

*Original Article*

## The safety of gadolinium in patients with stage 3 and 4 renal failure

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### Abstract

**Background.** Although there is a well-documented risk of acute renal failure (ARF) with the iodinated contrast agents, intravenous gadolinium-based contrast agents are considered non-nephrotoxic and have been widely used for magnetic resonance imaging (MRI). However, debate continues regarding the safety issue of gadolinium, especially in patients with kidney failure. Therefore, we aimed to evaluate the safety of gadolinium in patients with stage 3 and 4 renal failure as well as risk factors for nephrotoxicity.

**Method.** We retrospectively analysed 473 patients with chronic renal failure who underwent angiographic MRI procedures in our centre from February 1999 to March 2005 in whom gadolinium was used as the sole contrast agent at a dose of 0.2 ml/kg. Among them, 91 patients with stage 3 or 4 renal failure according to K/DOQI definition, who had available data in their files, were enrolled in the study. The ARF was defined as an increase of at least 0.5 mg/dl in serum creatinine level over baseline after using gadolinium.

**Results.** Eleven of 91 (52 males, 39 females; median age 59 years; median estimated glomerular filtration rate (eGFR) 33 ml/min/1.73 m<sup>2</sup>) patients developed ARF (12.1%). The median eGFR was lower in patients with ARF than in those who did not develop ARF. The risk factors for ARF were baseline eGFR, older age, diabetic nephropathy and low baseline haemoglobin and albumin levels. Baseline eGFR and diabetic nephropathy were determined as the independent risk factors in regression analysis.

**Conclusions.** An ARF can occur after gadolinium-based contrast agents in patients with moderate to severe chronic renal failure. Risk factors for ARF after gadolinium toxicity include diabetic nephropathy and low GFR.

**Keywords:** acute renal failure; chronic renal failure; contrast nephropathy; gadolinium

### Introduction

With the common use of contrast media in diagnostic and interventional procedures, contrast-induced nephropathy became a leading cause of hospital-acquired acute renal failure (ARF) [1]. It increases not only the cost of medical care by extending the hospital stay but also patient morbidity and mortality [2]. In the pathogenesis of contrast-induced nephropathy, renal haemodynamic alterations leading to medullary hypoxia and tubular epithelial cell toxicity are the main factors.

To date, despite the several therapeutic interventions such as hydration with saline infusion (the most convincing prophylactic procedure), N-acetylcysteine, fenoldopam, theophylline, haemofiltration and haemodialysis therapy, no treatment modality seems to be sufficient for the prevention of contrast medium-induced ARF [3]. Although radiocontrast nephropathy is an infrequent condition in the general population, it is reported at rates up to 50% in patients with high-risk clinical conditions such as renal insufficiency and diabetes [4].

Gadolinium is a well-known paramagnetic contrast agent used primarily for magnetic resonance (MR) investigations. The question of whether or not it can cause nephrotoxicity in high-risk patients, as has been observed with other iodinated contrast agents, has gained considerable clinical interest. Although gadolinium-based contrast agents are generally regarded as non-nephrotoxic in a healthy population, the safety issue of these agents is controversial in the high-risk patient group [5]. Therefore, the purpose of this study was to evaluate the safety of gadolinium in patients with moderate and severe renal failure (stage 3 and stage 4 according to National Kidney Foundation, Renal Failure Classification [6]) who underwent MR

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angiography. We also evaluated the risk factors for ARF in these patients.

## Patients and methods

Patients with stage 3 (moderate) and stage 4 (severe) renal failure according to the K/DOQI definition (glomerular filtration rate (GFR) between 15 and 59 ml/min/1.73 m<sup>2</sup>) [6], who underwent angiographic MR imaging (MRI) procedures in our centre from February 1999 to March 2005 and in whom gadolinium was used as the sole contrast agent, were included in the study. In this retrospective study, we analysed 473 patients with chronic renal failure.

Patients without stable renal function for at least a one month period prior to the gadolinium-based radiological procedure were excluded from the study. Patients receiving non-steroidal anti-inflammatory drugs, any nephrotoxic drugs including antibiotics, chemotherapy drugs or other forms of contrast media during the study period were also excluded. Patients who had serum creatinine levels recorded at the beginning, on the 1st, 3rd, and 7th day and 1 month after gadolinium administration, were included in the analyses. Patients with ARF, liver failure, severe heart failure (New York Heart Association (NYHA) Class III and IV), uncontrolled hypertension and pregnancy were excluded from the study. After exclusion, 91 patients were suitable for the analyses. Age, co-morbid conditions, anti-hypertensive medications and severity of renal failure were all considered in the analyses.

Acute renal failure was defined as an increase of at least 0.5 mg/dl in serum creatinine level over baseline values within 24–72 h after contrast administration in the absence of another etiology [7]. In this study, only three contrast agents were used for intravenous administration during MRI: Gd-DTPA (Magnevist; Schering AG, Germany), Gd-DTPA-BMA (Omniscan; Amersham Health, Ireland) and Gd-DOTA (Dotarem; Guerbet, France). The dose of gadolinium-based contrast was 0.2 mmol/kg body weight in all the patients. The estimated glomerular filtration rate (eGFR) was calculated using the 'four variable' (abbreviated) modification of diet in renal disease (MDRD) study equation [8].

Statistical analyses were performed with Statistical Package for Social Sciences for Windows version 11.5 (SPSS Inc; Chicago, IL, USA). Comparisons of two groups were made with unpaired Student's *t*-test. Chi-square test was used for non-numerical data. Regression analyses were performed to find independent variables for ARF. *P* value of less than 0.05 was considered significant.

## Results

Patients' characteristics at baseline are given in Table 1. Seventy-three patients had systemic hypertension, 18 had type 2 diabetes mellitus and six had heart failure (NYHA Class I, II). The causes of chronic renal failure were glomerulonephritis in 27 patients, hypertensive nephrosclerosis in 23 patients, diabetic nephropathy in 18 patients, interstitial renal diseases in nine patients, cystic renal diseases in four patients and other diseases/unknown etiologies in 10 patients.

**Table 1.** Patients' characteristics at baseline

Factors	All patients ( <i>n</i> = 91)
Age (years) <sup>a</sup>	59 (21–84)
Gender [n (%)]	
Male	52 (57.1%)
Female	39 (42.9%)
Baseline eGFR (ml/min/1.73 m <sup>2</sup> ) <sup>a</sup>	33 (15–58)
Diabetes mellitus [n (%)]	18 (19.8%)
Hypertension [n (%)]	73 (80%)
Heart failure [n (%)]	6 (6.6%)
Albumin (g/dl) <sup>a</sup>	3.4 (1.5–4.7)
Haemoglobin (g/dl) <sup>a</sup>	11 (7.3–17)

eGFR, estimated glomerular filtration rate.

<sup>a</sup>Data are expressed as medians and interquartile ranges.

Eleven of 91 patients (12.1%) developed ARF after gadolinium-based contrast administration. The median eGFR was 33 ml/min/1.73 m<sup>2</sup> (range, 15–58) for all patients. The median eGFR in patients who developed ARF was 16 ml/min/1.73 m<sup>2</sup> (range, 15–33), while it was 33.5 ml/min/1.73 m<sup>2</sup> (range, 15–58) in patients who did not develop ARF (*P* = 0.001). Although calculating eGFR can be associated with problems in rapidly rising creatinine (due to lack of steady state), we calculated the decline in eGFR in patients who developed ARF. Two of 50 patients (4%) with stage 3 and 9 of 41 patients (21%) with stage 4 renal failure developed ARF. The decline in eGFR [11 ml/min/1.73 m<sup>2</sup> (range, 9–13)] was 33% (range, 27.2–39.3%) in patients with stage 3 and [4 ml/min/1.73 m<sup>2</sup> (range, 3–9)] 22.2% (range, 18.7–33.3%) in patients with stage 4 renal failure. None of the patients required dialysis and no mortality was observed during the study period. Average age of the study population was 59 years (range, 21–84) and patients with ARF were older than those without ARF (72 years, range: 54–78 vs 56 years, range: 21–84, respectively; *P* = 0.014).

The relation between the etiology of renal failure and development of gadolinium-induced ARF was also evaluated. Diabetic nephropathy was present in 18 of 91 patients (19.8%), and six patients with diabetic nephropathy (6.5%) developed ARF. Patients with diabetic nephropathy had a higher risk for gadolinium-based contrast-induced nephropathy (*P* = 0.007). In addition, lower albumin and haemoglobin levels before contrast administration appeared to be significant risk factors for ARF (Table 2).

An increased risk for gadolinium-based contrast-induced nephropathy was found in patients with older age, lower baseline creatinine clearance, diabetic nephropathy and low haemoglobin and albumin levels. Logistic regression analyses were performed to determine independent variables. Lower eGFR and diabetic nephropathy were found as the statistically significant independent risk factors for gadolinium-based contrast-induced nephropathy (Table 3).

Eighty percent (73 patients) of patients were on antihypertensive medication including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (45%), diuretics (42%) and other

**Table 2.** Evaluation of risk factors

	ARF (n = 11)	Non-ARF (n = 80)	P Value
Age (years) <sup>a</sup>	72 (54–78)	56 (21–84)	0.014
Gender (F/M)	4/7	35/45	NS
Baseline eGFR (ml/min/1.73 m <sup>2</sup> ) <sup>a</sup>	16 (15–33)	33.5 (15–58)	0.001
Albumin (g/dl) <sup>a</sup>	3 (1.5–3.5)	3.4 (1.5–4.7)	0.014
Haemoglobin (g/dl)	9.5 (8.6–14.5)	11 (7.3–17)	0.011
DN [n (%)]	6 (6.5%)	12 (13.1%)	0.007

ARF, acute renal failure; eGFR, estimated glomerular filtration rate; DN, diabetic nephropathy; NS, not significant.

<sup>a</sup>Data are expressed as medians and interquartile ranges.

**Table 3.** Regression table showing significant independent variables

Variables	Exp (B)	95% CI	Significance
Diabetic nephropathy	6.910	1.408–33.906	0.017
Baseline eGFR	0.889	0.807–0.979	0.017

eGFR, estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>).

antihypertensive drugs (beta blockers, calcium channel blockers, alpha blockers, alpha methyl dopa and imidazoline receptor blockers). There was no statistical difference between gadolinium-induced nephropathy and the type of antihypertensive medication.

Systemic hypertension, heart failure and the other etiologies of chronic renal failure were not risk factors for gadolinium nephrotoxicity.

## Discussion

In this study, we showed that an intravenous 0.2 mmol/kg body weight dose of gadolinium caused ARF in 12.1% of patients with stage 3 and 4 renal failure. Older age, low baseline creatinine clearance, diabetic nephropathy and lower haemoglobin and albumin levels appear to be risk factors for ARF. Among them, lower eGFR and diabetic nephropathy were found to be independent risk factors.

It has been well demonstrated that contrast nephropathy due to iodinated agents increases with the presence of chronic renal failure, diabetes, older age and the simultaneous use of other nephrotoxic agents [9]; however, these risk factors have not been clearly demonstrated for gadolinium-based contrast nephrotoxicity. The use of low-dose gadolinium-based contrast agents (to 0.1 mmol/kg body weight) in patients with impaired renal function has been shown to be non-nephrotoxic [10], but results regarding the safety issue with a 0.2 mmol/kg body weight or higher dose are controversial in stage 3 and 4 renal failure patients.

Rieger *et al.* [11] found no significant change in serum creatinine level in 29 patients with renal failure who underwent diagnostic and interventional angiographic procedures with high doses of gadolinium dimeglumine

(0.34 mmol/kg). Conversely, Erley *et al.* [12] showed a significant decline in 50% of patients with severe renal impairment after gadolinium-based (>0.5 mmol/kg) digital subtraction angiography. They compared the safety issue of gadolinium-based contrast media with iodinated media (iohexol) and concluded that gadolinium-based contrast media showed no benefit over iodinated media for preventing GFR reduction in patients with renal failure. Sam *et al.* [13] also showed the nephrotoxic effects of gadolinium-based contrast media after both intravenous and intraarterial administration in patients with renal failure even with doses of less than 0.4 mmol/kg. They stated that intraarterial administration is no more problematic than intravenous administration.

Most of the studies showing the safety of intravenous gadolinium did not stratify the patients according to moderate and severe renal failure [14,15]. Townsend *et al.* [16] evaluated the patients with moderate and severe renal failure and found no significant change in renal function after intravenous gadolinium administration. In their study, the mean GFR was 52.2 ml/min/1.73 m<sup>2</sup> in moderate and 21.2 ml/min/1.73 m<sup>2</sup> in severe renal failure groups. Similarly, in our study patients who did not develop ARF had a median eGFR of 33.2 ml/min/1.73 m<sup>2</sup>, while those who did develop ARF had a lower eGFR (16 ml/min/1.73 m<sup>2</sup>). The lower eGFR in our patients seems to be the most important factor in the development of ARF after gadolinium-based contrast administration.

In this study, the incidence of ARF due to gadolinium was higher (12.1%) than reported in the literature (3.5–9.5%) [13]. The patients in our study had a lower GFR than reported in the literature, which may explain the higher ARF incidence.

The previously determined risk factors for occurrence of contrast-induced nephropathy include renal failure, diabetic nephropathy, congestive heart failure, volume depletion, contrast agent type and use of high doses of radiocontrast agent [17]. The use of ACE inhibitors may also increase the risk [18]. When the effects of antihypertensive medications in gadolinium-based contrast-induced nephropathy were evaluated, no association was found.

Nikolsky *et al.* [19] recently showed that low preprocedural haematocrit levels increased the rates of contrast-induced nephropathy in patients after percutaneous coronary interventions with any given GFR level. Anaemia-induced deterioration of renal ischaemia was thought to be the possible explanation [19]. In our study, although low haemoglobin and low albumin levels appeared to be risk factors for gadolinium toxicity, they were related to lower eGFR and diabetic nephropathy, respectively. They were not found to be the independent risk factors.

The dose of gadolinium-based contrast was 0.2 mmol/kg body weight in our study. However, in recent years, newer MR machines produce more accurate pictures especially for MR angiography by using less amounts of gadolinium, which may lower the nephrotoxicity incidence.

Our study, although limited by its retrospective nature and lack of a control group, demonstrated that gadolinium can be nephrotoxic in renal failure patients. Identification of the risk factors for patients with moderate to severe renal failure and application of prophylactic measures before gadolinium-based contrast administration should be considered to reduce the risk of nephrotoxicity.

*Conflict of interest statement.* None declared.

## References

1. Rudnick MR, Goldfarb S, Wexler L *et al.* Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. *Kidney Int* 1995; 47: 254–261
2. Persson PB, Patzac A. Renal haemodynamic alterations in contrast medium-induced nephropathy and the benefit of hydration. *Nephrol Dial Transplant* 2005; 20 [Suppl 1]: i2–i5
3. Detrenis S, Meschi M, Musini S, Savazzi G. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. *Nephrol Dial Transplant* 2005; 20: 1542–1550
4. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 1990; 89: 615–620
5. Thomsen HS. How to avoid CIN: guidelines from the European Society of Urogenital Radiology. *Nephrol Dial Transplant* 2005; 20 [Suppl 1]: i18–i22
6. National Kidney Foundation: K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2000; 39 [Suppl 1]: 1–237
7. Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. *N Engl J Med* 1994; 331: 1449–1450
8. Levey AS, Greene TG, Kusek JW, Beck GL. Modification of diet in renal disease study group: a simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000; 11: A0828 (abstract)
9. Berns AS. Nephrotoxicity of contrast media. *Kidney Int* 1989; 36: 730–740
10. Haustein J, Niendorf HP, Krestin G *et al.* Renal tolerance of gadolinium DTPA/dimeglumine in patients with chronic renal failure. *Invest Radiol* 1992; 27: 153–156
11. Rieger J, Sitter T, Toepfer M *et al.* Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. *Nephrol Dial Transplant* 2002; 17: 824–828
12. Erley CM, Bader BD, Berger ED. Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotaemic patients. *Nephrol Dial Transplant* 2004; 19: 2526–2531
13. Sam AD 2nd, Morasch MD, Collins J *et al.* Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. *J Vasc Surg* 2003; 38: 313–318
14. Arsenault TM, King BF, Marsh JW Jr *et al.* Systemic gadolinium toxicity in patients with renal insufficiency and renal failure: retrospective analysis of an initial experience. *Mayo Clin Proc* 1996; 71: 1150–1154
15. Hoffmann U, Fischereider M, Reil A, Fisher M, Link J, Kramer BK. Renal effects of gadopentetate dimeglumine in patients with normal and impaired renal function. *Eur J Med Res* 2005; 10: 149–154
16. Townsend RR, Cohen DL, Katholi R *et al.* Safety of intravenous gadolinium (Gd-BOPTA) infusion in patients with renal insufficiency. *Am J Kidney Dis* 2000; 36: 1207–1212
17. Barrett BJ. Contrast nephrotoxicity. *J Am Soc Nephrol* 1994; 5: 125–137
18. Kini AS. Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with the use of fenoldopam. *Am J Cardiol* 2002; 89: 999–1002
19. Nikolsky E, Mehran R, Lasic Z *et al.* Low hematocrit predicts contrast-induced nephropathy after percutaneous coronary interventions. *Kidney Int* 2005; 67: 706–713

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