Prevalence of Nephrogenic Systemic Fibrosis in Patients with Chronic Liver Disease

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Introduction: Nephrogenic Systemic Fibrosis (NSF) is a rare disease that has been associated with the use of gadolinium-based contrast agents (GBCA) in patients with compromised renal function. Recently the FDA has placed a black box warning on the use of GBCA in patients with renal failure. The black box warning specifically calls for vigilance in regards to "acute renal insufficiency of any severity due to hepatorenal syndrome or in perioperative liver transplant period." [1] This warning implies that patients with liver disease are at risk for NSF even in the setting of mild (estimated glomerular filtration rate [eGFR] 60-90 mL/min/1.73m^2) or moderate (eGFR 30-60 mL/min/1.73m^2) renal insufficiency. Historically, GBCA-enhanced MR imaging has played an important role in assessment of patients with chronic liver disease. Therefore, limiting the use of GBCA may have negative effects on the care of these patients. Our purpose was to determine the prevalence of NSF in chronic liver patients exposed to GBCA for clinical care.

Methods: We conducted a retrospective chart review of 500 patients with chronic liver disease who underwent 969 GBCA-enhanced MR scans from February 2004 to October 2007. The following data were recorded: (1) Demographics, (2) Liver related data (etiology of chronic liver disease, presence of cirrhosis, presence of hepatocellular carcinoma, history of liver transplant), (3) Renal related data (eGFR most proximate temporally to GBCA exposure, hemodialysis at the time of GBCA exposure), (4) GBCA related data (agent formulation, anatomical region scanned, number of exposures per patient), (5) Presence of conditions reported to be associated with NSF (inpatient status at time of GBCA exposure, major surgery within 6 weeks of GBCA exposure, documented thrombotic event such as deep vein thrombosis or pulmonary embolism at time of GBCA exposure)[2] and (6) Dermatopathology reports. Any dermatopathology result was reviewed and those with fibrosis possibly consistent with NSF were submitted for reevaluation by a board certified dermatopathologist. eGFR was estimated from serum creatinine levels using the Modification of Diet in Renal Disease scale. [2]

Results: The patient cohort had an average age of 54 years (range 18-85). Fifty-three percent of patients were Caucasian, 24% Hispanic, 10% African-American and 13% of other ethnicity. The most common cause of chronic liver disease was hepatitis C virus (Table 1). Of the 500 patients, 269 (54%) were cirrhotic, 97 (19%) had a diagnosis of HCC, and 34 (7%) underwent liver transplant. Six (18%) of the 34 liver transplant patients were exposed to GBCA within 6 weeks of surgery (3 prior to transplant, 3 after). Three-hundred and fifty-one patients (70%) had renal insufficiency (Table 2). Of these 351 patients with renal failure, one had a thrombotic event, 18 (5%) had major surgery within 6 weeks of GBCA exposure and 34 (10%) were inpatients during their GBCA exposure (Table 3). The most common GBCA used was Multihance® (Table 4). Almost half of the patients had multiple GBCA exposures (Table 5). For those with multiple GBCA exposures, the average time between exposures was 197 days (range 1-968). Of the 40 patients with dermatopathology the report mentioned fibrosis in five. None of the five biopsies were consistent with NSF upon focused review.

Table 1. Liver disease etiology

Hepatitis C Virus	270/500 (54%)
Hepatitis B Virus	56/500 (11%)
Alcoholic Liver Disease	77/500 (15%)
Non-Alcoholic Steatohepatitis	35/500 (7%)
Autoimmune Hepatitis	8/500 (2%)
Cryptogenic Cirrhosis	14/500 (3%)
Other Pathology	125/500 (25%)

Table 2. Renal status at time of exposure

Mild insufficiency (eGFR 60-90)	226/500 (45%)
Moderate insufficiency (eGFR30-59)	95/500 (20%)
Severe insufficiency (eGFR <30)	23/500 (5%)
On hemodialysis	7/500 (1%)

Note: eGFR units in mL/min/1.73m^2

Table 3. Additional risk factors for NSF in patients with renal failure

Thrombotic Event	1/351(<1%)
Major Surgery	18/351 (5%)
Inpatient GBCA exposure	34/351 (10%)

Table 4. GBCA formulation

Multihance®	206/500 (41%)
Optimark®	138/500 (28%)
Magnevist®	2/500 (<1%)
Not Recorded	155/500 (31%)

Table 5. GBCA exposures per patient

1 exposure	284/500 (57%)
2 exposures	102/500 (20%)
3 exposures	49/500 (10%)
4 exposures	31/500 (6%)
5 exposures	13/500 (3%)
6 exposures	10/500 (2%)
≥7 exposures	11/500 (2%)

Conclusion: Our cohort consisted of 500 patients with chronic liver disease, of whom 321 had mild-moderate and 30 had severe renal dysfunction. No patient was diagnosed with NSF after exposure to GBCA**.** Although the concern regarding NSF in patients with severe renal failure is well substantiated, the concern raised by the FDA regarding liver patients with any severity of renal failure may be premature. A large prospective multicenter evaluation of NSF in chronic liver patients receiving GBCA would be beneficial, as our study was limited by its retrospective design and may have underestimated the true prevalence of NSF, particularly of NSF with milder clinical manifestations that may not have led to deramtopathology assessment.

References:

1. Omniscan® (gadodiamide) [package insert] Princeton, NJ, US: GE Healthcare:2007

2. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, Djamali A. *Nephrogenic systemic fibrosis: risk factors and incidence estimation.* Radiology. 2007 Apr;243(1):148-57