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Research Article

Elevation of Serum Creatinine Levels Following IV Administration of Gadolinium Containing Contrast Media in the Pediatric Population

Naffaa LN, Nath R, Irani N, Anton C, Brody A
Department of Radiology, Akron Children's Hospital, USA
Department of Radiology, Cincinnati Childrens Hosiptal

***Corresponding author:** Naffaa LN, Department of Radiology, Akron Children's Hospital, One Perkins Square, Akron, OH 44308, USA, Tel: (407) 967-6540; Email: lenanaffaa@hotmail.com

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Abstract

Purpose: The renal safety profile of Gadolinium containing contrast agents, has been assumed to be impeccable. However, non-radiologic literature continues to report declining renal function following intravenous administration of these agents in patients with lower renal reserve. The purpose of our retrospective case-control study was to determine whether the intravenous administration of Gd-DTPA (Magnevist) in the pediatric population induces changes in serum creatinine.

Methods: MRI examinations between January and June 2016 (prior to the NSF black box warning from the FDA) who had creatinine levels within 1 week prior and following the examination. Exams meeting inclusion criteria were divided into controls (non-contrast) and age and gender matched cases (contrast-enhanced) for comparison. A difference of means test was used to compare the change in creatinine relative to pre-exam base line in cases and controls.

Results: During the study period, 233 cases met inclusion criteria. Of these, 73 non- contrast controls were identified with a mean age of (5.2 years+/- 6.5). The control group demonstrated a decline of 0.02+/- 0.34 mg/dL in their creatinine values after the exam compared to the pre-exam baseline. The age and gender-matched cases demonstrated an increase of 0.11 +/- 0.21 mg/dL. The difference of means test demonstrated the finding to be statistically significant with a p value of 0.005.

Conclusion: Our results indicate a small but significant rise in creatinine following intravenous administration of Gd-DTPA. The possibility of cumulative effects can't be excluded by this study and would be important in the context of existing literature on these compounds. Our findings should be verified by a prospective trial using a more sensitive and specific marker for renal injury.

Keywords: MRI, Intravenous Contrast, Nephrology, Statistics

Introduction

Gadolinium is a widely used element in Magnetic Resonance Imaging (MRI) including children. In its free ionic form, gadolinium is highly toxic. It must be sequestered in a chelate in order to be used as a contrast agent [1]. Most gadolinium chelates are almost exclusively eliminated by the kidneys unchanged with over 95%excreted within 24 hours [1].

A benign renal profile for Gadolinium-Based Contrast Agent (GBCA) was initially suggested in low risk patients [1,2]. A few cases of renal injury were subsequently reported following intravenous gadolinium administration. Two of these cases involved preexisting tuberous sclerosis and diabetic nephropathy with post-administration tubular necrosis [3]. Another case was of a 56 year old female with normal baseline creatinine who developed mesangial sclerosis following a total intravenous dose of 23.5 m Mol combined Omnis can and Magnevistina 24 hour period [4]. In both reports, elevation in creatinine was noticed 48 hours after gadolinium administration [3,4].

More worrisome are prospective analysis of 158 patients with baseline renal impairment in whom Gadolinium-based contrast media was administered and a rise in creatinine> 10% was observed within 72 hours [5]. Additional retrospective studies– some with control groups–involving patients with stage 3 or 4 renal impairment (GFR < 60 ml/min/1.73m^2) [6] demonstrated a12% incidence of acute renal injury attributable to gadolinium administration [7]. Unlike voluminous data on NSF related injury, many studies on gadolinium induced nephrotoxicity are not part of the radiology literature. The studies demonstrating nephrotoxicity have variable study design, are limited by small sample size, varying levels of renal function, and comparison of multiple GBCAs [1-4,7,8]. These studies were also performed predominantly in adults. Most radiology literature, moreover, does not reveal significant nephrotoxicity following GBCA since patients with otherwise normal renal function [8]. The existing literature leaves unexplored the possibility that a small rise in serum creatinine can occur in a pediatric population following intravenous administration of GBCAs which falls short of the level typically used to diagnose contrast-induced nephropathy. The significance of

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such a finding, if present, may indicate a subclinical injury that can be masked by sufficient renal reserve. When the reserve is lacking, as in the multiple studies of patients with renal failure, the contrast administration triggers long term deterioration in renal function and in some cases, NSF from coincident delay in rapid contrast excretion. Such small rises in creatinine levels may be difficult to detect in studies with small sample size, no control groups, and short-term follow up. In our case-control study, we aim to follow changes in serum creatinine from before to after GBCA administration in the pediatric population with sufficient sample size and post-administration follow up to detect small shifts in creatinine. The goal of our study is to determine whether increases in blood creatinine are present following contrast administration, thereby suggesting whether further evaluation of this phenomenon is warranted.

Methods

IRB approval for this single institution retrospective study was obtained. A computerized search of hospital records was used to generate a list of all MRI examinations performed between January and June of 2006. The time period was selected to avoid any changes in practice which may have resulted from the Food and Drug Administration's (FDA) announcement [9]. Inclusion criteria for the study was a creatinine level measured both within 1 week (up to and including 6 days) prior to and following the exam. For each exam that met inclusion criteria, the creatinine values (in mg/dL) prior to and following the exam were recorded along with age, gender, and status of the patient (inpatient, outpatient or emergency) at the time of the MRI examination.

Creatinine was chosen as an indicator of renal function due mainly to its wide use in routine clinical care, and associated availability for retrospective review. If multiple creatinine levels were available within the1 week window following the exam, we selected the highest value for use in our analysis. In the case of multiple creatinine values prior to an MRI, the value closest to the time of the MRI was used as the baseline. This algorithm was methodically applied to all cases without knowledge of contrast status at the time of exam selection.

Following selection using creatinine level availability, a review was performed to determine if the exam involved administration of gadolinium- diethylenetriaminepentaacetic acid (Magnevist, Berlex Laboratories, Wayne NJ) during the examination. Based upon this information the selected examinations were divided in to three groups. Group A included all patients obtaining an MRI during which intravenous contrast was administered. Group B served as a control group and included all patients obtaining an MRI without intravenous contrast administration. An age and gender matched subset of Group A formed a third group (Group C) which was used to perform a case-control analysis with Group B.

The change in creatinine values prior to and following the MRI were calculated by subtracting pre-examination value from post examination value. A mean and standard deviation of the change in creatinine was then calculated for each of the three groups. A difference of means test was used to compare Group B with Groups A and C. Given the sufficiently large sample sizes, we assumed normal distributions.

Results

7440 MRI exams (1039 in patients, 6356 out patients, 48 emergency room) were performed on 4842 patients (508 in patients, 4302 out patients, 32 emergency room) during the 6 month study period in 2006. Of the 7440 exams, 233 instances met inclusion criteria. The age of included patients at the time of exam ranged from 1 day to 25 years (mean of 7.6 ± 6.8 years). 116 patients (49.8%) were male and 117 (50.2%) were female. Of the 233 exams meeting inclusion criteria, 220 were on inpatients.

Group A (contrast administered) contained 160 patients with a mean age of 8.8 ± 6.7 years (range 0-25 years). The 73 patients in Group B had a mean age of 5.2 years ± 6.4 (range 0-20 years). The age and gender matched subset of Group A was composed of 73 cases with a mean age of 5.8 years ± 6.3 (range 0-20 years). The age difference between Group A and Group B was significant with a p-value of 0.01. The age difference between the case control subset of Group A and the controls from Group B was not statistically significant (Table1).

Group A demonstrated a slight rise in creatinine: 0.08 ± 0.34 (range of difference-1.4 to 3.4). Group B demonstrated a slight decline in creatinine: -0.02 ± 0.34 (range of difference -2.3 to 0.5). Group C revealed a larger rise in creatinine: 0.11 ± 0.21 (range of difference -0.2 to1). The difference of means test revealed a statistically significant comparison of the variation in creatinine for both Groups A and C when compared to the non-contrasted control exams of Group B; p-values of 0.03 and 0.005, respectively.

Baseline creatinine levels were not significantly different between the Group B controls and Group C cases even when the analysis was restricted to patients under 18 years of age (Table 2). In fact, the trend in the data demonstrated higher baseline creatinine (lower renal function) in the control group than those who received contrast.

89 (38%) of the exams in our study had only one creatinine value in the 6 day window following the MRI. Of the remaining patients, 29 had two values within the 6 day window, 26 had 3, 15 had 4, 9 had 5, 21 had 6, and the remaining had more than 6 values (multiple tests on the same day). Two patients had more than 20 creatinine labs drawn in the 6 day window; both were under a year of age and had abnormal creatinine prior to their MRI exam (one received contrast, the other did not). 201 of the patients included in the study had a pre-exam creatinine on the same day or the day prior to the date of exam.

Discussion

Our results indicate a statistically significant rise in creatinine levels in patients who receive intravenous Gd-DTPA when compared with patients who have non-contrast MRI exam. This finding is consistent with existing medical literature.

The data collection was intended to pre-date gadolinium policies which could have masked a small effect on creatinine by diverting patients with low renal function away from gadolinium administration. This concern is consistent with studies that have shown a drop in patients developing NSF/renal failure after policies for gadolinium were implemented [6].

Our data could therefore, have been skewed in the opposite direction–involving more patients with renal impairment for contrast enhanced MRI examination in order to avoid known contrast induced nephropathy from an iodinated study. The data suggest that this was not the case in our study, which is a peculiarity. The pediatric

patient only case- control comparison outlined in Table 2 had only three exams with baseline creatinine> 1.3 mg/dL, all of which were in the control group. The highest baseline creatinine in the contrast administered group was 1.3 mg/dL in an 11 year old female. She subsequently demonstrated a rise in creatinine to 1.9 mg/dL three days after the exam. The overall incidence of baseline renal failure, therefore, in our 73 cases was not greater than the 2% incidence of renal failure expected from a national survey of all hospitalized patients [10].

In the context of normal renal function, the gadolinium chelate's half life should be less than 2 hours [11]. These chelates should not undergo biologic transformation and are eliminated unchanged, almost exclusively by means of glomerular filtration, without any active tubular secretion. In this sense, gadolinium chelates are similar to creatinine, the commonly used indicator of glomerular filtration rates. Both are freely filtered by the glomeruli and not reabsorbed with the main difference being that approximately 15% of creatinine is also actively secreted by tubules [12].

Although the mechanism for a potential nephrotoxic effect from Gadolinium containing chelates is unknown, circumstantial evidence is increasing. Non-chelated Gadolinium is found in the tissues of patients with decreased renal function who have a longer effective half-life for chelate excretion. It is hypothesized that competing cations, such as iron and zinc, displace Gadolinium from its chelate, given enough time [11,13].

In patients with lower renal function, excretion time is prolonged and administering higher doses of GBCAs would also allow more of these interactions to occur [14]. It is possible that similar reactions could occur on a smaller scale during the normal process of urinary concentration and contrast excretion. Fibrosis occurs when free gadolinium is deposited in soft tissues [15]. The pathologic finding of mesangial sclerosis following gadolinium administration reported in the renal biopsy we cited as initial evidence meriting this study is also consistent with this mechanism [5].

The limitations of our study include the use of an assay that is relatively insensitive for renal injury and susceptible to multiple coincident factors. As with most retrospective studies, it is difficult to control for confounding variables and determine whether changes in creatinine were due to other events at the time of the MRI examination. What if patients receiving contrast were also more likely to be on nephrotoxic medications/have base line renal injury? This could be a confounding cause of rises in creatinine values when combined with contrast administration.

While we cannot completely exclude this possibility, there is evidence that counsels us otherwise. Most substantial is the preexamination creatinine values. If confounding nephrotoxicity was present in the contrast administered group we would expect the higher baseline creatinine to be in Group C. In fact, the opposite was true with baseline

Creatinine values being higher in the control group (Tables 1&2). Furthermore, a substance with no effect on renal function (if that accurately describes GBCAs), when administered in the setting of a pre-existing nephrotoxic condition or regimen should not lead to a rise in creatinine coincident with the administration event. This leaves us with the possibility that many contrast enhanced MRI examinations coincided with the start of a nephrotoxic drug regimen which had its effect within the 6 day follow-up window of our study.

Consideration in this regard may fall upon the potential effects of anesthetics administered for sedation during pediatric MRI exams. In our study, the use of controls who received similar anesthetic care serves to mitigate this variable as a cause of the observed difference in creatinine rise in our study.

Conclusion

Our results, therefore, could be expected if Gadolinium Based Contrast Media result in a sub clinical renal injury. This mechanism would reconcile the disparate but reproducible reports in the radiologic versus the non-radiologic literature which focus on different subsets of patients. Our findings, in conjunction with the reported literature, raise sufficient concern about the impact of repeated GBCA administration on the kidney to warrant further investigation.

More knowledge about long term renal effects maybe elucidated with a prospective study using a sensitive marker for renal injury such as Neutrophil gelatinase Associated Lipocalin (NGAL). This marker has been tested in the pediatric population and has demonstrated an association with acute renal injury within two hours of cardiopulmonary bypass as opposed to 1-3 days before a rise in creatinine was seen [16]. This property is helpful in an assay for tissue damage as it more closely temporizes the inciting event, distinguishing it from potential confounders.

An associated analysis of urinary proteins released coincident with contrast administration, or any reparative processes would help determine whether there is tissue damage associated with Gadolinium containing contrast media. Such a study would also help identify individuals at risk for injury from contrast administration and contribute to the growing body of knowledge regarding the effects of widely used Gadolinium containing chelates.

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