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Decreased Incidence of NSF in Patients on Dialysis After Changing Gadolinium Contrast-Enhanced MRI Protocols

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Abstract

Purpose—To retrospectively determine the incidence of nephrogenic systemic fibrosis (NSF) in patients on dialysis administered either a lower dose high-relaxivity linear gadolinium-chelate, gadobenate dimeglumine (Multi-Hance, MH), compared to a standard dose linear gadolinium chelate, gadodiamide (Omniscan, OM).

Materials and Methods—This study was Health Insurance Portability and Accountability Act (HIPAA)-compliant and Institutional Review Board (IRB)-approved. As per institution standardized contrast-enhanced magnetic resonance imaging (MRI) protocols, patients on dialysis were imaged using either MH, between 2/2007 to 9/2008, or OM between 10/2003 and 1/2007. Rates of NSF were compared using 95% score-based confidence intervals (CI). The Wilcoxon rank sum test was used to test similarity/difference between contrast doses given to each patient group.

Results—Overall, 312 patients on dialysis received OM and eight (2.6%) developed NSF (95% CI: 1.30%–4.98%). In all, 784 patients on dialysis received MH at a mean cumulative dose of 0.11 mmol/kg (0.05–0.75 mmol/kg) and no cases of NSF were identified (upper 95% confidence bound of 0.45%). The mean cumulative dose of OM was 0.16 mmol/kg (0.1–0.9 mmol/kg) for all patients and 0.28 mmol/kg (0.1–0.8 mmol/kg) for the patients with NSF. The median OM dose was greater in patients who developed NSF ($P = 0.03$), and was greater than the median MH dose ($P < 0.005$).

Conclusion—NSF incidence in at-risk patients receiving contrast-enhanced MRI can be reduced after changing contrast administration protocols that includes changing the type and dose of contrast agent.

Keywords

NSF; ESRD; dialysis; gadolinium; MRI

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Gadolinium-based contrast agents (GBCAs) are a family of gadolinium formulations that are used to improve the diagnostic quality of magnetic resonance imaging (MRI) scans. Overall, GBCAs have been found to be extremely safe, with about 200 million administrations worldwide (1) and, until recently, no known serious complications.

Nephrogenic systemic fibrosis (NSF), which was first recognized in 1997 and described in the literature in 2000 (2), is considered to be a systemic fibrotic disorder that clinically presents with nonspecific sclero-derma-like skin lesions (2–4). Collagen is deposited in tissues and the cutaneous findings of NSF include extensive thickening and hardening of the skin, hyperpigmentation, plaques, papules, and nodules (2–4). The severity of NSF varies, and has ranged from reports describing a transient disease, with clinical improvement, to severe progression and association with joint contractures, loss of ambulation, and even increased mortality risk (5–7). Deaths have been attributed to complications related to limited mobility and respiratory failure (6,7).

In early 2006 a possible relationship between GBCAs and NSF was reported (8). In addition, gadolinium has been detected in tissues affected by NSF (9). GBCAs are eliminated primarily by renal excretion and patients with impaired renal function have extended elimination times that can increase from a normal of ≈ 6 hours (equal to 5 times the half-life of the agent in the patient's blood) for most agents, to up to several days in patients with endstage renal disease (10–15). The delayed excretion and prolonged tissue exposure to circulating GBCA is likely a key factor in the relationship between renal insufficiency and NSF (12).

There are several different GBCAs available. Of particular note, the majority of NSF cases have been associated with one of the agents, gadodiamide (Omniscan, OM; GE Healthcare, Milwaukee, WI) (16,17). This agent is among the least stable formulations and stability of the chelate has been proposed as an important factor in relation to the development of NSF in patients unable to clear the agent through their kidneys. It has been noted that few if any of the reported NSF cases have occurred in relation to the most stable macrocyclic or higher relaxivity agents (15,17,18). A concern has been that most of the peer-reviewed reports on NSF have been from large centers using predominantly or exclusively OM (14,17,18). The need to similarly review and report NSF incidence in at-risk patients from centers using other agents than OM is viewed as a current urgent need in order to better understand the relative incidence or risks between the different GBCA formulations.

Our center has a large and expanding renal transplantation program and has used contrast-enhanced MRI increasingly as an important diagnostic methodology in patients on dialysis during assessments performed prior to transplantation to evaluate for neoplastic processes and vascular diseases. We have been primarily a single-agent user at any given time, particularly for patients with advanced renal disease, and have the capacity to track the type of GBCA given to these patients. In addition, we have previously used OM and then converted our protocols to use the higher relaxivity lower dose agent gadobenate dimeglumine (MultiHance, MH; Bracco Diagnostics, Milan, Italy) in response to the growing number of NSF cases with OM. MH has only been reported in association with two patients with NSF, but both associated with multiple contrast agent exposure: 1) a patient who received OM a week after MH and then developed NSF a month after the gadodiamide dose; and 2) a patient who received an unknown amount and type of GBCA followed by doses of MH greater than 0.1 mmol/kg at 48 and 39 days before developing NSF (17). However, to our knowledge, there have been no unconfounded published accounts of NSF in patients exposed to MH. Furthermore, MH has a higher chelate stability than OM. Hence, with the

higher relaxivity, greater potential safety profile, and higher chelate stability, we hypothesized that MH may provide a safer alternative to OM.

The purpose of this study was to compare the incidence of NSF in patients on dialysis, representing an at-risk population, who have been exposed to different imaging protocols including use of either standard dose OM or half-dose MH.

MATERIALS AND METHODS

This trial was approved by our Institutional Review Board (IRB) and was Health Insurance Portability and Accountability Act (HIPAA)-compliant.

Patients

To focus only on patients with the highest risk for developing NSF, patients were selected for severe renal insufficiency as identified by chronic dialysis dependency. The electronic radiology information system was searched for patients who had received contrast-enhanced MRI studies and this list was cross-referenced against orders generated by the renal transplant center and found on our transplantation center electronic medical records database. This search created a new database of patients who were on dialysis and underwent contrast-enhanced MR scans as part of a pretransplantation evaluation. The MRI scans (MRI or MRA) and the amount of GBCA was determined from reviewing each record individually. The medical records and the dermatopathology records were also reviewed for each case individually. The inclusion criteria were designed to capture all patients who were exposed to a GBCA while on routine dialysis at the time of MR scan(s). Institutional policy is that patients on dialysis have dialysis arranged within 1 day of the scan. Our institution safety committee policies and procedures specifically approved the use of GBCA administration in patients with renal disease when the benefits of enhanced MRI outweigh the risks of avoiding the test or using alternatives. Patients were included in this study only if clinical follow-up was available beyond 6 months after the last contrast-enhanced MRI. For exclusion criteria, all patients were reviewed to determine if there was cross-over between types of GBCA administration; there were no patients who fell into this category.

GBCA Utilization

Patients on dialysis were imaged using intravenous OM from 10/2003 through 1/2007. OM had been administered either at a standard dose of 0.1 mmol/kg of body weight or at a dose of 0.2 mmol/kg in angiographic examinations. Based on changed institutional policies and procedures in response to concerns over NSF, patients with endstage renal disease on routine dialysis who had a contrast-enhanced MRI, starting from 2/2007 and through 2/2009, were administered MH intravenously. This agent was given either as a standard-dose of 0.05 mmol/kg of body weight or at a dose of 0.1 mmol/kg in angiographic examinations. The incidence of NSF in these two groups of patients was compared. For each patient the dose of either agent was recorded. For patients who received multiple doses of either agent, both the individual and cumulative doses were determined.

Statistical Analysis

This study is a retrospective study of two patient cohorts studied in two different time intervals during which first OM and then MH was utilized. To determine if the rate of NSF cases was different between the two contrast agents, we constructed 95% score-based confidence intervals (CIs) for the proportion of NSF cases in each group of subjects. We considered nonoverlapping CIs as evidence for a difference in the incidence proportion. Wilcoxon rank sum test was used to test the following null hypotheses: 1) that the median

OM dose was equal in patients who did and did not develop NSF, and 2) that the median OM dose was equal to the median MH dose.

RESULTS

From October 2003 to February 2007, intravenous OM was administered to 312 dialysis-dependent patients (Table 1). In this group, eight patients (2.6%) developed NSF. The distributions of cumulative doses of OM with NSF and without NSF are shown in Figs. 1 and 2, respectively. The 95% CI was 1.30%–4.98%.

These eight patients have been previously included as part of an early report on NSF occurrence in association with GBCA (23). In this study, we extend the prior analysis with post-NSF diagnosis follow-up and more detailed chart review. Of particular note, no additional NSF cases were identified throughout the extended review window (Table 1). Table 2 summarizes the characteristics of the patients with NSF, the methods of treatment for NSF, and cumulative doses of OM. Of these patients with NSF on hemodialysis, the average delay to dialysis after OM exposure was 2 days, and this interval ranged from 1–3 days.

The patient with the highest cumulative dose of 0.8 mmol/kg developed mild skin changes that were not treated specifically. A patient with indurated plaques and weakness had physical therapy performed, with the patient indicating improved symptoms of “weakness.” This patient’s main concerns remained focused on symptoms of nausea and vomiting, attributed to previously diagnosed chronic mesenteric ischemia. This patient was transferred to hospice due to deconditioning from poor nutrition. Topical steroid cream was applied in two other patients, and it was noted that the skin findings attributed to NSF remained stable or improved, with no indication of debilitation from NSF.

Three patients had other serious comorbid conditions that were not attributed to NSF. A 67-year-old male died 2 months after diagnosis of NSF from pulmonary edema secondary to renal failure. The etiology of his renal disease was obstructive uropathy secondary to nephrolithiasis. A 70-year-old male with glomerulonephritis died from exacerbation of congestive heart failure, 18 weeks after NSF diagnosis. Another NSF patient developed metastatic renal cell carcinoma, diagnosed on contrast-enhanced MRI, originating within the renal transplant. In all of these patients NSF was not considered a major component to clinical management.

From 2/1/07 to 2/15/09, 784 patients with end-stage renal disease received intravenous MH for gadolinium-enhanced MRI or MRA (Table 1). The proportion of NSF cases was 0% and the upper bound of the 95% CI was 0.45%. The distribution of cumulative doses of OM and MH is summarized in Fig. 2. Of the 784 patients, 94% of patients had greater than 10 months of follow-up, and 6% had 8–10 months of follow-up, with no patient having less than 6 months clinical follow-up for development of skin lesions in keeping with NSF.

The mean cumulative doses of OM and MH are provided in Table 3. Since the distributions of patients in the various groups are not normal, nonparametric statistical analysis with the Wilcoxon test was used to compare the median cumulative doses. The median OM dose was not equal in patients who did and did not develop NSF ($P = 0.03$). The median cumulative dose of the total OM population was not equal to the median MH cumulative dose ($P < 0.005$). We could not ascertain any systematic changes in dialysis techniques, drug utilization, filters, or other elements related to medical treatment of the patients over the period of study.

The upper bound of the CI for the incidence of NSF cases with MH (0.46%) was much less than the lower bound of the CI for the incidence of cases with OM (1.3%). Thus, we are 95% confident that the proportion of NSF cases was lower in the group that received MH when compared to the group that received OM (Fig. 3).

DISCUSSION

At our institution we determined the incidence of NSF in patients with endstage renal disease to be significantly reduced from 2.6% to 0.0% after changing our contrast enhancement procedures from OM, at routine doses, to MH, at half the OM doses, per contrast-enhanced MRI or MRA procedure. By taking advantage of the higher relaxivity properties of MH a significantly lower dose was used on average when compared to OM.

NSF is known to be a disease affecting patients who have renal disease and impaired renal function. Although risk has been attributed to those patients with a renal function described by a glomerular filtration rate (GFR) of less than 30 mL/min (classified as at least moderately severe, Stage IV disease), NSF is primarily seen in patients with less than 15 mL/min (severe, Stage V disease) and mostly in patients on dialysis (1,11,13,16). Our study concentrated on patients on dialysis in order to isolate a well-documented population of patients who have the highest possible risk for developing NSF after GBCA exposure and who are easily identified for tracking purposes.

It appears that most cases of NSF will manifest clinically within 3 to 6 months of GBCA exposure, and all of our patients with NSF were documented within 3 months of GBCA exposure. We had a minimum of 6 months follow-up for any patient, but with the vast majority of cases having longer than 1 year beyond the time of contrast exposure and time of review for this report. The sensitivity for NSF disease detection can only have increased at our center as knowledge of this disease improved and vigilance with complete physical examination for skin lesions, documentation, and case reporting has become more systematic and formalized at our center. This transition has occurred since the end of 2006, when the relationship between GBCA and NSF became apparent. Despite an increased clinical vigilance, we noted a decline in NSF incidence.

It has been suggested that more severe clinical manifestations of NSF may arise in relation to delayed dialysis (11) but there are no data yet to show that the incidence of NSF may be altered by more aggressive multiple dialysis. The 2.6% incidence of NSF at our center in patients exposed to OM is in keeping with the range reported by other centers (16). The observation that none of our NSF patients on dialysis developed severe debilitating disease may be related to our long-standing policy of having dialysis performed as soon as possible after a contrast-enhanced MRI. This policy had been in place at our center throughout the period included in this retrospective study. The measurement of precise time-delay between GBCA exposure and dialysis for every patient was outside the constraints of this study. It may be possible that with greater vigilance, after realization of the link between NSF and GBCAs, that our patients had shorter time delays to dialysis after a contrast-enhanced MRI. While we were unable to show this result from our data, it remains another potential variable that may impact the incidence, or severity, of NSF.

The dose of GBCA and incidence of NSF has been thought to be related (11,13,18). It has been suggested that not only is the one-time dose related to the risk of developing NSF, but that the cumulative dose of contrast may be considered a risk factor (11,13,18). It remains unclear as to how long after a GBCA dose the effects of the exposure may persist and be additive to subsequent doses.

MH has approximately twice the relaxivity compared to OM (19), with the potential to lower the administered dose while preserving diagnostic effectiveness. We therefore modified our protocols, administering half the typical dose of OM (in moles per patient body weight) for MRI and MRA. In order to provide this information, we opted to review and show the dosing history for each patient with regard to single-study dose and cumulative dose in order to make comparisons between our dialysis population exposure to one or the other GBCA. Comparing diagnostic quality of our MRI results achieved using different contrast agents was not within the scope of our study. Diagnostic quality of the two gadolinium agents appears to be comparable when OM is administered at 0.1 mmol/kg, and MH at 0.05 mmol/kg, based on both in vitro in vivo comparisons (20–24).

Since this study was not a randomized clinical trial, the reduction in NSF cannot be definitely attributed to the specific contrast agent or dose of administration. We cannot state to what extent the reduction in NSF incidence in our study is attributable to a difference in the formulation of the agents, including relative chemical reactivity of the gadolinium chelates with other species, or to the reduction in dose used with the higher relaxivity agent. The role of increased vigilance and shorter time to dialysis may be another unmeasured variable. However, with increased vigilance there has also been implementation of integument examinations that may increase clinical sensitivity for NSF over the latter phase of this study. The increase in the rate of renal failure patients scanned was due to growth in our renal transplant program and increased use of MRI for preoperative evaluation of transplant recipients. We could not delineate a change or bias in the patient cross-section regarding types of medications, medical conditions, or dialysis equipment or techniques between the patients who received OM or MH, although this may be another source of difference affecting NSF incidence.

While other studies to date have compared relative NSF incidence between centers (11–15), these may have similar uncontrolled variables as noted for this study. However, our study is the first showing longitudinal changes in NSF incidence that is coincident with a change in contrast procedures within a single center. What we can conclude is that NSF incidence within our center has been reduced significantly based on modifications in procedures that include the type and administration dose of the gadolinium chelate. We believe that our report represents the largest documented NSF disease-free patient cohort of patients on dialysis exposed to a particular GBCA administration protocol from a single center, where NSF cases have been documented with another protocol. Having NSF cases identified at our center validates our capacity to detect and diagnose this disease at rates similar to prior reports from other centers (17). The as-yet undetectable incidence of NSF in a large number of patients on dialysis receiving contrast-enhanced MRI studies at our center should be a consideration for other facilities developing optimized dose-reduction protocols (25–28) designed to reduce risks of contrast-enhanced MRI in patients with renal disease who are expected to derive overall health benefits from the diagnostic MRI scan. Our findings help to establish safer practice protocols that facilitate performing a contrast-enhanced MRI in patients with renal disease when the study is diagnostically indicated.

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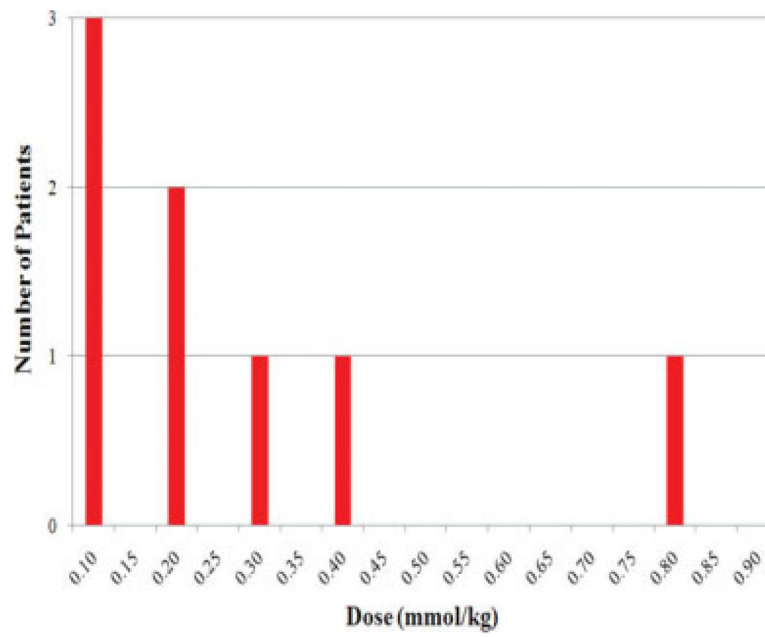


Figure 1. Distribution of cumulative doses in the gadodia-mide (OM) group with NSF.

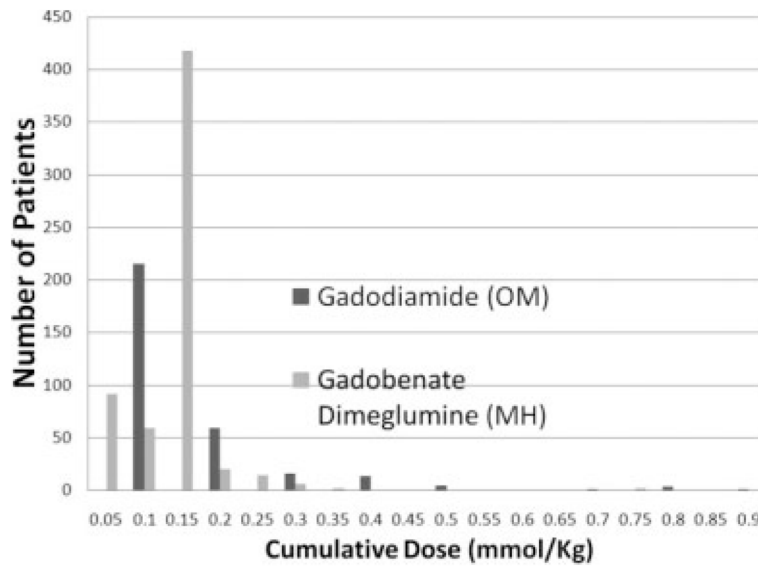


Figure 2. Distribution of cumulative doses by type of gadolinium agent, either gadodiamide (OM) or gadobenate dime-glumine (MH).

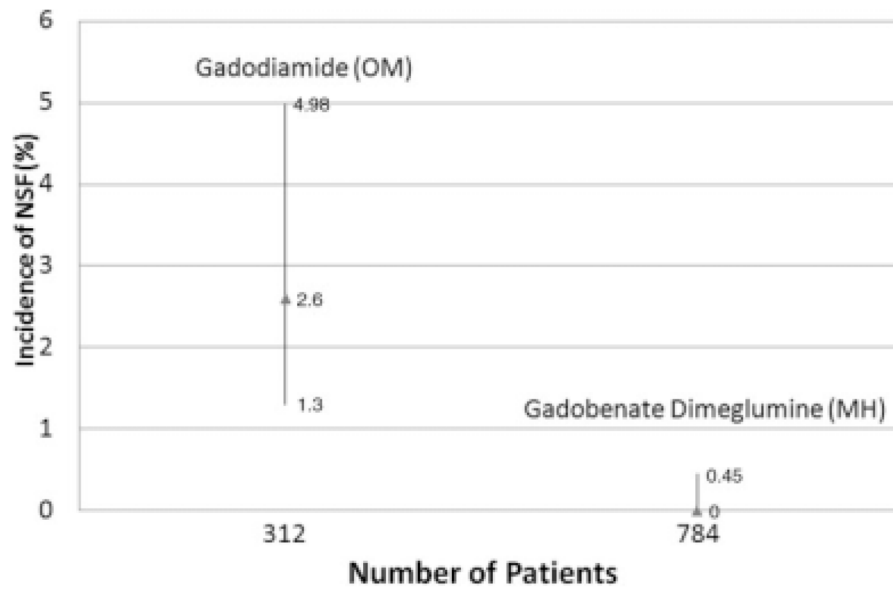


Figure 3. Incidence of NSF in patients with endstage chronic kidney disease on dialysis versus type of gadolinium agent and number of contrast-enhanced MRI exams performed, using either gadodiamide (OM) or gadobenate dimeglumine (MH). The 95% confidence limits are shown.

Table 1

Patient Study Population Characteristics

	Patients	Age (years)	Gender (M:F)	Dialysis
Gadodiamide (OM)	312	Mean 54, range 19–90	165:147	100%
With NSF	8	Mean 47, range 17–69	5:3	100%
Gadobenate (MH)	784	Mean 51, range 17–83	394:390	100%

NSF Patient Characteristics

Table 2

	Age (years)	Gender	Renal disease	Dialysis method	post-NSF	NSF signs/symptoms	Biopsy source	NSF treatment	Follow-up	Outcome	Dose
1	38	F	HTN	PD		Hyperpigmented confluent macules on arms, nodules on thighs, thickened/indurated lesions neck, abdomen	Left forearm and thigh	Topical steroid	3.5 years	Softening of some lesions	0.2
2	67	M	OU from stones	PD		Macular erythema back, buttocks and posterior thigh; scant scaly infiltrative erythematous plaques at right shoulder and bilateral axillae	Right shoulder	None	7 weeks	Death from pulmonary edema	0.4
3	17	M	OU and reflux	HD		Progressive indurated/pruritic scleroderma-like plaques on bilateral lower legs	Left shin and thigh	None	22 weeks	Lost to follow-up with no further NSF notes. Bowel perforation due to methotrexate	0.1
4	70	M	GN	PD		Lower extremities with shiny skin and swelling.	Legs	None	18 weeks	Death from CHF	0.3
5	48	F	RAS	HD		Indurated plaques of the arms, weakness	Left forearm	Physical therapy for weakness	3 weeks	Weakness improved with physical therapy, sent to home hospice with PEG tube feeds due to wasting from nausea and vomiting of unknown etiology	0.1
6	53	M	Adult PCKD	HD		Marked, right greater than left, induration of arm, hand, leg, and foot, musculoskeletal weakness	Right arm	Imatinib mesylate	3 years	Skin changes stable	0.8
7	35	F	Post strep GN	PD		Tan-orange firm papules confluent into irregular plaques on bilateral lower extremity	Left posterior lower leg	None	1 year	Died in hospice, RCC of the transplant kidney, metastatic to the lungs; failed sorafenib due to hypertension and nosebleeds. Skin changes stable.	0.1

Age (years)	Gender	Renal disease	Dialysis method	NSF	NSF signs/symptoms	Biopsy source	NSF treatment	Follow-up	Outcome	Dose
8	F	FSGN	HD		Bilateral arms and legs with annular / nummular red plaque	Medial lower legs	Topical steroid	4 years	Skin changes stable	0.2

PD, peritoneal dialysis; HD, hemodialysis; HTN, hypertension; OU, obstructive uropathy; GN, glomerulonephritis; RAS, renal artery stenosis; PCKD, polycystic kidney disease; CHF, congestive heart failure; RCC, renal cell carcinoma; FSGN, focal segmental glomerulonephritis.

Table 3

Characteristics of GBCA Dose Administrations in the Patient Subgroups

Patient population	<u>Cumulative dose (mmol/kg)</u>			
	Mean	Min	Max	Median
Gadodiamide (OM): Total	0.16	0.1	0.9	0.1
With NSF	0.28	0.1	0.8	0.1
Without NSF	0.15	0.1	0.9	0.2
Gadobenate (MH): Total	0.11	0.05	0.75	0.1