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Nephrotoxic Effects in High-Risk Patients Undergoing Angiography

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ABSTRACT

BACKGROUND

The use of iodinated contrast medium can result in nephropathy. Whether iso-osmolar contrast medium is less nephrotoxic than low-osmolar contrast medium in high-risk patients is uncertain.

METHODS

We conducted a randomized, double-blind, prospective, multicenter study comparing the nephrotoxic effects of an iso-osmolar, dimeric, nonionic contrast medium, iodixanol, with those of a low-osmolar, nonionic, monomeric contrast medium, iohexol. The study involved 129 patients with diabetes with serum creatinine concentrations of 1.5 to 3.5 mg per deciliter who underwent coronary or aortofemoral angiography. The primary end point was the peak increase from base line in the creatinine concentration during the three days after angiography. Other end points were an increase in the creatinine concentration of 0.5 mg per deciliter or more, an increase of 1.0 mg per deciliter or more, and a change in the creatinine concentration from day 0 to day 7.

RESULTS

The creatinine concentration increased significantly less in patients who received iodixanol. From day 0 to day 3, the mean peak increase in creatinine was 0.13 mg per deciliter in the iodixanol group and 0.55 mg per deciliter in the iohexol group ($P=0.001$; the increase with iodixanol minus the increase with iohexol, -0.42 mg per deciliter [95 percent confidence interval, -0.73 to -0.22]). Two of the 64 patients in the iodixanol group (3 percent) had an increase in the creatinine concentration of 0.5 mg per deciliter or more, as compared with 17 of the 65 patients in the iohexol group (26 percent) ($P=0.002$; odds ratio for such an increase in the iodixanol group, 0.09 [95 percent confidence interval, 0.02 to 0.41]). No patient receiving iodixanol had an increase of 1.0 mg per deciliter or more, but 10 patients in the iohexol group (15 percent) did. The mean change in the creatinine concentration from day 0 to day 7 was 0.07 mg per deciliter in the iodixanol group and 0.24 mg per deciliter in the iohexol group ($P=0.003$; value in the iodixanol group minus the value in the iohexol group, -0.17 mg per deciliter [95 percent confidence interval, -0.34 to -0.07]).

CONCLUSIONS

Nephropathy induced by contrast medium may be less likely to develop in high-risk patients when iodixanol is used rather than a low-osmolar, nonionic contrast medium.

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ACUTE RENAL FAILURE IS SERIOUS AND costly.^{1,2} Nephropathy induced by contrast medium remains one of the most clinically important complications of the use of iodinated contrast medium.²⁻⁶ Most commonly, it is defined as an acute impairment of renal function manifested by an absolute increase in the serum creatinine concentration of at least 0.5 mg per deciliter (44.2 μ mol per liter) or by a relative increase of at least 25 percent from the base-line value.⁷⁻¹¹ The serum creatinine concentration typically peaks on the second or third day after exposure to contrast medium and usually returns to the base-line value within two weeks.^{6,12} However, renal function may not return to its base-line level, contributing to an increased risk of death.^{2,12}

The incidence of nephropathy induced by low-osmolar contrast medium is low in the general population and has been calculated to be less than 2 percent.³ Patients at increased risk include those with renal impairment and diabetes, especially in combination.^{8,10,13} In such patients, the incidence is significantly higher, in the range of 12 to 50 percent.^{2,4,8,10,14-18} Large clinical studies and meta-analyses have indicated that the use of low-osmolar contrast medium substantially reduces the risk of nephropathy in high-risk patients as compared with the use of high-osmolar contrast medium.^{8,9,11,14,19,20}

Iodixanol, a nonionic, dimeric contrast medium, is iso-osmolar to blood at all concentrations, and its level of general toxicity is lower than that of low-osmolar contrast mediums.²¹⁻²³ Extensive investigations of iodixanol in low-risk patients (patients without diabetes who have normal renal function) have shown no difference between the frequency of nephropathy associated with iodixanol and that of nephropathy associated with low-osmolar contrast mediums.^{3,21,24} This absence of difference may reflect the low risk of nephropathy in low-risk patients.⁷ Two small studies found no differences in renal toxicity between iodixanol and low-osmolar contrast mediums used in angiography in patients without diabetes who had renal failure.^{25,26} The first study indicating a reduced incidence of nephropathy with iodixanol in patients with renal impairment (one third of whom had diabetes) was reported by Chalmers and Jackson, who found that iodixanol was less than half as nephrotoxic as iohexol.²⁷ We performed a randomized, prospective, double-blind, multicenter study comparing the nephrotoxicity of iodixanol with that of

iohexol in patients with stable diabetes mellitus and impaired renal function who underwent coronary or aortofemoral angiography.

METHODS

STUDY PATIENTS

Patients were considered to be eligible for the study if they were older than 18 years of age, had been referred for coronary or aortofemoral angiography, had diabetes mellitus (type 1 or 2) that was being treated with insulin or oral antidiabetic drugs, and had either a stable serum creatinine concentration (1.5 to 3.5 mg per deciliter [133 to 308 μ mol per liter] for men and 1.3 to 3.5 mg per deciliter [115 to 308 μ mol per liter] for women) as measured within three months before enrollment or a calculated creatinine clearance of no more than 60 ml per minute, according to the formula of Cockcroft and Gault. Criteria for exclusion were pregnancy, lactation, intravascular administration of an iodinated contrast medium within the previous seven days, treatment with metformin or nonsteroidal antiinflammatory drugs within the previous 48 hours, intake of nephrotoxic drugs within the previous seven days, history of serious reactions to iodinated contrast mediums, newly discovered unstable diabetes, severe concomitant disease, renal transplantation, or end-stage renal disease necessitating dialysis. Written informed consent was obtained from each patient before enrollment.

STUDY PROTOCOL

The study was conducted in 17 centers in five European countries (Denmark, France, Germany, Spain, and Sweden). It was designed to compare the renal effects of a nonionic, iso-osmolar, dimeric contrast medium, iodixanol (320 mg of iodine per milliliter; 290 mOsm per kilogram of water [Visipaque, Amersham Health]), with those of the nonionic, low-osmolar, monomeric contrast medium iohexol (350 mg of iodine per milliliter; 780 mOsm per kilogram of water [Omnipaque, Amersham Health]).

Each patient was randomly assigned to receive one of the two contrast mediums, which were placed in identical vials to ensure blinding. The volume used varied among patients and was not standardized. All patients were to be well hydrated before angiography, according to local regimens. It was recommended, but not required, that patients receive 500 ml of water orally, 500 ml of saline intravenously, or both before the angiography, followed

by 1 liter of 0.9 percent saline or similar fluids intravenously from the start of the procedure.

The follow-up period was seven days. Serum creatinine was measured before examination (at base line, or day 0) and on days 2, 3, and 7. Morning urine samples were collected on days 0, 2, and 7 for measurement of albumin and the renal tubular enzymes N-acetyl- β -glucosaminidase and alkaline phosphatase. Data from these urinalyses were correlated with the urine creatinine concentration. A central laboratory performed all analyses. Patients were observed and questioned regarding adverse events and were instructed to report any symptoms. All adverse events were recorded during the seven-day follow-up period.

The primary end point was the peak increase in the serum creatinine concentration between day 0 (when contrast medium was administered) and day 3. Secondary end points were the number of patients with a peak increase of at least 0.5 mg per deciliter and the number with a peak increase of at least 1.0 mg per deciliter (88.4 μ mol per liter) during days 0 through 3 (these are the two increments that are most commonly used to define nephrotoxic effects), as well as the change in the serum creatinine concentration from day 0 to day 7. The protocol was approved by the ethics committee of each institution and by the health authorities in accordance with the national regulations in each country.

STATISTICAL ANALYSIS

For the calculation of the sample size, we assumed a base-line serum creatinine concentration of 1.8 mg per deciliter (159.1 μ mol per liter). Assuming a peak increase in the serum creatinine concentration of 25 percent for iohexol and 15 percent for iodixanol and a common standard deviation for the increase of 0.35 mg per deciliter (30.9 μ mol per liter), the inclusion of 61 subjects in each group allowed for a two-sided significance level of 5 percent and 80 percent power, assuming a normal distribution. All the 95 percent confidence intervals except those for the odds ratios were determined by the bootstrap method.²⁸

The statistical analyses of the peak increase in the serum creatinine concentration from day 0 to day 3, the change in the concentration from day 0 to day 7, and the changes in urine variables from base line to day 2 and from base line to day 7 were performed with the use of a linear regression in which the covariates were the contrast-medium group, age, base-line serum creatinine concentra-

tion, total dose administered (grams of iodine), and center. Only the significant covariates were included in the final model. This analysis assumes a normal distribution of increases in the creatinine concentration. Since some patients had a significantly greater increase in serum creatinine than others, a natural logarithmic transformation was performed for all serum creatinine measures, so that the assumption of normal distribution would be closer to being met. When this transformation is used, the results are measures of relative change rather than absolute change. First-order interactions, except for interactions with center, were included in the model. The number of subjects with a peak increase in the serum creatinine concentration of 1.0 mg per deciliter or more between day 0 and day 3 and the number with a peak increase of 0.5 mg per deciliter or more between day 0 and day 3 were analyzed by logistic regression with the covariates listed above. No interim analysis was performed.

RESULTS

STUDY PATIENTS

Between January 1999 and September 2001, 135 patients from 17 centers (median number per center, 8; range, 1 to 18) were enrolled in the study. Of the 135 patients, 6 patients from four different centers were excluded from per-protocol analyses because of major protocol violations. Of the 129 patients in whom the protocol was followed and who were evaluated for renal outcomes, 64 received iodixanol and 65 received iohexol. The two groups appeared to be clinically similar with regard to demographic and other base-line characteristics, although there were statistically significant differences in mean body-mass index (the weight in kilograms divided by the square of the height in meters) and in the duration of diabetes (Table 1).

EFFECT ON SERUM CREATININE CONCENTRATION

Iodixanol induced a significantly smaller mean increase in the serum creatinine concentration than did iohexol. The peak increase in the serum creatinine concentration within three days after the administration of contrast medium was 0.13 mg per deciliter (11.2 μ mol per liter) in the iodixanol group, as compared with 0.55 mg per deciliter (48.2 μ mol per liter) in the iohexol group ($P=0.001$); the increase with iodixanol minus the increase with iohexol was -0.42 mg per deciliter (-37.0 μ mol per liter) (95 percent confidence interval, -0.73 to -0.22

Table 1. Demographic and Base-Line Characteristics of the Patients.*

Characteristic	Iodixanol Group (N=64)	Iohexol Group (N=65)	Iodixanol Group minus Iohexol Group (95% CI)
Age (yr)	71.1±6.0	70.6±8.6	0.5 (-1.9 to 3.2)
Sex (no. of patients)			
Male	41	35	
Female	23	30	
Weight (kg)	76.5±12.4	77.2±14.4	-0.7 (-5.3 to 4.0)
Body-mass index	26.8±3.4	28.5±5.1	-1.7 (-3.1 to -0.2)
Duration of diabetes mellitus (yr)	12.8±9.8	18.0±12.2	-5.2 (-9.5 to -1.0)
Base-line serum creatinine concentration (mg/dl)	1.49±0.53	1.60±0.52	-0.11 (-0.29 to 0.07)
Base-line creatinine clearance (ml/min)	50.1±12.8	47.3±16.6	2.8 (-2.5 to 7.7)
No. of previous examinations with iodinated contrast medium	75	46	
Coronary angiography performed (no. of patients)	62	64	
No. of diseased vessels identified (% of patients)			
1	14	22	
>1	72	65	
PTCA performed (% of patients)	17	25	
Aortofemoral angiography performed (no. of patients)	2	1	
Hydration given intravenously (ml)	977±853	934±596	43 (-183 to 316)
Volume of contrast medium (ml)	163±88	162±82	1 (-27.3 to 30.3)
Total dose of contrast medium (g of iodine)	52±28	57±29	-5 (-14.4 to 5.1)

* Plus-minus values are means ±SD. The mean difference between the groups is significant (at a two-sided significance level of 5 percent) when the confidence interval (CI) does not include 0. To convert values for creatinine to micromoles per liter, multiply by 88.4. PTCA denotes percutaneous transluminal coronary angioplasty.

mg per deciliter [-64.9 to -19.8 μ mol per liter]) (Table 2). The effect of the base-line serum creatinine concentration was different in the two groups. Among patients who received iohexol, but not among those who received iodixanol, a higher base-line serum creatinine concentration was associated with a higher peak increase between day 0 and day 3 (P for interaction <0.001).

The secondary end points also showed that iodixanol was significantly less nephrotoxic than iohexol. The mean change in the serum creatinine concentration between day 0 and day 7 (when it was measured in 116 patients) was 0.07 mg per deciliter (6.3 μ mol per liter) in the iodixanol group and 0.24 mg per deciliter (21.4 μ mol per liter) in the iohexol group (P=0.003); the increase with iodixanol minus the increase with iohexol was -0.17 mg per deciliter (-15.1 μ mol per liter) (95 percent confidence interval, -0.34 to -0.07 mg per deciliter

[-30.2 to -6.0 μ mol per liter]). When the most common definition of contrast-medium-induced nephropathy (an increase in the serum creatinine concentration of at least 0.5 mg per deciliter) was used, the incidence of nephropathy was 3 percent in the iodixanol group (2 of 64 patients) and 26 percent in the iohexol group (17 of 65 patients) (P=0.002). The odds ratio for nephropathy in the iodixanol group as compared with the iohexol group was 0.09 (95 percent confidence interval, 0.02 to 0.41). Ten patients in the iohexol group (15 percent) but none in the iodixanol group had an increase in serum creatinine concentration of at least 1.0 mg per deciliter (Fig. 1).

EFFECT ON URINE VARIABLES

At base line, 10 patients in the iodixanol group and 23 in the iohexol group had urinary excretion of at least 50 mg of albumin per millimole of creatinine,

meeting the criteria for proteinuria. However, a high ratio of urinary albumin to creatinine did not correlate with a high peak increase in the serum creatinine concentration. Neither contrast medium resulted in a significant change in the excretion of the urinary enzymes *N*-acetyl- β -glucosaminidase and alkaline phosphatase from base line to day 2 or day 7.

ADVERSE EVENTS

A total of 42 adverse events occurred in 31 of the 135 enrolled patients (23 percent) — 13 in the iodixanol group and 29 in the iohexol group (Table 3). All seven serious events deemed to be related to contrast medium occurred in the iohexol group; five patients in this group had acute renal failure related to the use of iohexol, and one patient had both acute renal failure and arrhythmia related to the use of iohexol. Three of these six patients recovered, two died, and one had persistent renal failure.

DISCUSSION

Our study found that the use of iodixanol resulted in a significantly smaller increase in the serum creatinine concentration than did the use of iohexol. The peak increase in the serum creatinine concentration between day 0 and day 3 was significantly lower in the iodixanol group than in the iohexol group. The difference was also significant at day 7. The incidence of contrast-medium-induced nephropathy, defined as an increase in the serum creatinine concentration of 0.5 mg per deciliter or more, was 3 percent in the iodixanol group and 26 percent in the iohexol group. The odds of nephropathy were 11 times as high with iohexol as with iodixanol. An increase in the serum creatinine concentration of 1.0 mg per deciliter or more did not occur in any patient in the iodixanol group but occurred in 15 percent of those in the iohexol group.

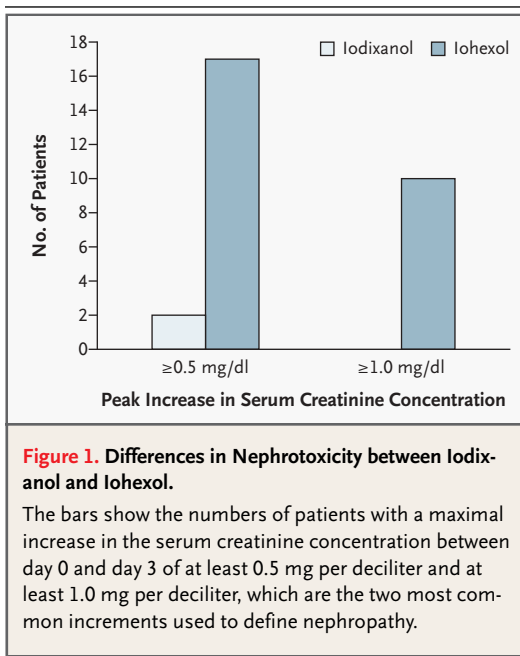
The first study to suggest that there was a reduced incidence of nephropathy with iodixanol was published by Chalmers and Jackson, who investigated 124 patients with serum creatinine concentrations of more than 1.7 mg per deciliter (150 μ mol per liter), one third of whom had diabetes.²⁷ In that unblinded study, patients were randomly assigned prospectively to receive either iodixanol or iohexol; the incidence of nephropathy (defined by an increase of 25 percent or more in the serum creatinine concentration) in the iodixanol group (3.7 percent) was less than half that in the iohexol group (10.0 percent). Our double-blind, randomized, controlled

Table 2. Peak Increase in the Serum Creatinine Concentration from Base Line to Day 3.*

Group	No. of Patients	Increase in Serum Creatinine Concentration		
		Mean \pm SD (95% CI)	Median	Range
Iodixanol	64	0.13 \pm 0.22 (0.08 to 0.18)	0.10	-0.21 to 0.84
Iohexol	65	0.55 \pm 0.98 (0.36 to 0.85)	0.21	-0.24 to 5.42

milligrams per deciliter

* To convert values for creatinine to micromoles per liter, multiply by 88.4. CI denotes confidence interval.



study not only confirms those results but also extends them to a population at higher risk for contrast-medium-induced nephropathy.

Why iso-osmolar contrast mediums are less nephrotoxic than low-osmolar contrast mediums is unclear. The difference might be explained by differences in either the osmolality or the chemotoxicity of the contrast mediums or their ionic composition.^{3,15,29} The osmotic diuresis induced by low-osmolar mediums is generally greater than that induced by iso-osmolar mediums. This diuresis may enhance distal sodium delivery, increasing medullary work and inducing hypoxia or volume depletion, with consequent activation of vasoreg-

Table 3. Adverse Events in 134 Patients in the Intention-to-Treat Population.*

Variable	Iodixanol Group (N= 67)		Iohexol Group (N= 67)	
	number			
Patients with an adverse event	9		22	
Adverse events	13		29	
Serious adverse events	4		11	
Related adverse events	2		8	
	<i>no. related to</i>		<i>no. related to</i>	
	<i>total no.</i>	<i>contrast medium</i>	<i>total no.</i>	<i>contrast medium</i>
Serious adverse events				
Arrhythmia	0	0	1	1
Cardiovascular event (angina pectoris, unstable angina pectoris, hematoma, myocardial infarction, or complications of myocardial infarction)	4	0	2	0
Multiple-organ failure	0	0	1	0
Pulmonary edema	0	0	1	0
Acute renal failure	0	0	6	6
Nonserious adverse events				
Cardiovascular event (angina pectoris, cardiac failure, hematoma, hypotension, or palpitation)	3	0	3	0
Gastrointestinal event (constipation, nausea, or vomiting)	2	1	5	1
Pain (abdominal pain, back pain, headache, or ischial neuralgia)	2	0	2	0
Skin-related event (increased sweating or urticaria)	1	1	1	0
Other event (C-reactive–protein positivity, epistaxis, hypoglycemia, hematuria, hemorrhage, or insomnia)	1	0	7	0

* One patient who, by mistake, received both contrast mediums was not included in the intention-to-treat analysis but did not have an adverse event. An adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not it was deemed to be related to the investigational product. A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, necessitated hospitalization or prolongation of hospitalization, or resulted in persistent or clinically significant disability or incapacity. A related adverse event was defined as an adverse event that was most likely caused by the investigational product.

ulatory hormones. If these vasoregulatory mechanisms are impaired (e.g., in patients with diabetes, renal impairment, or both), such impairment might be a major cause of renal damage after exposure to contrast medium and could explain the benefit of iso-osmolar contrast mediums.^{30,31}

That osmolality is an important factor in contrast-medium–induced nephropathy is supported by several studies. In a prospective, randomized study involving 1196 patients who underwent angiocardiology, Rudnick et al.⁸ found no differences in the incidence of nephropathy (defined as an increase of 0.5 mg per deciliter or more in the serum creatinine concentration within 72 hours after the administration of contrast medium) between patients receiving iohexol (low-osmolar; 780 mOsm per kilogram of water) and patients receiving diatrizoate (high-osmolar; 1870 mOsm per kilogram of water) among low-risk patients

(patients without diabetes who had a base-line serum creatinine concentration of less than 1.5 mg per deciliter [133 μ mol per liter]). However, among patients without diabetes whose serum creatinine concentrations were higher than 1.5 mg per deciliter, the incidence of nephropathy was reduced from 27.0 to 12.2 percent by the use of iohexol.⁸ Among patients with diabetes, the incidence was reduced from 47.7 to 33.3 percent. Overall, patients receiving high-osmolar contrast medium were 3.3 times as likely to have nephropathy induced by contrast medium as those receiving low-osmolar contrast medium.⁸ Our finding of a 26 percent incidence of nephropathy with iohexol is in agreement with the results of the study by Rudnick et al. Barrett and Carlisle performed a meta-analysis to determine the relative nephrotoxicity of contrast mediums using the results of 14 trials and concluded that the use of low-osmolar contrast medium rather than

high-osmolar contrast medium was beneficial to patients with preexisting renal failure.²⁰

In our study, base-line urinary albumin excretion did not correlate with the base-line serum creatinine concentration and was not a predictor of nephropathy. Our findings indicate that patients with a high base-line serum creatinine concentration and diabetic nephropathy were at lower risk when iodixanol was used.

The finding of a reduced incidence of nephropathy with the use of iodixanol presents an apparent contradiction to some of the experimental studies in rats that claim that the high viscosity of dimeric contrast mediums might be a risk factor because it might cause stasis in renal tubules.³² Our data also contradict some of the experimental studies in dogs, in which the use of iso-osmolar contrast medium conferred no advantage.^{33,34} These differences may reflect the difficulty of translating to patients the results of studies in animals.

Several approaches to the prevention of nephropathy induced by contrast medium have been reported, of which vigorous hydration may be the most important.^{5,29} Some medications, such as diuretics, mannitol, dopamine, calcium-channel blockers, endothelin-receptor antagonists, theophylline, and prostaglandin, have been tried without major success.^{11,35-38} Efforts to prevent nephropathy by administering acetylcysteine before the adminis-

tration of contrast medium have been discussed elsewhere.^{39,40} Acetylcysteine, a free-radical scavenger, has been shown to be renoprotective in some studies^{41,42} but not in others.^{43,44} In our study, only four patients in the iodixanol group and seven in the iohexol group received acetylcysteine. Exclusion of these patients from the analysis of the primary end point did not affect the results. A selective dopamine-1-receptor agonist, fenoldopam, has been reported to be useful in preventing contrast-medium-induced nephropathy.⁴⁵ Kini et al.⁴⁶ reported a protective effect of fenoldopam in patients with diabetes and impaired renal function who were undergoing coronary angiography; they found a 4 percent incidence of nephropathy, defined as a 25 percent increase in the serum creatinine concentration. However, that study was retrospective and lacked a control group.⁴⁶

Table 4 summarizes published data from controlled studies in which low-osmolar contrast mediums were used in patients with diabetes and renal impairment. Our study, which found a 3 percent incidence of contrast-medium-induced nephropathy with iodixanol, appears to have had a better outcome than previous studies that used low-osmolar contrast medium alone. The incidence of nephropathy in the iohexol group is consistent with earlier published results for similar groups of patients.^{8,9,11,14,20} The results in our iodixanol group

Table 4. Contrast-Medium-Induced Nephropathy in Patients with Diabetes in Controlled Studies with Low-Osmolar Contrast Mediums.*

Study	Medium Used (Mean Volume)	Procedure	Base-Line Serum Creatinine	Increase in Serum Creatinine Defining Contrast-Medium-Induced Nephropathy	Day on Which Peak Serum Creatinine Increase Was Measured	Incidence of Contrast-Medium-Induced Nephropathy
			mg/dl			no./total no. (%)
Barrett et al. ⁷	Low-osmolar contrast mediums (100 ml)	Angiocardiography, intravenous pyelography, computed tomography	≥1.4	>25%	2	3/24 (12)
Rudnick et al. ⁸	Iohexol (140 ml)	Angiocardiography	≥1.5 <1.5	>0.5 mg/dl	1-3	34/102 (33) 18/148 (12)
Taliercio et al. ⁹	Iopamidol (134 ml)	Angiocardiography	≥1.5	>0.5 mg/dl	1-5	6/20 (30)
Manske et al. ¹⁰	Iohexol or iopamidol (30 ml)	Angiocardiography	5.9±1.6	>25%	2	21/42 (50)
Wang et al. ¹¹	Low-osmolar contrast mediums (122 ml)	Angiocardiography	≥2.0	>0.5 mg/dl or >25%	2	15/39 (38)
Lautin et al. ¹⁴	Iohexol or ioxaglate (78 ml)	Peripheral (femoral) angiography	≥1.5 <1.5	>0.3 mg/dl and >20%	1-3	4/15 (27) 11/60 (18)

* To convert values for creatinine to micromoles per liter, multiply by 88.4. The plus-minus value is the mean ±SD.

were similar to or better than those in studies that included low-osmolar contrast mediums and acetylcysteine or fenoldopam. The use of iodixanol alone may eliminate many of the adverse effects or logistic problems created when prophylactic pharmacologic regimens are used. Thus, the likelihood

that contrast-medium-induced nephropathy will develop in high-risk patients appears to be significantly reduced when iodixanol, an iso-osmolar contrast medium, is used rather than a low-osmolar nonionic contrast medium.

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APPENDIX

In addition to the authors, the other investigators in the NEPHRIC study group are as follows: Denmark: J.K. Madsen, Rigshospitalet, Copenhagen; France: G. Grollier, Centre Hospitalier Universitaire de Caen, Caen; J.-M. Fauvel, Centre Hospitalier Universitaire de Rangueil, Toulouse; J.-L. Bonnet, Centre Hospitalier Universitaire de la Timone, Marseilles; J.-P. Beregi, Centre Hospitalier Général de Valenciennes, Valenciennes; Germany: J. vom Dahl, Klinikum der Technische Hochschule, Aachen; J. Petersen, Herzzentrum, Bad Krozingen; W. Rutsch, Universitätsklinikum Charité, Berlin; C. Özbek, Herzzentrum Klinikum Völklingen, Völklingen; Spain: A. Betriú, Hospital Clinic, Barcelona; C. Macaya, Hospital Clinico San Carlos, Madrid; Sweden: B. Lindvall, Huddinge University Hospital, Stockholm; B. Calissendorff, Huddinge University Hospital, Stockholm.

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