Manganese-Based Oral Contrast Agent for Liver Magnetic Resonance Imaging

Evaluation of the Time Course and Dose Response of Liver Signal Intensity Enhancement

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Objectives: Recently, an oral contrast agent (CMC-001, CMC Contrast, Lund, Sweden) containing manganese chloride tetrahydrate ($MnCl_2$) as active substance has been introduced for liver magnetic resonance imaging (MRI). The aim of this study was to evaluate the time course and dose response of liver signal intensity (SI) enhancement and liver-lesion contrast (LLC) after administration of 2 doses of CMC-001 corresponding to 0.8 g $MnCl_2$ and 1.6 g $MnCl_2$.

Materials and Methods: A total of 20 patients with liver metastases diagnosed by computed tomography were included in this prospective study. Patients were randomly assigned to receive either 0.8 g $MnCl_2$ (n = 11) or 1.6 g $MnCl_2$ (n = 9). MRI was performed precontrast (0 hour) and at 1, 2, 3, and 6 hours after contrast agent administration using a breath-hold T1-weighted gradient echo sequence (GRE). For quantitative analysis, SI was measured in regions of interest in the liver and in representative liver metastases. Liver SI enhancement and LLC were calculated. Area under the curve analysis was performed for liver SI enhancement and LLC in both dose groups. The dose groups were compared with a Wilcoxon rank-sum test for independent samples. Tests for pairwise differences between the time points were performed with paired Wilcoxon signed-rank tests.

Results: Area under the curve analysis revealed no statistical significant differences for liver SI enhancement and LLC between the 0.8 and 1.6 g $MnCl_2$ dose group ($P = 1.00$ and $P = 0.94$, respectively). Liver parenchyma showed significant SI enhancement until 3 hours after contrast agent administration (median of pooled data from both dose groups: 1 hour, 24.7%; 2 hours, 37.2%; 3 hours, 54.9%; 6 hours, 47.3%). LLC significantly increased until 2 hours after contrast agent administration (median of pooled data from both dose groups: 0 hour, 0.19; 1 hour, 0.29; 2 hours, 0.36; 3 hours, 0.37; 6 hours, 0.36). Liver SI enhancement and LLC showed no significant differences between 3 hours and 6 hours after contrast agent administration ($P = 0.75$ and $P = 0.25$, respectively). Mild adverse events occurred in 6 patients (30%) after contrast agent administration.

Conclusions: CMC-001 at doses corresponding to 0.8 and 1.6 g $MnCl_2$ offers robust liver SI enhancement with a diagnostic time window for liver MRI between 2 and 6 hours after oral administration.

Key Words: magnetic resonance, liver, oral, contrast, manganese

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Magnetic resonance imaging (MRI) is an established diagnostic modality for the evaluation of focal liver lesions. Liver-specific MR contrast agents have shown to improve lesion detection and characterization in comparison to unenhanced MRI or contrast-enhanced spiral computed tomography (CT).[1] To date, all approved liver-specific MR contrast agents including gadoxetic acid (Primovist, Bayer Schering Pharma, Germany), gadobenate dimeglumine (Multihance, Bracco, Italy), mangafodipir trisodium (Teslascan, GE Bioscience Healthcare, United Kingdom), and superparamagnetic iron oxide particles are given intravenously with liver-specific phases starting 10 to 60 minutes after administration.[2] Recently, an oral manganese-based contrast agent has been developed for liver MRI (CMC-001, CMC Contrast, Lund, Sweden), which contains manganese chloride tetrahydrate ($MnCl_2$) as active substance.[3–6] After oral administration of CMC-001, manganese is absorbed in the small bowel and transported to the liver through the portal venous system.[7] Approximately 95% of oral manganese is taken up by hepatocytes during the first pass through the liver with subsequent increase in liver signal intensity (SI) on T1-weighted MR images. In an initial study in 10 patients with extrahepatic malignancies, liver SI enhancement by CMC-001 improved delineation of liver metastases compared with unenhanced MRI.[3,5] Unlike intravenous liver-specific contrast agents, oral administration of CMC-001 offers the pharmacological property that only small amounts of manganese enter the general circulation, likely reducing the risk of systemic adverse reactions.[7,8]

Administration of the investigational product CMC-001 is fairly simple. CMC-001 is packed in 2 sachets, one containing the active ingredient $MnCl_2$, and the other containing L-alanine and vitamin D_3, which serve as promoters to increase absorption of manganese in the small bowel.[7] Both sachets are dispensed in tap water. According to initial reports, liver MRI can be performed within 2 to 4.5 hours (h) after oral contrast agent administration providing flexibility in planning of MR examinations.[5,6] However, the diagnostic time window for liver MRI after oral administration of CMC-001 has not yet been evaluated systematically.

The aim of this study was to evaluate the time course and dose response of liver SI enhancement and liver-lesion contrast (LLC) for 2 different doses of CMC-001 in patients with known liver metastases. Liver MRI was performed over a 6-hours period with 2 CMC-001 doses corresponding to either 0.8 g $MnCl_2$ or 1.6 g $MnCl_2$. These results are expected to provide information on the diagnostic time window for liver MRI after oral administration of CMC-001.

MATERIALS AND METHODS

Patients

Informed consent was obtained from all participants in this institutional review board approved, open label, randomized, paral-

lel group, single-center, phase II study. A total of 20 patients (8 women, 12 men) were included in this study. Patients had a maximum of 10 liver metastases diagnosed by contrast-enhanced dual-phase spiral CT performed within 2 to 21 days prior to MRI. CT determinations for patient enrollment were verified by a radiologist (M.T.) with 20 years of experience in abdominal CT and MR imaging. The primary tumors of the patients were as following: colorectal cancer (n = 6), renal cell carcinoma (n = 5), breast cancer (n = 3), malignant melanoma (n = 2), neuroendocrine tumor of the small intestine (n = 1), urothelial carcinoma of the bladder (n = 1), and pancreas carcinoma (n = 1). One patient had liver metastasis of an unknown primary tumor. Exclusion criteria were hepatitis, liver cirrhosis, icterus, impaired renal function with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2, and conditions which might interfere with gastrointestinal absorption such as previous surgical interventions of the stomach or small intestine.

Patients were randomized into either the 0.8 g $MnCl_2$ dose group (11 patients; 5 women and 6 men) or the 1.6 g $MnCl_2$ dose group (9 patients; 3 women and 6 men). The patients' median age was 63 years (range, 47–74 years) in the 0.8 g $MnCl_2$ dose group and 67 years (range, 55–73 years) in the 1.6 g $MnCl_2$ dose group. The patients′ median body weight was 80 kg (range, 44–124 kg) in the 0.8 g $MnCl_2$ dose group and 76 kg (range, 66–88 kg) in the 1.6 g $MnCl_2$ dose group. There was no statistical significant difference between the 2 dose groups regarding gender ($P = 0.67$), age ($P = 0.38$), and body weight ($P = 0.42$). Adverse events were registered up to 48 hours after contrast agent administration.

Contrast Agent

The contrast agent CMC-001 is composed of manganese chloride tetrahydrate ($MnCl_2$), L-alanine, and vitamin D_3. Patients in the 0.8 g $MnCl_2$ dose group received 200 mL of contrast agent preparation supplemented with 0.5 g L-alanine and 800 IU vitamin D_3. Patients in the 1.6 g $MnCl_2$ dose group received 400 mL of contrast agent preparation supplemented with 1.0 g L-alanine and 1600 IU vitamin D_3. Patients fasted for at least 10 hours before contrast agent administration to avoid inadvertent intake of additional manganese compounds in food. Patients were asked to drink the contrast agent preparation within 10 minutes.

Blood Test

Whole-blood manganese levels were determined in blood samples taken at baseline (0 hour), at 3 hours, and at 24 hours after contrast agent administration. The manganese levels were determined using Graphite Furnace Atomic Absorption Spectrometry with Zeeman background correction (Z-GFAAS), a highly selective method that precludes interference from other elements. The reference range for manganese levels in whole-blood was assumed at 100 to 271 nmol/L.[9,10]

MR Imaging

All patients were examined on a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) equipped with a high-performance gradient subsystem (maximum gradient amplitude of 40 mT/m along the x- and y-axis, maximum gradient amplitude of 45 mT/m along the z-axis, maximum slew rate of 200 mT/m/ms). A combination of the phased array surface coil and the spine array coil with a total of 12 radiofrequency channels was used. Patients were examined in the supine position. Precontrast MR imaging was performed immediately before oral administration of CMC-001. Postcontrast MR imaging was performed at 1, 2, 3, and 6 hours after contrast agent administration. The images were acquired in the axial plane, the field of view ranged between 225 × 300 mm and 338 × 450 mm depending on the patient's abdominal girth. A breath-hold T1-weighted gradient echo sequence was performed at each time point (fast low-angle shot sequence: repetition time, 218 milliseconds; echo time, 4.72 milliseconds; flip angle, 90 degrees; slice thickness, 7 mm; matrix, 115 × 256). Fat saturation was not applied.

Image Evaluation

One radiologist (M.R.) with 3 years of experience in liver MRI performed quantitative and qualitative image evaluation. The reader was blinded to the time point of image acquisition and the dose group. For each patient, circular regions of interest (ROIs) were positioned at the same anatomic location in all sequences to lower influence of local variation of coil sensitivity profiles. ROIs were placed outside of vessels and artifacts.

For quantitative evaluation, ROIs were placed in the right liver lobe, the gallbladder lumen, and in 1 representative liver metastasis. The SI of the liver parenchyma was measured in ROIs placed in the right liver lobe. The SI of the gallbladder was measured in ROIs placed in the lumen of the gallbladder with exclusion of nonenhancing bile, whereas 2 patients were excluded from analysis due to prior cholecystectomy. The liver SI enhancement was calculated using the following equation: liver SI enhancement = ([SI_P after contrast − SI_P before contrast]/[SI_P before contrast]) × 100; with P representing SI of liver parenchyma. The SI enhancement within the gallbladder lumen was calculated using the following equation: gallbladder SI enhancement = ([SI_G after contrast − SI_G before contrast]/[SI_G before contrast]) × 100; with G representing SI of bile within the gallbladder lumen. For the calculation of LLC, ROIs were placed in 1 representative liver metastasis and in normal liver parenchyma in close proximity to the liver metastasis in the same axial plane. LLC was calculated using the following equation: $LLC = (SI_P - SI_M)/(SI_P + SI_M)$; with P representing SI of normal liver parenchyma and M representing SI of liver metastasis. Moreover, homogeneity of liver enhancement was qualitatively evaluated on a three-point scale differentiating between homogeneous (1), circumscribed inhomogeneous (2), and diffusely inhomogeneous ("patchy") enhancement (3).

Statistical Analysis

The age and weight of the patients were analyzed descriptively and tested for differences between dose groups with a two-sided Wilcoxon rank-sum test. The patients′ gender was tested by Fisher exact test for differences between dose groups. Liver and gallbladder SI enhancement and LLC were recorded. Areas under the curves (AUCs) were calculated from 0 to 6 hours for liver and gallbladder SI enhancement and LLC to correct for baseline differences. The dose groups were compared with a Wilcoxon rank-sum test for independent samples. Tests for pairwise differences between the time points were performed with Wilcoxon signed-rank tests. AUCs were also calculated for changes from baseline of manganese levels in whole-blood. All tests were performed 2-sided, P less than 0.05 were regarded as statistically significant. Calculations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and R software (version 2.7.1, R Development Core Team, Vienna, Austria).

RESULTS

Adverse Events

Adverse events occurred in 3 patients in the 0.8 g $MnCl_2$ dose group and in 3 patients in the 1.6 g $MnCl_2$ dose group (Table 1). Four patients had diarrhea, 1 patient vomiting and diarrhea, and 1 patient increased urinary frequency. All adverse events resolved within 24 hours and did not require treatment. No serious adverse event occurred.

TABLE 1. Patient Characteristics, Liver SI Enhancement 3 hours After Administration of $MnCl_2$, Manganese Levels in Whole-Blood at Baseline and 3 hours After Administration of $MnCl_2$, and Occurrence of Adverse Events

Patient Number	Gender	Age (yr)	Body Weight (kg)	$MnCl_2$ (g)	Liver SI Enhancement (%) 3 h	Manganese Level in Whole Blood (nmol/L)		Adverse Events
						0 h	3 h	
01	Male	74	89	0.8	58.8	172	201	No
02	Male	69	69	1.6	74.0	145	165	No
03	Female	67	70	0.8	35.5	238	257	No
04	Female	49	97	0.8	76.4	170	187	No
05	Male	67	79	1.6	13.1	151	160	No
06	Female	60	72	1.6	40.4	270	293	No
07	Male	68	86	1.6	24.5	156	308	No
08	Female	60	78	1.6	60.5	257	230	No
09	Female	64	77	0.8	30.2	178	157	No
10	Male	53	80	0.8	90.6	234	253	Yes*
11	Male	71	93	0.8	59.0	139	220	No
12	Male	69	66	1.6	63.0	353	405	Yes*
13	Female	47	44	0.8	55.8	274	249	Yes†
14	Male	73	76	1.6	90.4	225	226	Yes†
15	Male	61	124	0.8	34.5	127	<100	Yes‡
16	Male	71	105	0.8	34.6	<100	137	No
17	Male	68	65	0.8	16.2	147	202	No
18	Female	58	66	0.8	67.4	138	156	No
19	Female	56	68	1.6	48.9	<100	<100	No
20	Male	71	88	1.6	74.2	178	220	Yes†

*Adverse events (diarrhea in patient 10, combined vomiting and diarrhea in patient 12) occurred between 1 and 2 hours after contrast agent administration.
†Adverse events (diarrhea in patient 13 and 20, urinary frequency increase in patient 14) occurred later than 6 hours after contrast agent administration.
‡Adverse event (diarrhea) occurred between 2 and 3 hours after contrast agent administration.
SI indicates signal intensity.

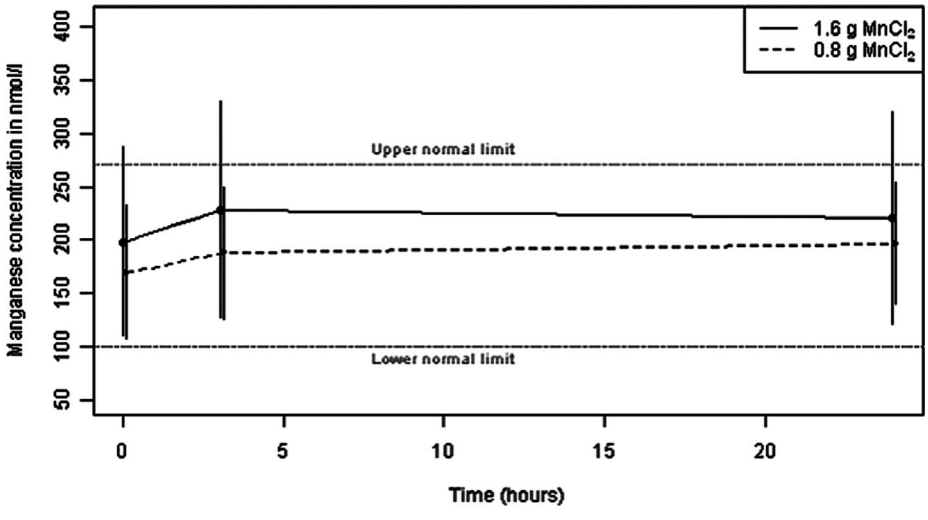

FIGURE 1. Time course of manganese levels in whole-blood at baseline (0 hour), 3 hours, and 24 hours after administration of 0.8 and 1.6 g $MnCl_2$ (mean ± SD).

Blood Test

The time course of manganese levels in whole-blood is shown in Figure 1. Elevated manganese levels (upper normal limit: 271 nmol/L) were detected in 4 patients as follows: In patients 12 and 13 (Table 1), manganese levels were already elevated at baseline. In patient 12 (353 nmol/L at baseline), the manganese level further increased at the 3 hours measurement to 405 nmol/L, while patient 13 (274 nmol/L at baseline) showed only a minimal increase to 286 nmol/L at the 24 hours measurement. Both patients had adverse events (vomiting and diarrhea in patient 12, diarrhea in patient 13). In patients 6 and 7, who had normal manganese levels at baseline, the manganese level increased to 293 nmol/L and 308 nmol/L at the 3 hours measurement. No adverse events were observed in these 2 patients. All other patients had manganese whole-blood levels

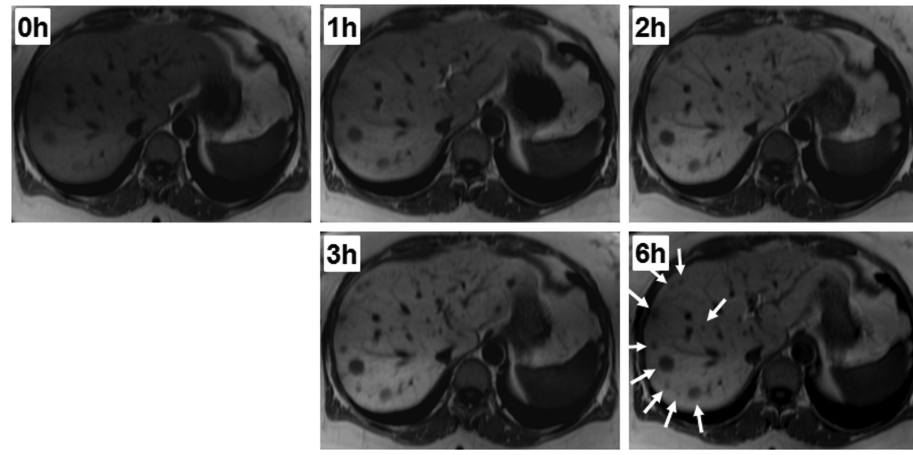

FIGURE 2. Axial T1-weighted GRE images obtained in a representative patient with liver metastases after oral administration of 0.8 g $MnCl_2$. Images were acquired immediately before (0 hour) administration of 0.8 g $MnCl_2$ and 1, 2, 3, and 6 hours thereafter. Liver metastases are indicated by arrows on the MR image acquired 6 hours after contrast agent administration.

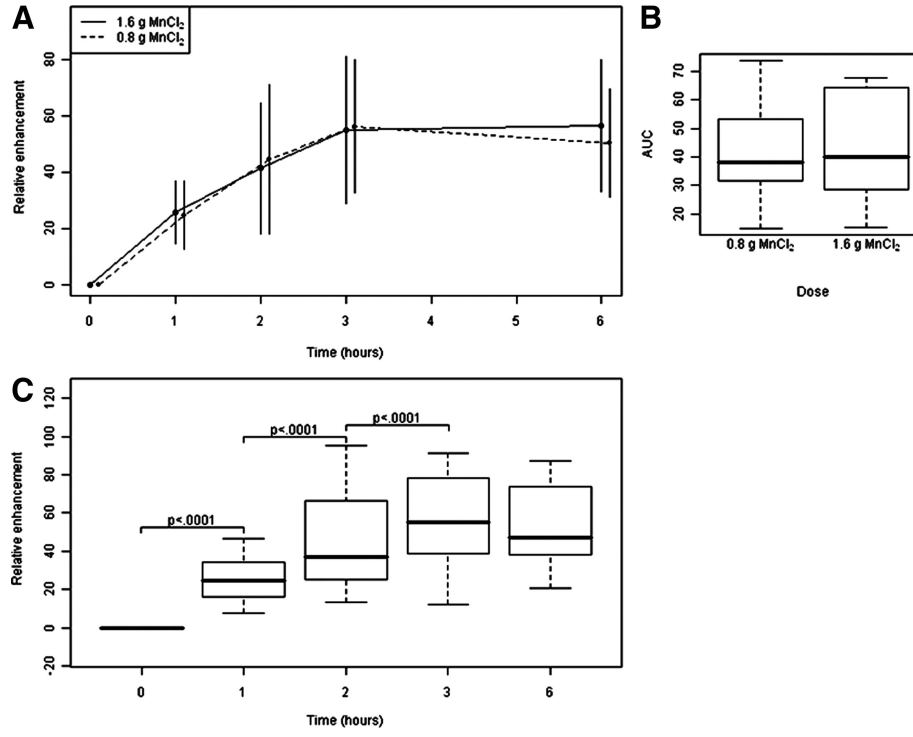

FIGURE 3. Time course of liver SI enhancement on T1-weighted GRE sequence. A, Time course of liver SI enhancement (%) after administration of 0.8 g $MnCl_2$ and 1.6 g $MnCl_2$ (mean ± SD). B, AUCs of liver SI enhancement after administration of 0.8 g $MnCl_2$ and 1.6 g $MnCl_2$. The AUCs were compared using Wilcoxon rank-sum test for independent samples ($P = 1.00$). C, Boxplots for liver SI enhancement (%) in pooled dose groups. Differences between the time points were evaluated using paired Wilcoxon signed-rank test.

within the given reference range or below at each time point. No significant differences regarding manganese levels in whole-blood were found between the 2 dose groups ($P = 0.88$).

Liver and Gallbladder SI Enhancement

The time course of liver SI enhancement on T1-weighted images after contrast agent administration is shown in Figures 2 and 3. As AUC analysis revealed no significant difference between the 0.8 and 1.6 g $MnCl_2$ dose group ($P = 1.00$; Figs. 3A, B) further analysis of liver SI enhancement was performed on the basis of pooled data (Fig. 3C). Liver parenchyma showed significant SI enhancement until 3 hours after contrast agent administration (median of pooled data from both dose groups: 1 hour, 24.7%; 2 hours, 37.2%; 3 hours, 54.9%; 6 hours, 47.3%). Liver SI enhancement showed no significant difference between 3 hours and 6 hours after contrast agent administration ($P = 0.75$). Qualitative evaluation demonstrated homogeneous liver enhancement in 15 patients and circumscribed inhomogeneous liver enhancement in proximity to focal liver lesions in 5 patients (Fig. 4). No patient showed diffusely inhomogeneous ("patchy") enhancement of liver parenchyma. SI enhancement of the bile was significant already 1 hour ($P < 0.001$) after contrast agent administration (median of pooled data from both dose groups: 1 hour, 373%; 2 hours, 450%; 3 hours, 441%; 6 hours, 356%) and no significant difference between the 0.8 and 1.6 g $MnCl_2$ dose group was found in the AUC analysis ($P = 0.10$).

Liver-Lesion Contrast

The time course of LLC on T1-weighted images after administration of 0.8 and 1.6 g $MnCl_2$ is shown in Figure 5A. AUC analysis revealed no significant difference between the 2 dose groups ($P = 0.94$; Fig. 5B). LLC significantly increased until 2 hours after contrast agent administration (median of pooled data from both dose groups: 0 hour, 0.19; 1 hours, 0.29; 2 hours, 0.36; 3 hours, 0.37; 6 hours, 0.36). LLC showed no significant differences

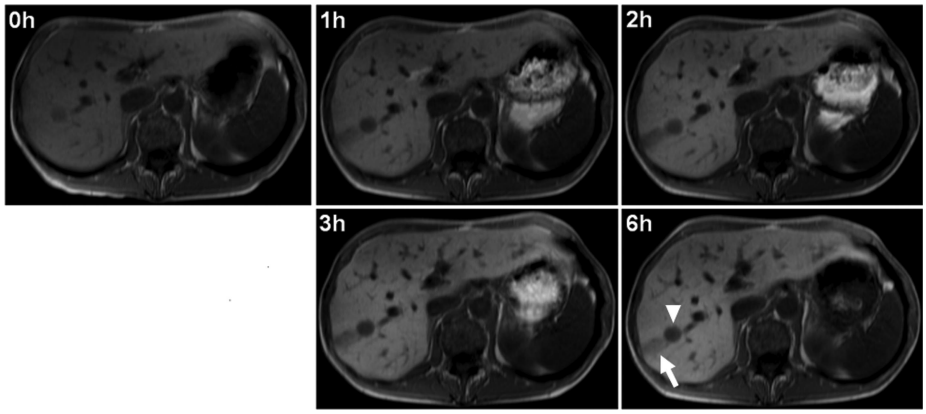

FIGURE 4. Axial T1-weighted GRE images obtained in a patient with liver metastases. Images were acquired immediately before (0 hour) administration of 1.6 g $MnCl_2$ and 1, 2, 3, and 6 hours thereafter. Circumscribed inhomogeneous liver enhancement was found in proximity to a liver metastasis (indicated by an arrow on the MR image acquired 6 hour after contrast agent administration). Liver metastasis is indicated by an arrowhead.

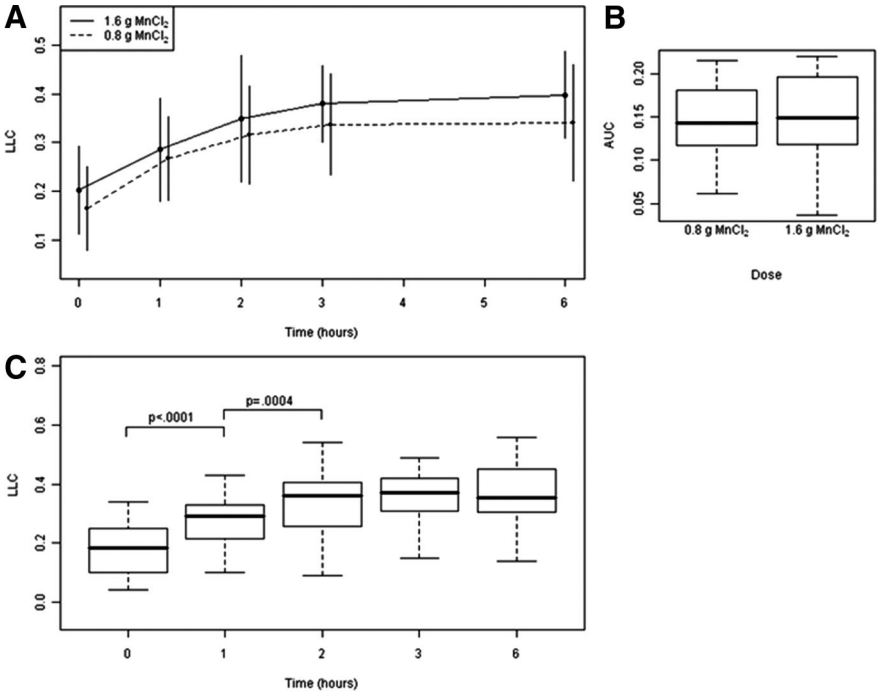

FIGURE 5. Time course of LLC on T1-weighted GRE sequence. A, Time course of LLC after administration of 0.8 g $MnCl_2$ and 1.6 g $MnCl_2$ (mean ± SD). B, AUCs of LLC after administration of 0.8 g $MnCl_2$ and 1.6 g $MnCl_2$. The AUCs were compared using Wilcoxon rank-sum test for independent samples ($P = 0.94$). C, Boxplots for LLC in pooled dose groups. Differences between the time points were evaluated using paired Wilcoxon signed-rank test.

between 2 and 3 hours ($P = 0.08$) or 3 and 6 hours ($P = 0.25$) after contrast agent administration (Fig. 5C).

DISCUSSION

In recent years, numerous studies established in particular gadolinium-based gadoxetic acid as a high standard for contrast-enhanced liver MRI with regard to lesion detection, localization, and characterization.[11–18] The rationale for developing the oral manganese-based contrast agent for liver MRI investigated in our study was based on the following considerations: (1) oral administration minimizes systemic exposure to manganese,[7] (2) accumulation of manganese in the liver provides a broad time window for postcontrast imaging, and (3) administration of oral manganese is simple with no need of injection or staff involvement.

Manganese is one of the least toxic of the trace elements.[19] After oral administration, manganese enters the portal venous system, from where it is taken up into hepatocytes during first passage of the liver.[19–22] Gastrointestinal absorption of manganese is enhanced by promoters such as vitamin D_3, ascorbic acid, and various amino acids.[7,23] Based on these observations, an oral contrast agent composed of $MnCl_2$, L-alanine and vitamin D_3 (CMC-001) was formulated. A phase I study in 12 healthy volunteers demonstrated that oral administration of CMC-001 was safe and resulted in significant SI enhancement of normal liver parenchyma. Other organs such as pancreas showed only minimal signal changes, which underlined the targeted properties of CMC-001 with regard to liver MRI. Initial results of the phase I study suggested that 1.6 g $MnCl_2$ caused a more pronounced increase in liver SI than 0.8 g $MnCl_2$.[4] In our dose-finding phase II study, no relevant differences between the 2 dose groups were observed, indicating the robustness of CMC-001 for liver-specific enhancement. The design of the phase I study precluded reliable information regarding the optimal time point of CMC-001-enhanced postcontrast MRI, as the examinations were performed at varying time points and at different field strengths.[4] In our study at 1.5 Tesla, liver parenchyma showed significant SI enhancement on T1-weighted MR images in both dose groups already 1 hour after oral administration of CMC-001. Liver SI enhancement peaked within 3 to 6 hours after contrast agent administration and LLC remained stable up to 6 hours after administration. These data suggest that CMC-001 is a robust liver-specific MR

contrast agent and promises flexible planning of postcontrast MR imaging.

To the best of our knowledge, data from 30 patients with hepatobiliary pathologies, who received CMC-001, were published so far.[3,5] In all 30 patients, CMC-001 was administered at a dose corresponding to 1.6 g $MnCl_2$. In the initial publication by Chabanova et al, data from 10 consecutive patients with known liver metastases were presented.[3] Two hours after oral administration of CMC-001, delineation of liver metastases was improved on T1-weighted MR images in comparison to unenhanced MRI. In a subsequent publication by Thomsen et al, 20 patients with focal liver lesions or biliary tract pathologies underwent MR examinations.[5] Again, liver MRI was performed 2 hours after contrast agent administration and CMC-001 caused robust liver SI enhancement in patients with focal liver lesions. Our data are in good accordance with these previous studies as we observed robust liver SI enhancement and high LLC 2 hours after contrast agent administration. Moreover, we detected pronounced SI enhancement in the gallbladder lumen already 1 hour after administration of CMC-001, indicating that biliary excretion of manganese starts within the first hour after oral contrast agent administration.

We observed circumscribed inhomogeneous liver SI enhancement in proximity to hepatic metastases in 5 of 20 patients. The low SI enhancement might be attributed to tumor compression of hepatic vessels causing reduced uptake of manganese by hepatocytes. Similar observations have been made by Chabanova et al who detected circumscribed inhomogeneous SI enhancement of liver parenchyma outside of metastatic lesions in 5 of 10 patients after administration of CMC-001.[3] Besides focal areas of reduced manganese uptake, a previous study on MRI with the liver-specific manganese-based contrast agent mangafodipir trisodium (Mn-DPDP) reported diffusely inhomogeneous enhancement patterns in patients with cirrhosis.[24] Thomsen et al also observed diffusely inhomogeneous ("patchy") enhancement patterns in several patients who underwent CMC-001-enhanced liver MRI.[5] However, the patchy enhancement pattern in their patient collective could not be conclusively explained and none of the patients showed histologic evidence of cirrhosis. Hence, further evaluations of inhomogeneous liver enhancement patterns after administration of CMC-001 are strongly warranted. In our patient collective, none of the patients showed diffusely inhomogeneous liver enhancement.

Liver MR imaging using intravenous liver-specific contrast agents requires an interval of 10 to 60 minutes between administration of the contrast agent and delayed hepatobiliary MR examination.[2] The acquisition of delayed MR images can greatly affect both imaging time and costs, which may be considered a drawback of intravenous liver-specific contrast agents. The novel oral administration route of CMC-001 could simplify liver MR imaging, as CMC-001 can be administered outside the MR examination room. Theoretically, CMC-001 could even be provided to patients for self-administration prior to arrival in the radiology department. Based on our data, an MRI protocol for detection of liver metastases should include administration of CMC-001 at 2 to 3 hours before liver MRI. Additional respiratory-triggered T1-weighted high spatial resolution MR images could potentially improve lesion detection and localization.[25] If further characterization of liver lesions is required, dynamic phase imaging could be performed using bolus injection of a conventional extracellular gadolinium-based contrast agent. In fact, a recent study demonstrated that dynamic MR imaging in already gadobenate dimeglumine-enhanced liver is feasible with similar information as dynamic MR imaging of the unenhanced liver.[26] Finally, considering the increase in cost by a double contrast agent administration and the lack of precontrast T1-weighted imaging, the use of CMC 001 appears especially targeted for liver metastasis detection and localization. These include follow-up MR examinations in patients with known liver metastases and examinations for planning therapeutic interventions such as liver surgery or radiofrequency ablation.

Broad clinical experience exists with the use of intravenously administered manganese-based contrast agents for liver MRI. In 1997, the manganese-based contrast agent Mn-DPDP was approved for liver MR imaging.[27] Mn-DPDP has to be administered as an intravenous infusion over 15 to 20 minutes. Intravenous infusion is considered an inconvenient mode of administration and precludes dynamic MR imaging. Moreover, intravenous infusion of manganese bypasses physiologic regulatory mechanisms for manganese homeostasis, which resulted in relatively high rates of adverse events.[24] Following intravenous infusion, Mn-DPDP slowly dissociates and free manganese is taken up by mitochondrial-rich cells such as hepatocytes, myocytes, pancreas cells, and kidney cells.[28] Increased concentration of manganese can act as calcium-blocker affecting cardiac contractility. Moreover, manganese uncouples myocardial as well as smooth muscle excitation causing decreased cardiac contractility and hypotension. Finally, manganese can cross the intact blood-brain barrier, which can lead to deposition of manganese in the basal ganglia with subsequent neurologic symptoms.[29] Orally administered manganese has the advantage of a selective portal venous perfusion with a high absorption rate during first pass in the liver.[30] Presystemic elimination of manganese in the liver should minimize the exposure of other organs and reduce the risk of cardiac and cerebral toxicity as seen with intravenously administered manganese. In fact, after oral administration of CMC-001, we did not observe a relevant increase in manganese levels in whole-blood. Two patients had slightly elevated manganese levels before administration of CMC-001, which reflects considerable individual variation in baseline levels of manganese. Six adverse events were reported during our study and all adverse events were mild and transient. The most frequent adverse events were gastrointestinal symptoms such as nausea and diarrhea. In conclusion, our safety data are in good accordance with previous studies indicating that administration of CMC-001 is safe and well-tolerated.[3–6]

Two limitations of our study should be acknowledged. First, the total number of patients included and the numbers randomized to the treatment groups were relatively small. Our observation of absence of significant differences in liver SI enhancement and LLC between the 0.8 and the 1.6 g $MnCl_2$ dose group is a preliminary result and should be validated in a larger number of subjects. Second, our evaluation was limited to quantitative parameters. Our conclusion has to be validated in terms of diagnostic accuracy against a high standard of reference for lesion detection and localization, ie, histopathologic evaluation of resected liver specimens and intraoperative ultrasound in the nonresected segments of the liver.

In conclusion, our study demonstrates that CMC-001 administered as single dose is a safe and effective oral contrast agent in patients who undergo MRI for evaluation of liver metastases. Considering the time course of liver SI enhancement and LLC, our results suggest that the diagnostic time window for liver MR imaging is between 2 hours and 6 hours after oral administration of CMC-001. From a logistic standpoint, CMC-001 could simplify liver-specific MR imaging and reduce imaging time and costs in carefully selected patients.

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