Journal of Radiology Nursing 38 (2019) 38–41

Contents lists available at ScienceDirect

Journal of Radiology Nursing

journal homepage: www.sciencedirect.com/journal/journal-of-radiology-nursing

The Rise of Off-Label Iron-Based Agents in Magnetic Resonance Imaging

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Keywords:
MRI
Contrast agents
Superparamagnetic iron oxide
Iron nanoparticle
Adverse reactions

A B S T R A C T

Gadolinium-based contrast agents (GBCAs) used in MRI have come under fire due to concerns about nephrogenic systemic fibrosis (NSF) and gadolinium retention. These concerns have prompted a search for alternatives to GBCAs. One attractive candidate is superparamagnetic iron oxide (SPIO). Over the past 20 years, several SPIO agents have been developed and approved for niche clinical applications in MRI. One interesting SPIO agent is ferumoxytol (Feraheme®), an FDA-approved intravenous medication used to treat iron-deficiency anemia in patients with chronic kidney disease. In preliminary studies examining its off-label use as an intravenous contrast agent, ferumoxytol appeared promising for MRI and MR angiography. However, experience with this agent remains limited. One key benefit of ferumoxytol is that it carries no risk of NSF in patients with impaired renal function. On the other hand, ferumoxytol has been reported to cause severe adverse events, including hypotension, hypersensitivity reactions, anaphylaxis, and death. Moreover, the rate of such events has been substantially greater than those observed with GBCAs or nonionic iodinated contrast media. In response to these data, the FDA issued a black box warning for ferumoxytol in 2015. To ensure patient safety, hospitals and imaging facilities must develop a plan to train MRI personnel to recognize and manage adverse reactions to ferumoxytol. Another challenge of using ferumoxytol concerns its pharmacokinetics and biodistribution, which differ from those of GBCAs. These differences can lead to unexpected patterns or persistence of tissue enhancement on MRI. In particular, ferumoxytol can remain in the body for days, weeks, or months after intravenous administration, potentially causing an unsuspecting radiologist to misinterpret an MRI. The decision to use ferumoxytol for a specific patient and clinical indication requires the radiologists to carefully weigh risk-benefit tradeoffs and consider alternative diagnostic tests.

In recent years, the gadolinium-based contrast agents (GBCAs) used in magnetic resonance imaging (MRI) have come under fire due to concerns about nephrogenic systemic fibrosis (NSF) and gadolinium retention in the brain, muscles, and bones (Marckmann et al., 2006; McDonald et al., 2015; Thomsen et al., 2008). First described in 2000, NSF is a rare, incurable syndrome affecting the skin and internal organs of patients with severe renal diseases. NSF was linked to GBCAs in 2006. Fortunately, NSF has nearly been extinguished due to restrictive clinical guidelines on GBCA administration and greater usage of safer macrocyclic gadolinium agents. Despite extensive research, investigators are yet to fully elucidate the mechanism by which GBCAs cause NSF, and they have not devised strategies to reduce or treat NSF (Mayo Clinic, 2018). In 2013, researchers made the surprising discovery that gadolinium is deposited and retained in human brain long after the

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Conflict of Interest: None of the authors have any financial ties to any companies based on the content of this article.
This article was written during official US Government time.

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https://doi.org/10.1016/j.jradnu.2018.11.004
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administration of GBCAs, although the clinical significance of this finding is currently unknown (Kanda et al., 2014; McDonald et al., 2015; US Food and Drug Administration, 2018). NSF and gadolinium retention are two reasons why the clinical MRI community is searching for alternatives to GBCAs (Bashir et al., 2015; Neuwelt et al., 2009; Nguyen et al., 2017; Toth et al., 2017; Wang, 2015).

Iron-oxide contrast agents, such as superparamagnetic iron-oxide and ultrasmall superparamagnetic iron-oxide (USPIO) nanoparticles, have been investigated for MRI for over 20 years. Several iron-oxide nanoparticles have undergone clinical testing, and a few have been approved for clinical use in certain countries, at least for a brief period. For example, Feridex I.V. (ferumoxide; AMAG Pharmaceuticals, Waltham, MA) was discontinued in 2008 due to poor sales, Resovist (ferucarbotran; Bayer Schering Pharma AG, Berlin, Germany) was withdrawn from the market in 2009, and GastroMARK (ferumoxsil; AMAG Pharmaceuticals, Waltham, MA) was discontinued by the manufacturer in 2012 (Wáng & Idée, 2017). Although iron-based contrast agents have been around for many years, they did not generate substantial clinical interest until the emergence of GBCA safety concerns. One iron-oxide agent that did survive the carnage was Feraheme® (ferumoxytol injection; AMAG Pharmaceuticals, Waltham, MA), a Food and Drug Administration (FDA)-approved intravenous medication to treat iron-deficiency anemia in patients with chronic kidney disease (Bashir et al., 2015; Knobloch et al., 2018; Lehrman et al., 2018; Neuwelt et al., 2009; Vasanawala et al., 2016; Wang, 2015). Several radiology groups around the world explored the use of ferumoxytol as a contrast agent for MRI and magnetic resonance angiography (MRA). Their initial experience was so encouraging that some may wonder why iron-oxide MRI contrast agents were not already being widely used.

The use of ferumoxytol as an MRI contrast agent is off label. Its safety and efficacy as a contrast agent have not been thoroughly and systematically studied (Varallyay et al., 2017). In 2015, the FDA issued a black box warning (the agency's most severe warning) for ferumoxytol in response to several reports of severe and fatal adverse events, including anaphylaxis (Bailie, 2012; Lu et al., 2010; U.S. Food and Drug Administration; U.S. Food and Drug Administration). In its warning, the FDA made several recommendations, including that ferumoxytol should be used only in patients who need intravenous iron therapy and then only when the benefits outweigh the risks (U.S. Food and Drug Administration). The European Medicines Agency (EMA) suspended the use of ferumoxytol in Europe in 2015 due to the high number of serious adverse events (European Medicines Agency, 2015a, b). In addition, the FDA and EMA warned that ferumoxytol can alter MRI signal for up to 3 months after administration, potentially degrading image quality and leading to errors in image interpretation (European Medicines Agency, 2015b; U.S. Food and Drug Administration). One strength of ferumoxytol is that, unlike GBCAs, it carries no risk of NSF in patients with impaired renal function.

Safety issues are not the only difference between iron-oxide agents and GBCAs. Iron-oxide molecules are much larger than GBCAs and, accordingly, have different pharmacokinetic properties and biodistribution and enhancement characteristics. To accommodate these differences, adjustments to MRI pulse sequences and imaging protocols may be required when using an iron-oxide agent (Toth et al., 2017; Neuwelt et al., 2009). Most GBCAs on the market are referred to as extracellular agents, which means that they are rapidly cleared from the intravascular space and then distributed in the tissue interstitial space. Owing to this behavior, GBCA-enhanced MRA is typically performed by using a first-pass technique (i.e., image quickly before contrast leaves the blood pool), and GBCA-enhanced tumor imaging is typically performed within seconds to minutes after the contrast injection. In contrast to GBCAs, USPIOs

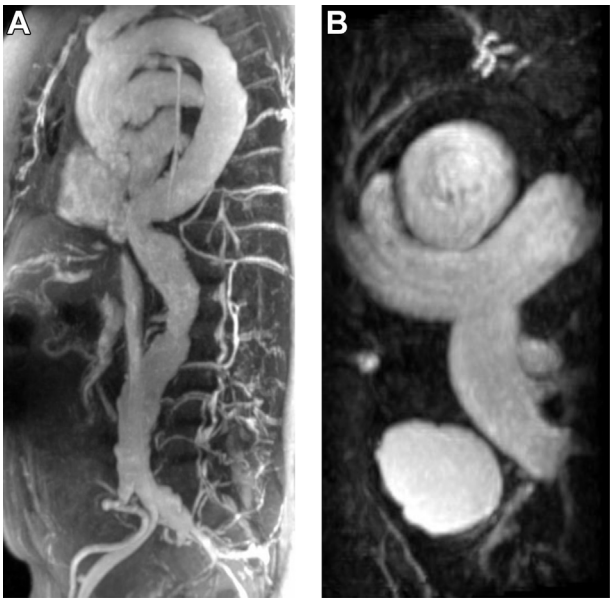

Figure 1. Ferumoxytol can be an excellent contrast agent for MRA in patients with severe kidney disease who should not get GBCA due to NSF risk. In this case, a 72-year-old man with an abdominal aortic aneurysm and stage 4 chronic kidney disease received a 5-mg/kg injection of ferumoxytol for a 3D MRA. (A) Maximum-intensity projection in the oblique sagittal plane showing the entire aorta, iliac bifurcation, and smaller collateral vessel. (B) Subvolume maximum-intensity projection in the oblique axial plane from the same 3D MRA data set showing the central pulmonary arteries. MRA, magnetic resonance angiography; GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

can remain in the blood pool for up to 15 hours and may require as long as 24-48 hours to produce maximum tumor enhancement due to slow contrast egress from the intravascular space. MRA with USPIOs offers the possibility of first-pass perfusion imaging, first-pass arterial imaging, or delayed imaging (minutes to hours) of both arteries and veins (Neuwelt et al., 2007) (Figure 1). However,

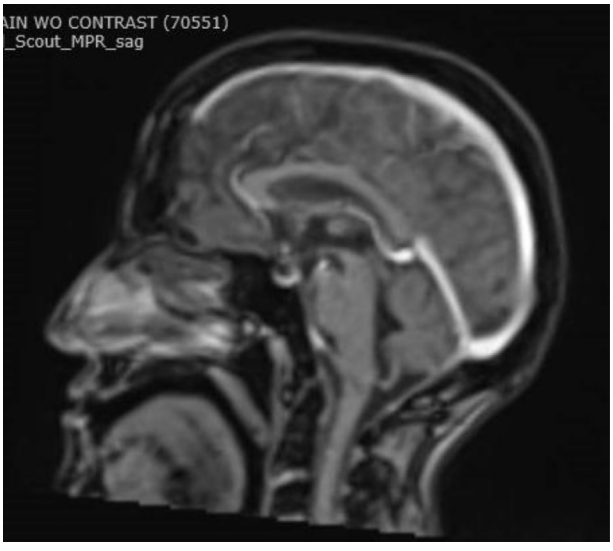

Figure 2. A 74-year-old woman with a history of lung cancer and atrial fibrillation presented with slurred speech. MRI was performed, but portions of the study were confusing to the neuroradiologist. The sagittal T1-weighted localizer shows bright enhancement of the dural sinuses, which was assumed to be artifactual or related to recent GBCA administration. A review of the electronic medical record revealed the true cause of the bright dural sinuses: 3 days earlier, the patient had received intravenous ferumoxytol to treat iron-deficiency anemia. MRI, magnetic resonance imaging; GBCA, gadolinium-based contrast agent.

the 2015 FDA black box warning forbids bolus injection of undiluted ferumoxytol, which effectively precludes first-pass imaging. Certain types of pathologies, such as small tumors, may enhance less well with iron-oxide agents than with GBCA or require higher doses to be effective (Neuwelt et al., 2007; Varallyay et al., 2017). Conversely, some USPIOs can improve the ability to distinguish between certain benign and malignant tumor characteristics (Daldrup-Link et al., 2003; Turkbey et al., 2015). An important downside to consider with ferumoxytol is related to its long half-life in the blood pool and the human body. Whether used as a contrast agent or an iron supplement, ferumoxytol can show up on magnetic resonance images days, weeks, or months after it is administered (Figure 2). Moreover, its presence can compromise the diagnostic accuracy and value of the MRI. The manufacturer warns that MRI should not be performed earlier than 4 weeks after ferumoxytol administration. When deciding whether to use an iron-oxide agent (versus GBCA or no contrast) for a particular patient, the radiologist must carefully weigh risk-benefit tradeoffs and consider alternative diagnostic testing.

There are financial considerations related to the use of ferumoxytol as an MRI contrast agent. Ferumoxytol is more expensive than GBCAs. It is also unknown if insurance companies or other payers will reimburse for ferumoxytol when used off label for MRI. The long dwell time of ferumoxytol in the human body, and the MR artifact it causes, may delay scheduling of patients for MRI. Also, imaging of patients may need to be rescheduled if recent ferumoxytol administration is not discovered until the day of the MRI appointment. This problem can result in unused scanner time and lost revenue for the facility.

Although the clinical experience with GBCAs is vastly greater than that with iron-oxide agents, the latter have been studied extensively as contrast agents for MRI for many years. In a patient with impaired renal function who requires contrast-enhanced imaging, it is reasonable to expect that a physician would consider using ferumoxytol, assuming the benefits outweigh the risks (Bashir et al., 2015; Hamilton et al., 2016; Neuwelt et al., 2009; Nguyen et al., 2017; Nguyen et al., 2018; Toth et al., 2017; Wang, 2015). In the past, the dose and rate of ferumoxytol administration were different for MRI and to treat iron-deficiency anemia (Bashir et al., 2015; Neuwelt et al., 2009; Toth et al., 2017; Vasanawala et al., 2016). But, these differences mostly disappeared when the FDA issued its black box warning, which required ferumoxytol to be diluted and infused slowly. The current label for ferumoxytol recommends using a diluted solution of ferumoxytol (in 50-200 mL of 0.9% sodium chloride or 5% dextrose) with a slow infusion of 510 mg (approx. 4-10 mg/kg) dose over 15 minutes (U.S. Food and Drug Administration). Bolus injections for MRI (where permitted) use smaller doses (1-7.3 mg/kg) (Varallyay et al., 2017; Vasanawala et al., 2016). Multiple small bolus injections have also been used for certain applications (Daldrup-Link, 2017; Lehrman et al., 2018; Lu et al., 2010; Nguyen et al., 2017; Nguyen et al., 2018; Wise-Faberowski et al., 2018).

In terms of patient management, the most important difference with the use of iron-oxide contrast agents (versus GBCAs) is the increased likelihood of adverse reactions and the need to manage those reactions appropriately. In a single-site study, Varallyay et al. (Varallyay et al., 2017) compared adverse reaction rates of various contrast agents to their experience using small, multiple bolus injections of ferumoxytol. Their adverse reaction rate for ferumoxytol was 10.6%, which is similar to the reaction rates for ionic iodinated contrast agents, about four times higher than the rate for nonionic iodinated contrast agents and about 15 times higher than that for GBCAs (Bleicher & Kanal, 2008; Katayama et al., 1990). The adverse reactions to watch for when using ferumoxytol are anaphylaxis, hypersensitivity reactions, and hypotension. Patients experiencing reactions may present with signs and symptoms of cardiac or cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness (U.S. Food and Drug Administration). Recommendations are to observe the patient for up to 30 min after ferumoxytol injection and to monitor the heart rate and blood pressure (Varallyay et al., 2017; U.S. Food and Drug Administration).

MRI personnel may be uncomfortable or unfamiliar with managing moderate to severe adverse reactions or adjusting to a work environment with a higher rate of adverse reactions. Therefore, institutions using ferumoxytol in MRI should develop a written plan to properly care for patients who have adverse events. Nurses and MRI technologists or radiographers should familiarize themselves with the types of adverse reactions to intravenous iron-oxide agents, should be prepared to recognize when their patients are having reactions, and should be ready to respond appropriately.

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