Questions and Answers (26 June 2007)

1. What is Magnetic resonance imaging (MRI)?

Magnetic resonance imaging (MRI) is a modern technology that allows doctors to have a detailed view of various parts of the body such as the brain, spinal cord, and heart.

2. What are MRI contrast agents?

MRI contrast agents are commonly used to improve the visibility of abnormal structures or lesions in the body. Gadolinium-containing MRI contrast agents are aqueous solutions that are injected into the body to improve the image quality and allow a more accurate picture to be observed. These agents, which contain the rare earth metal gadolinium, were first authorised for use in the European Union (EU) in the late 1980s. Because gadolinium is highly toxic, it is reversibly held in a complex structure with other molecules (called a chelate) in the contrast-agent solution.

3. In the EU what gadolinium-containing contrast agents are available?

Omniscan	(Gadodiamide)
Magnevist	(Gadopentetate dimeglumine)
MultiHance	(Gadobenate dimeglumine)
Primovist	(Gadoxetic acid disodium)
Vasovist	(Gadofosveset)
ProHance	(Gadoteridol)
Gadovist	(Gadobutrol)
Dotarem	(Gadoteric acid)

4. What are Omniscan (gadodiamide) and Magnevist (gadopentetate dimeglumine) used for?

Omniscan, the brand name of gadodiamide, is a gadolinium-containing contrast agent that is used in MRI examinations of the brain, spine, and other parts of the body. It is also used to detect coronary artery disease (disease of the arteries of the heart) that can lead to heart attacks. Omniscan is given by injection into a vein, and the recommended dose for adults is 0·1mmol/kg bodyweight.

Magnevist, the brand name of gadopentetate dimeglumine, is a gadolinium-containing contrast agent that is used in MRI examinations of the brain, spine, and other parts of the body including the joints. Magnevist is given by injection into a vein, and the recommended dose for adults is 0·2mL/kg bodyweight.

Full prescribing information is available in the Summary of Product Characteristics (SPC) for healthcare professionals and the Patient Information Leaflet (PIL) for patients.

5. What is nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy (NFD)?

Nephrogenic systemic fibrosis (NSF[1]), also known as nephrogenic fibrosing dermopathy (NFD), was first diagnosed in 1997. It is a condition that occurs only in patients with advanced kidney dysfunction. Patients with kidney dysfunction who have had, or who are awaiting, liver transplantation are also thought to be at increased risk of developing this disease.

NSF develops over a period of days to several weeks. The first symptoms are red or dark patches or papules that develop on the skin. The skin of the limbs, and sometimes the trunk, thickens and feels "woody". Furthermore, the skin surface can resemble an orange-peel texture. Patients may experience burning, itching, or severe sharp pains in the affected areas, and hands and feet might swell with blister-like lesions. In many cases, skin thickening prevents joint movements and might result in contractures (an inability to straighten the joints) and immobility. Other organs might be affected, including the lungs, liver, muscles, and heart. About 5% of patients have very rapid and progressive disease development, and some patients may die.

6. What causes NSF?

Since NSF was first recognised in 1997, researchers have proposed several theories about the cause of the disease. However, it was not until early 2006 that an association between NSF and gadolinium-containing contrast agents was made. In a pivotal study,[2] five of nine patients (average age 58 years) with end-stage renal failure (ie, advanced kidney impairment) who had NSF had received a gadolinium-containing MRI contrast agent (Omniscan [gadodiamide]) 2–4 weeks previously. This study was followed in short succession by further studies and case reports that show a similar association.

7. Who is at risk of developing NSF?

Patients with severe kidney impairment and those who have had, or who are awaiting, liver transplantation are at risk of NSF after Omniscan administration. Patients with severe kidney impairment should also not receive Magnevist because of an increased risk of NSF. Neonates and infants up to 1 year of age may also be at risk because their kidneys are not developed fully. Doctors should use other gadolinium-containing MRI contrast agents in patients with severe kidney impairment, and should use Omniscan and Magnevist in patients with moderate kidney impairment only after careful consideration.

8. Can NSF occur in those who have normal kidney function?

There are no known cases of NSF in patients with normal kidney function.

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[1] The International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) http://www.icnfdr.org considers NSF as the preferred term to use over NFD because they think it reflects more accurately the current understanding of the disorder.

[2] Grobner T. Gadolinium - a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006 Apr;**21**(4):1104-8. (Grobner, 2006). Erratum 2006 Jun;**21**(6):1745.

9. How many cases of NSF associated with gadolinium-containing contrast agents have been reported worldwide?

More than 250 cases of NSF have been associated with gadolinium-containing contrast agents worldwide.

10. How might gadolinium-containing contrast agents contribute to development of NSF?

The mechanism by which some gadolinium-containing contrast agents might trigger NSF is under investigation. However, several theories have been proposed. Kidney impairment is thought to be an important factor because NSF develops only in patients with advanced kidney dysfunction, who clear the contrast agent from the body at a much slower rate than do patients with normal kidney function.

In patients with severe kidney impairment, gadolinium ions (Gd^{3+}) may be released into the body from a chelate complex of the gadolinium-containing contrast agent by a transmetallation process with ions from the body (eg, zinc, iron, calcium, magnesium). Free Gd^{3+} can accumulate in tissues and organs and trigger fibrosis (formation of fibrous tissues), leading to NSF.

11. Are all gadolinium-containing contrast agents associated with the same risk of NSF?

No. Current evidence suggests that the risk of developing NSF is related to the physicochemical and pharmacokinetic properties of gadolinium-containing contrast agents. The physicochemical properties affect the release of toxic Gd^{3+} from the chelate complex, and the pharmacokinetic properties influence how long the agent remains in the body.

The risk of NSF is considered to be highest with Omniscan and OptiMARK[3], which carry no molecular charge, are arranged in a linear structure with excess chelate, and seem more likely to release free Gd^{3+} into the body. Those that are cyclical in structure (eg, ProHance, Gadovist, and Dotarem) are least likely to release free Gd^{3+} into the body. Between these two groups are those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist).

Worldwide to date, 180 cases of NSF have been associated with Omniscan, 78 cases of NSF with Magnevist, and a single case has been reported with MultiHance in a patient coadministered Omniscan. No cases of NSF have been associated with the other gadolinium-containing contrast agents[4]. This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary.

12. What is the regulatory position?

The UK Commission on Human Medicines (CHM) and one of its expert advisory groups reviewed the issue of NSF and gadolinium-based contrast agents in January, 2007 and more recently in May, 2007. CHM proposed a step-wise approach to restricting the use of gadolinium-based contrast agents in patients with kidney disease, in liver-transplant patients, and in neonates and infants up to 1 year of age.

[3] OptiMARK is not marketed in the EU, but it is available in the US.
[4] Cases of NSF have also been reported with OptiMARK in the US.

Likewise, a European committee on medicines safety, the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP), considered the worldwide spontaneous reports of NSF, published case reports and studies, and research about the properties of different gadolinium agents. They concluded that differences in the stability of gadolinium complexes might affect the likelihood of NSF development.

On the basis of the available evidence, the committees advised that Omniscan (and OptiMARK) should not be used in patients with severe kidney impairment (ie, those with a glomerular filtration rate [GFR] of <30 mL/min/1·73m^2) or in those who have had, or who are awaiting, liver transplantation. Patients with severe kidney impairment should also not use Magnevist because of the increased risk of NSF. On a precautionary basis, the committees advised that a warning should be added to the product information (the Summary of Product Characteristics, SPC, for healthcare professionals and the Patient Information Leaflet, PIL, for patients) about the use of Omniscan and Magnevist in patients with moderate renal impairment (ie, those with a GFR of 30–59 mL/min/1·73m^2) and in neonates and infants up to 1 year of age because of their immature kidney function.

For the other linear agents (MultiHance, Primovist, and Vasovist) and the cyclical agents (ProHance, Gadovist, and Dotarem), a warning about their use in patients with severe renal impairment has been added to the product information. The risk of NSF with MultiHance, Primovist, and Vasovist remains under investigation by the European committee.

13. Should patients be screened for renal function?

All patients, particularly those older than 65 years, should be screened for renal dysfunction by obtaining a history and/or laboratory tests before gadolinium-containing contrast agents are used.

14. What is the advice about dialysis?

Haemodialysis shortly after administration of a gadolinium-containing contrast agent in patients currently receiving haemodialysis may be useful for removal of a contrast agent from the body. However, there is no evidence to suggest that haemodialysis can prevent or treat development of NSF.

15. Is it safe to use Omniscan, Magnevist, and the other gadolinium-containing contrast agents in patients with normal renal function?

Yes. Omniscan has been used in more than 30 million patients and Magnevist in more than 80 million patients since they were first licensed. NSF has been observed only in patients with severe kidney impairment. These patients cannot excrete gadolinium-containing contrast agents from the body as quickly as those with normal kidney function, which possibly allows more time for gadolinium ions (Gd^{3+}) to be released from the contrast agent and subsequently damage the skin and other organs. No cases of NSF have been observed in patients with normal kidney function.

16. Where should I report a *suspected* adverse drug reaction to a gadolinium-containing contrast agent or any medicine?

Suspected adverse drug reactions should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) by use of a Yellow Card, which is available from MHRA, CHM Freepost, London SW8 5BR or electronically via the MHRA website (http://www.mhra.gov.uk).

17. What should patients do if they are concerned?

Anyone who is concerned should speak to their doctor at a routine appointment.

18. Where can I find further information about NSF and gadolinium-containing contrast agents?

Further information about NSF and gadolinium-containing contrast agents can be found at the following websites:

Medicines and Healthcare products Regulatory Agency (MHRA)
http://www.mhra.gov.uk
European Society of Urogenital Radiology (ESUR)
http://www.esur.org
International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR)
http://www.icnfdr.org