Public Assessment Report

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

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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.

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 EU member states to inform them of a possible association between gadodiamide with NSF. Further data were discussed 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.

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 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 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.

1http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2024695&ssTargetNodeId=221
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. 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.

Gadodiamide (Omniscan) was the first agent to be associated with the disorder nephrogenic systemic fibrosis (NSF). 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.
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. 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. 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.

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 Regulatory action to date

This issue 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.

During the same period, the US Food and Drug Administration (FDA) issued preliminary guidance that physicians should be cautious when using gadolinium-containing contrast agents in patients with advanced renal failure. In December, 2006, the FDA issued a further update, informing physicians that they had received 90 reports of patients with moderate to end-stage renal disease who developed NSF after MRI or magnetic resonance angiography with a gadolinium-based contrast agent. Onset ranged from 2 days to 18 months after exposure to gadolinium, and the FDA identified Omniscan, Magnevist, and OptiMARK as the suspect products in these cases. The FDA considers that there is a potential for NSF to occur with use of any of the five gadolinium contrast agents licensed in the USA.

Meanwhile 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.

http://www.fda.gov/cder/drug/infopage/gcca/default.htm
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. Because NSF is a newly diagnosed syndrome, several researchers suggest that a new agent or new examination technique might cause this syndrome.

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), erythropoietin, inhibitors of angiotensin-converting enzyme, and induced antibodies against phospholipids.

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. These cells enter sites of inflammation and tissue repair, secrete growth factors and cytokines, and contribute to matrix production in connective tissue. 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.

Cowper noted that development of NSF in many patients was associated temporally with vascular or thrombotic events, or with development of cancer. 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. Evidence of this association was later shown in a pivotal study by Grobner (see section 2.3).
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,\(^8\) photopheresis,\(^9\) 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, 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 properties of gadodiamide and other gadolinium-based agents

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 and gadoterate meglumine), where Gd\(^{3+}\) is caged in a cavity, and linear chelates (eg, gadodiamide and gadopentetate dimeglumine; figure 1).26 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 $\text{Gd}^{3+}$ through a process called transmetallation with endogenous ions from the body.\textsuperscript{27} These agents have the largest amount of excess chelate. Gadodiamide differs from other gadolinium-based contrast media, with the exception of gadoversetamide,\textsuperscript{2} because it has an excess of chelate and is more likely to release free $\text{Gd}^{3+}$ compared with other agents. Cases of NSF in association with gadoversetamide have been reported in the USA.

Table 1 (page 10) summarises the chemical structure and charge of the currently available marketed gadolinium contrast agents.

Cyclic molecules offer better protection and binding to $\text{Gd}^{3+}$ compared with linear molecules.\textsuperscript{2,26,28,29} Ionic cyclic chelates are least likely to release free $\text{Gd}^{3+}$: they need no excess chelate, and have the longest dissociation half-life. Non-ionic linear gadolinium chelates (such as gadodiamide) are most likely to release free $\text{Gd}^{3+}$ in the body; they have the highest amount of excess chelate.\textsuperscript{2,26,28,29} Furthermore, the charge of the molecule may increase the likelihood of release of free $\text{Gd}^{3+}$ through the available binding strength to the chelate.\textsuperscript{29}
Table 1: Currently marketed gadolinium contrast agents

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
<th>Acronym</th>
<th>Chemical structure</th>
<th>Charge</th>
<th>Cases of NSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omniscan</td>
<td>gadodiamide</td>
<td>Gd-DTPA-BMA</td>
<td>Linear</td>
<td>Non-ionic</td>
<td>Yes</td>
</tr>
<tr>
<td>OptiMARK*</td>
<td>gadoversetamide</td>
<td>Gd-DTPA-BMEA</td>
<td>Linear</td>
<td>Non-ionic</td>
<td>Yes</td>
</tr>
<tr>
<td>Magnevist</td>
<td>gadopentetate</td>
<td>Gd-DTPA</td>
<td>Linear</td>
<td>Ionic</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>dimeglumine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>gadobenate</td>
<td>Gd-BOPTA</td>
<td>Linear</td>
<td>Ionic</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>dimeglumine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primovist</td>
<td>gadoxetic acid</td>
<td>Gd-EOB-DTPA</td>
<td>Linear</td>
<td>Ionic</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>disodium salt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasovist</td>
<td>gadofosveset</td>
<td>Gd-DTPA</td>
<td>Linear</td>
<td>Ionic</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>trisodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProHance</td>
<td>gadoteridol</td>
<td>Gd-HP-DO3A</td>
<td>Cyclic</td>
<td>Non-ionic</td>
<td>No</td>
</tr>
<tr>
<td>Gadovist</td>
<td>gadobutrol</td>
<td>Gd-BT-DO3A</td>
<td>Cyclic</td>
<td>Non-ionic</td>
<td>No</td>
</tr>
<tr>
<td>Dotarem</td>
<td>gadoterate</td>
<td>Gd-DOTA</td>
<td>Cyclic</td>
<td>Ionic</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>meglumine</td>
<td></td>
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</table>

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

Transmetallation releases free gadolinium 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.\(^30\) 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,\(^26,31–34\) in vivo,\(^26,35–41\) and those involving human studies\(^42\) 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. Gadoteridol was found to be the most inert of the three drugs tested. Moreover, Kimura and co-workers 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.

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).

Gadolinium deposition occurs in human body tissues and has been identified in tissue samples of patients with NSF. High and colleagues 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.

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.

Boyd and colleagues also identified gadolinium deposition in patients with NSF, 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.
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, followed by OptiMARK (gadoversetamide, which is not licensed in Europe but is available in the USA), and a small number of cases have been reported with Magnevist (gadopentetate dimeglumine).

The latest figures suggest that 90 cases of NSF associated with Omniscan, OptiMARK, or Magnevist have 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. 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.

The Medicines and Healthcare products Regulatory Agency (MHRA) is aware of 21 cases of NSF associated with gadodiamide, five of which had a fatal outcome. The MAH for Magnevist has informed the UK of 13 non-UK cases of NSF associated with this agent. The causal role of Magnevist for some cases is unclear because several agents were given or because there is inadequate information about the case. However, for at least one case, in which the patient received high doses of Magnevist in a fairly short period, development of NSF seems related to Magnevist administration.

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. Therefore, NSF does not appear to occur in association with gadolinium-based contrast agents in patients without renal impairment. The population at risk are those with severely impaired renal function. Several researchers have suggested that liver transplant patients are prone to NSF. 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.

The different physicochemical properties of gadolinium-based contrast agents probably affect their behaviour in the body through the release of toxic free gadolinium (Gd^{3+}) (see section 2.4). Gadolinium-based contrast agents that consist of ionic cyclic chelate (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.
Magnevist is a linear chelate, but it has an ionic charge that might lower the likelihood of release of Gd$^{3+}$ into the body.$^{28,29}$ 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, gadodiamide interferes with measurement techniques of serum calcium that are commonly used in hospitals, which leads to spurious cases of hypocalcaemia.$^{43-45}$ Studies have shown that gadolinium deposition occurs in human body tissue.$^{46-48,50}$ 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.$^{14,16,52,53}$

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. 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.

In its recent communication of Dec 22, 2006, the US FDA does not differentiate between their five licensed gadolinium-based contrast agents and risk of NSF, although to date they have received only cases associated with Omniscan, OptiMARK, and Magnevist. The FDA recommends that treating physicians should assess carefully the benefits and risks associated with use of a gadolinium-based contrast agent in patients with moderate to end-stage renal disease, and that an alternative imaging method or contrast agent should be used when possible. In addition, they propose prompt dialysis to remove gadolinium if used as a contrast agent is in these patients. However, some researchers have debated the benefits of dialysis of gadolinium.$^{23,26,52}$ For instance, daily dialysis for three consecutive days starting on the day of gadodiamide administration did not prevent development of NSF in three patients.$^{23}$
4 Conclusion

A review of the available data does not suggest that the risk of NSF in patients with advanced renal insufficiency is the same for all gadolinium-based contrast agents because distinct physiochemical properties affect their stabilities and thus the release of free gadolinium ions.

The non-ionic linear chelates (Omniscan and OptiMARK) are associated with the highest risk of NSF; ionic cyclic chelates are associated with the lowest risk of NSF (Dotarem; see table 1, page 10). The ionic linear chelates (Magnevist, MultiHance, Vasovist and Primovist) and the non-ionic cyclic chelates (Gadovist and ProHance) have similar structures and these fall in between the other two groups.

4.1 UK regulatory position

CHM and PEAG (see page 5) reviewed the issue of NSF and gadolinium-based contrast agents in January, 2007. With no known effective treatment for NSF and no effective method of removing free gadolinium ions from the body, the Commission advised that creatinine levels should be measured in all patients before use of a gadolinium-based contrast agent. CHM proposed a step-wise approach to restricting the use of gadolinium-based contrast agents in at-risk patients. They advised that Omniscan (and OptiMARK) should not be used in at-risk patients, and that ionic linear chelates (Magnevist, MultiHance, Vasovist and Primovist) or non-ionic cyclic chelates (Gadovist and ProHance) should not be used in at-risk patients unless regarded clinically essential. They advised that the standard recommended dose of these agents should not be exceeded, and their use should not be repeated at a time interval of less than 1 week. For the ionic cyclic agent Dotarem, CHM proposed a warning for its use in at-risk patients.

CHM concluded that there is no robust evidence to suggest that haemodialysis is protective against NSF, and that dialysis in patients with severe renal impairment after gadolinium-containing contrast agent administration should not be recommended.

CHM concluded 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 recommendations.

The advice of CHM informed the UK position during discussions of the European Pharmacovigilance Working Party (PhVWP, see section 4.2).
4.2 European regulatory position

The PhVWP reviewed the issue of NSF and gadodiamide-based contrast agents in January, 2007 through data presented in an assessment report by the UK. On the basis of the current evidence, PhVWP concluded that there was strong suggestion of a causal association between gadodiamide and NSF in patients with severe renal failure. They noted that some gadolinium-containing products had been associated with few spontaneous reports of NSF, and some products had not been associated with any reports. PhVWP concluded that differences in the structure of gadolinium complexes may affect their propensity to trigger NSF.

PhVWP concluded that the balance of risks and benefits of gadodiamide in patients with severe renal failure was negative, and that its use should be strictly contraindicated. PhVWP considered that dialysis after gadolinium administration was not beneficial in preventing NSF in patients with severe renal impairment. On a precautionary basis, PhVWP advised that a warning should be added to the product information about the use of gadodiamide in neonates because of their immature kidney function.

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

<table>
<thead>
<tr>
<th>Section 4.3 Contraindications</th>
</tr>
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<tbody>
<tr>
<td>Gadodiamide is contraindicated in patients with severe renal impairment (GFR&lt; 30 ml/min/1.73m²), and those who have had or are undergoing liver transplantation (see section 4.4 for Special Warnings and Precautions).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 4.4 Special warnings and precautions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe renal impairment and liver transplant patients:</td>
</tr>
<tr>
<td>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 &lt;30ml/min/1.73m²) 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).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonates and Infants:</th>
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</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 4.8 Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of NSF have been reported with OMNISCAN®.</td>
</tr>
</tbody>
</table>

*Box 1: Proposed SPC changes for gadodiamide (Omniscan)*
PhVWP advised that for all other gadolinium-containing contrast agents, strong warnings about potential NSF in patients with impaired renal function should be added to the product information.

4.3 Proposed SPC wording for all other gadolinium-containing contrast agents

<table>
<thead>
<tr>
<th>Section 4.4 Special warnings and precautions for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 &lt;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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 4.8 Undesirable effects (for those products where cases have been reported)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of NSF have been reported.</td>
</tr>
</tbody>
</table>

Box 2: Proposed SPC wording for all other gadolinium-containing contrast agents

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

PhVWP advised that healthcare professionals in the European Union should be informed of this new information promptly.
References


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27 Thomsen HS, Morcos SK, Dawson P. Is there a causal relation between the administration of gadolinium based contrast media and the development of nephrogenic systemic fibrosis (NSF)? *Clin Radiol* 2006; **61**: 905–06.


31 Tweedle MF. Physicochemical properties of gadoteridol and other magnetic resonance contrast agents. *Invest Radiol* 1992; **27** (suppl 1): S2–6.30


34 Corot C, Idée JM, Hentsch AM, Santus R, et al. Structure-activity relationship of macrocyclic and linear gadolinium chelates: investigation of transmetallation effect on the


47 White GW, Gibby WA, Tweedle MF. Comparison of Gd (DTPABMA) (Omniscan) versus Gd (HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol* 2006; 41: 272–78.


53 Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: Is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? *In press*.
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
Photopheresis
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