Global reports and findings of NSF and its effects

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Background

The subject of nephrogenic systemic fibrosis (NSF), first addressed in the radiological community in 2006 [1], is a fast-moving topic with new details arising almost every day. NSF is a rare, debilitating and sometimes fatal condition that only occurs in patients with severe renal impairment. It is characterised by the formation of connective tissue in the skin, which becomes thickened, coarse and hard, sometimes leading to contractures and joint immobility. NSF has been associated with use of gadolinium-containing MRI contrast agents in patients with severe renal impairment [2-3]. Since its recognition in 1997 by Dr. Shawn E. Cowper, a dermatopathologist of Yale University [2], more than 215 cases have been recorded [4]. Recent reports by Grobner [5] and Marckmann [6] were among the first to suggest a link with gadolinium containing contrast agents. Subsequent to these reports the United States Food and Drug Administration (FDA) issued a public health advisory in June 2006 recommending that gadolinium containing contrast agents be used only if clearly necessary in patients with advanced kidney failure and that prompt dialysis is instituted in patients with advanced kidney failure who receive gadolinium-containing contrast agents [7]. In January of 2007 this was followed by an announcement of the pharmacovigilance working party of the European Medicines Agency (EMEA) who decided that it is contraindicated to use gadodiamide (Omniscan®, Gd-DTPA-BMA, GE Healthcare, Buckinghamshire, United Kingdom) in patients with a GFR below 30 ml/min, on dialysis and patients who have undergone liver transplantation. Due to immature kidney function in neonates and infants up to 1 of age, gadodiamide should only be used in these patients after careful consideration [8]. Today, this warning is in place not only for gadodiamide, but also for Gd-DTPA (Magnevist®, Bayer Schering Pharma, Berlin, Germany), Gadoteridol (ProHance®, Bracco Diagnostics, Milan, Italy), gadobenate dimeglumine (MultiHance®, Bracco Diagnostics, Milan, Italy), and gadoversetamide (OptiMARK®, Mallinckrodt, Inc, St. Louis, MO).
At present there is no established treatment for NSF although a number of therapies have been used with varying success. For a more detailed description of the clinical manifestations of NSF and the role of gadodiamide we refer the website of the International Center for Nephrogenic Fibrosing Dermopathy Research [3] and the editorial on this subject by Thomsen [1].

**Current Insights into the Pathophysiology of NSF**

Although the exact mechanism by which NSF develops remains elusive, recent publications have shed further light on the pathogenesis of NSF. Grobner found that patients with renal disease who were exposed to gadodiamide and did develop NSF were acidotic at the time of imaging, while those that did not develop NSF were not acidotic [5]. Furthermore, as the release of free Gd$^{3+}$ through a process of transmetallation in patients with reduced elimination of gadolinium-containing contrast agents via the kidneys is considered to be a possible trigger for NSF, the stability of the Gd-chelate complexes is an important factor in the overall risk assessment across the various contrast agents. In addition, the total cumulative dose of Gd-chelate that has been administered over time seems to be an important risk factor, with a higher risk of developing NSF in patients who have received larger cumulative doses [9].

Based on their chemical structures Gd-containing contrast agents may be divided into two groups: linear (open-chain) chelates and macrocyclic chelates. A further subdivision is made between ionic and non-ionic linear chelates [10]. Non-ionic linear chelates such as gadodiamide and gadoversetamide display clearly lower stability values than ionic linear chelates and are characterized by a comparably high concentration of excess free ligand in the formulation [10]. The ionic linear chelates such as Gd-DTPA are characterized by a much higher complex stability. However, a significant number of NSF cases have been associated with Gd-DTPA. Macrocyclic chelates differ significantly from linear chelates regarding the kinetics of complexation and decomplexation. Significant activation energy is necessary to both generate and dissociate the Gd-complexes, also resulting in high complex stability [10].

Two recent publications confirm the biological relevance of the difference between macrocyclic and ionic linear versus non-ionic linear chelates. Boyd et al have now convincingly demonstrated the presence of gadolinium in areas of calcium phosphate deposition in blood vessels in a skin biopsy obtained from a patient with clinical features consistent with NSF after administration of gadodiamide [11]. These results were corroborated in a report by High et al. who studied tissue from 7 patients with clinical and histopathological diagnosis of NSF after gadodiamide administration [4]. Gadolinium was detected in the histological specimens of 4 of these 7 patients. In all cases the gadolinium particles appeared to be intracellular, possibly in the lysosomes [4].
Scope of the problem – Number of Cases

At the time of preparation of this abstract (February 25, 2008) the FDA has received over 250 reports of NSF associated with exposure to gadolinium contrast agents [12]. Most cases involve exposure to gadodiamide and Gd-DTPA, but almost all other agents have been implicated as well. In many subjects more than one brand of contrast agent was used, further complicating establishing the exact cause.

Onset of NSF-symptoms in all available reports dates back up to several years. The time span between administration of MR-contrast medium and occurrence of symptoms ranges between several days and several years. However, in many cases the diagnosis of NSF has not been verified by deep skin biopsy and histopathology, and it remains to be determined if these represent true cases.

At present there are no known cases of NSF associated with the sole and exclusive administration of gadobutrol (Gadovist® Bayer Schering Pharma AG), gadofosveset trisodium (Vasovist®, Bayer Schering Pharma AG), gadoxetic acid (Primovist®, Bayer Schering Pharma AG), gadotertiol (ProHance®, Bracco Diagnostics, Milan, Italy) and gadoterate meglumine (Dotarem®, Guerbet S.A., Aulnay-sur-Bois, France). In addition, there has been a sharp drop in the number of reported cases in 2007 compared to 2006, probably reflecting altered practice patterns.

What to do clinically?

Despite the fact that at present not all gadolinium-based contrast agents have been associated with NSF it is paramount that these agents be used with caution in patients with renal insufficiency, especially considering the fact that the pathogenesis has not definitively been established. Reflecting these concerns, the Committee for Medicinal Products for Human Use (CHMP) of the EMEA has requested the marketing authorisation holders of MR contrast agents to introduce a warning in the summary of product characteristics (“package insert”) about the occurrence of NSF in patients with severe renal impairment.

How do these recent findings influence clinical practice? Based on the approach by Kuo et al., published in the March 2007-issue of Radiology [13], we recommend the following approach for patients with stage 4 or 5 chronic kidney disease (i.e. patients on peritoneal dialysis or hemodialysis) or patients with a GFR of less than 30 mL/min/1.73 m² and in patients with acute renal failure (who may not have immediately decreased GFR values):

1) In consultation with the ordering physician, we consider ultrasound, CT and non-contrast-enhanced MRA as alternative imaging modalities
2) We do not recommend administering gadodiamide, gadoversetamide of Gd-DTPA to a patient with a history of renal dysfunction. If administration of a gadolinium-based MR contrast agent is deemed necessary, we consider using the lowest dose needed to reliably provide the diagnostic information being clinically sought. If there is a diagnosis or clinical suspicion of NSF in the patient, we discourage exposure to any gadolinium chelates.
3) For patients maintained with hemodialysis, we ensure hemodialysis treatment as soon as possible, ideally within 3 hours after the administration of the gadolinium-containing contrast agent. A second dialysis session within 24 hours can also be performed if it is clinically safe to do so. For patients undergoing peritoneal dialysis, we ensure that patients have no periods with a dry abdomen (ie, peritoneal cavity contains no dialysate), and we perform more frequent manual exchanges or additional automated peritoneal dialysis cycles for at least 48 hours after administration.

At this time, the relationship between NSF and gadolinium chelates remains unclear. Further studies are now underway at the Centers for Disease Control Prevention, the FDA, and in the medical regulatory agencies of the European Union. If a patient with NSF is encountered the following should be done [13]:

1. A history of administration of a gadolinium-based MR contrast agent in the weeks or months preceding the initial diagnosis should be ascertained. In addition the date of administration, the dose and brand of the contrast agent administered, as well as the date of onset or diagnosis of NSF should be noted. It is important to note the cumulative dose of Gd that has been administered.
2. The event should be reported to the EMEA (http://www.emea.europa.eu) and FDA online through the MedWatch reporting program (http://www.fda.gov/medwatch/) or by phone (1-800-FDA-1088), or appropriate non-E.U. / non-U.S. regulatory agencies.
3. The case should be reported to the NSF registry at Yale University (http://www.icnfdr.org) and to the European Society of Urogenital Radiology (http://www.esur.org).
REFERENCES