Contrast-Induced Nephrotoxicity: The Effects of Vasodilator Therapy

D. A. Bull, K. E. McIntyre, V. M. Bernhard, and R. L. Misiorowski

Surgical and *Radology Services, Tucson VA Medical Center and the Departments of Surgery and *Radiology,
University of Arizona Health Sciences Center, Tucson, Arizona 85723

Submitted for publication May 28, 1991

The increasingly frequent use of contrast-enhanced imaging for diagnosis or intervention in patients with peripheral vascular disease has generated concern about the incidence and avoidance of contrast-induced nephrotoxicity (CIN). In this prospective study, we sought to identify those patients at greater risk of developing CIN and to evaluate the efficacy of vasodilator therapy with dopamine in limiting this complication. Baseline serum creatinine (Cr) concentrations were obtained on admission and daily for up to 72 hr after angiography in 222 patients undergoing 232 angiographic procedures. The preangiographic treatment was varied at 2-month intervals for 1 year. All patients received an intravenous infusion of 5% dextrose and 0.45% normal saline at a rate of 75 to 125 ml/hr. During the first interval patients received 12.5 g of 25% mannitol immediately prior to their contrast load, in addition to intravenous fluids. During the next 2-month period the patients were given renal dose dopamine intravenously (3 μg/kg/min) commencing the evening before angiography and continued to the next morning. During the latter half of the study the treatment regimens were modified so that the use of mannitol was restricted to patients with diabetes mellitus and dopamine to patients with serum creatinine concentrations of ≥2 mg/dl. Postangiographic elevation in Cr occurred in 2, 10.4, and 62% of studies in patients with baseline creatinine levels of ≤1.2 mg/dl, 1.3 to 1.9 mg/dl, and ≥2.0 mg/dl, respectively. None of the patients receiving dopamine experienced an elevation in creatinine. There was no statistical correlation between age, diabetes, or medication with calcium channel blockers and CIN. Our preliminary results suggest that renal dose dopamine may reduce the incidence of contrast-induced nephrotoxicity in high risk patients. © 1992 Academic Press, Inc.

INTRODUCTION

The frequent use of diagnostic studies and therapeutic interventions requiring iv contrast agents in patients with peripheral vascular disease (PVD) has engendered concern about the risk and consequences of contrast-induced nephrotoxicity (CIN). This complication, the third leading cause of renal failure in hospitalized patients, often prolongs the hospital stay and may occasionally cause irreversible renal damage [1, 2]. Patients with preexisting renal dysfunction and/or diabetes are believed to be at highest risk [3–6]. Intravenous fluid volume loading, mannitol, calcium channel blockers, and furosemide have all been used clinically or experimentally with varying results to prevent the renal dysfunction following the infusion of contrast agents [4–9]. The objectives of this study were to identify those patients at greater risk of developing CIN and to evaluate the efficacy of renal vasodilation with dopamine in reducing the incidence of this complication.

MATERIALS AND METHODS

Two hundred and twenty-two patients with peripheral vascular disease underwent 232 peripheral or visceral arteriograms at the Tucson VA or University Medical Center, Tucson, Arizona. The cases were compiled prospectively. Each patient's usual medication, including the use of calcium channel blockers, furosemide, and insulin, was recorded.

Angiography was performed with ioxaglate sodium meglumine (Hexabrix) using the Seldinger technique. The patients were maintained on their preangiographic medications throughout the duration of the study.

The preangiographic treatment was varied at 2-month intervals during the 12 months of the study. All patients received an intravenous infusion of 5% dextrose and 0.45% normal saline at a rate of 75 to 125 ml/hr. During the first interval patients received 12.5 g of 25% mannitol immediately prior to their contrast load, in addition to intravenous fluids. During the next 2-month period the patients were given renal dose dopamine intravenously (3 μg/kg/min) commencing the evening before angiography and continued to the next morning. During the latter half of the study the treatment regimens were modified so that the use of mannitol was restricted to patients with diabetes mellitus and dopamine...
to patients with serum creatinine concentrations of \( \geq 2 \) mg/dl.

Serum creatinine (Cr) and BUN concentrations were determined prior to the administration of the contrast agent (pre-Cr, pre-BUN) and at least daily for up to 72 hr after the procedure (post-Cr, post-BUN). Differences between baseline and peak postangiographic values were calculated. An increase in Cr of \( \geq 1.0 \) mg/dl or \( \geq 50\% \) of baseline was considered significant.

**Statistical Analysis**

The data were analyzed using the Student \( t \) test, Fisher's exact test, and ANOVA. A \( P \) value \( < 0.05 \) was accepted as significant. All data are expressed as the mean \( \pm \) SD.

**RESULTS**

Of the 222 patients with PVD, 209 were male and 13 were female with a mean age of 64 \( \pm \) 10 years. Sixty-nine patients (31\%) were already taking calcium channel blockers, 33 (15\%) had insulin-dependent diabetes mellitus, and 37 (17\%) were taking furosemide (Table 1). One hundred and fifteen patients (52\%) received mannitol, 11 (5\%) received verapamil, and 30 (14\%) dopamine in addition to intravenous fluid (Table 2).

The mean volume of contrast administered was 116 \( \pm \) 50 cc. There was no significant difference in the amount of contrast infused into patients of any of the treatment groups.

The incidence of contrast-induced nephrotoxicity was greater among patients with impaired renal function.

**TABLE 1**

Demographics of Patients Undergoing Angiography

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>24</td>
<td>60</td>
<td>148</td>
</tr>
<tr>
<td>Pre-Cr (mg/dl)</td>
<td>( \geq 2.0 )</td>
<td>1.3 - 1.9</td>
<td>( \leq 1.2 )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.3 ( \pm ) 15.6</td>
<td>68.1 ( \pm ) 9.5</td>
<td>63.7 ( \pm ) 9.4</td>
</tr>
<tr>
<td>DM</td>
<td>4</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>LASIX</td>
<td>11</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Ca channel</td>
<td>13</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Contrast load (cc)</td>
<td>100 ( \pm ) 53</td>
<td>117 ( \pm ) 42</td>
<td>117 ( \pm ) 53</td>
</tr>
</tbody>
</table>

**TABLE 3**

Changes in Serum Creatinine Levels in Patients with Baseline Levels \( \geq 2.0 \) mg/dl

<table>
<thead>
<tr>
<th></th>
<th>Preangiographic</th>
<th>Postangiographic</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>11</td>
<td>3.0 ( \pm ) 1.5</td>
<td>2.5 ( \pm ) 1.5</td>
</tr>
<tr>
<td>No dopamine</td>
<td>13</td>
<td>2.6 ( \pm ) 0.4</td>
<td>3.9 ( \pm ) 1.9</td>
</tr>
</tbody>
</table>

Note. Means \( \pm \) SD.

* \( P < 0.05 \).

Significant elevation in serum creatinine occurred in 2\% (3 of 141) of studies in patients whose baseline Cr was \( \leq 1.2 \) mg/dl, in 10.4\% (5 of 48) of studies when serum creatinine ranged between 1.3 to 1.9 mg/dl, and in 62\% (8 of 13) of studies when the initial creatinine was \( \geq 2.0 \) mg/dl. One of the 13 patients with a baseline Cr of 2.0 mg/dl who had received standard therapy (fluid and mannitol) developed oliguric renal failure requiring temporary hemodialysis. In contrast none of the patients with Cr \( > 2.0 \) mg/dl who received dopamine had an elevation in Cr (Table 3). Postangiographic serum creatinine concentrations in patients receiving dopamine were lower compared to patients receiving fluids and mannitol alone, irrespective of baseline Cr concentrations (Fig. 1). The differences in Cr concentrations between the two groups only reached statistical significance in patients with serum creatinine \( \geq 2.0 \) mg/dl. Postangiographic Cr was not different in patients with DM or those taking furosemide or calcium channel blockers routinely. There were no significant differences in pre- and post-BUN in patients receiving either fluids and mannitol or dopamine therapy. Pre-Cr and post-Cr concentrations in patients receiving calcium channel blockers or mannitol with serum Cr \( \leq 2.0 \) mg/dl remained unchanged. There was no statistical correlation

**FIG. 1.** The effect of dopamine on postangiographic creatinine levels.
between age, the volume of contrast administered, or the presence of insulin-dependent diabetes and pre- and postangiographic serum creatinine (P = NS).

DISCUSSION

The reported incidence of nephrotoxicity in patients requiring intravenous contrast for imaging procedures ranged from 0 to 22% [10]. A number of factors probably account for the wide variation in the reported incidence of CIN including severity of atherosclerosis, diabetes, preexisting renal disease, age, hydration status, the dose and type of contrast agent used, the presence of congestive heart failure, the concomitant use of nephrotoxic drugs, repeated angiographic procedures in close proximity, and dysproteinemia [3–6, 11]. Of these, diabetes and preexisting renal disease have been identified as major risk factors in the development of CIN but others may contribute cumulatively [4, 5, 11]. In the series reported by Parfrey et al., the incidence of contrast induced nephrotoxicity in diabetics with coexistent renal disease was 9.0% versus 2.4% in diabetic patients without renal impairment [11].

Renal dysfunction following exposure to contrast agents may vary from a transient elevation in creatinine concentrations to oliguric renal failure requiring dialysis. In a study of 364 vascular patients undergoing angiography, Gomes et al. reported renal dysfunction (defined as an increase of 1 mg/dl or 50% above baseline Cr) of 7.1% (26). Five (19%) of the 26 patients required dialysis; 4 patients required permanent dialysis [12].

The mechanisms responsible for CIN remain uncertain. Impaired renal perfusion, altered glomerular permeability to proteins, direct tubular injury, intraluminal nephron obstruction, and a hypersensitivity response to the contrast agent have been proposed. When contrast is injected selectively into the renal artery, a biphasic response is elicited: transient vasodilation and increased renal blood flow is followed by prolonged, severe vasoconstriction accompanied by a 10–25% reduction in blood flow. The severity of the renal vasoconstriction appears proportional to the osmolality of the contrast used [10]. While the cause of this contrast-induced vasoconstriction is uncertain, activation of the renin-angiotensin system has been suggested [13]. Workman et al., however, did not observe significant changes in either renin or angiotensin following a bolus injection of Conray 60 into the aorta of dogs [14]. Angiotensin II, a potent vasoconstrictor, increases preglomerular vascular resistance and thus reduces the glomerular filtration rate. This effect is countered by PGL, if the latter were reduced, vasoconstriction would result.

Observations that calcium channel blockers ameliorate CIN support the hypothesis that alterations in intracellular calcium and consequently, vascular smooth muscle tone may contribute to renal impairment. Intravenous calcium channel blockers given to healthy volun-
teers have been observed to relieve renal vasoconstriction. The electromechanical gradient in resting vascular smooth muscle favors calcium influx. The gradient is maintained by active extrusion of Ca\(^{2+}\) by Ca\(^{2+}\) ATPase present in the sarcolemma [15]. If the rate of Ca\(^{2+}\) entry into smooth muscle cells exceeds the rate of removal, vasoconstriction ensues. Calcium channel blockers, including verapamil, induce vasodilation by modulating calcium entry.

Experimentally, calcium channel blockers have been demonstrated to ameliorate ischemia-induced vasoconstriction [16, 17]. In our study, the efficacy of calcium channel blockers was difficult to assess due to the large number of patients already receiving them prior to angiography. It should be noted that Neumayer et al. have demonstrated that patients receiving nitrendipine, a calcium channel blocker, maintained a stable glomerular filtration rate in contrast to untreated patients, who experienced a mean reduction in GFR of 27% following the administration of contrast [9]. Although we did not discontinue calcium channel blockers in patients receiving them preangiographically in this study, future studies evaluating the potential benefits of calcium channel blockers in the management of CIN should take this variable into consideration.

Recent reports [3, 18, 19] suggest that low osmolality contrast agents such as ioxaglate can also cause CIN in high risk individuals. This implies that similar precautions should be taken as with conventional ionic agents.

The most significant increase in postangiographic Cr levels was observed within 72 hr and was more pronounced in patients with preexisting renal dysfunction. There was no statistical correlation between the presence of insulin-dependent diabetes or age and CIN in the patients evaluated in this study. There were however, too few patients with renal artery stenosis to permit statistical evaluation of the contribution of this risk factor to the development of CIN.

Intravenous fluids and mannitol have been used alone or in combination to prevent CIN. Mannitol, an osmotic diuretic, also increases circulating atrial natriuretic peptide and, as a consequence, the glomerular filtration rate. A possible explanation for the failure of fluid and mannitol to prevent a rise in Cr in our patients with baseline serum creatinine levels of ≥2.0 mg/dl may relate to the volume of fluid administered. Because of the common occurrence of coronary artery disease in vascular patients, the volume of fluid administered was carefully titrated. Furthermore, the rate of fluid infusion following the administration of mannitol was not always sufficient to compensate for the resulting osmotic diuresis.

In addition to its effects on renal blood flow, dopamine has been observed to increase or maintain glomerular filtration rate, enhance natriuresis, augment atrial natriuretic peptide, and blunt the mineralocorticoid and va-
sopressin response associated with the injection of contrast agents [20, 21].

These beneficial effects of dopamine are mediated via DA1 and DA2 receptors in the kidney. Activation of the DA1 receptor is associated with an increase in renal blood flow and adenylyl cyclase activity in the proximal tubule and inhibition of Na⁺/H⁺ transport. In the collecting system, dopamine antagonizes the action of mineralocorticoids and the hydrosomotic effect of vasopres-
sin. Stimulation of the DA2 is associated with an increase in the glomerular filtration rate [19, 20]. The administration of dopamine prevented the expected rise in Cr in patients with baseline Cr levels >2.0 mg/dl. The beneficial effects of renal dose dopamine appears to be related to its stimulatory effects on the dopaminergic receptors in the kidney, suggesting that vasoconstriction may be a major contributing factor to the development of CIN.

Our study supports earlier ones suggesting that patients with preexisting renal impairment are more susceptible to the development of CIN following the intraarterial injection of low osmolality contrast agents. The administration of renal dose dopamine commencing prior to the infusion of the contrast agent may limit or prevent renal impairment in such patients.

REFERENCES

6. Rich, M. W., and Creelius, C. A. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheter-
18. Spangler-Viklund, B., Nikonoff, T., Lundberg, M., Larsson, R., Skau, T., and Nyberg, P. Acute renal failure caused by low-osmo-
19. Aron, N. B., Feinfeld, D. A., Peters, A. T., and Lynn, R. I. Acute renal failure associated with ioxaglate, a low-osmolality radio-