Oral Magnetic Particles in MR Imaging of the Abdomen and Pelvis

Two phase 2 clinical trials of an oral superparamagnetic contrast agent for enhancement on magnetic resonance images of the intestine were performed. In trial 1, 31 male patients with cancer of the testis under went follow-up examinations of the abdomen at 0.5 and 1.5 T after oral administration of magnetic particles. In trial 2, 31 female patients with pelvic and lower abdominal disease were examined at 1.5 T after administration of the contrast material. The patients each ingested 800 mL of contrast material over approximately 2 hours. Concentrations of 0.25 and 0.5 g/L did not induce blurring or metallic artifacts. Distribution was homogeneous through the gastrointestinal tract. In all patients, a loss of signal intensity was observed on proton density-, T1-, and T2-weighted images. The diagnostic information from postcontrast images in trial 2 was greater in 16 patients (52%). Contrast enhancement was independent of field strength; no major side effects were observed. Artifacts from moving bowels were less troublesome, and delineation of intraabdominal and pelvic organs was better with the use of oral magnetic particles.

Index terms: Gastrointestinal tract, MR studies, 70.1214 + Iron + Magnetic resonance (MR), contrast enhancement

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Severe obstacles have slowed the progress of magnetic resonance (MR) imaging of the abdomen and, to a lesser extent, the pelvis. Motion artifacts due to peristalsis, blood flow, and respiration on the one hand, and lack of contrast between the bowel and adjacent organs on the other, adversely affect images and thus diagnostic quality of examinations. Hardware and software improvements have helped resolve some of the first problems, and the development of oral contrast agents seems to be promising to overcome the latter (1).

Potential contrast media include positive agents (ie, paramagnetic or T1 agents), which, at certain concentrations, reduce T1 and brighten signal intensity (2), and negative agents, including those which reduce the proton density to eliminate the signal intensity in the region of interest, and superparamagnetic and ferromagnetic (ie, T2 or bulk susceptibility) agents, which reduce T2 and thus darken the area of interest.

Details of the mechanism of action of superparamagnetic oral ferrite particles have been described previously (3–6). Initial clinical trials have shown the feasibility of using negative contrast agents with iron particles in MR imaging of the abdomen (7–10).

We performed two phase 2 clinical trials to evaluate a bulk susceptibility (negative) oral contrast agent: oral magnetic particles (OMP). Bound to monodisperse polymer particles as a carrier matrix, the active component of this agent is a ferrite-type crystalline magnetic iron oxide.

The aim of the trials was to evaluate the safety and efficacy of the agent. We present the results of these trials, summarizing data on contrast material enhancement, artifacts, diagnostic information, field strength issues, and adverse events.

Patients and Methods

Patients

Trial 1 involved 31 males aged 17–51 years (mean, 32.9 years) whose body weight ranged from 53 to 114 kg (mean, 80.1 kg). Trial 2 involved 31 women aged 42–79 years (mean, 60.2 years) whose body weight ranged from 52 to 108 kg (mean, 68.8 kg). In both trials, the first six patients were considered pilot patients. In the pilot phase, different concentrations of the agent were used to determine the best conditions for the final trials.

Exclusion criteria were relative, and absolute contraindications of MR imaging were as previously reported (12). The following exclusion criteria were added: gastric or duodenal ulcer, Crohn disease, fistulas, or colitis; known or suspected gastrointestinal damage due to radiation therapy, although spillage into the peritoneum was not considered threatening from a toxicologic point of view; nausea, vomiting, or severe diarrhea; laxative use during the past 12 hours; known human immunodeficiency virus or hepatitis positivity; previous entry into the present trial or simultaneous entry into another trial; and application of any other contrast agent within 36 hours before and 1 week after the examination.

The trials were performed according to the revised Helsinki Declaration of 1975. Both the regional ethical committee and the Norwegian Medicines Control Authority had assessed and approved the trials. Before examination, the nature of the procedure and the contrast agent was explained, and informed consent was obtained from all patients. All patients were conscious and cooperative.

Contrast Material

The OMP consisted of monodisperse polymer particles with a diameter of 3–4 μm as a carrier matrix. They were coated

Abbreviations: GRE = gradient echo, OMP = oral magnetic particles, SE = spin echo, TE = echo time, TR = repetition time.
with the active component, a ferrite-type crystalline iron oxide (50 nm in diameter), intermediate between magnetite and γ-iron III oxide. The iron content of the agent was approximately 20%–27% by weight. Because of their size, the particles were superparamagnetic.

Toxicology studies were performed in mice and rats. None of the rodents died after administration of the highest dose possible (9 g/kg in mice and 2 g/kg in rats); thus, the median lethal dose could not be calculated. A histologic examination of the gut in rats showed no local effect after administration of the clinical dose, and only minor unspecific and reversible changes were observed after the administration of doses 50 times the clinical dose (750 mg/kg).

An iron-59 absorption study in rats showed absorption of less than 1% of the iron ingested. The particles were excreted in the feces exclusively within 48 hours. Magnetic field exposure did not influence the gastrointestinal transfer of the particles.

During the pilot phases of the phase 2 trials described herein, the particles were applied in plain aqueous suspension; in the final trials, a viscosity-increasing agent was added to overcame aggregation and sedimentation, which had caused artifacts. This viscosity-increasing agent consisted of a commonly used food additive—a mixture of starch and cellulose. In trial 1, a high viscosity of 2,500 mPa·sec was evaluated; in trial 2, a lower viscosity of 700 mPa·sec was studied. Background information on the viscosity enhancement has been previously reported (11).

Dose

In the pilot phases, three different concentrations of the contrast agent were used: 0.25, 0.5, and 0.75 g/L. Because of metallic artifacts associated with the 0.75-g/L concentration, concentrations of 0.5 g/L were used in the final trials. The patients were given OMP in four portions of 200 mL each with a 40-minute interval between ingestions.

MR Imaging

The trials comprised two protocols. In the first protocol, 25 male patients and six male pilot patients with cancer of the testis were imaged at 0.5 and 1.5 T after ingestion of the contrast agent, with both computed tomography (CT) and ultrasound (US) as reference modalities. In the second protocol, 25 female patients and six female pilot patients with lower abdominal and pelvic diseases were imaged at 1.5 T before and after ingestion of the contrast agent, with US and surgery as reference methods. A comparative discussion of the results obtained with the different imaging modalities will not be presented here.

Imaging was performed with the use of two whole-body systems (S5 [0.5-T] and S15 [1.5-T] models; Philips Medical Systems, Eindhoven, The Netherlands). Transverse, sagittal, and coronal gradient-echo sequences (flip angle, 70°; repetition time [TR] msec/echo time [TE] msec = 28/13), T1-weighted sequences (450/20), T2-weighted sequences (2,100/100), and intermediately (proton density) weighted spin-echo (SE) sequences (2,100/29) were applied. Because of cardiac gating of the immediately weighted and T2-weighted sequences, TR depended on the length of the individual cardiac cycle (± 2,100 msec [standard deviation]). TR, TE, and pulse angle were not adjusted for different field strengths.

Additional Examinations

Before and 24 hours after ingestion of the contrast agent, vital signs (heart rate and blood pressure) were measured. A blood screening test was performed before the first MR image was obtained and 24 hours thereafter. At the same time, urine samples were obtained for white and red blood cell, protein, and glucose counts and microscopy.2

Adverse Events

The patients were closely observed for any kind of immediate reaction during, and for 24 hours after, MR imaging. The patients were asked about possible subjective reactions with use of a standardized nonsuggestive pattern of questioning. Patients were questioned further only if they stated a reaction. In addition, the patients were questioned about delayed adverse events during a 1-week period after MR imaging.

Image Reading and Assessment

Images were read and scored by two radiologists (P.A.R., O.S.) independently. Diagnostic information from the examinations was evaluated by considering "image quality" and "general contrast material effect" for all pulse sequences and image orientations. They were graded as "excellent," "sufficient," or "insufficient."

The organ delineation in the abdomen and pelvis was evaluated as sufficient or insufficient. The contrast material distribution in the various segments of the gastrointestinal tract was scored as "no distribution," "partial," or "good."

The diagnostic information from the MR images obtained before and after contrast agent intake was compared. The impact on diagnosis ("less," "equal," or "more") was scored. Better delineation of organ structures was not necessarily scored as "more information." For example, only the case depicted in Figure 1 was scored as more information, whereas the case depicted in Figure 2 was scored as "equal information."

Artifacts caused by the contrast medium for each pulse sequence and image orientation were noted. They were classified as "metallic" (high signal intensity surrounding a signal void), "blurring" (blurring effect of the contrast material on surrounding tissues), and "other" (method-inherent artifacts, such as flow and motion).

After the radiologic evaluation, all categorical variables were tabulated as counts and percentages. Continuous variables were presented by means, standard deviations, and maximums and minimums.

RESULTS

Pilot Phases 1 and 2

With the aqueous suspension of OMP, fast gradient echo (GRE) sequences led to both motion and metallic artifacts in the abdomen, interfering with image reading and obscuring relevant clinical information. Thus, none of the common gradient sequences was used in the final trials. Metallic artifacts were also created by the inhomogeneous distribution of the magnetic particles in the aqueous suspension with use of standard SE sequences.

As a result of the pilot-phase findings, a viscosity-increasing substance was added to the contrast agent, which improved the distribution of the particles and thus decreased the frequency of artifacts.

Final Trials 1 and 2

Adverse effects and reactions toward the contrast agent.—No severe side effects were observed. Two cases of nausea (one contrast agent–related and one of unknown cause), two cases of vomiting, and one case of nausea and vomiting were reported 24 hours after contrast material intake, and one case of exhaustion occurred because of the length of the procedure. The patient who reported nausea and vomiting 24 hours after the procedure felt nauseous before the procedure but did not state it at that time. Twenty-nine patients reported delayed events during the week after the examination. A change in bowel habits with looser stools was most commonly reported, but obstipation was also reported (by 25% of those who reported delayed reactions). The taste of the contrast agent was described as acceptable or tolerable by 59 of the patients (95%).

2 Clinicochemical parameters measured: hemoglobin, S-iron, iron saturation, S-total iron binding capacity, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, phosphate, calcium, potassium, creatinine, urea, ferritin, leukocytes, and differential cell count.
all said they would ingest the contrast agent again.

Vital signs and clinicochemical parameters.—No changes were noted in blood pressure or heart rate measured the day after contrast agent intake in any of the patients. The clinicochemical parameters showed normal variations, and no clinically significant changes were noted in the mean values of blood or urine parameters after the intake of oral magnetic particles. Individual changes were within expected normal variation.

Contrast material enhancement.—Sufficient or excellent signal intensity voids were observed with T2-weighted and intermediately weighted sequences, but T1-weighted sequences also yielded good contrast enhancement with a better signal-to-noise ratio than that of T2-weighted images (Figs 1-4).

Insufficient contrast enhancement was seen in 6% of the T1-weighted images; 68% of the T1-weighted images showed sufficient and 26% showed excellent contrast enhancement. Intermediately weighted and T2-weighted images of the upper abdomen showed sufficient (70%) or excellent (30%) contrast enhancement (compared with 72% and 28%, respectively, for images of the lower abdomen).

Figure 1. Precontrast (a) and postcontrast (b) images (450/20, 1.5 T) of a trial 2 patient with recurrent colon cancer. Two metastases are visible (arrowheads, a), and a third is suspected centrally. Postcontrast image reveals this structure to be part of the intestines.

Figure 2. Precontrast (a–c) and postcontrast (d–f) images ([a, d] 450/20, [b, e] 2,100/29, [c, f] 2,100/100; 1.5 T) of a trial 2 patient with uterine cancer. Blood-filled uterus is shown; tumor is not visible on these images. Precontrast images fail to delineate parts of the anterior wall of the uterus and in part of the bladder because of feces-filled intestines. The delineation of the uterus is clearer on postcontrast images. Note excellent contrast enhancement on T1-weighted, T2-weighted, and intermediately weighted images.
None showed insufficient contrast enhancement.

In some cases, particularly in the sigmoid and rectum, no differentiation could be made between air and signal intensity void created by OMP. There was no observable difference between the high- and low-viscosity preparations of the contrast agent.

General image contrast was better with the 0.5-T system. It was excellent on transverse intermediate and T2-weighted images in 12 patients (40%), compared with excellent contrast in four patients (13%) examined with the 1.5-T system. The remaining images showed sufficient contrast enhancement, except for one image, obtained with the 1.5-T system, that showed insufficient delineation.

Artifacts.—Common motion and flow artifacts were observed. Additional blurring and metallic artifacts were observed in 100% of the phase patients imaged with the aqueous suspension but in none of the patients imaged after administration of 0.25 and 0.5 g/L of the viscosity-enhanced OMP.

Diagnostic information.—In the majority of cases, the diagnosis was more certain when based on information obtained from postcontrast images. The overall postcontrast information from trial 2 was equal to precontrast information in 15 patients (48%); more information was available from postcontrast images in 16 patients (52%).

A comparison of postcontrast information obtained at 0.5 and 1.5 T in trial 1 revealed that the information was better at 0.5 T in 20 patients (65%) and equal in 11 patients (35%). These differences were due to increased inherent artifacts at higher field strengths and not to the contrast agent.

Field strength influence.—Contrast enhancement was independent of field strength. No difference in the signal intensity of the voids was observed between the 0.5- and the 1.5-T systems. This was mainly due to the fact that the concentration of the agent had been optimized for SE imaging at medium and high field strengths. In the SE images, no disturbing susceptibility artifacts were observed at 1.5 T.

**DISCUSSION**

MR imaging has not yet been established as a leading modality in the abdomen. US and CT are considered better and faster.

The shortcomings of MR imaging include motion artifacts created by respiration, cardiac motion and blood flow, and peristalsis. These problems can be partly overcome with cardiac and respiratory gating, special software that allows the elimination of certain kinds of motion disturbances, and, recently, ultrafast (i.e., subsecond) imaging.

Additional shortcomings are comparable with those of CT: Collapsed or feces- and fluid-filled intestines can hardly be differentiated from adjacent intraabdominal organs or pathologic lesions. As in conventional radiography and CT, orally or rectally administered contrast agents are thought to help resolve some of these problems.

A variety of substances have been proposed and studied in animals, human volunteers, and patients, including positive agents, mostly based on rare earth compounds and negative agents, among them bulk susceptibility agents, such as the one we studied.

The ideal contrast agent for MR imaging of the abdomen and for certain diagnostic examinations of the pelvis should possess the following properties: (a) it should be easy to administer and nontoxic; (b) its side effects should be minimal; (c) it should not change the gross anatomy of the intestines and the adjacent organs by enlarging them too much and thus leading to patient discomfort; (d) it should distribute uniformly throughout the entire gastrointestinal tract; (e) it should not induce additional image artifacts; (f) its enhancement should be unchanged throughout the entire gastrointestinal tract; (g) it should maintain its contrast enhancement on all pulse sequences, be they T1-weighted, T2-weighted, or intermediate weighted images; and (h) it should increase the sensitivity and, if possible, the specificity of the diagnosis.

Our data show that OMP fulfill most of these criteria. The administration of this contrast agent caused no problems for the patients. It passed through the entire gastrointestinal tract and is eliminated in total with no absorption of the particulate iron. It was well tolerated, with no serious side effects seen in our two trials. Patient discomfort as previously described was not observed.

The pilot-phase trials revealed problems similar to those encountered by other research groups: Sufficient contrast enhancement was achieved, but the distribution of the contrast agent was not homogeneous; parts of the bowel loops were not filled; and severe artifacts were created by the agent. After an evaluation of the causes, the composition of the image was improved.

**Figure 3.** Coronal postcontrast T1-weighted image (450/20, 0.5T) of a trial 1 patient with stage IIIC seminoma of the testis and metastasis in the left lower abdomen. The small bowel is well marked, and the encapsulated metastasis is well delineated.

**Figure 4.** Transverse postcontrast intermediate weighted (a) (2,100/29, 0.5T) and T2-weighted (b) (2,100/100, 0.5T) images of a trial 1 patient with cancer of the testis with lung metastases. CT and US reveal possible metastasis in the hilum of the left kidney. The contrast material-filled intestines help rule out a metastasis in the region.
the agent was changed. A viscosity-increasing agent made of common food additives was added, leading to uniform distribution of the contrast agent throughout the gastrointestinal tract. The additive induced a more homogeneous distribution of the contrast agent. We believed that the distribution of this contrast agent was better than that of any other oral agent used in computerized medical imaging. It also helped eliminate metallic and blurring artifacts created by the magnetic particles in aqueous suspension.

Unlike image noise associated with T1 (positive) agents, image noise was not worsened by OMP because of the signal intensity loss in the intestines. Thus, the deteriorating influence of motion artifacts on image quality diminished. OMP reduced or completely eliminated signal intensity throughout the entire gastrointestinal tract on all types of pulse sequences used in these two clinical trials. Although OMP had a stronger effect on T2-weighted sequences, it also led to signal intensity voids on intermediate-weighted and T1-weighted images, as well as on T1-influenced GRE and ultrafast (ie, subsecond) agents. The latter effect could be shown with slightly changed and newly developed pulse sequences. A separate study on the use of OMP with fast and ultrafast sequences is under way (Rinck PA, Kvaarness J, Jones R, et al, unpublished data).

One of the major problems to overcome is the increased blurring and susceptibility artifacts seen with common GRE and subsecond imaging. We attempted to solve these problems by adjusting the composition of the contrast agent. In general, the agent can be used successfully with all common T1-weighted or T1-influenced pulse sequences applied for efficient abdominal examinations. This is an advantage of OMP over paramagnetic (ie, commonly T1-influencing) agents, which can behave in a biphasic manner, depending on the concentration of the agent. With these agents, concentration during passage through the gastrointestinal tract may provoke T2 effects. This can cause unpredictable and thus unreliable contrast enhancement, as was reported with manganese chloride (15). Other research groups have reportedly overcome this problem by adding mannitol to their positive agent (1.0 mM gadopentetate dimeglumine in solution with 15 g of mannitol per liter) (2). This keeps water absorption low during gastrointestinal passage, induces an additional water influx, and results in sufficiently high signal intensity effect throughout the intestines, but helps cause diarrhea.

Other negative contrast agents, including gas, water, perfluorochemical compounds, and barium sulfate suspension, possess a number of disadvantages, such as pain at gas administration or absorption during passage through the gastrointestinal tract, as in the case of water; limited effectiveness in clinical imaging; and failure to fulfill the criteria of an ideal oral MR imaging contrast agent for the intestines, as discussed above (16–18).

Clinical efficiency and diagnostic value were found to be higher in many of those abdominal examinations in which OMP were used. Its application enhanced structures in the middle and lower abdomen and in the pelvis. It was helpful for specific diagnostic questions, particularly for the differentiation between bowel lumen and adjacent normal and pathologic structures. We used this agent successfully to rule out recurrent tumor and metastases to lymph nodes in the abdomen.

The preparation of patients for imaging with an oral contrast agent according to our phase 2 protocol was rather time-consuming. If an examination requires the administration of a gastrointestinal contrast agent to enhance the distal small bowel, it may be helpful to administer the agent the night before imaging.

In summary, these clinical trials showed that OMP are a promising gastrointestinal contrast agent. They increased diagnostic certainty and were safe and well tolerated by the patients.

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References

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