REVIEW ARTICLE

The Effects of Acetazolamide on Exercise Performance at Sea Level and in Hypoxic Environments: A Review

Alexander M. Posch, BS; Stewart Dandorf, MD, MPH, MS; David C. Hile, MD

From the Nova Southeastern University College of Osteopathic Medicine, Davie, FL (Mr Posch) and the Department of Emergency Medicine, Johns Hopkins University, Baltimore, MD (Drs Dandorf and Hile).

Lowlanders rapidly ascending to high altitude (>2500 m) often develop acute mountain sickness (AMS). While acclimatization is the most effective method of reducing symptoms of AMS (ie, headache, fatigue, nausea, gastrointestinal distress, etc.), it may take several days to become fully acclimated. Prophylactic use of acetazolamide (AZ), a carbonic anhydrase inhibitor, has become a popular alternative to staged acclimatization because it can be a less time-consuming method of reducing symptoms of AMS. While numerous studies have shown the effectiveness of AZ in mitigating the symptoms of AMS, a review of the existing literature regarding the effects of AZ on submaximal and maximal exercise performance at sea level and at altitude has not been performed. Literature search identified 17 peer reviewed articles examining the effects of AZ on exercise performance both at sea level and at altitude, as well as the associated side effects of prophylactic AZ use for the attenuation of AMS. This review finds that AZ treated cohorts experience a reduction in time to exhaustion during both submaximal and maximal exercise performance at sea level. At altitude, AZ treated cohorts' recorded widely variable submaximal and maximal exercise performance. At sea level, AZ impairs submaximal and maximal exercise performance. Due to the wide variation of findings of previously published studies, the effects of AZ on submaximal and maximal exercise performance at altitude remain unknown.

Keywords: carbonic anhydrase inhibitor, exercise endurance, altitude

Introduction

Unacclimatized lowlanders often rapidly ascend to high altitude (>2500 m) for leisure (eg, skiing, mountaineering), occupational demands (eg, mining, construction), or military operations. Without proper acclimatization, the hypoxic stress these individuals encounter on arrival to high altitude can have debilitating effects on their health and physical performance.

Although acclimatization is best achieved by a slow, gradual ascent to the desired altitude, this process can be lengthy, often driving sojourners to altitude to expedite the process through prophylactic use of carbonic anhydrase inhibitors such as acetazolamide (AZ).^{1,2} The ability of AZ to prevent acute mountain sickness has been well demonstrated;

however, the physiologic effects of AZ on exercise tolerance, an essential outcome for most traveling to altitude, are less clear. Although AZ increases blood oxygen saturation at sea level and at altitude, it also generates metabolic acidosis in both environments.³ For these reasons, there is little conclusive evidence regarding the prophylactic use of AZ and its effects on exercise performance. In this review we sought to evaluate the current knowledge regarding the physiologic effects on exercise tolerance and endurance of persons using AZ at sea level and altitude.

Methods

A literature review was performed beginning on October 16, 2015, with the last search conducted on February 6, 2016. Studies were identified by searching PubMed and ScienceDirect and by referencing UpToDate. The search terms used were “acetazolamide,” “acute mountain sickness,” “altitude,” “hypoxia,” “athlete,” “fitness,”

Corresponding author: Alexander M. Posch, 6960 SW 39th Street, Unit 303E, Davie, FL 33314; e-mail: ap2305@mynsu.nova.edu.

Submitted for publication January 2018.

Accepted for publication June 2018.

“exercise endurance,” “exercise performance,” “prophylaxis,” and “side effects.”

To be included in our analysis, articles were required to be peer-reviewed investigations of randomized comparisons of AZ to a control, to a placebo, or to a different treatment group. We included articles examining the effects of AZ at sea level, in normobaric hypoxia, and in hypobaric hypoxia (ie, chamber or terrestrial altitude). We collectively identified 15 articles for inclusion and individually retrieved and checked studies for inclusion criteria. Subsequently, relevant studies were reviewed by all authors for validation before inclusion. The articles included in the current review are listed in [Table 1](#).⁴⁻¹⁸

Results

EFFECTS OF ACETAZOLAMIDE ON EXERCISE AT SEA LEVEL

On review of the current literature, evidence suggests that using AZ at sea level negatively affects exercise performance. At sea level, AZ reduces exhaustion time (EXHt), increases ventilation (V_E), and has no effect on oxygen consumption during submaximal exercise. During maximal effort exercise at sea level, AZ use has been found to reduce EXHt and maximal work. AZ increases V_E and either reduces or has no effect on maximal oxygen consumption ($VO_{2\max}$) ([Table 2](#)).

EFFECTS OF ACETAZOLAMIDE ON EXERCISE AT ALTITUDE

At altitude, the effect of AZ on exercise is less clear. Although AZ increases V_E during both submaximal and maximal exercise, there is contrasting evidence regarding the effect of AZ on submaximal EXHt. Additionally, several reports indicate AZ reduces oxygen saturation, whereas it increases ratings of perceived exertion and results in less of a decrement in performance during submaximal exercise. Although one investigation reports an increase in maximal oxygen consumption after AZ administration, the majority of reports indicate that AZ either reduces or has no impact on maximal oxygen consumption or watt production at altitude. Furthermore, AZ has been found to reduce time to achieve maximal effort, increase V_E , and have no effect on oxygen saturation during maximal effort exercise ([Table 3](#)).

Discussion

After reviewing the available literature, AZ was found to consistently impair or have negligible effects on submaximal and maximal exercise performance at sea level. Several studies report that AZ reduces EXHt and either reduces or maintains $VO_{2\max}$ at sea level.^{7,8,11,14} These

findings may be explained by the metabolic acidosis generated by AZ use.^{4,5} During exercise, individuals using AZ experienced increased V_E , decreased arterial and venous blood bicarbonate ion concentrations, and decreased blood pH compared with control participants.^{10,11} Although designed to improve ventilation at altitude, a pharmacologically induced metabolic acidosis is unnecessary and ineffective at sea level.³ It may effectively reduce the available exercise capacity of an individual by further reducing the blood pH before the onset of exercise, thus resulting in decreased EXHt and $VO_{2\max}$.⁹ Furthermore, the AZ dose in most studies ranged from 500 to 750 mg/24 h, which exceeds the recommended dosage of 250 mg/24 h.³ The increased dose may contribute to the reduction in exercise performance and worsened side effects because they are known to be dose dependent.

Although AZ use at sea level is detrimental to exercise performance, it is primarily used at altitude. During resting conditions at altitude, it is widely accepted that AZ increases S_pO_2 and ventilation.^{11,12} However, the effect of AZ use on submaximal exercise performance at altitude has yielded confounding results ([Table 3](#)).

Several studies have suggested that AZ is beneficial to submaximal exercise performance at altitude. In a study of participants acclimatized to 4846 m, those being treated with AZ experienced less of a decrement in work achieved per minute while cycling at 85% maximal heart rate compared with those receiving placebo. Furthermore, this study reported that participants treated with AZ retained a larger percentage of muscle mass while at altitude compared with those receiving placebo.¹³ In another study, when unacclimatized participants completed a dynamic knee extension test at 4300 m, investigators found an increase in EXHt during the AZ trial vs the placebo.¹⁴

Alternatively, other investigations have indicated that AZ may be detrimental to submaximal exercise performance at altitude. While exercising at 90% of sea level $VO_{2\max}$ at a simulated altitude of 4200 m, EXHt was reduced in the AZ-treated trial compared with control.¹⁵ A 2014 study concluded that AZ-treated volunteers cycling at 60% sea level peak power output experienced a decrease in S_pO_2 compared with placebo-treated volunteers.¹⁶

Similarly, AZ appears to have varied effects on maximal exercise performance at altitude ([Table 3](#)). For instance, one study concluded that AZ treatment can improve maximal exercise performance at altitude by increasing $VO_{2\max}$.¹⁵ In contrast, other studies have found AZ to have either a detrimental effect or no effect at all on maximal exercise performance.

Table 1. Summary of the current literature investigating the effects of acetazolamide on exercise performance

<i>Authors</i>	<i>Journal</i>	<i>Date of publication</i>	<i>Dosage used</i>	<i>Exposure type</i>	<i>Altitude/Equivalent altitude</i>	<i>Exercise</i>	<i>Sample size</i>
Faoro et al ⁴	<i>J Appl Physiol</i>	2007	250 mg/8 h for 24 h	Natural hypobaric hypoxia	4700 m	Cycle	n=15, 8 F, 7 M (mean age 35 y)
Collier et al ⁵	<i>Pharmacol Res Perspect</i>	2016	250/500/1000 mg	Sea level	0 m	None	n=15 (18-32 y)
Ellsworth et al ⁶	<i>Am J Med</i>	1987	250 mg/8 h	Natural hypobaric hypoxia	4392 m	Active ascent	n=42
Stager et al ⁷	<i>Med Sci Sports Exerc</i>	1990	2 × 250 mg	Simulated (chamber)	4270 m	Treadmill	n=27
Schoene et al ⁸	<i>J Appl Physiol</i>	1983	250 mg/8 h for 24 h	Normobaric hypoxia (F _I O ₂ = 0.118)	0 m	Cycle	n=6
Hermansen et al ⁹	<i>J Appl Physiol</i>	1972	n/a	Sea level	0 m	Cycle or treadmill	n=13
Jonk et al ¹⁰	<i>J Physiol</i>	2007	250 mg/8 h for 24 h	Normobaric hypoxia (F _I O ₂ = 0.125)	0 m	Cycle	n=6 (26±1 y)
Gonzales et al ¹¹	<i>Respir Physiol Neurobiol</i>	2013	500 mg/8 h for 72 h	Sea level	0 m	Cycle	n=7 (28±5 y)
Harrison et al ¹²	<i>PLoS One</i>	2016	250 mg/12 h for 24-48 h	Natural hypobaric hypoxia	~3200 m	None	n=226
Bradwell et al ¹³	<i>Lancet</i>	1986			4846 m		n=11
Fulco et al ¹⁴	<i>Clin Sci</i>	2006	250 mg/8 h for 48 h	Simulated (chamber)	4300 m	Leg extension	n=6 (20±1 y)
McLellan et al ¹⁵	<i>Eur J Appl Physiol Occup Physiol</i>	1988	500 mg/24 h for 48 h	Simulated (chamber)	4200 m	Cycle	n=4
Bradwell et al ¹⁶	<i>Wilderness Environ Med</i>	2014	250 mg/12 h for 72 h	Natural hypobaric hypoxia	3459 m	Cycle	n=20 (18-67 y)
Hackett et al ¹⁷	<i>Med Sci Sports Exerc</i>	1985	250 mg/8 h for 24 h	Natural hypobaric hypoxia	6300 m	Cycle	n=4
Garske et al ¹⁸	<i>J Appl Physiol</i>	2003	500 mg/12 h for 60 h	Normobaric hypoxia (F _I O ₂ = 0.13)	—	Cycle	n=9

F, female; M, male.

Table 2. Indices of submaximal and maximal exercise performance after AZ administration at sea level

AZ dosage	Treatment length	Altitude (m)	Pb (mm Hg)	Exercise mode	Exercise intensity	Outcome metric	Result	P	Author
500 mg/24 h	24 h	1520	640	Treadmill	Submax	VO ₂ ; EXHt	↔ VO ₂ , ↓ EXHt	P≤0.05	Stager et al ⁷
250 mg/8 h	24 h	0	760	Cycle ergometer	Submax	V _E	↑ V _E	P<0.001	Jonk et al ¹⁰
500 mg/8 h	72 h	0	760	Cycle ergometer	Submax	EXHt	↓ EXHt	P=0.003	Gonzales et al ¹¹
250 mg/8 h	48 h	0	760	One-leg knee ext	Submax	EXHt	↓ EXHt	P<0.05	Fulco et al ¹⁴
250 mg/8 h	24 h	0	~760	Cycle ergometer	Max	VO _{2 max} ; EXHt	↓ VO _{2 max} ; ↓ EXHt	P≤0.05	Ellsworth et al ⁶
500 mg/24 h	24 h	1520	640	Treadmill	Max	VO _{2 max} ; watts	↔ VO _{2 max} ; ↓ watts	P≤0.05	Stager et al ⁷
250 mg/8 h	24 h	0	754–763	Cycle ergometer	Max	VO _{2 max}	↓ VO _{2 max}	P<0.025	Schoene et al ⁸
250 mg/8 h	24 h	0	760	Cycle ergometer	Max	V _E	↑ V _E	P<0.001	Jonk et al ¹⁰

AZ, acetazolamide; EXHt, exhaustion time; max, maximum; ext, extension; submax, submaximum; T_{max}, time to achieve exercise maximum; V_E, minute ventilation; VO_{2 max}, maximal aerobic capacity; watts, power output; watts_{max}, peak power achieved.

Table 3. Indices of submaximal and maximal exercise performance after AZ administration at altitude

AZ dosage	Treatment length	Altitude (m)	Acclimatization status	Exercise mode	Exercise intensity	Outcome metric	Result	P	Author
500 mg/24 h	24 h	4270	Unacclimatized	Cycle ergometer	Submax	EXHt	↓ EXHt	P≤0.05	Stager et al ⁷
250 mg/8 h	24 h	F _I O ₂ = 0.125	Unacclimatized	Cycle ergometer	Submax	V _E	↑ V _E	P<0.001	Jonk et al ¹⁰
500 mg/24 h	72 h	4846	Acclimatized to 4846 m	Cycle ergometer	Submax	Watts	↓ Watts	P<0.05	Bradwell et al ¹³
250 mg/8 h	48 h	4300	Unacclimatized	One-leg knee ext	Submax	EXHt	↑ EXHt	P<0.05	Fulco et al ¹⁴
500 mg/24 h	48 h	4200	Unacclimatized	Cycle ergometer	Submax	EXHt	↓ EXHt	P<0.05	McLellan et al ¹⁵
250 mg/12 h	72 h	3459	Unacclimatized	Cycle ergometer	Submax	S _p O ₂ ; RPE	↓ S _p O ₂ ; ↑ RPE	P<0.01	Bradwell et al ¹⁶
250 mg/8 h	24 h	4700	Unacclimatized	Cycle ergometer	Max	W _{max}	↔ Watts _{max}	n/a	Foaro et al ⁴
500 mg/24 h	24 h	4270	Unacclimatized	Cycle Ergometer	Max	VO _{2 max}	↔ VO _{2 max}	P≤0.05	Stager et al ⁷
250 mg/8 h	24 h	F _I O ₂ = 0.118 (~4500)	Unacclimatized	Cycle ergometer	Max	VO _{2 max}	↑ VO _{2 max}	P<0.05	Schoene et al ⁸
250 mg/8 h	24 h	F _I O ₂ = 0.125	Unacclimatized	Cycle ergometer	Submax	V _E	↑ V _E	P<0.001	Jonk et al ¹⁰
250 mg/8 h	24 h	6300	Unacclimatized	Cycle ergometer	Max	S _p O ₂ ; T _{max}	↔ S _p O ₂ ; ↓ T _{max}	P<0.05	Hackett et al ¹⁷
500 mg/12 h	60 h	F _I O ₂ = 0.13 (~3700)	Unacclimatized	Cycle ergometer	Max	VO _{2 max} ; watts _{max}	↓ VO _{2 max} ; ↓ watts _{max}	P<0.01	Garske et al ¹⁸

AZ, acetazolamide; EXHt, exhaustion time; F_IO₂, fraction of inspired oxygen; max, maximum; ext, extension; RPE, rating of perceived exertion; S_pO₂, blood oxygen saturation; submax, submaximum; T_{max}, time to achieve exercise maximum; V_E, minute ventilation; VO_{2 max}, maximal aerobic capacity; watts, power output; watts_{max}, peak power achieved.

The inconsistent conclusions across studies may arise from variance in methods used for exercise performance measures, altitude, acclimatization status, and AZ dosages. Furthermore, some studies were conducted in normobaric hypoxia with various inspired O₂ fractions, which many have also contributed to these inconsistent findings. Another limitation of many of the studies cited herein was the use of a cycle ergometer for exercise testing in the absence of trained cyclists. Without recruiting trained cyclists for testing, one cannot rule out the impact of a training effect on the associated results.

To date our knowledge base regarding the prophylactic use of AZ is limited to its effects on exercise performance at sea level. Future aims should include a standardized set of variables by which exercise performance at altitude is assessed. Additionally, researchers should standardize altitude exposure and mode of exercise used across investigations. Furthermore, AZ dosing either must be standardized or the effects of a higher than recommended dosage on exercise performance must be examined. By standardizing these variables, researchers may be able to determine the beneficial, detrimental, or inconsequential effects of using AZ during exercise at altitude.

Author Contributions: Study concept and design (DH); acquisition of the data (AP, DH, SD); analysis of the data (AP, DH, SD); drafting of the manuscript (AP, SD, DH); critical revision of the manuscript (DH); approval of the manuscript (AP, SD, DH).

Financial/Material Support: None.

Disclosures: None.

References

- Cheung SS. Mountaineering and high-altitude physiology. In: *Advanced Environmental Exercise Physiology*. 10th ed. Champaign, IL; 2010:147–63.
- Hackett PH, Roach RC. High altitude illness. *N Engl J Med*. 2001;345(2):107–14.
- Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med*. 2010;21(2):146–55.
- Faoro V, Huez S, Giltair S, Pavelescu A, van Osta A, Moraine JJ, et al. Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes. *J Appl Physiol*. 2007;103(4):1161–5.
- Collier DJ, Wolff CB, Hedges AM, Nathan J, Flower RJ, Milledge JS, et al. Benzolamide improves oxygenation and reduces acute mountain sickness during high-altitude trek and has fewer side effects than acetazolamide at sea level. *Pharmacol Res Perspect*. 2016;4(3):1–12.
- Ellsworth AJ, Larson EB, Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med*. 1987;83(6):1024–30.
- Stager JM, Tucker A, Cordain L, Engebretsen BJ, Brechue WF, Matulich CC. Normoxic and acute hypoxic exercise tolerance in man following acetazolamide. *Med Sci Sports Exerc*. 1990;22(2):178–84.
- Schoene RB, Bates PW, Larsen EB, Pierson DJ. Effect of acetazolamide on normoxic and hypoxic exercise in humans at sea level. *J Appl Physiol*. 1983;55(6):1772–6.
- Hermansen L, Osnes JB. Blood and muscle pH after maximal exercise in man. *J Appl Physiol*. 1972;32(3):304–8.
- Jonk AM, Van Den Berg I, Olfert IM, Wray DW, Arai T, Hopkins SR, et al. Effect of acetazolamide on pulmonary and muscle gas exchange during normoxic and hypoxic exercise. *J Physiol*. 2007;579(3):909–21.
- Gonzales JU, Scheuermann BW. Effect of acetazolamide on respiratory muscle fatigue in humans. *Respir Physiol Neurobiol*. 2013;185(2):386–92.
- Harrison MF, Anderson PJ, Johnson JB, Richert M, Miller AD, Johnson BD. Acute mountain sickness symptom severity at the South Pole: the influence of self-selected prophylaxis with acetazolamide. *PLoS One*. 2016;11(2):e0148206.
- Bradwell AR, Dykes PW, Coote JH, Forster PJ, Milles JJ, Chesner I, et al. Effect of acetazolamide on exercise performance and muscle mass at high altitude. *Lancet*. 1986;3(1):1001–5.
- Fulco CS, Muza SR, Ditzler D, Lammi E, Lewis SF, Cymerman A. Effect of acetazolamide on isolated quadriceps muscle endurance performance at sea level and during acute altitude exposure. *Clin Sci*. 2006;110(6):683–92.
- McLellan T, Jacobs I, Lewis W. Acute altitude exposure and altered acid-base states. II. effects on exercise performance and muscle and blood lactate. *Eur J Appl Physiol Occup Physiol*. 1988;57(4):445–51.
- Bradwell AR, Myers SD, Beasley M, Ashdown K, Harris NG, Bradwell SB, et al. Exercise limitation of acetazolamide at altitude (3459 m). *Wilderness Environ Med*. 2014;25(3):272–7.
- Hackett PH, Schoene RB, Winslow RM, Jr Peters RM, West JB. Acetazolamide and exercise in sojourners to 6,300 meters—a preliminary study. *Med Sci Sports Exerc*. 1985;17(5):593–7.
- Garske LA, Brown MG, Morrison SC. Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions. *J Appl Physiol*. 2003;94(3):991–6.