

Gadobenate Dimeglumine Administration and Nephrogenic Systemic Fibrosis: Is There a Real Risk in Patients with Impaired Renal Function?¹

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Purpose:

To determine the incidence of nephrogenic systemic fibrosis (NSF) in patients with renal disease who received gadobenate dimeglumine at a single medical center.

Materials and Methods:

This was an institutional review board–approved HIPAA-compliant retrospective study with waiver of informed consent. Patients either underwent dialysis or not, had an abnormal estimated glomerular filtration rate (eGFR), and underwent magnetic resonance (MR) imaging and/or MR angiography with gadobenate dimeglumine in 2010. Dialysis status, eGFR, time to transplantation, waiting list status, contrast material volume at index imaging, and additional imaging examinations between 2007 and 2014 were recorded. Clinical notes with and without integument examinations, pathologic records, and additional patient communication were evaluated for development of NSF through September 2014. Dates of latest documented integument examination and latest interaction were recorded. Mean, standard deviation, and median values were obtained, along with incidence percentage of NSF.

Results:

Of 401 patients (172 women, 229 men; mean age, 50 years), 75.5% were dialysis dependent ($n = 303$) and 24.4% ($n = 98$) were not undergoing dialysis, with a mean eGFR \pm standard deviation of 17 mL/min per 1.73 m² \pm 5.6 (range, 6–41 mL/min per 1.73 m²; median, 16.3 mL/min per 1.73 m²). Mean and median contrast material volume at index imaging were 24 mL \pm 5.7 (range, 9–45 mL). Additional contrast material volume administered was 23 mL \pm 12.9 (range, 6–64 mL; median, 20 mL; $n = 66$). One hundred twenty-six patients (31%) received a transplant; mean time to transplantation was 1.72 years \pm 1.25 (range, 0–4.46 years; median, 1.4 years). No patients received diagnoses of NSF. Mean follow-up was 2.35 years \pm 1.61 (range, 0.00–4.61 years; median, 2.75 years) with documented integument examination and 3.08 years \pm 1.36 (range, 0.16–4.66 years; median, 3.66 years) with direct patient communication.

Conclusion:

No patients undergoing peritoneal dialysis, hemodialysis, or nondialysis who experienced renal failure developed NSF after administration of gadobenate dimeglumine after more than 2 years' mean follow-up. Gadobenate dimeglumine may be safe in this population.

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Nephrogenic systemic fibrosis (NSF) is a rare but potentially fatal disorder characterized by skin fibrosis in patients with impaired renal function (1). A subset of individuals who develop NSF also develop systemic fibrosis, which may involve the myocardium, lungs, kidneys, diaphragm, and other muscles and may be fatal (2,3).

NSF was first identified in 1997 and first reported in 2000 (1). In 2006, a link between gadodiamide (Omniscan; GE Healthcare, Piscataway, NJ) and NSF was suggested (4). Subsequent investigations demonstrated gadolinium in the tissues of patients who developed NSF after the administration

of gadolinium-based contrast agents (GBCAs) (5,6). Individuals with impaired renal function are at increased risk for the development of NSF, believed to be attributed to prolonged tissue exposure to GBCAs, since these agents are primarily excreted renally (7). The mechanism that results in gadolinium stimulation of tissue fibrosis remains poorly understood but is an area of active research (8–10). Immunologic studies suggest that gadolinium results in increased expression of genes that encode proinflammatory and profibrotic cytokines (8–10).

In 2010, the U.S. Food and Drug Administration made several labeling recommendations regarding the administration of GBCAs (11). The American College of Radiology 2013 Manual on Contrast Media also provides recommendations regarding the administration of GBCAs to patients with renal failure (12). The manual classifies GBCAs into groups I–III on the basis of the association with reported cases of NSF and the duration of time that particular GBCA has been available. Group I agents (gadodiamide, gadopentetate dimeglumine, and gadoversetamide) are associated with the highest number of NSF cases. Group II agents (gadobenate dimeglumine [Multihance; Bracco Diagnostics, Princeton, NJ], gadoteridol, gadoterate meglumine [not Food and Drug Administration approved in the United States], and gadobutrol [Gadavist; Bayer Healthcare, Wayne, NJ]) are associated with few, if any, unconfounded cases of NSF. Group III agents (gadofosveset [Ablavar; Lantheus Medical Imaging, North Billerica, Mass] and gadoxetic acid [Eovist; Bayer Healthcare]) are those that have appeared on the market only relatively recently.

According to the American College of Radiology manual, administration of group I agents is contraindicated in patients at risk for NSF (12).

In 2007, our institution switched from gadodiamide to gadobenate dimeglumine in response to reports of individuals who developed NSF after administration of gadodiamide (7). Subsequent publications have documented a 0% incidence of NSF after administration of gadobenate dimeglumine, including patients with renal failure (7,13,14). At our institution, we routinely perform magnetic resonance (MR) imaging and MR angiography of the abdomen and pelvis in patients with end-stage renal disease (ESRD) as part of a pretransplant recipient evaluation to screen for malignancy and vascular abnormalities that could compromise a future renal transplant (15). This provides a large cohort of patients with ESRD who are exposed to gadobenate dimeglumine. The purpose of this investigation was to retrospectively determine the incidence of NSF through long-term follow-up of individuals with ESRD, including patients not undergoing dialysis and those undergoing peritoneal dialysis or hemodialysis who received gadobenate dimeglumine.

Advances in Knowledge

- No patients with impaired renal function were determined to have nephrogenic systemic fibrosis (NSF), regardless of dialysis type (peritoneal dialysis [$n = 57$] vs hemodialysis [$n = 246$]).
- No patients with impaired renal function were determined to have NSF after receiving multiple doses of gadobenate dimeglumine (66 patients, mean volume of 47 mL).
- No patients with impaired renal function were determined to have NSF in either the group not dependent on dialysis ($n = 98$, mean estimated glomerular filtration rate [eGFR] of 17 mL/min per 1.73 m²) or the group dependent on dialysis ($n = 303$; eGFR not applicable).
- No patients with impaired renal function were detected to have NSF after a mean of more than 2 years' follow-up (range, 0.00–4.61 years) with a documented integument examination only and a mean of more than 3 years' follow-up (range, 0.16–4.66) with direct patient communication (with or without a documented integument examination), suggesting that gadobenate dimeglumine may be safe to administer in this patient population.

Implication for Patient Care

- Contrast material–enhanced MR imaging with gadobenate dimeglumine in patients with impaired renal function may be safe and should remain a viable imaging option in this patient population.

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Abbreviations:

eGFR = estimated glomerular filtration rate
ESRD = end-stage renal disease
GBCA = gadolinium-based contrast agent
NSF = nephrogenic systemic fibrosis

Author contributions:

Guarantors of integrity of entire study, S.B.N., A.S., K.L.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, all authors; clinical studies, S.B.N., M.T.O., A.S., K.L.C.; statistical analysis, S.B.N., M.T.O., A.S.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

Materials and Methods

Institutional review board approval was obtained, and a waiver of informed consent was granted for this Health Insurance Portability and Accountability Act-compliant retrospective study. No industry support was provided for this study. The radiology report database in our department was searched to identify patients at least 18 years of age who underwent a combined MR imaging and MR angiography examination of the abdomen and pelvis with and without contrast material administered in the same session, with either “ESRD” or “renal transplant evaluation” listed in the clinical indication field of the report. Gadobenate dimeglumine was administered at a dose of 0.05 mmol per kilogram of body weight and 0.10 mmol/kg for MR imaging and MR angiography of the abdomen and pelvis, respectively, for a total off-label dose of 0.15 mmol/kg for all studies per our institutional protocol, which is higher than the approved dose of 0.10 mmol/kg. The search was limited to January 1, 2010, through December 31, 2010, to allow for longer-term follow-up of patients.

Each electronic medical record was reviewed by one board-certified radiologist (S.B.N., K.L.C., A.S., C.C.M., and M.T.O., with 3, 3, 4, 6, and 8 years of experience, respectively). The following factors were recorded: patient sex, age at the time of index imaging examination, and volume and type of GBCA administered. The estimated glomerular filtration rate (eGFR) closest to the date of the index imaging study was recorded only for patients not undergoing dialysis, since patients undergoing dialysis do not have an accurate filtration rate and by definition are classified as having ESRD. eGFRs were calculated according to the Modification of Diet in Renal Disease study (16). The dialysis status of patients at the time of the index imaging examination was also recorded, along with the type of dialysis (hemodialysis or peritoneal dialysis).

All additional contrast-enhanced MR examinations of any body part (eg, the brain, spine, abdomen, or joints) that occurred between 2007 and 2014

were recorded for each patient, along with the volume and type of GBCA administered. Records prior to 2007 were unavailable in the electronic database. Electronic medical records were also reviewed to determine whether these patients continued to have impaired renal function at the time of these additional imaging sessions. Volume of contrast material administered during these additional imaging examinations (performed either before or after the index imaging study between 2007 and 2014) was only documented if the patient had continued to undergo dialysis or had an eGFR of less than 60 mL/min per 1.73 m² without dialysis if the patient had already received a transplant at the time of additional imaging. Transplant status and time to transplantation were recorded for each patient in those who received a transplant to specifically evaluate the proximity of transplantation to the date of the index imaging study.

To determine whether any patients developed NSF, each patient's electronic medical record was reviewed, including review of the pathology database, transplantation notes, progress notes, consultation notes (including dermatology and rheumatology notes), and patient communications (eg, documented phone calls) for the mention of NSF or NSF-like symptoms, such as cutaneous lesions or skin thickening. The date of the last note that documented a physical examination with specific evaluation of the integumentary system was recorded. Specifically, these notes were required to have a separately filled in and manually selected field labeled “integument examination” or “skin examination” under the physical examination section and/or had to clearly include a description of any positive or negative skin findings under the physical examination section, without a separate heading. Additionally, the date of the latest direct communication with patients, including clinical visits, physical examinations, and documented phone conversations with the patient who did not specifically mention a skin evaluation, were also recorded in an attempt

to obtain any delayed self-reported symptoms beyond a formal integument examination. The number of days between index imaging examination and the date of the latest note documenting an integument examination and the date of latest communication with the patient were calculated. Patients were excluded if there was no follow-up beyond 60 days or if patients not undergoing dialysis had an eGFR of more than 59 mL/min per 1.73 m² at the time of index imaging to include patients with stage 3 and higher chronic kidney disease.

Statistical analysis included calculation of medians, means, and standard deviations for the following measures: eGFR, length of time between eGFR and index imaging examination, volume of contrast material administered during the index imaging examination, volume of contrast material administered for additional imaging, total cumulative contrast material volume, length of follow-up with integument examination, length of follow-up with direct patient communication, and time to transplantation (if applicable). Incidence percentage of NSF was calculated in the study population.

Results

We identified 573 patients who received gadobenate dimeglumine for the clinical indication of evaluation for renal transplant or ESRD between January 2010 and December 2010. One hundred seventy-two patients were excluded because of insufficient follow-up beyond the date of imaging (less than 60 days) or because of eGFR higher than 59 mL/min per 1.73 m². The study population consisted of 401 patients, including 229 men and 172 women with a mean and median age \pm standard deviation of 50 years \pm 13 (range, 18–77 years).

Of the 401 patients, 303 patients (75.5%) were dialysis dependent (246 hemodialysis, 57 peritoneal dialysis), and 98 patients (24.4%) were not dialysis dependent. Of the 98 patients who were not dialysis dependent, 94 had chronic renal failure and four had acute renal failure at the time of the index

Volume of Contrast Material Administered, Duration of Follow-up, and NSF Incidence in Patients with Renal Failure Who Received Gadobenate Dimeglumine

Dialysis Type	No. of Patients	eGFR (mL/min per 1.73 m ²)	Mean Dose Administration for Index Imaging Study (mL)	Mean Total Cumulative Dose (including index imaging study) (mL)	Mean Follow-up with Integument Examination (y)	Mean Follow-up with Direct Patient Communication (y)	Incidence of NSF (%)
No dialysis	98	17	24 ± 6.1	29 ± 13.3	2.6 ± 1.5	3.5 ± 1.0	0
Peritoneal dialysis	57	NA	24 ± 5.7	28 ± 10.6	2.6 ± 1.6	3.2 ± 1.4	0
Hemodialysis	246	NA	24 ± 5.5	28 ± 10.9	2.2 ± 1.7	2.9 ± 1.4	0
Total	401	NA	24 ± 5.7	28 ± 11.5	2.4 ± 1.6	3.1 ± 1.4	0

Note.—Unless indicated otherwise, data are means ± standard deviations. NA = not applicable.

imaging examination per electronic medical record clinical notes.

Mean eGFR for patients not undergoing dialysis ($n = 98$) was 17 mL/min per 1.73 m² ± 5.6 (range, 6–41 mL/min per 1.73 m²; median, 16.3 mL/min per 1.73 m²); most of these patients (93%) had an eGFR of less than 30 mL/min per 1.73 m² ($n = 91$). The mean time interval between recorded eGFR and the index imaging examination was 12 days ± 76 (range, 268–476 days; median, 22 days).

The mean and median volume of gadobenate dimeglumine received per patient was 24 mL ± 5.7 (range, 9–45 mL) during the index imaging examination (Table). Sixty-six patients underwent additional contrast-enhanced MR imaging between 2007 and 2014 at our institution. Volume of additional gadobenate dimeglumine administered during additional imaging that occurred between 2007 and 2014 ranged from 6 to 64 mL (mean, 23 mL ± 12.9; median, 20 mL). The mean total cumulative dose of gadobenate dimeglumine for those 66 patients was 47 mL ± 13.4 (range, 21–85 mL; median, 45 mL), including the dose received from the index imaging study.

Approximately 31% of patients went on to receive a renal transplant ($n = 126$), with the mean time to transplantation being 1.72 years ± 1.25 (range, 0–4.46 years; median, 1.4 years). Of the transplant recipients, 65 patients were undergoing hemodialysis, 24 patients were undergoing peritoneal dialysis, and 37 patients were not undergoing dialysis prior to receiving the

transplant. Only three patients received a transplant within 1 week of the date of the index imaging study. Two hundred seventy-five patients (68%) did not receive a transplant, and of those patients, 100 (36%) remained active on the waiting list.

No patients received a diagnosis of NSF as documented by means of chart review (0% incidence). The mean length of follow-up was 2.35 years ± 1.61 (range, 0.00–4.61 years; median, 2.75 years) with a documented evaluation of the integumentary system. The mean length of follow-up with documented direct patient communication with or without an integument examination was 3.08 years ± 1.36 (range, 0.16–4.66 years; median, 3.66 years) (Table). Only six of these 401 patients (1.5%) had direct communication follow-up that consisted of self-reported symptoms alone (ie, phone call), and 4.0% ($n = 16$) solely had a clinical visit or physical examination without a documented integument examination during follow-up visits. At some point in their follow-up care, 94.5% of all patients ($n = 379$) underwent a formal integument examination.

Discussion

According to the American College of Radiology manual, if the benefits of the diagnostic information obtainable in the contrast-enhanced MR examination outweigh the risk of the patient developing NSF, administration of a GBCA that is not a group I agent (such as gadobenate dimeglumine) could be considered

(12). However, weighing the benefit of obtaining diagnostic information against the risk of developing NSF can be challenging, especially since there is sparse published literature to adequately quantify the actual risk of NSF in patients with renal failure. Our study provides some reassurance regarding the safety of gadobenate dimeglumine in individuals with renal failure, since we found a 0% incidence of NSF in 401 patients after a mean of more than 2 years of follow-up with a documented skin examination and a mean of approximately 3 years of follow-up with direct patient communication.

Our study is consistent with prior publications, although the duration of follow-up in our study was longer than that in prior studies (7,14) and had a larger patient cohort (13). For example, Altun et al reported a 9-month follow-up for 402 patients undergoing dialysis and 147 at-risk patients with renal disease (14), and Martin et al reported a 10-month follow-up for 94% of 784 study patients with no mean follow-up reported (7). Wang et al reported a 6–36-month follow-up for a smaller cohort of 36 patients with impaired renal function similar to that in our study (13).

According to data presented from the NSF registry, approximately 80% of individuals who developed NSF were undergoing either peritoneal dialysis or hemodialysis (17). Approximately 75% of our study population was undergoing peritoneal dialysis or hemodialysis, with 57 patients (14%) exclusively undergoing peritoneal dialysis. These

data expand on prior reports by documenting the type of dialysis for dialysis-dependent patients. Prior studies have shown a decreased rate of gadolinium excretion via peritoneal dialysis, with only 69% of gadolinium excreted after 22 days of continuous peritoneal dialysis (18). In comparison, mean excretory rates of gadolinium are 78%, 96%, and 99% in the first to third hemodialysis sessions, respectively (19). This confers a theoretical higher risk of NSF in patients with peritoneal dialysis. In a small case series of documented patients with NSF reported by the Center for Disease Control, it was shown that patients undergoing peritoneal dialysis had higher estimated NSF rates than those undergoing hemodialysis (20). In our study, no patients undergoing peritoneal dialysis who received gadobenate dimeglumine developed NSF. To our knowledge, this is the largest series of peritoneal dialysis-dependent patients who received gadobenate dimeglumine reported in the literature.

We also observed a 0% incidence of NSF in 98 patients with ESRD (mean eGFR, 17 mL/min per 1.73 m²) who were not dialysis dependent. Our results are consistent with those of Wang et al, who reported no cases of NSF after a switch to gadobenate dimeglumine, including 36 patients with an eGFR of less than 30 mL/min per 1.73 m² who received gadobenate dimeglumine (13).

Approximately 31% of the study population ($n = 126$) received a renal transplant, with the mean time to transplantation being 1.72 years. Only three of these patients received a transplant within a week of the index imaging examination, possibly allowing for clearance of any remaining gadolinium from the index imaging study due to newly restored renal function. Therefore, it is unlikely that the time to transplantation contributed to the low incidence of NSF in this study, since most of the study population (99%) either did not receive a transplant or received a transplant well beyond the time that gadolinium would have already been cleared if the patient was undergoing dialysis.

It has been suggested that the cumulative dose of contrast material may

be a factor in the development of NSF (21,22). In prior studies, investigators have evaluated dose ranges between 0.05 and 0.15 mmol/kg gadobenate dimeglumine in at-risk patients, with investigators in one study limiting total volume of dose to 20 mL (13). In our study, patients routinely received an off-label dose of 0.15 mmol/kg of gadobenate dimeglumine, with the index imaging examination mean dose volume of 24 mL. Additionally, 66 patients underwent multiple contrast-enhanced studies with gadobenate dimeglumine, with a mean cumulative dose of 47 mL (range, 21–85 mL) between 2007 and 2014. There were no findings of NSF in this subset of patients, which could be used to argue against the cumulative dose of contrast material being a significant factor in developing NSF. However, additional studies with a larger patient population are needed for further evaluation.

As of 2013, approximately 85% of unconfounded cases of NSF were associated with gadodiamide, 13% were associated with gadopentetate dimeglumine, and a few were associated with gadoversetamide (14,23,24). A posited reason for the development of NSF in individuals exposed to those specific agents has been that they are of a relatively less stable formulation (25,26). To our knowledge, no unconfounded cases of NSF after exposure to single-agent gadobenate dimeglumine have been reported. Potential contributing factors to its higher safety profile include a relative higher relaxivity, which allows for relatively lower doses of contrast material administration (7). In addition, the partial hepatic clearance of gadobenate dimeglumine may lead to a higher safety profile in patients with renal failure (27).

At our institution, we routinely administer up to three individual lifetime doses of 0.15 mmol/kg of gadobenate dimeglumine to individuals with impaired renal function. All patients are screened for a history of dialysis, and any patient who receives GBCA is scheduled for dialysis within 36 hours (preferably within 24 hours).

Our study is limited by its retrospective nature. As such, we were

unable to call each patient and directly ask about NSF symptoms; we therefore relied solely on a thorough chart review for the detection of NSF. In addition, clinical notes with a dedicated skin examination, performed by physicians who are trained to detect NSF, along with those who may not have been specifically trained to detect NSF, were included to calculate the longest length of follow-up. At our institution, however, there are additional safeguards in place for the detection of NSF that may not have been captured by our chart review. This includes a dedicated annual interview for those active on the transplant waiting list in which any skin concerns are specifically addressed though may not always be documented in the electronic medical record, especially when negative. In addition, our posttransplant patient population routinely undergoes dedicated integument examinations by specialists who are familiar with NSF, since these patients have a higher incidence of both benign and malignant skin lesions, with the subsequent need for increased monitoring (28–30).

Additional limitations of this study include the possibility that some patients may have received care outside of our institution, and we did not have access to outside medical records, unless they were scanned into our institution's electronic medical record. Also, we could not determine the percentage of dialysis-dependent patients who underwent dialysis within the recommended 3-day period after administration of gadobenate dimeglumine. If patients underwent dialysis at an outside facility, this information was not available in the electronic medical record. Last, the time interval between eGFR and the date of imaging was somewhat variable, such that the recorded eGFR may not reflect the exact eGFR at the time of imaging in the nondialysis patient population. However, all patients were confirmed to have renal failure.

An inherent statistical limitation exists, since a power calculation could not be performed for this study because the incidence of NSF in patients with renal failure who were exposed to gadobenate dimeglumine is unknown (no

unconfounded cases were reported). However, a post hoc power calculation demonstrated that our sample size of 401 patients would be adequate to detect at least a 0.5% or 1% incidence of NSF with a statistical power of 0.85 and 0.98, respectively. While the overall incidence of NSF with any GBCA in the entire population is an extremely rare occurrence, prior studies have shown much higher incidences with other GBCAs that are known to be associated with NSF when evaluating patients with a similar profile to our study population of patients with renal disease. For example, larger studies have shown incidence rates of 2.6%–3.0% in the renal failure population exposed to gadodiamide (7,14), although a smaller study reports an incidence rate as high as 18% (31). Similarly, the reported incidence of NSF with gadopentetate dimeglumine exposure in patients with renal disease ranges from 1% to as high as 18% (32,33). The wide range of reported incidences may be due to the differences in contrast material dose administration, varying chronic kidney disease stages, detection techniques, and length of patient follow-up among studies.

In conclusion, we found a 0% incidence of NSF after administration of gadobenate dimeglumine to individuals with renal failure after a mean of more than 2 years' follow-up. Our work contributes to a growing body of literature that allows for a more comprehensive understanding of the safety profiles of different GBCAs and the risk of NSF. Specifically, our data suggest that gadobenate dimeglumine administration may be safe in patients with impaired renal function, including those undergoing peritoneal dialysis, hemodialysis, or no dialysis.

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