

Letters

DOI:10.2214/AJR.06.1651

WEB—This is a Web exclusive article.

Nephrogenic Systemic Fibrosis and Nonionic Linear Chelates

We read with great interest the article by Broome et al. [1] and Editor in Chief Dr. Robert Stanley's editorial [2] highlighting a possible causal relationship between gadodiamide and nephrogenic systemic fibrosis. These cases are in agreement with the findings of previous reports [3–6] and bring the total number of published cases of nephrogenic systemic fibrosis associated with gadodiamide to 47. These cases are probably the so-called “tip of an iceberg” because a significant number of unreported cases have been brought to our attention [7].

We have explored the possible mechanisms that may explain the association between gadodiamide and nephrogenic systemic fibrosis, and it becomes apparent that the stability of the chelate and the release of free gadolinium could be involved in triggering the fibrotic process [8, 9]. In recent reports, investigators have documented the presence of gadolinium atoms in skin biopsies of patients with nephrogenic systemic fibrosis [10, 11]. Of the extracellular chelates in clinical use, the least stable molecules in terms of the physicochemical properties are the nonionic linear chelates (i.e., gadodiamide and gadoversetamide) and the most stable molecules are the cyclic chelates.

We agree with Dr. Stanley's recommendation that gadodiamide use should be strictly avoided in patients on dialysis and in patients with end-stage renal disease or acute hepatorenal syndrome. However, we believe that the warning should extend to include all the nonionic linear chelates that share the same physicochemical properties as ga-

dodiamide and gadoversetamide. Although to our knowledge no data that associate gadoversetamide with nephrogenic systemic fibrosis have been published to date, there is a genuine theoretic concern that nonionic linear chelates probably can release gadolinium like gadodiamide under similar conditions. The absence of reported cases of nephrogenic systemic fibrosis associated with gadoversetamide could be partly because it is not marketed in Europe and its use in the United States is unknown. On the other hand, more than 30 million patients have received gadodiamide worldwide since its introduction in 1993 [7].

At this stage of our understanding, we believe that it would be safer to avoid the use of all nonionic linear chelates, including gadodiamide and gadoversetamide, in patients on dialysis and in those with chronic kidney disease (grade 3 or more or a glomerular filtration rate < 60 mL/min [Sadowski et al., presented at the 2006 annual meeting of the Radiological Society of North America]) or acute hepatorenal syndrome. In addition, we agree with the observation of Broome et al. [1] that prophylactic hemodialysis immediately after contrast-enhanced MRI examination does not offer any protection against the development of nephrogenic systemic fibrosis.

Henrik S. Thomsen
Sameh K. Morcos

Copenhagen University Hospital at Herlev
DK-2730 Herlev, Denmark

References

1. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR* 2007; 188:586–592
2. AJR Website. Stanley RJ. Alert: MRI contrast agent use in patients with renal failure. Available at:

www.ajronline.org. Accessed December 15, 2006

3. Evenepoel P, Zeegers M, Segaert S, et al. Nephrogenic fibrosing dermopathy: a novel, disabling disorder in patients with renal failure. *Nephrol Dial Transplant* 2004; 49:469–473
4. Grobner T. Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; 21:1104–1108
5. Maloo M, Abt P, Kashyap R, et al. Nephrogenic systemic fibrosis among liver transplant recipients: a single institution experience and topic update. *Am J Transplant* 2006; 6:2212–2217
6. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected etiological role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; 17:2359–2362
7. Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol* 2006; 16:2619–2621
8. Idée J-M, Port M, Raynal I, Schaefer M, Le Grenier S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol* 2006; 20:563–576
9. 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? *Br J Radiol* 2007; [Epub ahead of print]
10. High W, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007; 56:21–26
11. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol* 2007; 56:27–30