

Information for Healthcare Professionals and other Stakeholders

NEPHROGENIC SYSTEMIC FIBROSIS: AN UNCOMMON AND DEBILITATING DISEASE POSSIBLY ASSOCIATED WITH GADOLINIUM CHELATES

Villepinte, 12 August 2009

Any significant information (eg publication of results of a new study, results of the investigation of a pharmacovigilance case) may cause the issue of a new version of this document.

What is Nephrogenic Systemic Fibrosis (NSF)?

NSF was first recognized in 1997 in 15 dialyzed patients and described in 2000 (1). This rare and highly debilitating disorder is characterized by extensive thickening and hardening of the skin associated with skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with an “peau d’orange” appearance. Nodules are sometimes also described. Joint contractures may develop, with patients progressively becoming wheelchair-dependent. Patients often complain of pruritus, causalgia and sharp pains (2). The distal extremities are the most common area of involvement (with a distribution from ankles to mid-thighs and from wrists to mid-upper arms), followed by the trunk. The lesions are typically symmetrical. It is worth noting that the face and neck are virtually never involved (3). NSF always occurs in patients with severe or end-stage chronic kidney disease (CKD) (eGFR < 30 ml/mn/1.73 m²) (1-3), usually in those requiring a treatment by dialysis (2).

NSF can occur in all age-groups and there is no predilection for a geographic region, race or gender.

So far, there is no recognized treatment for NSF. It has been suggested that improving renal function may slow down the development of the disease and, in some cases, may reverse its course (2).

The mechanism of this highly debilitating disease remains unknown. Current literature suggests a multifactorial aetiology (4).

So far, several factors have been suggested to be frequently associated with the onset of NSF (Table 1) :

Table 1
Recognized or possibly associated factors for NSF

- | |
|---|
| <ul style="list-style-type: none">• Severe or end-stage renal failure (1-3)• High cumulative dose of gadolinium chelate (5)• High dose of erythropoietin (5,6)• High serum phosphate levels (5)• High serum calcium levels (5)• Coexisting proinflammatory event (major surgery, infection, vascular event) (7)• Iron mobilization (4)• Metabolic acidosis (8) (debated: 7,9)• History of hypothyroidism (10) |
|---|

In 2006, two European teams independently suggested a link between the administration of gadolinium chelates used as contrast media for magnetic resonance imaging (MRI) and the occurrence of NSF in patients with renal failure (8,9). Numerous retrospective analyses rapidly followed and confirmed this temporal link (7,11-13).

The time to onset of the symptoms ranges between a few days and a few years following exposure to the gadolinium chelate. The majority of published cases occurred within 3 months (2).

The link between gadolinium-containing contrast media and NSF is considered probable (8, 9, 14, 15, 16) and awareness of this potential adverse reaction to gadolinium chelates is a major requirement for radiologists and specialists in patients with stage 4 and 5 chronic kidney disease.

Current Position of European Health Authorities

In February 2007, the European Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency (EMA) initially advised all contrast media marketing authorization holders to add warnings about the possibility that NSF may occur with gadolinium chelates to section 4.4 of the Summary of Product Characteristics (SPC).

Guerbet immediately complied with this requirement.

To date, no further changes were requested by the PhVWP with regard to the SPC of meglumine gadoterate (Dotarem®).

On June 26th, 2007, the Commission on Human Medicines together with the PhVWP issued a public assessment report stating that an updated review of available data suggests that the risk of NSF in patients with advanced renal failure is not the same for all gadolinium chelates.

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

There are two generally recognised categories of gadolinium chelates: macrocyclic molecules where Gd^{3+} is caged in the pre-organised cavity of the ligand (20), and the linear open chain molecules (20). Gadolinium chelates differ in their thermodynamic stability constants and in their kinetic stability. In general, in vitro studies have suggested that, macrocyclic molecules are more stable than linear molecules (15-19).

Further, the PhVWP recommended that gadodiamide (Omniscan) and gadopentate dimeglumine (Magnevist) be contraindicated in patients with severe renal impairment. For patients with moderate renal impairment (ie, GFR or eGFR 30-59mL/min/1.73m²) or neonates and infants up to 1 year of age, Omniscan should be used only after careful consideration.

Guerbet Pharmacovigilance Data

Guerbet markets meglumine gadoterate (Dotarem[®]), a macrocyclic, ionic gadolinium chelate associated with a high thermodynamic and kinetic stability (15-19).

With respect to NSF, Guerbet has been reported to date ten medically confirmed reports of patients who have received Dotarem[®] and developed NSF afterwards (table 2):

- one case currently under investigation
- nine “confounded” cases (cases where the patient has received Dotarem[®] and at least one another gadolinium-based contrast agent).

On the basis of the available information, the causality of Dotarem[®] is doubtful for several reasons such as the lack of detailed information on the clinical history, the injection of linear gadolinium chelates, the chronology of the injections, potential other causality factors such as pro-inflammatory events.

In these cases there is no data to suggest that Dotarem[®] may have triggered the disease.

In addition to these cases, Guerbet has been reported one case of a patient who developed NSF after injection of linear gadolinium chelates, and for whom the disease worsened after injection of Dotarem (table 3). On the basis of the available information the causality of Dotarem[®] is also doubtful in that case for several reasons such as the absence of information regarding the renal function and its course, the unknown precise chronology of the events, potential other factors such as pro-inflammatory events.

Table 2
Cases where occurrence of NSF could be associated
with the administration of Dotarem®

#	Report date	NFS onset	Associated products	Country
1	2007	2000	Omniscan® or Prohance® (2000), Dotarem® (2000, 2001, 2002)	Switzerland
2	2008	2002	Dotarem® (2000), Omniscan® (2002)	Switzerland
3	2007	2002	Omniscan® (1997, 2000, 2002), Dotarem® (2002) Omniscan® (2003, 2004, 2005)	Switzerland
4	2007	2003	Dotarem® (1999), Omniscan® (2003)	Switzerland
5	2008	2004	Omniscan® (2000, 2004), Dotarem® (2002)	Switzerland
6	2007	2004	Omniscan® (2003, 2004, 2006), Dotarem® (2003, 2004), Magnevist® (2004, 2005)	France
7	2007	2005	Magnevist® (1999, 2000?), Gadovist® (2000, 2005), Dotarem® (2004, 2005)	Switzerland
8	2008	2006	Dotarem® (2003), Omniscan® (2006)	Austria
9	2009	2006	Unknown GBCA (1997), Dotarem® (2006)	Denmark
10	2009	2004	Omniscan® (1998), Magnevist® (2002), Dotarem® (2003, 2004)	Austria

* Adverse Events are managed in accordance with the regulatory Pharmacovigilance reporting standards; in particular Volume 9A of the Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use – September 2009. The causality assessment scales used by the International Pharmacovigilance department of Guerbet is based on the French method of imputation in force with correlation to the international imputation (the wording "doubtful" being consistent with both methods).

Table 3
**Cases where worsening of NSF could be associated
with the administration of Dotarem®**

#	Report date	NFS onset	Associated products	Country
1	2008	1999	Magnevist® (1998), Omniscan® (1999), Dotarem® (2003, 2004)	Austria

All the patients presented with renal insufficiency. In nine cases the NSF was confirmed by skin biopsy; one case was not biopsied; one case is doubtful regarding the biopsy. The date of the onset of NSF is not always clearly established by the reporter.

Position Statement

At Guerbet, we significantly contribute to improving diagnosis for major disease areas (cardiovascular diseases, cancer, inflammatory and neurodegenerative diseases).

We are strongly committed to providing radiologists and cardiologists with a comprehensive range of innovative and effective contrast media to achieve their aim to provide optimum diagnosis for their patients.

A complete research programme is in progress at Guerbet and in cooperation with recognized academic centres to better understand the mechanism of NSF and thoroughly study the role of physicochemical properties of gadolinium chelates in its pathogenesis. The research programme includes a prospective clinical analysis of the safety of Dotarem.

We are in full collaboration with Health Authorities for Pharmacovigilance issues with total transparency and consistently acting in the best interests of the patients is a fundamental principle at Guerbet. This is particularly true in the case of NSF and will remain so.

Further information about NSF and gadolinium chelates

Medicines and Healthcare products Regulatory Agency (MHRA)

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

European Society of Urogenital Radiology (ESUR)

http://www.esur.org/Nephrogenic_Fibrosis.39.0.html

International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR) (Yale University)

<http://www.icnfd.org>

References

1. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; 356: 1000-1001
2. Cowper SE, Kuo PH, Bucala R. Nephrogenic systemic fibrosis and gadolinium exposure: association and lessons for idiopathic fibrosing disorders. *Arthritis Rheum* 2007; 56: 3173-3175
3. Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). *Curr Opin Rheumatol* 2006; 18: 614-617
4. Swaminathan S, Shah SV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol* 2007; 18: 2636-2643
5. Marckmann P, Skov L, Rossen K, Heaf JG, Thomsen HS. Case-control study of gadodiamide-related nephrogenic systemic fibrosis. *Nephrol Dial Transplant* 2007; 22: 3174-3178
6. Swaminathan S, Ahmed I, McCarthy JT, Albright RC, Pittelkow MR, Caplice NM, Griffin MD, Leung N. Nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy. *Ann Intern Med* 2006; 145: 234235
7. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, Djamali A. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; 243: 148-157
8. Grobner T. Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis ? *Nephrol Dial Transplant* 2006; 21: 1104-1108
9. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; 17: 2359-2362
10. Kallen AJ, Jhung MA, Cheng S, Hess T, Turabelidze G, Abramova L, Arduino M, Guarner J, Pollack B, Saab G, Patel PR. Gadolinium-containing magnetic resonance imaging contrast and nephrogenic systemic fibrosis: a case-control study. *Am J Kidney Dis* 2008; 51: 966-975

11. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *Am J Roentgenol* 2007; 188: 586-592
12. Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris STW, Simpson K, Roditi GH. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology* 2007; 245: 168-175
13. Khurana A, Runge VM, Narayanan M, Greene Jr JF, Nickel AE. Nephrogenic systemic fibrosis. A review of 6 cases temporally related to gadodiamide injection (Omniscan). *Invest Radiol* 2007; 42: 139-145
14. Abraham JL, Thakral C. Tissue distribution and kinetics of gadolinium and nephrogenic systemic fibrosis. *Eur J Radiol* 2008; 66 : 200-207
15. Morcos SK. Extracellular gadolinium contrast agents: differences in stability. *Eur J Radiol.* 2008; 66: 175-179
16. Perazella MA, Rodby RA. Gadolinium use in patients with kidney disease: a cause for concern. *Sem Dialysis* 2007; vol 20, No 3 (May-June): 179-185
17. Wedeking P, Kumar K, Tweedle MF. Dissociation of gadolinium chelates in mice: relationship to chemical characteristics. *Magn Reson Im* 1992; 10: 641-648
18. Caravan P, Ellison JJ, McMurry TJ, Lauffer RB. Gadolinium (III) chelates as MRI contrast agents : structure, dynamics, and applications. *Chem Rev* 1999 ; 99 : 2293-2352
19. Laurent S, Vander Elst L, Copoix F, Muller RN. Stability of MRI paramagnetic contrast media. A proton relaxometric protocol for transmetallation assessment. *Invest Radiol* 2001; 36: 115-122
20. Laurent S, Vander Elst L, Muller RN. Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. *Contrast Med Mol Imaging* 2006; 1: 128-137
21. Frenzel T. Stability of gadolinium-based contrast agents in human serum. *Proc. 20th Annual Meeting of the European Society of Radiology. Eur. Radiol.* 2008; 18 (suppl. 1): B-095.

P 0844 – October 2008