Group II GBCM can be used safely for imaging in stage 4/5 CKD patients: PRO

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Primum no nocere. Few things speak louder in medicine. It seems so simple. But it is also too easy to hide behind these three powerful words. The truth is we put patients at risk every day, but we try do so with close attention to risk vs benefit. The benefit of gadolinium is obvious, but the risk has changed as gadolinium has changed over the last 20 years. In the following I will argue that risk is minimal, and that gadolinium-based contrast media can be used safely for imaging in stage 4/5 CKD patients. But first let’s review some background.

Gadolinium-based contrast media (GBCM) for magnetic resonance imaging (MRI) have been available since the late 1980s. Radiographic studies with MRI and GBCM provided improved imaging for many conditions compared to studies that utilized iodine-based contrast media (IBCM). Because the combination of MRI with GBCM was considered to be safe and specifically did not have the concerns of anaphylaxis and acute kidney injury that may be seen with IBCM, GBCM imaging became extremely popular with millions of uneventful studies being performed every year. Thus, it is rather surprising that it took almost a decade for reports to emerge of a debilitating chronic fibrosing skin condition in patients with end-stage kidney disease (ESKD). By 2000 it was realized that the disease was not limited to skin and this entity was entitled nephrogenic systemic fibrosis (NSF) describing its systemic involvement and its association with kidney failure. It still took 6 more years before this potentially fatal condition was linked to exposure to gadolinium, almost 20 years after GBCM MRI studies became available (1)!

Once the association of NSF to GBCM was made, the FDA in 2007 issued a “black box warning” for patients with “severe kidney insufficiency” (2). While reports of NSF were limited to patients predominantly with ESKD, there was not enough information to know exactly what level of kidney disease qualified for GBCM avoidance. Thus, many Nephrologists, hospitals and Radiologists took the conservative position to simply avoid GBCM in anyone with CKD 4/5. This policy persists today for the majority of clinicians involved in the decision to use GBCM. The purpose of this paper is to convince the reader that this is a flawed position and that when chosen properly, GBCM can be used safely for imaging in stage 4/5 CKD patients.

Gadolinium is a lanthanide element with paramagnetic properties that make it an excellent contrast media for MRI by significantly improving diagnostic efficacy. However, “free” gadolinium that exists as a salt, e.g. GdCl, is extremely toxic as it can interact with calcium-dependent biologic processes resulting in various cytotoxic effects. To avoid these potential toxicities, gadolinium is chelated to organic ligands. These gadolinium chelates maintain their paramagnetic properties while essentially trapping the gadolinium and preventing it from roaming free to wreak havoc on the skin and visceral organs (NSF). Most GBCM remain in the extracellular fluid and as the majority are not protein bound are rapidly excreted by the kidneys. Delayed excretion occurs in CKD and while GBCM are significantly removed with hemodialysis (HD), there is no evidence that strategies using HD after GBCM prevents NSF (3).

There are nine GBCM chelates that differ in structure of the organic chelating ligand (linear or macrocytic) and net charge (ionic or nonionic) Table 1 (4). While there is no hard and fast rule relating the thermodynamic stability (ability to prevent free circulating gadolinium) to these properties, the macrocytic GBCM are better at preventing dissociation of gadolinium from its...
chelate than linear GBCM. When NSF was first reported, the GBCM most commonly used were the linear Group I agents gadodiamide, gadoversetamide and gadopentetate. Indeed, almost all cases of NSF have been related to Group I GBCM agents (often in repeated or higher than recommended doses) and these agents are no longer marketed or available in the United States (5,6).

By 2012 there were >1500 cases of NSF reported to the FDA, but this dropped dramatically after 2008 to single digits. The reason for this decrease is likely a combination of decreased administration in CKD related to the FDA warning and a decreased usage of Group I GBCM (7,8). One problem is the difficulty in confidently relating NSF to a specific GBCM. Many patients with NSF did not have adequate documentation of the specific GBCM utilized as many of these cases presented months to years after the purported MRI study. In addition, other patients received more than one MRI study with different GBCM agents. Therefore, cause and effect needs to be limited to “unconfounded” cases in which it is certain that there was only one specific GBCM administered prior to the development of NSF. In fact, the Table 1 GBCM Group I-III designation was created by the American College of Radiology based on the risk of NSF using unconfounded cases, with NSF having been essentially limited to the use of one of the Group I GBCM agents. Since these agents are no longer available in the United States for this reason, the issue at hand is the use of Group II and III GBCM in patients with CKD 4/5.

To answer this, we must scrutinize the data regarding safety of the GBCM Groups II and III in CKD 4/5. There are essentially no unconfounded cases of NSF associated with Group II GBCM. It is noteworthy that all three of the GBCM Group I chelates that have been linked to NSF are linear. Group II GBCM consists of 4 macrocytic and one linear GBCM. So, it may come as a surprise that a linear GBCM gadobenate is included in Group II. However, the ACR designated it as such because there is extensive data showing that there is minimal to no risk of NSF with its usage. Clearly there is more to the development of NSF than just molecular structure. Gadobenate does have some hepatobiliary excretion that may play a role in its safety despite it being a linear gadolinium chelate (9-11).

There are two ways to assess the risk of Group II GBCM and NSF. One can look at cases of NSF and determine what GBCM was administered, and the other way is to assess the development of NSF in patients with CKD 4/5 that received a Group II agent. In a series of 405 patients that developed NSF, there were 23 that were related to Group II exposure, however only two of these were unconfounded (5,9,12). In a meta-analysis of 4,931 Group II GBCM administrations in patients with CKD 4/5, there were no cases of NSF conferring a risk of 0% (11). Since the risk may be greater in CKD 5 than CKD 4 a sub-analysis was performed separating these groups and found the upper limit of the 95% CI of risk to be 0.2% (1/500) for CKD 5D (ESKD on dialysis) based on zero cases in 1,849 exposed ESRD individuals, and 0.5% (1/200) for CKD 5 not receiving dialysis also based on zero cases in 732 exposed individuals. For the CKD 5 group as a whole, the 95% CI upper limit was 0.1% (1/1000), again based on zero cases. While these exposure numbers may be small relative to the potential risk, there is not even a signal that utilizing Group II GBCM in patients with CKD 4/5 puts them at any significant risk of NSF. I would reiterate, zero cases of NSF in 4,931 Group II exposures in patients with CKD 4/5.
When NSF was first recognized, Group I GBCM had the majority market share in United States. Realizing this could bias the risk assessment, a balanced market share analysis was performed and determined that Group I GBCM had a 190-fold increased rate of NSF compared to Group II GBCM (1.52 v 0.008/million average risk exposures p<0.001) (5).

There is also a dose relationship to NSF risk when Group I agents were used that is relevant to this discussion. It was not uncommon to administer a “double” or greater dose of GBCM. In one review of patients that developed NSF, only 10% had received a standard single dose (17). In another retrospective study of 74,124 patients (all levels of renal function) that received the standard single 0.1 mmol/kg of GBCM, there were no cases of NSF, while 15 of 8,997 (0.17% p,0.001) who received 0.2-0.4 mmol/kg developed NSF (14). Additionally, all cases of NSF were related to Group I GBCM. Since double doses of Groups II GBCM are not typically performed, this may play an independent role in their safety in patients with CKD.

The only Group III GBCM in Table 1 is gadoxetate, a linear ionic gadolinium chelate. It has 50% biliary excretion which may be protective in the setting of CKD. No unconfounded cases of NSF have been reported using gadoxetate but the data on its use in CKD is limited. The largest series included 85 patients with CKD 4/5 and there were no reported cases of NSF (15). Because of the limited experience using this GBCM in advanced CKD, an opinion regarding its use in advanced CKD will not be offered in this discussion.

To conclude, while NSF seemed epidemic at one-point, new cases appear to have been eliminated by avoiding the high-risk Group I linear GBCM chelates. Lower dosing may be also playing a role. Regardless, the data do not support the avoidance of Group II GBCM in patients with CKD 4/5 in whom the study is felt necessary over standard imaging using IBCM. There is also no role for increased or accelerated HD following GBCM administration.

Primum no nocere is a basic tenet of medicine, but it must be based on facts and not irrational fear.

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References:


Table 1: American College of Radiology GBCM Group designations

<table>
<thead>
<tr>
<th>U.S. Trade Name</th>
<th>Generic Name</th>
<th>Structure</th>
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<tbody>
<tr>
<td>Omniscan</td>
<td>Gadodiamide</td>
<td>Linear nonionic</td>
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</tr>
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<td>Gadoversetamide</td>
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