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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 (Spo_2), Lake Louise acute mountain sickness (AMS) score, and perceived difficulty.

Results.—At altitude, resting Spo_2 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 Spo_2 ($P < .05$). During the exercise test, Spo_2 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 Spo_2. 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 Spo_2, 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

selected as the PPO. Peak pulse rate was recorded and compared with the theoretical peak pulse rate of 220 minus age to provide some assurance that individuals were exercising at or near their maximum. On completion of each test at altitude, the individual was asked to indicate whether the perceived exertion was easy, medium-hard, or hard, to which was added an involuntary category of fail.

ASCENT PROFILE AND ALTITUDE STUDIES

Individuals travelled from sea level to Cervinia in Italy (2050 m) or Zermatt in Switzerland (1608 m) during a 12-hour period. Final ascent to Refugio Testa Grigia (3459 m), in Italy, was by cable car over a 1-hour period to arrive at 4:00 PM.

Altitude exercise tests were commenced at 8:00 AM the following day and completed by 7:00 PM. Paired individuals were tested within an hour of each other so that altitude exposure times were similar. Pairs tested early had approximately 16 hours of altitude exposure, whereas later pairs had up to 27 hours of altitude exposure. Each person was asked immediately before the exercise test by the investigators as to their view of which medication they thought they were taking, but the allocation code was unknown.

Self-assessed questionnaires of the Lake Louise Scoring System for AMS[14] were recorded on the evening of arrival, the following morning, and immediately before and after the exercise tests. Because subjects were tested at different times of the day, a mean AMS score was obtained as a measure of accumulated AMS symptoms in relation to hypoxia exposure. This was the mean value of the morning Lake Louise score and that immediately before the exercise test. Spo_2 and pulse rate were measured using an Ohmeda Biox 3740 Pulse Oximeter (Datex-Ohmeda Ltd, Hatfield, UK). Three recordings were made before the exercise test, and the mean was calculated. Measurements were also recorded every 5 minutes during the test. The calculated reduction in Spo_2 was from the mean preexercise level to the lowest level recorded during exercise.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS version 21 (IBM Corp, Portsmouth, UK). Box and whisker plots for medians and ranges, Mann-Whitney test for differences of means, and Spearman's correlation for comparison of groups were used.

ETHICS

The study was approved by Chichester University Research Ethics Committee (protocol number: 121339) and was performed according to the Declaration of Helsinki. All individuals gave signed informed consent.

Results

The 2 treatment groups were well matched for susceptibility to AMS, male/female ratio, and age (Az, 41 years; placebo, 44 years; >50 years: Az, 4; placebo, 5). Median PPO achieved at sea level was not significantly higher in the placebo group (mean ±1 SD: Az, 210 ± 29 vs placebo, 250 ± 47). The trial capsules were taken by all individuals successfully. A questionnaire recorded immediately before the exercise test (but analyzed later) indicated that 15 had correctly guessed their medication.

At altitude (Figure 1), resting Spo_2 before the exercise tests were higher in the Az group compared with placebo (Mann-Whitney test, mean ±1 SEM: Az, 91.7 ± 0.08; Pl, 85.4 ± 0.83; $P < .001$), and the 4 individuals with the lowest resting Spo_2 had the highest AMS scores (Spearman's correlation; $P < .05$). Comparison of Spo_2 for subjects paired for AMS susceptibility showed that all those taking Az had higher values than their placebo partners ($P < .001$). There were insignificant trends to a lower Spo_2 with increasing age, plus lower AMS scores and rising Spo_2 as the day progressed. Seven of 10 matched pairs had higher AMS scores in the placebo individual compared with their Az partner and 1 was the same.

The exercise test was technically satisfactory in all subjects. Spo_2 fell in all but 1 subject during the test (mean ± SEM: Az group, 91.7% ± 0.8% to 81.7% ± 2.4%; placebo group, 85.4% ± 0.83% to 79.2% ± 1.1%; $P < .001$) and the fall was greater in the Az group ($P < .01$). In the 6 youngest subjects, the 3 taking Az

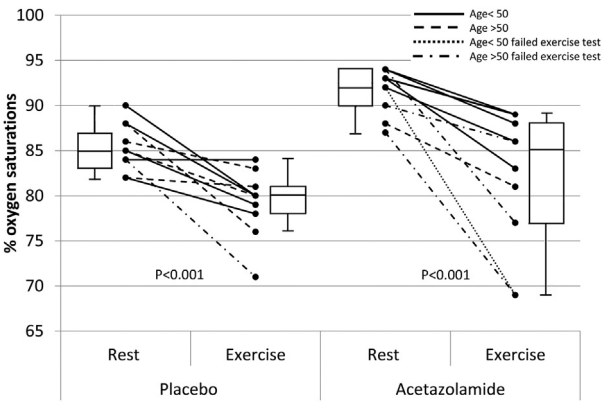

Figure 1. Peripheral O_2 saturations (Spo_2) in placebo and acetazolamide groups at 3459 m before and during exercise. Acetazolamide individuals had higher concentrations before exercise ($P < .001$) and had a greater fall during exercise ($P < .005$) than placebo individuals. Box and whisker plots show medians and ranges for the 2 groups.

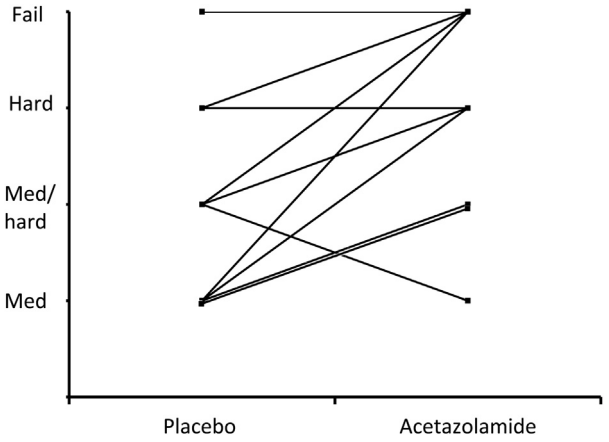

Figure 2. Perceived exercise difficulty for placebo individuals at 3459 m compared with their matched acetazolamide partners ($P < .01$).

had the highest Spo_2 at altitude (Figure 1) and higher than their corresponding control partners, both at rest (Az, 94%, 94%, 92% vs placebo, 90%, 88%, 85%) and during the exercise test (Az, 89%, 89%, 88% vs placebo, 80%, 80%, 79%), and Spo_2 fell less during the exercise test (Az fall: 8%, 6%, 4% vs placebo fall, 10%, 9%, 8%). There were insufficient subjects for statistical analysis.

Five subjects failed to complete the exercise test, with 4 of the 5 having the largest fall in percentage Spo_2 (Figure 1). Furthermore, the placebo subject who failed had the highest AMS score of 8 on awakening and 4 before the exercise test. Four of the subjects complained of dyspnea as the limiting factor, and in the fifth subject it was leg fatigue. No objective measurements of ventilation were made. There was an age relationship with exercise failure: 4 of the 9 subjects older than 50 years failed the test, whereas only 1 of 11 younger than 50 years failed and there were no failures in those younger than 30 years ($P < .05$). The perception of difficulty was higher in the Az subjects compared with the placebo subjects (Figure 2; Spearman's correlation, $P < .01$) in spite of a higher starting Spo_2. There were insufficient subject numbers to show a relationship between AMS susceptibility and exercise failure. The 1 individual taking ramipril (and Az) successfully completed the test.

Discussion

The results show that exercise performance at 3459 m was reduced in many subjects taking Az. The reduction was in terms of its perceived difficulty and the failure to complete the test in 4 subjects of whom 3 had large reduction in Spo_2. This was not related to AMS susceptibility. It was also not related to exercise performance requirements because each subject had to perform at 60% of their sea level PPO. As expected, the Az group had higher resting Spo_2 at altitude before the test and they had fewer AMS symptoms. In contrast, placebo subjects had lower Spo_2 at rest, but these were better maintained during the exercise tests compared with the Az subjects. The 1 placebo exercise test failure had the highest Lake Louise AMS score of 8 on awakening and the highest of 4 before the exercise. We speculate that his exercise performance was compromised by accumulated edema fluid that may have reduced pulmonary gas exchange.

There have been several detailed publications of the effect of Az on exercise at reduced oxygen concentrations during early exposure to hypoxia. All were for subjects exposed to hypoxic gas mixtures commencing immediately before the exercise tests. Schoene and colleagues investigated 6 men (age, 23–35 years) in a crossover study of 3 250-mg doses of Az over 24 hours and using an FIO_2 of 0.118 (~4800 m), compared with an FIO_2 of 0.21 at sea level.[4] On Az, arterial oxygenation was higher during exercise with an increase in exercise endurance at maximal oxygen consumption (Vo_{2max}). Jonk and colleagues investigated 6 trained men (age, 26.3 ± 4.6 year) in a crossover study at an FIO_2 of 0.125 (~4400 m) and used 3 250-mg doses of Az over 24 hours; they noted improved arterial oxygenation during exercise but there were no exercise endurance data.[8] Three studies have shown a reduction in exercise performance on Az during hypoxia. McLellan and colleagues performed a crossover study in 4 subjects using 500 mg Az daily for 2 days at a simulated altitude of 4200 m, and noted a slightly reduced time to exhaustion at 90% Vo_{2max} on Az.[6] Stager and colleagues investigated 27 subjects (age, 28.7 ± 2.9 years) in a crossover study using 2 250-mg doses of Az over 24 hours at a simulated altitude of 4270 m and showed a 26% reduction in time to exhaustion on a submaximal exercise test.[5] Garske and colleagues investigated 9 subjects (age, 27.9 ± 2.9 years) in a crossover study and used 500 mg of Az twice daily for 5 doses at an FIO_2 of 0.13 (~4200 m); they showed improved arterial oxygenation at maximal exercise, but maximal power was reduced and leg fatigue was greater.[7] Interestingly, the first 2 studies at 4800 m and 4400 m showed benefit from Az, whereas the latter 3 at slightly lower altitudes (~4200 m) showed reduced exercise performance.

Our study differed from these reports in 3 main aspects. First, subjects were exposed to altitude for 18 to 27 hours before the exercise test and, importantly, during a period of sleep with its attendant hypoxia. This caused a measureable amount of AMS symptoms, which were slightly less in the Az group (although not significant). Second, the altitude of our study at 3459 m (FIO_2 ~0.13) was considerably lower than the reported laboratory experiments but still showed

impaired exercise performance on Az. By comparison, a study at 4846 m and after 10 days of altitude exposure had shown superior exercise performance on Az.[12] These contrasting results suggest that there may be a critical combination of altitude gain or hypoxia duration above which Az improves exercise performance by reducing the incidence of AMS. The third difference in our study was the wide age profile. The 3 subjects taking Az who were younger than 30 years performed well with no exercise test failures. Furthermore, Spo_2 was considerably higher during exercise than in aged-matched placebo controls. If we had investigated only these 6 young subjects (as for most laboratory studies), we would have concluded that Az had no adverse effect on exercise and had a beneficial effect on Spo_2. Why older individuals were compromised by exercise is unclear. Maybe they had age-related cardiovascular impairment, altered alveolar ventilation, or renal impairment, but there was no evidence of disease and all were fit individuals. One might also speculate that older people metabolize Az differently. There are more than a dozen different carbonic anhydrase isoenzymes, and some may be inhibited differently with age or in dissimilar individuals. Whatever the mechanism, more studies on older subjects and at higher altitudes are warranted.

It is important to remember that maximal or submaximal exercise cannot be maintained for long periods, so bears little resemblance to the prolonged periods of lower-intensity exercise that occurs on treks. Brief periods of excessive oxygen desaturation that might occur with Az during exercise are insignificant compared with oxygen saturations that are 15% to 20% higher throughout the day and night.[15] Over many days this could have an important accumulative effect resulting in better sleep, less appetite suppression, and greater retention of muscle mass, any of which could lead to better exercise performance.

LIMITATIONS OF THIS STUDY

The investigation contained only 20 individuals so was relatively small but nevertheless larger than most laboratory series. In addition, the altitude attained was modest, and there was no crossover trial. The latter is difficult to achieve as a mountain study. A week or more is required to deacclimatize and to wash out Az, so all individuals would need to return to sea level, the United Kingdom in our case. As regards the exercise test, a Vo_{2max} or endurance test might have provided more information. However, such studies are more complicated, and we wanted to complete the study in a single day so that altitude exposure would not be too disparate between individuals. We chose 500 mg per day of Az to be comparable with existing chamber experiments. A commonly recommended dose for trekking is 250 mg per day, which might have less effect on exercise performance and merits further study.[1] Exercise performance using a horizontal bicycle ergometer is slightly less than that on a vertical bicycle, but all subjects were studied in the same manner. Other limitations are the lack of continuous recordings of Spo_2, pulse rate, blood pressure, etc, and we had no measure of pulmonary gas exchange.

Conclusions

We have shown that during early acclimatization to 3459 m, 500 mg of Az daily reduces the ability to exercise hard. Placebo subjects experienced more AMS than those on Az but were able to exercise to a greater degree, had lower Spo_2, and experienced less fatigue. In this small study group, exercise limitation was more frequent in the older members, an age effect that has not been observed previously. These results add to the uncertainty of the effect of Az on exercise at altitude. Although it is entirely appropriate that Az should be widely used for preventing AMS, more studies on exercise performance are required, particularly using different medication doses, different ascent profiles, and on elderly people.

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