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EDITORIAL

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Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide

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Recently, it has been reported [1, 2] that a serious adverse reaction called nephrogenic systemic fibrosis (NSF) may occur after exposure to the extracellular nonionic low osmolar gadolinium-based contrast agent gadodiamide (Omniscan®, GE Health Diagnostic, Amersham, United Kingdom). Nephrogenic systemic fibrosis was recognized in 1997 in California [3]. The typical patient is middle-aged and has end-stage renal disease (ESRD) [4]. Most patients, but not all, are on regular dialysis treatment. The typical course begins with subacute swelling of distal parts of the extremities followed during subsequent weeks by severe skin induration and sometimes anatomical extension involving thighs, antebrachium, and lower abdomen. The skin induration may be aggressive and associated with constant pain, muscle restlessness, and loss of skin flexibility. In some cases, NSF leads to serious physical disability including wheelchair requirement. NSF was initially observed in and thought to solely affect the skin—therefore, it was initially called nephrogenic fibrosing dermopathy—but it is now known that several organs such as liver, lungs, muscles and heart may be involved. Organ involvement may explain the suspected increased mortality of NSF patients [4].

Grobner was the first to propose that MR contrast media containing Gd might be a trigger of NSF [2]. Marckmann [1] reported 13 patients who had been exposed to gadodiamide prior to the development of NSF. The authors could not identify any other common exposure/event. The delay from exposure to first sign of the disease was 2–75 days (median 25 days). Odds ratio for acquiring the disease if gadodiamide-exposed was 32.5 (95% CI: 1.9–549.2) ($p<0.0001$). Seven patients (54%) became severely disabled and one died 21 months after exposure. Evenepoel et al. reported already in 2004 two cases of severe NSF [5]. A common factor for the three European reports is that all 20 patients had had gadodiamide ([6]; Oyen, personal communication, August 2006). The official site of the nephrogenic fibrosing dermopathy (NFD/NSF) registry [3] states that all registry cases, in which records can be located, have at least one known exposure to gadolinium within 2 to 8 weeks prior to clinical symptoms. However, it is not mentioned to which gadolinium-based contrast agent the patients had been exposed. In a personal communication, Dr. Cowper writes that the registry has information that the majority had had gadodiamide.

In August 2006, all members of the European Society of Urogenital Radiology (ESUR) received an electronic mail asking them to report cases of NSF to the chairman of the ESUR contrast media safety committee in request for material for the upcoming meeting of the committee. The complete material will be analyzed, but

already within 1 week three striking responses were obvious: (1) I have never heard about NSF (most frequent answer); (2) we have never seen a case of NSF; (3) yes, we have seen cases of NSF after administration of Gd-based contrast media. If the answer belonged to group 2 or 3, the responder was asked which contrast agent they had used. In Europe, it turned out that all patients who developed NSF had had gadodiamide within a few weeks before developing NSF. In the US, the overwhelming majority of patients who had had a gadolinium agent had had gadodiamide. Four patients may have had one of the other agents with a linear chelate (gadoversetamide and gadopentate dimeglumine). It was unclear what the rest had had; it will be checked, but it may be difficult as some of the examinations took place outside the contacted institution and some had multiple injections of various agents.

Based on the obtained information, it seems appropriate to draw the following conclusions:

(1) It is striking that many radiologists were unaware that nephrogenic systemic fibrosis may be a serious late adverse reaction to gadolinium-based contrast media despite the fact that the Food and Drug Administration issued a warning 8 June 2006 [7]. Furthermore, the warning from the vendor of gadodiamide issued 6 June 2006 [8] had not been distributed in several countries. No other vendors have issued a warning.
(2) More than 150 patients have developed NSF after exposure to a Gd-based contrast medium. The overwhelming majority (~90%) had had gadodiamide with certainty. Regarding the remaining patients it is still unknown what they had. At least three patients, who developed NSF, had gadodiamide after 8 June 2006. Two patients got it in August 2006.
(3) NSF after exposure to gadodiamide has been seen in Caucasian and Afro-Americans. It has been observed also in the United Kingdom, USA, the Netherlands, France, Belgium, Austria and Denmark. The patients were either on dialysis or had reduced renal function (highest GFR reported: 20 ml/min.).
(4) There are no reports of NSF in patients with normal kidney function. Around 200 million patients have had injections of a gadolinium-based contrast agent since the early 1980s. A population of more than 30 million patients has received gadodiamide. So, in patients without ESRD, all gadolinium-based contrast agents seem to be safe.
(5) Exposure to a gadolinium-based contrast agent cannot be documented in all patients developing NSF.

Gadodiamide is almost exclusively excreted renally and therefore has a markedly prolonged half-life in renal failure patients, including dialysis patients [9]. The molecular structure of chelate (DTPA-BMA) binding Gd is linear. Gadodiamide formulation differs from most other non-tissue specific extracellular MR imaging agents on the European market by having an excess chelate (12 mg/ml) and being less stabile [9]. The excess chelate is considered necessary because of the possibility of transmetallation with endogenous ions [9]. Transmetallation results in release of free Gd^{+++}, which is extremely toxic, but it can also cause binding of other ions. Agents susceptible to transmetallation have the largest amount of excess chelate. Thus, it seems possible that transmetallation is easier with gadodiamide than in other gadolinium-based contrast agents [10]. Of course, transmetallation is more likely to occur when gadolinium-based agents remain inside the body for a long period as is the case in patients with renal failure. Whether transmetallation plays a crucial role in the development of NSF in patients with renal failure remains unproven [1].

Several NSF cases reported by Marckmann [1] were exposed to gadodiamide earlier without developing signs of NSF. This observation suggests that gadodiamide was a necessary, but not a sufficient cause of NSF. Certain other factors must have played a role, but they were not able to identify any such cofactor. Also, the fact that NSF can develop in patients in whom it cannot be documented that they have had a gadolinium-based agent speaks in favour of a cofactor.

NSF is a serious late adverse reaction in patients with end-stage renal failure or on dialysis. Recently published reports [1, 2, 5] and a simple and rapid survey suggest a possible causal relationship between gadodiamide and NSF. Whether other gadolinium-based contrast agents can trigger the development of NSF is not yet clear. There are no published reports at the time of writing (September 2006). Careful analyses of the current data as well as new research are strongly warranted. All radiologists should be informed about this serious late adverse reaction. Cases with a positive history of exposure to gadolinium-based contrast agents should be reported to the National Medicines Agencies. The ESUR Contrast Media Safety Committee (http://www.esur.org) will appreciate receiving information. Adverse events to gadolinium contrast agents can also be reported at http://www.fda.gov/medwatch/index.html. At this stage, based on the available information, gadodiamide should not be administered to patients with renal impairment, including those on dialysis.

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