European Medicines Agency

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Questions and answers on the review of gadolinium-containing contrast agents

The European Medicines Agency has completed a review of the risk of nephrogenic systemic fibrosis (NSF) in patients receiving gadolinium-containing contrast agents. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that a number of measures need to be introduced into the prescribing information for these medicines, to minimise the risk of NSF associated with their use.
The review was carried out under 'Article 31'[1] and 'Article 20'[2] referrals.

What are gadolinium-containing contrast agents?
Gadolinium-containing contrast agents are diagnostic agents used in patients undergoing a magnetic resonance imaging (MRI) scan. They contain gadolinium, a 'rare earth' metal, which is used as a 'contrast enhancer' to help make the inside of the body more visible on the scan. The medicines are only used by MR specialists. Patients receive an injection of the contrast agent just before or during the scan.

Gadolinium-containing contrast agents include nine different active substances: gadobenic acid, gadobutrol, gadodiamide, gadofosveset, gadopentetic acid, gadoteric acid, gadoteridol, gadoversetamide and gadoxetic acid.

Most of these medicines are authorised nationally. Two of these products – OptiMARK (gadoversetamide) and Vasovist (gadofosveset) – have received a marketing authorisation that is valid throughout the European Union (EU).

Why were gadolinium-containing contrast agents reviewed?
An association between the use of gadolinium-containing contrast agents and NSF was first observed in January 2006, when cases of the disease were reported in Denmark and Austria in patients with kidney problems undergoing MRI scans. NSF is a rare disease that causes thickening of the skin and connective tissues in patients with severe kidney problems. It may affect several organs such as the liver, lungs and heart.

During 2007, more cases of the disease were reported and the CHMP's Pharmacovigilance Working Party (PhVWP) held several discussions to establish how the risk of NSF could be reduced.

[1] Article 31 of Directive 2001/83/EC as amended, referral under Community interest.

[2] Article 20 of Regulation (EC) No 726/2004.

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In December 2007, the Scientific Advisory Group (SAG) for Diagnostics of the CHMP was convened to discuss the approach of the PhVWP. The SAG agreed with the PhVWP that the risk of developing NSF depends on the type of gadolinium-containing contrast agent used, and advised that these agents should be categorised into three groups:

- **high risk:** gadoversetamide (OptiMARK), gadodiamide (Omniscan) and gadopentetic acid (Magnevist, Magnegita, and Gado-MRT-ratiopharm);
- **medium risk:** gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance);
- **low risk:** gadoteric acid (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).

The SAG also highlighted the need to harmonise the prescribing information regarding the use of these agents particularly in high-risk groups, such as pregnant and breast-feeding women, children, the elderly and patients undergoing liver transplant.

Consequently, in November 2008 the Danish medicines regulatory agency asked the CHMP to carry out an assessment of the risk of NSF for the non-centrally authorised gadolinium-containing contrast agents, and to recommend measures that could be taken to reduce this risk. At the same time, the European Commission requested the CHMP to carry out the same assessment for the centrally authorised agents.

Which data has the CHMP reviewed?
The CHMP has assessed all of the available information on the risks of NSF associated with the use of gadolinium-containing contrast agents, particularly those used in patients with kidney problems and patients receiving a liver transplant, in neonates and infants, the elderly and women who are pregnant or breastfeeding. This included information from preclinical and clinical studies, as well as information provided by the companies that make the medicines.

What are the conclusions of the CHMP?
Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP agreed with the SAG classification of gadolinium-containing contrast agents into high-, medium- and low-risk agents based on their risk of causing NSF. However, the CHMP recognised that within the high-risk group the risk of NSF with gadoversetamide and gadodiamide appears higher than with gadopentetic acid, based on physicochemical properties, studies in animals and the number of cases of NSF reported worldwide. The Committee also concluded that an additional factor that may contribute to the risk of NSF is the way these medicines are used (such as the dose, how often they are given and for how long).

To minimise the risk of NSF the Committee recommended a number of changes to the prescribing information of these medicines, depending on the risk classification of the agents.

For high-risk gadolinium-containing contrast agents, the CHMP recommended that:
- they must not be used in patients with severe kidney problems, in patients around the time of liver transplantation, and in newborn babies less than four weeks of age, who are known to have immature kidneys;
- their dose should be restricted to the minimum recommended dose in patients with moderate kidney problems and infants up to one year of age, and there should be at least a period of seven days between scans;
- as a precaution, breastfeeding should be discontinued for at least 24 hours after the patient has received a high-risk agent;
- all patients should be screened for kidney problems using laboratory tests before receiving these agents.

For medium- and low-risk agents the CHMP recommended that:

- warnings should be added to the prescribing information for their use in patients with severe kidney problems and patients receiving a liver transplant;
- their dose should be restricted to the minimum recommended dose in patients with severe kidney problems, patients around the time of liver transplantation and neonates and infants up to one year of age, and there should be at least a period of seven days between scans;
- the decision to continue or suspend breastfeeding for at least 24 hours after a scan should be taken by the doctor and the mother;
- screening for kidney problems using laboratory tests is recommended for all patients before receiving these agents.

In addition, the prescribing information of all gadolinium-containing contrast agents should include:

- a warning that the elderly may be at particular risk of NSF, because their kidneys are less able to remove gadolinium from the body;
- a statement that there is no evidence to support the initiation of haemodialysis (a blood clearance technique) to prevent or treat NSF in patients not already undergoing haemodialysis;
- information on the cases of NSF reported for each agent.

Finally, the CHMP recommended that further studies should be carried out on the long-term retention of gadolinium in human tissues (such as bone) released from gadolinium-containing contrast agents.

A communication containing the key messages of this review will be distributed to doctors at national level.

What are the recommendations for patients and prescribers?

- Gadolinium-containing contrast agents remain suitable diagnostic agents for use in patients undergoing an MRI scan, but doctors should be aware of the associated risk of NSF especially in patients with kidney problems, and other high-risk groups.
- These medicines should only be used in accordance with the updated prescribing information.
- Doctors should record in the patient's notes the type and dose of contrast agent used.
- Patients who have any questions should speak to their doctor.

The European Commission issued a decision on 1 July 2010.