Prevention of Contrast-Induced Nephropathy With Sodium Bicarbonate: A Randomized Controlled Trial

Gregory J. Merten, MD  
W. Patrick Burgess, MD, PhD  
Lee V. Gray, MD  
Jeremiah H. Holleman, MD  
Timothy S. Roush, MD  
Glen J. Kowalchuk, MD  
Robert M. Bersin, MD  
Arl Van Moore, MD  
Charles A. Simonton III, MD  
Robert A. Rittase, PharmD  
H. James Norton, PhD  
Thomas P. Kennedy, MD, MPH

Context  Contrast-induced nephropathy remains a common complication of radiographic procedures. Pretreatment with sodium bicarbonate is more protective than sodium chloride in animal models of acute ischemic renal failure. Acute renal failure from both ischemia and contrast are postulated to occur from free-radical injury. However, no studies in humans or animals have evaluated the efficacy of sodium bicarbonate for prophylaxis against contrast-induced nephropathy.

Objective  To examine the efficacy of sodium bicarbonate compared with sodium chloride for preventive hydration before and after radiographic contrast.

Design, Setting, and Patients  A prospective, single-center, randomized trial conducted from September 16, 2002, to June 17, 2003, of 119 patients with stable serum creatinine levels of at least 1.1 mg/dL (≥97.2 µmol/L) who were randomized to receive a 154-mEq/L infusion of either sodium chloride (n=59) or sodium bicarbonate (n=60) before and after iopamidol administration (370 mg iodine/mL). Serum creatinine levels were measured at baseline and 1 and 2 days after contrast.

Interventions  Patients received 154 mEq/L of either sodium chloride or sodium bicarbonate, as a bolus of 3 mL/kg per hour for 1 hour before iopamidol contrast, followed by an infusion of 1 mL/kg per hour for 6 hours after the procedure.

Main Outcome Measure  Contrast-induced nephropathy, defined as an increase of 25% or more in serum creatinine within 2 days of contrast.

Results  There were no significant group differences in age, sex, incidence of diabetes mellitus, ethnicity, or contrast volume. Baseline serum creatinine was slightly higher but not statistically different in patients receiving sodium bicarbonate treatment (mean [SD], 1.71 [0.42] mg/dL [151.2 [37.1] µmol/L] for sodium chloride and 1.89 [0.69] mg/dL [167.1 [61.0] µmol/L] for sodium bicarbonate; P=.09). The primary end point of contrast-induced nephropathy occurred in 8 patients (13.6%) infused with sodium chloride but in only 1 (1.7%) of those receiving sodium bicarbonate (mean difference, 11.9%; 95% confidence interval [CI], 2.6%-21.2%; P=.02). A follow-up registry of 191 consecutive patients receiving prophylactic sodium bicarbonate and meeting the same inclusion criteria as the study resulted in 3 cases of contrast-induced nephropathy (1.6%; 95% CI, 0%-3.4%).

Conclusion  Hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure.

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iodixanol and hemofiltration before and after contrast injection have been recently described to reduce renal failure following contrast but are expensive strategies that tax the financial resources of health care systems.

All protocols to prevent contrast-induced nephropathy include the infusion of sodium chloride. However, in prophylactic hydration, it is possible that the most efficacious anion for sodium is not chloride but bicarbonate. Free-radical formation is promoted by an acidic environment typical of tubular urine but is inhibited by the higher pH of normal extracellular fluid. Because free radicals are postulated to mediate contrast-induced nephropathy, alkalinizing renal tubular fluid with bicarbonate may reduce injury. Pretreatment with sodium bicarbonate is more protective than sodium chloride for prophylaxis against contrast-induced nephropathy. We examined the hypothesis that the bicarbonate anion results in better outcomes than the chloride anion in hydration fluids administered before and after exposure to radiographic contrast.

**METHODS**

**Study Population**

This single-center, randomized controlled trial compared infusion of sodium chloride vs sodium bicarbonate as the hydration fluid to prevent renal failure in patients with stable renal insufficiency undergoing diagnostic or interventional procedures requiring radiographic contrast. A subsequent registry was established to additionally test the hypothesis that patients receiving sodium bicarbonate treatment experience a low incidence of contrast-induced renal failure. During the randomized study, consecutive eligible patients scheduled for exposure to the nonionic radiographic contrast agent iopamidol (796 mOsm/kg H₂O, 755 mg of iopamidol per milliliter, and 370 mg iodine per milliliter) were considered for enrollment. Eligible patients included individuals aged 18 years or older with stable serum creatinine levels of at least 1.1 mg/dL (≥97.2 µmol/L) who were scheduled to undergo cardiac catheterization, computed tomography, diagnostic or therapeutic arteriography, or transjugular intrahepatic portal systemic shunt placement. Exclusion criteria included serum creatinine levels of more than 8 mg/dL (≥707 µmol/L), change in serum creatinine levels of at least 0.5 mg/dL (≥44.2 µmol/L) during the previous 24 hours, preexisting dialysis, multiple myeloma, pulmonary edema, uncontrollable hypertension (treated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg), emergency catheterization, recent exposure to radiographic contrast within 2 days of the study, allergy to radiographic contrast, pregnancy, and administration of dopamine, mannitol, fenoldopam, or N-acetylcysteine during the intended time of the study.

The study was reviewed and approved by the institutional review board of the Carolinas Health Care System. All patients gave written informed consent for participation in the randomization trial or the subsequent registry phase.

**Protocol**

Patients were identified as study candidates based on preliminary laboratory test results and referral from the physician scheduled to perform the contrast study. Qualified patients who agreed to enter the study were sequentially assigned to 1 of 2 treatment groups by the pharmacy based on a computer-generated randomization schedule. Patients allocated to the sodium chloride group received 154 mEq/L of sodium chloride in 5% dextrose and H₂O. Patients allocated to the sodium bicarbonate group received 154 mEq/L of sodium bicarbonate in dextrose and H₂O, mixed in the hospital pharmacy by adding 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of 5% dextrose in H₂O, slightly diluting the dextrose concentration to 4.23%. After appropriate nursing evaluation and initial measurement of blood pressure and weight, the precontrast fluid was administered. The initial intravenous bolus was 3 mL/kg per hour for 1 hour immediately before radiocontrast injection. Following this, patients received the same fluid at a rate of 1 mL/kg per hour during the contrast exposure and for 6 hours after the procedure. For patients weighing more than 110 kg, the initial fluid bolus and drip were limited to those doses administered to a patient weighing 110 kg. Diuretics were routinely held on the day of contrast injection. A basic metabolic panel of serum chemistries was obtained on the morning of the procedure and on postprocedure days 1 and 2, and until any increase of serum creatinine resolved. Urinary pH was measured after infusion of the bolus when the patient next spontaneously voided. No diuretics were administered after a patient received contrast.

This study was partially but not completely blinded. The primary end point, serum creatinine level, was determined in a fully blinded fashion by laboratory personnel who measured serum creatinine by autoanalyzer without knowledge of patient study groups. Patients were not told to which group they were randomized. Although the investigators theoretically could have determined the results of randomization by inspection of solutions infused, their direct contact with patients consisted solely of obtaining informed consent before randomization.

**Data Collection and Management**

Clinical data were prospectively collected by 3 investigators (G.J.M, W.P.B, L.V.G.), coded, and entered into a computerized database. An independent physician data and safety monitoring board periodically assessed safety throughout the study. The clinical management of the patient was the responsibility of the attending physician.

**Study End Points and Statistical Analysis**

The primary outcome measure was development of contrast-induced nephropathy, defined by an increase in serum creatinine of 25% or more within...
2 days after administration of the radiographic contrast. This definition is identical to that used in a recent large meta-analysis in contrast-induced nephropathy. Postcontrast creatinine was assessed the mornings of days 1 and 2. The highest serum creatinine on postcontrast days 1 or 2 was used to calculate the change in serum creatinine (the primary end point), the estimated glomerular filtration rate (a secondary end point) by using the Modification of Diet in Renal Disease Study group formula, and incidence of contrast-induced nephropathy.

Before beginning the study, the institution’s biostatistician (H.J.N.) estimated the sample size needed for the primary end point of contrast-induced nephropathy, assuming development of contrast-induced renal failure in 15% of the sodium chloride group and 5% of the sodium bicarbonate group. Analysis indicated that a sample size of 260 patients would be required to detect a statistically significant difference with a power of 80% (α = .05).

Tests for significance were conducted using the t test for continuous variables and χ² test or Fisher exact test for categorical variables. All analyses were conducted using SAS software version 8.2 (SAS Institute Inc, Cary, NC). Data are expressed as mean (SD). All tests are 2-tailed, with differences reported as significant if P < .05. The study analysis was modified intention to treat and did not include protocol violators. Ten patients (5 per group) who did not return for follow-up laboratory tests were excluded. Inclusion of their baseline data in the analysis as last-observation-carried-forward was not informative and did not affect the results.

Study Termination
Midway through accumulation of the planned number of study patients, the safety monitor, who was not a study investigator and was blinded to the intervention groups, asked for an interim analysis to ensure that the sodium bicarbonate treatment group was experiencing an incidence of contrast-induced nephropathy no worse than that of the control group hydrated with sodium chloride. Although there were no prospectively established stopping rules, the study was halted after a review of the data because of ethical concern about continuing to expose the control group to the substantially higher risk of contrast nephropathy associated with sodium chloride hydration. Subsequent eligible patients were treated with the sodium bicarbonate prophylaxis and asked to enroll in a registry.

The registry comprised all patients who met the same inclusion criteria as the study. Outcomes were collected in the same way as the randomized trial. To simplify the sodium bicarbonate preparation for registry patients, the sodium bicarbonate solution was prepared by adding 3 ampules (150 mEq) of sodium bicarbonate to 1 L of 5% dextrose in H₂O, yielding a 130-mEq/L concentration of sodium bicarbonate and 4.35% dextrose. To obtain the same sodium bicarbonate load as those patients in the randomized phase, these registry patients received a 3.3-mL/kg initial bolus for 1 hour immediately before contrast injection, followed by an infusion of 1.18 mL/kg per hour thereafter for 6 hours.

RESULTS

Randomized Study
Between September 16, 2002, and June 17, 2003, 137 patients were randomized to receive sodium bicarbonate (n=69) or sodium chloride (n=68), with 119 patients completing the study (Figure 1). A total of 18 patients did not complete the study. Five outpatient study patients in each group neglected to follow instructions to return for follow-up laboratory studies but had good urine output at discharge. Although measurements of serum creatinine are not available for these individuals, none are known to have developed clinical renal failure following contrast exposure. Eight patients were protocol violators: 5 were not candidates because serum creatinine values were too low (≤ 1.0 mg/dL [≤ 88.4 µmol/L]) on the morning of the procedure, 2 had received another prophylactic agent (dopamine or N-acetylcysteine), and 1 was identified before contrast injection as hav-
ing an increasing serum creatinine level from bladder outlet obstruction. One patient’s prophylaxis regimen was arbitrarily changed by the attending physician from sodium chloride to sodium bicarbonate but this patient was included in the sodium chloride group analysis based on the intention-to-treat principle.

Characteristics of the 119 patients completing the study are shown in Table 1. There were no statistically significant differences between the groups in age, sex, ethnicity, incidence of diabetes mellitus, or weight. Cardiac catheterization was the most frequent radiocontrast procedure in this study (Figure 1). Treatment groups did not differ significantly by mean volume of contrast administered or in volumes of contrast received by individuals in either treatment group undergoing cardiac catheterization, computed tomography, or other miscellaneous procedures (Table 2). The mean baseline serum creatinine was slightly but not statistically higher (P = .09) and the glomerular filtration rate lower in patients receiving sodium bicarbonate treatment compared with those patients receiving sodium chloride. More patients with severe renal insufficiency (serum creatinine, ≥2.5 mg/dL [≥221 µmol/L]) were randomized to receive sodium bicarbonate (n = 8) than sodium chloride (n = 2) (Figure 2). Because elevated serum creatinine is an important risk factor for development of contrast-induced nephropathy, our nonstratified randomization procedure could have biased the study outcome against patients receiving sodium bicarbonate.

Postcontrast data for serum creatinine levels increased for those patients receiving sodium bicarbonate. Despite a higher mean baseline serum creatinine and a higher number of individuals with a baseline creatinine level of at least 2.5 mg/dL (≥221 µmol/L), the group receiving sodium bicarbonate treatment incurred only a 1.7% (1 of 60) incidence of contrast-induced nephropathy compared with 13.6% (8 of 59) in patients who received sodium chloride (mean difference, 11.9%; 95% confidence interval [CI], 2.6%–21.2%; P = .02) (Table 2). Post hoc analysis revealed that the percentage change in glomerular filtration rate after contrast (Figure 3) was significantly improved in patients receiving sodium bicarbonate treatment (+8.5%) compared with those receiving sodium chloride (–0.1%) (mean difference, –8.6%; 95% CI, –17.0% to –0.2%; P = .02). When results were analyzed by another common definition of contrast nephropathy, at least 0.5 mg/dL (≥44.2 µmol/L) change in serum creatinine, 7 (11.9%) of 59 patients who were treated with sodium chloride developed contrast nephropathy vs only 1 (1.7%) of 60 who received sodium bicarbonate (mean difference, 10.2%; 95% CI, 1.3%–19.1%; P = .03). The absolute risk reduction of contrast-induced nephropathy (defined as ≥25% change in serum creatinine), using sodium bicarbonate as the referent, was 10.6% (95% CI, 1.8%–19.4%; P = .02) (Table 2). The absolute risk reduction of contrast-induced nephropathy, at least 0.5 mg/dL (≥44.2 µmol/L) change in serum creatinine, 7 (11.9%) of 59 patients who were treated with sodium chloride developed contrast nephropathy vs only 1 (1.7%) of 60 who received sodium bicarbonate (mean difference, 10.2%; 95% CI, 1.3%–19.1%; P = .03). The absolute risk reduction of contrast-induced nephropathy (defined as ≥25% change in serum creatinine), using sodium bicarbonate as the referent, was 10.6% (95% CI, 1.8%–19.4%; P = .02) (Table 2).
compared with sodium chloride was 11.9%, resulting in a number needed to treat of 8.4 patients to prevent 1 case of renal failure.

All cases of contrast-induced nephropathy occurred in patients undergoing cardiac catheterization (8 [17%] of 48 patients who were treated with sodium chloride and 1 [2%] of 49 patients who were treated with sodium bicarbonate). When patients undergoing cardiac catheterization were analyzed independently, the benefit of sodium bicarbonate treatment was even larger (incidence of contrast-induced nephropathy, 16.7% for sodium chloride vs 2.0% for sodium bicarbonate; mean difference, 14.7%; 95% CI, 3.4%-25.9%; \( P = .02 \)). All individuals with contrast-induced nephropathy experienced prolonged hospitalization as a consequence of this complication but none required dialysis. Of the 9 randomized patients who experienced contrast-induced nephropathy, the mean (SD) baseline serum creatinine was 1.66 (0.56) mg/dL (146.7 [49.5] µmol/L) among the 8 patients receiving sodium chloride and 2.1 mg/dL (185.6 µmol/L) in the single patient treated with sodium bicarbonate. In the cases of contrast-induced nephropathy, the 8 patients who received sodium chloride had a mean (SD) contrast volume of 151 (50) mL (range, 100-250), not statistically different from the overall sodium chloride cohort. The only patient in the sodium bicarbonate treatment group who developed contrast-induced nephropathy received only 65 mL of contrast but experienced 24 hours of profound hypotension associated with an acute myocardial infarction. After restoration of this patient’s hemodynamic stability, the serum creatinine level returned to the baseline of 2.1 mg/dL (185.6 µmol/L) 4 days after contrast.

In each group, bolus administration of hydration fluid caused a moderate increase in both systolic and diastolic blood pressures that was not significantly different between groups (Table 2). The medical records of all patients who had a serum creatinine level increase of 25% or more were reviewed in detail. Other than the single patient in the sodium bicarbonate treatment group who developed contrast-induced nephropathy, no other patient was found to have an alternative explanation for deterioration of serum creatinine. No patient developed clinical heart failure or respiratory distress. One patient in the sodium bicarbonate treatment group had a blood pressure increase of more than 30 mm Hg with the administration of the bolus. The fluid bolus administration was discontinued and diuretic therapy was administered before proceeding with contrast injection. Following diuretics and contrast, the infusion was continued and the patient did not develop contrast-induced nephropathy.

Urine pH measurements after the initial bolus of fluid confirmed that patients receiving sodium bicarbonate experienced urinary alkalization (Table 2). A small but significant increase in serum bicarbonate occurred in patients receiving sodium bicarbonate. There was a small nonsignificant decrease in serum potassium in the sodium bicarbonate group, indicating that the alkaline load from sodium bicarbonate did not induce a decrease in serum potassium sufficient to create a risk for disturbances of cardiac rhythm.
Registry Phase

When randomization was discontinued, all subsequent patients meeting the original inclusion criteria were treated with sodium bicarbonate and asked to enroll in the registry until February 8, 2004. The demographic data of these 191 patients were not statistically different from either of the randomized groups. The mean (SD) serum creatinine level of registry patients was 1.79 (0.62) mg/dL (158.2 [54.8] μmol/L). The mean (SD) percentage change in serum creatinine was 0% (13.5%) and the mean (SD) percentage change in estimated glomerular filtration rate was +2.5% (16.9%). Contrast-induced nephropathy occurred in 3 (1.6%) of 191 patients (95% CI, 0%-3.4%).

COMMENT

In this study, we showed that replacing chloride ion with bicarbonate as the anion in sodium-containing hydration fluids significantly reduced nephropathy following radiographic contrast injection. In a recent meta-analysis, the incidence of contrast-induced nephropathy ranged from 2% to 26% in patients receiving N-acetylcysteine plus sodium chloride and 11% to 45% in those patients administered sodium chloride hydration alone.\(^\text{12}\) The cumulative incidence of contrast-induced nephropathy in our patients in the sodium bicarbonate treatment group (1.7% in randomized patients and 1.6% in the subsequent registry) is equal to or less than the lowest rate of injury reported with N-acetylcysteine\(^\text{12}\) and is far less than the published experience in patients hydrated with sodium chloride.\(^\text{5-11,16-18}\) These studies were performed with so-called nonionic low osmotic contrast agents of approximately 600 to 900 mOsm/L, similar to that of the iopamidol used in our study (796 mOsm/L). The subsequent data registry further confirms that preprocedure intravenous administration of sodium bicarbonate reduces renal injury from radiographic contrast. We envision that sodium bicarbonate could also be combined with other agents such as N-acetylcysteine, which alone does not always prevent contrast nephropathy.\(^\text{27-30}\)

The apparent success of sodium bicarbonate in reducing contrast-induced nephropathy is not likely the result of better volume expansion from sodium bicarbonate\(^\text{11,32}\) but is consistent with the hypothesis that contrast injury is from free radicals\(^\text{13-15}\) generated within the acid environment of the renal medulla. Contrast-induced nephropathy appears to be caused by the hyperosmolar nature of most contrast agents.\(^\text{1,3,16}\) Hyperosmolar stress triggers prompt cellular generation of reactive oxygen species.\(^\text{33-34}\) Effects from hyperosmolar stress might be compounded in the renal medulla, which is normally deficient in oxygen, with a PaO\(_2\) of 10 to 20 mm Hg.\(^\text{35}\) Radiocontrast causes vasoconstriction,\(^\text{35,14,16}\) a decrease in renal blood flow, and a further increase in medullary hypoxia\(^\text{37}\) that is exacerbated by the already compromised renal circulation in diabetes mellitus or preexisting kidney damage,\(^\text{33}\) or by nonsteroidal anti-inflammatory agents, which block normal prostaglandin enhancement of medullary blood flow.\(^\text{37,38}\)

Paradoxically, decreased tissue oxygen tension promotes mitochondrial generation of reactive oxygen species.\(^\text{39,40}\) Oxidant stress could also be magnified by the enhanced neutrophil adherence and emigration that is stimulated by local hypoxia.\(^\text{41}\) Thus, local conditions in the renal medulla after contrast favor oxidant injury, a hypothesis supported by the abrupt increase of malondialdehyde in renal venous plasma immediately following contrast-induced vasoconstriction and the reduction in experimental contrast-induced nephropathy by superoxide dismutase or allopurinol.\(^\text{13,15}\) The superoxide (O\(_2^-\))–driven Haber-Weiss reaction,

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\begin{align*}
\text{Fe}^{3+} + \text{O}_2^- & \rightarrow \text{Fe}^{2+} + \text{O}_2 \\
\text{Fe}^{2+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^- 
\end{align*}
\]

accounts for free-radical production in many oxidant-mediated human diseases.\(^\text{20}\) The reaction is catalyzed by minute amounts of iron in the biologic environment and is most active at acid pH (pKa = 4.9). However, at neutral pH, uncomplexed ferric ions precipitate as insoluble ferric hydroxides,\(^\text{21}\) reducing the production of injurious hydroxyl (OH) radicals.\(^\text{22}\) By increasing medullary pH, bicarbonate might protect from oxidant injury by slowing Haber-Weiss radical production. Also, superoxide generated by ischemia might react with medullary nitric oxide to form the potent oxidant peroxynitrite.\(^\text{43}\) At physiologic concentrations, bicarbonate scavenges peroxynitrite and other reactive species generated from nitric oxide.\(^\text{43}\) Thus, several oxidant mechanisms of renal injury might be disrupted by sodium bicarbonate.

The potential effect of sodium bicarbonate on these events is not surprising in light of pH conditions within the nephron. Near the end of the proximal tubule in the medulla, as a consequence of active reabsorption, the tubular bicarbonate concentration has declined to about 6 mEq/L, and the tubular fluid pH is approximately 6.5.\(^\text{19}\) In the descending Loop of Henle, water and chloride are passively reabsorbed,\(^\text{19}\) and urine pH increases to about 7.4 at the tip of the papilla, which is spared from contrast nephropathy,\(^\text{19}\) suggesting that higher pH is protective. In fact, patients with enhanced urinary acid excretion from high aldosterone (eg, dehydration, congestive heart failure, nephrotic syndrome, and cirrhosis) have increased risk of contrast-induced nephropathy.\(^\text{4}\) The beneficial effect of higher proximal tubular pH is supported by a report that acetazolamide, which blocks proximal tubular bicarbonate reabsorption, is protective in a rat model of contrast-induced renal failure.\(^\text{44}\)

A recent study advocated hemofiltration before and after contrast to prevent contrast-induced renal failure from coronary angiography.\(^\text{17}\) All dialysis procedures are alkalinizing and as reported, this study left open the question of whether its major benefit was from the increased clearance conferred by this invasive and expensive procedure or by the infusion of alkalinizing replacement solution.

Our study has several limitations. The results are from a single institution, sample sizes are small although adequately powered, and dropouts oc-
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curred in both study groups from outpatient participants who failed to return for postcontrast measurement of serum creatinine. Also, the study was terminated early when significant differences were found between groups, because of ethical concern about continuing to expose control patients to the substantially higher risk of contrast nephropathy associated with sodium chloride hydration alone. Nevertheless, the results suggest that hydration with sodium bicarbonate is efficacious and practical, requiring pretreatment only an hour before contrast injection. Although confirmation in a larger multisite institution study would be appropriate, infusion of sodium bicarbonate may provide an inexpensive, safe, practical, and simple method for preventing contrast-induced renal failure.

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