# Manganese Based MR Contrast Agents: Formulation and Clinical Applications

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**Abstract:** This paper discusses the development and clinical applications of positive manganese based MR contrast agents, including both intravenous (i.v.) and oral formulations. The i.v. formulation is a manganese–dipyridoxyl diphosphate chelate which is commercially available; whereas the oral formulation is a mixture of MnCl2, alanine and Vitamin D3, which is currently under clinical trials. The compositions, preclinical studies and pharmacokinetics of both formulations are discussed. The main reported clinical difference between the two formulations is that i.v. administration exposes all the organs, whereas oral ingestion exposes only the enterohepatic circulation. Manganese based MR contrast agents are particularly suitable for detection of focal liver lesions due to their uptake by the mitochondria rich hepatocytes, and biliary delineation due to their biliary excretion; it can provide useful information in diffuse liver lesions. Further, the i.v. formulation can be used for focal pancreatic lesions.

**Keywords:** Manganese, metabolism, Mangafodipir, CMC-001, positive contrast agent, liver, gallbladder, biliary tree, cancer, metastases, cirrhosis, pancreas, chemotherapy.

## 1. INTRODUCTION

Manganese ($Mn^{2+}$) is an essential trace element that plays an important role in various aspects of metabolism in humans, animals, plants and microorganisms [1]. In man, the normal whole body content of Mn is 220–360 μmol, with a daily turn over of 90–140 μmol, and up to 25% stored in the skeleton which is not readily accessible. The highest concentrations of manganese are found in the liver (22–38 μmol/kg) and pancreas, and lesser quantities in kidneys (11–16 μmol/kg). Manganese is interchangeable with other ions such as cobalt, zinc and nickel in the activation of enzymes.

Manganese is also a cofactor in a variety of enzymes including pyruvate carboxylase, superoxide dismutase, glutamine synthetase and alkaline phosphates. Therefore it is involved in oxidation–reduction processes, phosphorylation, fermentation, and in the synthesis of cholesterol, fatty acids and mucopolysaccharides. Manganese is also present in many intracellular organelles, especially mitochondria, where it has an important metabolic function as a coenzyme in protein synthesis.

The main route of manganese absorption is the gastrointestinal tract, but in man, rats and mice less than 5% of the oral intake is absorbed. In contrast to many other minerals in the body, manganese is actively excreted *via* hepatocytes into the bile, and only minimal amounts are excreted *via* the kidney.

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When used as a contrast agent, manganese ion ($Mn^{2+}$) belongs to the same group of paramagnetic ions as gadolinium ($Gd^{3+}$) and copper ($Cu^{2+}$), which are capable of shortening the T1 of water protons, thus increasing the signal intensity of T1 weighted (T1w) Magnetic Resonance (MR) images; but manganese has also a minor T2 effect which reduces the signal intensity [2-10]. Biologically manganese is involved in mitochondrial function of cells, and thus the more mitochondria in the tissue, the higher its uptake. As hepatocytes are rich in mitochondria, $Mn^{2+}$ is an excellent contrast agent for MR imaging of the liver and other mitochondria rich organs like pancreas and kidneys.

This article discusses the development and use of both intravenous (i.v.) and oral manganese based contrast agents, including their formulation, preclinical evaluations, pharmacokinetics and clinical applications.

## 2. FORMULATION OF MANGANESE BASED MR CONTRAST AGENTS

Manganese based MR contrast agents are used in two forms:

- Intravenous formulation: Mangafodipir trisodium, manganese–dipyridoxyl diphosphate chelate (MnDPDP manganese-5, 5'-bis(phosphate) sodium salt, which is commercially available and used for slow injection (in Europe) or bolus injection (in the US).
- Oral formulation: A mixture of $MnCl_2$, alanine and vitamin D3, designated as CMC-001, and is currently undergoing phase 3 clinical trial for oral intake.

Following i.v. injection, manganese ion accumulates in the liver, bile, pancreas, kidneys and cardiac muscle [11, 12],

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but following oral intake, it accumulates only in the liver and bile [9]. The orally administered manganese formulation overcomes such problems as the cumbersome i.v. administration and exposure of total body to $Mn^{2+}$. Oral ingestion of CMC-001 also results in higher visualization due to its higher accumulation in the liver and bile. Fig. (**1**) shows the uptake of manganese by hepatocytes leading to higher signal intensity, whereas metastasis remains hypointense.

### Intravenous Manganese MR Contrast Agent: Mangafodipir Trisodium

Mangafodipir trisodium (formerly known as Mn-DPDP, Teslacan, GE Healthcare) (Fig. **2**), is a paramagnetic agent developed as an MR contrast material for the hepatobiliary system.

The large linear ligand dipyridoxyl diphosphate (DPDP) is a vitamin $B_6$ (pyridoxine hydrochloride) analog; it reduces the acute i.v. toxicity of free $Mn^{2+}$ [13, 14]. The metal chelate has a net electric charge of $3^-$, resulting from the $2^+$ charge of the manganese ion and the $5^-$ charge of DPDP, counterbalanced by the presence of three sodium ions in the solution. Following i.v. administration, Mangafodipir trisodium is metabolized by dephosphorylation to Mn–dipyridoxyl monophosphate (Mn-DPMP) and Mn–dipyridoxyl-ethylenediamine-diacetate (Mn-PLED), and also transmetallated by zinc to the corresponding zinc compounds.

Biodistribution studies of Mangafodipir in rats [15] have shown that at 30 min after i.v. injection, 13% of the paramagnetic agent and its metabolites are present in the liver, 9% in small intestine, 3% in blood, 1.3% in kidneys, and less than 1% in other organs. In rats, fecal excretion amounts to 47% and renal elimination to 43% after 6 h, with 6% retained in the body after 7 days. According to the manufacturer's brochure, in humans, the $Mn^{2+}$ content of Mangafodipir is eliminated 15% *via* the urine in 24 h and 59% in the feces in 5 days.

### Oral Manganese MR Contrast Agent: CMC-001

The oral formulation of manganese based MR contrast agent, CMC-001, is a mixture of manganese chloride ($MnCl_2$), alanine ($C_3H_7O_2N$) and Vitamin $D_3$ ($C_{27}H_{44}O$) (Fig. **3**) [7, 9].

Addition of alanine and Vitamin $D_3$ to $Mn^{2+}$ increase its uptake in absence of competing ions like $Ca^{2+}$ and $Fe^{2+}$. Absorption of manganese also decreases when the diet is rich in phylates and phosphorus. This is most likely the result of

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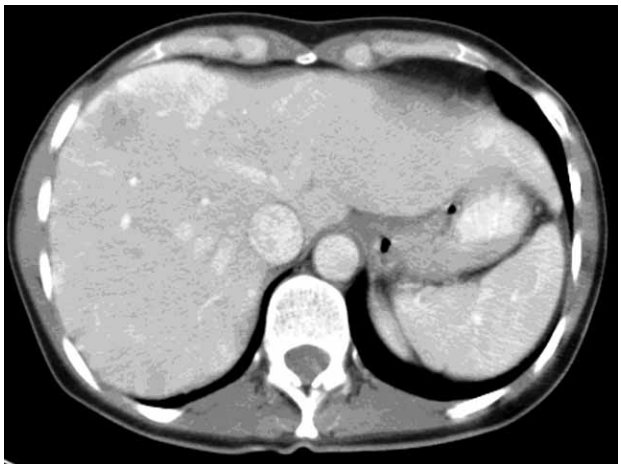

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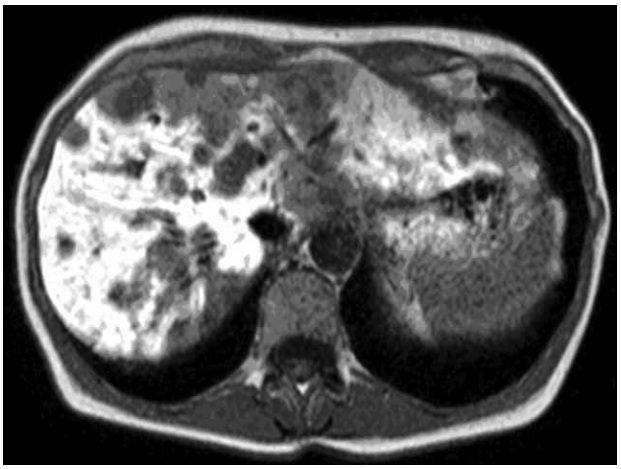
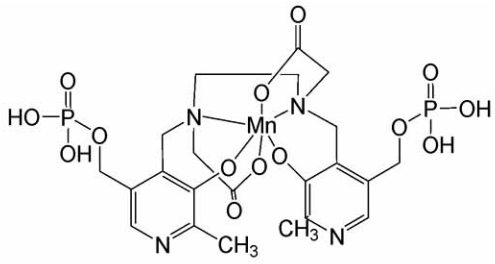


**Fig. (1).** Computed tomography (CT) (**A**) and MR liver images (**B**) of a 52-year old female with bladder cancer. CMC-001 enhanced MRI shows multiple metastases relatively to CT (adapted from [16]).



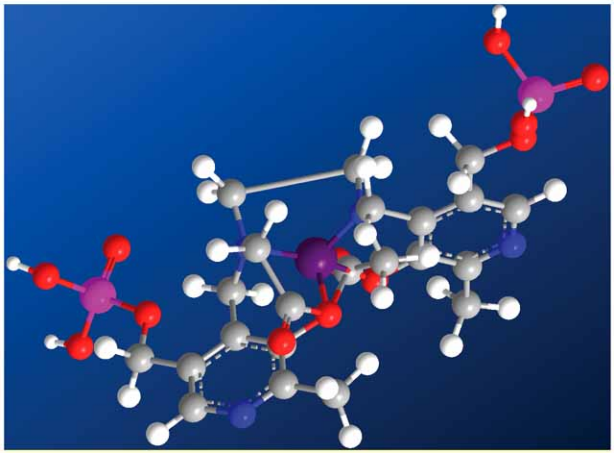



**Fig. (2).** Chemical structure and molecular model of Manganese–dipyridoxyl diphosphate chelate (MnDPDP), known as Mangafodipir manganese-5,5'-bis(phosphate) sodium salt.

Its full chemical name is trisodium trihydrogen {(OC-6-13)-[[N,N-1,2-ethanediylbis[N-[ [3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato]] (8-)] manganate}6–; C22H27-MnN4Na3O14P2; molecular weight 757.33.

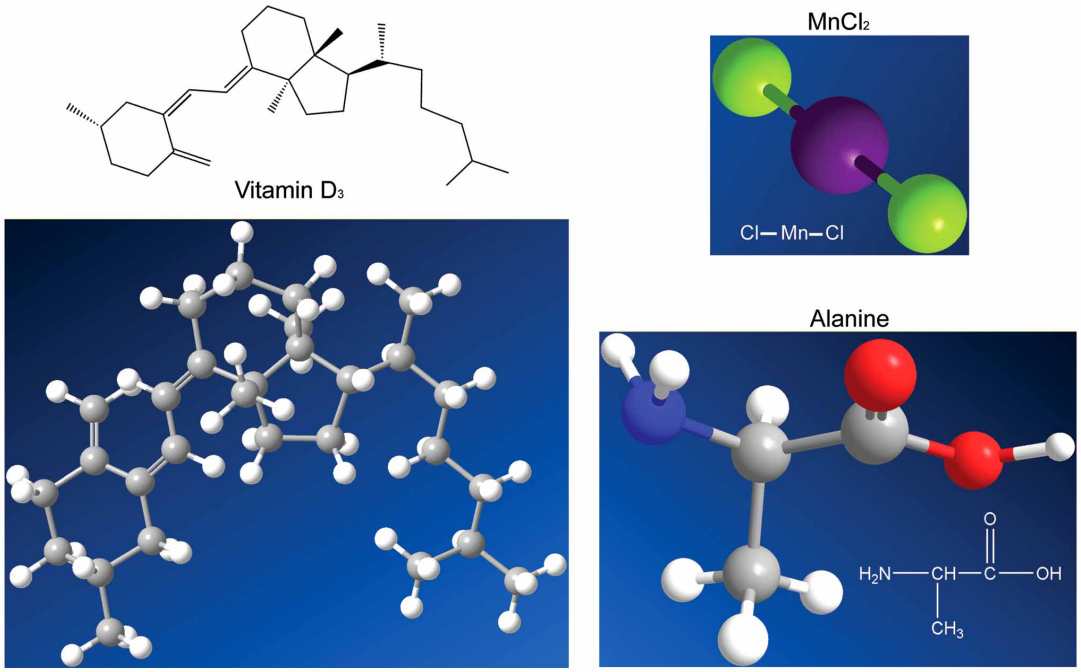



**Fig. (3).** Chemical structures of MnCl2, alanine and vitamin D3, formulated as oral manganese based MR contrast agent currently under clinical trial as CMC-001.

lower solubility of manganese with increasing concentrations of these compounds in the intestines.

Manganese absorption is mediated by a high affinity, low capacity and saturable active transport mechanism. In patients with iron deficiency or hepatic cirrhosis, manganese absorption is twice that in normal adults. This is likely due to higher concentrations of proteins that participate in the carrier mediated transport of both iron and manganese. The majority of absorbed manganese binds to α2-macroglobulin in the portal circulation. Both free and bound manganese are taken up by the liver, and then rapidly excreted into the bile. Vitamin $D_3$ primarily affects the intestinal absorption of manganese.

The higher uptake of oral manganese over the bowel wall is due to the use of promoters. Secondarily, the uptake of manganese in the hepatocytes increases. During the first passage through the liver approximately 95% of oral manganese is taken up by the liver leaving only trace amounts in liver veins. For instance, Chabanova *et al.* [7] did not observe any increased levels of manganese in peripheral blood in healthy volunteers 25 h after intake of CMC-001 (Fig. **4**). This is also confirmed by the lack of any pancreas and kidney MR enhancement after administration of the i.v. formulation.

## Recommended Dosage and Administration of Manganese MR Contrast Agents

Mangafodipir is available in two preparations— one at a concentration of 0.05 mol/l for a 1–2 min injection (in the US), and one with a concentration of 0.01 mol/l for 10–15 min infusion (in Europe). But the actual Mn dose used for the two preparations is equal, 5 µmol/kg body weight (b.w.). During the infusion it is necessary to observe the patient for adverse effects.

The recommended dose for the oral CMC-001 is much higher than that of Mangafodipir, but it is still modest— only 10 fold higher than the average daily intake in man (10 µmol/kg). However, the intake may vary considerably depending on the type of food ingested. A diet consisting of nuts, cereals, legume seeds, tea and coffee can provide 360–450 µmol/kg Mn on dry weight basis, whereas fish, cheese and poultry provide only 9 µmol/kg. CMC-001 can be administered at home at least 2 h before MR examination.

When a lesion with no uptake of $Mn^{2+}$ has been identified, it is possible to characterize the lesion with dynamic contrast enhancement (DCE) using an extracellular gadolinium based contrast agent.

Manganese ion has 5 unpaired electrons, and is the second most powerful positive contrast agent for MRI after gadolinium. The effect of manganese in shortening the $T_1$ and $T_2$ relaxation times is dependent on its dose [9].

The use of manganese based MR contrast agent for abdominal MR imaging may have several advantages. First, the signal intensity of the normal liver increases on T1w images as manganese is taken up by the hepatocytes. Second, the signal intensity of gallbladder and of biliary tree also increases on T1w images due to manganese excretion into the biliary system. In addition the oral manganese formulation increases the signal intensity of the bowel lumen.

Abdominal MRI with manganese based contrast agent is typically performed on a 1.5 T MR scanner using a "breath-hold" scanning protocol [16-19]. The pre-contrast part of the protocol includes acquisition of high spatial resolution T1w gradient-recalled echo (GRE) images with thin slices. The post-contrast images are usually obtained 10–60 min after the end of administration of Mangafodipir, or 2 h after drink-

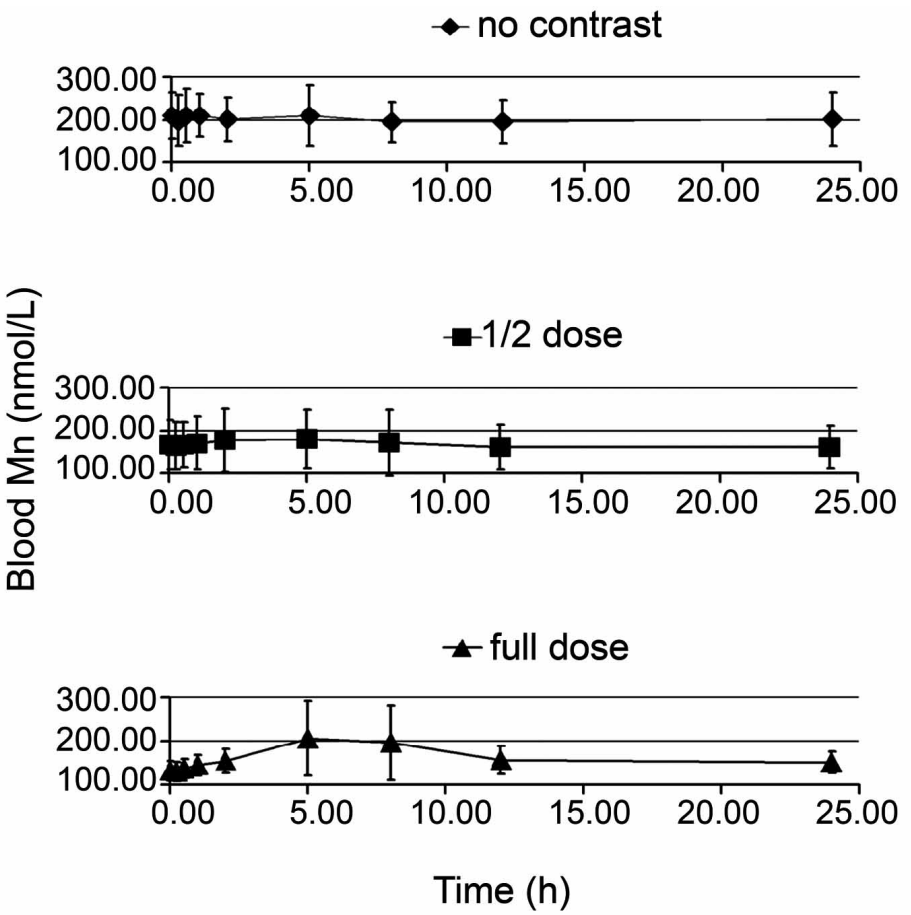



**Fig. (4).** Whole blood manganese levels before and after oral manganese in healthy volunteers (n = 12). The full dose corresponds to 1.6 g manganese chloride tetrahydrate, 1 g alanine and 1600 IU vitamin D3.

ing the oral CMC-001. The post-contrast MRI includes the same T1w sequence for detection of liver lesions. For observation of the biliary system a high resolution 3D GRE sequence is also added.

In patients with diseases such as colorectal cancer, a routine workup of the liver pre-contrast imaging is often unnecessary for saving room time. For instance, Mangafodipir can be infused in a different room, or sachets of oral CMC-001 can be sent to the patient and ask them to drink the contrast medium when they wake up in the morning before going for examination. The imaging can then be done upon room availability within the next few hours.

If no lesions or no new lesions are observed, the procedure can stop. If a new lesion appears, one can obtain repetitive thin slices covering the lesion of interest after injection of a Gd based contrast agent in order to characterize the lesion by its dynamic contrast uptake. This strategy is the opposite of what is suggested for other liver specific agents in which the contrast uptake is done first. The strategy suggested here saves room time and guarantees that the lesion of interest is included in the field of view. Most MR scanners cannot cover a complete liver with thin slices for a contrast uptake study. Thus the lesion of interest may not be included, as its presence is not known.

## 3. PHARMACOKINETICS OF MANGANESE MR CONTRAST AGENTS

### Pharmacokinetics of Intravenous Manganese MR Contrast Agent

Mangafodipir, manganese–dipyridoxyl diphosphate chelate (MnDPDP) is metabolized *via* transmetallation with zinc into the corresponding metabolites, as listed below and is shown in Fig. (**5**).

After bolus injection, Mn-DPDP reaches the highest average plasma concentration in less than 2 min, and is then rapidly eliminated to low levels within 15 min (Fig. **6**). Mn-PLED reaches a peak plasma concentration at 10 min and is eliminated after 2 h. Zn-PLED concentration in plasma increases slowly to its peak of after 30 min, and is still detectable after 12 h as the only metabolite.

Following a 20 min infusion, Mn-DPDP is not detectable in plasma already at 2 min after the end of infusion, while Zn-PLED reaches a peak plasma concentration of 9 ±2 μ M between 10–30 min after the end of infusion. As with the bolus injection, Zn-PLED is the only detectable metabolite in plasma after 8 h.

The maximal plasma concentration of Mn for a dose of 5 μmol/kg b.w. after administration of MnDPDP is 38 μmol/l

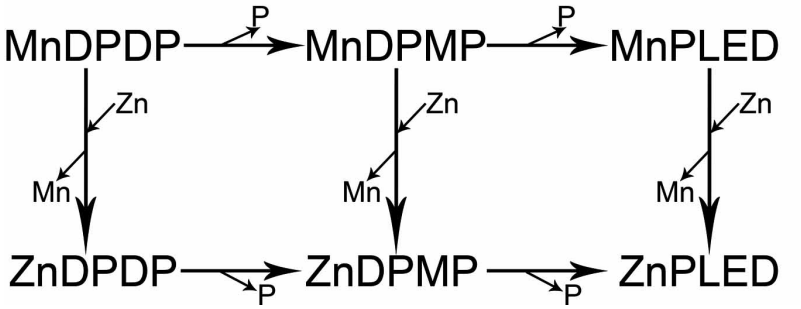



**Fig. (5).** *In vivo* metabolism (transmetallation) of MnDPDP following administration of Mn based contrast agents.

Mn-DPMP: Manganese dipyridoxyl monophosphate;

Mn-PLED: Manganese dipyridoxyl ethylenediamine diacetate;

ZnDPDP: Zinc dipyridoxyl diphosphate;

ZnDPMP: Zinc dipyridoxyl monophosphate;

Zn-PLED: Zinc dipyridoxyl ethylenediamine diacetate.

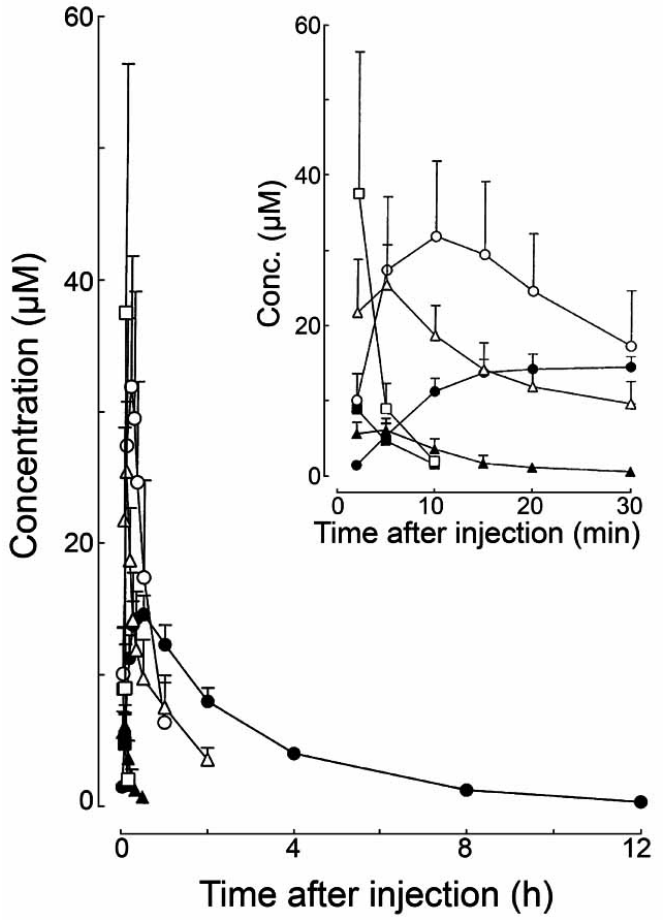



**Fig. (6).** Plasma concentration of MnDPDP (❒) and its main metabolites after a bolus injection (<1 min) in volunteers receiving 10 μmol MnDPDP/kg bw. Values are means for 5 volunteers, error bars represent SD (adapted from [20]).

MnDPMP (△), MnPLED (❍), ZnDPDP (■), ZnDPMP (▲), ZnPLED (●)

for bolus injection, and 14 μmol/l for a 20 min infusion; the corresponding dose for the ligand DPDP, is 38 and 26 μmol/l, respectively. The corresponding distribution volumes are 1–1.5 l/kg for Mn, and 0.24–0.28 l/kg for the ligand. The initial plasma half lives are below 20 min for Mn, and 50 min for the ligand and plasma clearance is 0.44–0.57 l/h kg, depending on the administration form. The $Mn^{2+}$ fraction of the excretion is irrespective of the administration form, bolus or infusion— approximately 15% is excreted in the urine within the first 24 h, and 57–61% in feces over 4 days. Most of the ligand is excreted solely in the urine during 24 h [20].

### Pharmacokinetics of Oral Manganese MR Contrast Agent

Following oral administration of $MnCl_2$, $Mn^{2+}$ is taken up from the gastrointestinal tract, and introduced into the portal system. $Mn^{2+}$ is strongly absorbed during the first passage, leading to high gastrointestinal uptake, thus exposing the bowel and the liver to high doses of manganese and avoiding all other organs. The level of $Mn^{2+}$ in the hepatic artery is within normal range, but it is higher than normal in the portal vein. This difference is observed only in oral administration, and its diagnostic value is still unknown. This active uptake of oral manganese is essentially the same as those of calcium, iron and zinc, and the uptake of manganese and calcium can be increased by the use of promoters such as vitamin $D_3$ and various amino acids. In the phase 1 trial of the oral $MnCl_2$, $Mn^{2+}$ concentration in blood samples was at the same level as the placebo group, and no increased signals intensity of the liver was observed in patients with normal biliary excretion 24 h after administration [7].

### Safety of Manganese MR Contrast Agents

Manganese is among the least toxic of the trace elements in mammals and birds [1, 21]. Excess body manganese in humans working in manganese mines or plants has been observed as an occupational disease [1, 22, 23]. $Mn^{2+}$ may also accumulate, with deleterious effects, in the body of patients receiving parenteral nutrition over a long period. The principal organ affected by chronic manganese toxicity is the brain, probably because of its slower turnover of the element relative to other tissues. The neuronal injury is associated with degeneration in the striatum and globus pallidus (Fig. **7**) [24]; the clinical symptoms are similar to those of Parkinson's disease.

### Safety of Manganese Intravenous MR Contrast Agent

Adverse events observed in clinical trials of Mangafodipir trisodium include feeling of warmth and flushing, nausea, pounding heart and dizziness. The first large scale trials conducted with this agent was reported in 1991 [25]. It was a phase 2 trial involving 141 patients, 38 (27%) of whom exhibited minor side effects. Flushing and feeling of warmth were reported in 21 (14%), and nausea in 3 (2.1%) [25].

Aicher *et al.* also reported side effects in 6/20 (30%) patients, including flushing, warmth and/or metallic taste [26].

A small European phase 3 trial that included 82 patients also produced mild or moderate adverse events in 17% of patients, and infusion related discomfort in 4% [27]. The rate of adverse events observed in a larger European phase 3 clinical trials was 7 % in 624 patients [8], as listed in Table **1**.

The largest study of efficacy and safety reported so far is a multicenter phase 3 clinical trial that included 404 adult patients in 18 institutions in the United States [13]. In this study 23% of patients reported experiencing at least one adverse reaction and a total of 146 adverse events were reported.

The most frequent adverse reactions associated with the administration of Mangafodipir trisodium are nausea, headache and pruritus. Sensations of heat and flushing are most common with high injection rates, and are probably related to peripheral vasodilatation. However, facial flushing is not significantly higher in slow bolus injection lasting 2–2½ min than that of infusion lasting 10–20 min. Transient decrease in

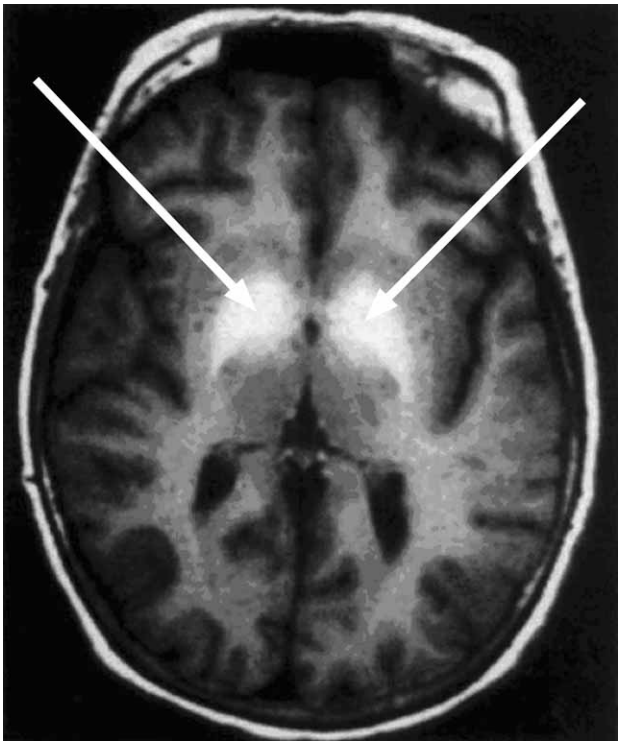


**Fig. (7).** T1w image of a female brain receiving total parenteral nutrition for 3 years. Increased signal intensity is observed in the globus pallidus as a result of manganese deposit (adapted from [24]).

**Table 1. Incidence of Discomfort and Adverse Events of MnDPDP in a European Phase 3 Trial (n = 624) (Adapted from [8])**

| Discomfort or Adverse Event | Patients Affected | |
|---|---|---|
| | Number | % of total |
| **Discomfort** | | |
| Sensation of warmth on infusion | 20 | 3.2 |
| Sensation of cold | 3 | 0.5 |
| Injection site pain | 2 | 0.3 |
| Pressure at injection site | 1 | 0.2 |
| **Adverse event** | | |
| Headache | 12 | 1.9 |
| Vomiting | 9 | 1.4 |
| Nausea | 8 | 1.3 |
| Feeling of warmth/flushing | 7 | 1.1 |
| Others | 10 | 1.6 |

alkaline phosphatase levels with the use of Mangafodipir trisodium have also been reported [13].

The exact mechanism of these adverse events to Mangafodipir trisodium is not known, but may be due, at last partly, to *in vivo* dechelation of $Mn^{2+}$, with rapid incorporation of manganese ion into hepatocytes. After dechelation, manganese ion binds to serum proteins. Cardiovascular effects may also be seen due to increased circulating concentrations of manganese. $Mn^{2+}$ given intravenously interferes with myocardial processing of $Ca^{2+}$, and can act as a $Ca^{2+}$ blocker, thus affecting cardiac contractility and muscle physiology. Manganese also uncouples myocardial and smooth muscle excitation and contraction, leading to further decrease in cardiac contractility and hypotension. In the brain, too, manganese may interfere with the electrochemical potential of cell membranes. Hyperacute toxicity is mainly the result of cardiovascular effects. Animal studies have shown [28-30] that the acute toxicity of intravenously administered manganese is due to cardiovascular effects caused by interference of $Mn^{2+}$ with myocardial processing of $Ca^{2+}$.

### Safety of Manganese Oral MR Contrast Agent

Clinical experience with oral Mn contrast agent CMC-001 is at present limited. Adverse reactions have not been seen so far, but patients may experience discomfort due to a 400 ml large volume intake [7] As CMC-001 is formulated with only nutritional products, it can be administered outside the imaging facility, e.g. in small clinics or at home. Oral administration of an excessive dose of manganese to rats (3600 µmol/kg, i.e. about 36 times the amount used in CMC-001), increases the billiary excretion of manganese, leading to its tissue retention. On the other hand, 1800 µmol/kg given daily for 3 months does not result in significant tissue accumulation [31]. One healthy volunteer has ingested approximately 200 µmol/kg daily for one month without feeling any adverse reactions [32].

## 4. PRECLINICAL EVALUATIONS OF MANGANESE MR CONTRAST AGENTS

The toxic effect of manganese is on the cardiovascular system because the inhibition of calcium entry interferes with electrical conductivity. In rats, for instance, repeated doses of excessive manganese (1.8 mmol/kg) given every other day for 3 months caused very small manganese accumulation in organs [31]. It was shown that acute toxic effects of manganese in organs might be avoided by using oral manganese administration instead of intravenous injection [33] Kreft *et al*. have reported liver contrast enhancement with oral dose of 1000 µmol/kg $MnCl_2$ in rats, similar to that of an i.v. dose of 20 µmol/kg [33]. Thomsen *et al*. did not find any increased concentration of manganese in the liver of rats receiving 100 µmol/kg pure $MnCl_2$ [15].

Infusion of up to 300 µmol/kg Mn-DPDP in conscious dogs caused no significant cardiovascular side effects, whereas a bolus injection of 100 µmol/kg increased the blood pressure moderately [34]. In dogs with ischemic heart failure an infusion of 300 µmol/kg MnDPDP caused minor hemodynamic and eletrophysiological effects, with no further deterioration in cardiac function [34]. Teratogenic effects have also been observed in pregnant rats, resulting in Mn induced skeletal malformations in the fetus [35]. Similar studies have been performed on rabbits with no observed malformations [36].

Approximate dose of MnCl2 at which 50% mortality occurred for mice, dogs and rats are shown in Table **2** [37].

**Table 2. Median Lethal dose ($LD_{50}$) of $MnCl_2$ After Intravenous Injection (Adapted from [37])**

| Species | lethal dose (µmol/kg) |
|---|---|
| Mice | 250–300 |
| Rats | 300–450 |
| Dogs | 3676.7 |

In comparison with MnCl2, MnDPDP was shown to have a much better safety profile suitable as an hepatobiliary MR contrast agent for i.v. administration [38].

Southon *et al*. compared the efficacy of MnDPDP as a tissue-specific MR agent with that of $MnCl_2$ in rats and pigs [39]. No loss of the efficacy was observed at the intended clinical dose of 5 µmol/kg. Both MnDPDP and $MnCl_2$ showed dose dependent R1 relaxation rates, but no R2 changes were observed on T2w images. The highest R1 was observed for the liver, reflecting $Mn^{2+}$ accumulation in this organ. The signal intensity enhancement peak was reached within 10–20 min irrespective of administration form, bolus or infusion. Doubling the dose from 10 to 20 µmol/kg, the signal intensity increased, but the difference was only moderate [39].

## 5. CLINICAL APPLICATIONS OF MANGANESE MR CONTRAST AGENTS

In a European phase 3 trials, Mangafodipir-enhanced images showed more lesions than contrast enhanced CT in 31% of cases, and fewer lesions in 13% of cases [8, 25]. In another phase 3 trials in the US, Mangafodipir-enhanced MRI was comparable or superior to CT [27]. Also according to Bartolozzi Mangafodipir-enhanced MRI showed more lesions than unenhanced MRI in up to 36% of patients [40]. In later studies also contrast enhanced MRI was equivalent or superior to helical CT in lesion detection [41, 42].

Sahani *et al*. has also reported that in patients with colon and pancreatic adenocarcinoma, high partial-spatial resolution Mangafodipir enhanced liver MRI reveals significantly more and smaller liver metastases than does the 2-[$^{18}$F] fluoro-2-deoxy-D-glucose and positron emission tomography (FDG PET) [43]. Similarly, improved lesion detection compared to CT and unenhanced MRI has also been reported by others [16, 40]. Thus, Mangafodipir enhanced MRI is likely to influence patient management in surgical candidates with liver tumors by detecting small metastases not detectable by CT and PET.

Cirrhosis may cause heterogeneity in Mangafodipir MRI enhancement, and fibrosis may account for low enhancement. However, a meta-analysis comparing the safety and efficacy of Mangafodipir in patients with liver lesions and cirrhosis showed that significantly higher numbers of lesions

were found on post-contrast images than in pre-contrast images, in both cirrhotic group (n = 137 patients) and non-cirrhotic group (n = 480 patients), and the higher detection was not influenced by liver cirrhosis. Mangafodipir also significantly improved lesion characterization in cirrhotic patients, but not in non-cirrhotic patients [44].

Fig. (**8**) shows hepatic dysfunction as a result of changes in portal flow due to tumor compression of the vessels, or early focal cirrhosis due to chemotherapy or diffuse lesions. The oral Mn formulation is especially suitable for detection of corresponding pseudolesions as it is delivered into the liver solely by the portal vein. However, the relationship between biliary and portal obstruction, either partial or total, with liver enhancement needs further evaluation, and the difference between arterial and portal doses may result in important diagnostic information. Theoretically, patients with partial portal thrombosis and abnormal venous contribution to the liver may have lower liver enhancements.

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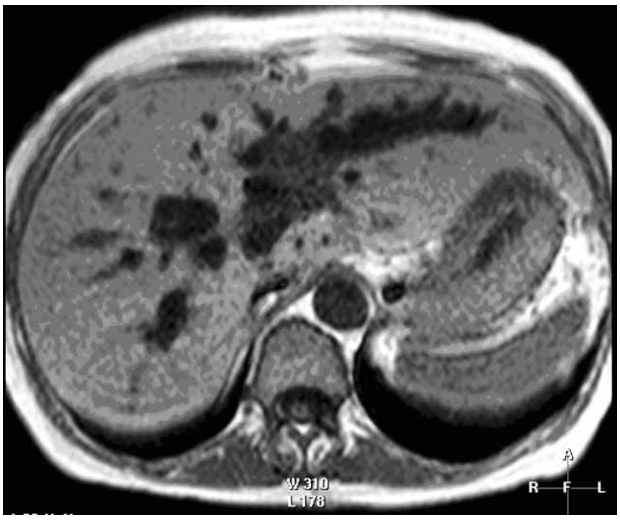


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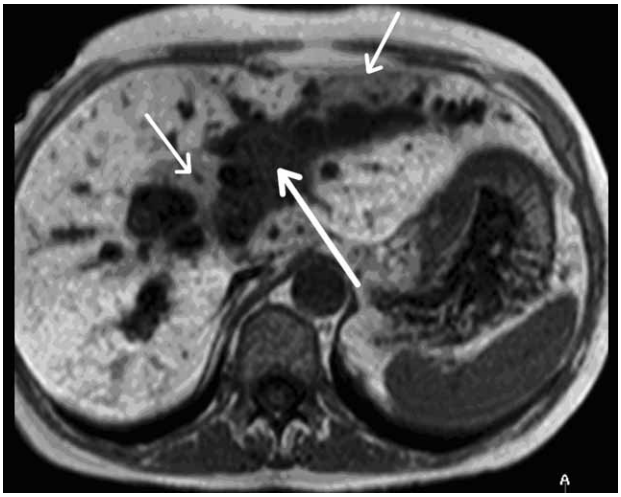


**Fig. (8).** T1w MRI of liver before (**A**) and 2 h after (**B**) ingestion of CMC-001. Biliary obstruction caused by a choleangiocarcinoma (large arrow). The pseudo lesions (small arrows) are probably caused by tumor compression of the vessels.

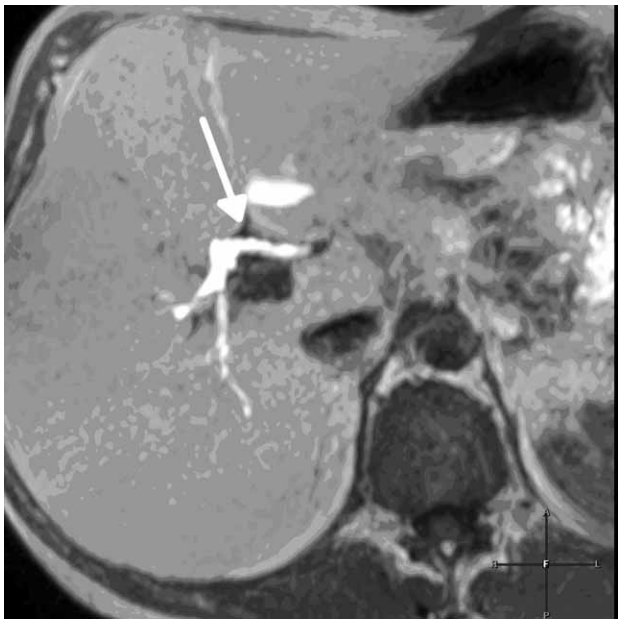


**Fig. (9).** T1w MRI of liver obtained following oral intake of CMC-001. Maximum intensity projection of internal biliary tree shows excretion of manganese through the bile. The ribbed appearance of the common bile duct (arrow) is caused by an endoprothesis.

The oral Mn formulation may also provide significant information in liver cirrhosis with reduced functioning hepatocytes and portal hypertension, sometimes with hepatofugal flows.

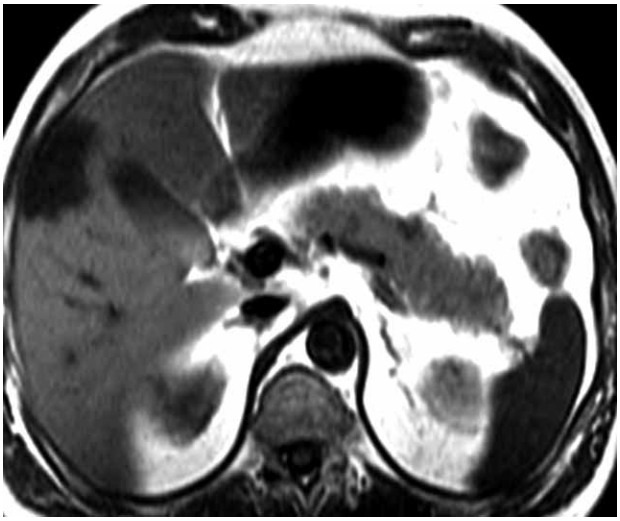
MR cholangiography for visualization of the bile ducts is based on the excretion of Mn into the bile vessels. Because T1w 3D GRE sequences can be performed in higher in-plane resolutions than T2w sequences, the intrahepatic bile ducts can be mapped, thus helping to find anatomical variants before surgery and evaluation of complex biliary–enteric anastomoses. Other structures, nonmetallic biliary stents and filling defects can also be delineated, as seen in Fig. (**9**) where the biliary system is visualized due to Mn excretion through the bile [45].

Intravenous administration of Mn based contrast agent leads to enhancement of pancreatic tumors to a lower degree than normal pancreatic tissue, and thereby provides negative contrast visualization [46]. Although the detection rate of focal areas is increased (Fig.**10**), differentiation between benign and malignant lesions is not possible on signal enhancement patterns alone. Thus a combination of both T2w and unenhanced images must be used for the fine differentiation of focal areas.

## 6. CONCLUSION REMARKS

Manganese is an essential trace element and a paramagnetic ion. Manganese based positive contrast agents may be administered both intravenously and orally. The two administration routes lead to different biodistribution patterns— in i.v. injection all organs are exposed, but in oral administration only the enterohepatic circulation is involved. Clinically $Mn^{2+}$ is excellent in detection of focal liver lesions due to its uptake in mitochondria rich hepatocytes, and also for biliary delineation due to its biliary excretion, thus providing useful

**A**



**B**

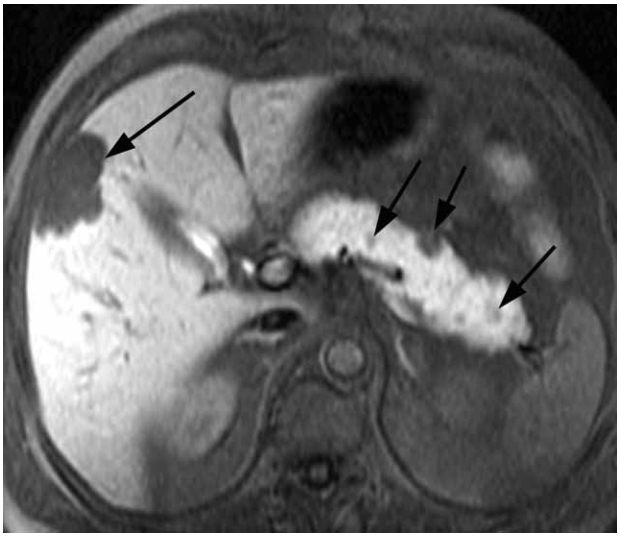


**Fig. (10).** T1w MRI of liver and pancreas before (**A**), and T1w fatsat MRI after (**B**) administration of Mangafodipir. Both normal liver and pancreas tissue are enhanced after injection of manganese, with better delineation of focal lesions in both liver and pancreas (arrows). Images courtesy of Dr Dushyant Sahani, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA.

information on diffuse liver lesions. The i.v. formulation can be used for imaging focal pancreatic lesions. In comparison with CT and PET scans, Mn enhanced MRI reveals more and smaller metastasis in the liver, thus leading to a more correct staging of cancer patients.

Manganese based MR contrast agents are in general well tolerated with few mild adverse events. Both oral and i.v. formulations can be given outside the scanner room in order to save scanner time and the oral formulation can also be sent to the patient in advance to save hospital time for both patient and staff. However, as yet there are no reported studies comparing Mn contrast agents for detection of pathology with those of gadolinium and liver specific iron oxide contrast agents.

Manganese agents are also used for experimental studies of, for example, cardiac ischemia and olfactory system neural connection, though the clinical value of these remains to be demonstrated.

## 7. DISCLOSURE

Thomsen HS. Manganese-containing magnetic resonance contrast agent. US patent no. 6,015,545/ 18 January 2000.

## 8. ABBREVIATIONS

| | | |
|---|---|---|
| $Mn^{2+}$ | = | Manganese |
| $Gd^{3+}$ | = | Gadolinium |
| $Cu^{2+}$ | = | Copper |
| $Zn^{2+}$ | = | Zinc |
| MR | = | Magnetic Resonance |
| CT | = | Computed tomography |
| MnCl | = | Manganese chloride |
| DPDP | = | Dipyridoxyl diphosphate |
| DPMP | = | Dipyridoxyl monophosphate |
| PLED | = | Dipyridoxyl ethylenediamine-diacetate |
| DCE | = | Dynamic contrast enhancement |
| ALAT | = | Alanine aminotransferase |
| ASAT | = | Aspartate aminotransferase |
| GRE | = | Gradient recalled echo |
| T1w | = | T1 weighted |
| T2w | = | T2 weighted |
| i.v. | = | Intravenous |
| R1 | = | Reciprocal of T1 |
| R2 | = | Reciprocal of T2 |
| b.w. | = | Body weight |

## REFERENCES

[1] Santamaria AB, Sulsky SI. Risk assessment of an essential element: manganese. J Toxicol Environ Health A 2010; 73: 128-55.

[2] Caravan P, Farrar CT, Frullano L, Uppal R. Influence of molecular parameters and increasing magnetic field strength on relaxivity of gadolinium- and manganese-based T1 contrast agents. Contrast Media Mol Imaging 2009; 4: 89-100.

[3] Balci NC, Semelka RC. Contrast agents for MR imaging of the liver. Radiol Clin Noth Am 2005; 43: 887-98.

[4] Reimer P, Schneider G, Schima W. Hepatobiliary contrast agents for contrast-enhanced MRI of liver: properties, clinical development and applications. Eur Radiol 2004; 14: 559-78.

[5] Martin DR, Semelka RC. Magnetic resonance imaging of the liver: review of techniques and approach to common diseases. Semin Ultrasound CT MR 2005; 26: 116-31.

[6] Balci NC, Semelka RC. Contrast agents for MR imaging of the liver. Radiol Clin Noth Am 2005; 43: 887-98.

[7] Chabanova E, Thomsen HS, Logager V, *et al.* Effect of new manganese contrast agent on tissue intensities: comparison of 0.23 T, 0.6T and 1.5 T MRI. A part of a phase I trial. MAGMA 2004; 17: 28-35.

[8] Torres CG, Lundby B, Sterud AT, McGill S, Gordon PB, Bjerknes H. MnDPDP for MR imaging of the liver. Results from the European phase III studies. Acta Radiol 1997; 38: 631-7.

[9] Thomsen HS, Loegager V, Noergaard H, Chabanova E, Moller JM, Sonne J. Oral manganese for liver imaging at three different field strengths. Acad Radiol 2004; 11: 630-6.

[10] Bellin M-F, Webb JAW, Van Der Molen AJ, Thomsen HS, Morcos SK. Safety of MR liver specific contrast media. Eur Radiol 2005; 15: 1607-16.

[11] Gallez B, Bacic G, Swartz HM. Evidence for the dissociation of the hepatobiliary MRI contrast agent Mn-DPDP. Magn Reson Med 1996; 35: 14-9.

[12] Hustvedt SO, Grant D, Southon TE, Zech K. Plasma pharmacokinetics, tissue distribution and excretion of MnDPDP in the rat and dog after IV administration. Acta Radiol 1997; 38: 690-9.

[13] Federle MP, Chezmar JL, Rubin DL, *et al.* Safety and efficacy of Mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: results of the U.S. multicenter phase III clinical trials (safety). J Magn Reson Imaging 2000; 12: 186-97.

[14] Elizondo G, Fretz CJ, Stark DD. Preclinical evaluation of MnDPDP: new paramagnetic hepatobiliary contrast agent for MR imaging. Radiology 1991; 178: 73-8.

[15] Thomsen HS, Svendsen O, Klastrup S. Increased manganese concentration in the liver after oral intake. Acad Radiol 2004; 11: 38-44.

[16] Chabanova E, Logager V, Moller JM, Dekker H, Barentsz J, Thomsen HS. Imaging liver metastases with a new oral manganese-based contrast agent. Acad Radiol 2006; 13: 827-32.

[17] Thomsen HS, Barentsz JO, Burcharth F, *et al*. Initial clinical experience with oral manganese (CMC-001) for liver MR imaging. Eur Radiol 2007; 17: 273-8.

[18] Kim HJ, Kim KW, Byun JH, *et al*. Comparison of mangafodipir trisodium- and ferucarbotran-enhanced MRI for detection and characterization of hepatic metastases in colorectal cancer patients. Am J Roentgenol 2006; 186: 1059-66.

[19] Kanematsu M, Kondo H, Goshima S, *et al.* Imaging liver metastases: review and update. Eur J Radiol 2006; 58: 217-28.

[20] Toft KG, Hustvedt SO, Grant D, *et al*. Metabolism and pharmacokinetics of MnDPDP in man. Acta Radiol 1997; 38: 677-89.

[21] Underwood EJ. Manganese. In: Underwood EJ, Ed. Trace elements in human and animal nutrition. New York, NY Academic Press 1971; pp. 177-207.

[22] Mena I. Manganese. In: Bronner F, Coburn JW, Ed. Disorders on mineral metabolism. New York, NY Academic Press 1981; pp. 233-70.

[23] Cooper WC. The health complications of increased manganese in the environment resulting from combustion of fuel additives: a review of the literature. J Toxicol Environ Health 1984; 14: 23-46.

[24] Mirowitz SA, Westrich TJ, Hinsch JD. Hypertensive basal ganglia on T1-weighed MR images in patients receiving parenteral nutrition. Radiology 1991; 181: 117-20.

[25] Rummeny E, Ehrenheim C, Gehl HB, *et al*. Manganese-DPDP as a hepatobiliary contrast agent in the magnetic resonance imaging of liver tumors. Results of clinical phase II trials in Germany including 141 patients. Invest Radiol 1991; 26(Suppl 1): S142-5; discussion S150-5.

[26] Aicher KP, Laniado M, Kopp AF, Gronewaller E, Duda SH, Claussen CD. Mn-DPDP-enhanced MR imaging of malignant liver lesions: efficacy and safety in 20 patients. J Magn Reson Imaging 1993; 3: 731-7.

[27] Wang C, Ahlstrom H, Ekholm S, *et al*. Diagnostic efficacy of Mn DPDP in MR imaging of the liver. A phase III multicenter study. Acta Radiol 1997; 38: 643-9.

[28] Wolf GL, Baum SL. Cardiovascular toxicity and tissue proton T1 response to manganese injection in the dog and rabbit. Am J Roentgenol 1983; 141: 193-7.

[29] Conrad LL, Trendly RL, Baxter DJ. Positive inotropic effect of manganese in dog myocardium. Am J Physiol 1966; 210: 357-9.

[30] Brurok H, Schøojtt J, Berg K, Karlsson JOG, Jynge P. Effects of manganese dipyridoxyl diphosphate, dipyridoxyl diphosphate- and manganese chloride on cardiac function: An experimental study in the langendorff perfused rat heart. Invest Radiol 1955; 30: 159-67.

[31] Kojima S, Hirai M, Kiyozumi M, Sasawa Y, Nakagawa M, Shin-O T. Studies of poisonous metals. X metabolic fate og manganese after oral administration of excessive manganese chloride in rats. Chem Pharm Bull 1983; 31: 2459-65.

[32] Mahoney JP, Small WJ. Studies of manganese: III. The biological half-life of radiomanganese in man factors which affect this lifetime. J Clin Invest 1968; 47: 643-53.

[33] Kreft BP, Baba Y, Tanimoto A, Finn JP, Stark DD. Orally administered manganese chloride: Enhanced detection of hepatic tumours in rats. Radiology 1993; 186: 543-8.

[34] Jynge P, Brurok H, Asplund A, Towart R, Refsum H, Karlsson JO. Cardiovascular safety of MnDPDP and MnCl2. Acta Radiol 1997; 38: 740-9.

[35] Grant D, Blazak WF, Brown GL. The reproductive toxicology of intravenously administered MnDPDP in the rat and rabbit. Acta Radiol 1997; 38: 759-69.

[36] Blazak WF, Brown GL, Gray TJ, Treinen KA, Denny KH. Developmental toxicity study of Mangafodipir trisodium injection (MnDPDP) in New Zealand white rabbits. Fundam Appl Toxicol 1996; 33: 11-5.

[37] Misselwitz B, Muhler A, Weinmann HJ. A toxicologic risk for using manganese complexes? A literature survey of existing data through several medical specialties. Ivest Radiol 1995; 30: 611-20.

[38] Larsen E, Grant D. General toxicology of MnDPDP. Acta Radiol 1997; 38: 770-9.

[39] Southon TE, Grant D, Bjornerud A, *et al*. NMR relaxation studies with MnDPDP. Acta Radiol 1997; 38: 708-16.

[40] Bartolozzi C, Donati F, Cioni D, *et al.* Detection of colorectal liver metastases: a prospective multicenter trial comparing unenhanced MRI, MnDPDP-enhanced MRI, and spiral CT. Eur Radiol 2004; 14: 14-20.

[41] Regge D, Campanella D, Anselmetti GC, *et al*. Diagnostic accuracy of portal-phase CT and MRI with Mangafodipir trisodium in detecting liver metastases from colorectal carcinoma. Clin Radiol 2006; 61: 338-47.

[42] Kim KW, Kim AY, Kim TK, *et al*. Small (<or = 2 cm) hepatic lesions in colorectal cancer patients: detection and characterization on Mangafodipir trisodium-enhanced MRI. Am J Roentgenol 2004; 182: 1233-40.

[43] Sahani DV, Kalva SP, Fischman AJ, *et al*. Detection of liver metastases from adenocarcinoma of the colon and pancreas: comparison of Mangafodipir trisodium-enhanced liver MRI and whole-body FDG PET. Am J Roentgenol 2005; 185: 239-46.

[44] Marti-Bonmati L, Fog AF, de Beeck BO, Kane P, Fagertun H. Safety and efficacy of Mangafodipir trisodium in patients with liver lesions and cirrhosis. Eur Radiol 2003; 13: 1685-92.

[45] Fayad LM, Kamel IR, Mitchell DG, Bluemke DA. Functional MR cholangiography: Diagnosis of functional abnormalities of the gallbladder and biliary tree. Am J Roentgenol 2005; 184: 1563-71.

[46] Boraschi P, Donati F, Gigoni R, *et al*. Mangafodipir trisodium-enhanced MR imaging of pancreatic disease. Eur Radiol 2006; 16: 988-97.

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