Questions and Answers

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)
Gadovist	(Gadobutrol)
Vasovist	(Gadofosveset)
Dotarem	(Gadoteric acid)
ProHance	(Gadoteridol)
Primovist	(Gadoxetic acid disodium)

4. What is Omniscan (gadodiamide) 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[1].

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

Nephrogenic systemic fibrosis (NSF[2]), 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 who have had, or who are awaiting, liver transplantation are also thought to be at increased risk of developing this disease.

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

[2] 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.

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,[3] 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 gadodiamide administration. Neonates and infants up to 1 year of age may also be at risk because their kidneys are not developed fully. Doctors should give careful consideration to the use of other gadolinium-containing MRI contrast agents in patients with severe kidney impairment.

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

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

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

Approximately 200 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. Omniscan is excreted from the body via the kidneys, and patients with kidney impairment clear the contrast agent from the body at a much slower rate than do patients with normal kidney function.

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[3] 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.

Gadolinium-containing contrast agents have different properties that affect their behaviour in the body. Contrast agents such as Omniscan and OptiMARK that carry no molecular charge and are arranged in a linear structure with excess chelate seem to be more likely to release free gadolinium ions (Gd3+) into the body. Those that carry a molecular charge and have a linear structure (eg, Magnevist, MultiHance, Primovist, and Vasovist), and those that carry no molecular charge and have a cyclical structure (eg, Gadovist and ProHance), seem to be less likely to release free Gd3+ into the body. Dotarem has a molecular charge and a cyclical structure, and is least likely to release free Gd3+ into the body. The exact mechanism by which free gadolinium ions that might be deposited in tissues and organs can stimulate NSF is unknown, but is thought to trigger fibrosis (formation of fibrous tissues).

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

Current evidence suggests that the risk of developing NSF may be related to the structure of the gadolinium-containing contrast agent (see question 10). Most cases of NSF have been associated with agents Omniscan and OptiMARK[4], which have similar structures. A small number of cases have been associated with Magnevist, and, to date, no cases of NSF have been associated with some gadolinium-containing contrast agents. This issue will be monitored closely as evidence accumulates, and new advice will be issued when necessary.

12. What is the UK 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. 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. They advised that Omniscan (and OptiMARK) should not be given to these patients, and that Magnevist, MultiHance, Vasovist, Primovist, Gadovist, ProHance should not be given to these patients unless regarded clinically essential. For Dotarem, a warning for its use in at-risk patients was also proposed. Together with other European member states, the UK position helped to form the regulatory recommendations for Europe (see question 13).

13. What are the regulatory recommendations of European medicines authorities?

A European committee on medicines safety considered the worldwide spontaneous reporting data for reports of NSF, published case reports and studies, and data on the properties of different gadolinium agents. They concluded that differences in the stability of gadolinium complexes might affect the likelihood of NSF.

On the basis of the available evidence, the committee concluded that the balance of risks and benefits of gadodiamide in patients with severe kidney failure was negative, and that gadodiamide should not be used in these patients or in those who have had, or who are awaiting, liver transplantation. On a precautionary basis, the committee 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

[4] OptiMARK is not licensed for use in the EU, but it is available in the US.

gadodiamide in neonates because of their immature kidney function. They advised strong warnings about the occurrence of NSF should be added to the product information for all other gadolinium-containing contrast agents.

14. What is the advice about dialysis?

There is not enough evidence to advise initiation of dialysis in patients at risk of NSF after use of a gadolinium-containing contrast agent. In a recent study, dialysis of ten patients within 2 days of gadodiamide administration did not prevent these patients from developing NSF[5].

15. Is it safe to use Omniscan (gadodiamide) and the other gadolinium-containing contrast agents in patients who are not at risk of NSF?

Yes. Omniscan has been used in more than 30 million patients since it was first licensed. NSF has been observed only in patients with severe kidney impairment. These patients cannot excrete gadodiamide from the body as quickly as those with normal kidney function, which allows more time for gadolinium ions (Gd^{3+}) to be released from the contrast agent and 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

[5] Broome DR, Girguis MS, Baron PW, Cottrell AC *et al.* Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am. J. Roentgenol.* 2007 Feb; **188** (2): 586-92.