Theophylline for the prevention of radiocontrast nephropathy: a meta-analysis

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Abstract

Background. Radiocontrast nephropathy is a common cause of acute renal failure in hospitalized patients. Several studies have examined the capacity of theophylline or aminophylline to prevent radiocontrast nephropathy, with conflicting results. We conducted a meta-analysis of published randomized controlled trials to determine if the pre-procedural administration of theophylline or aminophylline prevents radiocontrast-induced declines in kidney function.

Methods. We searched MEDLINE, EMBASE, the Cochrane Collaboration Database, bibliographies of retrieved articles, and consulted with experts to identify relevant studies. Randomized controlled trials of theophylline or aminophylline in hospitalized patients receiving radiocontrast were included. Studies were excluded if they did not report changes in serum creatinine or creatinine clearance within 48 h after radiocontrast exposure.

Results. Seven randomized controlled trials satisfied all inclusion criteria and were included in the analysis (pooled sample size $n = 480$). The difference in mean change in serum creatinine was 11.5 μmol/l (95% confidence intervals 5.3–19.4 μmol/l, $P = 0.004$) lower in the theophylline- or aminophylline-treated groups than controls. One participant (0.6%) required dialysis.

Conclusions. Prophylactic administration of theophylline or aminophylline appears to protect against radiocontrast-induced declines in kidney function. Whether these agents reduce the proportion of patients who experience large decrements in serum creatinine concentration, or require dialysis, is unknown.

Keywords: aminophylline; meta-analysis; prevention; radiocontrast nephropathy; theophylline

Introduction

Radiocontrast nephropathy is a common cause of acute renal failure (ARF) in hospitalized patients [1] and has been associated with increased in-hospital and long-term mortality and increased length of hospital stay [2–4]. Several studies have identified factors associated with the development of radiocontrast nephropathy including diabetes mellitus, high doses of contrast medium, volume depletion, co-administration of nephrotoxic medications and pre-existing chronic kidney disease (CKD). Given the burden of radiocontrast nephropathy and the increasingly complex nature of patients undergoing coronary angiography and other invasive radiological procedures, efforts to prevent or ameliorate radiocontrast-induced nephropathy are warranted.

Radiocontrast nephropathy has attracted considerable interest not only because of its clinical impact, but also because, unlike other causes of ARF, its timing can be anticipated. Previous investigational prevention strategies have included intravenous sodium chloride, osmotic and loop diuretics [5], dopamine [6] and other purported vasodilators [7], agents with antioxidant properties such as N-acetylcysteine [8] and, more recently, intravenous sodium bicarbonate [9]. Studies in animals suggest that the renal haemodynamic response to radiocontrast is biphasic—there is an initial vasodilation, followed by prolonged vasoconstriction, which may contribute to ARF [10]. This vasoconstrictive response is partly mediated by adenosine. As the vasoconstrictive response can be blunted with theophylline in experimental animals, multiple investigators have evaluated the competitive adenosine antagonists (theophylline and aminophylline) as a potential means of reducing the risk of radiocontrast nephropathy in human subjects. However, these studies have been limited by small sample size, variation in timing and dosage of drug administration, and variation in the definition of radiocontrast nephropathy. Therefore, we aimed to perform a meta-analysis of
these studies to resolve whether a strategy of theophylline or aminophylline administration would be expected to reduce the risk of radiocontrast-induced declines in kidney function in humans.

Methods

Literature review

To identify relevant studies, we searched MEDLINE (January 1966–August 2003), EMBASE (January 1974–August 2003) and the Cochrane Collaboration Database (January 1996–August 2003), using the keywords aminophylline, theophylline, kidney disease and clinical trials. This strategy was combined with a manual search of reference lists from identified articles and consultation with experts in nephrology, radiology and cardiology. Studies in all languages were included when the following criteria were met: planned as a prospective, randomized, controlled trial; included patients receiving radiocontrast media intravenously or intra-arterially for diagnostic or therapeutic procedures; use of theophylline or aminophylline before radiocontrast exposure; reported sufficient data to calculate either a mean change in serum creatinine or estimated creatinine clearance in each group before and within 48 h after contrast administration; and published as an abstract or article. Studies that were retrospective, case-control, non-randomized or did not have placebo arms were excluded.

Data extraction

Two authors independently reviewed each of the identified studies to determine eligibility and perform data abstraction. Using a standardized form, the reviewers recorded sample size, study setting, patient characteristics, methods and timing of theophylline or aminophylline administration, presence of and type of pre-procedure volume expansion, baseline and final serum creatinine or creatinine clearance, and other reported outcome variables. Disagreements were resolved by discussion. The methodological quality of the included randomized trials were assessed by the Jadad score from 0 to 5, with higher scores indicating higher quality reporting [11].

Statistical analysis

Mean change in serum creatinine from baseline was calculated by subtracting the baseline serum creatinine from the final reported serum creatinine. Differences between placebo and treatment groups were compared as the primary outcome measure. Two studies [12,13] reported only mean creatinine clearances between treatment groups rather than serum creatinine. For these studies, the Cockcroft–Gault equation was used to back-calculate the expected mean serum creatinine before and after radiocontrast exposure by incorporating mean creatinine clearance, age and weight and the percentage of subjects of each sex reported in each study [14]. We used a random effects meta-analysis in which studies are weighted inversely proportional to \(\sigma^2\) within-study variance, \(\rho\) is the ratio between the two variances, and \(n_{\text{trt}}\) and \(n_{\text{placebo}}\) are the sample sizes in the treatment and placebo groups, respectively. Since we did not have access to the raw data and hence could not calculate \(\sigma^2\), we performed the meta-analysis for a range of weighting schemes ranging from the extremes of \(\rho\) equal to 0 (when all the studies are equally weighted) up to \(\rho\) equal to \(\infty\) (when the studies are weighted inversely proportional to sample sizes). We present the most conservative estimates (\(\rho\) equal to \(\infty\)) as our primary results. To explore the possibility of publication bias, we conducted Begg’s test using the range of weights described above. To test the robustness of our findings to different assumptions, we performed additional sensitivity analyses limiting the meta-analysis to: (i) double-blinded placebo-controlled trials \((n = 277)\); (ii) studies that reported outcomes at 48 h after radiocontrast exposure \((n = 422)\); (iii) studies that gave exclusively non-ionic radiocontrast agents \((n = 307)\); (iv) studies that co-administered theophylline or aminophylline with specified intravenous hydration protocols \((n = 342)\); (v) studies in which >100 ml of radiocontrast was administered \((n = 352)\); (vi) studies that included only participants undergoing coronary angiography \((n = 303)\); and (vii) studies that gave the first dose of theophylline or aminophylline <1 h before radiocontrasts exposure \((n = 290)\). All analyses were performed using Stata Version 8.0 (Stata Corporation, College Station TX).

Results

Study inclusion

We identified 10 studies in which theophylline or aminophylline was used for prevention of radiocontrast nephropathy [12,13,15–22]. One was a letter to the editor and was excluded on the basis that the authors did not report change in serum creatinine or creatinine clearance within 48 h of radiocontrast exposure [22]. Another was excluded on the basis of case-control design [21]. A third study included a subset of participants that overlapped with participants included in a separate study by the same author; therefore, to avoid including any individual participant more than once, one of these studies was excluded [20]. As the two studies were of similar methodological quality and identical in sample size, we chose to incorporate the study that was restricted to participants undergoing coronary angiography to increase the statistical power of this subset in sensitivity analysis. Thus, seven studies fulfilled all inclusion criteria and constituted the final sample evaluated in the meta-analysis [12,13,15–19].

Sample size and baseline characteristics

The seven studies were reported between 1994 and 2003. The studies varied in sample size from 39 to 100 participants, with a total sample size of 480 included in the meta-analysis. Sixteen participants (3%) were excluded because of no post-exposure serum creatinine or creatinine clearance. The mean age of study participants ranged from 41 to 75 years (overall mean age 60 years); women accounted for
between 9 and 33% of participants (overall fraction of women 23%). The prevalence of heart failure ranged from 0 to 28% (overall fraction with heart failure 5%) and prevalence of diabetes ranged from 0 to 100% (overall fraction with diabetes 46%). The baseline mean serum creatinine varied from 88.4 to 185.6 μmol/l (overall mean serum creatinine 123.7 μmol/l). The mean quantity of radiocontrast administered ranged from 78 to 261 ml (overall mean 134 ml). Four studies used exclusively non-ionic radiocontrast [12,13,15,16], two used ionic radiocontrast [17,19], and one study used both, but reported results separately based on type of radiocontrast medium used [18]. In sum, 307 participants (64%) received non-ionic radiocontrast. Four studies enrolled subjects undergoing coronary angiography, requiring intra-arterial delivery of radiocontrast [15–18], while three others did not specify or allowed either intravenous or intra-arterial delivery [12,13,19]. Theophylline or aminophylline was co-administered with intravenous fluids in five studies (71% of subjects). The first dose of theophylline or aminophylline was given within 1 h of radiocontrast exposure in five studies (60% of subjects). Details of the characteristics of these seven trials are outlined in Table 1.

**Changes in serum creatinine concentration**

Subjects randomized to theophylline or aminophylline vs placebo had similar pre-treatment serum concentrations (125.5 and 123.7 μmol/l, respectively). Subjects randomized to placebo had a rise in serum creatinine from baseline that was a mean 11.5 μmol/l higher than those randomized to theophylline or aminophylline. With the most conservative estimate (weighting of samples proportional to the inverse of sample size), the 95% confidence interval for the mean change in serum creatinine was 5.3–19.4 (P = 0.004, Figures 1 and 2). Results were similar when analyses were limited to double-blinded placebo-controlled studies (point estimate 17.5 μmol/l), studies that reported outcomes at 48 h after radiocontrast exposure (point estimate 9.7 μmol/l), studies that gave exclusively non-ionic radiocontrast (point estimate 10.6 μmol/l), studies that had specific intravenous volume expansion protocols prior to radiocontrast exposure (point estimate 9.8 μmol/l) and studies that delivered >100 ml of radiocontrast (point estimate 8.8 μmol/l). Analyses limited to those studies that included only subjects undergoing coronary angiography (point estimate 8.0 μmol/l, P = 0.08) and those which administered theophylline or aminophylline ≤1 h before radiocontrast exposure (point estimate 12.0 μmol/l, P = 0.08) had similar point estimates but failed to reach statistical significance (Table 2).

**Radiocontrast nephropathy and the need for dialysis**

Four of the seven studies evaluated the incidence of radiocontrast-induced ARF, defined as a rise in serum creatinine ≥25% from baseline in two studies [15,17] and a rise of 0.5 mg/dl (i.e. 44 μmol/l) from baseline in two others [13,16]. The overall incidence of radiocontrast-induced ARF was 12% (34 of 290 subjects). Three of the studies included in our analysis provided data on the provision of dialysis [13,15,17]. In this subgroup, dialysis was required in only one of 179 participants, or 0.6%. This individual was randomized to the aminophylline arm [15].

**Adverse effects**

One study reported on the occurrence of side effects attributable to theophylline or aminophylline including hypotension, dysrhythmia or anaphylaxis [18]. No side effects were noted amongst the 48 subjects in this study, but a low dose of theophylline was used, resulting in a relatively low mean serum level (6.8 μg/ml). In this study, no benefit on kidney function was noted. Two other studies measured serum theophylline concentrations and found an improvement in serum creatinine with theophylline administration (levels 10.6 ± 1.9 and 13.9 ± 6.1 μg/ml, respectively) but did not report on incidence of side effects [12,13].

**Test for publication bias**

Using the broad array of weighting schemes, P-values for Begg’s test ranged from 0.71 to 1.00, suggesting no evidence for publication bias.

**Discussion**

The primary finding of this meta-analysis is that prophylactic administration of theophylline or aminophylline appears to prevent radiocontrast-induced declines in kidney function. By the most conservative estimate, prophylactic theophylline or aminophylline administration was associated with a relative decline in serum creatinine of 11.5 μmol/l. This finding provides clinical evidence that, similar to animal studies, adenosine-mediated vasoconstriction may contribute to radiocontrast-induced nephrotoxicity in humans and that adenosine blockade may be protective. The protective benefit appeared robust regardless of the study design, form or volume of radiocontrast delivered, and presence or absence of intravenous volume expansion.

The pathogenesis of radiocontrast-induced nephropathy remains incompletely understood. Radiocontrast may be nephrotoxic through two proposed mechanisms; alterations in renal haemodynamics, and direct tubular toxicity, in part due to oxygen free radicals. These mechanisms are suggested to contribute synergistically to the development of ARF [14]. In laboratory animals, the haemodynamic response of the kidney to radiocontrast is biphasic. Shortly after radiocontrast exposure, there is initial vasodilation, followed by a period of prolonged vasoconstriction that occurs primarily in the renal cortex [10]. While the cortical vasoconstrictive effect may be protective early after
<table>
<thead>
<tr>
<th>Study (Jadad score)</th>
<th>No. of patients</th>
<th>Procedure and radiocontrast agent</th>
<th>Theophylline or aminophylline</th>
<th>Hydration</th>
<th>Primary end-point (time after radiocontrast exposure)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abizaid [15] (2)</td>
<td>40</td>
<td>Coronary angiography, hexabrix (non-ionic)</td>
<td>Aminophylline 4 mg/kg bolus followed by 0.4 mg/kg/h drip beginning 2 h before procedure</td>
<td>0.45% saline 1 ml/kg/h 12 h before and 12 h after</td>
<td>SCR ≥25% (at 48 h)</td>
<td>1 patient required dialysis</td>
</tr>
<tr>
<td>Erley [12] (3)</td>
<td>39</td>
<td>CT or angiography, iopromide (non-ionic)</td>
<td>Theophylline 5 mg/kg i.v. once, 45 min before procedure</td>
<td>0.43% saline 1 l/h 4 h after procedure</td>
<td>Change in GFR (inulin) (at 48 h)</td>
<td></td>
</tr>
<tr>
<td>Erley [13] (3)</td>
<td>80</td>
<td>CT or angiography, iopromide (non-ionic)</td>
<td>Theophylline 240 mg p.o. q.a.m., 540 mg p.o. q.h.s. for 2 days before until 3 days after radiocontrast</td>
<td>No specific hydration protocol</td>
<td>SCR ≥0.5 mg/dl (any time before 72 h)</td>
<td>16 patients lost to follow-up, no patient required dialysis</td>
</tr>
<tr>
<td>Huber [16] (2)</td>
<td>100</td>
<td>Coronary angiography, iomeprol</td>
<td>Theophylline 200 mg i.v. once 30 min before radiocontrast</td>
<td>0.9% saline (2 l) over 24 h starting after radiocontrast</td>
<td>SCR ≥0.5 mg/dl (at 48 h)</td>
<td></td>
</tr>
<tr>
<td>Kapoor [17] (1)</td>
<td>70</td>
<td>Coronary angiography, diatrizoate (ionic)</td>
<td>Theophylline 200 mg p.o. b.i.d. beginning 24 h before to 24 h after radiocontrast</td>
<td>0.9% saline (1 mg/kg/h) for 12 h before to 12 h after radiocontrast</td>
<td>SCR ≥25% (at 48 h)</td>
<td>No patient required dialysis</td>
</tr>
<tr>
<td>Katholi [18] (2)</td>
<td>93</td>
<td>Coronary angiography, iopamidol (non-ionic), 45 patients diatrizoate (ionic)</td>
<td>Theophylline 2.88 mg/kg p.o. Q 12 h starting 1 h before until 48 h after radiocontrast</td>
<td>D5W (1 mg/kg/h) from 1 h before until 72 h after radiocontrast</td>
<td>Change in CrCl (12 h urine) (at 48 h)</td>
<td></td>
</tr>
<tr>
<td>Kolonko [19] (2)</td>
<td>58</td>
<td>Intravenous injection uropolinum (ionic)</td>
<td>Aminophylline 165 mg i.v. 30 min before radiocontrast once</td>
<td>No i.v. hydration</td>
<td>Change in S_{Cr} (at 24 h)</td>
<td></td>
</tr>
</tbody>
</table>

S_{Cr} = serum creatinine (μmol/l); DM = diabetes mellitus; CHF = congestive heart failure, or EF < 30%; CV = contrast volume; coronary angiography = coronary angiography with or without percutaneous intervention; CrCl = creatinine clearance; CT = computed tomography.

*Data are mean (SD) or percentage.
exposure by re-directing blood flow towards the renal medulla, prolonged vasoconstriction associated with radiocontrast may result in ischaemic damage to the cortical tubular epithelial cells. This haemodynamic response is thought to be mediated by endogenous intrarenal adenosine. Since the discovery that theophylline, a competitive adenosine antagonist, might attenuate, and dipyridamole, a potentiator of adenosine, might accentuate radiocontrast nephropathy in animals [23], multiple investigators have evaluated theophylline and aminophylline as a means of preventing radiocontrast nephropathy in humans. However, previously published randomized trials have been limited in their ability to conclude whether these agents are effective in preventing declines in kidney function primarily due to small sample size. Our meta-analysis demonstrates that these agents do appear to provide renal protection in humans, although the clinical significance of the changes observed remains uncertain.

Over the past decade, multiple therapies have been investigated for prevention of radiocontrast nephropathy. Despite modest early reports, several subsequent high-profile studies ([8] and others) and meta-analyses suggested a benefit of the antioxidant N-acetylcysteine. However, a more recently published meta-analysis suggested substantial inter-study heterogeneity, and no conclusion on efficacy was reached [24]. Nevertheless, N-acetylcysteine is inexpensive and relatively well tolerated and has been increasingly utilized. Merten and colleagues recently reported impressive results with intravenous sodium bicarbonate, reducing the risk of radiocontrast nephropathy to \( \frac{1}{24^2} \% \), relative to 14% among saline-treated control subjects [9]. To our knowledge, no study has evaluated whether theophylline or aminophylline provides additive or synergistic effects in combination with N-acetylcysteine or sodium bicarbonate.

Only one study included in our analysis reported on the occurrence of side effects with theophylline or aminophylline therapy. With short-term administration, significant toxicity from theophylline is rarely observed when serum concentrations are held below 100 \( \mu \)g/ml [25]. Two of the three studies that reported on serum theophylline concentrations demonstrated benefit with serum theophylline concentrations at \( \sim 10-20\% \) of toxic levels. A single dose of 250mg of aminophylline given intravenously would not be expected to yield a serum concentration above the range of 100 \( \mu \)g/ml in most patients.
Our meta-analysis has several important limitations. While many patients who are exposed to radiocontrast experience minimal changes in renal function, some have larger declines. With a non-linear distribution of changes in kidney function, a discrete outcome (e.g. ‘radiocontrast nephropathy’—yes or no) might be more clinically relevant than a change in serum creatinine, and would have been preferred as a summary effect measure. Unfortunately, three studies included in our analysis failed to report on the proportion of subjects who developed discrete changes in serum creatinine, and the four studies that did report on the fraction of subjects experiencing discrete changes in serum creatinine used varying definitions for radiocontrast nephropathy. As with many meta-analyses, we had insufficient access to primary data. Therefore, regardless of the definition employed, we could not calculate the rate of radiocontrast nephropathy in many of the theophylline- and control-treated subjects. Other outcomes or events, such as the provision of dialysis, lengthening of hospital stay and mortality, were either rare or not documented. Bias may have been introduced in non-blinded trials. However, a sensitivity analysis limited to randomized double-blinded placebo-controlled trials showed a similar point estimate and statistically significant protective effect with theophylline therapy. The mean serum creatinine concentrations in published studies were relatively low, indicating that some subjects might have been at relatively low risk of radiocontrast-induced injury. If there is a clinically meaningful benefit to the provision of theophylline or aminophylline, it might be more potent (and more easily observed) among patients with more extensive CKD. It is possible that other studies showing no effect of theophylline or aminophylline were not published, thereby leading to an overestimation of the summary effect observed in this study. We were unable to provide some of the conventional measures by which study heterogeneity and publication bias are usually judged. We employed a random effects analysis to allow for heterogeneity (rather than test for heterogeneity, with a Q-test), since residual variance could not be uniformly determined in all seven studies. A funnel plot could not be constructed, although Begg’s test suggested no evidence of publication bias. As stated, in our primary analysis, we made conservative assumptions to bias against finding a difference between theophylline- and placebo-treated groups. Extensive sensitivity analyses confirmed the robustness of our findings.

In summary, we conducted a meta-analysis of studies employing theophylline or aminophylline for prevention of radiocontrast nephropathy, and identified a statistically significant effect on the decline in kidney function after radiocontrast exposure. Whether a modest improvement in kidney function following radiocontrast exposure would translate into a clinically meaningful benefit (reduced need for dialysis or in-hospital mortality) is unknown. Future studies evaluating the effects of theophylline or aminophylline on prevention of ARF or treatment of established ARF would be of considerable interest. In addition, the use of theophylline or aminophylline in combination with other preventive strategies (e.g. sodium bicarbonate, antioxidants, inhibitors of apoptosis, etc.) may be worth pursuing, based on unique and potentially complementary mechanisms of action.

Conflict of interest statement. None declared.

References


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