

ORIGINAL RESEARCH

Exercise Limitation of Acetazolamide at Altitude (3459 m)

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Objective.—To assess the effect of acetazolamide (Az) on exercise performance during early acclimatization to altitude.

Methods.—Az (250 mg twice daily) or placebo was administered for 3 days in a double-blind, randomized manner followed by a rapid ascent to 3459 m in the Italian Alps. Twenty healthy adults (age range, 18–67 years) were tested at 60% of sea-level peak power output for 15 minutes on a bicycle ergometer after 16 to 27 hours of altitude exposure. Exercise performance was measured in relation to peripheral oxygen saturations measured from pulse oximetry (SpO₂), Lake Louise acute mountain sickness (AMS) score, and perceived difficulty.

Results.—At altitude, resting SpO₂ was higher in the Az group compared with placebo ($P < .001$). The highest AMS scores were in 4 of the placebo individuals with the lowest resting SpO₂ ($P < .05$). During the exercise test, SpO₂ fell in all but 1 subject ($P < .001$) and was reduced more in the Az group ($P < .01$). Four Az and 1 placebo subject were unable to complete the exercise test; 4 of these 5 had the largest fall in SpO₂. The perception of exercise difficulty was higher in the Az subjects compared with those taking the placebo ($P < .01$). There was an age relationship with exercise limitation; 4 of the 9 older than 50 years failed to complete the test whereas only 1 of 11 younger than 50 years failed, and there were no failures in the 6 younger than 30 years ($P < .05$).

Conclusions.—In this study group, and despite higher resting SpO₂, Az may have compromised exercise at 3459 m altitude during early acclimatization, particularly in older subjects.

Key words: acetazolamide, exercise, altitude

Introduction

The use of acetazolamide (Az) for the prevention of acute mountain sickness (AMS) has been debated for 50 years, but 2 recent meta-analyses have strongly supported its effectiveness. In 2012, Kayser and colleagues reviewed 24 placebo-controlled trials comparing 1011 Az-treated individuals with 854 placebo-treated individuals and showed convincing evidence of its value.¹ Escalating doses from 250 mg, to 500 mg and 750 mg per day revealed increasing reduction in AMS symptoms by 45%, 50% and 55%

respectively, compared with placebo. Another systematic review and meta-analysis again scrutinized the published studies and confirmed the overall positive benefits of Az.² This study was supported by a linked editorial suggesting a more personalized approach was indicated.³

In spite of this overwhelming evidence, many are unwilling to take medication that may have unpleasant side effects. Paresthesias and the altered taste of carbonated drinks can be most irritating, although they are less apparent with lower doses. In addition, there are concerns that exercise capacity might be reduced at altitude because this has been observed when taking Az at sea level.^{4,5} Moreover, exercise tests using hypoxic gas mixtures to simulate altitude in the laboratory have not been consistent. Some have demonstrated impaired

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exercise performance,^{6,7} whereas others showed the opposite, that Az improved arterial oxygenation during exercise.^{4,8} However, the total numbers of individuals investigated have been small, typically 6 per study. In addition, the participants have been young, whereas trekkers to altitude often tend to be older. For example, in one Japanese report 70% of the subjects were older than 50 years.⁹ When Az is commenced at high altitude in acclimatized individuals, there is again uncertainty about its effect on exercise. One early study showed 2 of 4 people had reduced exercise capacity at 6300 m,¹⁰ whereas a study of 15 subjects showed no adverse effects at 4700 m after 10 days of acclimatization.¹¹ Unfortunately, none of these studies addressed the use of Az in practice. Normally, Az is taken prophylactically for 1 to 2 days before altitude exposure.¹ Typically, individuals then ascend to between 3500 m and 5500 m over the following week or so. Such altitude exposure is much longer than that undertaken in laboratory experiments, and there is usually some degree of AMS. Only 1 study has evaluated this treatment schedule.¹² Twenty individuals prophylactically took 500 mg of Az or placebo daily on an ascent to 4,846 m. At 10 days, the Az group performed better with 20% less reduction in exercise performance than the placebo group, and this was associated with retention of muscle mass. Clearly, Az was having a quite different effect from its use in short-term treatment studies.

These differing data and limited long-term studies do not provide a consensus regarding the altitude or the stage in acclimatization when Az is beneficial, neutral, or possibly detrimental to exercise. The purpose of this investigation was to assess whether Az affected exercise performance at modest altitude in the early phase of altitude acclimatization. A height of 3459 m was chosen as this was sufficient to induce a modest degree of AMS, and the availability of a comfortable, easily accessible refuge allowed well-controlled exercise testing.

Methods

SUBJECTS AND DRUG TRIAL OF AZ VS PLACEBO

Twenty healthy individuals were recruited. Ages ranged from 18 to 67 years (mean age, 43 ± 16.5 years). There were 6 women, 4 between 20 to 23 years and 2 older than 50 years. Menstrual cycle phase was not recorded. Sixteen individuals had previous experience of altitude and were classified into low, medium, or high AMS susceptibility, but none had suffered from pulmonary or cerebral edema. In 4 individuals, AMS susceptibility was unknown. No participant had resided above 1500 m in the previous 2 months. Apart from 1 subject with mild

hypertension who was taking the angiotensin-converting enzyme inhibitor, ramipril (5 mg/d), none was taking any relevant medication and all had refrained from intense physical activity on the days before testing. All were kept naive regarding the medication and expected outcomes of the study. Because of obvious side effects from Az administration such as paresthesias, individuals were requested not to discuss any aspects of their medication with others, including the investigators.

Individuals were paired for similar characteristics by hierarchy of importance for 1) previous AMS susceptibility, 2) male/female, and 3) age. There were no significant differences between the groups for these 3 variables, nor weight or resting pulse rate. Each pair received 250-mg capsules of Az or placebo (starch) randomly allocated by independent observers, with blinding to subjects and investigators alike. Capsules were taken twice daily starting 3 days before the altitude exposure for a total of 9 doses.

EXERCISE TEST

This was performed on a specially constructed, lightweight (25 kg), horizontal bicycle designed for altitude studies (Alti Cycle).¹³ In use, the individual lay supine, constrained by a shoulder harness, with feet strapped into the pedals. Multistage gearing provided high inertia from a 2-kg flywheel rotating at 2900 rpm at 60 rpm pedaling speed, thereby mimicking the sensation of cycling on a normal bicycle. A remotely controlled brake acted on the flywheel to provide controllable resistance, and power output and cadence were measured via a strain-gauged crank-set (Schoberer Rad MeBtechnik, Julich, Germany) linked to a laptop computer. This mode of exercise was chosen because it allowed other studies.

A submaximal exercise test was selected to induce considerable pulse oxygen saturation (SpO_2) desaturation at altitude and with the expectation that it would be completed by all individuals. To establish the exercise intensity required before ascent, 1 individual was exercised on different days for 15 minutes at 80%, 70%, and 60% of their peak power output (PPO) in a normobaric hypoxic chamber (TISS Model 201003-1; TIS Services, Mestead, UK) at an oxygen depletion similar to 3,459 m (fractional inspired oxygen [FiO_2], 0.13). Only the 60% PPO was sustainable for 15 minutes, and this was used at altitude for all subjects.

The exercise test at sea level was undertaken on days 6 and 7 before ascent by each individual in the following manner. After a warm-up for 2 to 3 minutes at 50 to 80 W and 60 rpm, the brake resistance was increased by 10- to 20-W intervals every 60 seconds until power could not be sustained. The last minute of constant power was

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