

# Magnetic Resonance Imaging Modalities with Contrast Enhancing Nanomaterials



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**Abbreviations:** BBB: Blood Brain Barrier; Ca: Calcium; CT: Computed Tomography; EM: Electro-Magnetic; EMA: European Medicines Agency; FDA: (U.S.) Food And Drug Administration; Fmri: Functional Magnetic Resonance Imaging; Gd: Gadolinium; GI: Gastro-Intestinal; IV: Intra-Venous; Mn: Manganese; MEMRI: Manganese-Enhanced MRI; Mn-DPDP: Chelated Manganese Nanoparticles; MRA: Magnetic Resonance Angiography; MRI: Magnetic Resonance Imaging; NCTR= (U.S.) National Center For Toxicological Research; NFD: Nephrogenic Fibrosing Dermopathy; NSF: Nephrogenic Systemic Fibrosis; RF: Radio-Frequency; SIPP: Superparamagnetic Iron Platinum Particles; SPIO: Super-Paramagnetic Ion Oxide; T1,2: Relaxation Times; USPIO: Ultra Small Super-Paramagnetic Ion Oxide

**Diseases Listed:** Cancer (Brain; Prostate); Nephrogenic Fibrosing Dermopathy; Nephrogenic Systemic Fibrosis; Scleroderma

**Drugs Cited:** Ablavar; Datarem; Gadavist; Gadobenate (Multihance); Gadobutrol (Gadovist); Gadodiamide (Omniscan); Gadocoletic Acid; Gadofosveset (Ablavar, Formerly Vasovist); Gadomelitol; Gadomer; GadoMRT Ratiopharm; Gadopentetate (Magnevist, Magnegita, Gado-MRT Ratiopharm); Gadoterate (Datarem); Gadoteridol (Prohance); Gadoversetamide (Optimark); Gadoxetate (Primavist); Magnevist; Manganese (Chelated; Enhanced); Multihance; Omniscan; Optimarse; Primovist; Prohance

**Discontinued:** Clariscan (PEG-Fero, Feruglose NC100150); Feridex I.V. (Endorem, Ferumoxides); Lumirem (Gastromark); Resovist (Cliavist); Sinerem (Combidex).

Various contrast materials are used in radiological imaging [particularly, computed tomography (CT) and the several modalities of magnetic resonance imaging (MRI)]. However, some of these agents can be toxic and their molecular size too large to provide highly contrasted images. In opposition, nanocontrast agents offer greater safety and enhanced contrast [1]. The purpose of this paper is to provide a comparative assessment of both types of contrast materials (conventional and nanomaterials).

## MRI Contrast Agents

These agents comprise a group of contrast media used to improve the visibility of internal body structures imaged with magnetic resonance. Most used agents are gadolinium (Gd)-based. Contrast agents alter the relaxation times of bodies within body tissues where they are present after oral administration (case of the gastro-intestinal (GI) tract) or intra-venous (IV) injection (for most other scans)]. To better appreciate their roles, the following analyses were performed.

## MRI Technique

A brief understanding of the MRI technique will be helpful. After administration of the appropriate contrast agent, sections of the patient's body are exposed to a very strong magnetic field, which causes the constituent hydrogen protons to align with this field (whether in the same or opposite directions). A radiofrequency (RF) pulse is then applied causing some of the protons (including those in the contrast agents) to spin and then relax after the pulse stops. This relaxation emits energy which is detected by the scanner and subsequently mathematically converted into an image. Depending on the application pursued, the MRI image can be weighted in different ways giving a higher or lower signal.

## Contrast Agents Types

Most clinically-used MRI contrast agents work through shortening the T1-relaxation time of protons located nearby (case of paramagnetic Gadolinium (Gd). T1 shortens with an increase in the rate of stimulated emission from higher energy states (spins anti-aligned with the main field) to lower energy states (spins aligned). Thermal vibration of the strongly magnetic metal ions in the contrast agent creates oscillating electromagnetic (EM) fields at frequencies corresponding to the energy difference between the spin states (via the classical equation:  $E = hv$ , where  $E$ =energy,  $h$ = Planck's constant and  $v$ =EM radiation frequency), resulting in the requisite stimulation.

### Classification of Nanocontrast Agents

Nanocontrast agents are numerous in their types, administration and properties. They may be classified in many different ways such as by their:

- a. Chemical composition;
- b. Administration route;
- c. Magnetic properties;
- d. Effect on the image;
- e. Metal center's presence and nature; and
- f. Biodistribution and applications:
  - i. Extra-cellular fluid agents (also known as IV contrast agents);
  - ii. Blood pool agents (also known as intravascular contrast agents);
  - iii. Organ specific agents (i.e. gastrointestinal contrast agents and hepatobiliary contrast agents);
  - iv. Active targeting cell labelling agents (e.g., tumor-specific agents);and
  - v. Response (also known as smart or bioactivated) agents.

It is not the purpose of this article to describe in detail such classification.

### Gadolinium Paramagnetic Contrast Agents

Gadolinium paramagnetic contrast agents are most often used in vessel enhancement when utilizing Magnetic Resonance Angiography (MRA) or for tumor enhancement associated with the degradation of the blood-brain barrier (BBB). For large vessels (aorta and its branches), a dose as low as 0.1 mmol/kg body mass is employed whereas a higher concentration is employed for finer vasculature.

It is important to note Gd (III) chelates do not pass through the brain's protective barriers because they are hydrophilic, thus they are useful in enhancing lesions and tumors where the Gd (III) leaks out. In the rest of the body, Gd (III) initially remains in the circulation but then distributes into the interstitial space or is eliminated by the kidneys.

### Categorization of Gadolinium Paramagnetic Contrast Agents

Gd(III) is categorized into:

- a. Extra-cellular fluid agents;
- b. Ionic agents(Magnevist, Dotarem);
- c. Neutral agents (Omniscan, Prohance, Gadavist, OptiMARK);
- d. Blood-pool Agents: Of which there are two categories:

- e. Albumin-bridging gadolinium complexes (Ablavar, Gadocoletic acid); and
- f. Polymeric gadolinium complexes (Gadomelitol, Gadomer);
- g. Organ-Specific Agents (Primovist, MultiHance (hepatobiliary agents).

In both the U.S. And Europe, eight Gd contrast agents have been approved for human use. They are all Gd-chelated. Thus, the European Medicines Agency (EMA) has approved the following:

- a. Gadobenate (MultiHance);
- b. Gadobutrol (Gadovist);
- c. Gadodiamide (Omniscan);
- d. Gadopentetate (Magnevist, Magneqita, Gado-MRT ratiopharm);
- e. Gadoterate (Datarem);
- f. Gadoteridol (ProHance);
- g. Gadoversetamide (OptiMARK); and
- h. Gadoxetate (Primavist).

In the U.S.A., the Food and Drug Administration (FDA) has also approved the same contrast agents except that Gadofosveset (Ablavar, formerly Vasovist) is used in place of Gadoterate (Datarem).

### Safety of Gadolinium Contrast Agents

Gd contrast agents are safer than iodinated contrast agents used in X-ray radiography or CT. Anaphylactoid reactions are rare, occurring in ~ 0.05-0.1% of the cases. As a free solubilized ion, GdIII is somewhat toxic, but is regarded as safe when administered as a chelated compound. Its 50% lethal dose is:

LD50 (50% lethal dose) ~ 100-200 mg/kg in animals; ~ 1000-2000 mg/kg if chelated (comparable to iodinated X-ray contrast compounds) in humans.

The chelatic compounds can be classified as: macro-cyclic, have linear geometry, are ionic or not:

- a) Macro-cyclic ionic compounds are least likely to release the GdIII ion, and hence are the safest.

However, in the presence of renal disease, they can lead to a severe complication: nephrogenic fibrosing dermopathy (NFD) also known as nephrogenic systemic fibrosis (NSF), which resembles scleromyxedema or scleroderma. The risk is greater for patients in dialysis than in patients with renal insufficiency (4);

- b) Have linear geometry; and
- c) Can be ionic or not.

Gd containing agents (Optimark, Omniscan, Magnevist, Magnegita, Gado-MRT ratiopharm) present high risk for patients with severe kidney problems, in patients who are scheduled for or have received a transplant, and in newborn babies up to 4 weeks of age (WHO, 2009). Further, following recent reports that deposits of gadolinium-based contrast agents remain in the brains of some patients who have had four or more contrast MRI scans, long after their last dose, the FDA has issued a warning to that effect. The Agency has urged physicians to question the need for repeated gadolinium-enhanced MRI scans in established treatment protocols. Although there are no known health risks at this time, the FDA is investigating whether these brain deposits could become problematic. Note that the warning does not affect other contrast-enhancing agents such as those that use iodine or other radioisotopes.

The FDA is investigating the risk in conjunction with the National Center for Toxicological Research (NCTR), but is not at this time requiring any label changes for gadolinium-enhancing contrast agents.

### Superparamagnetic Ion Oxide Contrast Agents

These agents reduce the T<sub>2</sub>-signal of absorbing tissues. There are two types used for liver tumor enhancement:

- a. Superparamagnetic Iron Oxide (SPIO); and
- b. Ultra-Small Superparamagnetic Iron Oxide (USPIO).

Although approved in the past, the following are no longer available:

- a. Feridex I.V. (Endorem, Ferumoxides): discontinued by AMAG Pharma in 11/2008;
- b. Resovist (Cliavist): Approved for Europe in 2001; discontinued in 2009;
- c. Sinerem (Combidex): Guerbet withdrew marketing application in 2007;
- d. Lumirem (Gastromark): FDA-approved in 1996; and
- e. Clariscan (PEG-fero, Feruglose, NC100150): Discontinued due to safety concerns.

### Iron Platinum Superparamagnetic Contrast Agents

At this point, iron platinum superparamagnetic contrast agents are only investigational, and have not been tried in humans as far as is known. Super-paramagnetic Iron Platinum Particles (SIPP) provides a significantly better T<sub>2</sub>-relaxivity compared with SPIO and USPIO. Encapsulated with phospholipids to create multifunctional SIPP, they provide stealth immuno-micelles that specifically target human prostate cancer cells.

**Manganese-Based Nanoparticles Paramagnetic Contrast Agents**

Chelated manganese nanoparticles (Mn-DPDP) enhance the T<sub>1</sub>-signal. They are used for the detection of liver lesions. The

chelate dissociates in vivo into manganese and DPDP, where the chelate is absorbed intra-cellularly and is excreted in the bile while the manganese is eliminated via the renal filtration.

These agents have been used in animal studies under the identification MEMRI (Manganese Enhanced MRI). Due to the ability of Mn<sup>2+</sup> to enter cells through calcium channels (Ca<sub>2</sub> channels), it can be used for functional brain imaging [2,3,4].

### Manganese Enhanced Magnetic Resonance Imaging (Memri)

Manganese ion (Mn<sup>2+</sup>) is an essential metal that participates as a co-factor in a number of critical biological functions, such as electron transport, detoxification of free radicals and synthesis of neurotransmitters. Mn<sup>2+</sup> can enter excitable cells using some of the same transport systems as Ca<sup>2+</sup> and it can bind to a number of intracellular sites because it has high affinity for Ca<sup>2+</sup> and Mg<sup>2+</sup> binding sites on proteins and nucleic acids.

Paramagnetic forms of manganese ions are potent MRI relaxation agents. Indeed, Mn<sup>2+</sup> was the first contrast agent proposed for use in MRI. Recently, there has been renewed interest in combining the strong MRI relaxation effects of Mn<sup>2+</sup> with its unique biology in order to further expand the already broad assortment of useful information that can be measured by MRI. Such an approach has been continuously developed in the past several years to provide unique tissue contrast, to assess tissue viability, to act as a surrogate marker of calcium influx into cells, and to trace neuronal connections.

### Conclusion

Traditional MRI contrast agents (formulated as chelates) can be toxic and in certain cases may even lead to a debilitating disease (NSF/NFD). They also lack the required sensitivity and often do not provide satisfactory contrast images, particularly in early disease stages. On the other hand, nanoparticulates are essentially and generally non-toxic, however, some concern still remains. They offer greater sensitivity and enhanced spatial resolution in both imaging and the dynamics of blood flow. They provide a new imaging method of the blood microcirculation (of importance to predict the onset of sepsis in the Emergency Room).

### References

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