The role of theophylline in contrast-induced nephropathy: a case-control study

Aditya Kapoor1, Sudeep Kumar1, Sanjeev Gulati2, Sanjay Gambhir3, Ravindra S. Sethi3 and Nakul Sinha1

1Department of Cardiology, 2Department of Nephrology and 3Department of Nuclear Medicine, Sanjay Gandhi PGIMS, Lucknow, India

Abstract

Background. Various strategies for the prevention of contrast-induced nephropathy (CN) have been studied, with conflicting results. Adenosine may play an important role in the pathogenesis of CN. This study prospectively assessed the role of oral theophylline in the prevention of CN.

Methods. We randomized into two groups 70 patients with diabetes mellitus who were undergoing coronary angiography (CAG) with high-osmolar contrast media. Group I (n = 35) underwent routine CAG, and group II (n = 35) received oral theophylline 200 mg b.d. 24 h before and for 48 h after CAG. Serum Na+, K+, blood urea nitrogen (BUN), creatinine, osmolality, glomerular filtration rate (GFR) and urinalysis were performed before and after CAG. The 99mTc-DTPA-clearance method was used to assess GFR.

Results. Following angiography, patients in the control group showed a significant rise in serum creatinine (1.19 ± 0.23 vs 1.44 ± 0.32 mg/dL, P = 0.003) and BUN (13.95 ± 2.61 vs 17.55 ± 3.9 mg/dL, P = 0.01) along with a fall in GFR (85.4 ± 14.7 vs 66.85 ± 14.8 ml/min, P = 0.008). The mean percentage fall in GFR was 35.8%. There was no significant change in serum creatinine (1.16 ± 0.18 vs 1.24 ± 0.21 mg/dL), BUN (12.8 ± 3.36 vs 14.8 ± 2.5 mg/dL) and GFR (86.8 ± 15.8 vs 80.3 ± 16.0 ml/min) in those receiving theophylline. No patient in the theophylline group had a > 25% rise in serum creatinine, compared with 7/35 in the control group (P = 0.017). In the control group, 11/35 (31%) developed CN, as demonstrated by a > 25% fall in GFR, while only one patient in the theophylline group had a fall in GFR (P = 0.004). None of the pre-angiographic variables could predict the development of CN.

Conclusions. Following the use of high-osmolar contrast media for routine CAG, CN may develop in 31% of diabetic patients. Patients who received prophylactic oral theophylline had a significantly lower risk of CN than those who did not.

Keywords: acute renal failure; angiography; cardiac catheterization; radiocontrast-induced nephropathy; renal haemodynamics; theophylline

Introduction

Nephrotoxicity due to the administration of radiocontrast agents is a common and preventable cause of acute renal failure (ARF). Contrast-induced nephropathy (CN) is the third leading cause of ARF in hospitalized patients [1]. The incidence of CN, which varies from 0 to 23% in patients undergoing cardiac catheterization and angiography, depends on the definition of CN used and the risk profile of the patient population included in the study [2]. Usually, CN is defined as a rise in serum creatinine of ≥25%, or ≥50% of the baseline value, and appears to be the result of a synergistic combination of direct tubular epithelial cell toxicity and alterations in renal hemodynamics with renal medullary ischaemia. Although the mediators of these changes are still not very clearly defined, alterations in the metabolism of prostaglandins, nitric oxide, endothelin, and adenosine may play a role.

Various preventive strategies have been employed to reduce the incidence of CN. These include administration of intravenous fluids [3,4], frusemide [5], mannitol [5,6], low-dose dopamine [7–9], atrial natriuretic peptide (ANP) [10], and calcium-channel blockers [11,12]. However, the results of most studies are conflicting, and more evidence is required before
any therapeutic measures are recommended for routine use.

Since adenosine may have a role in the pathogenesis of CN, an adenosine antagonist (theophylline) has been investigated as a means of reducing the risk of CN [9,13–15]. However, data on use of oral theophylline for this purpose is scant and inconsistent. The purpose of this prospective study was to determine whether alterations in renal function after administration of radiocontrast agents can be prevented by oral theophylline.

Materials and methods

We prospectively studied 70 consecutive patients of diabetes mellitus, aged 18–70 years, who were referred to our Institute for coronary angiography and had a serum creatinine < 3.0 mg/dl. A written informed consent was obtained from each patient prior to inclusion in the study and the study protocol conformed to the ethical guidelines of the Institute’s Human Research Committee. Exclusion criteria included (i) pre-existing renal failure with serum creatinine ≥ 3.0 mg/dl, (ii) maintenance dialysis, (iii) a history of acute myocardial infarction, (iv) left ventricular ejection fraction (EF) < 25%, (v) allergy to contrast media, (vi) pregnancy, and (vii) diuretic therapy.

Prior to angiography, all patients had tests to measure serum Na⁺, K⁺, blood urea nitrogen (BUN), creatinine, and osmolality. A baseline assessment of serum Na⁺, K⁺, urea, creatinine, and osmolality was also done. GFR was calculated using the 99mTc-DTPA-clearance method. Two blood samples at 90 and 120 min were taken after 99mTc-DTPA injections to measure GFR adjusted to the body surface area [16]. The patients were randomized into two groups: group I (n = 35), who underwent routine coronary angiography, and group II (n = 35), who received oral theophylline 200 mg b.d. starting 24 h before the angiography and continuing for 48 h thereafter. In addition, all patients received intravenous normal saline (1 ml/kg/h) commencing 12 h before and continuing for 12 h after the procedure. Coronary angiography was performed using a high-osmolar contrast medium, diatrizoate meglumine (76% Urograffin; Schering AG, Berlin, Germany). All laboratory tests and renal scans were repeated 48 h after angiography.

Case definition

Clinically significant renal impairment was defined as a ≥ 25% rise in serum creatinine compared to a patient’s baseline value [17] or a ≥ 25% fall in GFR, documented by renal scan.

Statistical analysis

Student’s t-test and χ² test were used to calculate the significance of the results. A P-value < 0.05 was taken as significant. All data are expressed as means ± SD. Regression analysis was performed for predictors of CN.

Results

There was no difference between the groups in terms of mean age at angiography (51.9 ± 8.16 vs 54.52 ± 9.16 years), mean left ventricular (LV) function (EF 56.6 ± 4.3 vs 57.8 ± 3.9%), gender distribution (31 males, 4 females in group I, 33 males, 2 females in group II) and mean dose of contrast used (77.8 ± 9.6 vs 80.2 ± 8.6 ml of 76% Urograffin) (Table 1).

Prior to angiography the two groups had comparable serum creatinine (1.19 ± 0.23 in group I vs 1.16 ± 0.18 mg/dl group II), BUN (13.95 ± 2.61 vs 12.8 ± 3.36 mg/dl), uric acid (69.0 ± 9.57 vs 70.1 ± 14.04 mg/dl) and urine creatinine levels (1.13 ± 0.17 vs 1.27 ± 0.48 mg/dl). There were also no significant differences in serum Na⁺, K⁺, osmolality, serum uric acid, and urine Na⁺, K⁺ or urine osmolality. Fractional excretion of sodium (FeNa) was also similar in both groups (1.38 ± 0.31 vs 1.53 ± 0.49, P = 0.27). The mean GFR as estimated by the plasma method was also not significantly different between the two groups (85.4 ± 14.7 vs 86.8 ± 15.8 ml/min (Table 1).

Following angiography, there were no significant changes in serum creatinine concentrations (1.16 ± 0.18 vs 1.24 ± 0.21 mg/dl) and BUN levels (12.8 ± 3.36 vs 14.8 ± 2.5 mg/dl) in the theophylline group (group II). The mean GFR also did not change significantly in this group (86.8 ± 15.8 vs 80.3 ± 16.0 ml/min) compared with pre-angiographic values (Table 2). FeNa levels increased significantly in the theophylline group after angiography from 1.53 ± 0.49 to 1.69 ± 0.53 (P = 0.02). There was no significant change in any of the other biochemical parameters following angiography in this group.

In contrast, patients who did not receive theophylline (group I) had a significant rise in serum creatinine (1.19 ± 0.23 vs 1.44 ± 0.32 mg/dl, P = 0.03) after angiography (Figure 1). This group also had a significant rise in BUN levels (13.95 ± 2.6 vs 17.55 ± 3.9 mg/dl, P = 0.01) (Figure 2). There was a correspondingly significant fall in GFR following angiography.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (group I)</th>
<th>Theophylline (group II)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.52 ± 9.16</td>
<td>51.9 ± 8.16</td>
<td>NS</td>
</tr>
<tr>
<td>S. creatinine (mg/dl)</td>
<td>1.19 ± 0.23</td>
<td>1.16 ± 0.18</td>
<td>NS</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>13.9 ± 2.61</td>
<td>12.8 ± 3.36</td>
<td>NS</td>
</tr>
<tr>
<td>S. uric acid (mg/dl)</td>
<td>4.47 ± 0.47</td>
<td>4.32 ± 0.71</td>
<td>NS</td>
</tr>
<tr>
<td>S. sodium (mEq/l)</td>
<td>134.78 ± 4.64</td>
<td>136.4 ± 3.73</td>
<td>NS</td>
</tr>
<tr>
<td>S. potassium (mEq/l)</td>
<td>4.3 ± 0.55</td>
<td>4.12 ± 0.58</td>
<td>NS</td>
</tr>
<tr>
<td>Blood osmolality (mOsm/l)</td>
<td>288.47 ± 35.17</td>
<td>292 ± 16.9</td>
<td>NS</td>
</tr>
<tr>
<td>Urine urea (mg/dl)</td>
<td>1.13 ± 0.17</td>
<td>1.27 ± 0.48</td>
<td>NS</td>
</tr>
<tr>
<td>Urine creatinine (mg/dl)</td>
<td>69.0 ± 9.57</td>
<td>70.1 ± 14.04</td>
<td>NS</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/l)</td>
<td>308.3 ± 41.56</td>
<td>294.7 ± 36.0</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>85.4 ± 14.7</td>
<td>86.8 ± 15.8</td>
<td>NS</td>
</tr>
<tr>
<td>FeNa (ml/min)</td>
<td>1.38 ± 0.31</td>
<td>1.53 ± 0.49</td>
<td>NS</td>
</tr>
</tbody>
</table>
Higher in group I patients. Post-angiography, GFR (17.5 ± 3.9 vs 14.8 ± 2.5 mg/dl, P = 0.02) was also higher in group I patients. Post-angiography, GFR was significantly lower in group I as compared with group II (15.4 ± 1.9 vs 13.0 ± 3.05 mg/dl), mean GFR (85.8 ± 7.9 vs 86 ± 16.2 ml/min), and FeNa (1.38 ± 0.29 vs 1.48 ± 0.44) were not significantly different between them. Following angiography, as expected, the mean serum creatinine was significantly higher in those who developed CN (1.72 ± 0.2 vs 1.27 ± 0.23 mg/dl, P = 0.001). The BUN was also slightly higher in these patients (19.43 ± 3.99 vs 15.65 ± 3.2 mg/dl, P = 0.04). There were no significant differences in any other biochemical parameters. Post angiography GFR was significantly lower in those who developed CN (56.02 ± 5.56 vs 76.57 ± 15.96 ml/min, P < 0.0001). FeNa levels after angiography were slightly higher in those who developed CN (1.73 ± 0.42 vs 1.64 ± 0.47) but this difference did not reach statistical significance. None of the patients required dialysis. All patients had normalization of their serum creatinine by 72 h.

On univariate analysis, development of CN did not correlate significantly with any pre-angiographic biochemical variable, nor with the pre-angiographic GFR. There was a significant correlation with the mode of treatment (P = 0.006, r = −0.422). On multivariate analysis, none of the pre-angiographic variables could predict development of CN.

### Table 2. Renal parameters in the two groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (group I)</th>
<th>Theophylline (group II)</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. creatinine (mg/dl)</td>
<td>1.19 ± 0.23</td>
<td>1.44 ± 0.32</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>13.95 ± 2.6</td>
<td>17.55 ± 3.9</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>GFR (plasma) (ml/min)</td>
<td>85.4 ± 14.7</td>
<td>66.8 ± 14.8</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>FeNa</td>
<td>1.38 ± 0.31</td>
<td>1.61 ± 0.39</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

GFR, glomerular filtration rate; FeNa, fractional excretion of sodium.

(85.4 ± 14.7 vs 66.8 ± 14.8 ml/min, P = 0.008) (Figure 3).

The mean percentage fall in GFR was 35.8% (Table 2).

FeNa levels showed a significant rise following angiography (from 1.38 ± 0.31 to 1.61 ± 0.39, P = 0.006).

### Incidence of CN

None of the patients in the theophylline group had more than a 25% rise in serum creatinine, but seven of 35 (20%) in the control group did (P = 0.017). Of those seven, five had an absolute increase in serum creatinine levels of ≥0.5 mg/dl. The more reliable GFR estimation revealed that CN developed in 11 of 35 patients (31%) in the placebo group (a ≥25% fall in GFR), while only one patient in the theophylline group showed a fall in GFR (P = 0.004). Interestingly, all seven patients who had a rise in serum creatinine following angiography also demonstrated a fall in GFR. In addition, four patients who did not have a rise in serum creatinine had a ≥25% fall in GFR. It was observed that the mean percentage fall in GFR in the seven patients who had a rise in serum creatinine was greater (38.6% fall) when compared with the four patients who had only a fall in GFR without a change in serum creatinine (their percentage fall in GFR being 31.1).

Post-angiography, the mean serum creatinine was significantly higher in the placebo group (group I) as compared to those who received theophylline (group II) (1.44 ± 0.3 vs 1.24 ± 0.2 mg/dl P = 0.03). The mean BUN (17.5 ± 3.9 vs 14.8 ± 2.5 mg/dl, P = 0.02) was also higher in group I patients. Post-angiography, GFR was greater (38.6% fall) when compared with the seven patients who had a rise in serum creatinine (P = 0.004). Interestingly, the more reliable GFR estimation revealed that CN developed in 11 of 35 patients (31%) in the placebo group (a ≥25% fall in GFR), while only one patient in the theophylline group showed a fall in GFR (P = 0.004). FeNa levels after angiography were slightly higher in those who developed CN (1.73 ± 0.42 vs 1.64 ± 0.47) but this difference did not reach statistical significance. None of the patients required dialysis. All patients had normalization of their serum creatinine by 72 h.
dehydration, and may also counter the osmotic effect of intravenous contrast media (CN). Saline hydration [3,4] may correct any pre-existing dehydration, and may also counter the osmotic effect of intravenous contrast media (CN). Whilst only saline hydration has been shown to be effective in preventing CN, other preventive strategies have also been used to reduce the chance of developing CN. Saline hydration [3,4] may correct any pre-existing dehydration, and may also counter the osmotic effect of intravenous contrast media (CN).

Discussion

Intravenous administration of contrast continues to be an important and often preventable cause of hospital-acquired ARF. Although various definitions of CN appear in the literature, it is commonly defined as an acute decline in renal function after the administration of intravenous contrast agents, and in the absence of other causes. Patients with CN typically present with an acute rise in serum creatinine 24–48 h after the contrast study. Serum creatinine usually peaks at 3–5 days and usually returns to normal after 7–10 days. Almost all patients revert to normal renal function, and dialysis is rarely required.

CN may result from a synergistic combination of direct tubular epithelial-cell toxicity and renal tubular ischaemia [17]. The nature of a contrast medium, the ions associated with it, and the ischaemia that results during a contrast study are critical determinants of the degree of cellular damage, while the osmolality of the solution is possibly only of secondary importance. The injection of contrast induces biphasic haemodynamic changes in the kidney, with a transient vasoconstriction and an increase in renal blood flow followed by more prolonged vasoconstriction and decrease in the blood flow. Alterations in the renal renin–angiotensin system, prostaglandins, endothelin, nitric oxide, and adenosine have all been implicated in the pathogenesis of this phenomenon.

Whether or not clinically significant renal impairment occurs, depends on the risk profile of a patient. Risk factors include baseline renal impairment, diabetes mellitus, congestive heart failure, reduced effective arterial volume (e.g. dehydration), concomitant use of nephrotoxic drugs, and administration of high doses of contrast. Preventive strategies are vital, especially in high-risk patients.

Preventive strategies

Whilst only saline hydration has been shown to be effective in preventing CN, other preventive strategies have also been used to reduce the chance of developing CN. Saline hydration [3,4] may correct any pre-existing dehydration, and may also counter the osmotic effect of intravenous contrast media (CN).

Role of non-ionic or low-osmolar contrast media (LOCM)

These contrast media, with one-half to one-third the osmolality of standard high-osmolar contrast media (HOCM), were developed in an attempt to reduce the incidence of CN. However, the risk of CN is not totally eliminated by the use of LOCM, although it is reduced when compared with the use of HOCM. Based on accumulated evidence and the high cost of these agents, it is prudent to use LOCM for patients with pre-existing renal impairment to minimize the risk of CN. It is perhaps unnecessary to use LOCM in a patient with normal renal function who is at a low risk of developing CN after angiography [17]. We used only HOCM in the diabetic patients in our study and observed that CN developed in 31% of patients in the placebo arm.

Role of adenosine

Adenosine has been shown to reduce renal blood flow and glomerular perfusion pressure by means of A1-receptor-mediated renal afferent arteriolar vasoconstriction and A2-receptor-mediated efferent arteriolar vasodilatation. The administration of contrast in human subjects is known to be associated with the production of endogenous intrarenal adenosine. The vasoconstrictive and potentially deleterious effects of adenosine on renal blood flow can be significantly reduced with adenosine antagonists (e.g. theophylline) and potentiated by dipyridamole, an inhibitor of adenosine re-uptake.
Erley et al. [13] studied the role of intravenous theophylline (5 mg/kg) and found that, compared with placebo, it prevented the fall in creatinine, inulin, and para-aminohippurate clearances. However, in their cohort, which included only 15% of diabetics, there were no significant changes in renal function in any of the patients they studied. In a study comparing saline hydration, saline hydration plus dopamine, and saline hydration plus intravenous aminophylline infusion, Abizaaid et al. [9] reported that neither dopamine nor aminophylline reduced the incidence of CN when compared with saline hydration alone. Data for oral theophylline in the prevention of CN is scant and contradictory. Katholi et al. [14] studied the effect of 2.88 mg/kg oral theophylline (every 12 h, four doses) compared with placebo in the prevention of CN. They reported that although serum creatinine did not change significantly, theophylline completely prevented the fall in creatinine clearance seen within 24 h after non-ionic contrast and reduced that seen after ionic contrast by about half. Another study, however, using 810 mg oral theophylline, indicated that it did not offer any benefit over routine saline hydration for the prevention of CN in patients with serum creatinine $\geq 1.5$ mg/dl receiving contrast media [18].

We chose to include only diabetics in our patient population (compared with previous studies in which only 15–20% of the subjects were diabetics), as they are more prone to develop CN, and we expected that any possible benefit of the drug would be highlighted. There is data suggesting that most of the increased risk in diabetics is related to underlying chronic renal insufficiency rather than the presence of diabetes mellitus per se [18]. However, other studies have reported diabetes (especially the insulin-dependent type) to be an independent risk factor for the development of CN [19,20].

In our patient population, the two groups (group I, who received saline hydration only, and group II, who received saline hydration plus oral theophylline) were comparable in terms of mean age, gender, LV function, and mean dose of contrast used. There were no significant differences among them in terms of pre-angiographic serum creatinine (1.19 $\pm$ 0.23 vs 1.16 $\pm$ 0.18 mg/dl), BUN (13.95 $\pm$ 2.61 vs 12.8 $\pm$ 3.6 mg/dl), urine creatinine (69.0 $\pm$ 9.57 vs 70.1 $\pm$ 14.04 mg/dl), urine urea levels (1.13 $\pm$ 0.17 vs 1.27 $\pm$ 0.48 mg/dl) and mean GFR (85.4 $\pm$ 14.7 vs 86.8 $\pm$ 15.8 ml/min). There was also no significant difference with respect to serum Na/K, osmolality, serum uric acid, and urine Na/K or osmolality.

Although no patient in the theophylline group demonstrated a rise in serum creatinine $\geq 25\%$ following angiography, such a rise was seen in seven of 35 (20%) in the control group. Estimation of GFR demonstrated that only one of 35 (2%) in the theophylline group had a $>25\%$ reduction in GFR, while CN occurred in 11 of 35 patients in the placebo arm (31%). Interestingly, all seven patients in the control group who had a rise in serum creatinine also had a fall in GFR. In addition, three patients (in the control group) and one patient (in the theophylline group) also had a measurable reduction in GFR despite no significant change in serum creatinine levels.

Post-angiography, the mean serum creatinine was significantly higher in the control group ($1.44 \pm 0.32$ vs $1.24 \pm 0.21$ mg/dl, $P = 0.03$). Patients who did not receive theophylline also had higher BUN ($17.55 \pm 3.9$ vs $14.8 \pm 2.5$ mg/dl, $P = 0.02$) and significantly lower GFR following angiography ($66.8 \pm 14.8$ vs $80.2 \pm 16$ ml/min, $P = 0.02$). The other biochemical parameters were not significantly different between these two groups. Overall, the renal dysfunction in our study was mild and no patient required dialysis. This could be because we excluded diabetic patients with moderate to severe renal failure (serum creatinine $\geq 3$ mg/dl). It could also be due to the use of saline hydration even in the control group.

None of the pre-angiographic variables predicted development of CN. The fact that no pre-angiographic biochemical or demographic parameter can predict accurately which patient will develop CN highlights the need to develop adequate prophylactic preventative measures. We found oral theophylline (an adenosine antagonist) to be safe and effective for the prevention of CN in diabetic patients undergoing coronary angiography with ionic contrast media.

Conclusions

We conclude that CN may develop in 31% of diabetic patients undergoing routine coronary angiography with high-osmolar contrast media. Although the biochemical changes may be subtle, abnormalities in GFR (especially by the plasma method of GFR estimation) are more frequent (31%) and detectable, if looked for. In this study we found theophylline to have additional benefit when combined with saline hydration, compared with saline hydration alone, in preventing CN. Further work is required to compare the efficacy of theophylline monotherapy with that of saline hydration for the prevention of CN.

References


Received for publication: 18.1.02
Accepted in revised form: 27.5.02