Citrate-coated (184th variant) very small superparamagnetic iron oxide particles

VSOP-C184

The MICAD Research Team

Created: September 1, 2006; Updated: September 27, 2006.

Chemical name:	Citrate-coated (184th variant) very small superparamagnetic iron oxide particles
Abbreviated name:	VSOP-C184
Synonym:	
Agent Category:	Iron oxide
Target:	Non-targeted
Target Category:	Phagocytosis
Method of detection:	Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA)
Source of signal:	Iron oxide
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Humans

Background

[PubMed]

Superparamagnetic iron oxide (SPIO) particles are potent and versatile contrast media for magnetic resonance imaging (MRI), and their efficacy has been shown to increase as their diameter decreases (1) SPIO particles were originally developed as liver MRI contrast agents to improve tumor detection at T_2-weighted imaging. Nevertheless, SPIO particles administered as a bolus (e.g., ferucarbotran (2)) only produce moderate signal enhancement, especially in the early stage of a dynamic T_1-weighted MRI. Ultrasmall superparamagnetic iron oxide particles (USPIO), such as ferumoxtran-10 (3), can only be administered as an infusion. Current SPIO and USPIO particles present very limited

NLM Citation: The MICAD Research Team. Citrate-coated (184th variant) very small superparamagnetic iron oxide particles. 2006 Sep 1 [Updated 2006 Sep 27]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

benefits compared with the low-molecular weight gadolinium-based contrast media (4, 5), which acquire their blood pool effect by binding to plasma proteins after intravenous injection.

VSOP-C184, a citrate-coated very small iron oxide paramagnetic particle (VSOP) with a T_1/T_2 ratio higher than most SPIO and USPIO particles studied so far (e.g., NC 100150 (6) and SHU 555 C (7)), is being investigated as a novel contrast medium for magnetic resonance angiography (MRA). First results from preclinical and phase I studies have been reported in the literature (8, 9).

VSOP-C184 is the 184th variant of 200 synthesized particles in the optimization process of the core size and citrate coating, which is designed to achieve a minimum ratio of the relaxivities R_1 and R_2 while maximizing the blood half-life of the contrast medium. The respective values for R_1 and R_2 (at 0.94 T) reported by Wagner et al. (8) are 20.1 l/mmol.sec and 37.1 l/mmol.sec, respectively. VSOP-C184 has a core diameter of 4 nm and a hydrodynamic diameter of 7.0 ± 0.15 nm. Contrary to ultra SPIO particles (USPIO), which are stabilized sterically, VSOP particles are stabilized electrostatically by a complex binding mechanism between citrate and the surface of the iron particles (9).

Synthesis

[PubMed]

VSOP-C184 consists of an aqueous solution of superparamagnetic iron oxide particles (core diameter of 4 nm) coated with a citrate layer. Taupitz et al. (9) reported a total diameter of the particles of 7.0 ± 0.15 nm. The concentration of the active substance used by the authors was 29 g (0.52 mol) Fe/l. The solution also contained citric acid at a concentration of 4.16 g/l and mannitol at 60 g/l (8).

Details about the manufacturing process for coating iron oxide particles (overall size of 8.6 mm) with monomeric material were previously reported by Pilgrimm et al. (10). The values for R_1 and R_2 (determined in demineralized water at 0.94 T) reported by Wagner et al. (8) were 20.1 l/mmol.sec and 37.1 l/mmol.sec respectively. VSOP-C184 has an osmolality of 376 mOsm/kg H_2O and a pH of 7.0. At room temperature, VSOP-C184 has so far proved to be stable for six months (8).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

Rodent studies were performed by Wagner et al. (8) on six male Wistar rats (85 days old, ≈420 g each) with VSOP-C184 at 0.015, 0.045, and 0.075 mmol Fe/kg. After intravenous injection, MRI was performed for 30 min (seven acquisitions) using a 3D gradient-echo sequence. Signal intensities were measured for selected regions of interest (ROIs) by collecting signal values inside the target tissue (of the ROI) and outside the body, without inclusion of motion artifacts (noise). Results showed that the rats exhibited a pronounced and long-lasting increase in vessel signal-to-noise ratio SNR_{blood} for all Fe concentrations. Compared with mean non-enhanced values, the mean SNR_{blood} values for the three tested doses were higher by a factor of 5.8, 10.9, and 11.4 at 2 min post-contrast. At 26 min post-contrast, mean values remained higher by a factor of 3.9, 8.8, and 9.3, respectively. This allowed excellent visualization of the thoracic and abdominal vasculature in rats, even at the lowest concentration of 0.015 mmol Fe/kg. The plasma elimination half-life of VSOP-C184 observed at 0.045 mmol Fe/kg was 21.3 ± 5.5 min.

Pharmacokinetic data were obtained by quantitatively measuring iron in the liver, spleen, and carcass, and by determining the signal intensity (SI) of liver and spleen 24 hours and 28 days after injection (for all three doses in Fe). Results showed that the T_1 relaxation time of plasma (a critical parameter for the angiographic effect in MRI) was reduced to below 100 ms for up to 20 min post-injection of VSOP-C184 at 45 µmol Fe/kg, and for ≈40 min at 75 µmol Fe/kg (8).

Toxicity studies were performed by Wagner et al. (8) using mice and rats administered with a single bolus injection of VSOP-C184 at the following dose levels: 0.83, 1,79, 3.85, 8.3, and 17.9 mmol Fe/kg. The animals were inspected before injection and immediately, 5, 15, 30, 60 min, 3, 6, and 24 hours after injection, and the median lethal dose ("lethal dose, 50%" or LD_{50}) was calculated by regression analysis (using the mortality rates at 24 h and 14 days). Results showed that the acute tolerance of VSOP-C184 was similar to that of polymer-coated SPIO and USPIO particles (11, 12). An LD_{50} in mice >17.9 mmol Fe/kg was determined for VSOP-C184, exceeding the maximum dose to be applied in humans during an examination (0.075 mmol Fe/kg) by a factor of at least 230. The LD_{50} determined in rats showed a high safety factor of at least 116.

Other Non-Primate Mammals

[PubMed]

Schnorr et al. (13) investigated the suitability of VSOP-C184 for first-pass MRA using three male mini pigs (≈6 months old, weight 16.75–20 kg), injected with VSOP-C184 at doses of 0.015, 0.025, or 0.035 mmol Fe/kg. Comparison was also made with the low-molecular weight contrast medium gadopentetate dimeglumine (Gd-DTPA) at concentrations of 0.1 and 0.2 mmol Gd/kg. Results showed that the differences between VSOP-C184 and Gd-DTPA were statistically not significant (p > or = .05), and that image quality, contrast, and delineation of vessels with VSOP-C184 at doses of 0.025 and 0.035 mmol Fe/kg were similar to those of Gd-DTPA at 0.1 and 0.2 mmol Gd/kg. The following signal enhancement values were obtained with VSOP-C184 for 0.015, 0.025, or 0.035 mmol Fe/kg: 9.4 ± 2.6; 12.31 ± 1.2; 16.53 ± 1.7 (aorta); 7.6 ± 2.2; 9.9 ± 1.0; 13.2 ± 0.5

(renal arteries). Vessel edge definition values were as follows for the three doses of VSOP-C184 were: 106.3 ± 31.0; 135.3 ± 58.8; 141.3 ± 71.0 (aorta); 102.2 ± 24.3; 146.8 ± 63.0; 126.9 ± 37.6 (renal arteries).

Other pig studies performed by Wagner et al. (8) showed that the plasma elimination half-life of VSOP-C184 (at 0.045 mmol Fe/kg) was 36.1 ± 4.2 minutes, resulting in a T_1 relaxation time <100 ms for 30 min in the animals. The particles were shown to be mostly cleared by the liver. MRA of VSOP-C184 at a dose of 0.045 mmol Fe/kg showed an excellent depiction of the coronary arteries.

Schnorr et al. (14) performed MRI studies using VSOP-C184 on 20 rabbits (5 for each contrast agent and dose) bearing liver tumors (VX-2 carcinoma) imaged at 1.5 T. Results showed that VSOP-C184 administered at 0.015 mmol Fe/kg produced high contrast in delayed imaging, similar to the contrast observed with ferucarbotan at identical dose. Like ferucarbotran, VSOP-C184 appeared to be taken up by liver Kupffer cells, while tumors remained unaffected. Although VSOP-C184 exhibited a much longer blood half-life in humans (≈35 min for 0.015 mmol Fe/kg (9)), experiments performed by Schnorr et al. (14) showed that, similarly to ferucarbotran, VSOP-C184 produced a signal decrease reaching noise levels as early as 5 min after intravenous injection when used in combination with a moderately T_2-weighted sequence. Schnorr et al. (14) suggested that the amount of VSOP-C184 accumulated in the liver during that time produced a sharp T_2-shortening effect after it was phagocytosed.

At T_1-weighted dynamic MRI, VSOP-C184 with 0.015 mmol and 0.025 mmol Fe/kg, Gd-DTPA, and ferucarbotran, the median peak contrast-to-noise ratio (CNR) values were 20.7 (25th percentile, 16.3; 75th percentile, 22.6), 24.2 (25th percentile, 19.3; 75th percentile, 28.5), 16.4 (25th percentile, 13.7; 75th percentile, 20.3), and 14.0 (25th percentile, 11.4; 75th percentile, 16.8), respectively. At T_2-weighted imaging using the same contrast agents and same concentrations, the measured median CNR values were 15.0 (25th percentile, 13.4; 75th percentile, 21.3), 15.7 (25th percentile, 14.5; 75th percentile, 19.8), 11.3 (25th percentile, 8.2; 75th percentile, 12.2), and 15.7 (25th percentile, 12.5; 75th percentile, 22.4), respectively.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Taupitz et al. (9) performed phase I clinical studies of VSOP-C184 on 18 healthy male subjects (19–43 years old) at concentrations of 0.015, 0.045, or 0.075 mmol Fe/kg ($n = 5$) or placebo ($n = 1$). After intravenous injections, blood samples were collected for

chemical and clinical analysis and relaxometry (0.94 T). Urinalyses were performed for up to 2 weeks after administration of the contrast medium.

None of the subjects showed significant abnormalities in safety laboratory parameters, and no serious adverse events were observed. Iron blood concentrations for all subjects showed no significant change (compared with baseline) after injection of VSOP-C184, for all subjects. However, plasma and serum iron concentrations increased significantly, reaching a peak level between 2 and 5 min post-injection, in correlation with the injected dose. The observed half-life was 0.5 to 1.5 h.

Results showed a reduction of T_1 relaxation times of blood to <100 ms, for a time period of 17 ± 5 min after intravenous injection of VSOP-C184 at 0.045 mmol Fe/kg, and for 60 ± 9 min at 0.075 mmol Fe/kg. The values obtained for plasma were 68 ± 12 (0.045 mmol Fe/kg) and 148 ± 16 (0.075 mmol Fe/kg), respectively. Values obtained for serum were 59 ± 7 (0.045 mmol of Fe/kg) and 132 ± 21 (0.075 mmol Fe/kg). Some significant differences between the three dose groups were observed with respect to the minimum values of relaxation times T_1 and T_2 obtained for blood, plasma, and serum ($p < 0.05$). Ferritin levels were found to be normal both before and after injection of VSOP-C184, yet a dose-dependent increase was observed 2–8 days after administration of the contrast media at 0.045 and 0.075 mmol Fe/kg.

The results obtained in the study by Taupitz et al. (9) suggest that 0.015 mmol Fe/kg (the lowest of the three doses investigated) cannot produce an adequate effect for MRA in the equilibrium phase, whereas the highest dose, 0.075 mmol, causes overdose effects. A dose of about 0.045 mmol Fe/kg seems to be optimal for equilibrium MRA.

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