Boost or Barrier? Acetazolamide's Effects on Exercise Performance: A Systematic Review

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Background

When mountaineers ascend to altitudes >2,500m the are at risk of developing a serious illness known as acute mountain sickness (AMS). Acetazolamide (AZ) is a carbonic anhydrase inhibitor (CA) and is widely accepted as the medication of choice to avoid AMS (1).

Numerous side effects may discourage climbers from using AZ. One of particular concern is its queried effect on exercise performance. Seeing as climbing is a physically active activity in an occasionally dangerous environment, understanding whether a medication could limit performance is crucial. Also, there is an increasing number of climbers over 50 years old, it is important to understand how acetazolamide may affect them specifically (2).

Two previous reviews of acetazolamide's effect on exercise performance exist but neither has focused on older climbers (3,4).

Aims & Objectives

This study aims to evaluate how acetazolamide effects exercise performance at high altitude (>2,500m), particularly in those over 50 years old.

- To review studies assessing the effect of acetazolamide on exercise performance at high altitude.
- To extract and synthesize age-specific data from the available literature

Method

Literature search and study selection

A systematic literature search for peer-reviewed articles was conducted through Medline, Embase, and Web of Science following PRISMA guidelines.

Population	Healthy, unacclimatised, human lowlanders (living at and born below 2,500m)	Outcomes	Studies must examine exercise capacity as an outcome measure, which may be reported as aerobic capacity (e.g., VO2max, time to exhaustion, or other).
Intervention	Acetazolamide	Study Design	Primary randomised control trials
Comparison	Placebo / Control	Setting	Conducted at altitude or under simulated conditions (e.g., hypobaric chamber)

Figure 1. *Eligibility criteria using the PICOSS model*

Risk of bias assessment

The risk of bias of the included studies was evaluated using the Cochrane Risk of Bias 2 tool.

Data extraction

- Study characteristics: study name, publication date, study design, altitude, time to acclimatisation
- Participant characteristics: Sex, age range, whether or not a study included participants aged >50, sample size of AZ and comparator group
- Acetazolamide characteristics: dosage, treatment length and washout time (if a crossover study)
- Outcome measures: VO_{2max}, VO_2, P_{max}, HR_{max}, time to exhaustion, V_E and oxygenation. Any relevant >50s outcome measures
- Statistical data: mean and standard deviation along with any p values available from the studies.

Data analysis

Meta-analysis would have been performed if suitable data were available, but this was not possible due to the heterogeneity of results. A narrative synthesis was instead chosen.

Results

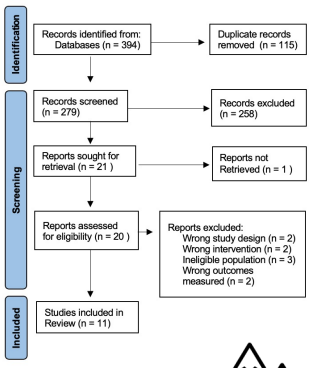

Figure 1. *PRISMA flow diagram*

Included studies

394 records were identified in the search. 11 were selected for analysis.

Study Characteristics

- 11 studies included 159 participants, 77% men.
- Five studies were crossover design.
- Participants exposed to real and simulated altitudes ranging from 3,459m to 4,846m.
- Most studies used a cycling ergometer to test at maximal and/or submaximal intensities.
- Acetazolamide doses ranged from 125 mg every six hours for 24 hours to 500 mg every 12 hours for 60 hours.

Quality of Studies

All studies had small numbers of participants, and all had 'some concerns' on the ROB2 risk of bias. No studies were excluded due to quality.

Effect of acetazolamide on exercise performance

- Overall exercise performance results were inconclusive.
- VO_2 was not impaired by AZ use.
- Most studies showed increases or no change in oxygenation and V_E with AZ, but this did not corelate to increases in $VO2_{max}$.
- Only 2 studies had data for >50s. Pmax, HRmax and time to failure were reduced in people over 50 with AZ use.

Study	M/SM	VO_{2Max}	VO_2	P_{max}	HR_{max}	EXHt	V_E	Oxy.	>50s Pmax	>50s HRmax	>50s TF
Schoene *et al.* 1983	M	↑				↔		↑			
Bradwell *et al.* 1986	M			↓				↑			
	SM 85%			↑				↑			
Stager *et al.* 1990	M	↔*			↔		↔	↔			
	SM (60%)		↔		↔	↓**	↔	↔			
Garske *et al.* 2003	M	↓		↓		↓	↔	↑			
Faoro et al. 2007	M	↔		↔	↔		↑	↑			
Jonk et al. 2007	SM 30-90%		↔				↑	↑			
Lalande *et al.* 2009	SM 40%		↔				↑	↑			
Bradwell et al. 2014	SM 60%							↓			↓
Ernst *et al.* 2017	M	↓		↔	↔		↔	↔			
	SM (NS)		↔		↔		↔				
Bradwell *et al.* 2018	M	↔		↓	↓		↓	↔	↓	↓	
	SM 40%		↔		↔			↔			
Bradbury *et al.* 2020	SM 40-45%		↔				↑	↑			
	TT							↑			

Table 1. *Simplified Results Table.* M = Maximal exercise test, SM = submaximal exercise test, *VO_2 peak, **T_{max}. ¹ Exercise duration time. Oxy = oxygenation, TT = self-paced time trial. ↑ = acetazolamide group result was higher than placebo group with statistical significance. ↓ = acetazolamide group result was lower than placebo group with statistical significance. ↔ = no statistical difference between acetazolamide and placebo results. TF = time to failure. NS = submaximal intensity not stated. ($p = \leq 0.05$)

Key findings

- Most results indicate that acetazolamide did not appear to impede exercise performance during submaximal exercise at high altitude.
- The effects of AZ on maximal exercise performance at high altitude remain inconclusive.
- Acetazolamide seems to impair exercise performance in individuals older than 50.

Discussion

- Extreme demands placed on the body at maximal intensity might mean any small changes have large effects leading to inconclusive results. Study heterogeneity may exacerbate this.
- Submaximal exercise may be more representative of high altitude climbing.
- While the majority of oxygenation and V_E was increased in AZ groups, it did not have a correlation to AZ groups suggesting other elements at play e.g. cardiovascular or muscular factors.
- Impacted exercise performance in people over 50 may be due to slower renal clearance.
- Limitations were the lack of homogenous data and the small number of participants.

Conclusions

Further studies with homogenous methodology and larger participant groups are recommended to provide a more definitive conclusions and facilitate statistical meta-Studies at testing submaximal exercise are needed to represent the requirements of day-to-day recreational climbing, and maximal tests to represent emergency climbing requirements.

Individuals over 50 should consider the implications that impaired exercise performance may have on their safety while climbing at high-altitude, but more age specific research is required to draw more robust conclusions.

Photograph 1. *Own photography, Ecuador 2023 at 5,000m.*

Photograph 2. *Background Photo, permission granted from NMR, Kanchenjunga 2022.*

SCAN ME

Please scan for the link to the full report with the more detailed results table.

References

1. Ritchie, N.D., Baggott, A.V. and Todd, W.T.A., (2012). Acetazolamide for the prevention of acute mountain sickness: a systematic review and meta-analysis. Journal of Travel Medicine, 19(5), 298-307.
2. The Himalayan Database [online] Available from https://www.himalayandatabase.com/ (Accessed on 15th November 24).
3. Doherty, C.J., Chang, J.C., Thompson, B.P., Swenson, E.R., Foster, G.E., & Dominelli, P.B. (2023) The Impact of Acetazolamide and Methazolamide on Exercise Performance in Normoxia and Hypoxia. High Alt Med Biol. 24(1): 7-18.
4. Posch, A.M., Dandorf S., Hile D.C. (2018) The Effects of Acetazolamide on Exercise Performance at Sea Level and in Hypoxic Environments: A Review. Wilderness Environ Med, 29(4): 541-545.