Catheterization and Cardiovascular Interventions 71:687–693 (2008)

PERIPHERAL VASCULAR DISEASE

Interventional Rounds

Does Gadolinium-Based Angiography Protect Against Contrast-Induced Nephropathy?: A Systematic Review of the Literature

Thomas F. Boyden, MD and Hitinder S. Gurm,* MD

We evaluated the incidence of contrast-induced nephropathy (CIN) in patients exposed to gadolinium for diagnostic or therapeutic procedures. Background: CIN with iodinated contrast agents is a leading cause of acute renal failure. Gadolinium is often used as an alternative to iodinated contrast in patients at increased risk of CIN. The safety of gadolinium in patients at increased risk of CIN has not been established. Methods and Results: The authors performed a systematic review by searching MEDLINE, ISI Web of Knowledge, Current Contents, Embase, and the Cochrane Central Register of Controlled Trials to identify relevant studies evaluating gadolinium and its associated incidence of CIN. They identified 17 studies that reported both favorable and negative results with regard to the association of gadolinium and CIN. The differences in the results appeared to be dose related. When gadolinium was used in doses of 0.4 mmol/kg or higher, there appeared to be an increased incidence of ARF particularly in patients with preexisting renal insufficiency. Conclusions: Although the evidence base is limited, gadolinium does not appear to be safer than iodinated contrast in patients at risk of CIN. Given the lack of randomized data to support its safety, gadolinium in lieu of iso-osmolar iodinated contrast cannot be advocated in patients at high risk of contrast nephropathy. © 2008 Wiley-Liss, Inc.

Key words: contrast-induced nephropathy; angiography; gadolinium; contrast media; renal failure

INTRODUCTION

Diagnostic and therapeutic procedures requiring contrast media have risen dramatically over the past two decades [1,2]. With this increase, the incidence of contrast-induced nephropathy (CIN) has also risen, and CIN now stands as the third most common cause of acute renal failure [3,4]. The incidence of CIN has been reported to be as high as 10–30% in patients with preexisting chronic renal insufficiency receiving intravascular iodinated contrast [2,4–8].

CIN is a major predictor of early and late mortality in patients undergoing coronary artery interventions [9–11]. Although hydration, pretreatment with *N*-acetylcysteine, and use of iso-osmolar contrast have reduced the incidence of CIN [1], it still remains a major concern in patients scheduled to undergo vascular imaging especially in those with preexisting renal insufficiency.

Gadolinium has long been used as a contrast medium in magnetic resonance imaging. As it was originally believed to be nonnephrotoxic, gadolinium has been used as a replacement for iodinated contrast in patients deemed to be at high risk of CIN undergoing vascular imaging. However, there are conflicting data with respect to gadolinium's safety in patients at high risk of CIN [7,8,12–22]. Although no large randomized trials have been undertaken to elucidate gadolinium's safety com-

Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan

*Correspondence to: Hitinder S. Gurm, MD, Division of Cardiovascular Medicine, University of Michigan Cardiovascular Center, 2A394, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5853. E-mail: hgurm@med.umich.edu

Received 31 October 2007; Revision accepted 22 November 2007

DOI 10.1002/ccd.21459
Published online 24 March 2008 in Wiley InterScience (www.interscience.wiley.com).

pared with iodinated agents, multiple small, randomized trials as well as prospective observational and retrospective studies have examined this relationship. We performed a systematic review to assess the data evaluating gadolinium's safety when used as a contrast medium for patients undergoing vascular angiography.

METHODS

We performed our systematic review using guidelines from the Cochrane Collaboration. A computerized search was performed to identify relevant articles (through December 31, 2006) in the MEDLINE, ISI Web of Knowledge, Current Contents, Embase, and the Cochrane Central Register of Controlled Trials. We combined exploded medical subject headings and keyword searches for gadolinium, CIN, nephropathy and angiography. Published meta-analyses, review articles, case reports and editorials were reviewed for potential trials of interest.

A study was included if gadolinium was a contrast agent of study and included outcome data on renal function before and after administration of this contrast agent. Information was abstracted using a standardized form. Abstracted information included patient characteristics (mean age, chronic renal insufficiency, and diabetes mellitus), amount of gadolinium used during procedure, baseline creatinine, postprocedure creatinine, and inclusion and exclusion criteria for enrollment if provided.

We selected trials based on evaluation of gadolinium in human subjects. These included randomized and observational studies (both prospective and retrospective). The primary outcomes of interest included postprocedural CIN. No single definition of CIN exists among the various studies examined in this review. Criteria used to define CIN ranged from a rise in creatinine >0.3–0.5 mg/dL within 48 hr of contrast administration to a decrease in glomerular filtration rate $>50\%$.

RESULTS

Our search identified 17 relevant studies from 1996 through 2007: four randomized controlled trials, nine prospective observational studies, and four retrospective analyses. Primary endpoints differed among each study. The amount of gadolinium used also varied based on procedural characteristics among the studies included in this analysis.

Baseline patient characteristics were similar among each trial and included patients with chronic renal insufficiency and diabetes mellitus. Follow up was similar in each study; however, outcome data based on preexisting comorbidities prior to procedure were not reported.

In each trial, patients received intravenous fluid hydration prior to and after their procedure. Type of intravenous fluid used was at the discretion of the individual investigators. Acetylcysteine was also administered at the discretion of the investigator and was predominately used in patients with preexisting renal insufficiency.

The 17 studies in our review reported both favorable and negative results with regard to the association of gadolinium and CIN [7,8,12–22]. The differences in the results appeared to be possibly dose related with an increased incidence of ARF when gadolinium was used in doses of 0.4 mmol/kg or higher. As each study in this systematic review varied in its design and outcomes of interest, each study is described below with total dose of gadolinium administration and resultant change in kidney function. See Tables I and II for details with respect to preprocedure and postprocedure kidney function and dose of gadolinium administered.

Randomized Trials

Of the four randomized trials included in this review, one examined the effects of gadolinium at high doses, defined in this review as ≥ 0.4 mmol/kg, while three reported outcomes with gadolinium used at low doses, defined as <0.4 mmol/kg. In only two of these trials was gadolinium administration compared to iso-osmolar contrast media administration.

Randomized Comparison of Gadolinium and Iodinated Contrast

In the high dose trial, Erley et al. examined patients with renal insufficiency undergoing digital subtraction angiography [17]. Ten patients received 0.57 ± 0.17 mmol/kg gadobutrol vs. 11 receiving 0.60 ± 0.27 mmol/kg iohexol. Baseline serum creatinine was similar in both groups with an average of 3.4 ± 1.4 mg/dL in the gadobutrol group and 3.0 ± 1.2 mg/dL in the iohexol group. Mean glomerular filtration rate (GFR) decreased in both groups at 48-hr follow up and was not statistically different between the groups ($P = 0.3226$). GFR decreased from 31 ± 21 to 21 ± 21 ml/min/1.73 m^2 in the gadobutrol group vs. 29 ± 11 to 19 ± 11 ml/min/1.73 m^2 in the iohexol group. Five patients in each group developed contrast media induced acute renal failure defined as a decrease in GFR by $\geq 50\%$ of baseline within 48 hr of contrast media administration. Erley et al. data suggest no benefit of using gadolinium in lieu of iso-osmolar contrast.

Spinosa et al. randomly assigned 40 patients undergoing lower extremity arteriography to CO_2 alone, iodinated contrast media and CO_2 or gadolinium and CO_2 [8]. In the seven procedures using CO_2 alone, including two interventions, none of the patients experienced a rise in serum creatinine greater than 0.5 mg/dL at 48 hr. Fifteen procedures in 15 patients were

TABLE I. Comparison of Gadolinium and Iodinated Contrast Agents on Renal Function

			Contrast agent dosing		Precontrast renal function		Postcontrast renal function		Percent developing ARF	
Author	Study design	Type of imaging	Gadolinium	Control	Gadolinium (mg/dL)	Control (mg/dL)	Gadolinium (mg/dL)	Control (mg/dL)	Gadolinium (%)	Control (%)
Erley et al. [17]	Randomized	DSA	0.57 ± 0.17 mmol/kg	0.60 ± 0.27 mmol/kg	3.40 ± 1.45	3.04 ± 1.19	3.98 ± 1.94	3.20 ± 1.58	50	45
Spinosa et al. [8]	Randomized	Lower extremity arteriography	0.29 mmol/kg	53 mL (33–100 mL)	2.3	2.1	2.3	2.5	5	40
Brigouri et al. [20]	Prospective observational	Coronary angiography	0.6 ± 0.3 mmol/kg	122 ± 58 mL	2.30	2.24	2.38	2.25	28	6.5
Prince et al. [22]	Retrospective	MRA	0.2–0.4 mmol/kg	N/A[b]	2.21 ± 1.60	2.14 ± 1.58	1.99 ± 1.40	2.34 ± 1.80	0	29
Reed et al. [23]	Retrospective	Coronary angiography	151 ± 79 mL[a]	136 ± 72 mL	2.36 ± 0.9	2.10 ± 0.5	2.44 ± 1.2	2.17 ± 0.7	16	14

[a]Gadolinium was administered as a dilution with iodinated contrast and the value listed represents total volume of the dilution.
[b]Iodinated contrast agent was not recorded sufficiently to provide an average dose.

TABLE II. Effect of Low-Dose Vs. High-Dose Gadolinium on Renal Function

Author	Study design	Type of imaging	Gadolinium dose	Precontrast renal function	Postcontrast renal function	Percent developing ARF (%)
Low dose						
Haustein et al. [14]	Randomized	MRI	0.1 mmol/kg	N/A	mean change 0.0 mg/dL	0
			0.3 mmol/kg	N/A	mean change 0.0 mg/dL	0
Tombach et al. [19]	Randomized	MRI	0.1 mmol/kg	175.0 μmol/L	183.4 μmol/L	0
			0.3 mmol/kg	158.9 μmol/L	157.2 μmol/L	0
Robert et al. [24]	Prospective observational	DSA	0.15 mmol/kg	187 μmol/L	186 μmol/L	3
Sancak et al. [25]	Prospective observational	DSA	0.3 mmol/kg	1.5 mg/dL	1.6 mg/dL	0
Spinosa et al. [12]	Prospective observational	Renal arteriography	0.3 mmol/kg	3.1 mg/dL	3.2 mg/dL	8
Wagner et al. [15]	Prospective observational	DSA	34 ± 19 mL	2.6 ± 1.5 mg/dL	2.3 ± 1.0 mg/dL	0
Ergun et al. [21]	Retrospective	MRA	0.2 mmol/kg	33 ml/min/ 1.73 m^2	N/A	12
High Dose						
Hammer et al. [26]	Prospective observational	DSA	0.4 mmol/kg	3.44 mg/dL	3.46 mg/dL	3
Rieger et al. [13]	Prospective observational	Arteriography and angiography	0.23–0.44 mmol/kg	3.6 ± 1.5 mg/dL	3.6 ± 1.4 mg/dL	3
Zeller et al. [27]	Prospective observational	DSA	136 ± 46 mL	2.57 ± 1.43 mg/dL (no intervention)	2.40 ± 1.28 mg/dL	0
			136 ± 46 mL	3.53 ± 1.75 mg/dL (intervention)	2.36 ± 1.15 mg/dL	0
Ailawadi et al. [16]	Prospective observational	Renal arteriography	40–264 mL	3.0 ± 1.4 mg/dL	2.9 ± 1.3 mg/dL	0
Sam et al. [18]	Retrospective	MRA and DSA	0.25–0.42 mmol/kg	2.2 mg/dL	N/A	3.5

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

performed with the use of CO_2 and nonionic contrast media, including six interventions. Of these patients, 6 developed CIN at 48 hr. Of the 20 procedures, including 15 interventions, utilizing gadolinium at 0.13–0.40 mmol/kg and CO_2, one patient with a baseline creatinine of 3.3 mg/dL experienced a serum creatinine increase greater than 0.5 mg/dL at 48 hr. This patient received a total dose of 70 mL of gadodiamide (0.3 mmol/kg). The authors concluded that gadolinium, when used in small volumes, provided a statistically significant ($P = 0.03$) benefit with respect to renal function when compared to nonionic contrast media. Furthermore, the authors determined the gadolinium-based images to be inferior to those obtained using nonionic contrast media.

High Dose Versus Low Dose Gadolinium

Studies comparing high and low dose gadolinium administration in patients undergoing MRI have not confirmed a dose response with respect to renal safety of gadolinium. Tombach et al. randomly assigned 21 patients with impaired renal function undergoing magnetic resonance imaging for any indication to receive either 0.1 mmol/kg or 0.3 mmol/kg of gadolinium [19]. Follow up occurred at 6, 24, 48, and 72 hr following administration of contrast media. No adverse events related to the administration of gadobutrol occurred at either dose during follow up. No patients developed acute renal failure or anuria and none required hemodialysis.

In a similar trial, Haustein et al. randomly assigned 199 patients undergoing magnetic resonance imaging of the central nervous system to receive either 0.1 or 0.3 mmol/kg gadopentate [14]. Eight adverse events occurred in the group assigned to receive 0.1 mmol/kg gadopentate vs. seven adverse events that occurred in the group that received 0.3 mmol/kg. There were no cases of acute renal failure reported in either group. Thus, it is not clear if the different results seen in the two randomized results comparing iodinated constrast to gadolinium are secondary to use of a lower dose.

Prospective Analyses

Of the nine prospective analyses identified for this review, four reported effects of gadolinium on kidney function when used at high doses. Briguori et al. examined 25 patients with CRI undergoing coronary artery procedures [20]. Gadolinium chelates were diluted 3:1 with iodixanol and compared to a control group of 32 patients with CRI selected from a database who had received iodinated iso-osmolality contrast agent. CIN occurred in 7 of 25 patients receiving the gadolinium chelate dilution vs. 2 of 32 that received the iodinated contrast agent alone ($P = 0.034$). Hemodialysis was required in two patients in the gadolinium-based group vs. none in the iodinated-based group. This was not statistically significant ($P = 0.19$).

Ailawadi et al. performed renal arteriography in 21 patients with a baseline creatinine of 3.0 mg/dL [16]. In 25 procedures performed using 124 ± 74 mL of gadolinium (ie. 0.4 mmol/kg), no patients suffered adverse events including acute renal failure, defined as a rise in serum creatinine greater than 0.3 mg/dL within 48 hr of contrast administration.

Hammer et al. reported effects of gadolinium in digital subtraction angiography in patients with renal insufficiency [26]. Patients received up to but not exceeding a total of 0.4 mmol/kg of gadolinium. One patient suffered ARF defined as a rise in creatinine of >0.5 mg/dL following administration of gadolinium. However, this patient presented with intraperitoneal and retroperitoneal hemorrhage following renal biopsy 8 days after renal transplant.

Zeller et al. examined the use of gadodiamide as the sole contrast agent in patients with iodinated contrast allergy for digital subtraction angiography and angioplasty with or without stent placement [27]. The volume of gadodiamide administered ranged from 60 to 200 mL (mean volume being 136 ± 46 mL). No serious side effects were noted in this study including no change in renal function from baseline.

Sancak et al. reported no ARF following administration of gadolinium when used for digital subtraction angiography in patients with moderate renal insufficiency at a dose limited to 0.3 mmol/kg [25]. Similarly, Robert et al. reported only one patient who developed ARF (defined as a rise in creatinine >0.5 mg/dL) when using gadolinium dosed at a total of 0.15 mmol/kg for digital subtraction angiography among 39 patients undergoing 42 procedures [24]. The patient who did develop ARF received both gadolinium and iodine-based contrast agents.

Spinosa et al. examined the use of gadolinium in the diagnosis and treatment of renal artery stenosis in patients with preexisting renal insufficiency [12]. Gadodiamide was administered at 0.3 mmol/kg along with CO_2 intra-arterially in 24 patients for a total of 25 procedures. Follow up occurred at 24 and 48 hr. In 23 of the 25 procedures, there was no significant rise in serum creatinine, defined as an increase in serum creatinine level greater than 0.5 mg/dL. Of the two patients who did have a significant increase in serum creatinine, one underwent renal transplant six years before being enrolled in the study and was experiencing an increasing serum creatinine for two months prior to angiography. The second patient was found to have bilateral renal artery stenosis and severe abdominal aortic atherosclerosis. This patient underwent angioplasty and renal artery stenting. It was believed the elevation in serum creati-

nine was secondary to cholesterol emboli as the patient developed skin changes consistent with livedo reticularis following the procedure.

Rieger et al. prospectively examined 29 patients undergoing 32 angiographic procedures including renal, iliac and lower extremity arteriography as well as upper extremity and central venous angiography [13]. Total dose of gadopentate administered was 0.34 ± 0.06 mmol/kg. Serum creatinine remained stable after 31 of the 32 procedures. As in the prior study, the one patient who developed acute renal failure underwent angioplasty and stent placement for renal artery stenosis and he was noted to have severe atherosclerosis of the abdominal aorta. As the patient developed postprocedural skin changes consistent with livedo reticularis, it was believed this patient suffered from cholesterol embolism.

Wagner et al. investigated the use of gadolinium for digital subtraction angiography in patients with contraindication to iodinated contrast media [15]. Thirty digital subtraction angiographies were performed in 22 patients using a 0.5 mol/L solution with an average volume of 34 ± 19 mL administered per patient. No patients developed CIN.

Retrospective Analyses

In the retrospective studies included in this review, Reed et al. identified 169 patients with CRI that underwent diagnostic cardiac catheterization or percutaneous intervention [23]. They compared a mixture of gadolinium-iodinated contrast to iodinated contrast alone with CIN as the primary outcome. There were no differences in the postprocedural serum creatinine levels or creatinine clearance; however, there was an increased incidence of dialysis and in-hospital death in the gadolinium-iodinated contrast mixture group. Total dose of gadolinium was not specified, but the gadolinium mixture group received 151 ± 79 mL of contrast compared to 136 ± 72 mL with the iodinated contrast group.

Sam et al. identified 260 patients that received gadolinium for magnetic resonance angiography or digital subtraction angiography [18]. Gadolinium was dosed at a minimum of 0.25 mmol/kg in all patients. 195 of the 260 patients had a baseline renal insufficiency. Of those with normal baseline renal function, none developed acute renal failure. Of those patients with chronic renal insufficiency, 3 of 153 patients undergoing MRA and 4 of 42 undergoing DSA developed acute renal failure. In those who developed ARF, the average dose of gadolinium was 0.31–0.41 mmol/kg for MRA and 0.27–0.42 mmol/kg for DSA.

Prince et al. performed a retrospective analysis of patients who underwent aortic, pelvic or renal artery magnetic resonance angiography with high-dose gadolinium, 0.2–0.4 mmol/kg, to identify patients who may have developed CIN [22]. Of the 110 patients identified that had serum creatinine checked two days prior to and postprocedure, none had clinically significant change in renal function or evidence of CIN following the administration of gadolinium.

Ergun et al. also conducted a retrospective analysis of 91 patients with stage III or IV renal failure who underwent MRA [21]. All patients received a total dose of gadolinium of 0.2 mmol/kg. Eleven of these patients developed ARF, defined as a serum creatinine increase of 0.5 mg/dL over baseline after administration of gadolinium.

DISCUSSION

The key finding of our review is that while observational data support a low incidence of CIN in patients with impaired renal function that received gadolinium, randomized data do not suggest a statistically significant benefit over iso-osmolar contrast media when used in similar doses.

With an ever-increasing number of contrast-based procedures, the risk of developing CIN remains a serious concern particularly in patients with underlying renal insufficiency. It has been reported that CIN occurs in 10–30% of patients with chronic renal insufficiency that undergo diagnostic angiographic or interventional procedures with iodinated contrast agents [2,5,7,28,29]. This has led to an incidence of renal replacement therapy that approaches 25% in patients developing CIN, particularly those who develop oliguria [30,31]. Additionally, nearly one-third of patients who develop CIN may never return to their baseline renal function [28,30].

Multiple risk factors have been identified for CIN including preexisting renal insufficiency, diabetes mellitus, congestive heart failure, volume depletion and the dose of contrast agent administered [4,6].

Given the high prevalence and significant morbidity associated with CIN, identification and utilization of a safe contrast agent is critical for reducing this iatrogenic adverse outcome. Gadolinium has been considered safer than iodinated contrast agents with regard to inducing acute renal failure. As gadolinium has been increasingly used in clinical practice, it is clear that it may be more nephrotoxic than originally thought. In fact, when gadolinium is used in doses that produce equal attenuation as iodinated contrast agents, use of gadolinium appears to be associated with a risk of renal dysfunction that is similar to iodinated agents [32,33].

While iodinated contrast causes CIN by ischemic injury to the medulla via the vasoconstrictive response to the contrast agent, the mechanism by which gadolinium causes nephropathy remains unclear [3,4]. A recent study of renal biopsy specimens from patients with gadolinium-associated nephropathy suggests that gadolinium may induce global sclerosis, tubular atrophy, and interstitial fibrosis, thus leading to permanent renal impairment [3].

Furthermore, multiple sources have documented nephrogenic systemic fibrosis following the administration of gadolinium in patients with preexisting renal failure [34,35]. This condition, which causes thickening of the skin leading to joint immobility and potential inability to walk, was first documented in the late 1990s as a fibrotic skin disorder in patients with renal failure [36,37]. The Centers for Disease Control in the Morbidity and Mortality Weekly Report for the week of February 23, 2007, published a case–control analysis submitted by a hospital in St. Louis, MO, which independently associated the use of gadolinium with this rare condition.

Our analysis of the available data suggest that gadolinium provides no clear benefit over iodinated contrast agents with respect to CIN in patients undergoing diagnostic angiographic and interventional procedures, particularly when used in doses approaching equal attenuation to iodinated contrast media.

Our findings should be interpreted in the context of the inherent flaws of a systematic review of the literature that include study selection bias, publication bias and the inability to adjust for baseline differences among study subjects. These conclusions are based on small numbers and may be underpowered to detect a true difference in the relative renal safety of gadolinium over iodinated contrast.

CONCLUSION

In patients with preexisting renal insufficiency, use of Gadolinium for vascular angiography appears to be associated with postprocedural renal dysfunction when given in doses approaching or exceeding 0.4 mmol/kg. Given the absence of randomized controlled data to support its safety, and concerns about serious multiorgan toxicity, albeit rare, use of gadolinium in lieu of iso-osmolar iodinated contrast cannot be advocated in patients at high risk of contrast nephropathy.

ACKNOWLEDGMENTS

The authors are grateful to Drs Brahmajee Nallamothu, Stanley Chetcuti, and P. Michael Grossman for their helpful suggestions.

REFERENCES

1. Gami A, Garovic V. Contrast nephropathy after coronary angiography. Mayo Clin Procedure 2004;79:211–219.
2. Solomon R, DuMouchel W. Contrast media and nephropathy: Findings from systematic analysis and food and drug administration reports of adverse events. Invest Radiol 2006;41:651–660.
3. Akgun H, Gonlusen G, Cartwright J, Suki W, Truong L. Are gadolinium-based contrast media nephrotoxic? A renal biopsy study. Arch Pathol Lab Med 2006;130:1354–1357.
4. Solomon R, Cohen J, Harrington J, Madias N, Zusman C. Contrast-medium-induced acute renal failure. Kidney Int 1998;53: 230–242.
5. Brezis M, Epstein F. A Closer Look at radiocontrast-induced nephropathy. New Engl J Med 1989;320:179–181.
6. Barrett B. Contrast nephrotoxicity. J Am Soc Nephrol 1994;5: 125–137.
7. Parfrey P, Griffiths S, Barrett B. Contrast-material-induced renal failure in patients with diabetes mellitus, renal insufficiency or both. New Engl J Med 1989;320:143–149.
8. Spinosa D, Angle J, Hagspiel K, Kern J, Hartwell G, Matsumoto A. Lower extremity arteriography with use of iodinated contrast material or gadodiamide to supplement CO_2 angiography in patients with renal insufficiency. J Vasc Interv Radiol 2000;11: 35–43.
9. Gupta R, Gurm H, Bhatt D, Chew D, Ellis S. Renal failure after percutaneous coronary intervention is associated with high mortality. Catheter Cardiovasc Interv 2005;64:442–448.
10. Rihal C, Textor S, Grill D, Berger P, Ting H, Best P, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105:2259–2264.
11. Best P, Lennon R, Ting H, Bell M, Rihal C, Holmes D, Berger P. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–1119.
12. Spinosa D, Matsumoto A, Angle J, Hagspiel K, McGraw J, Ayers C. Renal insufficiency: usefulness of gadodiamide-enhanced renal angiography to supplement CO_2-enhanced renal angiography for diagnosis and percutaneous treatment. Radiology 1999;210:663–672.
13. Rieger J, Sitter T, Toepfer M, Linsenmaier U, Pfeifer K, Schiff H. Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. Nephrol Dialysis Transplant 2002;17: 824–828.
14. Haustein J, Laniado M, Niendorf H, Louton T, Beck W, et al. Triple-dose versus standard-dose gadopentetate dimeglumine: A randomized study in 199 patients. Radiology 1993;186:855–860.
15. Wagner H, Kalinowski M, Klose K. The use of gadolinium chelates for X-ray digital subtraction angiography. Invest Radiol 2001;36:257–265.
16. Ailawadi G, Stanley J, Williams D, Dimick J, Henke P, Upchurch G. Gadolinium as a nonnephrotoxic contrast agent for catheter-based arteriographic evaluation of renal arteries in patients with azotemia. J Vasc Surgery 2003;37:346–352.
17. Erley C, Bader B, Berger E, Tuncel N, Winkler S, Tepe G, Risler T, Duda S. Gadolinium-based contrast media compared with iodinated media for digital subtraction angiography in azotemic patients. Nephrol Dialysis Transplant 2004;19:2526–2531.
18. Sam A, Morasch M, Collins J, Song G, Chen R, Pereles F. Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. J Vasc Surg 2003;38:313–318.
19. Tombach B, Bremer C, Reimer P, Kisters K, Schaefer R, Geens V, Heindel W. Renal tolerance of a neutral gadolinium chelate

(gadobutrol) in patients with chronic renal failure: Results of a randomized study. Radiology 2001;218:651–657.
20. Briguori C, Colombo A, Airoldi F, Melzi G, Michev I, Carlino M, Montorfano M, Chieffo A, Bellanca R, Ricciardelli B. Gadolinium-based contrast agents and nephrotoxicity in patients undergoing coronary artery procedures. Catheter Cardiovasc Intervent 2006;67:175–180.
21. Ergun I, Keven K, Uruc I, Ekmekci Y, Canbakan B, Erden I, Karatan O. The safety of gadolinium in patients with stage 3 and 4 renal failure. Nephrol Dialysis Transplant 2006;21:697–700.
22. Prince M, Arnoldus C, Frisoli J. Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. J Magn Reson Imag 1996;1:162–166.
23. Reed P, Dixon S, Boura J, O'Neill W, Kahn J. Comparison of the usefulness of gadodiamide and iodine mixture versus iodinated contrast alone for prevention of contrast-induced nephropathy in patients with chronic kidney disease undergoing coronary angiography. Am J Cardiol 2007;100:1090–1093.
24. Robert A, Bonneville F, Miralbes S, Huart J, Cattin F, Quantin N, Bonneville J. Gadolinium utilization in digital subtraction angiography and interventional radiology: About 39 Cases. J Radiol 2002;83:1759–1763.
25. Sancak T, Bilgic S, Sanlidilek U. Gadodiamide as an alternative contrast agent in intravenous digital subtraction angiography and interventional procedures of the upper extremity veins. Cardiovasc Intervent Radiol 2002;25:49–52.
26. Hammer F, Goffette P, Malaise J, Mathurin P. Gadolinium dimeglumine: An alternative contrast agent for digital subtraction angiography. Eur Radiol 1999;9:128–136.
27. Zeller T, Muller C, Frank U, Burgelin K, Sinn L, Horn B, Flugel P, Roskamm H. Gadodiamide as an alternative contrast agent during angioplasty in patients with contraindications to iodinated media. J Endovasc Therapeut 2002;9:625–632.
28. Spinosa D, Kaufmann J, Hartwell G. Gadolinium chelates in angiography and interventional radiology: A useful alternative to iodinated contrast media for angiography. Radiology 2002;223:319–325.
29. Barrett B, Carlisle E. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993;188:171–178.
30. Porter G. Contrast associated nephropathy. Am J Cardiol 1989;64:22E–26E.
31. Fenves A, Allgren R. Radio contrast dye-induced acute tubular necrosis (ATN): Atrial natriuretic peptide (anp) vs. placebo (abstract). Am Soc Nephrol 1995;6:463.
32. Nyman U, Elmstahl B, Leander P, Nilsson M, Golman K, Almen T. Are gadolinium-based contrast media really safer than iodinated media for digital subtraction angiography in patients with azotemia? Radiology 2002;223:311–318.
33. Davidson C, Stacul F, McCullough P, Tumlin J, Adam A, Lameire N, Becker C. Contrast Medium Use. The American Journal of Cardiology 2006;98(6A):42K–58K.
34. Food and Drug Administration. Public health advisory: Gadolinium-containing contrast agents for magnetic resonance imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance.http://www.fda.gov/cder/drug/advisory/gadolinium_agents.htm, 2006.
35. Marckmann P, Skov L, Rossen K. Nephrogenic systemic fibrosis: Suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006;17:2359–2362.
36. Cowper S, Robin H, Steinberg S, Su L, Gupta S, LeBoit P. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000;356:1000–1001.
37. Ting W, Stone M, Madison K, Kurtz K. Nephrogenic fibrosing dermopathy with systemic involvement. Arch Dermatol 2003;139:903–906.