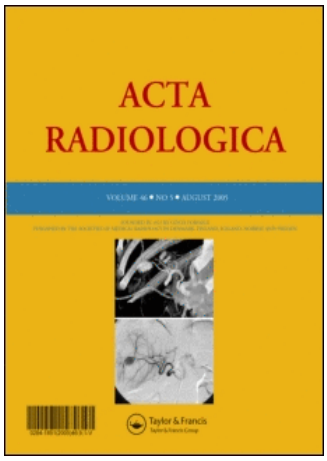

Acta Radiologica
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713394674

Enhanced Computed Tomography or Magnetic Resonance Imaging: A Choice between Contrast Medium-Induced Nephropathy and Nephrogenic Systemic Fibrosis?

To cite this Article: Thomsen, H. S., Marckmann, P. and Logager, V. B. , 'Enhanced Computed Tomography or Magnetic Resonance Imaging: A Choice between Contrast Medium-Induced Nephropathy and Nephrogenic Systemic Fibrosis?', Acta Radiologica, 48:6, 593 - 596
To link to this article: DOI: 10.1080/02841850701370717
URL: http://dx.doi.org/10.1080/02841850701370717

EDITORIAL ACTA RADIOLOGICA

Enhanced Computed Tomography or Magnetic Resonance Imaging: A Choice between Contrast Medium-Induced Nephropathy and Nephrogenic Systemic Fibrosis?

For more than 10 years, it has been believed that it would be better for the kidneys if patients with reduced renal function were referred to enhanced magnetic resonance imaging (MRI) rather than undergoing radiography (e.g., arteriography, computed tomography [CT]) with iodinated contrast media (CM) (20). It may indeed be better for the kidneys, but recently it has been shown that it may be associated with another severe adverse reaction: a potentially disabling and life-threatening disease, nephrogenic systemic fibrosis (NSF), may occur in the weeks following exposure to certain extracellular gadolinium-based contrast media (13, 19). Thus, a patient with reduced renal function (chronic kidney disease [CKD] stage 4 and 5: glomerular filtration rate [GFR] <30 ml/min) faces the unpleasant choice of risking contrast medium-induced nephropathy (CIN) after administration of iodine-based CM or NSF after exposure to gadolinium-based CM (17). This new knowledge has complicated work in the imaging department.

Patients at risk of CIN and NSF

Reduced renal function is the most important risk factor regarding CIN and NSF. The poorer the function (GFR), the higher the risk is. Therefore, it is of utmost importance to identify patients with reduced renal function. Several studies have shown that it is not cost effective to measure serum creatinine level and estimate GFR in all patients. As a matter of fact, formulas such as the Cockroft-Gault and Modification of Diet in Renal Disease (MRMD) are only useful in patients with reduced renal function (<60 ml/min). The two formulas do not provide identical results; however, they are definitely better than no estimate at all. The Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) (21) recommends that serum creatinine is measured and GFR calculated in patients: 1) with previously raised serum creatinine, 2) who take metformin for diabetes, 3) who will receive intraarterial contrast medium, and 4) who have a history suggesting the possibility of raised serum creatinine (renal disease, renal surgery, proteinuria, diabetes mellitus, hypertension, gout, and recent intake of nephrotoxic drugs). Based on these results, the radiologist can take necessary precautions and recommend the best imaging examination for an individual patient who is not on dialysis.

In patients on hemodialysis without residual renal function, CIN is irrelevant, whereas use of gadolinium-based agents that may trigger NSF, e.g., gadodiamide, would be inappropriate. When it comes to renal failure patients with some residual kidney function, CIN becomes relevant. This is particularly true for patients on continuous ambulatory peritoneal dialysis (CAPD), who depend on their remnant function. At the same time, these patients have an increased risk of NSF due to the prolonged half-life of the contrast agent. The incidence of NSF is probably higher in the CAPD population than in the hemodialysis population (3).

NSF

The administration of certain extracellular gadolinium-based contrast media may trigger the development of NSF in patients with severely reduced renal function (<30 ml/min) or those on dialysis (3). The incidence of this condition in this group of patients has been estimated to range between 3 and 6%, and onset seems to vary from a few days to 3 months after exposure (2–4, 13, 15, 16). The disease is characterized by scleroderma-like skin changes that mainly affect the limbs and trunk. The induration of skin can progress to cause flexion contracture of joints. The fibrotic changes may also affect other organs such as muscles, heart, liver, and lungs. The disease can be aggressive in some patients, leading to serious physical disability or even death (Fig. 1). Strikingly, the overwhelming majority ($\sim$90%) of reported cases occurred after administration of the nonionic agent gadodiamide (16, 18, 19). As of March 12, 2007, a total of 74 cases have been reported in the literature. Seventy-two of these had gadodiamide, one gadopentate,

informa
healthcare

DOI 10.1080/02841850701370717

and in one no exposure could be verified (2, 4, 5, 7, 8, 11–13, 15, 16, 18, 22). NSF has not been reported after gadoterate meglumine, gadoteridol, gadobenate dimeglumine, or gadobutrol, some of which have been used in many patients at imaging centers serving nephrology centers. Today, it is contraindicated to use gadodiamide in patients with reduced or absent renal function (see below).

Stability

The stability of the binding of the gadolinium ion (Gd^{+++}) within the chelate could be an important factor in the pathogenesis of NSF, and may explain the strong association between gadodiamide and this condition. The stability of the Gd-chelates is influenced by the configuration of the molecule, whether linear or cyclic, and ionicity (10, 14). In general, cyclic chelates offer better protection and binding to Gd^{+++} in comparison to linear molecules. In patients with reduced renal function, the contrast agent remains in the body for a long period; during this period, transmetallation with endogenous ions may result in free Gd^{+++}, which has been found in the skin (1, 9).

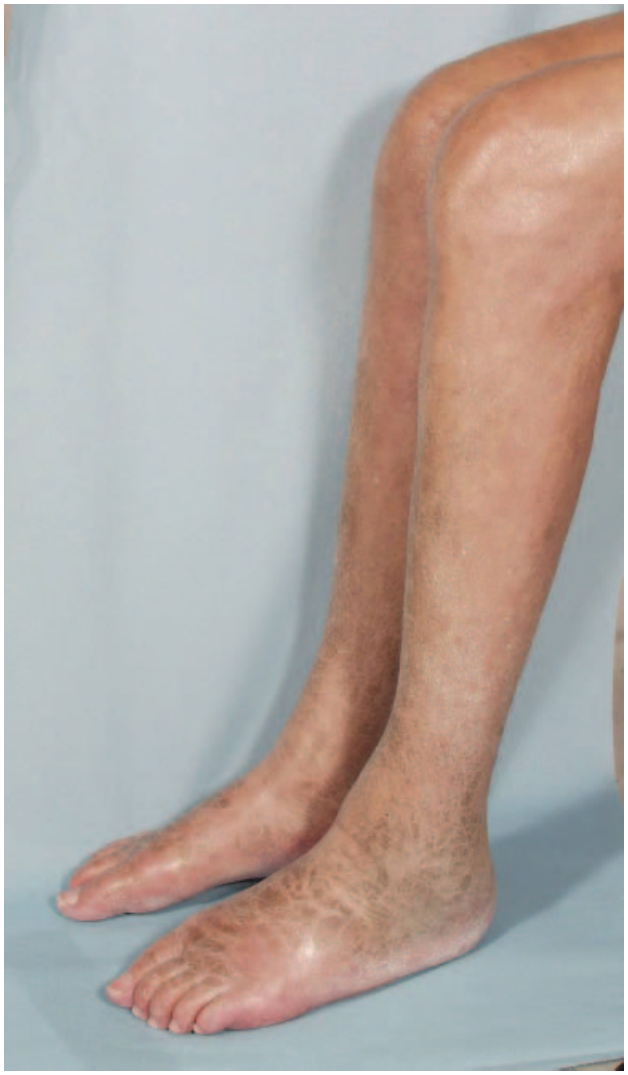

Fig. 1. Female patient aged 35 years and on regular hemodialysis for several years with late-stage severe, disabling nephrogenic systemic fibrosis primarily affecting the lower limbs and causing contractures, loss of walking ability, and wheelchair requirement. (Photo by Fie Sløk, Department of Plastic Surgery, Herlev Hospital, Denmark.)

Factors other than Gd^{+++}

In five studies, the incidence of NSF after gadodiamide has been reported to range between 3 and 6% (2, 4, 13, 15, 16). Furthermore, patients developing NSF seem to have had a larger dose of gadodiamide. There is no doubt that free Gd^{+++} is a factor stimulating the fibrocytes. Many cofactors have been proposed in various reports: increased doses of erythropoietin (EPO), metabolic acidosis, iron and ferritin, chronic inflammation, anion gap, and increased phosphate (7, 8, 11, 16). However, no universal cofactor apart from renal failure has been identified. MARCKMANN et al. (13) could not identify any exposure/event other than gadodiamide common to more than a minority of patients who developed NSF. The Center for Disease Control and Prevention found that only exposure to gadolinium-containing CM during the preceding 6 months or preceding year remained static in their case-control study of 19 cases with NSF (3). At this state of our current knowledge, it seems likely that there may be several cofactors that may increase the risk of NSF after certain gadolinium-based CM.

Contraindication

All over Europe, it is now contraindicated to use gadodiamide (Omniscan; GE Healthcare, Amersham, UK) in patients with GFR $<$ 30 ml/min, those on dialysis, or those who have had or are waiting for liver transplantation (6). Gadodiamide should be used in neonates and infants up to 1 year of age only after careful consideration.

Personal experience

At our center, 24 patients have developed NSF. Based on the clinical suspicion of gadodiamide causing NSF, we immediately stopped the use of gadodiamide in March 2006 and switched to a more stable agent. For more than 1 year, we have not seen

any new cases of NSF developing. We found it unethical to continue to administer gadodiamide to patients with normal renal function when a severe adverse reaction had been seen with this CM in a subgroup of patients. Furthermore, the control of kidney function in all patients would be troublesome, as only about 40% of our patients undergo enhanced MRI. An unexpected benefit from this decision has been that patients no longer complain spontaneously about bad taste.

Our current strategy is to employ ultrasonography, enhanced ultrasonography, unenhanced CT, or unenhanced MRI whenever possible as the primary examination in the workup of clinical problems in patients with increased risk of CIN and NSF. However, we still perform enhanced MRI in renal failure patients when other modalities are considered inadequate and if the clinical benefit of the imaging procedure outweighs the risk of NSF.

Conclusion

Both CIN and NSF are important adverse reactions to contrast media. The concern regarding CIN/NSF should not have the undesirable consequence that we do not diagnose important diseases. There are stable gadolinium-based contrast agents that have not been correlated to NSF. There are ways to reduce the incidence of CIN, which is lower after intravenous than after intraarterial injection. Any imaging procedure should be undertaken only after careful consideration of the benefits and risks of the imaging technique. This was also the case before NSF.

H. S. THOMSEN, P. MARCKMANN & V. B. LOGAGER
Departments of Diagnostic Radiology and Nephrology, Copenhagen University Hospital, Herlev, Denmark

Henrik S. Thomsen, Department of Diagnostic Radiology 54E2, Copenhagen University Hospital, Herlev, Herlev Ringvej 75, DK-2730 Herlev, Denmark (tel. +45 44 88 32 12, fax. +45 44 91 04 80, e-mail. hentho01@heh.regionh.dk)

References

1. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. J Am Acad Dermatol 2007;56:27–30.
2. Broome DR, Girguis M, Baron P, Cottrel A, Kjellin I, Kirk G. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. Am J Roentgenol 2007;188:586–92.
3. Center for Disease Control and Prevention (CDC). Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents – St. Louis, Missouri, 2002–2006. MMWR Morb Mortal Wkly Rep 2007;56:137–41.
4. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. J Am Soc Nephrol 2007:Epub.
5. Dharnidharka VR, Wesson SK, Fennell RS. Gadolinium and nephrogenic fibrosing dermopathy in pediatric patients. Pediatr Nephrol 2006:Epub.
6. EMEA Decision, February 7, 2007. Available at URL: www.esur.org. Accessed: March 14, 2007.
7. Evenepoel P, Zeegers M, Segaert S, Claes K, Kuypers D, Maes B, et al. Nephrogenic fibrosing dermopathy: a novel, disabling disorder in patients with renal failure. Nephrol Dial Transplant 2004;49:469–73.
8. Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 2006;21:1104–8.
9. 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;56:27–30.
10. Idée J-M, Port M, Raynal I, Schaefer , Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. Fundam Clin Pharmacol 2006;20:563–76.
11. Khurana A, Runge VM, Narayanan M, Greene JF, Nickel AE. Nephrogenic systemic fibrosis. A review of 6 cases temporally related to gadodiamide injection (Omniscan). Invest Radiol 2007;42:139–45.
12. Maloo M, Abt P, Kashyap R, Younan D, Zand M, Orloff M, et al. Nephrogenic systemic fibrosis among liver transplant recipients: a single institution experience and topic update. Am J Transpl 2006;6:2212–7.
13. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, et al. Nephrogenic systemic fibrosis: suspected etiological role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006;17:2359–62.
14. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast molecule an important factor in the pathogenesis of this condition? Br J Radiol 2007:Epub.
15. Roditi G, Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine A, et al. A retrospective case-control study of gadolinium-enhanced magnetic resonance imaging and nephrogenic systemic fibrosis in patients with renal failure. ECR'07; B-100.
16. Sadowski E, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. Radiology 2007;243:148–57.
17. Thomsen HS. Current evidence on prevention and management of contrast induced nephropathy. Eur Radiol 2007:in press.
18. Thomsen HS. Extracellular gadolinium agents: latest evidence in tolerance and complications. ECR'07; A-384.

19. Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. Eur Radiol 2006;16:2619–21.
20. Thomsen HS, Almén T, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology. Gadolinium-containing contrast media for radiographic examinations: a position paper. Eur Radiol 2002;12:2600–5.
21. Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). In which patients should serum-creatinine be measured before contrast medium administration? Eur Radiol 2005;15:749–54.
22. Yerram P, Saab G, Karuparthi PR, Hayden M, Khanna R. Nephrogenic systemic fibrosis: a mysterious disease in patients with renal failure – role of gadolinium-based contrast media in causation and the beneficial effect of intravenous sodium thiosulfate. J Am Soc Nephrol 2007:Epub.