RENAL DISEASE, GADOLINIUM-BASED MR CONTRAST AGENTS, AND NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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For access to the above paper please click here.

RECOMMENDATIONS

Section L.3.g. of guidance document: At this stage, the following guidelines are recommended when considering administering a gadolinium-based MR contrast agent (GBMCA) to patients with renal failure/disease.

The development of NSF in patients with renal disease has followed the administration of some, but not all, of the FDA-approved GBMCAs. To date, the development of NSF has been associated with the isolated prior administration of—especially, and clearly predominantly—Omniscan (at rates that exceed those associated with simple market share), but also Magnevist and OptiMARK. Nevertheless, it is thought to be appropriate to assume for now that a potential association might exist for all five FDA-approved gadolinium-based MR contrast agents until there are more definitive data to suspect otherwise.

At this time, no special treatment or handling is recommended for kidney disease patients with stage 1 or 2 chronic kidney disease (defined as presence of kidney damage with GFR > 90mL/min/1.73 m^2 or GFR between 60 and 89 mL/min/1.73 m^2, respectively). The only exception to this is that patients with any level of renal disease should not receive Omniscan for their contrast-enhanced MR examinations. This is an opinion shared by others [57] and seems prudent for all renal disease patients.

Prospectively checking patient renal function, serum creatinine level, or glomerular filtration rate prior to accepting a patient for an MR imaging or angiographic examination is specifically not required. Among the reasons for this is that roughly 90% of NSF patients seem to already be on dialysis and the majority of the remainder seem to be stage 5 or stage 4. Add to this the fact that one could avoid administering any of the agents with which NSF has been most strongly associated, and the fact that even in patients with severe or end-stage renal disease the incidence of developing NSF seems to be around 3–5%. Therefore, specific prospective hematologic screening is not felt to be warranted. Instead, it is recommended that all requests for MR be prescreened, with an additional question inquiring about the presence of a history of "kidney disease or dialysis." If the disease is present but quite mild (stages 1 or 2), modification of how the study should be performed (relative to a patient with no renal disease) does not appear to be indicated except for the avoidance of Omniscan. Conversely, if the disease is present and severe or end-stage in nature, the patient will often be aware of this level of kidney disease and will likely be under physician care for this condition. *The American Journal of Kidney Diseases* states [54]: "In general, patients with GFR <30 mL/min/1.73 m^2 should be referred to a nephrologist." Thus, selecting patients with a GFR threshold of roughly 30 mL/min/1.73 m^2 or already on dialysis (i.e., stages 4 and/or 5) as the level for which special consideration (including possibly

hemodialysis) should be given, might represent a medically reasonable approach to, and compromise on, this issue. For patients with stage 3 CKD, the potential risks associated with holding an MR imaging or angiographic examination could outweigh the potential risk of developing NSF, given the very few number of patients with putative GFR < 60 mL/min/m^2 who have been reported to have developed NSF. Further data are clearly needed to clarify the potential risk for stage 3 CKD patients given the few cases reported and the large number of patients with stage 3 CKD and who are predominantly older than age 70 who would be affected.

For all patients with stage 3, 4, or 5 kidney disease or those with acute kidney injury (AKI), it is recommended that one consider refraining from administering any GBMCAs unless a risk–benefit assessment for that particular patient indicates that the benefit of doing so clearly outweighs the potential risk(s). Similar reasoning applies equally to patients with protected regions which the gadolinium chelate might enter but from which it might not be readily cleared. An example of such a space is the amniotic fluid, in which these contrast agents can accumulate shortly after intravenous administration (personal observation and verbal communication, Emanuel Kanal, 1988).

When risk–benefit assessments warrant administration of a GBMCA to patients with stages 3–5 renal disease (moderate to end-stage) or AKI, consideration should be given to administering the lowest dose that would provide the diagnostic benefit being sought, with a half-dose, if clinically acceptable, being considered the default standard dose for such patients. The study should be monitored during its execution and prior to contrast administration to ensure that the administration of the GBMCA is still deemed necessary and indicated at that time. Postponing the examination in patients with AKI until renal function has recovered should also be considered if clinically feasible.

Standard medical practice dictates that for all patients who receive a contrast agent, the type, dose, and route of administration are to be documented in a physician order and in the report. However, patients with moderate to end-stage (stages 3–5) renal disease who are to undergo contrast-enhanced MR imaging examinations of any kind must have a written order to this effect for this agent from the radiologist approving the examination. This order must arise explicitly from the radiologist and NOT from either a referring physician or an MR imaging protocol standing order. The name of the patient, the name and specific brand of GBMCA, dose, route, and rate of administration should all be explicitly specified on the order, along with the date and signature of the requesting radiologist.

Prospective documentation of a risk–benefit assessment for each such patient is considered advisable. It is recommended that all patients identified as having moderate to end-stage (stages 3–5) kidney disease in whom a GBMCA is to be administered provide informed consent when practical, which includes a review of known risks and benefits as well as the possible availability of alternative imaging methods, if any.

As noted above, early data suggest that elevated levels of phosphate, iron, zinc, or copper might serve as efficient competitors for the" attention" of the chelate molecule [46]. These might therefore result in increased levels of free gadolinium (Gd^{3+}) ion in the patient, which might in turn increase the potential of the patient to develop NSF. Other cations such as lanthanum, now used as lanthanum carbonate (Fosrenol) for phosphorus binding in end-stage renal disease patients, could also present similar transmetallation and free gadolinium concerns. A history of multiple prior GBMCA administrations or hepato-renal disease also seems to be associated with an increased incidence of subsequent development of NSF. The existence of acidosis or active inflammatory and/or thrombotic processes as possible increased risk factors has been entertained

but has not been reproducibly established at this point. This information should be taken into account during the risk–benefit assessment of each individual patient.

For administration of GBMCAs to patients on hemodialysis, the patient is to be transported to hemodialysis immediately upon the termination of the MR imaging examination. Arrangements should be made with the treating dialysis centers to provide them with as much notice as possible prior to the arrival of that patient for hemodialys is. It is recommended that hemodialys is be initiated no later than 2 hours following the administration of the GBMCA. This applies equally to emergent or urgent gadolinium chelate administration to these patients and to inpatients as well as outpatients. An additional hemodialysis session should be considered within 24 hours of this first contrast-enhanced treatment session for the reasons noted above.

For administration to patients on chronic ambulatory peritoneal dialysis (CAPD) or continuous cycler-assisted peritoneal dialysis (CCPD) (also known as automated peritoneal dialysis, or APD), there appears to be strong reason to hesitate to administer these agents. As noted above, this process of dialysis seems to be relatively ineffective at clearing the gadolinium from the body. Thus, special caution should be exercised when deciding whether a peritoneal dialysis patient should receive gadolinium-based MR contrast agents. If it is decided that they should be administered such agents, administration of the lowest reasonable dose is strongly recommended. In the past, it had been recommended that the patient avoid periods of a dry abdomen (i.e., no dialysate in the peritoneal cavity) and that the patient be advised to begin additional dialysis self-treatments or CCPD treatments immediately upon the termination of the MR examination in which the GBMCA was administered. These suggestions seemed prudent, although the efficacy of these recommendations had not been established. However, in light of the near-total apparent ineffectiveness of peritoneal dialysis at clearing the gadolinium from the body, it may well be worth considering immediate initiation of hemodialysis in peritoneal dialysis patients who receive even a low dose of a GBMCA, or not administering the agent if clinically feasible. Investigations are ongoing at this time to attempt to assess prevalence rates of NSF in peritoneal dialysis versus hemodialysis patients; although at this time it is too early for definitive conclusions.

Historically, as a result of the high atomic number associated with GBMCAs, these agents have occasionally been administered to (especially renal failure) patients in an off-label manner for such X-ray based diagnostic tests as conventional angiography (including access angiography and fistulography) and even CT scanning. The rationale behind this practice was to avoid the administration of iodinated contrast agents to these patients and to decrease the incidence or likelihood of the development of contrast-induced nephropathy. In an attempt to prevent inadvertent GBMCA administration to renal disease patients by nonradiologists (who may at this point still not be fully aware of the issues and risks associated with GBMCAs), for now it is thought prudent to ensure that all GBMCAs are to be administered only by radiologists. If there is a request for a GBMCA to be administered by a nonradiologist to a patient for an off-label use, such as intra-arterial administration for vascular assessment in renal failure patients, this must be made in the form of a written order. All such requests must be prospectively reviewed and approved by either a radiologist or a pharmacist knowledgeable in the issues raised above, a risk–benefit assessment should be prospectively performed, and, where practical, informed consent should be provided by the patient.

For patients in whom a diagnosis of NSF has already been established, it might be appropriate to consider avoiding entirely any administration of a gadolinium-based MR contrast agent.

For patients not already on hemodialysis, the FDA's December 22, 2006 advisory [47] notwithstanding, the decision to initiate hemodialysis following gadolinium administration should

not be taken lightly. The vast majority of NSF cases developed in patients with severe or end-stage renal disease, and most were already dialysis patients. The numbers of patients with moderate, as opposed to severe or end-stage, renal disease that have been diagnosed with NSF is exceedingly small, if they exist at all. At this time, it seems reasonable to assume that as the renal function/GFR decreases from 60 mL/min/m^2 through 30mL/min/m^2, 15 mL/min/m^2, and below, the greater the concern and the greater the likelihood of subsequent NSF development. Therefore, we think that at the present time insufficient data exist to advise consideration for hemodialysis in this population of patients with moderate chronic kidney disease (stage 3) in the same manner or same perceived risk as those with severe or end-stage renal disease (stages 4 and5). The risks of initiating hemodialysis must be seriously weighed against those of developing NSF in each particular case before a decision is made one way or the other. Finally, withholding clinically indicated GBMCAs can also be associated with its own risks, which should be considered in the decision-making process for all patients with kidney disease.

Should a new diagnosis of NSF be made, it is recommended that the FDA be notified through their MedWatch program (http://www.fda.gov/medwatch/) [11] or by phone (1-800-FDA-1088), and that the international NSF registry at Yale University be notified as well (http://www.icnfdr.org) [39] to ensure that each database is kept as current as possible on this rapidly changing environment.

In the weeks and months to come, it is anticipated that there will be much further study of this issue, and that more information will be forth coming that will hopefully shed more light on this important issue [56].