Acetazolamide for the treatment of acute mountain sickness

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Abstract

Introduction

Acute mountain sickness is the most prevalent illness related to acute exposure to high altitude, secondary to the hypobaric hypoxia effects in our body. Acetazolamide has been traditionally used for its prevention and treatment, however, there is still controversy regarding the degree of usefulness of this medication as monotherapy.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified a systematic review that included two primary studies, both corresponding to randomized trials. We conclude that it is not possible to establish clearly whether treatment with acetazolamide reduces the symptoms of acute mountain disease or increases the risk of adverse effects, because the certainty of the existing evidence has been evaluated as very low.

Problem

When the organism is exposed to acute high-altitude hypobaric hypoxia, it develops a series of adaptive responses. However, if these responses are insufficient or abnormal, a spectrum of high-altitude illnesses that mainly include acute mountain sickness, high-altitude pulmonary edema and high-altitude cerebral edema, can occur. Of the three conditions previously indicated, acute mountain sickness is the most frequent, with its main symptoms being headache, fatigue, dizziness, nausea, vomiting, sleep disturbances and anorexia[1].

For the prevention and treatment of this syndrome, a series of non-pharmacological and pharmacological measures have been used. One of them is acetazolamide, which inhibits the carbonic anhydrase enzyme at the renal level and causes urinary bicarbonate excretion and metabolic acidosis. Its effect triggers compensatory hyperventilation and respiratory alkalosis, which promote the physiological response to the hypoxic stimulus. Despite being traditionally used, there is still controversy about the usefulness of acetazolamide as a treatment for acute mountain sickness[1].

Key messages

- We are uncertain whether treatment with acetazolamide decreases the symptoms of acute mountain sickness or if it increases the risk of adverse effects as the certainty of the evidence has been assessed as very low.
- The outcomes mortality and acute mountain sickness symptoms resolution were not reported.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found one systematic review[1], which included two primary studies[2,3], both corresponding to randomized trials.
What types of patients were included*	Both trials included patients with acute mountain sickness, that is, subjects acutely exposed to high-altitude, presenting symptoms of headache, fatigue, dizziness, nausea, vomiting, sleep disturbances and anorexia. The patients included were adult mountaineers. In one trial[2] 91% of the participants were male, while in the other sex was not reported[3]. One trial[2] defined the syndrome according to the AMS (Acute Mountain Sickness) Symptom Questionnaire, with a score greater than or equal to two (with onset of symptoms over 4,200 masl and maximum 24 hours before inclusion) and excluded patients with previous use of acetazolamide, confirmed diagnosis of high-altitude pulmonary or cerebral edema, or with severe comorbidity. The other trial[3] included patients with a score greater than or equal to three in a self-administered acute mountain sickness questionnaire (18 questions and a maximum score of 180) and excluded patients with severe comorbidity, obese and previous acclimatation.
What types of interventions were included*	Both trials evaluated the use of acetazolamide orally. One trial[2] administered 250 mg at 0 and 8 hours and the other[3] 20 mg/kg at baseline and then 500 mg daily for 5 days. Both trials compared against placebo.
What types of outcomes were measured	The trials reported multiple outcomes, which were grouped by systematic review as follows: Primary outcomes: • Mortality • Acute mountain sickness symptoms resolution Secondary outcomes: • Acute mountain sickness symptoms reduction, measured with AMS Symptom Questionnaire[2] and self-administered questionnaire[3] • Adverse effects The average follow-up of the trials was 3 days, with a range between 24 hours[2] and 5 days[3].

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of findings

The information on the effects of acetazolamide for the treatment for acute mountain sickness is based on two randomized trials that included 25 patients.
Two trials reported acute mountain sickness symptoms decrease (25 patients)[2,3], only one trial reported adverse effects, with incomplete results (12 patients)[2]. No trial reported the outcomes mortality or acute mountain sickness symptoms resolution.

The summary of findings is as follows:

- We are uncertain whether treatment with acetazolamide decreases acute mountain sickness symptoms as the certainty of the evidence has been assessed as very low.
- We are uncertain whether treatment with acetazolamide increases the risk of adverse effects as the certainty of the evidence has been assessed as very low.
- No studies were found to evaluate the reduction of mortality with treatment with acetazolamide.
- No studies were found to evaluate acute mountain sickness symptoms resolution with acetazolamide treatment.

Acetazolamide for the treatment of acute mountain sickness

Patients Patients with acute mountain sickness
Intervention Acetazolamide
Comparison Placebo

Outcome	Effect	Certainty of evidence (GRADE)
Acute mountain sickness symptoms decrease	The symptoms improvement/decrease scale was on average 1.15 standard deviations smaller than the group without acetazolamide. SMD: 1.15 units less (Margin of error: 2.56 less to 0.27 more)**	⨁◯◯◯[1,2] Very low
Adverse effects	The outcome adverse effects was only reported by one trial [2], which reported zero adverse effects in the intervention group, while the number of adverse effects in the control group was not reported.	⨁◯◯◯[1,2] Very low
Acute mountain sickness symptoms resolution	The outcome acute mountain sickness symptoms resolution was not measured or reported by the systematic review.	--
Mortality	The outcome mortality was not measured or reported by the systematic review.	--

Margin of error: 95% confidence interval (CI).
SMD: Standard mean difference
GRADE: Evidence grades of the GRADE Working Group (see later).

** The standard mean difference is used when the outcome has been measured in different scales and it is hard to interpret clinically. A general rule is that values close to 0.2 would have little clinical relevance, values of 0.5 would be of moderate relevance (clinically recognized) and values greater than 0.8 would be of high relevance.

[1] The certainty of evidence was downgraded two levels due to high risk of bias. Both trials presented problems with random sequence generation, blinding of participants, blinding of outcome assessment and selective reporting.
[2] The certainty of evidence was downgraded one level due to imprecision of the results. In the case of the "symptom improvement" outcome, each end of the confidence interval leads to different decisions. In the outcome "adverse effects" the certainty of the evidence was decreased due to the sample size used (n = 12).

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary applies to adult patients with acute mountain sickness.

The patients included in the trials were male adults, however, it is reasonable to extrapolate these results to female patients.

The evidence presented in this summary should not be extrapolated to the pediatric population or pregnant women, due to the different requirements and risks of these groups that were not evaluated in the included trials.

About the outcomes included in this summary

The selected outcomes are those considered critical for decision-making according to the opinion of the authors of this summary, coinciding with the identified systematic review.

Balance between benefits and risks, and certainty of the evidence

There is no clarity regarding the effectiveness or safety of acetazolamide as a treatment for acute mountain disease because the certainty of the evidence is very low. Additionally, there is no evidence on the benefit of treatment in mortality and resolution of symptoms of patients with acute mountain sickness, since these were not evaluated.

In consideration of the above, the balance between benefits and risks should be assessed individually, taking into account additional factors associated with the experience and preferences of both patients and physicians regarding the use of acetazolamide.

Resource considerations

There are no studies evaluating the cost-effectiveness of acetazolamide as a treatment for acute mountain disease. However, even if the economic value of acetazolamide is not high, it is not possible to make an adequate cost/effectiveness balance because the certainty of the evidence is very low.

What would patients and their doctors think about this intervention

Travelers and mountaineers who are exposed to high-altitude are the main ones affected by acute mountain sickness, whose symptoms constitute an important impediment to the realization of their recreational and/or sports activities.

In this scenario, given the uncertainty about the benefits and risks, patients and physicians could both lean in favor of its use and against it. The final decision should be individualized considering the values and preferences of the patients and explaining the existing uncertainty.

Differences between this summary and other sources

The conclusions of this summary are consistent with those of the systematic review identified[1].

The results of this summary partially coincide with those of the guidelines of the International Society of Travel Medicine [4] and Wilderness Medical Society[5] in which the use of acetazolamide is recommended as an alternative treatment for acute mountain sickness, despite the uncertain evidence and its very low level of certainty of the evidence.

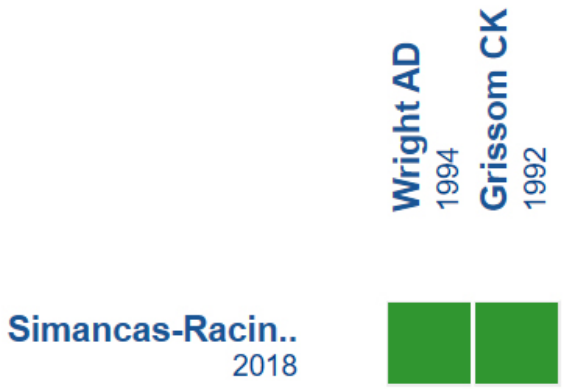
Could this evidence change in the future?

It is very likely that future research will modify the conclusions of this summary, mainly due to the very low certainty of the evidence available and the low number of randomized trials and patients evaluated.

No ongoing trials or systematic reviews of acetazolamide were found as a treatment for acute mountain disease in PROSPERO database or in the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Acetazolamide for the treatment of acute mountain syndrome.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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