Safety Assessment of Double-Contrast MR Imaging of Liver Disease

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Introduction: Magnetic resonance (MR) imaging plays a major role in the diagnosis and surveillance of chronic liver disease. Double-contrast (SPIO/Gd) enhanced MR imaging has been used to assess hepatocellular carcinoma and liver fibrosis [1,2] and may be more accurate for characterization of liver nodules than single-contrast MR imaging [2,3]. Although each of these types of contrast agents are individually FDA-approved for MR imaging, their sequential use is not FDA-approved. To our knowledge, no study has prospectively assessed the risk of sequential double-contrast use. Our aim is to assess the safety of sequential double-contrast MR imaging in patients with liver disease.

Methods: This was a prospective study of 56 subjects (37 Male, 19 Female; Age 18-89, average 52) with known or suspected liver disease who underwent double-contrast MR imaging in 2007. Forty-one were cirrhotic. The study was IRB-approved, HIPAA-compliant, and performed in accordance with FDA IND #75,779. All subjects signed informed consent. The contrast agents used were ferumoxides injectable solution (Feridex®) and gadopentetate dimeglumine (Magnevist®). Ferumoxide (dose, 0.56 mg iron/kg = 0.05 ml ferumoxide suspension/kg) was diluted in 100 ml of 5% dextrose solution and infused through a 5 micron filter over 16-62 min (mean 30 min) at a rate of 1.7-6.4 ml/min (mean 3.8 ml/min). Gadopentetate (dose, 0.1 mmol/kg) was injected at 2 ml/sec using a power injector, followed by a 20 ml saline flush. A physician collected data on each subject at five phases (Table 1). Each AE's severity was graded. Whether each AE was a serious AE was further determined. It was also determined whether each AE was due to administration of either contrast agent or the sequential administration of the two agents. Data were summarized descriptively. Observed AE frequency was compared to the AE frequency described in the product inserts.

Table 1. Phases of data collection for safety assessment of double-contrast administration.

Baseline	Pre-contrast; including medical history, brief physical examination, demographics, weight, pain assessment (Likert scale score 0-10), vital signs (heart rate, blood pressure, and respiratory rate), basic metabolic panel, liver function test, complete blood count, and electrocardiogram.
Phase 1	Pre-MR imaging (ferumoxide infusion); including pain assessment (before, two minutes after initiation, and upon completion), vital signs (before and q15 min), dose, infusion rate, and AEs.
Phase 2	During MR imaging (gadopentetate injection); including heart rate (q5 min), dose, injection rate, and AEs.
Phase 3	After MR imaging; including vital signs (q15 min for up to 1 hour), and AEs.
Phase 4	Follow-up visit (24-72 hrs post-MR imaging); including interim history, physical exam, and AEs

Results: There were seven AEs (five back pain reactions, one nausea reaction, and one allergic reaction) in five subjects due to ferumoxide administration (Table 2). Our patient sample had a similar frequency of back pain compared to that described in the ferumoxide product insert for subjects with and without cirrhosis (Table 3). Compared to the frequency of ferumoxide-related AEs described in the product insert, our patient sample had a similar frequency of nausea (2%, 1/56 vs. 0.7%, 11/1535) and allergic reaction (2%, 1/56 vs. 0.7%, 12/1535). All AEs associated with ferumoxide infusion occurred before gadopentetate administration; we observed no AEs during gadopentetate administration. Thus, all of the AEs described above were judged as not due to gadopentetate administration, nor due to sequential administration of ferumoxide and gadopentetate. There were no unexpected or serious AEs related to either agent.

Table 2. Summary of AEs (all ferumoxide-related).

Subject	**#11**	**#12**	**#12**	**#20**	**#20**	**#37**	**#40**
AE	Back pain	Back pain	Allergic reaction	Back pain	Nausea	Back pain	Back pain
Severity	Mild, 4/10	Moderate, 5/10	Mild, cutaneous	Moderate, 7/10	Mild	Severe, 10/10	Mild, 2/10
Onset	7 min	10 min	33 min	4 min	4 min	10 min	32 min
Resolution	Complete, spontaneous, 5 min	Complete, spontaneous, 3 min	Complete, resolved after diphenhydramine 25mg IV, 30 min	Complete, spontaneous, 5 min	Complete, spontaneous, 5 min	Complete, spontaneous, 15 min	Complete, spontaneous, 5 min

Conclusion: In subjects undergoing sequential administration of ferumoxide and gadopentetate, the incidence of AEs is comparable to that described in product inserts. In our study sample, all AEs were due to ferumoxide infusion. There were no serious AEs. Based on these observations, there does not appear to be a greater risk with sequential use of ferumoxide and gadopentetate than with individual use of either agent alone.

Table 3. Back pain AE frequency to ferumoxide.

	Our Study	**Ferumoxide Product Insert**
Cirrhotic Subgroup	12% (5/41)	12.5% (18/144)
Non-Cirrhotic Subgroup	0% (0/15)	1.8% (10/545)

References:

1. Aguirre D, et al. Radiology 2006; 239:425-437.
2. Ward J, et al. Radiology 2000; 216:154-162.
3. Bhartia B, et al. American Journal of Roentgenology 2003; 180:577-584.