Citrate-coated Superparamagnetic Iron Oxide Particles as a New MR Contrast Medium: Results of a Clinical Phase I Trial

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Synopsis
A new iron oxide MRI blood-pool contrast medium with citrate-coating (VSOP-C184) was investigated for its tolerance and effectiveness. VSOP-C184 (diameter: 8.6 nm; R1 and R2: 20.1 and 37.1 l/(mmol*s)) was administered intravenously at 15, 45, and 75 µmol Fe/kg in 5 healthy volunteers each. Possibly substance-related adverse events that showed complete resolution without medication occurred in 2 subjects of the 75 µmol group. Otherwise, bolus injection of VSOP-C184 was well tolerated. At the intended clinical dose of 45 µmol Fe/kg, plasma T1 is < 100 ms over a period of 68±12 min, and minimum plasma T1 is 50±6 ms.

Introduction
The tolerance and pharmacokinetic properties of a new MRI bloodpool contrast medium based on very small iron oxide particles (VSOP) were investigated in a clinical phase I trial. In contrast to the iron oxide contrast media already available, which have polymer coats (e.g. dextran), VSOP particles are coated by a monomer (citrate) (1-3). This coating allows for producing very small particles (<10 nm) with a narrow size range and favorable magnetic properties.

Material and methods
Contrast medium: The citrate-stabilized iron oxide preparation VSOP-C184 was investigated. The particles have a total diameter of 8.6 nm with a core size of 4 nm. R1 and R2 relaxivities at 0.94 T in water are 20.1 and 37.1 l/(mmol*s), respectively.

Subjects and dosages: Three dosages of VSOP-C184, 15, 45, and 75 µmol Fe/kg body weight, were investigated in a total of 18 healthy subjects. In each dose group 5 subjects received the study drug and one a placebo. The dose of 15 µmol Fe/kg was infused over 10 min. The doses of 45 and 75 µmol Fe/kg were injected as an intravenous bolus at a rate of 1 ml/s.

Tolerance: Analysis comprised subjective sensations, ECG, oxygen saturation, blood pressure, clinicochemical and immunologic parameters, iron metabolism, and urinary status. Blood was collected before intravenous injection of VSOP-C184 as well as 1, 4, and 24 hours and 2 weeks thereafter.

Pharmacokinetics: Determination of T1 and T2 relaxation times in serum, plasma, and whole blood at 0.94 T and measurement of plasma iron levels by AAS (atom absorption spectrometry). Blood was collected before contrast medium injection as well as 1, 2, 5, 15, 30, 45 min and 1, 4, 24 hours thereafter. The data served to calculate elimination half-lives.

Results
Tolerance: Infusion and intravenous bolus injection of VSOP-C184 were well tolerated. In the highest dose group (75 µmol Fe/kg) one subject showed a slight decrease in blood pressure and another shortness of breath, dizziness, and abdominal pain starting 45 min after injection. These possibly substance-related symptoms receded completely within a short time and without requiring medication. In general, slight increases in transferrin, total iron, and ferritin were observed. None of the other laboratory parameters investigated showed any abnormal changes.

Pharmacokinetics: Injection of VSOP-C184 produces a prolonged shortening of T1 and T2 relaxation times in serum, plasma, and whole blood (see Table 1). Elimination takes a monoexponential course. The different methods (T1 and T2 relaxation times, iron determination) demonstrate nearly identical elimination kinetics.

Table 1: Pharmacokinetic data of VSOP-C184

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Serum</th>
<th>Plasma</th>
<th>whole blood</th>
<th>Serum</th>
<th>Plasma</th>
<th>whole blood</th>
<th>Serum</th>
<th>Plasma</th>
<th>whole blood</th>
<th>Serum</th>
<th>Plasma</th>
<th>whole blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 µmol Fe/kg</td>
<td>33±5</td>
<td>35±4</td>
<td>52±7</td>
<td>192±29</td>
<td>161±31</td>
<td>266±26</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>45 µmol Fe/kg</td>
<td>50±6</td>
<td>54±5</td>
<td>59±5</td>
<td>59±7</td>
<td>50±6</td>
<td>86±7</td>
<td>59±7</td>
<td>68±12</td>
<td>17±5</td>
<td></td>
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<tr>
<td>75 µmol Fe/kg</td>
<td>71±13</td>
<td>68±8</td>
<td>74±3</td>
<td>37±9</td>
<td>30±4</td>
<td>58±5</td>
<td>132±21</td>
<td>148±16</td>
<td>60±9</td>
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</tr>
</tbody>
</table>

*AAS: atom absorption spectrometry; *time interval after injection, in which the T1 relaxation time remains below 100 ms

Conclusion:
VSOP-C184 is a safe and well-tolerated bloodpool contrast medium suitable for MR angiography based on its prolonged and strong T1-relaxation-time-shortening effect.

References
3) Taupitz et al, Radiology 2002; 222: 120-126

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