Public Assessment Report

Increased risk of nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis and gadolinium-containing MRI contrast agents

Executive summary

Magnetic resonance imaging (MRI) contrast media are used to enhance the contrast of images and to facilitate visualisation of abnormal structures or lesions in various parts of the body. In January, 2006, gadolinium-containing MRI contrast agents were postulated to contribute to the development of a rare and sometimes fatal disorder called nephrogenic fibrosing dermopathy (NFD) or nephrogenic systemic fibrosis (NSF). Nephrogenic fibrosing dermopathy (NFD) was first recognised in the USA in 1997 as an idiopathic skin condition characterised by thickening and hardening of the skin of the extremities and sometimes of the trunk, with an increase in the number of dermal fibroblast-like cells associated with collagen remodelling and mucin deposition.

Initially 20 cases of NSF from Denmark, and a further five cases from Austria were identified in which all patients had renal impairment and were noted to have received the MRI contrast agent gadodiamide (Omniscan) before development of the disorder. To date, there have been no reports of NSF in patients with normal kidney function. Since the 1980s, more than 200 million patients have been exposed to gadolinium-based contrast agents, more than 30 million of whom have received Omniscan and 80 million of whom have received Magnevist.

This issue was discussed at the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) in June, 2006. Following this discussion, the marketing authorisation holder (MAH) for Omniscan sent a letter to radiologists and nephrologists in some European Union (EU) member states to inform them of a possible association between gadodiamide with NSF[i]. Further data were discussed at the November, 2006, PhVWP meeting. In February, 2007, 48 (validated) and 40 (under validation) cases of NSF were associated with gadodiamide (Omniscan), two possible cases were associated with gadopentetate dimeglumine (Magnevist), and no cases were identified with other gadolinium-containing contrast agents. PhVWP contraindicated the use of Omniscan in patients with severe renal impairment and in patients who have had, or are undergoing, liver transplantation and communicated this advice throughout the EU. By March, 2007, new data emerged to suggest that Magnevist is also associated with increased risk of NSF, with more than 70 cases of NSF reported. One case of NSF has also been reported with MultiHance in a patient co-administered Omniscan.

NSF and the role of gadolinium-based contrast agents is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical and pharmacokinetic properties of gadolinium-containing agents might affect their behaviour in the body and the amount of free gadolinium released in patients with renal impairment. Currently, there is no effective treatment for NSF; the most effective treatment options are related to improvement

[i] http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2024695&ssTargetNodeId=221

in renal impairment. Therefore, it is imperative that radiologists, nephrologists, and other relevant healthcare professionals receive guidance as to how to avoid this very debilitating and sometimes fatal disorder.

This report discusses the current available data and summarises the advice of the Pharmacovigilance Working Party on appropriate regulatory action to provide guidance about this disorder to radiologists, nephrologists, and other healthcare professionals.

1 Introduction

1.1 Magnetic resonance imaging (MRI) contrast agents

MRI contrast media are used to enhance the contrast of images and to facilitate visualisation of abnormal structures or lesions in various parts of the body. Contrast media affect the relaxation times of protons in their vicinity. The most common MRI contrast media are based on paramagnetic compounds that contain metal ions from the transition or lanthanide series of the periodic table such as manganese, iron, and gadolinium. These metal ions have a large magnetic moment and can shorten the longitudinal (T1) and transversal (T2) relaxation times of protons in the water of tissues. The lanthanide metal ion gadolinium has the strongest effect of all elements on T1 relaxation time because it has seven unpaired electrons. To differentiate between normal and pathological structures, gadolinium selectively changes the signal intensity of protons in the vicinity of either normal or pathological tissues.

Gadolinium alone is highly toxic in vivo because it distributes to bone and to the liver, where it rapidly produces liver necrosis. Therefore, all MRI products that contain gadolinium are based on chelates, which modify its bodily distribution to overcome toxicity while maintaining its contrast enhancement. Gadolinium chelates have different physical properties (see section 2.4).

Unlike agents used to enhance x-rays, gadolinium chelates do not have a toxic effect on the kidneys.[1] Therefore, in recent years, patients with severe renal impairment or previous severe reactions to iodine-containing contrast media were recommended to receive gadolinium-based MRI contrast agents instead of traditional radiographic contrast agents.[2]

Gadodiamide (Omniscan) was the first agent to be associated with the disorder nephrogenic systemic fibrosis (NSF).[3] Gadodiamide is a contrast medium used for cranial MRI, spinal MRI, and general MRI of the body; it is given intravenously. For cardiac MRI, gadodiamide is indicated for assessment of coronary artery disease (CAD). The recommended dose of gadodiamide for adults for imaging of the central nervous system, whole body, heart, and breasts is 0·1 mmol/kg bodyweight (equivalent to 0·2 mL/kg bodyweight) up to 100 kg. The recommended dose for assessment of cardiac perfusion is 0·15 mmol/kg bodyweight (equivalent to 0·3 mL/kg bodyweight) given as two separate doses of 0·075 mmol/kg bodyweight at an interval of 10 minutes or longer (one at pharmacological stress followed by one at rest). Gadodiamide is also indicated for imaging of the central nervous system and whole body in children at a dose of 0·1 mmol/kg bodyweight.

Cases of NSF have also been reported with gadopentetate dimeglumine (Magnevist), the first MR contrast agent approved in Europe. Gadopentetate dimeglumine is used for cranial MRI, spinal MRI and general MRI of the body. The recommended dose for adults is 0·2 mL/kg bodyweight up to a maximum of 0·6 mL/kg bodyweight. For children (including neonates and

infants younger than 2 years), 0·2 mL/kg bodyweight is generally recommended, although doses of 0·4 mL/kg bodyweight may be used if necessary for children older than 2 years. Gadopentetate dimeglumine is also used for contrast enhancement in direct magnetic resonance arthrography at a dose of 2 mmol/L up to 20 mL (knee joint up to 50 mL) for adults.

1.2 Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis

Nephrogenic fibrosing dermopathy (NFD) was first recognised in the USA in 1997 as an idiopathic skin condition characterised by thickening and hardening of the skin of the extremities and sometimes of the trunk, with an increase in the number of dermal fibroblast-like cells associated with collagen remodelling and mucin deposition.[4] In all of the first 15 cases of NFD, the patient had received, or was receiving, renal dialysis.

A variant of NFD—nephrogenic systemic fibrosis (NSF)—has more prominent and visible effects on the skin than does NFD, and is associated with systemic involvement of other organs including the lungs, liver, muscles, and heart.[5–7] 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. Thus throughout this report, the term NSF will be used to denote NFD and NSF.

NSF develops over a period of days to several weeks. The skin changes start as reddened or darkened patches, papules, or plaques. Over time, the skin feels “woody”, and the surface may have an appearance of texture of orange peel. Diagnosis is confirmed by the presence of specific histopathological features on skin biopsy—thickened collagen bundles with surrounding clefts, mucin deposition, and proliferation of fibroblasts and elastic fibres without signs of inflammation.[8,9]

Skin lesions are commonly symmetrical, with zones between the ankles and thighs; later lesions can develop between the wrist and upper arms. Patients may have burning, itching, or severe sharp pains in areas of involvement, and may have swelling of the hand and foot with blister-like lesions. Some patients have reported yellow papules or plaques on or near the eyes. Rapid, new-onset fluctuating hypertension of unknown cause has also been reported before onset of skin lesions.

For many patients, the skin thickening inhibits the flexion and extension of joints, resulting in contractures. Those severely affected may be unable to walk or extend fully the arm, hand, leg, and feet joints; complaints of muscle weakness are common. Radiography might show calcification of soft tissue, and deep bone pain has been described in the hips and ribs.

About 5% of patients have a rapidly progressive severe disease course. NSF might contribute to death by scarring of body organs (which impairs normal function), restriction of effective ventilation, or restriction of movement leading to an accidental fall that might be further

exacerbated by fractures and clotting complications. Other patients have died as a result of renal disease or transplant surgery.

NSF occurs only in patients with renal impairment (see section 2.1), and the onset of this syndrome is associated with hypercoagulability, thrombotic events, recent vascular surgery, or recent renal transplant failure.

1.3 Initial regulatory action

This issue was discussed at a European level at the June, 2006 meeting of the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP). All European marketing authorisation holders (MAHs) of gadolinium-containing MRI contrast agents were requested to submit safety update reports to regulatory authorities to identify cases of NSF.

In the UK, the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines (CHM) was informed of this issue in June, 2006. In August, 2006, a Dear Healthcare Professional letter was circulated to all UK radiologists and nephrologists to inform them of a possible association between gadodiamide with NSF[ii].

In Europe, Member States assessed the safety update reports at the November, 2006, PhVWP meeting. 48 (validated) and 40 (under validation) cases of NSF were associated with gadodiamide (Omniscan), two possible cases were associated with gadopentetate dimeglumine (Magnevist), and no cases were identified with other gadolinium-containing contrast agents. The PhVWP proposed further investigation to elucidate the mechanism by which gadolinium-containing contrast agents might cause NSF.

[ii] http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2024695&ssTargetNodeId=221

2 Data assessed

2.1 Postulated triggers of NSF

The cause of NSF has been the subject of great interest since it was first diagnosed in 1997.[4] Because NSF is a newly diagnosed syndrome, several researchers suggest that a new agent or new examination technique might cause this syndrome.[5,7,8,10]

Common factors of patients who develop NSF have been reviewed extensively. There seems to be no gender predisposition for development of NSF. Severe renal impairment is a common factor; however, neither the duration of renal disease nor its underlying causes seem to be related to development of NSF (see http://www.icnfdr.org). Other conditions that have been associated with NSF include coagulation abnormalities and deep venous thrombosis, recent surgery, failed kidney transplantation, and sudden-onset kidney disease with severe swelling of the extremities (see http://www.icnfdr.org). Patients with NSF have commonly had a vascular surgical procedure or have had a thrombotic episode about 2 weeks before the onset of skin changes.

Several agents or contributory factors have been postulated to trigger this syndrome, including: dialysate fluid (or a contaminant),[5] erythropoietin,[11] inhibitors of angiotensin-converting enzyme,[12] and induced antibodies against phospholipids.[13]

Cowper and Bucala suggested that circulating fibrocytes (bone-marrow derived, connective-tissue cells found in the peripheral circulation and mesenchymal tissue) may have a role in NSF.[14] These cells enter sites of inflammation and tissue repair, secrete growth factors and cytokines, and contribute to matrix production in connective tissue.[15] Mediators such as transforming growth factor β, a potent stimulus for production of type I collagen by some cell types and a mediator of interstitial fibrosis, can induce fibrocytes to differentiate into myofibroblasts—cells that seem to represent a small proportion of spindle cells present in NSF. Other researchers have recorded increased levels of transforming growth factor β in the skin and muscle of some affected patients.[16]

Cowper noted that development of NSF in many patients was associated temporally with vascular or thrombotic events, or with development of cancer.[10] Because many of these patients had received angiography that used a contrast agent (eg, for clot detection, surgery planning, and assessment of vascularity of brain neoplasms), Cowper and colleagues propose that radiographic contrast deposited in the peripheral circulation might be a target for circulating fibrocytes.[17] Evidence of this association was later shown in a pivotal study by Grobner (see section 2.3).[3]

2.2 Current treatment options for NSF

At present, there is no known effective treatment for NSF. Physical therapy or treatment with topical and systemic steroids has variable benefit; immunosuppressive therapy is ineffective.[3] Plasmapheresis,[18] photopheresis,[19] and thalidomide[20] have led to an improvement in some patients. Others have improved after restoration of normal renal function either spontaneously or as a result of a renal transplantation.[10]

LeBoit proposes that a dose reduction in erythropoietin might improve NSF because recombinant erythropoietin has potential fibrogenic properties.[5] Maloo and colleagues suggest that calcineurin inhibitors and erythropoietin might play a part in NSF because both have profibrogenic potential through upregulation of transforming growth factor β.[21]

Grobner (see section 2.3) gave two patients pentoxifylline, a substance with activity against tumour necrosis factor.[3] Skin changes in one patient who had late-stage disease seemed to slow or arrest; the second patient had stabilisation and a slight reversal of disease. Grobner adds that the role of vasodilation, with possible beneficial effects of renal perfusion and antifibrotic activity, in disease stabilisation is unclear.

2.3 Gadolinium as a trigger for NSF

In January, 2006, a study in Austria suggested that a magnetic resonance contrast medium containing gadolinium might trigger NSF.[3] Five of nine patients with end-stage renal disease (mean age 58 years) who had magnetic resonance angiography with gadodiamide contrast medium developed NSF within 2–4 weeks. The five patients developed thickening and induration of the skin on the legs and feet, which eventually spread to the trunk and upper body. The five affected patients had signs of metabolic acidosis, whereas the unaffected patients had normal pH values and bicarbonate levels at the time of magnetic resonance angiography. Affected patients had a longer mean time of dialysis than did unaffected patients, but no other differences were found with respect to age, sex, medication, underlying renal disease, dialysis modalities, and comorbidities.

A large study from Denmark reported an association between gadolinium-containing contrast agents and NSF.[22] Between August 2005 and May 2006, a review of case notes of all patients with NSF from a nephrology department in Copenhagen showed that all 13 patients with end-stage renal disease (mean age 50 years) with NSF had been exposed to gadodiamide before the first signs of NSF.[22] Seven patients developed severe disabilities, and one patient died 21 months after exposure; the remaining six patients were not as severely affected. Interestingly, six of the 13 patients were previously exposed to gadodiamide without any onset of NSF symptoms.

By contrast with Grobner's suggestion that acidosis might be an essential contributing factor in NSF,[3] Marckmann and colleagues found no evidence to support this idea.[22] Rather, they suggest that gadodiamide might be the causative factor: no further cases were observed after withdrawal of gadodiamide from their centre in March, 2006.

Broome and colleagues have shown that patients on dialysis are at risk of NSF after gadodiamide administration from a review of 12 identified cases of NSF from 301 people exposed to gadodiamide exposed, compared with no cases of NSF from 258 people who were not exposed to gadodiamide (odds ratio for development of NSF after gadodiamide exposure 22·3 [95% CI 1·3–378·9]).[23] Broome and colleagues noted that the risk was significantly higher when a dose twice the normal recommended dose of gadodiamide had been used.[23]

In another study, seven of 254 patients with renal insufficiency developed NSF after administration of a gadolinium-containing MRI contrast agent—an incidence of 3% for this population.[24] Moreover, prevalence of NSF in dialysis patients who were exposed to Omniscan was reported as 4% (odds ratio for NSF after Omniscan exposure 22·3 [95% CI 1·3–378·9]).[23] Those who have received liver transplantation have also been identified as at risk of NSF.[18,21]

Gadodiamide is almost exclusively excreted by the kidney, and it has a prolonged half-life in patients with impaired renal function: the half-life of gadodiamide in healthy volunteers is 1·3 hours, in patients with end-stage renal failure is 34·3 hours, in haemodialysis patients is 2·6 hours, and in patients having peritoneal dialysis is 52·7 hours.[22,25]

Cowper and colleagues propose that NSF is the result of a combination of events that begin with renal disease, followed by deposition of allergens then circulating fibrocytes. Broome and colleagues speculate that if this idea is true, contrast media such as gadodiamide and gadoversetamide, which have different structures to other gadolinium-containing contrast agents, would be more likely to release free gadolinium (see section 2.4).[23]

2.4 Physicochemical and pharmacokinetic properties of gadolinium-based agents

The current understanding of CHM and PhVWP is that gadolinium-based agents are associated with different levels of NSF risk based on their physicochemical and pharmacokinetic properties. Table 1 (page 10) summarises the properties of the currently available marketed gadolinium contrast agents.

Table 1: Currently marketed gadolinium contrast agents

Brand name	Generic name	Acronym	Chemical structure	Charge	Elimination pathway	Protein binding	Cases of NSF
Omniscan	gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Kidney	None	Yes
OptiMARK*	gadoversetamide	Gd-DTPA-BMEA	Linear	Non-ionic	Kidney	None	Yes
Magnevist	gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Kidney	None	Yes
MultiHance	gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	97% Kidney 3% Bile	<5%	Yes
Primovist	gadoxetic acid disodium salt	Gd-EOB-DTPA	Linear	Ionic	50% Kidney 50% Bile	<15%	No
Vasovist	gadofosveset trisodium	Gd-DTPA	Linear	Ionic	91% Kidney 9% Bile	>85%	No
ProHance	gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	Kidney	None	No
Gadovist	gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	Kidney	None	No
Dotarem	gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	Kidney	None	No

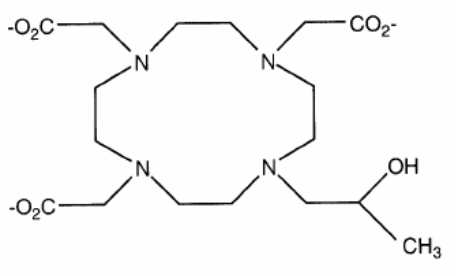
*OptiMARK is not yet marketed in Europe, but is available in the USA

Physicochemical properties

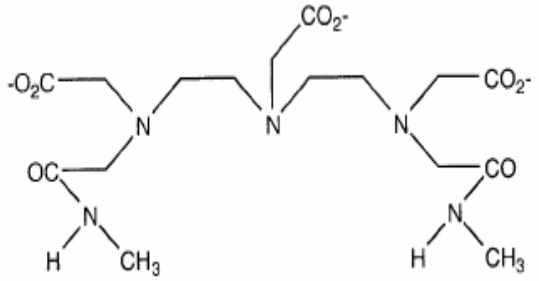
All available gadolinium contrast agents are chelates that contain the gadolinium ion (Gd^{3+}). There are two structurally distinct categories of gadolinium chelates—cyclic chelates (eg, gadoteridol, gadobutrol and gadoterate meglumine), where Gd^{3+} is caged in a cavity, and linear chelates (eg, gadodiamide and gadopentetate dimeglumine).[26] Examples of structures of some cyclic and linear chelates are provided in figure 1. For some gadolinium contrast agents (eg, gadodiamide and gadoversetamide), excess chelate is included in the contrast-agent preparation to ensure the absence of toxic free gadolinium (Gd^{3+}) in solution. High chelate concentration is an indirect marker of the likelihood that free gadolinium will be released more easily from the chelate complex.[2,26]

Some gadolinium-based contrast media are more likely than others to release free Gd^{3+} through a process called transmetallation with endogenous ions from the body.[27] Gadodiamide differs from other gadolinium-based contrast media, with the exception of gadoversetamide,[2] because it has an excess of chelate and is more likely to release free Gd^{3+} compared with other agents. Cases of NSF in association with gadoversetamide have been reported in the USA.

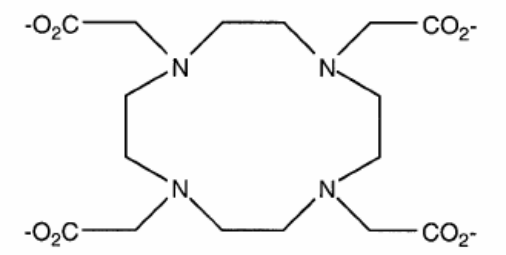
Figure 1. Chemical Structures of some cyclic chelates (ProHance [gadoteridol] and Dotarem [gadoterate meglumine]) and linear chelates (Omniscan [gadodiamide] and Magnevist [gadopentetate dimeglumine])



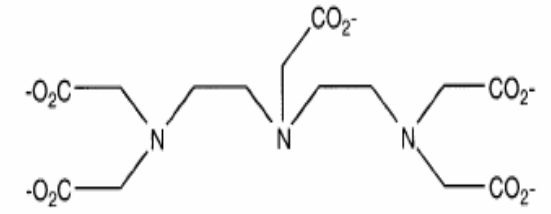
ProHance (gadoteridol)



Omniscan (gadodiamide)



Dotarem (gadoterate meglumine)



Magnevist (gadopentetate dimeglumine)

Cyclic molecules offer better protection and binding to Gd^{3+} compared with linear molecules.[2,26,28,29] For example, the ionic cyclic chelate gadoterate meglumine has a much longer dissociation half-life and higher thermodynamic stability than the non-ionic chelate gadodiamide.[26] Cyclic chelates (eg, gadoteridol, gadobutrol, and gadoterate meglumine) need no excess chelate for the purpose of ensuring the absence of toxic Gd^{3+} in solution and are least likely to release free Gd^{3+} from the chelate complex.[30] Non-ionic linear gadolinium chelates (such as gadodiamide) are most likely to release free Gd^{3+} in the body; they have the highest amount of excess chelate.[2,26,28,29] Furthermore, the charge of the molecule may increase the likelihood of release of free Gd^{3+} [28] through reduced binding strength to the chelate.[29]

Transmetallation releases free gadolinium from the chelate complex through replacement of Gd^{3+} in the chelate by cations such as zinc or copper.[2] Transmetallation occurs more easily with gadodiamide than with other gadolinium-based contrast media.[31] Moreover, transmetallation might occur more readily when a gadolinium contrast agent remains inside the body for a long period, such as in patients with renal failure.[27]

Studies done in vitro,[26,32–35] in vivo,[26,36–42] and those involving human studies[43] lend support to these findings about the physicochemical properties of gadolinium-based contrast agents.

Human studies

Puttagunta and colleagues showed that gadodiamide underwent more transmetallation than did two other gadolinium-containing contrast media (gadoteridol and gadopentetate dimeglumine) in healthy volunteers.[43] Gadoteridol was found to be the most inert of the three drugs tested. Moreover, Kimura and co-workers[40] showed that gadodiamide administration to patients resulted in the highest increase of zinc in urine (which suggests transmetallation) compared with two other gadolinium-containing contrast media (gadoterate meglumine and gadopentetate dimeglumine). Idée and colleagues reported transient increases in serum iron levels after injection of gadodiamide.[26]

Gadodiamide interferes with the techniques of measurement of calcium in serum commonly used in hospitals. Cases of spurious hypocalcaemia have been reported with gadodiamide and gadoversetamide, which is caused by the formation of a complex between Gd^{3+} and a reagent used in the measurement technique (o-cresol-phthalein, OCP).[44–46]

Gadolinium deposition occurs in human body tissues,[47,48] and has been identified in tissue samples of patients with NSF. High and colleagues[49] showed gadolinium deposition in four of 13 tissue samples from seven patients with NSF who were previously exposed to gadodiamide; interestingly, they were able to detect gadolinium in tissue samples up to 11 months after exposure. No gadolinium was identified in a tissue sample from a patient without NSF. Other metals found in the tissue of NSF patients included large deposits of iron, copper, and zinc.[23,49,50]

High and colleagues speculate that gadolinium retained in tissue is phagocytosed by macrophages because the gadolinium in the tissue samples was associated with cell bodies. Intracellular gadolinium might increase the number of profibrotic cytokines or growth factors, leading to dermal or systemic fibrosis.[49]

Boyd and colleagues also identified gadolinium deposition in patients with NSF,[51] which seemed to be restricted to areas where there was also deposition of calcium phosphate. The researchers conclude that cutaneous gadolinium deposition may have a role in the development of NSF.

Pharmacokinetic properties

Distinct pharmacokinetic properties of gadolinium-based agents contribute to the risk of NSF: the longer a gadolinium-based agent remains in the body the greater the level of risk. All gadolinium-based agents have some degree of renal elimination, which varies from 50% for Primovist (with 50% hepatic elimination) to 100% for most other agents (see table 1). The elimination pathway is especially important for patients who have renal dysfunction. Other unique pharmacokinetic properties may also have a contributory role. For example, Vasovist has a prolonged serum half-life due to its unique binding properties to serum albumin.

3 Discussion

In the past year, evidence to support a causal association between gadodiamide (Omniscan) and development of NSF has increased. Of the marketed gadolinium-based contrast agents, most cases of NSF have been associated with Omniscan. Cases have also been reported with OptiMARK (gadoversetamide), which has similar properties to Omniscan. However, these cases are fewer in number compared with Omniscan possibly because OptiMARK is available in the USA, but is not yet marketed in Europe. More recently, 78 cases of NSF have been reported with Magnevist (gadopentetate dimeglumine), and a single case has been reported with MultiHance (gadobenate dimeglumine) in a patient co-administered Omniscan.

As at December, 2006, 90 cases of NSF associated with Omniscan, OptiMARK, or Magnevist had been reported to the US FDA. Elsewhere, more than 150 patients have developed NSF after exposure to a gadolinium-based contrast medium, more than 90% of which were exposed to Omniscan.[52] The reports, collated by the European Society of Urogenital Radiology (ESUR), showed that patients who developed NSF had received Omniscan a few weeks before. Four patients may have received another linear chelate (eg, OptiMARK and Magnevist), and for the remaining cases the causative agent is not known because several agents were given or because there is inadequate information about the case.[52]

Latest figures suggest that 180 worldwide cases of NSF have been associated with Omniscan. Recently, the MAH for Magnevist informed the UK and other European Member States of 78 non-UK cases of NSF associated with this agent. Many patients had received higher than the recommended dose, but this did not negate the causal association with Magnevist.

To date, there have been no reports of NSF in patients with normal kidney function. Since the 1980s, more than 200 million patients have been exposed to gadolinium-based contrast agents, more than 30 million of whom have received Omniscan and 80 million of whom have received Magnevist. Therefore, NSF does not appear to occur in association with gadolinium-based contrast agents in patients without renal impairment.[52] The population at risk are those with severely impaired renal function. Several researchers have suggested that liver transplant patients with renal dysfunction are also prone to NSF.[18,21,23] Gadodiamide is almost exclusively excreted by the kidneys. Importantly, the half-life of gadodiamide in healthy volunteers is 1·3 hours, compared with 34·3 hours for those with end-stage renal failure.[25]

Risk of NSF depends on the different physicochemical and pharmacokinetic properties of the gadolinium-based contrast agents. The physicochemical properties affect the release of toxic free gadolinium (Gd^{3+}) from the chelate complex, and the pharmacokinetic properties influence how long the agent remains in the body (see section 2.4). Gadolinium-based contrast agents that consist of cyclic chelate (eg, ProHance, Gadovist, and Dotarem; see table 1, page 10) are least likely to release free Gd^{3+} into the body. By contrast, gadolinium-

based contrast agents that consist of non-ionic linear chelate (eg, Omniscan and OptiMARK; table 1) are most likely to release free Gd^{3+} into the body.[2,26,28,29]

Magnevist is a linear chelate, but it has an ionic charge that might lower the likelihood of release of Gd^{3+} into the body.[28,29] New pre-clinical and spontaneous reporting data suggest that Magnevist is associated with an increased risk of NSF, albeit lower than the risk of NSF associated with Omniscan and OptiMARK. In vitro and in vivo studies lend support to the idea that gadodiamide can release gadolinium ions through a process called transmetallation with endogenous ions from the body such as zinc, iron, calcium, and magnesium.

In humans, Omniscan interferes with measurement techniques of serum calcium that are commonly used in hospitals, which leads to spurious cases of hypocalcaemia.[44–46]. Studies have shown that gadolinium deposition occurs in human body tissue.[47–49,51]Deposition of gadolinium in tissue has been postulated to stimulate development of NSF through various mechanisms such as involvement of circulating fibrocytes and transforming growth factor β.[14,16,53,54]

NSF and the role of gadolinium-based contrast agents is an emerging science. The exact disease mechanism has yet to be elucidated, but physicochemical properties of gadolinium-containing agents might affect the amount of free gadolinium released in patients with renal impairment. Researchers have debated the benefits of initiating dialysis as a means of removing gadolinium from the body.[23,26,53] For instance, daily dialysis for three consecutive days starting on the day of gadodiamide administration did not prevent development of NSF in three patients.[23] Currently, there is no effective treatment for NSF; the most effective treatment options are related to improvement in renal impairment. Therefore, it is imperative that radiologists, nephrologists, and other relevant healthcare professionals receive guidance as to how to avoid this very debilitating and sometimes fatal disorder.

4 Conclusion

A review of the available data does not suggest that the risk of NSF in patients with advanced renal impairment is the same for all gadolinium-based contrast agents. Distinct physicochemical properties affect their stabilities and thus the release of free gadolinium ions, and pharmacokinetic properties influence how long the contrast agent remains in the body.

The non-ionic linear chelates (Omniscan and OptiMARK) are associated with the highest risk of NSF because they are more likely to release Gd^{3+} from the chelate complex in patients with severe renal impairment than are other agents. By contrast, the cyclical chelates (Gadovist, ProHance, and Dotarem; see table 1, page 10) are considered the most stable and likely to have the lowest risk of NSF. New data suggest that the ionic linear chelate Magnevist is associated with an increased risk of NSF in patients with severe renal impairment, albeit not as great a risk as that with Omniscan and OptiMARK. The risk of NSF associated with the other ionic chelates (MultiHance, Vasovist, and Primovist) remains under investigation.

4.1Regulatory position

In the UK, CHM and PEAG (see page 6) reviewed the risk of NSF with gadolinium-based contrast agents in January, 2007, and during the same month the European PhVWP reviewed the same data. On the basis of the current evidence, CHM and PhVWP proposed a step-wise approach to restricting the use of gadolinium-based contrast agents in at-risk patients based on their physicochemical and pharmacokinetic properties that affect their propensity to trigger NSF.

CHM and PhVWP concluded that haemodialysis shortly after administration of a gadolinium-based contrast agent in patients who are currently receiving haemodialysis may help remove the contrast agent from the body. However, there is no robust evidence to suggest that haemodialysis can prevent or treat the development of NSF.

4.1.1 Non-ionic linear agents (Omniscan and OptiMARK[iii])

CHM and PhVWP concluded that the balance of risks and benefits of Omniscan in patients with severe renal impairment was clearly negative, and recommended that its use should be strictly contraindicated in this patient group (GFR <30mL/min/1·73m^2) and in those who have had (or who are undergoing) liver transplantation due to hepatorenal syndrome. PhVWP also recommended a warning for use of Omniscan in patients with moderate renal impairment (GFR <60mL/min/1·73m^2). On a precautionary basis, CHM and PhVWP advised that a warning should be added to the product information about its use in neonates and infants up to 1 year of age because of their immature kidney function.

[iii] The non-ionic linear agent OptiMARK (gadoversetamide) is not yet marketed in the EU.

Summary of Product Characteristics (SPC) wording for gadodiamide (Omniscan)

Section 4.3 Contraindications

Gadodiamide is contraindicated in patients with severe renal impairment (GFR< 30 ml/min/1.73m^2), and those who have had or are undergoing liver transplantation (see section 4.4 for Special Warnings and Precautions).

Section 4.4 Special warnings and precautions for use

Severe renal impairment and liver transplant patients:

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of gadodiamide and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30ml/min/1.73m^2) and those who have had or are undergoing liver transplantation. Therefore OMNISCAN® should not be used in these populations (see section 4.3 for Contraindications). Cases of NSF have also been reported in patients with moderate renal impairment (GFR <60 mL/min/1·73m^2) with gadodiamide. Omniscan should be used in these patients with caution.

Haemodialysis shortly after Omniscan administration in patients currently receiving haemodialysis may be useful at removing Omniscan from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Neonates and Infants:

Due to immature kidney function in neonates and infants up to 1 year of age, OMNISCAN® should only be used in these patients after careful consideration.

Section 4.8 Undesirable effects

Cases of NSF have been reported with OMNISCAN®.

Box 1: SPC changes for gadodiamide (Omniscan)

4.1.2 Ionic linear agents (Magnevist, MultiHance, Primovist, Vasovist)

In May, 2007, CHM and PhVWP recommended that use of Magnevist should be contraindicated in patients with severe renal impairment (GFR <30mL/min/1·73m^2) based on new pre-clinical and spontaneous reporting data that suggest that Magnevist is associated with an increased risk of NSF. As a precautionary measure, doses of Magnevist that are higher than those recommended should be used with caution in patients with moderate renal impairment (GFR 30–59mL/min/1·73m^2). CHM advised that all patients, particularly those who are elderly, should be screened for renal dysfunction by obtaining a history or through tests. A warning was also advised for neonates and infants up to 1 year of age because of their immature kidney function.

SPC wording for gadopentetate dimeglumine (Magnevist)

Section 4.3 Contraindications

Use of Magnevist is contraindicated in patients with severe renal impairment (GFR <30mL/min/1·73m^2).

Section 4.4 Special warnings and precautions for use

Impaired renal function

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of Magnevist and some other gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30mL/min/1·73m^2). Therefore Magnevist should not be used in these patients (see section 4.3 for Contraindications).

The risk for the development of NSF in patients with moderate renal impairment is unknown, therefore Magnevist should be used with caution in patients with moderate renal impairment (GFR 30–59 mL/min/1·73m^2).

All patients should be screened, in particular patients over the age of 65, for renal dysfunction by obtaining a history and/or laboratory tests.

Haemodialysis shortly after Magnevist administration in patients currently receiving haemodialysis may be useful at removing Magnevist from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Newborns and infants

In neonates and infants up to 1 year of age Magnevist should only be used after careful consideration due to their immature renal function.

Section 4.8 Undesirable effects

Cases of NSF have been reported with Magnevist.

Box 2: SPC changes for gadopentetate dimeglumine (Magnevist)

PhVWP advised that for all other gadolinium-containing contrast agents, strong warnings about potential NSF in patients with severely impaired renal function should be added to the product information.

SPC wording for all other gadolinium-containing contrast agents

Section 4.4 Special warnings and precautions for use

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR <30mL/min/1·73m^2). As there is a possibility that NSF may occur with xxxx, it should only be used in these patients after careful consideration.

Haemodialysis shortly after xxxx administration in patients currently receiving haemodialysis may be useful at removing xxxx from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Section 4.8 Undesirable effects *(for those products where cases have been reported)*

Cases of NSF have been reported.

Box 3: SPC wording for all other gadolinium-containing contrast agents

PhVWP advised that appropriate wording should be added to the Patient Information Leaflets (PILs).

The risk of NSF with the other ionic linear chelates (MultiHance, Vasovist, and Primovist) remains under investigation by PhVWP.

4.1.3 Cyclic agents (ProHance, Gadovist, Dotarem)

The cyclical chelates (ProHance, Gadovist, and Dotarem) are considered to have the most stable structure and are likely to be associated with the lowest risk of NSF. PhVWP recommended the addition of a warning to the product information of these products as outlined in box 3 (section 4.1.2).

4.2 Communication

CHM and PhVWP recommended that communications should be sent to relevant healthcare professionals (ie, radiologists, nephrologists, and all physicians who may request MRI radiological investigations in patients with severe renal impairment such as geriatricians and cardiologists) to inform them of these new information promptly[iv].

CHM and PhVWP continue to monitor closely this safety issue and will provide further updates as they become available.

[iv] Communication documents were made available on the MHRA website in February, 2007 http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2030229&ssTargetNodeId=221

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Glossary

Antifibrotic

Events or factors that prevent the laying down of fibrous scar tissue

Bicarbonate

A bodily substance that controls the acidity of blood; levels are regulated by the kidney

Bone marrow

The spongy component of blood that produces blood cells

Brain neoplasm

New growth of cells in the brain, which may develop into cancer

Calcification

The process by which bodily tissues become hard due to deposition of calcium

Calcineurin inhibitors

Agents that block the binding protein calcineurin

Cation

A positively charged atom or molecule

Central nervous system

The nerves of the brain and spinal cord

Chelate

A metal that is complexed with other molecules, sometimes in a ring

Coagulation

The process of blood clotting

Collagen (type I)

The protein component of connective tissue, it is also present in skin, bone, cartilage, and ligaments

Comorbidities

Presence of more than one disease or disorder in a person at the same time

Contractures

Resistance to the stretch of a muscle

Cranial

Relating to the skull

Creatinine

A bodily waste product that is passed in urine, which can be used to measure kidney function

Cutaneous

Relating to the skin

Cytokines

Proteins that circulate in the body that have a signalling and regulatory role

Deep vein thrombosis

Blood clotting in the legs

Dermal

Relating to the skin

Dialysate fluid

The mixture of fluid that flows during kidney **dialysis**

Dialysis

A process of filtering waste products from the body

Electrons

Negatively charged particle

End-stage renal disease

A patient with impaired liver function who requires kidney dialysis

Endogenous

Developing or originating in an organism

Erythropoietin

A bodily substance that regulates production of red blood cells in the **bone marrow**

Fibroblast

A cell present in connective tissue

Fibrocyte

A cell present in connective tissue that can form **collagen** and has an important role in wound healing

Fibrogenic

Events or factors that promote the laying down of fibrous tissue

Glomerular filtration rate

A measure of the ability of the kidneys to filter waste

Haemodialysis

The process of filtering products from the blood

Half-life

The time taken by a substance to decrease to half its value

Histopathological

Signs of disease that are evident through a microscope

Hypercoagulability

A bodily state of heightened ability of the blood to clot

Hypocalcaemia

Low concentration of calcium in the blood, which can cause muscular problems such as cramp

Idiopathic

Of unknown cause

Immunosuppressive

An agent that decreases that activity of the immune system

Induration

Hardening

Inert

Unreactive, stable

Inhibitors of angiotensin-converting enzyme

Drugs that block the activity of an enzyme that has role in the regulation of blood pressure

Intracellular

Inside cells

In vitro

Experiments or studies done in an artificial environment such as a test tube

In vivo

Experiments or studies done with a living organism

Ionic

A substance that separates into **ions**

Ions

Atoms that carry a positive or negative charge

Liver necrosis

Death of cells in the liver

Macrophages

Important cells of the body's immune system that engulf and kill some foreign bodies such as bacteria

Magnetic resonance angiography

A non-invasive method of imaging blood vessels

Magnetic resonance imaging

A non-invasive method of imaging bodily structures

Marketing Authorisation Holder

An organisation that holds a licence for a medicine (a pharmaceutical company)

Matrix

A meshwork in which cells are embedded

Mean

Average

Mesenchymal tissue

Connective tissue that describes a developmental pathway in the embryo that leads to the formation of connective tissue

Metabolic acidosis

An abnormal level of acidity in the blood, which can lead to symptoms such as dehydration and shock

Mucin

A component of mucous

Myofibroblast

A **fibroblast** cell that contains muscle filaments such that they may contract

Non-ionic

A substance that does not separate into **ions**

Odds ratio

A measure of the risk or likelihood of an event occurring; a 95% CI (confidence interval) estimates the precision of this measurement

Paramagnetic

A substance with magnetic properties

Pathological

A diseased state

Peripheral circulation

The blood supply to the extremities of the body such as the arms and legs

Peritoneal

Relating to the lining of the abdomen

pH

The scale that measures acidity

Phagocytose

The process by which a **macrophage** engulfs foreign bodies

Pharmacological

Relating to the action of medicines

Phospholipids

A type of fatty molecules that have an important role in cell membranes

Photophoresis

Destruction of cells by use of ultra-violet light, which activates a drug

Plasmapheresis

Separation of blood into the a cellular component and a plasma component

Protons

Positively charged particles

Topical

An agent applied to the skin

Radiographic

Relating to the procedure of taking x-rays

Renal

Relating to the kidneys

Serum

The clear portion of bodily fluid or of blood

Skin biopsy

A method of measuring the cellular components of a skin sample

Systemic

Relating to the whole body

Thalidomide

A drug that is able to modulate the immune system

Thrombotic

Agents or events that promote blood clotting or thrombus formation

Transforming growth factor β

A bodily substance that stimulates the growth of some cells

Transmetallation

A chemical reaction, in which one metal attached to other molecules is substituted for another

Tumour necrosis factor

A bodily substance that promotes inflammation

Vasodilation

Widening of blood vessels