IRISH MEDICINES BOARD

31/01/2011

IMPORTANT SAFETY INFORMATION ON THE RISK OF NEPHROGENIC SYSTEMIC FIBROSIS WITH GADOLINIUM CONTAINING CONTRAST AGENTS

Dear Healthcare Professional,

Further to previous communications regarding the risk of Nephrogenic Systemic Fibrosis (NSF) with the gadolinium-containing contrast agents (GdCAs), the IMB is writing to you now to communicate the recommendations of the European Medicines Agency following completion of an EU-review and subsequent issuance of a European Commission Decision.[1] It would be appreciated if the contents of this letter and in particular the risk minimisation measures could be highlighted to relevant staff at your hospital. It is essential that the up to date product information for the individual products is also consulted for detailed information on contraindications and recommendations and warnings for safe use (www.ema.europa.eu and www.imb.ie).

Based on current available evidence, the CHMP agreed with the NSF risk classification for the GdCAs as follows:

High risk:
Omniscan (gadodiamide), OptiMARK (gadoversetamide), Magnevist (gadopentetic acid)
Medium risk:

MultiHance (gadobenic acid), Primovist (gadoxetic acid), Vasovist (gadofosveset)
Low risk:

Gadovist (gadobutrol), ProHance (gadoteridol), Dotarem (gadoteric acid)

Advice for healthcare professionals

Details of the risk minimisation measures for the GdCAs according to their respective classifications are described below:

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High risk GdCAs (Omniscan, OptiMARK, Magnevist)

- All patients should be screened for renal dysfunction using laboratory tests prior to use. It is particularly important to screen patients aged 65 years and older for renal dysfunction.
- Use of high risk GdCAs is contraindicated in patients with severe renal impairment (glomerular filtration rate, GFR < 30 ml/min/1.73m^2), in patients in the perioperative liver transplantation period and in neonates.
- For patients with moderate renal impairment (GFR 30-59 ml/min/1.73 m^2) and infants, if following careful evaluation of the risks and benefits of using a high risk GdCA, it is considered clinically indicated, use should be restricted to the single lowest dose possible. Use of a GdCA should not be repeated for at least 7 days.
- Breast-feeding should be discontinued for at least 24 hours after use.
- Use in pregnancy is not recommended unless the clinical condition of the woman requires its use.
- There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.
- Peel-off tracking labels found on the vials/syringes/bottles should be stuck onto the patient record to accurately record the name of the gadolinium contrast agent used. The dose used should also be recorded in the patient record.

Medium risk GdCAs (MultiHance, Primovist, Vasovist)

More stringent warning apply to the medium risk GdCAs compared with the low risk GdCAs (refer to the Summary of Product Characteristics)

- It is recommended that all patients are screened for renal dysfunction using laboratory tests prior to use. It is particularly important to screen patients aged 65 years and older for renal dysfunction.
- For patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and patients in the perioperative liver transplantation period use a single lowest dose possible if use cannot be avoided. Use of a GdCA should not be repeated for at least 7 days.
- For neonates and infants use a single lowest dose possible. Use of a GdCA should not be repeated for at least 7 days.
- The decision of whether to continue or suspend breast-feeding for 24 hours should be at your discretion in consultation with the mother.
- Use in pregnancy is not recommended unless the clinical condition of the woman requires its use.
- There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.
- Peel-off tracking labels found on the vials/syringes/bottles should be stuck onto the patient record to accurately record the name of the gadolinium contrast agent used. The dose used should also be recorded in the patient record.

Low risk GdCAs (Gadovist, ProHance, Dotarem)

Less stringent warning apply to the low risk GdCAs compared with the medium risk GdCAs (refer to the Summary of Product Characteristics)

- It is recommended that all patients are screened for renal dysfunction using laboratory tests prior to use. It is particularly important to screen patients aged 65 years and older for renal dysfunction.
- For patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and patients in the perioperative liver transplantation period use a single lowest dose possible if it is necessary to use the GdCA. Use of a GdCA should not be repeated for at least 7 days.
- For neonates and infants use a single lowest dose possible. Use of a GdCA should not be repeated for at least 7 days.
- The decision of whether to continue or suspend breast-feeding for 24 hours should be at your discretion in consultation with the mother.
- Use in pregnancy is not recommended unless the clinical condition of the woman requires its use.
- There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.
- Peel-off tracking labels found on the vials/syringes/bottles should be stuck onto the patient record to accurately record the name of the gadolinium contrast agent used. The dose used should also be recorded in the patient record.

Background

Nephrogenic Systemic Fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy (NFD), is a serious and life-threatening condition characterised by the formation of connective tissue in the skin which becomes thickened, coarse and hard, sometimes leading to contractures and joint immobility. Patients with NSF can have systemic involvement of other organs including the lungs, liver, muscles, and heart.

There are nine gadolinium-containing contrast agents authorised in the EU including Omniscan® (gadodiamide), OptiMARK® (gadoversetamide), Magnevist® (gadopentetic acid), MultiHance® (gadobenic acid), Primovist® (gadoxetic acid), Vasovist® (gadofosveset), Gadovist® (gadobutrol), ProHance® (gadoteridol) and Dotarem® (gadoteric acid).

The risk of NSF with the GdCAs has been kept under close regulatory review since the association was first observed in January 2006[2]. In December 2007 the Scientific Advisory Group for Diagnostics (SAG-D) of the CHMP categorised the GdCAs into three groups of NSF risk based on their thermodynamic and kinetic properties. The SAG-D raised concern about the lack of harmonisation in the GdCAs Summaries of Product Characteristics (SPCs) on several issues and highlighted the need for further research to clarify the issue of NSF.

Within the recent review of the GdCAs, the CHMP has considered data relating to the risk of NSF in patients with renal impairment; patients in the perioperative liver transplantation period; use in infants, neonates and the elderly; use during pregnancy and lactation; the need for renal dysfunction screening prior to use and dose restrictions; measures to accurately record the GdCA used and what further studies are required.

Request for adverse reaction reporting

Healthcare professionals are requested to be alert to adverse reactions and to report them to the Pharmacovigilance Unit of the Irish Medicines Board using the yellow card reporting system or the online reporting system (www.imb.ie). For further information on this safety concern or the European review, please consult the EMA website at www.ema.europa.eu .

Yours sincerely,

Joan Gilvarry

Dr. Joan Gilvarry, MB., FRCPI.,
Director of Human Products Monitoring

[1]The review was conducted under Article 31 referral procedure of Council Directive 2001/83/EC (as amended) for all non-centrally authorised GdCAs and under Article 20 referral procedure of Regulation EC 726/2004 for all centrally authorised GdCAs.

[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.
Erratum 2006 Jun;**21**(6):1745.