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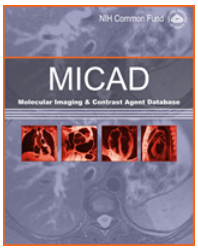

Ferumoxtran

USPIO

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Chemical name:	Ferumoxtran	
Abbreviated name:	USPIO	
Synonym:	Ultrasmall Superparamagnetic Iron Oxide, AMI-227, NC100150	
Agent Category:	Superparamagnetic Iron Oxide	
Target:	Reticuloendothelial system	
Target Category:	Internalized by phagocytes	
Method of detection:	Magnetic Resonance imaging (MRI)	
Source of signal\contrast:	Iron oxide	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans	No structure is available in PubChem.

Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used to create images because of their abundance in water molecules. Water comprises about 80% of most soft tissues. The contrast of proton MRI depends mainly on the density of nuclear (proton spins), the relaxation times of the nuclear magnetization (T1, longitudinal and T2, transverse), the magnetic environment of the tissues, and the blood flow to the tissues. However, insufficient contrast between normal and diseased tissues requires development of contrast agents. Most of the contrast agents affect the T1 and T2 relaxation of the surrounding nuclei, mainly the protons of water. T-2* is the spin-spin relaxation time composed of variations from molecular interactions and intrinsic magnetic heterogeneities of tissues in the magnetic field (1).

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Superparamagnetic iron oxide (SPIO) structure is composed of ferric iron (Fe^{3+}) and ferrous iron (Fe^{2+}). The iron oxides particles are coated with a layer of dextran or other polysaccharide. These particles have a large combined magnetic moments or spins which are randomly rotated in the absence of an applied magnetic field. SPIO is used mainly as a T2 contrast agent in MRI though it can shorten both T1 and T2/T2* relaxation processes. SPIO particle uptake into reticuloendothelial system (RES) is by endocytosis or phagocytosis. SPIO particles are taken up by phagocytic cells such as monocytes, macrophages, and oligodendroglial cells. A variety of cells can also be labeled with these particles for cell trafficking and tumor-specific imaging studies. SPIO agents are classified by their sizes with coating material (about 20 nm to 3,500 nm in diameters) as large SPIO agents (Ferumoxsil or AMI-121, Ferucarbotran, OMP), standard SPIO (SSPIO) agents (Ferumoxides or AMI-25, SHU 555), ultrasmall SPIO (USPIO) agents (Ferumoxtran or AMI-227, NC100150) and monocrystalline iron oxide nanoparticles (MION) agents (1).

Ferumoxtran is composed of iron particles of about 4-6 nm and the hydrodynamic diameter is about 20-40 nm. The crystals are covered with a layer of dextran. Ferumoxtran is classified as USPIO with significant T1 relaxation effects. Ferumoxtran has a long plasma half-life due to improved coating. In humans, the blood pool half-life of plasma relaxation times is calculated to be more than 24 h (2). Because of its long blood half-life, ferumoxtran can be used as blood pool agent during the early phase of intravenous administration (3). In the late phase, ferumoxtran is suitable for the evaluation of RES in the body, particularly in lymph nodes (4).

Synthesis

[PubMed]

SPIO agents are produced by controlling the precipitation of iron oxide in an aqueous solution of ferric salt, ferrous salt, and coating material by addition of an alkaline solution while active stirring or sonication is applied. The desired SPIO size of the agent is isolated and purified by differential column chromatography, centrifugation, and dialysis. Electron microscopy, X-ray diffraction and laser light scattering are used to measure median diameter of the nanoparticles. Relaxivities are measured by NMR spectroscopy (1).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

It was shown that the uptake of SPIO by human monocytes was dependent on size, concentration, and time. SSPIO uptake was higher than USPIO (AMI-227) uptake as measured by iron content and T2* relaxivity. The uptakes of both were directly proportional to concentration and time. The surface property of SPIO is also an important factor. MION was also taken up by T-cells, glioma cells and macrophages. MION can be attached to monoclonal and polyclonal antibodies for cell-surface markers of tumor cells and inflammatory cells accessible via blood circulation (5) (6).

Using monolayers of cultured pig endothelial cells to measure transcytosis of particles, 45% of USPIO nanoparticles were translocated in 5.5 h, whereas only 11% of SSPIO nanoparticles were translocated (7). On a human activated monocyte THP-1 cell assay, SSPIO showed a higher macrophage uptake (1.1-3.0%) compared with USPIO, ferumoxtran (0.03-0.12%) (6). These differences are attributed to the larger size of SSPIO nanoparticles.

Animal Studies

Rodents

[PubMed]

The blood half-life of ferumoxtran (the hydrodynamic diameter is about 11 nm) in rats was 81 min, considerably longer than that of larger SPIO preparations, such as AMI-25 (6 min). Electron microscopy demonstrated that ferumoxtran particles transmigrate the capillary wall by means of vesicular transport and through interendothelial junctions. Twenty-four h after intravenous administration, 3.6% of the injected dose/gram (ID/g) of tissue was found in lymph nodes, 2.9% ID/g in bone marrow, 6.3% ID/g in liver, and 7.1% ID/g in spleen (7). In another study, ferumoxtran was found to be mainly as an extracellular agent for at least 1 h in the rats (0.15 mmol Fe/kg). Liver RES accumulation peaked at 8-24 hours. There was no substantial uptake within hepatocytes (8).

Non-Human Primates

[PubMed]

Bourrinet et al. (9) performed pharmacokinetic, safety pharmacology, single- and repeat-dose toxicity, reproduction toxicity, and genotoxicity studies with ferumoxtran-10 given intravenously in mice, rats, rabbits, dogs, and monkeys. Ferumoxtran-10 was taken up by macrophages in liver, spleen, and lymph nodes within 24 hours after injection and underwent progressive metabolism. The blood clearance pattern in monkeys exhibited a two-phase model with a half-life ($t_{1/2}\alpha$) of 52 min during the distribution phase and a half-life ($t_{1/2}ß$) of 342 min during the elimination phase. Toxicity was observed only at very high exposure levels, well above the intended human dose of 2.6 mg Fe/kg.

Other Non-Primate Mammals

[PubMed]

Ferumoxtran contrast agents have been studied in renal perfusion, portal angiography, cardiac ischemia, inflammation, and atherosclerosis using dogs [PubMed], pigs [PubMed], and rabbits [PubMed].

Human Studies

[PubMed]

AMI-227 was studied in 41 healthy subjects. Relaxation time measurements in plasma samples showed a strong, dose-dependent, and persistent decrease in T1 and T2 values. Significant changes in MR signal intensity of the blood pool and well-perfused organs (liver and spleen) were noted on both T1- and T2- weighted images. Changes in signal intensity of cervical lymph nodes were also observed at the higher doses and late imaging times (2). The major potential applications for USPIO nanoparticles are as (a) an intravenous contrast agent for the lymph nodes [PubMed], (b) a bone marrow contrast agent (10), [PubMed], (c) a perfusion agent for angiography [PubMed], (d) a perfusion agent for the brain and kidneys [PubMed], and (e) a monitoring agent for macrophage infiltration in pathological tissues [PubMed].

References

1. Wang Y.X., Hussain S.M., Krestin G.P. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. Eur Radiol. 2001; **11** (11):2319–31. PubMed PMID: 11702180.
2. McLachlan S.J., Morris M.R., Lucas M.A., Fisco R.A., Eakins M.N., Fowler D.R., Scheetz R.B., Olukotun A.Y. Phase I clinical evaluation of a new iron oxide MR contrast agent. J Magn Reson Imaging. 1994; **4** (3):301–7. PubMed PMID: 8061425.
3. Stillman A.E., Wilke N., Li D., Haacke M., McLachlan S. Ultrasmall superparamagnetic iron oxide to enhance MRA of the renal and coronary arteries: studies in human patients. J Comput Assist Tomogr. 1996; **20** (1):51–5. PubMed PMID: 8576482.

4. Anzai Y., Piccoli C.W., Outwater E.K., Stanford W., Bluemke D.A., Nurenberg P., Saini S., Maravilla K.R., Feldman D.E., Schmiedl U.P., Brunberg J.A., Francis I.R., Harms S.E., Som P.M., Tempany C.M. Evaluation of neck and body metastases to nodes with ferumoxtran 10-enhanced MR imaging: phase III safety and efficacy study. Radiology. 2003; **228** (3):777–88. PubMed PMID: 12954896.
5. Metz S., Bonaterra G., Rudelius M., Settles M., Rummeny E.J., Daldrup-Link H.E. Capacity of human monocytes to phagocytose approved iron oxide MR contrast agents in vitro. Eur Radiol. 2004; **14** (10):1851–8. PubMed PMID: 15249981.
6. Raynal I., Prigent P., Peyramaure S., Najid A., Rebuzzi C., Corot C. Macrophage endocytosis of superparamagnetic iron oxide nanoparticles: mechanisms and comparison of ferumoxides and ferumoxtran-10. Invest Radiol. 2004; **39** (1):56–63. PubMed PMID: 14701989.
7. Weissleder R., Elizondo G., Wittenberg J., Rabito C.A., Bengele H.H., Josephson L. Ultrasmall superparamagnetic iron oxide: characterization of a new class of contrast agents for MR imaging. Radiology. 1990; **175** (2):489–93. PubMed PMID: 2326474.
8. Van Beers B.E., Sempoux C., Materne R., Delos M., Smith A.M. Biodistribution of ultrasmall iron oxide particles in the rat liver. J Magn Reson Imaging. 2001; **13** (4):594–9. PubMed PMID: 11276104.
9. Bourrinet P., Bengele H.H., Bonnemain B., Dencausse A., Idee J.M., Jacobs P.M., Lewis J.M. Preclinical safety and pharmacokinetic profile of ferumoxtran-10, an ultrasmall superparamagnetic iron oxide magnetic resonance contrast agent. Invest Radiol. 2006; **41** (3):313–24. PubMed PMID: 16481915.
10. Daldrup-Link H.E., Rummeny E.J., Ihssen B., Kienast J., Link T.M. Iron-oxide-enhanced MR imaging of bone marrow in patients with non-Hodgkin's lymphoma: differentiation between tumor infiltration and hypercellular bone marrow. Eur Radiol. 2002; **12** (6):1557–66. PubMed PMID: 12042968.