26 June 2007

Dear Colleague,

Gadolinium-containing MRI contrast agents and Nephrogenic Systemic Fibrosis (NSF) - Update

In February 2007 I wrote[1] to inform you of the debilitating and sometimes fatal condition Nephrogenic Systemic Fibrosis (NSF) that has been associated with some intravenous gadolinium-containing magnetic resonance imaging (MRI) contrast agents in patients with severe renal impairment.

NSF, also known as nephrogenic fibrosing dermopathy (NFD), is a rare condition that involves fibrosis of the skin and connective tissues, which can lead to contractures and joint immobility. NSF usually starts in the extremities, sometimes involving the trunk, and other organs can become affected later including the lungs, liver, muscles, and heart, in some cases leading to a fatal outcome. NSF has occurred only in patients with renal dysfunction; there are no known cases of NSF in patients with normal renal function.

After a review of additional data, I would like to update you on the current regulatory position.

The UK Commission on Human Medicines (CHM) together with the European Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) recommend that:

- Use of **Omniscan (gadodiamide)** is contraindicated in patients with severe renal impairment (ie, GFR [glomerular filtration rate] or eGFR [estimated GFR] <30mL/min/1·73m^2) or in patients with renal dysfunction who have had, or who are awaiting, liver transplantation. For patients with moderate renal impairment (ie, GFR or eGFR 30–59mL/min/1·73m^2) or neonates and infants up to 1 year of age, Omniscan should be used only after careful consideration.

- Use of **Magnevist (gadopentetic acid)** is contraindicated in patients with severe renal impairment (ie, GFR or eGFR <30mL/min/1·73m^2). Magnevist should be used with caution in patients with moderate renal impairment (ie, GFR or eGFR 30–59mL/min/1·73m^2), and should be used in neonates and infants up to 1 year of age only after careful consideration.

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

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

- Careful consideration should be given to the use of the **other gadolinium-containing MRI contrast agents** in patients with severe renal impairment (ie, GFR or eGFR <30mL/min/1·73m^2).

Mechanism

The mechanism by which some gadolinium-containing contrast agents might trigger NSF is under investigation. Patients with severe renal impairment have an increased risk of NSF because they take longer to eliminate the contrast agent from the body compared with those without renal impairment. Gadolinium ions (Gd^{3+}) may be released into the body from a chelate complex of the gadolinium-containing contrast agent by transmetallation with ions from the body (eg, zinc, iron, calcium, magnesium). Free Gd^{3+} can accumulate in tissues and organs and trigger fibrosis, leading to NSF[1].

Current evidence suggests that the risk of developing NSF is related to the gadolinium-containing contrast agents' physicochemical properties that affect the extent to which they release free Gd^{3+} from the chelate complex, and to their pharmacokinetic properties that influence how long the contrast agent remains in the body.

Eight gadolinium-containing contrast agents are currently authorised in the UK:

Brand name	Generic name	Chemical structure	Charge	Elimination pathway	Protein binding	Cases of NSF
Omniscan	gadodiamide	Linear	Non-ionic	Kidney	None	Yes
OptiMARK*	gadoversetamide	Linear	Non-ionic	Kidney	None	Yes
Magnevist	gadopentetic acid	Linear	Ionic	Kidney	None	Yes
MultiHance	Gadobenic acid	Linear	Ionic	97% Kidney, 3% Bile	<5%	Yes
Primovist	gadoxetic acid	Linear	Ionic	50% Kidney, 50% Bile	<15%	No
Vasovist	gadofosveset	Linear	Ionic	91% Kidney, 9% Bile	>85%	No
ProHance	gadoteridol	Cyclic	Non-ionic	Kidney	None	No
Gadovist	gadobutrol	Cyclic	Non-ionic	Kidney	None	No
Dotarem	Gadoteric acid	Cyclic	Ionic	Kidney	None	No

*OptiMARK is not yet licensed in Europe, but is available in the USA

Risk of NSF is considered to be highest with Omniscan and OptiMARK, 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).

Continuing investigation

To date 180 worldwide cases of NSF have been reported with Omniscan, 78 cases of NSF reported with Magnevist, and a single case of NSF reported with MultiHance in a patient co-administered Omniscan. Cases of NSF have also been reported with OptiMARK in the USA. This issue will remain under continuous review, and new information and prescribing advice will be communicated as necessary.

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 http://www.mhra.gov.uk.

Further information about NSF and gadolinium-containing MRI contrast agents can be found at the websites of MHRA http://www.mhra.gov.uk; the European Society of Urogenital Radiology (ESUR) http://www.esur.org; and the International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) http://www.icnfdr.org.

Yours faithfully,

Professor Sir Gordon Duff
Chairman, Commission on Human Medicines

[1]http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2030229&ssTargetNodeId=221