Meta-analysis: allopurinol in the prevention of postendoscopic retrograde cholangiopancreatography pancreatitis

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CRD summary
The review concluded that prophylactic allopurinol may not be useful for postendoscopic retrograde cholangiopancreatography pancreatitis. This was a reasonably well conducted review. The authors’ conclusions reflected the results of the review and appear likely to be reliable, but the lack of study details and statistical heterogeneity should be borne in mind.

Authors’ objectives
To assess the effect of prophylactic allopurinol compared with placebo on pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP).

Searching
MEDLINE, EMBASE, The Cochrane Library and Science Citation Index were searched up to March 2008. Major conference abstracts were also searched. Search terms were not reported. Reference lists of trials were scanned for further relevant studies. Only full paper articles were included.

Study selection
Studies were eligible if they were RCTs reported in a full paper article comparing prophylactic administration of allopurinol compared with placebo in patients receiving endoscopic retrograde cholangiopancreatography (ERCP) and which assessed the incidence of post-ERCP pancreatitis.

The included trials used different dosing schemes: one used 200 mg of allopurinol at 15 hours and three hours before ERCP; one used 600 mg at 15 hours and three hours before ERCP; one used 600 mg at four hours and 300 mg at one hour before ERCP; and the fourth used 300 mg at one hour before ERCP. All studies included diagnostic and therapeutic ERCP. The definition of post-ERCP pancreatitis was based on standard criteria in all trials included.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Two authors independently assessed study quality using the following criteria: generation of allocation sequence; allocation concealment; and double blinding. Low risk of bias was defined as all criteria being met, moderate risk of bias as one or more of the criteria being partly met and high risk of bias as one or more criteria not being met. Any disagreement between the reviewers was resolved by discussion.

Data extraction
Two reviewers independently extracted the data using a standardised form and entering data into the Cochrane Review Manager software.

Methods of synthesis
Differences between groups were expressed as relative risks (RR) with 95% confidence intervals. Data were summarised in a meta-analysis using a random-effects model (DerSimonian and Laird). Statistical heterogeneity between studies was assessed using the Q (with p<0.1) and I² statistics. Heterogeneity was explored using the following subgroup analyses: single centre versus multicentre; high (>600 mg) versus low dose of allopurinol; high versus low pre-treatment risk of post-ERCP pancreatitis; and high versus low/moderate risk of bias (as determined by the validity assessment). Publication bias was examined using a funnel plot.

Results of the review
Four trials with a total of 1,730 participants were included. The funnel plot suggested that there may have been some publication bias. Three of the trials had a low risk of bias (all quality criteria fulfilled) and one had a moderate risk of bias (unclear allocation concealment).

No significant difference in the incidence of post-ERCP pancreatitis was found in the meta-analysis when comparing allopurinol with placebo (RR 0.86, 95% CI: 0.42, 1.77, p=0.68). The number of patients developing post-ERCP pancreatitis was 78 in the allopurinol groups and 83 in the placebo groups. There was evidence of significant statistical heterogeneity ($\chi^2 p=0.006, I^2=75.8\%$). Of the four included RCTs, one found a significant effect in favour of allopurinol (possibly linked to some demographic differences between the comparison groups) and the other three did not.

A prophylactic effect of allopurinol was not found in any of the subgroups examined (single centre versus multicentre, high versus low dose of allopurinol, high versus low pre-treatment risk of post-ERCP pancreatitis and high versus low/moderate risk of bias).

**Authors’ conclusions**

Prophylactic allopurinol may not be useful for post-ERCP pancreatitis reduction.

**CRD commentary**

This was a carefully conducted and well-reported systematic review addressing a clearly stated research question. Appropriate inclusion criteria were defined and measures were taken to avoid the introduction of error and bias during the review process. The literature search included a variety of relevant databases, but search terms were not listed and it was unclear whether there was a language restriction. Publication bias was reported to have been assessed, but would have been difficult to interpret in view of the small number of studies included. The methodological quality of the included studies was restricted to three criteria and subgroup analyses based on study quality were included in the meta-analysis. The use of meta-analysis appeared appropriate, but the use of a heterogeneity assessment to determine the employment of a fixed- or random-effects model may not have been advisable. Information on the patients included in the trials was limited. The authors’ conclusions followed from the data presented, but the lack of information regarding the population and the significant statistical heterogeneity raised some questions.

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

Practice: The authors made no specific recommendations for practice.

Research: The authors stated that further trials with the following characteristics were needed: multicentre prospective trials sufficiently powered to detect a difference between comparison groups; trials that include only patients with high risk factors regarding post-ERCP pancreatitis who may undergo high-risk procedures; and trials that report more details allowing an association of risk of post-ERCP pancreatitis with patient-related and procedure-type-related information. Additionally, further trials investigating other medical prophylaxis that is safe, inexpensive and easy to administer were needed.

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