Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness: systematic review and meta-analysis

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CRD summary
The authors concluded that 250mg, 500mg and 750mg doses of acetazolamide were effective for acute mountain sickness in healthy participants, and the lowest effective dose found was 250mg. This was a well-conducted review. There were methodological limitations to the included trials, but their results consistently favoured acetazolamide and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To examine the efficacy of acetazolamide at different doses for preventing acute mountain sickness and to identify the lowest effective dose.

Searching
MEDLINE and EMBASE were searched for articles from their inception to January 2012; search terms were reported. The references of included articles, reviews, and selected journals on high-altitude medicine were searched. No language restrictions were applied. Researchers were contacted to identify unpublished studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) comparing acetazolamide with placebo in healthy participants, who were over 16 years old, to prevent acute mountain sickness when ascending to an altitude over 3km. Trials had to provide a clear definition, and the incidence among participants, of acute mountain sickness. Trials that did not state the administered dose, that included indigenous or local populations, or in which ascent was simulated in a hypobaric chamber, were excluded.

The mean age (where reported) ranged from 20 to 39 years. The percentage of males ranged from 58 to 100. The median altitude at enrolment was 3,440m and the mean final altitude was 4,619m. The first dose was taken on the day of ascent or at least one day before ascent. Most trials assessed acute mountain sickness using the Lake Louie scoring system.

Two reviewers independently selected trials for inclusion with any disagreements resolved through discussion.

Assessment of study quality
Trial quality was assessed using the Cochrane Collaboration’s risk of bias tool. Two reviewers independently assessed quality.

Data extraction
Data on acute mountain sickness were extracted from each trial to calculate odds ratios and 95% confidence intervals. The incidence of adverse events was extracted. The data were extracted by one reviewer and checked by another with any disagreements resolved through discussion. Where trials had two intervention arms compared with the same control group, the control group was divided into two to avoid unit of analysis errors (repeated counting of the same data). Trial authors were contacted for missing data.

Methods of synthesis
The trial data were pooled to provide an overall odds ratio and 95% confidence interval, using a fixed-effect and a random-effects model. Heterogeneity was assessed using X² and I². A sensitivity analysis was conducted, using only data from the Lake Louie scoring system for acute mountain sickness. The impact of variations in interventions, participants, outcomes and trial quality was examined. Publication bias was assessed using a funnel plot.

Results of the review
Eleven RCTs were included in the review (over 1,500 participants; range 12 to over 330). Eight of the 11 trials had
adequate sequence generation, 10 had concealed allocation, six reported blinding for patients and staff, three reported blinding of outcome assessors, and six avoided attrition bias.

Overall, compared with placebo, acetazolamide significantly reduced the incidence of acute mountain sickness (OR 0.36, 95% CI 0.28 to 0.46; I²=0; 12 comparisons from 11 trials). There were statistically significant reductions in the incidence of acute mountain sickness with acetazolamide, compared with placebo, at doses of 250mg (OR 0.41; 95% CI 0.26 to 0.64; I²=15%; NNT six; four trials) 500mg (OR 0.37; 95% CI 0.26 to 0.52; NNT seven; I²=0; six trials) and 750mg (OR 0.20; 95% CI 0.10 to 0.41; NNT three; I²=44%; two trials).

Sensitivity analyses including only the eight trials using the Lake Louie scoring system found similar results. There were no substantial differences between fixed-effect and random-effects analyses. The authors stated that there was no evidence of funnel plot asymmetry.

There was a substantially higher incidence of paraesthesia with acetazolamide, compared with placebo. There were smaller increases in the incidence of dysgeusia, and frequency of micturition with acetazolamide.

**Authors' conclusions**
Acetazolamide was effective compared with placebo at doses of 250mg, 500mg and 750mg, and the lowest effective dose, with evidence available, was 250mg.

**CRD commentary**
The review question and inclusion criteria were clear. An adequate search of electronic databases was undertaken and no language restrictions were applied, which minimised language bias. Attempts were made to obtain unpublished material. Acceptable processes were used to minimise error and bias in the review. The trials appear to have been sufficiently similar to provide valid pooled estimates for the effectiveness data.

Appropriate criteria were used to assess trial quality; there were high drop-out rates and unclear reporting of blinding of the outcome assessor. The number of participants lost to follow-up was not provided and the impact of the trial limitations was not examined in sensitivity analyses. Three trials were small (the smallest had just 12 participants). There were some inconsistencies between the trial descriptions in the table and the text. For example, two trials had the same participant numbers and dose in the table, but different numbers in the text and forest plots. The authors stated that there was no evidence of publication bias, but there were two few trials to draw firm conclusions.

This was mainly a well-conducted review. Most of the trials were either high quality, but small or were of low quality, but all found consistent reductions in acute mountain sickness and the authors’ conclusions appear to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should discuss with their patients the benefits and harms of higher doses compared with lower ones.

**Research:** The authors suggested a number of avenues for further research, including recruiting at low altitude (most of the trials recruited at high altitude), including participants from the general population (rather than mountain enthusiasts), and assessing the drug's effectiveness for rapid ascent to altitude.

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