Theophylline for Prevention of Contrast-Induced Nephropathy

A Systematic Review and Meta-analysis

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Background: Contrast-induced nephropathy (CIN) is an important cause of declines in kidney function and is related to greater morbidity, health care costs, and mortality. Adenosine has been proposed to contribute to the pathophysiological process of CIN. We performed a systematic review and meta-analysis of theophylline, an adenosine antagonist, for the prevention of CIN.

Data Sources: Studies were identified in all languages by search of MEDLINE (1966 through November 2003), EMBASE (1980 through week 44 [November] of 2003), and the Cochrane Controlled Clinical Trials Register (1996 through November 2003) databases and selected conference proceedings.

Study Selection: We searched for randomized controlled trials comparing theophylline vs control in patients receiving radiocontrast media for angiography or computed tomography.

Data Extraction: Our primary outcome measures were the risk of CIN, the difference in serum creatinine levels between theophylline and control groups at 48 hours and need for dialysis.

Data Synthesis: Nine randomized controlled trials involving 585 patients were identified and included for analysis. Theophylline protocols and definitions of CIN varied across studies. There was evidence of heterogeneity of results across trials ($Q=9.77; P=0.08$); therefore, pooled values require cautious interpretation. The overall pooled odds ratio (OR) using a conservative random-effects model was $0.40$ ($95\%$ confidence interval [CI], $0.14$ to $1.16$; $P=0.09$) indicating a trend toward reduction in the incidence of CIN with theophylline use. The pooled estimate for the difference in 48-hour serum creatinine levels between the theophylline and control groups was $-0.17$ mg/dL ($95\%$ CI, $-0.28$ to $-0.06$ mg/dL) ($-15.2$ µmol/L [95% CI, $-24.6$ to $-5.7$ µmol/L]) ($P=0.002$), indicating that theophylline may be protective in CIN. The incidence of CIN requiring dialysis was uncommon and reported in only 1 case.

Conclusions: Theophylline may reduce the incidence of CIN with an efficacy that is perhaps comparable to that reported in studies of N-acetylcysteine. However, findings are inconsistent across studies. A large, well-designed trial that incorporates the evaluation of clinically relevant outcomes is required to more adequately assess the role for theophylline in CIN prevention.

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also searched. We derived 3 comprehensive review filter method. The second theme, "adenosine antagonists," was created by a search using an exploded MeSH heading and text word search for the terms theophylline or aminophylline.

STUDY SELECTION CRITERIA

We independently evaluated articles for eligibility on the basis of 4 inclusion criteria: (1) study design (RCTs), (2) target population (patients receiving contrast media for intravascular angiography or computed tomography), (3) intervention (trials of adenosine antagonists vs control), and (4) outcome (a priori explicit definition of CIN or use of change in serum creatinine level or glomerular filtration rate prior to and following contrast administration for the primary outcome).

DATA EXTRACTION

We independently extracted data from all primary studies fulfilling eligibility criteria. Any discrepancies in extracted data were resolved by consensus. Data extracted included identifying information, focus of the study, details of study protocol, and demographic data. The primary outcome measures were the incidence of CIN, change in serum creatinine levels, and change in glomerular filtration rate. The secondary outcome measures were requirement of renal replacement therapy and adverse reactions to adenosine antagonists. Authors of the studies were contacted for additional information when applicable.

ASSESSMENT OF METHODOLOGICAL QUALITY

We independently assessed the methodological quality of individual studies. Any disagreements were resolved by consensus. Items used to assess study quality were methods of randomization, any blinding, use of a placebo, reporting of losses to follow-up or missing outcome assessments, and evidence of important baseline differences between the groups. An overall quality score was determined for each study as described by Jadad et al.

STATISTICAL ANALYSIS

Data from all of the selected RCTs were combined to estimate the pooled odds ratio (OR) with 95% confidence intervals (CIs) using a random-effects model as described by DerSimonian and Laird and Senn et al. The presence of heterogeneity across trials was evaluated using a test for homogeneity. Because the test has a low sensitivity for detecting heterogeneity, a P value of ≤ .10 was considered significant for the presence of statistical heterogeneity. Meta-regression was performed to analyze for potential clinical and study quality factors that may influence treatment effects. We tested for potential publication bias using both the Begg test for funnel plot asymmetry and the Egger test. An additional sensitivity analysis was performed to determine the impact that the addition of a varying number of hypothetical negative trials would have on the pooled results. All statistical analyses were performed with Stata version 8.0 (StataCorp, College Station, Tex).

RESULTS

STUDY IDENTIFICATION

A total of 57 unique citations were identified by our search strategy (Figure 1). After the initial screen, 26 citations warranted further review. Among these, 17 articles were excluded. Overall, 9 studies were identified and fulfilled our inclusion criteria. All of these citations were identified by the electronic search strategy. There was excellent overall agreement for inclusion of individual studies (κ = 0.74).

STUDY CHARACTERISTICS

The RCTs were published between 1992 and 2003. Table 1 and Table 2 present the characteristics and quality indicators of the 9 trials. A total of 585 patients were examined in these 9 trials, among whom 295 received adenosine antagonists and 290 were in control groups. There were 257 patients (44%) with diabetes mellitus, of whom 123 were assigned to receive adenosine antagonists and 134 were assigned to a control group. One study excluded patients with diabetes mellitus and another did not report the proportion of diabetic patients. Four studies had a priori hydration protocols, and 2 studies advised intake of greater than 2 L of hydration.
of fluid prior to contrast media exposure,24,25 and 3 did not detail whether hydration was provided.17,18,20 The type of contrast media used varied across studies. Patients either received ionic or high osmolar,20,21,23 nonionic or low osmolar,18,22,24,25 or both17,19 contrast media.

The definitions of CIN and protocols for administration and total cumulative dosages of theophylline varied across studies (Table 1). Key elements of study methods and reporting also varied across studies (Table 2).

META-ANALYSIS OF INCIDENCE OF CIN

The incidence of CIN varied across studies reporting primary dichotomous outcomes. Table 3 and Figure 2 present information on the incidence of CIN for available studies. Three studies provided evidence of a risk reduction for developing CIN with theophylline use23-25 whereas 3 studies did not find a statistically significant reduction in risk associated with theophylline treatment.17,21,22 The overall pooled OR for developing CIN using a random-effects model was 0.40 (95% CI, 0.14-1.16; P = .09), suggesting a trend toward a reduced incidence of CIN with theophylline use that is not statistically significant in the more conservative random-effects analysis (Figure 2). However, the pooled effect estimate comparing the

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Table 1. Characteristics of Studies Reporting the Use of Adenosine Antagonists for Prevention of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Diabetes, No. (%)</th>
<th>Elective Procedure</th>
<th>Primary Outcome</th>
<th>THEO Protocol</th>
<th>Hydration Protocol</th>
<th>Contrast Media</th>
<th>Contrast Media Volume, mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandhi et al17</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>THEO Protocol</td>
<td>Hydration Protocol</td>
<td>Iopromide</td>
<td>Iopromide</td>
</tr>
<tr>
<td>Erley et al18</td>
<td>39</td>
<td>7 (18)</td>
<td>Yes</td>
<td>NR</td>
<td>5 mg/kg IV 45 min prior</td>
<td>1.43 mL/(kg - h) PO or D5W IV × 3 d</td>
<td>Iopamidol or diatrizoate meglumine</td>
<td>Iopamidol</td>
</tr>
<tr>
<td>Katholi et al19</td>
<td>93</td>
<td>74 (80)</td>
<td>Yes</td>
<td>NR</td>
<td>2.88 mg/kg PO every 12 h × 4 doses starting 1 h prior</td>
<td>0.45% NS 2-2.5 L 24 h prior and after</td>
<td>Amiodarone meglumine</td>
<td>Ioxaglate</td>
</tr>
<tr>
<td>Kolonko et al20</td>
<td>58</td>
<td>Excluded</td>
<td>Yes</td>
<td>NR</td>
<td>165 mg IV 30 min prior</td>
<td>NA</td>
<td>Iopromide</td>
<td></td>
</tr>
<tr>
<td>Abizaid et al21</td>
<td>40</td>
<td>22 (55)</td>
<td>NR</td>
<td>&gt;25% Increase (SCr)</td>
<td>4-mg/kg bolus, then 0.4-mg/kg infusion per hour</td>
<td>NS 1 mL/(kg- h) 12 h prior and after</td>
<td>Iopromide</td>
<td>Iopromide</td>
</tr>
<tr>
<td>Erley et al22</td>
<td>64</td>
<td>19 (30)</td>
<td>Yes</td>
<td>&gt;0.5-mg/dL increase (SCr)</td>
<td>270 mg PO qam, 1040 mg PO qpm 24 h prior and 72 h after</td>
<td>NS 1 mL/(kg - h) 12 h prior and after</td>
<td>Iodixanol</td>
<td>Iodixanol</td>
</tr>
<tr>
<td>Kapoor et al23</td>
<td>70</td>
<td>70 (100)</td>
<td>NR</td>
<td>&gt;25% Increase (SCr)</td>
<td>200 mg PO bid 24 h prior, 48 h after</td>
<td>NS 1 mL/(kg- h) 12 h prior and after</td>
<td>Diatrizoate meglumine</td>
<td>Iomeprol</td>
</tr>
<tr>
<td>Huber et al24</td>
<td>100</td>
<td>34 (34)</td>
<td>No</td>
<td>&gt;0.5-mg/dL (SCr at 48 h)</td>
<td>200 mg IV 30 min prior</td>
<td>Advised &gt; 2 L</td>
<td>Iomeprol</td>
<td>Iomeprol</td>
</tr>
<tr>
<td>Huber et al25</td>
<td>100</td>
<td>31 (31)</td>
<td>No</td>
<td>&gt;0.5-mg/dL (SCr at 48 h)</td>
<td>200 mg IV 30 min prior</td>
<td>Advised &gt; 2 L</td>
<td>Iomeprol</td>
<td>Iomeprol</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; D/W, 5% dextrose (in water) injection; IV, intravenous; NA, not applicable; NR, not recorded or available; NS, normal saline; PO, by mouth; qam, every morning; qpm, every night; SCr, serum creatinine; THEO, theophylline.

*SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 88.4.

Table 2. Quality of Studies Reporting the Use of Adenosine Antagonists for Prevention of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th>Source</th>
<th>Jadad Score*</th>
<th>Inclusion/Exclusion Criteria Specified</th>
<th>Randomization Process Described</th>
<th>Use of Any Blinding</th>
<th>Placebo-Controlled</th>
<th>Reported Loss to Follow-up</th>
<th>Reason for Loss to Follow-up Provided</th>
<th>Baseline Differences Between Groups</th>
<th>Power Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandhi et al17</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NS</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Erley et al18</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Katholi et al19</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NS</td>
<td>NS</td>
<td>No</td>
</tr>
<tr>
<td>Kolonko et al20</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NS</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Abizaid et al21</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Erley et al22</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kapoor et al23</td>
<td>0</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Huber et al24</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Huber et al25</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
occurance of CIN across all studies needs to be viewed with caution given the evidence of statistical heterogeneity of results across studies ($\chi^2=9.77; P=.08$).

There was no evidence to suggest publication bias according to both the Begg test ($P=.85$) and Egger test (coefficient, 0.81; 95% CI, −7.52 to 5.90; $P=.75$). **Figure 3** demonstrates this by the relative symmetry in the Begg funnel plot. The occurrence of CIN requiring dialysis was uncommon and reported in only 1 case.

**META-ANALYSIS OF CHANGE IN SERUM CREATININE LEVEL WITH THEOPHYLLINE USE**

Table 3 gives a summary of the changes in serum creatinine level available across all studies. The pooled estimate (using a random-effects model) for the difference in 48-hour serum creatinine level between the theophylline and control groups was $-0.17 \text{ mg/dL} \ (95\% \text{ CI, } -0.28 \text{ to } -0.06 \text{ mg/dL}) (\sim 15.2 \text{ µmol/L} \ (95\% \text{ CI, } -24.6 \text{ to } -5.7 \text{ µmol/L}) \ (P=.002) based on data available from 7 studies (**Figure 4**). This pooled estimate also requires cautious interpretation due to availability of data from only 7 studies and given evidence of statistical heterogeneity of creatinine results across studies ($Q=21.7; P<.001$).

**META-REGRESSION**

Meta-regression was performed to assess a number of clinical and study quality factors that may have contributed to heterogeneity across studies. These analyses suggest that the heterogeneity across studies may partially account for the year of study publication (coefficient, 1.31; 95% CI, 0.25 to 2.37; $P=.02$). When the analysis was restricted to the 4 studies with overall Jadad scores of 2 or higher, the overall pooled OR for CIN using a random-effects model was 0.77 (95% CI, 0.29 to 2.04; $P=.60$), whereas for studies with an overall Jadad score of less than 2, the pooled OR was 0.12 (95% CI, 0.03 to 0.42; $P<.001$), suggesting that studies with lower quality report

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**Table 3. Outcomes of Studies Reporting the Use of Adenosine Antagonists for Prevention of Contrast-Induced Nephropathy**

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Odds Ratio (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandhi et al, 1997</td>
<td>1.27 (0.16-16.8)</td>
<td>11.3</td>
</tr>
<tr>
<td>Erley et al, 1998</td>
<td>1.26 (0.24-6.9)</td>
<td>22.7</td>
</tr>
<tr>
<td>Kolonko et al, 1999</td>
<td>1.26 (0.33-4.7)</td>
<td>12.1</td>
</tr>
<tr>
<td>Abizaid et al, 1999</td>
<td>1.27 (0.10-16.8)</td>
<td>14.6</td>
</tr>
<tr>
<td>Huber et al, 1999</td>
<td>0.01 (0.01-0.53)</td>
<td>14.6</td>
</tr>
<tr>
<td>Huber et al, 1999</td>
<td>0.17 (0.03-0.81)</td>
<td>19.8</td>
</tr>
<tr>
<td>Overall</td>
<td>0.40 (0.14-1.16)</td>
<td>19.8</td>
</tr>
</tbody>
</table>

### Abbreviations:
- CI: confidence interval
- CIN: contrast-induced nephropathy
- GFR: glomerular filtration rate
- NR: not recorded or available
- OR: odds ratio
- RR: relative risk
- SCr: serum creatinine
- THEO: theophylline

### SI conversion factor:
To convert serum creatinine to micromoles per liter, multiply by 88.4.
greater reductions in the incidence of CIN with theophylline use.

Other meta-regression analyses demonstrated that the heterogeneity could not be accounted for by differences in patient age (coefficient, 0.11; 95% CI, –0.04 to 0.27; P = .16), baseline serum creatinine levels (coefficient, 0.03; 95% CI, –0.01 to 0.07; P = .16), diabetes mellitus (coefficient, –0.02; 95% CI, –0.06 to 0.03; P = .52), whether the procedure was performed electively or emergently (coefficient, 2.19; 95% CI, –0.51 to 4.89; P = .11), or periprocedure hydration administered (coefficient, 1.08; 95% CI, –1.17 to 3.33; P = .35). In addition, the heterogeneity was not accounted for by differences in the total dose of adenosine antagonist administered (coefficient, 0.001; 95% CI, –0.002 to 0.001; P = .73) or the volume of contrast media administered (coefficient, 0.004; 95% CI, –0.02 to 0.03; P = .71). There was a trend for reduction in CIN when ionic vs nonionic contrast media was used (coefficient, 2.14; 95% CI, –0.59 to 4.86; P = .13). This was further supported in the study by Kapoor and colleagues in which ionic radiocontrast media was used. That study demonstrated the largest reduction in incidence of CIN with an estimated OR of 0.06 (95% CI, 0.01 to 0.53), a finding that suggests that theophylline may be more protective for patients receiving ionic as opposed to nonionic contrast media.

SENSITIVITY ANALYSIS

To explore the sensitivity of our final results to the existence of potential unpublished “negative” trials, we modeled the existence of a varying number of hypothetical negative trials, each enrolling 100 patients, with an estimated event rate of CIN of 19% in each control group and yielding an OR of 1.2. Using a random-effects model, the addition of 7 such trials would result in a pooled OR of 1.01 (95% CI, 0.73 to 1.39; P = .90). If fewer than 7 such trials exist, the pooled OR point estimate remains below 1.0. These results imply that the pooled OR results suggesting benefit with theophylline use are relatively robust to the addition of new negative trials.

This systematic review combines results from 9 randomized studies assessing the efficacy of adenosine antagonists (theophylline or aminophylline) for the prevention of CIN and acute elevations in serum creatinine level in patients administered radiocontrast media. There is a pathophysiologic rationale for the prophylactic administration of adenosine-receptor antagonists to potentially attenuate the renal toxic effects observed with radiocontrast media. Our results indicate that the use of adenosine antagonists is associated with a trend toward reduced incidence of CIN and a small reduced pooled mean difference in serum creatinine level at 48 hours.

The pooled results that we report need to be interpreted with some caution, given the evidence of significant heterogeneity of results across studies. Given this heterogeneity, we have elected to present the more conservative random-effects pooled estimate for dichotomous outcome of CIN, and the resulting pooled OR has a 95% CI that surpasses 1.0.

Meta-regression analysis revealed 3 factors that may partially contribute toward this trend for heterogeneity. First, differences in study quality can represent a potentially important source of heterogeneity. In general, the trial quality scores were uniformly low. We found that studies with lower overall quality scores were associated with a greater reduction in risk for CIN. Similarly, studies that were more recently published were associated with a greater reduction in incidence of CIN. Second, ionic radiocontrast media is associated with an increased incidence of CIN in patients with reduced baseline kidney function. We demonstrated a trend for a reduced incidence of CIN with theophylline administered prior to exposure with ionic radiocontrast media (as opposed to nonionic contrast). This raises the possibility that theophylline may be more protective for patients receiving more “toxic” ionic contrast. Finally, variation in the theophylline protocols (ie, total dose and schedule) across studies may also represent a source of heterogeneity. We found that theophylline prophylaxis was associated with a larger overall benefit for studies with no predefined hydration protocol, suggesting that theophylline may render some additional benefit in patients not receiving any hydration. In a test of this hypothesis, Bader and colleagues administered theophylline prior to radiocontrast media exposure to 19 patients with congestive heart failure and reduced baseline kidney function unable to receive hydration. The overall incidence of CIN was 21%, with no patient requiring acute dialysis in this cohort. Although this trial had no control group, the authors suggested a preservation of glomerular filtration and avoidance of dialysis with the use of theophylline. Similarly, Bader and colleagues compared prophylactic theophylline to N-acetylcysteine in patients with reduced baseline kidney function un-
Our findings indicate that the evidence supporting the use of theophylline for the prevention of CIN, though promising, remains inconclusive. The results of the trials that we reviewed to date should be viewed as being collectively suggestive of possible benefit; however, a larger, more definitive, well-designed trial for confirmation and assessment of risks in certain populations is needed before theophylline could be recommended routinely for the prevention of CIN. Such a trial should include a hydration protocol and routine use of low or iso-osmolar nonionic contrast media, since these are the current standard of care. Finally, although absolute or relative changes in serum creatinine level are reasonable surrogate end points, more important and clinically relevant end points should also be primarily addressed.

CONCLUSIONS

Our findings indicate that the evidence supporting the use of theophylline for the prevention of CIN, though promising, remains inconclusive. The results of the trials that we reviewed to date should be viewed as being collectively suggestive of possible benefit; however, a larger, more definitive, well-designed trial for confirmation and assessment of risks in certain populations is needed before theophylline could be recommended routinely for the prevention of CIN. Such a trial should include a hydration protocol and routine use of low or iso-osmolar nonionic contrast media, since these are the current standard of care. Finally, although absolute or relative changes in serum creatinine level are reasonable surrogate end points, more important and clinically relevant end points should also be primarily addressed.

REFERENCES

14. Arend L, Bakris G, Burnett J. Role for intrarenal adenosine in the renal hemodynamic response to radiocontrast media exposure. A total of 36 patients were randomized to receive either theophylline or N-acetylcysteine intravenously prior to the procedure. Theophylline was superior, with a greater reduction in the incidence of CIN compared with N-acetylcysteine (28% vs 39%; P=.045). At 1 week of follow-up, no patient required rescue dialysis in the theophylline group compared with 2 in the N-acetylcysteine group.

Few studies reported whether any significant adverse effects occurred with use of theophylline. Huber and colleagues24 reported a temporary increase in heart rate (<15/min) immediately following administration of theophylline, 200 mg intravenously, without significant adverse sequelae. However, use of theophylline in select populations may be limited by relative contraindications, particularly patients with active coronary ischemia, arrhythmias, or preexisting seizure disorders. Only 2 studies measured serum theophylline levels. Gandhi and colleagues17 reported a mean serum theophylline level of 5.8 µg/mL (32.2 µmol/L) immediately prior to angiography after receiving three 125-mg doses in the proceeding 24 hours. Erley and colleagues18 administered theophylline, 5 mg/kg (mean weight of patients, 74 kg), 45 minutes prior to radiocontrast media exposure and reported a mean serum theophylline level of 7.2 µg/mL (40.1 µmol/L) 1 hour after the procedure. To our knowledge, no studies to date have assessed whether serum theophylline level corresponds to a dose-response reduction in the incidence of CIN. Despite the relative low dose of theophylline administered in these trials, any future studies should incorporate potential adverse effects as an important secondary outcome.

To our knowledge, this is the first study to assess the pooled evidence for prophylactic use of theophylline for the prevention of CIN. This meta-analysis suggests that theophylline may reduce the incidence of CIN; however, the currently available evidence remains inconclusive and warrants renewed interest to establish whether patients may derive a clinical benefit. Our sensitiv-


