Prophylaxis of Contrast Material–induced Nephropathy in Patients in Intensive Care:

Acetylcysteine, Theophylline, or Both? A Randomized Study[1]

Wolfgang Huber, MD
Florian Eckel, MD
Michael Hennig, PhD
Hilkea Rosenbrock, PhD
Annette Wacker, MD
Dieter Saur, MD
Angelika Sennefelder, MD
Romain Hennico, MD
Cordula Schenk, MD
Alexander Meining, MD
Renate Schmelz, MD
Ralph Fritsch, MD
Wolfgang Weiss, MD
Peter Hamar, MD
Uwe Heemann, MD
Roland M. Schmid, MD

Purpose: To prospectively compare the protective effect of acetylcysteine, theophylline, and both agents combined in patients who are admitted to the intensive care unit with at least one risk factor for contrast material–induced nephropathy and who receive at least 100 mL of iodinated contrast medium.

Materials and Methods: Institutional ethics review board approval and informed consent were obtained. A total of 91 patients (mean age, 58.5 years ± 14.8 [standard deviation]; 31 women, 60 men; 150 examinations) were admitted to the intensive care unit with at least one risk factor for contrast-induced nephropathy and received either *(a)* 200 mg theophylline 30 minutes before contrast medium administration (group T), *(b)* 600 mg acetylcysteine twice daily on the day of and (if possible) the day before the examination (group A), or *(c)* both agents combined (group AT). The primary endpoint for this study was the incidence of contrast-induced nephropathy (χ^2 test).

Results: Groups T, A, and AT were comparable with regard to baseline creatinine levels and the amount of contrast medium administered. The incidence of contrast-induced nephropathy in groups T, A, and AT was 2%, 12%, and 4%, respectively, and was significantly lower in group T than in group A ($P = .047$). There was no significant difference in the incidence of contrast-induced nephropathy between groups A and AT ($P = .148$) or between groups T and AT ($P = .53$). For group A, serum creatinine did not change after 12, 24, or 48 hours compared with baseline. Creatinine levels in group T decreased 12 hours (1.19 mg/dL ± 0.58; $P = .008$) and 48 hours (1.16 mg/dL ± 0.55; $P = .034$) after contrast material injection compared with baseline (1.25 mg/dL ± 0.61). In group AT, creatinine significantly decreased 24 hours (1.21 mg/dL ± 0.74; $P = .003$) and 48 hours (1.17 mg/dL ± 0.69; $P < .001$) after contrast material injection compared with baseline (1.28 mg/dL ± 0.74). Group A had significantly higher maximal increases in creatinine than groups T and AT ($P = .014$).

Conclusion: For prophylaxis of contrast-induced nephropathy in patients who are admitted to the intensive care unit and who receive 100 mL or more of contrast medium, theophylline is superior to acetylcysteine.

© RSNA, 2006

Despite the use of low-osmolarity contrast media and prophylactic hydration, the impairment of renal function after contrast medium administration continues to be a clinical problem. With a prevalence of 12%, contrast material–induced (hereafter, contrast-induced nephropathy) nephropathy is the third most frequent cause of acute renal failure (1). The frequency of contrast-induced nephropathy strongly depends on a number of risk factors, including already impaired renal function, high amounts of contrast medium, and diabetes (Fig 1). Although the incidence is low in the absence of risk factors, in the worst case contrast-induced nephropathy occurs in more than 50% of patients (2–4,7–12). Contrast-induced nephropathy, which is defined according to Barrett and Parfrey (10) as an increase in serum creatinine levels of at least 0.5 mg/dL within 48 hours after the administration of contrast medium, results in longer hospitalization (11) and increased mortality (2,12). The in-hospital mortality of patients with contrast-induced nephropathy who require dialysis can be as high as 35.7% (2).

Most of these risk factors are frequently found in patients who have been admitted to the intensive care unit. Therefore, substantial effort has been invested in preventing contrast-induced nephropathy. Despite the protective effects of hydration that are described in several studies (13–15), other research-

ers have reported incidences of between 20% and 50% in patients who were thoroughly hydrated (8,9). Furthermore, it is often not possible to delay contrast medium radiography until adequate hydration has been achieved in emergency situations. Additionally, the resulting volume load of approximately 2 L/d is not without risk, especially for patients in the intensive care unit who have poor left ventricular function, adult respiratory distress syndrome, or decompensated cirrhosis.

The results of several studies (5,6,16–18) and those of a recent meta-analysis (19) have demonstrated a considerable reduction in the incidence of contrast-induced nephropathy by using medical prophylaxis with theophylline 30 minutes before contrast medium administration in patients with impaired renal function or other risk factors. Acetylcysteine administered 24 hours (9,20,21) or immediately (22,23) before contrast medium injection was preventive in patients with impaired renal function in five studies but was not preventive in at least 16 trials (24–32).

To our knowledge, there have been no clinical studies to date that compare these two prophylactic agents. Therefore, the purpose of our study was to prospectively compare the protective effect of acetylcysteine, theophylline, and both agents combined in patients who are admitted to the intensive care unit with at least one risk factor for contrast-induced nephropathy and who receive at least 100 mL of iodinated contrast medium.

Materials and Methods

Our institutional ethics review board approved this study, and informed consent was obtained from all patients or their relatives.

A power analysis was performed according to previous data on theophylline prophylaxis (5,6), with contrast-induced nephropathy incidences of 20% in the group without theophylline prophylaxis and 4% in the groups with theophylline prophylaxis. Assuming an additional prophylactic effect of acetylcysteine, the incidence of contrast-induced

nephropathy in the combined group was estimated as 1%. On the basis of the assumed incidences of contrast-induced nephropathy (1%, 4%, and 20%), a sample size of 47 cases per group was calculated for detecting a difference between these three rates with a power of 90% (nQuery, version 4.0; Statistical Solutions, Saugus, Mass).

Study Design

Between August 20, 2000, and May 27, 2002, 91 patients (31 women, 60 men) who were admitted to the intensive care unit with at least one risk factor listed in Figure 1, who had stable serum creatinine levels, and who were undergoing 150 consecutive radiographic imaging examinations with a minimum of 100 mL of parenteral contrast medium were randomly selected to receive either theophylline (group T), acetylcysteine (group A), or both agents combined (group AT).

Theophylline (200 mg) was administered intravenously as a short infusion 30 minutes before contrast medium injection. Acetylcysteine was given intravenously at a dose of 600 mg twice daily on the day before and the day of contrast medium administration. In case of emergency examination on the day of randomization, 600 mg of acetylcysteine was administered exclusively 30 minutes before and 12 hours after contrast medium injection. Patients in group AT received 200 mg of theophylline 30 minutes before contrast medium injection and 600 mg of acetylcysteine, as described for patients in

Advances in Knowledge

- In this prospective randomized study of 150 patients who were admitted to the intensive care unit and who received at least 100 mL of contrast medium, theophylline was superior to acetylcysteine with regard to prevention of contrast material–induced nephropathy.
- Compared with other prophylactic agents, theophylline (200 mg administered intravenously 30 min before the injection of contrast medium) is "easy to handle" and straightforward in emergency examinations.

group A (ie, two to four doses of 600 mg acetylcysteine).

Patients who were already undergoing pretreatment with theophylline or acetylcysteine were exclusively randomized into groups that included the preexisting prophylactic agent. Patients undergoing pretreatment with both agents were excluded. Figure 2 schematically shows the randomization procedure.

In a setting that included patients with acute renal failure, only those with stable renal function were eligible. The stability of renal function was verified by comparing the baseline creatinine value obtained immediately before contrast medium administration with at least one screening value obtained during the preceding 2 days. Patients with a difference of more than 0.4 mg/dL were excluded.

A total of 30 of 91 patients underwent repeat (up to four) radiographic examinations. To avoid the influence of previous examinations and randomization, patients who had undergone previous examinations were eligible for repeat examinations only after a minimum of 4 days had elapsed since their last examination and, in case of the absence of contrast-induced nephropathy, after the preceding contrast material–enhanced procedure. The criteria for the second randomization were the same as for the first randomization. Therefore, the same patient could be randomized according to different regimens for repeat examinations. The mean patient age ± standard deviation was 58.5 years ± 14.8 (range, 21–89 years). A total of 31 women underwent 54 examinations, and 60 men underwent 96 examinations.

Of the 151 radiographic procedures, 129 (85.4%) were performed with computed tomography, 11 (7.3%) with coronary angiography, four (2.6%) with a transjugular intrahepatic portosystemic shunt procedure, one (0.7%) with pulmonary angiography, three (2.0%) with celiac and mesenteric angiography, and three (2.0%) with cerebral arteriography. One patient underwent two consecutive radiographic examinations within 30 minutes. Therefore, the total amount of con-

trast medium that was administered during both examinations (CT and pulmonary angiography) was added, and this case was evaluated as a single examination for a total of 150 examinations.

All patients received at least 100 mL (100–400 mL) of the low-osmolarity contrast medium iomeprol (Imeron 350, Byk-Gulden, Germany [coronary angiography procedures, $n = 11$] or Imeron 300, Byk-Gulden [all other examinations, $n = 139$]).

The most frequent underlying diseases and/or indications for radiography were sepsis (24 [16%] of 150 cases), pancreatitis (27 [18%] of 150 cases), complications of liver cirrhosis (15 [10%] of 150 cases), other gastrointestinal disorders (24 [16]% of 150 cases), and cardiac (18 [12%] of 150 cases), pulmonary (21 [14%] of 150 cases), and central nervous system (21

[14%] of 150 cases) impairment. Exclusion criteria were pregnancy or contraindications to theophylline (untreated high-grade arrhythmia or history of seizures) or acetylcysteine (previous allergy).

Hydration was performed according to clinical data, laboratory results (fractional excretion of sodium), radiographic evidence (chest radiography), and hemodynamic findings (central venous pressure and hemodynamic monitoring by using a pulmonary arterial catheter or PiCCO [Pulse Conture Cardiac Output; Pulsion Medical Systems, Munich, Germany]) if available. The choice of hydration solution was made with respect to underlying disease and to the results of serum electrolyte analysis in patients admitted to the intensive care unit.

Serum creatinine and blood urea nitrogen levels were determined once

Figure 1

Risk Factors for Contrast–induced Nephropathy

- Impaired renal function (2–6)
  - Serum creatinine level of 1.2 mg/dL or more
  - Decreased creatinine clearance
- Diabetes mellitus (only in cases of renal impairment) (2)
- Dehydration, diuretics (5)
- High dose of contrast medium (2,5,6)
  - More than 2 mL of contrast medium per kilogram body weight
- Cigarroa quotient of greater than 5.0 (3,5,6)
  - Contrast medium (mL) × serum creatinine level (mg/dL) per kilogram body weight
  - 21% versus 2% increase in creatinine of 1 mg/dL or more ($P < .001$) (3)
- Old age (4)
- Hypertension (5,6)
- Intraarterial administration of contrast medium
- Heart insufficiency
  - New York Heart Association score of III or greater
  - Ejection fraction of less than 50%
- Nephrotoxic medication (5)
  - Nonsteroidal anti-inflammatory drugs
  - Aminoglycoside
  - Vancomycine
  - Amphotericine B
- Repeat exposure to contrast medium
- Proteinuria
- Plasmocytoma and/or paraproteinuria

Figure 1: Risk factors for contrast-induced nephropathy. Where available, references are listed in parentheses.

12–48 hours before ("screening"), immediately before ("baseline"), and 12, 24, and 48 hours after contrast medium administration.

Urinary excretion of *N*-acetyl-β-glucosaminidase, creatinine, total protein, albumin, and α-1-microglobulin were determined 0, 12, 24, and 48 hours after the administration of contrast medium. To exclude the dilution effects of osmotic diuresis induced by the contrast medium, proteinuria markers were calculated in relation to urinary creatinine concentration.

Urine volume and fluid balance were determined at 12-hour intervals before and up to 48 hours after the administration of contrast medium. Follow-up was performed in patients with contrast-induced nephropathy and included daily determination of serum creatinine levels until discharge or death.

Endpoints

The incidence of contrast-induced nephropathy was the primary endpoint. Secondary endpoints included the time course of renal retention parameters for serum creatinine and blood urea nitrogen levels (compared with baseline values), a regression analysis with regard to the maximum increase in serum creatinine levels (see below), a comparison of the prevalence of risk factors between patients with and those without contrast-induced nephropathy, the follow-up of patients with contrast-induced nephropathy until discharge or death, and the documentation of side

Figure 2

Pretreatment	Prophylaxis
Theophylline: no / Acetylcysteine: no	Theophylline
Theophylline: yes / Acetylcysteine: no	Acetylcysteine
Theophylline: no / Acetylcysteine: yes	Theophylline **and** Acetylcysteine

Figure 2: Chart demonstrates randomization procedure. Patients who were already undergoing pretreatment with theophylline or acetylcysteine were randomized into groups that included the preexisting prophylactic agent. Patients undergoing pretreatment with both agents were excluded.

effects attributable to theophylline or acetylcysteine.

The monitoring of patients and the decisions regarding hydration were performed by authors who were working in the intensive care unit (W.H., F.E., A.W., D.S., A.S., R.H., C.S., A.M., R.S., R.F.). The data acquisition and evaluation were performed by four authors (W.H., F.E., M.H., H.R.).

Statistical Analysis

Dichotomous parameters were compared by using the χ^2 test. The Wilcoxon test for unpaired samples was used to compare continuous parameters between the treatment groups, and the Wilcoxon test for paired samples was used to compare follow-up results with respective baseline values within each treatment group.

Risk factors pertaining to contrast-induced nephropathy (Fig 1) were documented prospectively. An explorative analysis was performed by using a multiple regression analysis (backward selection) with Y = maximum increase in serum creatinine level, as compared with baseline values, within 48 hours, as well as variables for group (A, T, or AT), age, weight, diabetes (yes or no), hypertension (yes or no), serum creatinine and blood urea nitrogen levels at baseline, Cigarroa quotient at baseline (contrast medium [in milliliters] × serum creatinine level [in milligrams per deciliter] per kilogram body weight), amount of contrast medium administered, nephrotoxic medication (yes or no), pathologic urinary screening, and pathologic renal ultrasongraphy (US). All statistical analyses were performed by using a commercially available software program (SAS, version 6.12; SAS Institute, Cary, NC).

Results

Risk Factors and Baseline Characteristics

Patients receiving theophylline, acetylcysteine, or both agents combined were comparable with regard to risk factors for contrast-induced nephropathy, including baseline creatinine levels (1.25 mg/dL ± 0.61 for group T vs 1.25 mg/

dL ± 0.74 for group A vs 1.28 mg/dL ± 0.74 for group AT), screening creatinine levels (1.24 mg/dL ± 0.61 for group T vs 1.33 mg/dL ± 0.81 for group A vs 1.38 mg/dL ± 0.89 for group AT), amount of contrast medium administered (163.4 mL ± 58.1 for group T vs 150.6 mL ± 33.4 for group A vs 157.0 mL ± 45.0 for group AT), Cigarroa quotient (2.76 ± 1.54 for group T vs 2.62 ± 1.52 for group A vs 2.86 ± 1.87 for group AT), and prevalence of diabetes (29% for group T vs 32% for group A vs 20% for group AT) (Table 1). Differences were not significant for any of these factors. The only significant difference between the three groups was a higher baseline value for blood urea nitrogen levels in group AT (34.3 mg/dL ± 20.0; *P* = .035) compared with group T (25.2 mg/dL ± 14.8) and group A (28.3 mg/dL ± 21.3). The mean baseline and screening creatinine levels were not significantly different between any of the three groups.

Primary Endpoint: Incidence of Contrast-induced Nephropathy

The overall incidence of contrast-induced nephropathy, which was assessed according to the definition by Barrett and Parfrey (10), was low and occurred after only nine (6%) of 150 examinations. As shown in Figure 3, the incidence of contrast-induced nephropathy according to Barrett and Parfrey's definition was significantly lower (*P* = .047) among patients who received only theophylline (one of 51 cases) compared with those who received only acetylcysteine (six of 50 cases). No statistically significant difference in the incidence of contrast-induced nephropathy was found between groups A and AT (*P* = .148) or between groups T and AT (*P* = .53).

A subgroup analysis of patients with serum creatinine levels of more than 1.5 mg/dL gives further evidence that theophylline is superior to acetylcysteine for prophylaxis of contrast-induced nephropathy in these patients: The incidence of contrast-induced nephropathy in patients with creatinine levels of more than 1.5 mg/dL was significantly higher in group A (five [45%] of 11
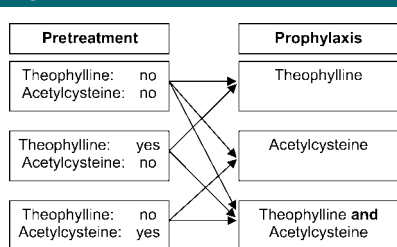
Table 1

Demographic Data and Main Risk Factors

Main Risk Factors	Group A	Group T	Group AT	P Value*
Age (y)†	55.4 ± 15.4	59.6 ± 14.3	60.6 ± 14.4	NS
Baseline creatinine level (mg/dL)†	1.25 ± 0.74	1.25 ± 0.61	1.28 ± 0.74	NS
Body weight (kg)†				
Before contrast material	74.3 ± 11.4	73.6 ± 12.9	72.7 ± 12.0	NS
After contrast material	74.5 ± 11.4	73.3 ± 12.9	72.6 ± 11.9	NS
Baseline BUN level (mg/dL)†	28.3 ± 21.3	25.2 ± 14.8	34.3 ± 20.0‡	.035‡
Amount of contrast medium (mL)				
Mean†	150.6 ± 33.4	163.4 ± 58.1	157.0 ± 45.0	NS
Range	100–280	100–400	100–300	
Cigarroa quotient‡	2.62 ± 1.52	2.76 ± 1.54	2.86 ± 1.87	NS
Diabetes mellitus	32 (16/50)	29 (15/51)	20 (10/49)	NS
Hypertension	38 (19/50)	53 (27/51)	55 (27/49)	NS
Sepsis	46 (23/50)	45 (23/51)	43 (21/49)	NS
Previous shock	44 (22/50)	49 (25/51)	49 (24/49)	NS
Catecholamines	24 (12/50)	31 (16/51)	31 (15/49)	NS
Emergency examination	44 (22/50)	63 (32/51)	41 (20/49)	NS
Pathologic urinary screening	66 (33/50)	71 (36/51)	45 (22/49)	NS
Pathologic renal US	8 (4/50)	20 (10/51)	14 (7/49)	NS
Diuretics	66 (33/50)	59 (30/51)	65 (32/49)	NS
Aminoglykoside	22 (11/50)	22 (11/51)	18 (9/49)	NS
Amphotericine B	4 (2/50)	6 (3/51)	12 (6/49)	NS
Vancomycine	26 (13/50)	24 (12/51)	35 (17/49)	NS
NSAID	20 (10/50)	35 (18/51)	20 (10/49)	NS
Nephrotoxic medication	90 (45/50)	86 (44/51)	86 (42/49)	NS
Fluid balance (mL/h)†				
Before contrast material	30.3 ± 65.5	19.0 ± 70.8	15.0 ± 72.5	NS
After contrast material	29.3 ± 58.3	3.3 ± 47.6	7.8 ± 35.8	NS
Urine volume (mL/h)†				
Before contrast material	106.8 ± 49.7	133.8 ± 66.1	119.8 ± 81.5	NS
After contrast material	112.3 ± 47.9	134.8 ± 69.0	144.3 ± 78.8	NS
Pretreatment with acetylcysteine	38 (19/50)	0 (0/51)	61 (30/49)	NS
Pretreatment with theophylline	0 (0/50)	10 (5/51)	16 (8/49)	NS

Note.—Unless otherwise indicated, data are percentages, with raw data in parentheses. BUN = blood urea nitrogen. NSAID = nonsteroidal antiinflammatory drug.

* NS = not significant.

† Data are the mean ± standard deviation.

‡ Cigarroa quotient = contrast medium (in milliliters) × serum creatinine level (in milligrams per deciliter) per kilogram body weight. Data are the mean ± standard deviation.
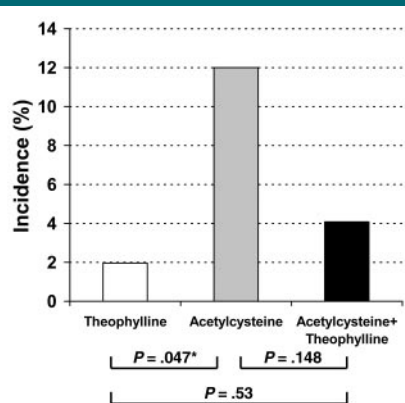
Figure 3

Figure 3: Bar graph demonstrates that the incidence of contrast-induced nephropathy was significantly lower among patients who received theophylline alone (one of 51 cases) than among those who received acetylcysteine alone (six of 50 cases) (P = .047). All other comparisons were not significant.

mg/dL ± 0.75; P = .46), 24 hours (1.25 mg/dL ± 0.77; P = .78), and 48 hours (1.27 mg/dL ± 0.84; P = 1.00) after the administration of contrast medium did not change compared with baseline (1.25 mg/dL ± 0.74).

In contrast, serum creatinine levels for patients in group T decreased 12 hours (1.19 mg/dL ± 0.58; P = .008) and 48 hours (1.16 mg/dL ± 0.55; P = .034) after the administration of contrast medium compared with baseline (1.25 mg/dL ± 0.61). In group AT, serum creatinine levels significantly decreased 24 hours (1.21 mg/dL ± 0.74; P = .003) and 48 hours (1.17 mg/dL ± 0.69; P < .001) after the administration of contrast medium compared with baseline (1.28 mg/dL ± 0.74).

Blood urea nitrogen levels were stable in groups T and A but decreased in group AT 12 (33.02 mg/dL ± 19.76; P = .009) and 24 (31.27 mg/dL ± 17.34; P = .014) hours after the administration of contrast medium compared with baseline (34.3 mg/dL ± 20.0).

Multiple regression analysis of risk factors.—The multiple regression analysis demonstrated that prophylactic agent (P = .014), age (P = .019), and hypertension (P = .049) were independent risk factors for the maximal increase in serum creatinine after con-

cases) than in group T (zero [0%] of 12 cases; P = .008) or group AT (one [7%] of 14 cases; P = .026). The incidence of contrast-induced nephropathy was not significantly different between groups T and AT (P = .345).

Secondary Endpoints

Time course of renal retention parameters.—Figure 4 shows the time course for two renal retention parameters—that is, serum creatinine and blood urea nitrogen levels—within the three groups.

Neither mean serum creatinine level nor mean blood urea nitrogen level increased in any group 12, 24, or 48 hours after the administration of contrast medium.

Overall, the time course for retention parameters was slightly more favorable among patients who received theophylline alone or in combination with acetylcysteine than in those who received acetylcysteine alone.

For patients in group A, serum creatinine levels obtained 12 hours (1.28

trast medium injection compared with baseline. Among the three different groups, patients who received acetyl-cysteine alone had a significantly higher maximal increase in serum creatinine ($P = .014$) compared with those who received theophylline alone or in combination with acetylcysteine.

Proteinuria.—Complete proteinuria diagnostics could be performed in 119 cases (42 in group T, 44 in group A, and 33 in group AT). Baseline levels for all five proteinuria markers were comparable in all three treatment groups (Table 2). For all patients, there was no increase in any proteinuria marker at any time. In contrast, urinary total protein concentration decreased significantly after 12 hours ($P = .028$), and urinary albumin concentration decreased significantly after 12 hours ($P = .006$) and 48 hours ($P = .031$).

Comparing the three different treatment groups yielded an increase in α-1-microglobuline ($P = .032$) and *N*-acetyl-β-glucosaminidase ($P = .007$) after 12 hours in group AT; this increase was not observed in the other two treatment groups. Additionally, total protein concentration decreased after 12 ($P = .034$) and 24 ($P = .031$) hours in group A but not in the two other groups. In group T, there was no change in any proteinuria marker at any time.

Characteristics and outcomes of patients with contrast-induced nephropathy.—Table 3 summarizes the characteristics of patients with and those without contrast-induced nephropathy. Comparisons of the incidences and means of risk factors for contrast-induced nephropathy between patients with and those without contrast-induced nephropathy reveal that the mean baseline values for creatinine, blood urea nitrogen, and Cigarroa quotient were significantly higher in patients with contrast-induced nephropathy (Table 3). Furthermore, the prevalence of sepsis and the use of catecholamines were significantly more frequent among patients with contrast-induced nephropathy. Patients with and those without contrast-induced nephropathy, however, were not different with regard to the amount and application (intravenous or intraarterial) of contrast medium or the prevalence of diabetes and hypertension.

Figure 5 shows the time course for the nine patients with contrast-induced nephropathy according to the definition by Barrett and Parfrey (10). A total of

Figure 4

a.

b.
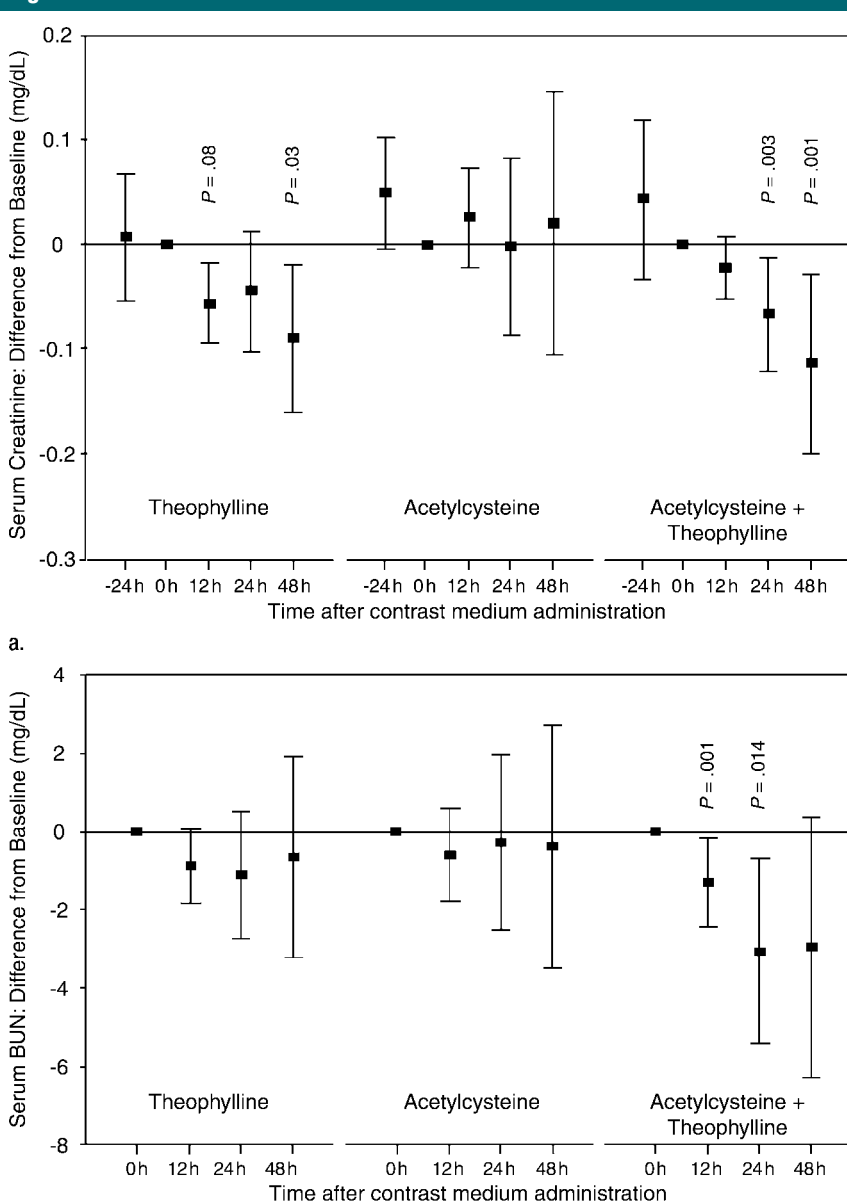
Figure 4: Time course of **(a)** serum creatinine and **(b)** blood urea nitrogen levels presented as the difference from baseline with 95% confidence intervals. Serum creatinine and blood urea nitrogen levels did not increased in any group after 12, 24, or 48 hours. In group A, serum creatinine did not change after 12, 24, or 48 hours compared with baseline. In group T, serum creatinine levels significantly decreased after 12 and 48 hours compared with baseline. In group AT, serum creatinine levels significantly decreased after 24 and 48 hours. Blood urea nitrogen levels were stable in groups T and A and decreased in group AT after 12 ($P = .009$) and 24 ($P = .014$) hours. Values for serum creatinine can be converted to micromoles per liter by multiplying by 88.4.

Table 2

Time Course of Proteinuria after Contrast Material Administration

Proteinuria Marker	All Patients	Group A	Group T	Group AT
Creatinine (mg/dL)				
0 h*	62.99 ± 47.64†	63.44 ± 34.10†	64.10 ± 61.03†	61.03 ± 45.53†
12 h	49.23 ± 35.06	51.50 ± 30.46	47.10 ± 33.35	48.77 ± 44.03
24 h	59.69 ± 35.06	66.43 ± 113.04	61.77 ± 56.66	46.20 ± 35.69
48 h	54.84 ± 40.36	57.45 ± 37.66	57.14 ± 42.34	48.82 ± 42.54
Total protein‡				
0 h*	1.14 ± 1.23†	0.96 ± 0.87†	1.38 ± 1.57†	1.10 ± 1.13†
12 h	1.05 ± 1.20 (.028)§	0.77 ± 0.64 (.034)§	1.41 ± 1.74	0.97 ± 0.76
24 h	1.05 ± 1.30	0.75 ± 0.64 (.031)§	1.27 ± 1.62	1.22 ± 1.52
48 h	0.93 ± 1.19	0.94 ± 1.56	0.79 ± 0.80	1.06 ± 0.98
Albumin‡				
0 h*	2.37 ± 4.03†	2.10 ± 3.64†	2.03 ± 3.65†	3.14 ± 4.19†
12 h	1.61 ± 2.95 (.006)§	1.20 ± 1.82	1.67 ± 3.89	2.13 ± 2.83
24 h	2.18 ± 5.93	1.24 ± 2.12	1.93 ± 5.19	4.03 ± 9.67
48 h	1.92 ± 4.16 (.031)§	1.33 ± 2.18	1.78 ± 3.73	2.86 ± 6.15
α-1-Microglobulin‡				
0 h*	2.09 ± 2.86†	1.41 ± 1.43†	2.81 ± 3.77†	2.09 ± 2.83†
12 h	2.23 ± 2.75	1.53 ± 1.45	2.70 ± 3.38	2.66 ± 3.11 (.032)§
24 h	2.15 ± 3.03	1.54 ± 1.65	2.51 ± 3.57	2.62 ± 3.77
48 h	1.87 ± 2.38	1.41 ± 1.37	1.70 ± 2.28	2.68 ± 3.28
N-Acetyl-β-glucosaminidase‖				
0 h*	0.86 ± 1.27†	0.80 ± 0.70†	1.04 ± 1.87†	0.74 ± 0.97†
12 h	0.91 ± 1.26	0.87 ± 0.96	0.78 ± 1.04	1.15 ± 1.82 (.007)§
24 h	0.98 ± 2.35	0.87 ± 0.97	0.79 ± 0.99	1.39 ± 4.28
48 h	0.75 ± 0.99	0.94 ± 1.30	0.60 ± 0.78	0.66 ± 0.64

Note.—Data are the mean ± standard deviation.

* Values obtained immediately before contrast medium administration.

† Baseline values were comparable in all groups.

‡ Measured in milligrams per gram creatinine.

§ Numbers in parentheses are P values. Significant differences were demonstrated when compared with baseline.

‖ Measured in international units per gram creatinine.

four patients died after contrast medium administration: one after 2 days (group AT), one after 5 days (group A), one after 10 days (group A), and one after 12 days (group A). The overall mortality of patients with contrast-induced nephropathy (four [44%] of nine patients) was significantly higher ($P <$ .001) than that of patients without contrast-induced nephropathy (three [4%] of 82 patients).

In one patient with contrast-induced nephropathy and anuric acute renal failure, dialysis was started 2 days after contrast medium administration and continued until death, which occurred 10 days after contrast medium administration. The other three of four lethal cases were caused by malignant diseases (esophageal carcinoma, cholan-giocellular carcinoma, and multiple myeloma). With respect to the underlying malignancies and written declarations of all three patients, no dialysis was performed. All three patients had clinical and laboratory signs of oliguric or anuric acute renal failure at the time of death.

Two of the five surviving patients recovered from contrast-induced nephropathy and were discharged with normalized serum creatinine levels. One of them died 4 months after the administration of contrast medium. Among the four patients who survived long term, three were discharged with increased serum creatinine levels (0.3, 0.7, and 0.8 mg/dL) compared with baseline. In two of these patients, long-term follow-up demonstrated normal-ization of renal function within 4 weeks. Mean serum creatinine levels were not significantly increased compared with baseline values at discharge or death (2.84 mg/dL ± 1.77 vs 2.09 mg/dL ± 1.02; $P = $ .110).

Side effects.—None of the patients developed side effects that required therapeutic interventions. Particularly, there were no malignant arrhythmias after treatment with theophylline and no allergic side affects attributable to acetylcysteine.

Discussion

The overall incidence of contrast-induced nephropathy in our study (6%) is low compared with the results of several other studies in patients at similar

risk, including studies performed with no prophylaxis except hydration. The incidence of contrast-induced nephropathy among the hydrated control groups for Tepel et al (9), Shyu et al (20), Diaz-Sandoval et al (22), and Koch et al (8) was 21%, 25%, 45%, and 52%, respectively. Thus, a beneficial effect of at least one of the three different prophylactic approaches in our study is highly probable.

In general, the incidence of contrast-induced nephropathy was significantly associated with more severe renal impairment before contrast medium administration, sepsis, or the use of catecholamines. All these risk factors were comparable within the three study groups. A comparison of the three different groups in our study shows an advantage for those receiving theophylline alone or in combination with acetylcysteine compared with those receiving acetylcysteine alone. The incidence of contrast-induced nephropathy among patients receiving theophylline alone (2%) was significantly lower than the incidence of contrast-induced nephropathy among patients receiving acetylcysteine alone (12%) ($P = .047$). This effect is even more pronounced in patients with creatinine levels of more than 1.5 mg/dL ($P = .008$). Mean serum creatinine levels decreased in the two groups that received theophylline alone or in combination with acetylcysteine. Serum creatinine levels, however, did not decrease in group A.

The decrease in creatinine for patients in groups T and AT, despite the administration of contrast medium, can be explained by the benefits of radiographic diagnosis and intervention: The benefits of demonstrating sepsis and

Table 3

Characteristics of Patients with Contrast-induced Nephropathy and Comparison with Baseline Values

Characteristics and Risk Factors	Patient No.									Contrast-induced Nephropathy ($n = 9$)	No Contrast-induced Nephropathy ($n = 141$)	P Value*
	1	2	3	4	5	6	7	8	9			
Age (y)	68	77	52	70	59	79	61	74	57	66.3 ± 9.5[†]	58.0 ± 15.0[†]	NS
Prophylactic agent	T	A	A	A	A	A	A	Both	Both	...	...	...
Contrast medium												
Amount (mL)	140	100	100	120	170	170	240	140	120	144.4 ± 44.2[†]	157.9 ± 46.9[†]	NS
Type	Imeron 300	Imeron 300	Imeron 300	Imeron 300	Imeron 300	Imeron 300	Imeron 300	Imeron 300	Imeron 300	...	...	...
Administration route	IV	IV	IV	IV	IV	IV	IV	IV	IV	9/9 (100)[‡]	124/141 (88)[‡]	NS
Previous administration	No	No	No	No	Yes	No	No	Yes	No	2/9 (22)[§]	28/82 (34)[§]	NS
Baseline creatinine level (mg/dL)	1.5	1.8	3.9	1.2	1.9	2.5	2.2	3.3	0.7	2.11 ± 1.00[†]	1.21 ± 0.64[†]	.003
Baseline BUN level (mg/dL)	25	33	110	30	36	48	29	62	13	42.9 ± 28.8[†]	28.4 ± 18.2[†]	.046
Change in BUN level												
24 h	27	37	109	48	38	64	41	70	15	...	...	...
48 h	33	53	114	32	49	56	46	79	23	...	...	...
Cigarroa quotient	3.2	2.3	6.0	1.9	4.4	5.7	7.0	6.1	1.3	4.21 ± 2.10[†]	2.65 ± 1.57[†]	.026
Diabetes	No	Yes	No	No	No	No	No	Yes	No	2/9 (22)[#]	39/141 (28)[#]	NS
Hypertension	No	No	Yes	No	Yes	Yes	No	Yes	No	4/9 (44)[#]	69/141 (49)[#]	NS
Aminoglycoside	No	Yes	Yes	No	No	No	Yes	No	No	3/9 (33)[#]	28/141 (20)[#]	NS
Diuretic	No	Yes	No	Yes	Yes	No	No	Yes	Yes	5/9 (56)[#]	90/141 (64)[#]	NS
Nephrotoxic medication	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7/9 (78)[#]	124/141 (88)[#]	NS
Catecholamines	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	7/9 (78)[#]	36/141 (26)[#]	.003
Emergency examination	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	6/9 (67)[#]	68/141 (48)[#]	NS
Sepsis	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8/9 (89)[#]	59/141 (42)[#]	.012
Examination type	CT	CT	CT	CT	CT	CT	CT	TIPS	CT	...	...	...
Acetylcysteine doses	0	2	3	4	4	4	2	4	4	...	...	...

Note.—A = acetylcysteine, BUN = blood urea nitrogen, IV = intravenous, T = theophylline, TIPS = transjugular intrahepatic portosystemic shunt.

* NS = not significant.

[†] Data are the mean ± standard deviation.

[‡] Data are the number of examinations during which patients received contrast medium through intravenous administration. Numbers in parentheses are percentages.

[§] Data are the number of patients who received previous administration of contrast medium. Numbers in parentheses are percentages.

[ǁ] A total of 30 of 91 patients underwent repeat examinations; two of these patients developed contrast-induced nephropathy and 28 did not.

[#] Data are the number of examinations performed in patients who had the specific risk factor. Numbers in parentheses are percentages.

performing consecutive therapy on the source of sepsis may outweigh the potential noxious side effects of the contrast medium. This phenomenon has been previously described in patients who were admitted to the intensive care unit (17), as well as in other studies on contrast-induced nephropathy (9,21,22).

The multiple regression analysis demonstrated a significant reduction in the maximal increase in serum creatinine levels within 48 hours after contrast medium administration in patients who received theophylline (group T and group AT) compared with those who received acetylcysteine (group A). The time course for blood urea nitrogen levels was significantly more favorable among patients in group AT than among those in groups T or A. The latter might be a hint for an additive effect of the two agents. Both agents interfere with crucial steps of the multifactorial pathophysiologic process of contrast-induced nephropathy.

Contrast media cause renal vasoconstriction and medullary ischemia due to modulation of renal synthesis and the release of several vasoactive mediators such as nitric oxide (33), prostaglandins (8,34), and endothelin (35). One of the most important vasoconstrictive mediators is adenosine, which increases in renal concentration after the administration of contrast material (36–38). Theophylline is a nonselective adenosine A1 and A2 receptor antagonist that has prevented contrast-induced and adenosine A1 receptor–mediated afferent renal vasoconstriction in several experimental studies (37,38). The results of a number of clinical studies have shown substantial prophylactic effects after the administration of contrast material, especially in patients with impaired renal function (5,6,16–18,39–41). In addition to medullary ischemia, contrast material can induce postischemic reperfusion injuries that are mediated by reactive oxygen metabolites in the kidneys (42–44). Therefore, antioxidants such as superoxide dismutase, acetylcysteine, and allopurinol have been successfully used in experimental (45) and clinical trials (9,20–23,46).

The less pronounced prophylactic effect of acetylcysteine compared with theophylline in our study might be related to several reasons: To date, at least 16 randomized controlled studies on acetylcysteine prophylaxis have been published (9,20–32). Only five of these studies reported a significant benefit (9,20–23). The largest trial (32), which included 397 patients, and the most recent meta-analysis (31), which included 20 studies with a total of 2195 patients, did not show a statistically significant benefit for acetylcysteine prophylaxis. By contrast, another meta-analysis (19) demonstrated a significant reduction of contrast-induced renal impairment with theophylline ($P = .004$). Nevertheless, acetylcysteine might be effective in patients who receive smaller amounts of contrast medium (between 75 and 140 mL), as suggested by the results of three studies (9,20,21) and two subgroup analyses (24,31). The mean amount of contrast medium in our study, however, was 157 mL.

Theophylline, on the other hand, was effective in two studies that included patients who received larger amounts of contrast medium (207 and 249 mL) (5,18). Furthermore, the results of a previous study (47) demonstrate that acetylcysteine might interfere with the analysis of serum creatinine concentrations. These results suggest that acetylcysteine artificially decreases serum creatinine levels without improving renal function, as determined by superior parameters such as cystatin C. Creatinine metabolism is affected by acetylcysteine, either through direct activation of creatinine kinase or through reversal of inhibition by free radicals (48). Therefore, the authors classified the preventive effects of acetylcysteine as "questionable" (47).

Another explanation of the lower prophylactic efficiency of acetylcysteine might be the emergency setting of our study, which deliberately included patients who underwent contrast- enhanced procedures immediately after randomization. Therefore, only 28 (56%) of 50 cases that were randomized to receive acetylcysteine

Figure 5

Legend:
—□— Patient 1: T
—✕— Patient 2: A
—●— Patient 3: A; death after 5d
—— Patient 4: A; dialysis; death after 10d
—▲— Patient 5: A
—✕— Patient 6: A; death after 12d
—■— Patient 7: A
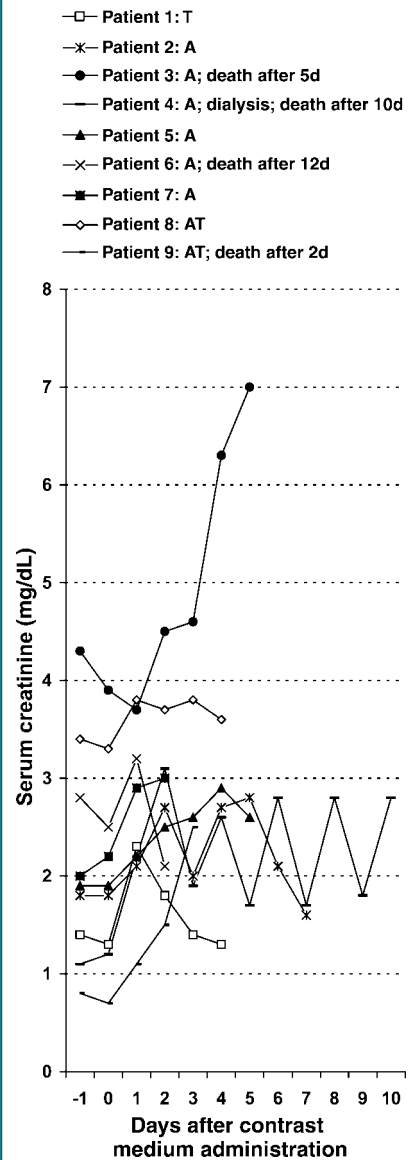—◇— Patient 8: AT
—— Patient 9: AT; death after 2d

Figure 5: Time course for serum creatinine in patients with contrast-induced nephropathy. Values for serum creatinine can be converted to micromoles per liter by multiplying by 88.4.

could be pretreated 24 hours before contrast medium administration, as suggested by the protocols of three trials with effective acetylcysteine prophylaxis (9,20,21). Other patients received only two doses of 600 mg acetylcysteine on the day of examination (16 [32%] of 50 cases) or two doses of 600 mg acetylcysteine on the day of

the examination and three doses of 300 mg acetylcysteine on the day before the examination (six [12%] of 50 cases) (three doses of 300 mg acetylcysteine is the standard mucolytic regimen in our intensive care unit).

Among the six patients who developed contrast-induced nephropathy despite acetylcysteine administration, only three received four doses of acetylcysteine starting 24 hours before the examination; the other three received acetylcysteine only two or three times but at least once before contrast medium administration. Comparisons of the incidence of contrast-induced nephropathy among patients who received four doses of acetylcysteine (three [11%] of 28 cases) and the incidence of contrast-induced nephropathy among patients who received theophylline (one [2%] of 51 cases) did not yield a statistically significant difference ($P = .090$). However, the incidence among the patients who received two or three doses of acetylcysteine (three [14%] of 22 cases) was significantly higher than that among patients who received theophylline alone (one [2%] of 51 cases, $P = .044$) and among all patients who received theophylline (ie, group T and AT together) (three [3%] of 100 patients, $P = .037$). Nevertheless, this subgroup analysis was not a prospective endpoint of the study.

Furthermore, a clinical study should be as close to clinical praxis as possible, including emergency examinations with high amounts of contrast material. Many of the emergency contrast-enhanced procedures in the intensive care unit cannot be delayed for 24 hours. Therefore, the immediate effect of theophylline given once 30 minutes before contrast medium injection is one of the main advantages of using this agent compared with 24-hour pretreatment with acetylcysteine. Additionally, the intensive care setting included patients with paralytic ileus and doubtful gastrointestinal absorption, which required rapid intravenous administration of both prophylactic agents. The efficiency of oral (18) and intravenous theophylline (5,6,17) has been demonstrated. Acetylcysteine was effective in four

studies (9,20–22) with oral administration and in one trial with intravenous administration (23). Therefore, it is not likely that the lower prophylactic efficiency of acetylcysteine resulted from intravenous administration.

Patients who underwent repeat examinations were deliberately included because repeat exposure to contrast medium is an important risk factor for contrast-induced nephropathy. Excluding patients with higher risk does not make sense in a study on prophylaxis. From a pathophysiologic viewpoint, a combination of theophylline and acetylcysteine might be superior to the administration of each agent alone. Indeed, the time course for serum creatinine and blood urea nitrogen levels was most favorable among the patients who received both agents, although these patients had significantly higher baseline blood urea nitrogen levels than those in the other two groups. The latter might be a bias induced by our randomization procedure given the opportunity to include patients who were pretreated with theophylline or acetylcysteine. Acetylcysteine is used frequently in the intensive care unit to liquefy mucus. Therefore, a large number of patients would have been withdrawn from the study if those who had undergone this treatment were excluded.

Nevertheless, a greater number of patients in group AT (38 [77%] of 49 cases) than in groups A and T (24 [24%] of 101 cases) had been pretreated with one of the prophylactic agents. Therefore, one might argue that these patients might have been more seriously ill than those in the other two groups. However, all other baseline characteristics, including the prevalence of multiple organ failure, catecholamine therapy, emergency examination, and baseline creatinine levels, were comparable.

Another limitation of our study might be the number of patients included. Despite the inclusion of a greater number of patients than most of the previous clinical studies concerning contrast-induced nephropathy, the statistical power is low with regard to the primary endpoint, especially for comparisons between groups T and AT.

However, to detect a difference between these two groups, which had incidences as low as 2% and 4%, with sufficient statistical power would require a study population of 1626 in each group (χ^2 test; power of 90% [nQuery, version 4.0; Statistical Solutions]).

Nevertheless, our study gives several hints for better prophylactic efficacy with theophylline versus acetylcysteine. Until studies that include the above-mentioned number of patients are available, prophylaxis of contrast-induced nephropathy should include theophylline, if possible in combination with acetylcysteine twice daily on the day before the contrast-enhanced procedure. Another limitation might be the absence of a strict hydration regimen for all patients. This, however, would have been unethical in patients who were admitted to the intensive care unit with a variety of different requests for fluid and electrolyte substitution. Nevertheless, our data concerning fluid balance and urine output demonstrate sufficient volume support, with a mean of more than 2.5 L/d over the complete observation period of 48 hours after contrast medium administration, which is much longer than the suggested hydration of more than 12 hours at 1 (mL · kg^{-1})/h. The mean amounts of urine output and fluid balance were comparable for all three groups; thus, a bias is not likely.

In addition to the prophylactic effect of theophylline, the overall low incidence of contrast-induced nephropathy (6%) might be partly the result of thorough hydration according to clinical, radiographic, hemodynamic, and laboratory data, which are usually unavailable in patients who are admitted to the intensive care unit. With respect to the absence of a control group without any medical prophylaxis, a prophylactic effect of acetylcysteine cannot be excluded. Finally, all our patients were white. There are, however, no data on ethnic susceptibility to contrast-induced nephropathy or racial differences with regard to the efficacy of theophylline or acetylcysteine.

In conclusion, for prophylaxis of contrast-induced nephropathy in pa-

Radiology

tients who are admitted to the intensive care unit and who receive 100 mL or more of contrast medium, theophylline is superior to acetylcysteine.

References

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983;74:243–248.

2. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368–375.

3. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 1989;86:649–652.

4. Rich MW, Crecelius CA. Incidence, risk factors and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years and older. Arch Intern Med 1990;150:1237–1242.

5. Huber W, Ilgmann K, Page M, et al. Effect of theophylline on contrast material–induced nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. Radiology 2002;223:772–779.

6. Huber W, Schipek C, Ilgmann K, et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. Am J Cardiol 2003;91:1157–1162.

7. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. Am J Med 1990;89:615–620.

8. Koch JA, Plum J, Grabensee B, Modder U; and the PGE_1 Study Group. Prostaglandin E_1: a new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? Nephrol Dial Transplant 2000;15:43–49.

9. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180–184.

10. Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med 1994;331:1449–1450.

11. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999;83:260–263.

12. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. JAMA 1996;275:1489–1494.

13. Eisenberg RL, Bank WO, Hedgock MW. Renal failure after major angiography can be avoided with hydration. AJR Am J Roentgenol 1981;136:859–861.

14. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast-media associated nephropathy: randomized comparison of 2 hydration regimes in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002;162:329–336.

15. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephropathy. Nephron Clin Pract 2003;93:C29–C34.

16. Erley CM, Duda SH, Schlepckow S, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kidney Int 1994;45:1425–1431.

17. Huber W, Jeschke B, Page M, et al. Reduced incidence of radio-contrast induced nephropathy in ICU patients under theophylline prophylaxis. Intensive Care Med 2001;27:1200–1209.

18. Kapoor A, Kumar S, Gulati S, Gambhir S, Sethi RS, Sinha N. The role of theophylline in contrast-induced nephropathy: a case-control study. Nephrol Dial Transplant 2002;17:1936–1941.

19. Ix JH, McCulloch CE, Chertow GM. Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis. Nephrol Dial Transplant 2004;19:2747–2753.

20. Shyu KG, Cheng JJ, Peiliang K. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol 2002;40:1383–1388.

21. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention. JAMA 2003;289:553–558.

22. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol 2002;89:356–358.

23. Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol 2003;41:2114–2118.

24. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast-agent-associated nephrotoxicity. J Am Coll Cardiol 2002;40:298–303.

25. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial on N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int 2002;62:2202–2207.

26. Allaqaband S, Tumuluri R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Interv 2002;57:279–283.

27. Boccalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheter Cardiovasc Interv 2003;58:336–341.

28. Vallero A, Cesano G, Pozzato M, et al. Contrast nephropathy in cardiac procedures: no advantages with prophylactic use of N-acetylcysteine (NAC) [in Italian]. G Ital Nefrol 2002;19:529–533.

29. Fung JW, Szeto CC, Chan WW, et al. Effect of N-acetylcysteine for prevention of contrast nephropathy in patients with moderate to severe renal insufficiency: a randomized trial. Am J Kidney Dis 2004;43:801–808.

30. Goldenberg I, Shechter M, Matetzky S, et al. Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography: a randomized controlled trial and review of the current literature. Eur Heart J 2004;25:212–218.

31. Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? a meta-analysis. Am J Med 2004;117:938–947.

32. Azmus AD, Gottschall C, Manica A, et al. Effectiveness of acetylcysteine in prevention of contrast nephropathy. J Invasive Cardiol 2005;17:80–84.

33. Touati C, Idee JM, Deray G. Modulation of the renal effects of contrast media by endothelium derived nitric oxide in the rat. Invest Radiol 1993;28:814–820.

34. Lund G, Einzig S, Rysavy J, Salomonowitz E, Castaneda-Zuniga W, Amplatz K. Effect of prostaglandin inhibition on the renal vascular response to ionic and non-ionic contrast media in the dog. Acta Radiol Diagn (Stockh) 1984;25:407–410.

35. Oldroyd S, Slee SJ, Haylor J, Morcos SK, Wilson C. Role for endothelin in the renal

responses to radiocontrast media in the rat. Clin Sci (Lond) 1994;87:427–434.

36. Osswald H, Schmitz HJ, Kemper R. Tissue content of adenosine, inosine and hypoxanthine in the rat kidney after ischemia and postischemic recirculation. Pflugers Arch 1977;371:45–49.

37. Arakawa K, Suzuki H, Naitoh M, et al. Role of adenosine in the renal responses to contrast media. Kidney Int 1996;49:1199–1206.

38. Oldroyd SD, Fang L, Haylor JL, Yates MS, El Nahas AM, Morcos SK. Effects of adenosine receptor antagonists on the responses to contrast media in the isolated rat kidney. Clin Sci 2000;98:303–311.

39. Erley CM, Duda SH, Rehfuss D, et al. Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline.

Nephrol Dial Transplant 1999;14:1146–1149.

40. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media: attenuation with theophylline. Radiology 1995;195:17–22.

41. Kolonko A, Wiecek A, Kokot F. The nonselective adenosine antagonist does prevent renal dysfunction induced by radiographic contrast agents. J Nephrol 1998;11:151–156.

42. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast-media-induced renal injury in volume depletion. Kidney Int 1992;41:1008–1015.

43. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Am J Kidney Dis 1997;29:465–477.

44. Bakris GL, Lass N, Gaber AO, Jones JD,

Burnett JC. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol 1990;258(1 pt 2):F115–F120.

45. DiMari J, Megyesi J, Udvarhelyi N, Price P, Davis R, Safirstein R. N-acetylcysteine ameliorates ischemic renal failure. Am J Physiol 1997;272(3 pt 2):F292–F298.

46. Katholi RE, Woods WT, Taylor GJ, et al. Oxygen free radicals and contrast nephropathy. Am J Kidney Dis 1998;32:64–71.

47. Hoffmann U, Fischereder M, Krüger B, Drobnik W, Krämer BK. The value of *N*-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol 2004;15:407–410.

48. Genet S, Kale RK, Baquer NZ. Effects of free radicals on cytosolic creatine kinase activities and protection by antioxidant enzymes and sulfhydryl compounds. Mol Cell Biochem 2000;210:23–28.