Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis

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CRD summary
This review assessed the use of theophylline for the prevention of contrast-induced nephropathy. The authors concluded that current evidence appears promising but is inconclusive, and that further research is required. The results of this well-conducted review are likely to be reliable, and the authors' recommendations appear appropriate.

Authors' objectives
To assess the efficacy of theophylline, an adenosine antagonist, for the prevention of contrast-induced nephropathy (CIN).

Searching
Several electronic databases were searched to November 2003: MEDLINE (from 1966), PubMed, EMBASE (from 1980) and the Cochrane Controlled Trials Register (from 1996). The search terms were reported and no language restrictions were applied. Further studies were sought through the reference lists of identified articles, conference proceedings of three large meetings, and contact with experts in the field. All types of publication were considered.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing adenosine antagonists with control were eligible for inclusion. All included studies used theophylline. There was variation across the studies in the dose and protocol for administration used.

Participants included in the review
Studies of patients receiving contrast media for intravascular angiography or computed tomography were eligible for inclusion. The proportion of participants with diabetes mellitus varied between studies (from 0 to 100%), as did the type of contrast media used and the hydration protocol of the procedure.

Outcomes assessed in the review
Studies reporting incidences of CIN (defined explicitly a priori), change in serum creatinine level or glomerular filtration rate prior to and following contrast administration, were eligible for inclusion. The secondary outcomes included adverse reactions and dialysis requirement.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The following methodological factors were considered in the review: methods of randomisation; use of blinding; use of placebo control; reporting of loss to follow-up and missing data; baseline differences between the groups; statistical power calculation. Jadad criteria were also used to determine a quality score out of 5 for each study. Two reviewers independently assessed the methodological quality of the studies. Any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data. The incidence of CIN, use of dialysis, and baseline and change in serum creatinine levels and glomerular filtration rate, were extracted for the intervention and control arms of each trial. The odds ratio (OR) for developing CIN was calculated for each study.

**Methods of synthesis**

How were the studies combined?
The incidence data were combined using a random-effects model to give a pooled OR with 95% confidence intervals (CIs). The mean changes in serum creatinine level was also combined using a random-effects model. Publication bias was assessed using a funnel plot analysis and the statistical tests proposed by Begg and Egger.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test. Regression analyses were performed to investigate potential sources of heterogeneity, including clinical and study quality factors. The robustness of the pooled results was tested in a sensitivity analysis where the impact of additional hypothetical negative trials was assessed.

**Results of the review**

Nine RCTs involving 585 participants were included in the review.

There was no statistically significant reduction in the incidence of CIN with the use of theophylline (OR 0.40, 95% CI: 0.14, 1.16, P=0.09), but there was a statistically significant reduction in serum creatinine (-0.17 mg/dL, 95% CI: -0.28, -0.06, P=0.002). There was evidence of statistical heterogeneity in both analyses (P=0.08, P<0.001). CIN requiring dialysis was uncommon and was reported in only 1 case.

Regression analyses on the incidence of CIN showed that more recent and poorer quality studies were associated with greater protective effects of theophylline. No statistically significant influences of clinical factors were detected.

There was no evidence of publication bias, and the pooled results were robust to the addition of new negative trials.

**Authors' conclusions**
The evidence on the use of theophylline for the prevention of CIN is suggestive of possible benefit but remains inconclusive.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria. The search for primary studies incorporated a range of sources and was not restricted by language or publication status. Publication bias was also formally investigated and it is unlikely that relevant studies were missed. Each stage of the review process was carried out in duplicate, which should have minimised the introduction of errors and bias. The assessment of study quality and the investigation of heterogeneity were both thorough.

The results of this well-conducted review are likely to be reliable, and the conclusion appears appropriately cautious.

**Implications of the review for practice and research**

Practice: The authors stated that more evidence is needed before theophylline can be recommended routinely for the prevention of CIN.

Research: The authors stated that a large trial is required to assess the effectiveness and risks of theophylline for the prevention of CIN. Such a trial should use a hydration protocol, low or iso-osmolar nonionic contrast media and clinically relevant end points.

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