Ibuprofen versus acetazolamide for prevention of acute mountain sickness

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Abstract

Introduction

Acute mountain sickness is a common condition occurring in healthy subjects that undergo rapid ascent without prior acclimatization, as low as 2500 meters above sea level. The classic preventive agent has been acetazolamide, although in the last decade there has been evidence favoring ibuprofen. However, it is unclear which method is more efficient.

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 two systematic reviews that included only one primary study, which is a randomized trial. We concluded it is not possible to establish whether ibuprofen is better or worse than acetazolamide because the certainty of evidence has been evaluated as very low.

Problem

Acute mountain sickness or high altitude illness is a condition that can arise when a subject ascents to more than 2500 meters above sea level without prior acclimatization. Classically, it presents as headache plus one of the following symptoms: anorexia, nausea, insomnia, fatigue or dizziness, and can progress to more severe forms of illness such as high altitude cerebral edema or high altitude pulmonary edema[1,2].

Acetazolamide has been the most used pharmacological prevention. It inhibits carbonic anhydrase at renal level, causing bicarbonate excretion through urine and metabolic acidosis. Its effect would offset hyperventilation and respiratory alkalosis, thus favoring the physiological response to hypoxic stimuli. However, the minimum dose (from 250 mg to 750mg per day) is still controversial.

An alternative treatment that has gained support during the last years has been ibuprofen, due to its availability and easy access[4-6]. This drug inhibits the synthesis of prostaglandin, which increases microvascular permeability at the brain as a physiopathological mechanism of acute mountain sickness.

However, it is unclear which treatment is more effective.

Key messages

- It is not possible to establish whether ibuprofen is better or worse than acetazolamide because the certainty of evidence has been evaluated as very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews[1-2] that included one primary study[3], which is a randomized trial.
What types of patients were included*	The trial included healthy patients, between 18 to 65 years, at risk of developing acute mountain sickness; without prior acclimatization. Criteria of exclusion were use of NSAIDs or acetazolamide one to three days prior to enrollment, symptoms of acute mountain sickness or concomitant infection[3].
What types of interventions were included*	The trial divided the participants into three groups: acetazolamide (75 mg tid), ibuprofen (600 mg tid) and placebo. All three groups had a prior three nights period of acclimatization[3].
What types of outcomes were measured	The trials reported multiple outcomes, which were grouped by systematic reviews as follows: • Risk of developing acute mountain sickness. • Risk of developing high altitude cerebral edema. • Risk of developing high altitude pulmonary edema. • Adverse events. • Differences in diagnostic test scores. The follow-up was one day[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 about the effects of ibuprofen for prevention of acute mountain sickness is based on one randomized trial that included 343 subjects, from which 129 were randomized to ibuprofen, 125 to acetazolamide and 89 to placebo[3]

The summary of findings is as follows:

- It is not clear whether ibuprofen is better or worse than acetazolamide for prevention of acute mountain sickness because the certainty of the evidence was evaluated as very low.
- The outcome high altitude cerebral edema was not measured or reported.
- The outcome high altitude pulmonary edema was not measured or reported.
- It is not clear whether ibuprofen has more or less adverse events than acetazolamide for prevention of acute mountain sickness because the certainty of the evidence was evaluated as very low.

Ibuprofen versus acetazolamide for acute mountain sickness

Patients Healthy subjects at risk of developing acute mountain sickness.
Intervention Ibuprofen.
Comparison Acetazolamide.

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITH Acetazolamide	**WITH Ibuprofen**		
	Difference: patients per 1000			
Acute mountain sickness	144 per 1000	192 per 1000	RR 1.33 (0.69 to 2.55)	⨁◯◯◯[1,2] very low
	Difference: 48 patients more per 1000 (Margin of error: 45 patients less to 223 patients more)			
High altitude cerebral edema	The outcome high altitude cerebral edema was not measured or reported in the study		--	--
High altitude pulmonary edema	The outcome high altitude pulmonary edema was not measured or reported in the study		--	--
Adverse Events	The study reported no adverse event in any group			⨁◯◯◯[1,2] very low

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITH acetazolamide** is based on the risk in the control group of the trials. The risk **WITH ibuprofen** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in one level for risk of bias, since attrition bias was detected (22.7% of patients lost to follow up) and it was not clear the selection, performance or detection bias.
[2] The certainty of the evidence was downgraded in two levels due to imprecision, since each end of the confidence interval would lead to very different decisions.

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

These results are applicable to healthy subjects between 18 to 65 years old, with prior acclimatization averaging three nights.
Considering the wide use of acetazolamide for prevention of acute mountain sickness without prior acclimatization, it is reasonable to extrapolate these results to those patients.
These results do not apply to patients with contraindication for nonsteroidal anti-inflammatory drugs, pregnant or patients with nephropathy.

About the outcomes included in this summary

The outcomes included are those considered critical to decision-making, as per the opinion of the authors of this review, being in line with those selected in the systematic reviews.
We considered the incidence of acute mountain sickness as the critical outcome for decision-making, considering it can present in severe forms such as high altitude cerebral edema and high altitude pulmonary edema.

Balance between benefits and risks, and certainty of the evidence

Considering the uncertainty of ibuprofen being better or worse than acetazolamide for prevention of acute mountain sickness, the authors of this review concluded that the use of acetazolamide is preferable since it is the standard pharmacological preventive measure.

Resource considerations

Since ibuprofen is a more costly treatment in comparison with acetazolamide, and that acetazolamide is considered the first choice of treatment for prevention of acute mountain sickness, cost-benefit slightly favors acetazolamide.

What would patients and their doctors think about this intervention

Patients and providers should incline in favor of acetazolamide as the first choice for the prevention of acute mountain sickness. However non-pharmacological measures such as acclimatization could gain support considering the current uncertainty.

Differences between this summary and other sources

The conclusions hereby presented are aligned with the ones from the identified systematic reviews.

Also, these results agree with those of the international wilderness medicine guidelines, such as Wilderness Medical society, that favors the use of acetazolamide as the first choice pharmacological measure for preventing acute mountain sickness[7,8].

Could this evidence change in the future?

It is very likely that the conclusions of this summary would change with new evidence, considering the current level of uncertainty

We identified one clinical trial [9] that has not been included in any systematic review.

We did not identify any ongoing trial on 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:** Ibuprofen versus acetazolamide in acute mountain sickness.

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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