya M, Ohtomo K, *et al.* Comparison of gadobenate dimeglumine with gadopentetate dimeglumine for magnetic resonance imaging of liver tumors. Invest Radiol 2001; 36: 632–41.

[8] Nakayama M, Yamashita Y, Mitsuzaki K, *et al.* Improved tissue characterization of focal liver lesions with ferumoxide-enhanced T1 and T2-weighted MR imaging. J Magn Reson Imaging 2000; 11: 647–54.

[9] Liou J, Lee JK, Borrello JA, Brown JJ. Differentiation of hepatomas from nonhepatomatous masses: use of MnDPDP-enhanced MR images. Magn Reson Imaging 1994; 12: 71–9.

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

[11] Lim KO, Stark DD, Leese PT, Pfefferbaum A, Rocklage SM, Quay SC. Hepatobiliary MR imaging: first human experience with MnDPDP. Radiology 1991; 178: 79–82.

[12] Rummeny EJ, Torres CG, Kurdziel JC, Nilsen G, Op de Beeck B, Lundby B. MnDPDP for MR imaging of the liver. Results of an independent image evaluation of the European phase III studies. Acta Radiol 1997; 38: 638–42.

[13] Wang C. Mangafodipir trisodium (MnDPDP)-enhanced magnetic resonance imaging of the liver and pancreas. Acta Radiol Suppl 1998; 415: 1–31.

[14] Oudkerk M, Torres CG, Song B, *et al.* Characterization of liver lesions with mangafodipir trisodium–enhanced MR imaging: multicenter study comparing MR and dual-phase spiral CT. Radiology 2002; 223: 517–24.

[15] Rofsky NM, Weinreb JC, Bernardino ME, Young SW, Lee JK, Noz ME. Hepatocellular tumors: characterization with Mn-DPDP-enhanced MR imaging. Radiology 1993; 188: 53–9.

[16] Murakami T, Baron RL, Peterson MS, *et al.* Hepatocellular carcinoma: MR imaging with mangafodipir trisodium (Mn-DPDP). Radiology 1996; 200: 69–77.

[17] Coffin CM, Diche T, Mahfouz A, *et al.* Benign and malignant hepatocellular tumors: evaluation of tumoral enhancement after mangafodipir trisodium injection on MR imaging. Eur Radiol 1999; 9: 444–9.

[18] Hottat N, Winant C, Metens T, Bourgeois N, Deviere J, Matos C. MR cholangiography with manganese dipyridoxyl diphosphate in the evaluation of biliary-enteric anastomoses: preliminary experience. AJR Am J Roentgenol 2005; 184: 1556–62.

[19] Kirchin MA, Pirovano GP, Spinazzi A. Gadobenate dimeglumine (Gd-BOPTA). An overview. Invest Radiol 1998; 33: 798–809.

[20] Spinazzi A, Lorusso V, Pirovano G, Kirchin M. Safety, tolerance, biodistribution, and MR imaging enhancement of the liver with gadobenate dimeglumine: results of clinical pharmacologic and pilot imaging studies in nonpatient and patient volunteers. Acad Radiol 1999; 6: 282–91.

[21] Spinazzi A, Lorusso V, Pirovano G, Taroni P, Kirchin M, Davies A. Multihance clinical pharmacology: biodistribution and MR enhancement of the liver. Acad Radiol 1998; 5: (Suppl 1) S86–89 (discussion S93–84).

[22] Grazioli L, Kirchin M, Pirovano G, Spinazzi A. MultiHance in the dynamic phase of contrast enhancement: a pictorial assessment. J Comput Assist Tomogr 1999; 23 (Suppl 1): S61–64.

[23] Caudana R, Morana G, Pirovano GP, *et al.* Focal malignant hepatic lesions: MR imaging enhanced with gadolinium benzyloxypropionictetra-acetate (BOPTA) – preliminary results of phase II clinical application. Radiology 1996; 199: 513–20.

[24] Manfredi R, Maresca G, Baron RL, *et al.* Delayed MR imaging of hepatocellular carcinoma enhanced by gadobenate dimeglumine (Gd-BOPTA). J Magn Reson Imaging 1999; 9: 704–10.

[25] Grazioli L, Morana G, Federle MP, *et al.* Focal nodular hyperplasia: morphologic and functional information from MR imaging with gadobenate dimeglumine. Radiology 2001; 221: 731–9.

[26] Grazioli L, Federle MP, Brancatelli G, Ichikawa T, Olivetti L, Blachar A. Hepatic adenomas: imaging and pathologic findings. Radiographics 2001; 21: 877–92 (discussion 892–74).

[27] Grazioli L, Morana G, Kirchin MA, Schneider G. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. Radiology 2005; 236: 166–77.

[28] Schuhmann-Giampieri G, Schmitt-Willich H, Frenzel T, Schitt-Willich H. Biliary excretion and pharmacokinetics of a gadolinium chelate used as a liver-specific contrast agent for magnetic resonance imaging in the rat. J Pharm Sci 1993; 82: 799–803.

[29] Hamm B, Staks T, Muhler A, *et al.* Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology 1995; 195: 785–92.

[30] Weissleder R, Stark DD, Engelstad BL, *et al.* Superparamagnetic iron oxide: pharmacokinetics and toxicity. AJR Am J Roentgenol 1989; 152: 167–73.

[31] Hahn PF, Saini S. Liver-specific MR imaging contrast agents. Radiol Clin North Am 1998; 36: 287–97.

[32] Gandon Y, Heautot JF, Brunet F, Guyader D, Deugnier Y, Carsin M. Superparamagnetic iron oxide: clinical time-response study. Eur J Radiol 1991; 12: 195–200.

[33] Ros PR, Freeny PC, Harms SE, *et al.* Hepatic MR imaging with ferumoxides: a multicenter clinical trial of the safety and efficacy in the detection of focal hepatic lesions. Radiology 1995; 196: 481–8.

[34] Muller M, Reimer P, Wiedermann D, *et al.* [T1-weighted dynamic MRI with new superparamagnetic iron oxide particles (Resovist): results of a phantom study as well as 25 patients]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1998; 168: 228–36.

[35] Strotzer M, Gmeinwieser J, Schmidt J, *et al.* Diagnosis of liver metastases from colorectal adenocarcinoma. Comparison of spiral-CTAP combined with intravenous contrast-enhanced spiral-CT and SPIO-enhanced MR combined with plain MR imaging. Acta Radiol 1997; 38: 986–92.

[36] Kehagias DT, Gouliamos AD, Smyrniotis V, Vlahos LJ. Diagnostic efficacy and safety of MRI of the liver with superparamagnetic iron oxide particles (SH U 555 A). J Magn Reson Imaging 2001; 14: 595–601.

[37] Reimer P, Jahnke N, Fiebich M, *et al.* Hepatic lesion detection and characterization: value of nonenhanced MR imaging, superparamagnetic iron oxide-enhanced MR imaging, and spiral CT-ROC analysis. Radiology 2000; 217: 152–8.