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Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial

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Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: A randomized trial. The incidence of nephrotoxicity occurring with the nonionic contrast agent, iohexol, and the ionic contrast agent, meglumine/sodium diatrizoate, was compared in 1196 patients undergoing cardiac angiography in a prospective, randomized, double-blind multicenter trial. Patients were stratified into four groups: renal insufficiency (RI), diabetes mellitus (DM) both absent ($N = 364$); RI absent, DM present ($N = 318$); RI present, DM absent ($N = 298$); and RI and DM both present ($N = 216$). Serum creatinine levels were measured at −18 to 24, 0, and 24, 48, and 72 hours following contrast administration. Prophylactic hydration was administered pre- and post-angiography. Acute nephrotoxicity (increase in serum creatinine of ≥1 mg/dl 48 to 72 hours post-contrast) was observed in 42 (7%) patients receiving diatrizoate compared to 19 (3%) patients receiving iohexol, $P < 0.002$. Differences in nephrotoxicity between the two contrast groups were confined to patients with RI alone or combined with DM. In a multivariate analysis, baseline serum creatinine, male gender, DM, volume of contrast agent, and RI were independently related to the risk of nephrotoxicity. Patients with RI receiving

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diatrizoate were 3.3 times as likely to develop acute nephrotoxicity compared to those receiving iohexol. Clinically severe adverse renal events were uncommon ($N = 15$) and did not differ in incidence between contrast groups (iohexol $N = 6$; diatrizoate $N = 9$). In conclusion, in patients undergoing cardiac angiography, only those with pre-existing RI alone or combined with DM are at higher risk for acute contrast nephrotoxicity. The incidence of acute nephrotoxicity in these high-risk patients is significantly less with the nonionic contrast media iohexol compared to the ionic contrast agent diatrizoate.

Intravascular iodinated contrast media administration continues to be a common cause of hospital-acquired acute renal failure [1, 2]. Both pre-existing renal insufficiency and diabetes mellitus have been frequently demonstrated to significantly increase the risk of this acute event (so-called "high-risk" patients) [3, 4]. During the past decade nonionic (low-osmolality) contrast media have become increasingly popular for radiographic procedures requiring intravascular contrast because they are associated with a decreased incidence of systemic and organ toxicity compared to conventional ionic (high-osmolality) contrast media [5]. Moreover, data from animal studies have suggested that nonionic contrast media are less nephrotoxic than ionic contrast media [6–11]. Despite these observations, clinical experience with nonionic contrast media has clearly demonstrated that these newer contrast agents are capable of causing contrast media-induced acute renal failure in humans [12–26]. Whether nonionic contrast media is less likely to cause acute renal failure compared to ionic contrast media remains unclear. Several recent investigations addressing this question have failed to demonstrate a difference in the incidence of nephrotoxicity between nonionic and ionic contrast media [16, 18, 19, 22, 23, 25, 26]. However, the small number of subjects with pre-existing renal insufficiency alone or combined with diabetes mellitus evaluated in these previous trials, limits any conclusions regarding the relative nephrotoxicity of nonionic contrast media in these "high-risk" patients.

The goal of our randomized prospective study was to compare the incidence of contrast nephrotoxicity between the nonionic contrast agent, iohexol, and the ionic contrast agent, diatrizoate, in a large population of both "low" and "high-risk" patients undergoing cardiac angiography.

Methods

Organization

The Iohexol Cooperative Study enrolled patients from 23 participating centers across the United States. A Safety Monitoring Committee independently reviewed study data periodically to assure that neither treatment was associated with excess patient risk. The Committee did not recommend termination of the trial at any point. The trial was approved by the respective Institutional Review Boards at each participating center and all patients gave informed consent.

Patient recruitment

Study enrollment began in July 1988 and ended in March 1991. Hemodynamically stable male and female adult patients who were referred for non-emergent diagnostic cardiac angiography were eligible for recruitment. Patients who had recently received iodinated contrast media or nephrotoxic agents, had undergone recent surgery, had acute renal failure, malignant hypertension or a recent change in dosage of diuretics, antihypertensives or calcium antagonists were ineligible. Women of child bearing potential were required to have a negative pregnancy test prior to study participation. Pregnant or lactating women were excluded from participation as were patients who had received any investigational drug in the 30 days prior to study entry.

Patients were categorized as "Diabetic" if they required insulin or oral hypoglycemic agents to control hyperglycemia. Patients with diet controlled diabetes mellitus were ineligible as were those patients who were newly found to have hyperglycemia (plasma glucose >140 mg/dl).

Chronicity of renal insufficiency was defined by a serum creatinine level at the time of study entry of ≥1.5 mg/dl, a prior history of chronic (≥6 weeks) renal insufficiency, and documentation of previously elevated serum creatinine levels.

Patients

On entry, patients were assigned to one of four stratified study groups: Group 1 Non-diabetic, serum creatinine <1.5 mg/dl; Group 2 Diabetic, serum creatinine <1.5 mg/dl; Group 3 Non-diabetic, serum creatinine ≥1.5 mg/dl; Group 4 Diabetic, serum creatinine ≥1.5 mg/dl. Within each group and at each center, patients were randomized to receive either the nonionic contrast agent iohexol (Omnipaque 350) or the ionic contrast agent diatrizoate meglumine/sodium (Renografin 76). The goal of the study was to evaluate renal function (defined below) in 320 patients in each of the four groups.

A complete medical history and physical examination was carried out on each patient.

Clinical and laboratory data collection

Information regarding all concomitant medications was collected at time of study entry and all medication changes during the course of the study were recorded. Intravenous fluids (D51/2NSS or its equivalent at a recommended rate of 100 ml/hr) were administered beginning at least four hours prior to angiography and were continued for 24 hours post-procedure unless clinically contraindicated. Diagnostic cardiac angiography was carried out according to the standard procedure of each center with the exception of "blinded" administration of contrast media. Preprocedural and procedural medications were recorded, as were details of the angiography including procedures performed, time of first injection of contrast and total volume administered.

A venous blood specimen for the serum creatinine value which determined the stratified group assignment at the time of study enrollment was drawn between 18 to 24 hours prior to the administration of contrast medium and the analysis was performed in the hospital laboratory at each of the study centers. In addition, blood specimens for serum creatinine determination were drawn at the same time, at 0 hours (just prior to contrast medium administration), and 24, 48 and if possible 72 hours following contrast medium administration and were analyzed at a central laboratory facility (SciCor, Indianapolis, IN, USA).

Statistical analysis

The primary outcome measure for this study was prospectively defined as an increase in serum creatinine from baseline (0 hour specimen) of 1.0 mg/dl or more within 48 to 72 hours following contrast administration. A patient was evaluable for renal outcome if creatinine was followed from baseline for at least 48 hours

post-procedure without the use of any additional contrast medium. A sample size of 1160 enrolled in the four groups combined would provide 90% power at an alpha level of 0.05 to detect the difference between overall study incidence rates of 10 and 5% for the two contrast media. At the same time, a sample size of 290 enrolled patients in each of the four groups would provide 80% power at an alpha level of 0.05 to detect the difference between group incidence rates of 15% and 7.5% for the two contrast media. The sample size was set at 320 per group to allow for the exclusion of patients who would require further contrast medium or imminent surgery within 48 hours of the study procedure. The occurrence of an increase in serum creatinine by ≥0.5 mg/dl above baseline as well as the mean peak change from baseline in serum creatinine were specified as secondary outcome measures.

The incidence rate for each center, patient group and treatment was calculated and analyzed with log-linear modelling (Module 4F of BMDP) [27] for differences between treatments and for lack of uniformity of that treatment difference across centers and across patient groups. Means were analyzed with an analogous three way analysis of variance model.

The main effects of other cofactors upon the primary incidence rate were assessed with logistic regression (Proc LOGIST of SAS) [28]. A stepwise procedure was used to select among the following: NYHA Classification, laboratory determined renal insufficiency (baseline serum creatinine ≥1.5 mg/dl vs. <1.5 mg/dl), baseline serum creatinine, diabetes mellitus, congestive heart failure, hypertension (diastolic blood pressure ≥90 mm Hg, <90 mm Hg) left ventricular ejection fraction (<35%, ≥35%), volume of contrast (milliliters), age (years), gender, and use of aspirin, non-aspirin nonsteroidal anti-inflammatory agents, heparin, angiotensin converting enzyme inhibitors, beta-blockers, calcium antagonists, and diuretics. In the case of angiotensin converting enzyme inhibitors, beta-blockers, calcium antagonists and diuretics, patients were required to receive stable doses for at least three days preceding study entry. Heparin use referred to intravenous heparin other than flush solution.

A similar procedure was used to investigate interactions of the cofactors with treatment. The only cofactor-interactions that were considered were renal insufficiency, diabetes mellitus, the drug classes described above, plus all other terms mentioned above that contributed significant main effects.

All statistical tests were two-tailed; P values of 0.05 or less for tests for hypothesis treatment effects were considered significant; P values of 0.10 or less were considered significant for the exploratory tests of the interactions with treatment and for all tests (of main effects and interactions) in the cofactor analysis.

Results

Patient entry

A total of 1390 of the 1462 patients who enrolled received study contrast media. The 72 patients who did not receive study contrast media were equally likely to have been assigned to iohexol (N = 34) or diatrizoate (N = 38).

Of those receiving contrast, 1196 were followed for at least 48 hours post-catheterization and were considered evaluable for the primary renal outcome analysis. The 194 patients who were not evaluable for renal function were as likely to have received iohexol (N = 102) as diatrizoate (N = 92). The reasons for non-evaluability of these patients were an immediate requirement for cardiac surgery or coronary angioplasty (N = 74), missing laboratory specimens (N = 61), administration of nephrotoxic drugs (N = 21), refusal to cooperate with protocol follow-up (N = 17), and other (N = 21).

The distribution of the 1196 patients who were evaluable for renal function by stratification groups was as follows: normal renal function without diabetes, N = 364 (30.4%); normal renal function with diabetes, N = 318 (26.6%); renal insufficiency without diabetes, N = 298 (24.9%); and renal insufficiency with diabetes, N = 216 (18.1%).

Table 1. Clinical characteristics and catheterization data[a]

	Iohexol (N = 594)	Diatrizoate (N = 602)	P value
	Percent		
Gender			0.75
Male	70.9	71.9	
Female	29.1	28.1	
Mean age *years*	63.8 ± 10.5	63.7 ± 10.3	0.92
Age distribution			
≥50 years	90.1	89.2	
≥70 years	32.1	30.4	
Cardiac status (NYHA Class)			0.73
I or II	68.9	69.9	
III or IV	31.0	29.8	
History of:			
Renal insufficiency	44.8	46.8	
Diabetes mellitus	43.1	46.5	
Prior reaction to contrast media	5.5	8.7	
Physical examination			
Mean weight *Kg*	82.1 ± 15.9	81.9 ± 16.9	0.63
Mean height *cm*	170.9 ± 9.9	171.7 ± 10.7	0.14
Mean supine blood pressure *mm Hg*	134/76 ± 22/12	136/76 ± 23/11	
Mean standing blood pressure *mm Hg*	131/76 ± 22/12	133/77 ± 23/11	
Concomitant medications			
Calcium antagonists	66.3	65.6	
Diuretics	47.5	43.4	
ACE inhibitors	26.1	23.6	
NSAIDS	10.9	10.8	
Oral hypoglycemic agents	21.7	22.8	
Insulin	24.9	25.6	
Catheterization Data			
Selective coronary arteriography	98.8	99.7	
Left ventriculography	88.4	86.4	
Mean LVEF %	54.2 ± 16.4	54.2 ± 15.9	
Mean volume of contrast *ml*	140.0 ± 56.6	139.1 ± 54.9	0.83
Mean volume of contrast */kg body weight*	1.78 ± 0.8	1.78 ± 0.8	0.53
Mean total volume intravenous hydration *ml*[b]	2393 ± 1362	2434 ± 1426	

Abbreviations are: NYHA, New York Heart Association; LVEF, Left ventricular ejection fraction.

[a] Plus-minus values are means ± SD

[b] Total intravenous hydration given pre, during and post-catheterization

Clinical characteristics and catheterization data

As presented in Table 1, clinical characteristics and catheterization data of the iohexol and diatrizoate patients who were evaluable for renal function did not disclose any significant differences between these two treatment groups. Recruitment (−18 to −24 hr) and baseline (0 hr) serum creatinine values are described in Table 2. The lower mean serum creatinine values at

Table 2. Recruitment (R) and baseline (B) serum creatinine values (mg/dl)[a]

	Iohexol[b]	Diatrizoate[b]
Total		
R	1.50 ± 0.67	1.53 ± 0.74
B	1.36 ± 0.64	1.39 ± 0.71
(−)RI(−)DM		
R	1.16 ± 0.24	1.14 ± 0.24
B	1.02 ± 0.19	1.00 ± 0.21
(−)RI(+)DM		
R	1.11 ± 0.26	1.14 ± 0.23
B	0.98 ± 0.21	0.99 ± 0.20
(+)RI(−)DM		
R	1.89 ± 0.66	1.95 ± 0.79
B	1.75 ± 0.60	1.78 ± 0.72
(+)RI(+)DM		
R	2.13 ± 0.83	2.20 ± 0.90
B	2.00 ± 0.81	2.06 ± 0.87

Abbreviations are: RI, renal insufficiency, DM, diabetes mellitus.
[a] Plus-minus values are means ± SD.
[b] The total patients in each treatment and stratification group are the same as the *N* values in Table 3 and Figure 1.

baseline compared to the recruitment values in each stratification group undoubtedly reflects the parenteral hydration administered pre-angiography.

Renal outcome data

Figure 1 shows the number and percent of evaluable patients who developed nephrotoxicity (**Methods**) by treatment and stratification group. In the iohexol group, 3.2% (19 of 591) of patients had an increase in the serum creatinine value of ≥1.0 mg/dl compared to 7.1% (42 of 592) of patients in the diatrizoate group, a difference which was highly significant ($P = 0.002$). Nephrotoxicity in both treatment groups was almost exclusively limited to patients who had renal insufficiency without or with diabetes (Fig. 1).

The renal outcome data was also analyzed using a secondary definition of nephrotoxicity as an increase in the baseline serum creatinine value of ≥0.5 mg/dl within 48 to 72 hours after contrast administration (Table 3). As expected, application of this more sensitive definition resulted in an increased incidence of nephrotoxicity in all groups but this did not effect the significant differences in nephrotoxicity between iohexol and diatrizoate ($P < 0.001$). Similar to the primary definition of nephrotoxicity, this analysis demonstrated that differences in nephrotoxicity between iohexol and diatrizoate groups were most evident in patients with either renal insufficiency alone or combined with diabetes mellitus.

For the entire population, the mean ± SE change in the serum creatinine value from baseline was significantly less in the iohexol compared to the diatrizoate patients at 24 hours (0.15 ± 0.01 mg/dl vs. 0.23 ± 0.01 mg/dl, $P < 0.001$) and 48 hours (0.22 ± 0.01 mg/dl vs. 0.28 ± 0.02 mg/dl, $P = 0.003$). There were only 324 patients with evaluable data at 72 hours. An interaction of stratification group with treatment was significant at 24 hours ($P = 0.002$) and 48 hours ($P = 0.003$) but not at 72 hours. The differences between iohexol and diatrizoate groups in the mean change from baseline in the serum creatinine were most pronounced in the patients who had renal insufficiency without or with diabetes mellitus, with the largest changes demonstrated in the latter group (Fig. 2).

The mean ± SD peak change in serum creatinine for patients who received iohexol was 0.28 ± 0.35 mg/dl compared to 0.35 ± 0.50 mg/dl for patients who received diatrizoate. Among patients with an increase from baseline in serum creatinine of ≥1.0 mg/dl, the mean ± SD peak changes in serum creatinine were 1.73 ± 0.82 mg/dl for patients who received iohexol and 1.82 ± 0.76 mg/dl in patients who received diatrizoate.

Cofactors associated with nephrotoxicity

The results of the logistic regression model used to analyze cofactors which were associated with an increased risk of nephrotoxicity (an increase in serum creatinine ≥1.0 mg/dl) are described in Table 4. Only those cofactors and their interactions which were significantly associated ($P \leq 0.10$) with nephrotoxicity are presented. The presence of renal insufficiency (baseline serum creatinine ≥1.5 mg/dl), diabetes mellitus, and male gender were each significantly associated with an increased risk of nephrotoxicity. Patients with renal insufficiency demonstrated a 21.1 times (CI 7.8 to 57.4) greater risk for nephrotoxicity than patients without renal insufficiency. Although the presence of diabetes mellitus was associated with a 3.4 times (CI 1.8 to 6.5) greater risk for nephrotoxicity, the frequency analysis of nephrotoxicity presented in Figure 1 demonstrates that the risk among patients without renal insufficiency was low regardless of the diabetic status. Cofactors analyzed in a continuous manner which were significantly associated with an increased risk of nephrotoxicity included baseline serum creatinine value and volume of contrast agent administered at angiography. An analysis of the interaction between type of contrast agent and the presence of baseline renal insufficiency demonstrated that patients with renal insufficiency who received diatrizoate were 3.3 times (CI 1.6 to 6.6) more likely to develop nephrotoxicity compared to similar patients who received iohexol. There was no significant difference between type of contrast agent in patients without renal insufficiency.

Clinical outcome

This study was not designed to examine differences in the clinical consequences of the various severities of nephrotoxicity following contrast administration. Nonetheless, 15 of 61 patients with acute nephrotoxicity were identified by the Safety Monitoring Committee to have developed unusually serious adverse renal events. Criteria for inclusion in this group included either oliguria, a requirement for acute dialysis, or an increase in the serum creatinine of sufficient magnitude to consider dialysis. In a few cases, limited follow-up data suggested that the nephrotoxicity was due to factors other than contrast (such as, cholesterol atheroemboli). An analysis of the clinical characteristics of these 15 patients revealed that 80% were male, mean age was 68.1 ± 10.7 years, and 66.6% had a NYHA class of III or IV. All of the patients had pre-existing renal insufficiency with a mean baseline creatinine value of 2.7 ± 1.2 mg/dl (range 1.5 to 5.4 mg/dl), 73% had concomitant diabetes mellitus, and the mean volume of contrast administered was 144 ± 52 ml (range 62 to 240 ml). The type of contrast agent administered was iohexol in six patients and diatrizoate in nine patients. Eight of the patients ultimately required acute dialysis ($N = 5$ iohexol; N = 3 diatrizoate) commencing 24 hours to 6 weeks after contrast administration.

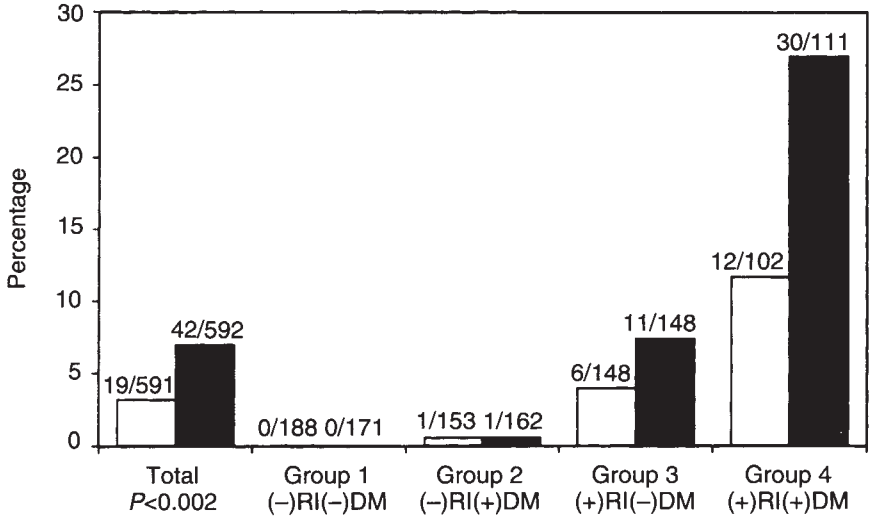

Fig. 1. *Percent of evaluable patients who developed nephrotoxicity for each treatment and stratification group following cardiac angiography.* Nephrotoxicity is defined as increase in serum creatinine of ≥1.0 mg/dl from baseline (0 hour) within 48 to 72 hours after contrast administration. Abbreviations are: RI, renal insufficiency; DM, diabetes mellitus. Symbols are: (□) iohexol; (■) meglumine/sodium diatrizoate.

Table 3. Frequency of nephrotoxicity: Defined as an increase in serum creatinine ≥0.5 mg/dl by treatment and stratification group

Group	Iohexol	Diatrizoate
	n/N (%)	
(−)RI(−)DM	16/188 (8.5)	14/171 (8.2)
(−)RI(+)DM	11/153 (7.2)	18/162 (11.1)
(+)RI(−)DM	18/148 (12.2)	40/148 (27.0)
(+)RI(+)DM	34/102 (33.3)	53/111 (47.7)
Total[a]	79/591 (13.4)	125/592 (21.1)

Abbreviations are: RI, renal insufficiency; DM, diabetes mellitus.
[a] Iohexol vs. diatrizoate, $P < 0.001$

Discussion

The introduction of nonionic (low-osmolality) contrast media in the 1980's was accompanied by expectations of reduced nephrotoxicity with these newer contrast agents as a result of observations in animal studies [6–11]. Although subsequent clinical studies demonstrated a nephrotoxic potential of nonionic contrast media [12–26], it remains unsettled if these newer contrast agents are associated with a lower incidence of nephrotoxicity compared to conventional ionic contrast media, especially in patients who are at high-risk for contrast-induced renal injury.

The purpose of the present study was to compare the incidence of nephrotoxicity following administration of the nonionic contrast agent iohexol and the ionic contrast agent diatrizoate in patients undergoing elective cardiac catheterization who were both at "low" and "high-risk" for contrast media nephrotoxicity. It is significant that this evaluation of 1196 patients, 514 of whom had renal insufficiency alone or combined with diabetes mellitus, is the largest prospective randomized trial performed to date which has compared the incidence of nephrotoxicity between nonionic and ionic contrast media, especially in "high-risk" patients.

In addition to the large sample size, other features in the design of our study also deserve comment. Randomization of the study population resulted in an equal distribution between the iohexol and diatrizoate treatment groups in those clinical characteristics and catheterization methods which may have affected renal outcomes (Tables 1 and 2). Of the 1,196 patients, renal function data were obtained in 99% at 48 hours and in 27% at 72 hours after contrast media administration, minimizing the possibility of acute nephrotoxicity escaping detection as a result of a post-contrast follow up period which was too brief (that is, ≤24 hours). The *a priori* selection of an increase in the baseline serum creatinine value of ≥1.0 mg/dl within 48 to 72 hours after contrast exposure as the primary outcome measure for evidence of contrast media nephrotoxicity was based on our opinion that a change of this magnitude was clinically relevant and sufficiently large to exclude laboratory variation as causal. Finally, strict enrollment criteria were developed to exclude patients in whom acute nephrotoxicity may have been caused by factors other than contrast media administration.

The results of our study demonstrate that the nonionic contrast agent iohexol is associated with significantly less nephrotoxicity than the ionic contrast agent diatrizoate in "high-risk" azotemic patients undergoing elective cardiac angiography. In addition, our findings demonstrate that in non-azotemic patients, regardless of the presence or absence of diabetes mellitus, there is no evidence of reduced nephrotoxicity by the use of the nonionic agent iohexol compared to the ionic agent diatrizoate. Although as a result of lower than expected incidence rates of nephrotoxicity, groups 1 to 3 (Fig. 1) were under powered to definitively exclude a difference between contrast media types, the extremely low incidence of nephrotoxicity in groups 1 and 2 make it unlikely that any differences between ionic and nonionic contrast media in these two groups which might be demonstrated with larger sample sizes would be clinically meaningful.

Our findings of a "selective" nephrotoxic benefit of the nonionic contrast agent iohexol conflict with previous studies which did not demonstrate a significant difference in nephrotoxicity between nonionic and ionic contrast media [16, 18, 19, 25, 29] or concluded that any differences which exist are of insufficient magnitude to be clinically significant [22, 23]. In a study by Moore et al [26], a reduced risk of nephrotoxicity was observed in patients with pre-existing renal insufficiency with nonionic compared to ionic contrast media (similar to our findings) although the statistical significance of the interaction was marginal ($P < 0.06$). The discrepancy in findings between our study and these earlier

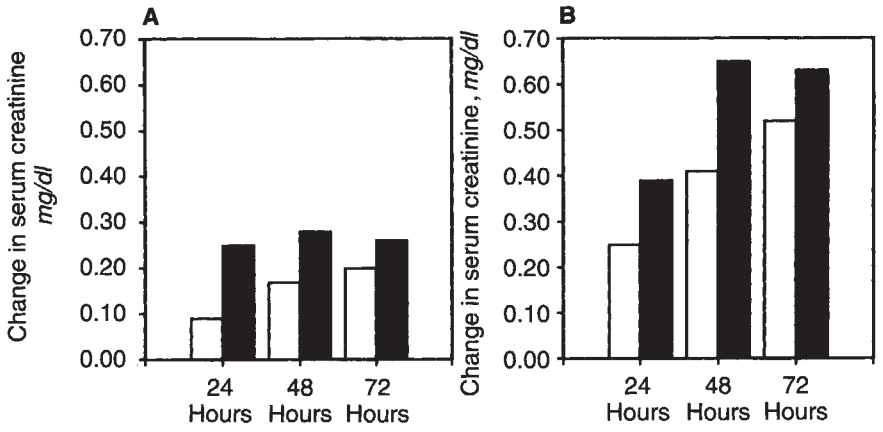

Fig. 2. *Mean ± SE changes in serum creatinine levels (mg/dl) from baseline (0 hour) in patients with renal insufficiency without (A) or with (B) diabetes mellitus for each treatment group at each time point following cardiac angiography.* Symbols are: (□) iohexol; (■) meglumine/sodium diatrizoate.

Table 4. Summary of logistic analysis: Significant[a] cofactors

Term	Parameter estimate	Standard Error	*P* value	Estimated odds ratio	95% Confidence interval
Gender *male vs. female*	+0.79	0.32	0.014	2.2	(1.2, 4.2)
Baseline serum					
Creatinine *mg/dl*	+0.83	0.18	<0.001	—	—
Diabetes mellitus	+1.12	0.33	<0.001	3.4	(1.8, 6.5)
Volume of contrast *ml*	+0.01	0.003	<0.001	—	—
Renal insufficiency					
baseline serum creatinine ≥1.0 mg/dl	+3.05	0.51	<0.001	21.1	(7.8, 57.4)
Contrast:					
diatrizoate versus iohexol	+0.27	0.21	NS	—	—
Renal insufficiency - contrast interaction	+0.91	0.29	0.001	—	—
Within subgroups: Diatrizoate versus iohexol					
Normal renal function	+0.03	0.21	—	1.3	(0.9, 2.0)
Renal insufficiency	+1.18	0.36	—	3.3	(1.6, 6.6)

Outcome was ≥ 1.0 mg/dl increase in serum creatinine.
[a] $P \leq 0.10$

investigations is most likely due to differences in sample size and study design. The number of patients with pre-existing renal insufficiency alone or combined with diabetes mellitus evaluated in previous studies was considerably smaller compared to the number of similar "high-risk" patients in this investigation. Given the incidences of nephrotoxicity found in our study for patients with chronic renal insufficiency alone or combined with diabetes mellitus, it is likely that previous studies [18, 22, 23, 25, 26] had insufficient power to avoid a Type II error in these populations of "high-risk" patients. This opinion is supported by a recent meta-analysis which concluded that nonionic contrast media are less nephrotoxic than ionic contrast media in patients with pre-existing renal insufficiency [30]. The absence of any differences in the incidence of nephrotoxicity between diatrizoate and iohexol in our patients with normal renal function without or with diabetes mellitus is, however, in agreement with previous studies, which have primarily evaluated similar "low-risk" patients [18, 19, 24, 26, 31].

Other design characteristics of earlier investigations which may have contributed to the discrepancy in findings between these studies and the present investigation include a failure to prospectively randomize patients into nonionic and ionic contrast media groups [16, 19, 24], the use of historic controls [16, 24], limited post-contrast periods for evaluation of renal function [23, 26], a disproportionate distribution of risk factors between contrast groups [16, 25, 26], and the administration of contrast media in settings other than cardiac catheterization [19, 22, 24–26]. In regards to this latter point, Moore et al [26] have demonstrated a higher incidence of contrast media-induced nephrotoxicity in patients undergoing cardiac catheterization compared to patients undergoing contrast media-enhanced body computed tomography. This difference may have been due to greater renal vasoconstriction with intraarterial injections as well as the larger volume of contrast media employed during cardiac catheterization [26]. Finally, we cannot exclude the possibility that differences between our study and previous investigations may, in part, be due to dissimilarities in the nephrotoxic potential of the specific formulations of contrast media evaluated. It is reasonable to consider that iohexol may be less nephrotoxic and/or diatrizoate (as Renografin) more nephrotoxic than other formulations investigated.

Using a logistic regression model, we found that pre-existing renal insufficiency, diabetes mellitus, and volume of contrast agent administered were significant independent risk factors for contrast media nephrotoxicity. These findings are in agreement with previous studies which have demonstrated similar risk factors for contrast media-induced nephrotoxicity [3, 4, 12, 16, 20, 22, 23, 25, 26, 32, 33].

Since there was no apparent difference in the incidence of more severe forms of nephrotoxicity between iohexol and diatrizoate in our study, and only a small number of patients required acute dialysis, similar to previous studies [3, 17, 18, 22, 23, 25, 26], the clinical implications of the findings in this study may be questioned. In view of the low incidence of clinically-severe acute renal failure inherent with contrast media exposure, any conclusions of a benefit of nonionic contrast media in reducing this form of nephrotoxicity will require the evaluation of an even greater number of "high-risk" patients or patients with more severe baseline azotemia. In this regard, we agree with the comments of Schwab et al [18] that the incidence of clinically serious nephrotoxicity in clinical practice may be greater than that demonstrated in research studies such as ours in which patients are carefully selected, optimally hydrated, and free of other factors which may predispose them to contrast nephrotoxicity. The incidence of severe forms of nephrotoxicity in this study may have also been reduced by the relatively high percentage of patients in both treatment groups who were on calcium antagonists which may have exerted a prophylactic benefit [34–36]. Until additional data are available, it remains speculative whether the differences in nephrotoxicity demonstrated in this study would also be evident for more severe forms of nephrotoxicity (that is, requiring acute dialysis) if a larger number of "high-risk" patients were evaluated.

Although not part of our study, we believe that the reduction by nonionic contrast media in milder forms of nephrotoxicity demonstrated in this study will affect clinical management and be cost-effective. In our experience, in the hospital setting an acute elevation of the serum creatinine of 1 mg/dl or more following contrast administration commonly leads to additional laboratory testing and postponement of further radiographic contrast exposure or surgical interventions, extending the period of hospitalization. Since one cannot prospectively identify which patients with contrast nephrotoxicity will progress to more clinically serious forms of acute renal failure once serum creatinine levels start to rise, such delays are inevitable. In an analogous manner, acute nephrotoxicity from aminoglycosides, which is also typically mild in nature, has been shown to substantially increase the cost of hospital care in affected individuals [37].

In conclusion, the results of this investigation demonstrate that the nonionic contrast agent iohexol is less nephrotoxic than the ionic contrast agent diatrizoate in patients with pre-existing renal insufficiency alone or combined with diabetes mellitus who undergo cardiac angiography. In contrast, in patients with normal renal function, regardless of the presence or absence of diabetes mellitus, nonionic contrast media are not less nephrotoxic compared to ionic contrast agents. Additional studies in high-risk patients will be required to determine if nonionic contrast media are also associated with a reduced incidence of severe nephrotoxicity (such as what would require acute dialysis) and if a reduction by nonionic contrast media of less severe forms of nephrotoxicity is cost-effective.

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References

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT: Hospital-acquired renal insufficiency: A prospective study. *Am J Med* 74:243–248, 1983
2. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G: Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. *Am J Med* 83:65–71, 1987
3. Coggins CH, Fang LS-T: Acute renal failure with antibiotics, anesthetic agents, and radiographic contrast agents (Chapt 11), in *Acute Renal Failure,* edited by Brenner BM, Lazarus JM, 2nd edition, New York, Churchill Livingstone, 1988, 295
4. Berns A: Nephrotoxocity of contrast media. *Kidney Int* 36:730–740, 1989
5. McClennan BL, Stolberg HO: Intravascular contrast media. Ionic versus nonionic: Current status. *Radiol Clin N Am* 29:437–454, 1991
6. Morris TW, Katzberg RW, Fisher HW: A comparison of the hemodynamic responses to metrizamide and meglumine/sodium diatrizoate in canine renal angiography. *Invest Radiol* 13:74–78, 1978
7. Thomsen HS, Dorph S, Mygind T, Hemmingsen MS, Holm J, Larsen S, Nielsen H, Rygaard H, Skaarup P: Urine profiles following intravenous diatrizoate, iohexol, or ioxilan in rats. *Invest Radiol* 23(Suppl 1):S168–S170, 1988
8. Lund G, Rysavy J, Salomonowitz E, Cragg A, Vlodaver Z, Bendell W, Castaneda-Zuniga W, Amplatz K: Nephrotoxicity of contrast media assessed by occlusion arteriography. *Radiology* 152: 615–619, 1984
9. Golman K, Almen T: Contrast media induced nephrotoxicity. Survey and present state. *Invest Radiol* 20: (Jan-Feb Supplement)S92–S97, 1985
10. Tornquist C, Almen T, Golman K, Holtos S: Renal function following nephroangiography with metrizamide and iohexol. Effects on renal blood flow, glomerular permeability and filtration rate and diuresis in dogs. *Acta Radiol* 26:483–489, 1985
11. Messana JM, Cieslinski DA, Nguyen VD, Humes HD: Comparison of the toxicity of the radiocontrast agents, iopamidol and diatrizoate, to rabbit renal proximal tubule cells in vitro. *J Pharmacol Exp Ther* 244:1139–1144, 1988
12. Cedgard S, Herlitz H, Geterud K, Attman P-O, Aurell M: Acute renal insufficiency after administration of low-osmolar contrast media. (letter) *Lancet* 2:1281, 1986
13. Evans JR, Shankel SW, Cutler RE: Low osmolar contrast agents and nephrotoxicity. (letter) *Ann Intern Med* 107:116, 1987
14. Cacoub P, Deray G, Baumelou A, Jacobs C: Nephrotoxicity of low osmolar radiocontrast agents in patients with chronic renal failure. (letter) *Nephron* 48:324–325, 1988.
15. Aron NB, Feinfeld DA, Peters AT, Lynn RI: Acute renal failure associated with ioxaglate, a low-osmolality radiocontrast agent. *Am J Kidney Dis* 13:189–193, 1989
16. Gomes AS, Lois JF, Baker JD, McGlade CT, Bunnell DH, Hartzman S: Acute renal dysfunction in high-risk patients after angiography: Comparison of ionic and nonionic contrast media. *Radiology* 170:65–68, 1989
17. Davidson CJ, Hlatky M, Morris KG, Pieper K, Skelton TN, Schwab SJ, Bashore TM: Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med* 110:119–124, 1989
18. Schwab SJ, Hlatky MA, Pieper KS, Davidson CJ, Morris KG, Skelton TM, Bashore TM: Contrast nephrotoxicity: A randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 320:149–153, 1989
19. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, Farid N, McManamon PJ: Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. *N Engl J Med* 320:143–149, 1989

20. MANSKE CL, SPRAFKA JM, STRONY JT, WANG W: Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 89:615–619, 1990
21. DERAY G, FAUCHER C, BRILLET G, BENHMIDA M, BLETRY O, JACOBS C: Acute renal failure caused by iopamidol, a nonionic, low-osmolar radiocontrast agent. *Am J Nephrol* 11:78–79, 1991
22. HARRIS KG, SMITH TP, CRAGG AH, LEMKE JH: Nephrotoxicity from contrast material in renal insufficiency: Ionic versus nonionic agents. *Radiology* 179:849–852, 1991
23. TALIERCIO CP, VLIETSTRA RE, ILSTRUP DM, BURNETT JC, MENKE KK, STENSRUD SL, HOLMES DR: A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. *J Am Coll Cardiol* 17:384–390, 1991
24. LAUTIN EM, FREEMAN NJ, SCHOENFELD AH, BAKAL CW, HARAMITI N, FRIEDMAN AC, LAUTIN JL, BRAHA S, KADISH EG, SPRAYREGEN S, BELIZON I: Radiocontrast-associated renal dysfunction: A comparison of lower-osmolality and conventional high-osmolality contrast media. *Am J Radiol* 157:59–65, 1991
25. BARRETT BJ, PARFREY PS, VAVASOUR HM, MCDONALD J, KENT G, HEFFERTON D, O'DEA F, STONE E, REDDY R, MCMANAMON PJ: Contrast nephropathy in patients with impaired renal function: High versus low osmolar media. *Kidney Int* 41:1274–1279, 1992
26. MOORE RD, STEINBERG EP, POWE NR, BRINKER JA, FISHMAN EK, GRAZIANO S, GOPALAN R: Nephrotoxicity of high-osmolality versus low-osmolality contrast media: Randomized clinical trial. *Radiology* 182:649–655, 1992
27. *BMDP.* BMDP Statistical Software Inc., Los Angeles, 1990
28. *SAS.* SAS Institute Inc., Cary, 1985
29. DERAY G, BELLIN M-F, BOULECHFAR H, BAUMELOU B, KOSKAS F, BAUMELOU A, GRELLET J, JACOBS C: Nephrotoxicity of contrast media in high-risk patients with renal insufficiency: Comparison of low- and high-osmolar contrast agents. *Am J Nephrol* 11:309–312, 1991
30. BARRETT BJ, CARLISLE EJ: Metaanalysis of the relative nephrotoxicity of high and low-osmolality iodinated contrast media. *Radiology* 188: 171–178, 1993
31. JEVNIKAR AM, FINNIE KJC, DENNIS B, PLUMMER DT, AVILA A, LINTON AL: Nephrotoxicity of high- and low-osmolality contrast media. *Nephron* 48:300–305, 1988
32. TALIERCIO CP, VLIETSTRA RE, FISHER LD, BURNETT JC: Risk for renal dysfunction with cardiac angiography. *Ann Intern Med* 104:501–504, 1986
33. CIGARROA RC, LANGE RA, WILLIAMS RH, HILLIS LD: Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 86:649–652, 1989
34. BAKRIS GL: Pathogenesis and therapeutic aspects of radiocontrast-included renal dysfunction (Chapt 13), in *Toxicology of the Kidney,* edited by HOOK JB, GOLDSTEIN RJ, 2nd edition, New York, Raven Press Ltd, 1993, 361
35. BAKRIS GL, BURNETT JC JR: A role for calcium in radiocontrast-induced reductions in renal hemodynamics. *Kidney Int* 27:465–468, 1985
36. RUSSO D, TESTA A, VOLPE LD, SANSONE G: Randomized prospective study on renal effects of two different contrast media in humans: Protective role of a calcium channel blocker. *Nephron* 55:254–257, 1990
37. EISENBERG JM, KOFFER H, GLICK HA, CONNELL ML, LOSS LE, TALBOT GH, SHUSTERMAN NH, STROM BL: What is the cost of nephrotoxicity associated with aminoglycosides? *Ann Intern Med* 107:900–909, 1987