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

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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 (MDRD) 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 intravascular 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 (~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,
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).

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.

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