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From New Indications to Novel Tissue-Specific Contrast Agents

Hanns-Joachim Weinmann, PhD
Research Laboratories of Schering AG, Berlin, Germany
D 13342 Berlin Germany
email: hannsjoachim.weinmann@schering.de

Introduction

The first paramagnetic metal chelate, gadopentetate dimeglumine (**1**, GdDTPA= gadolinium complex of diethylenetriaminepentaacetic acid) received marketing authorization (Magnevist, Schering AG, Berlin, Germany) in 1988. Less than ten years after the first approval in Europe, Japan, and the US, metal chelates became an important tool for routine clinical MRI. More than 20 million applications have been performed with this first paramagnetic chelate. Other gadolinium chelates with similar imaging properties have been introduced. These agents belong to the group of open-chain (**2** gadodiamide, **3** gadoversetamide) and macrocyclic complexes (**4** gadoterate, **5** gadoteridol, **6** gadobutrol) (fig.1).

This article describes new specific formulations of these agents and mentions also new and more specific contrast agents.

Special formulations

The neutral macrocyclic complex gadobutrol can be formulated as 1.0 mol/L solutions with acceptable viscosity (1). The highly concentrated material will be useful in fast dynamic studies such as brain perfusion and fast Magnetic Resonance Angiography (MRA). When high peak concentrations of gadolinium and strong susceptibility effects are desirable, the 1.0-molar media are advantageous.

Standard formulations (0.5 mol/L) used for intravenous injection must be substantially diluted (0.5 and 5 mmol/L) to produce optimal signal intensity in a local volume (e.g. stomach). Diluted gadopentetate formulations were used as oral contrast medium (Magnevist enteral) or in MR arthroscopy, MR cisternography and myelography (2, 3, 4). Magnevist enteral contains mannitol and GdDTPA (1 mmol/L). Mannitol and the gadolinium chelates are not absorbed from the GI tract and produce a strong and homogenous enhancement in the entire GI lumen. A 2 mmol/L formulation of gadopentetate is in clinical use for arthroscopy in some European countries.

Transcatheter arterial embolization and percutaneous ethanol injection (PEI) are widely used in the therapy of primary hepatocellular carcinoma or metastases(5). MR-guided ethanol administration can be performed by using a gadolinium-doped ethanol formulation. 90% ethanol

solution containing 1 mmol/L GdDTPA is easily detectable using T1-weighted imaging techniques.

Liver-specific contrast agents

One of the disadvantages of currently available contrast agents is their relatively non-specific distribution in the organism. Targeting compounds to liver-specific cells such as hepatocytes or Kuppfer cells were the first successful approach to reach tissue-specificity. These include water-soluble paramagnetic chelates with hepatobiliary uptake such as Mn-DPDP (Mangafodipir = Teslascan®, Nycomed, Norway), GdBOPTA (gadobenate = MultiHance®, Bracco, Italy), Gd-EOB-DTPA (Gd-ethoxybenzyl-DTPA, gadoxetate, Eovist®, Schering AG, Germany), and superparamagnetic iron particles accumulating in the reticulo endothelial system (RES) such as AMI-25 (Feridex®, Berlex, USA and Endorem®, Guerbet, France) and SH U 555A (Resovist® Schering, Germany).

Because of its five unpaired electrons the Mn^{2+} ion is a powerful T_1-relaxation agent. Mangafodipir demonstrates both biliary and renal excretion and has been shown to be a positive and very effective liver enhancer. Its chemical similarity to vitamin B_6 is cited as the reason for uptake by hepatocytes. In addition, free Mn2+ released from the unstable complex caused tissue enhancement in the liver and pancreas (6, 7). Although general tolerance was favorable, transient facial flushing has been observed.

The Gd-EOB-DTPA (Eovist®) molecule has a lipophilic residue that targets the agent to a special carrier in the sinusoidal plasma membrane of the hepatocyte. Because of the overall high hydrophilicity and low protein binding the agent displays a favorable tolerance profile. After intravenous injection, the compound is completely eliminated from the body in equal parts by the hepato-biliary and renal routes. Because of the hepatocellular accumulation and high relaxivity, as little as 10 -25 mmol /kg of Eovist® is sufficient for an improved detection and characterization of liver tumors.

Special superparamagnetic iron oxide (SPIO) aggregates are extremely effective T2-relaxation agents (8, 9). These iron particles are coated with polysaccharides (e.g. dextranes) and form a mahogany-colored aqueous solution. After intravenous administration, SPIO particles are sequestered by normal phagocytic Kupffer cells, but they are not retained in metastases and no uptake was observed in hepatocytes. SPIO caused a strong susceptibility effect that is especially apparent in T2-weighted sequences. Just 3 mg Fe/g liver will cause a signal decrease of 50% in a standard T2-weighted sequence. The iron oxides are metabolized into a soluble, and non-superparamagnetic form of iron within a few days.

With T2-weighted imaging techniques, a dose of about 10 mmol Fe/kg produced excellent clinical results (10, 11). SPIO-enhanced images during the retention phases offer improved diagnostic accuracy in detecting focal liver lesions. No clinically relevant adverse reactions or changes in laboratory parameters were observed with the latest SPIO formulations (Resovist®).

Blood-Pool Agents

MR angiography (MRA) has been revolutionized by the introduction of paramagnetic gadolinium chelates. Extracellular agents permits arterial blood imaging within 30 sec or less. However, some indications may require a longer lasting contrast effect, these indications are coronary MRA, high resolution imaging and interventional MR techniques. Para- and superparamagnetic agents are, in principle, both suitable for enhancing the blood signal intensity at

low concentrations.

A strong protein-binding derivative of gadopentetate (MS-325, Epix, Cambridge, USA) display vascular distribution and a high T1-relaxivity. Reports from initial clinical studies demonstrate excellent angiograms (venous and arterial enhancement) and indicate that the compound may be safe and effective .

Polymeric gadolinium complexes have been investigated extensively. Such large molecules do not diffuse quickly out of the blood into the interstitial space and elicit a prolonged elimination from the vascular lumen because of a slower glomerular excretion. Several groups tried covalently binding gadolinium chelate to polymeric backbones such as albumin, dextran, polylysine, and novel polymeric structures (12, 13, 14).

A lot of attention is being focused on gadolinium containing dendrimers such as Gadomer-17, a 24 gadolinium atom-carrying compound. This molecule has an apparent molecular weight of about 35 kDa, that is, small enough to guarantee renal excretion and large enough to reduce diffusion through the endothelial wall of intact blood vessels. A dose of 12.5 to 50 μmol Gd/kg of body weight is sufficient to produce excellent angiograms. In addition, such polymeric agents have the potential to improve differential diagnosis by measuring the permeability surface area product of the endothelial wall in malign and benign lesions (15).

Recently, ultra-small superparamagnetic iron oxides (USPIOs) have been used as effective T1 blood pool contrast agents. Using heavily T1-weighted sequence doses of 1 to 3 mg (15 to 50 μmol) Fe/kg body weight produced excellent contrast enhancement of the vascular system (16). Like macrophage-specific SPIOs, these iron oxides are subject to intracellular degradation.

Necrosis-specific agents

Although not tumor-specific, a metalloporphyrin derivatives (bis-GdDTPA mesoporphyrin, Gadophrin-2, Schering AG Berlin, Germany) accumulates in necrotic tissue. The agent enhances small necrotic zones three to twenty-four hours after a dose of 25-50 mmol Gd/kg (17). This technique may be useful for visualizing spontaneous necrosis such as acute myocardial infarct or necrosis following imaging guided tumor ablation.

Lymph Node-Specific Agents

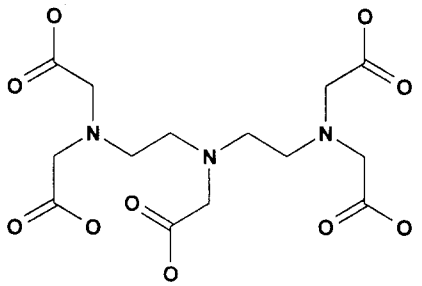
Since endolymphatic administration is an invasive and cumbersome procedure, agents that accumulate in the lymphatics after interstitial or intravenous injection were desired. Lymphotropic paramagnetically labeled substances would result in increased signal intensity of the normal tissue. Special carbohydrated polymers labeled with GdDTPA accumulate in the lymph nodes of rats after intravenous injection (18).

SPIOs are potent contrast agents for lymphography. After endolymphatic administration, trace amounts caused a darkening of the lymphatic vessels and lymph nodes (19). A significant reduction of the signal intensity of the normal lymph nodes occurs 24 h after intravenous injection of a dose of about 50 mmol/kg. Promising results have been reported in a clinical phase III study using AMI 7227 (Advanced Magnetics, USA) (20).

Monoclonal Antibodies

Paramagnetic chelate-labeled monoclonal antibodies are believed to be the ultimate tumor-seeking materials. Experimental studies in small animals revealed that it was possible to

achieve a higher and more specific concentration of the magnetic label at the target (21). Studies confirmed that special iron oxide formulations (MION) exhibit a specific enhancement after an intravenous dose of 2 mg antibody/kg (22). Monoclonal antibodies conjugated with MION particles may provide a method to obtain specific diagnoses of tumor involvement. However, the required dose of an antibody is still very high to make commercial development promising.



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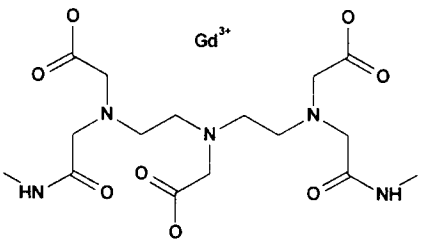

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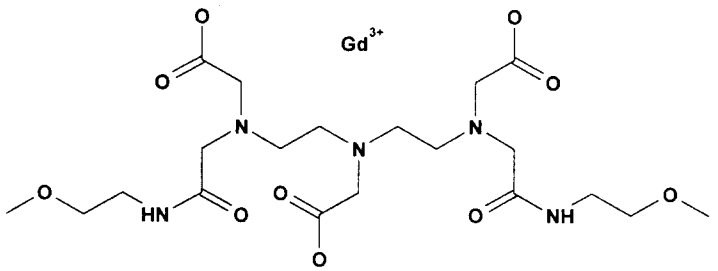

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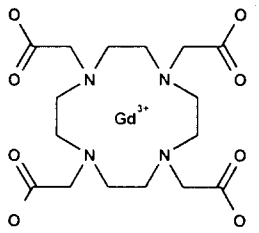

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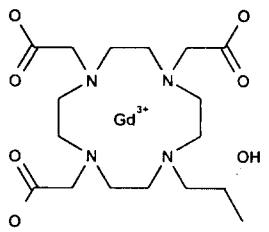

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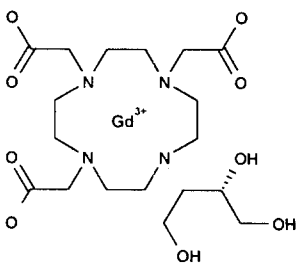

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Fig. 1: Chemical structure of clinically used extracellular gadolinium chelates.
1 (gadopentetate=Magnevist), **2** (gadodiamide=Omniscan), **3** (gadoversetamide=Optimark), **4** (gadoterate=Dotarem), **5** (gadoteridol=ProHance), **6** (gadobutrol=Gadovist).
The corresponding cations ions of **1** and **4** were omitted.

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