

Acetazolamide reduces exercise capacity following a 5-day ascent to 4559 m in a randomised study

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ABSTRACT

Objective To assess whether acetazolamide (Az), used prophylactically for acute mountain sickness (AMS), alters exercise capacity at high altitude.

Methods Az (500 mg daily) or placebo was administered to 20 healthy adults (aged 36±20 years, range 21–77), who were paired for age, sex, AMS susceptibility and weight, in a double-blind, randomised manner. Participants ascended over 5 days to 4559 m, then exercised to exhaustion on a bicycle ergometer, while recording breath-by-breath gas measurements. Comparisons between groups and matched pairs were done via Mann-Whitney U and Pearson's χ^2 tests, respectively.

Results Comparing paired individuals at altitude, those on Az had greater reductions in maximum power output (P_{\max}) as a percentage of sea-level values (65±14.1 vs 76.6±7.4 (placebo); $P=0.007$), lower $VO_{2\max}$ (20.7±5.2 vs 24.6±5.1 mL/kg/min; $P<0.01$), smaller changes from rest to P_{\max} for VO_2 (9.8±6.2 vs 13.8±4.9 mL/kg/min; $P=0.04$) and lower heart rate at P_{\max} (154±25 vs 167±16, $P<0.01$) compared with their placebo-treated partners. Correlational analysis (Pearson's) indicated that with increasing age P_{\max} ($r=-0.83$; $P<0.005$) and heart rate at P_{\max} ($r=-0.71$, $P=0.01$) reduced more in those taking Az.

Conclusion Maximum exercise performance at altitude was reduced more in subjects taking Az compared with placebo, particularly in older individuals. The age-related effect may reflect higher tissue concentrations of Az due to reduced renal excretion. Future studies should explore the effectiveness of smaller Az doses (eg, 250 mg daily or less) in older individuals to optimise the altitude–Az–exercise relationships.

INTRODUCTION

Acetazolamide (Az) is an important medication for the prevention of acute mountain sickness (AMS). This was demonstrated initially by Forward *et al*,¹ followed by a large study on Everest trekkers,² with an accompanying editorial.³ In controlled studies, Az has been shown to increase arterial oxygen saturations at all altitudes and to assist in ascents to Everest Base Camp, the summit of Kilimanjaro and elsewhere.^{4–6} A meta-analysis of 24 placebo-controlled trials comparing 1011 Az-treated with 854 placebo-treated

Key messages

What are the new findings?

- ▶ Acetazolamide (Az) decreased maximum power output at 4559 m.
- ▶ Effects of Az were greater in those over 50 years of age.
- ▶ Doses of Az may need to be optimised especially in older subjects to minimise adverse effects.

How might it impact on clinical practice in the near future?

- ▶ Findings indicate that smaller doses of Az may be more appropriate for older individuals visiting and exercising at altitude.

individuals showed convincing evidence of its value for the prevention of AMS.⁷ Escalating doses of Az from 250 mg to 500 mg and 750 mg per day reduced AMS relative risk by 45%, 50%, and 55% respectively, although current recommendations suggest 125 mg twice daily.

An important but controversial aspect of Az use is its effect on exercise at altitude. Five chamber studies examining the impact of Az during short-term exposure to hypoxia, three of these showed reduced $VO_{2\max}$ and/or time to exhaustion,^{8–10} one a slight increase in $VO_{2\max}$,¹¹ and one no effect.¹² Similar inconsistent findings have been reported in natural high-altitude environments. Hackett *et al*¹³ gave Az acutely to well-acclimatised individuals and observed a reduction in exercise performance (time at maximum workload), whereas Faoro *et al*¹⁴ observed no effect. Results are again inconsistent when Az is used prophylactically. Specifically, after a 14-day trek to 4846 m, $VO_{2\max}$ and exercise endurance were greater on Az compared with placebo.¹⁵ Conversely, when used during early acclimatisation (18–24 hours), Az reduced exercise performance, but only in individuals over 50 years of age.¹⁶



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Table 1 Participant characteristics (mean±SD) at baseline (150 m)

| | Placebo (10) | Acetazolamide (10) |
|------------------------------------|----------------------|----------------------|
| Sex: male/female | 8/2 | 8/2 |
| Age (range of years) | 33±17 (21–66) | 40±23 (21–77) |
| Height (cm) | 176±8 (159–185) | 177±11 (154–189) |
| Weight (kg) | 73±13.6 (46.7–91.2) | 73±13 (48.1–91.8) |
| AMS history: mild:moderate:unknown | 3:4:3 | 6:2:2 |
| VO _{2max} (mL/kg/min) | 40.3±6.3 (29.3–47.7) | 35.9±6.1 (26.9–44.4) |
| Maximum power output (W) | 234±51 (155–305) | 215±39 (155–260) |
| Heart rate maximum (beats/min) | 185±20 (150–208) | 169±26 (122–198) |
| Peak respiratory exchange rate | 1.11±0.2 (0.7–1.3) | 1.16±0.05 (1.1–1.2) |

*There were no significant differences (all $P>0.05$) between groups (Mann-Whitney U test). AMS, acute mountain sickness.

Surveys of trekkers add no further information, despite Az being widely used with no reported adverse effects on exercise. For instance, on Kilimanjaro, 35% of climbers use Az yet the overall summit success rate can be as low as 50%–60% during ascents over 3 and 4 days. Those affected by Az might ascend more slowly and ascribe any perceived weakness to altitude or poor fitness. Nevertheless, exercise capability is an important issue when there are time-restricted climbing schedules or in some emergency situations. There are also questions about the use of Az in older individuals. Az is excreted unmetabolised in urine,^{17,18} so drug levels increase in line with reduced glomerular filtration rates (GFR). Given the known age-related decline in renal function, Az concentrations might increase sufficiently to induce excess acidosis in older individuals, thereby inhibiting exercise. Given that increasing numbers of older people are exploring high mountains,¹⁹ questions regarding the effect of Az on exercise need to be answered, particularly as older people may be less susceptible to AMS.²⁰ Against this background the purpose of the current study was to assess the effects of Az on exercise performance in young and older individuals during a typical alpine high-altitude climb.

METHODS

Subjects

Twenty healthy individuals were recruited (16 male), mean age 36 years (range 21–77 years): 13 were under 26 years and 6 were males over 50 years. Fifteen individuals had previous experience of high altitude allowing their self-reported susceptibility to AMS to be categorised into mild or moderate, but no participant had suffered from high-altitude pulmonary or cerebral oedema. All subjects had resided below 1500 m in the previous 2 months, none were taking medication affecting the cardiovascular system, all were non-smokers and no intense physical activity had been undertaken for 7 days before baseline testing. All participants had free access to fluids during the studies, but no formal measurements of hydration status or urine volumes were undertaken.

Individuals were paired for similar characteristics according to the following hierarchy: (1) age, (2) sex, (3) previous AMS susceptibility and (4) body mass (table 1). Each member of the pairs was randomised to Az 250 mg twice daily or placebo (lactose powder), in identical capsule form, following a double-blind design. Medication was started the day before altitude exposure and continued for a total of 10 doses over 5 days. Because of potential unblinding linked to Az side effects, individuals were requested not to discuss any aspects of their medication.

Baseline experiments and equipment

Two weeks before ascent, graded baseline exercise tests were carried out in Birmingham (150 m above sea-level) to determine maximum power output (P_{max}) and maximum oxygen uptake (VO_{2max}). Exercise tests were performed on a light-weight (25 kg), recumbent bicycle ergometer designed for altitude studies (Alticycle) as previously described.¹⁶

After a 5 min, self-paced warm-up, participants commenced at 50–100 W depending on their self-reported level of fitness. Using a cadence of 60 rev/min, power was increased every 3 min by 25 W or 15 W, for men or women, respectively, until 80% of the predicted maximum. Thereafter, power steps were increased every minute until volitional exhaustion. Breath-by-breath gas measurements were recorded of minute ventilation (VE), end-tidal oxygen ($P_{et}O_2$) and carbon dioxide ($P_{et}CO_2$) concentrations, oxygen uptake (VO_2) and expired CO_2 (VCO_2) using a Cosmed K4b² (Cosmed, Rome, Italy).²¹ Heart rate (HR), peripheral blood O_2 saturations (SpO_2) and perceived exertion were recorded at rest and for every exercise stage. The maximum VO_2 attained (VO_{2max}) was determined as the highest 20 s moving average in VO_2 , together with the corresponding P_{max} .

Baseline serum creatinine measurements were used to estimate GFR (eGFR) using the Cockcroft-Gault equation.²²

Table 2 Altitude performance (4559 m) at rest, 45%, and maximum power (P_{max}) for placebo and Az groups, and comparisons between matched pairs

| Test variable | Comparison of placebo versus Az for groups | | Comparison of placebo versus Az for matched pairs | |
|--|---|--|---|---|
| | Placebo versus Az at rest* P_{max} | Placebo versus Az at 45% P_{max} | Placebo versus Az at P_{max} * | Change from rest to P_{max} † |
| P_{max} (W) as % of sea-level values | – | – | \$76.6 (7.4) versus 65 (14.1) P=0.03 | – P = 0.007 |
| Heart rate (b/min) | 92 (18.4) versus 93 (15.7) P=0.88 | 146 (17) versus 140 (17) P=0.43 | 167 (16) versus 154 (25) P=0.33 | 75 (21) versus 61 (20) P=0.1 |
| RPE (Borg scale: 6–20) | 10(2) versus 9 (1) P=0.36 | 14(2) versus 14(1) P=0.56 | 17(2) versus 17 (2) P=0.81 | 7 (2) versus 8 (2) P=0.36 |
| VE (L/min) | 34(9) versus 37(10) P=0.48 | 75(13) versus 88(22) P=0.11 | 150(22) versus 125(27) P=0.04 | 116 (21) versus 88 (28) P=0.05 |
| SpO ₂ (%) | 79.0 (4.1) versus 84.6 (4.7) P=0.004 | 74.1 (5.2) versus 75.5 (5.1) P=0.55 | 77.0 (4.4) versus 77.2 (6.3) P=0.7 | –2.4 (5.7) versus –7.4 (6.3) P=0.13 |
| PetO ₂ (mm Hg) | 54.9 (2.7) versus 58.4 (2.7) P=0.007 | 57.8 (2.7) versus 61.9 (3.8) P=0.01 | 64.2 (2.0) versus 65.0 (2.0) P=0.45 | 9.3 (1.8) versus 6.6 (2.3) P=0.009 |
| PetCO ₂ (mm Hg) | 21.0 (1.5) versus 17.5 (1.5) P=0.0006 | 20.5 (2.1) versus 16.6 (2.7) P<0.01 | 16.8 (1.5) versus 15.2 (1.5) P=0.05 | –4.2 (1.37) versus –2.3 (0.95) P=0.0003 |
| VO ₂ uptake: (mL/kg/min) | 10.8 (3.2) versus 10.9 (2.8) P=0.97 | 19.5 (5.5) versus 18.4 (2.8) P=0.56 | 24.6 (5.1) versus 20.7 (5.2) P=0.063 | 13.8 (4.9) versus 9.8 (6.2) P=0.0003 |
| VCO ₂ production (mL/kg/min) | 8.7 (2.5) versus 8.7 (2.3) P=0.91 | 18.7 (4.8) versus 18.3 (2.3) P=0.82 | 29.5 (4.6) versus 23.4 (5.5) P=0.01 | 20.8 (5.0) versus 14.7 (6.0) P=0.0003 |
| VE/VO ₂ produced | 44 (5.8) versus 50 (6.8) P=0.04 | 55.0 (8.0) versus 70.8 (18.2) P=0.03 | 86 (16.0) versus 88 (11.5) P=0.78 | 42 (13.0) versus 38 (7.1) P=0.68 |
| VE/VCO ₂ produced | 55 (4.1) versus 64 (5.3) P=0.001 | 56.9 (6.7) versus 70.8 (14.2) P=0.02 | 70 (6.3) versus 79 (9.7) P=0.04 | 15 (5.2) versus 15 (4.8) P=0.80 |
| CO ₂ prod [‡] /O ₂ uptake (RER) | 0.81 (0.07) versus 0.78 (0.06) P=0.44 | 0.96 (0.06) versus 0.99 (0.07) P=0.44 | 1.23 (0.16) versus 1.12 (0.1) P=0.14 | 0.42 (0.12) versus 0.34 (0.09) P=0.19 |

Data are mean values (\pm SD) with P values in bold when $P=0.05$ or less. Symbols indicate type of statistical test used:

*Mann-Whitney U test for differences of means.

†Pearson's correlation for changes in paired individuals.

‡Pearson's χ^2 test for observed differences between matched pairs.

§Percentage reduction of individuals mean values between baseline and altitude.

Az, acetazolamide; PetCO₂, end tidal CO₂; PetO₂, end tidal O₂; RER, respiratory exchange ratio; RPE, rate of perceived effort; SpO₂, peripheral blood O₂ saturation; VCO₂, CO₂ production; VE, ventilation; VO₂, O₂ uptake.

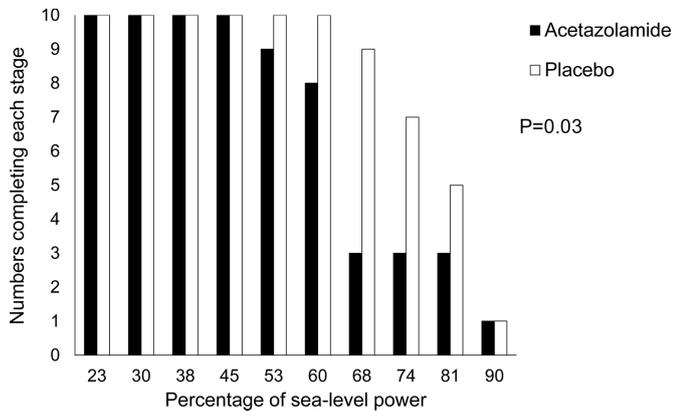


Figure 1 Numbers of individuals taking placebo or acetazolamide (Az) completing each exercise stage (ranging from 23% to 90% of baseline values) at 4559m. For example, at 68% of baseline power, the test was completed by three Az and nine placebo individuals. $P=0.03$ by Mann-Whitney U test for differences of means.

Ascent profile and altitude studies

Individuals travelled by sea and overland from the UK to Gressonay (1640 m) in Italy over an 18-hour period, followed by a 2-night stay that included an acclimatisation ascent to 2800m. Participants ascended in two groups on consecutive days to 2646m, 3647m and 4559m at the Margherita Hut, which involved 3–5 hours of moderate to strenuous exercise daily. Matched pairs ascended together. Self-assessed questionnaires using the Lake Louise (LL) scoring system for AMS²³ were recorded morning and evening to produce twice daily AMS scores. At the Margherita Hut (4559m), individuals were tested on the exercise bicycle between 2 and 10 hours after arrival, with matched pairs being assessed within 90 min of each other. Exercise tests at high altitude were performed in a similar manner, using the same incremental steps as baseline, but at 40% less power in accordance with a previous report of power reduction at

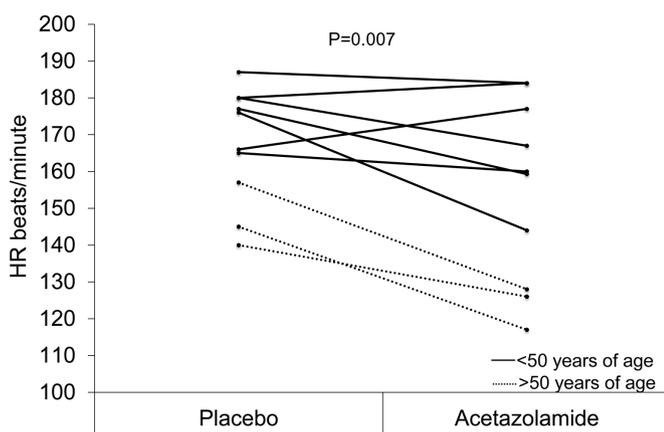


Figure 2 Studies at 4559m showing maximum heart rate (HR) for the matched pairs of participants. Pairs <50 years are shown as solid lines and >50 years are shown as dotted lines. Pearson's χ^2 test for observed differences between matched pairs at altitude.

altitude.²⁴ Individuals were asked after their exercise test which medication they thought they were taking.

Analysis of results and statistics

Comparisons of Az and placebo groups were made for reduction of maximum power from baseline to altitude. In addition, changes in altitude performance were compared between the groups, and between Az/placebo treatments within paired individuals. Statistical analyses were performed using SPSS V.21. Mann-Whitney U test was used to analyse differences of means; Pearson's χ^2 test was used to analyse observed differences between matched pairs; Pearson's correlation was used to test the relationship between variables of interest (age vs HR_{max}). Results are given as mean \pm SD throughout, and results reaching $P<0.05$ were considered significant. No a priori decisions were made regarding the effects of Az on any variable.

RESULTS

Baseline studies

Baseline measures are shown in table 1. There were no significant differences between placebo and Az groups.

Exercise test

Results are shown in table 2 and figures 1–3. At rest, VO_2 , VCO_2 and respiratory exchange ratios were similar between groups, while resting SpO_2 and $PetO_2$ were higher and $PetCO_2$ was lower in the Az-treated group compared with the placebo-treated group.

During exercise at altitude, all participants were able to achieve 45% of their baseline performance, but at higher power, there was progressive failure until only one individual in each group was able to perform at 90% of baseline P_{max} (figure 1). At 45% of baseline performance, VE and $PetO_2$ were on average higher, while $PetCO_2$ was lower in the Az group compared with the placebo group (table 2). Greater maximum power was generated by placebo participants, both as a group ($P=0.03$) (figure 1) and in the matched pairs ($P=0.007$) (table 2). VO_{2max} was higher in the placebo group within the matched pairs ($P=0.0003$), but as a whole group, the difference did not reach significance ($P=0.063$). VCO_2 was higher on placebo at maximum performance both as a group and in the matched pairs (table 2). While resting HRs were not different between groups, those on Az had lower HR at P_{max} compared their placebo-matched pair (figure 2).

Correlation analysis of the matched pairs was used to assess the relationship between age and the effect of Az on exercise parameters at altitude. With increasing age of the matched pairs, there was a greater reduction in HR_{max} on those taking Az compared with their placebo partners ($r=-0.71$, $P=0.01$; figure 3A). Similarly, there was a greater reduction in P_{max} from baseline performance in those taking Az ($r=-0.83$; $P<0.005$; figure 3B). There was a negative correlation between baseline eGFR of participants and their age ($r=-0.69$; $P=0.001$).

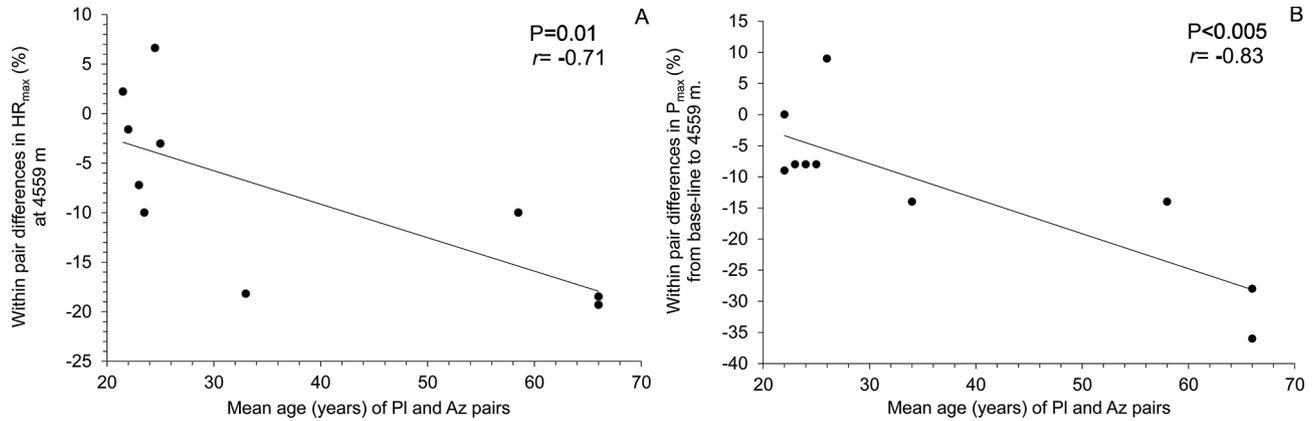


Figure 3 Studies on paired participants (placebo vs acetazolamide (Az)) for P_{\max} at altitude showing (A) the relationship between mean age of each pair and within pair differences for maximum heart rate (HR_{\max}), and similarly for (B) mean age of each pair and differences in reduction in maximum power (P_{\max}) from baseline (Pearson's correlation).

Questionnaires recorded immediately after the exercise test indicated that 11 had correctly guessed their medication (eight on Az and three on placebo), seven did not know (two on Az and five on placebo), while two on placebo thought they were taking Az. On the day of the exercise test, the mean of the summated morning and evening LL AMS scores were similar in the two groups (Az vs placebo: 2.1 ± 2.0 vs 2.1 ± 1.3 , $P=0.7$). Only two individuals had scores over 3 on the exercise test day, one in the placebo group and one in the Az group, both of whom completed the exercise test satisfactorily.

DISCUSSION

Main findings

The main finding of this study was the greater reduction in P_{\max} at altitude in individuals taking Az compared with those on placebo, particularly in those over 50 years old. Despite the stimulation of respiratory centres by Az, leading to higher SpO_2 and $PetO_2$ at rest, this did not translate into an improvement in exercise performance. Indeed, during the incremental increases in exercise intensity, the fall in SpO_2 was greater in the Az group. In contrast, VO_2 and VCO_2 showed larger increases in the placebo group, indicating a greater exercise capacity. At altitude, resting HRs were similar in both groups, but at P_{\max} Az-treated participants showed smaller increases from baseline. This was apparent in the matched pairs and more so in individuals over 50 years.

Previous studies

Our finding of impaired P_{\max} in subjects on Az is consistent with our previous study at lower altitude (3459 m), which did not use a progressive exercise test to P_{\max} or examine detailed metabolic data.¹⁶ It is also consistent with a detailed chamber study at a simulated altitude of 4200 m.¹⁰ The latter study reported reduced blood pH at near-peak exercise on Az. Such pH changes reflect the slowed CO_2 excretion kinetics and the renal-metabolic acidosis mediated by Az, via inhibition of carbonic anhydrases (CA).²⁵

Field-based studies at altitude previously reported have produced conflicting results. Comparison is difficult because studies were undertaken at different altitudes, using different Az doses and with a variety of ascent profiles. In particular, larger doses are likely to have the greatest inhibiting effect on exercise ability, as shown in the data of Garske *et al.*,¹⁰ who used 1000 mg per day for 2.5 days prior to testing. Since Az has a half-life of 8–12 hours,²⁶ it would accumulate to produce a greater effect in those taking the drug for several days, rather than only 24 hours (as frequently used in chamber studies). Field-based studies have generally been over longer periods and in individuals who were acclimatised. We chose to study the effect of Az during early acclimatisation, which is pertinent to the ascent of mountains such as Mt Blanc and Kilimanjaro.

Mechanism of action of Az

The mechanism of action of Az has been widely studied.²⁷ Multiple effects include a metabolic acidosis when sufficient bicarbonate has been excreted, which typically takes 24 hours or more.²⁸ At altitude, this provides a beneficial ventilatory stimulus that opposes and limits the braking effect of hypocapnia on the full ventilatory response to hypoxia. However, CA isoenzymes are widespread throughout the body including the heart. The heart has high concentrations of the CA-IV isoenzyme, which is 3.5 times more sensitive to Az inhibition than CA-II (widespread in tissues) and is threefold more enzymatically active.²⁹ This suggests important cardiac functionality.³⁰ Indeed, we observed that HR failed to increase as much in the Az group during exercise, particularly in older participants where Az retention may have been higher due to age-related changes in renal function (discussed below). Skeletal muscle, however, contains predominantly CA-III, which is minimally inhibited by Az.³¹ However, other factors should also be considered in relation to impaired exercise performance in hypoxia, especially the role of the central nervous system. In particular, altitude alters autonomic nervous system functions, which are thought

to play an important role in the regulation of cardiac output and ventilation.³²

Older people

The greater effect of Az on exercise performance in older people raises important questions regarding dosage, especially given the increasing numbers of older people trekking at altitude.¹⁹ Since Az is largely excreted unchanged in urine (90% of an oral dose is excreted within 24 hours) and GFR decreases with age, tissue concentrations may be higher in older people. For example, toxicity is frequently observed when Az is used for treating glaucoma, a disease of older people. In particular, patients with reduced GFR or who are on dialysis are prescribed doses of 125 mg per day or less.¹⁸ In such patients, fatigue and lethargy are well-known side effects, but there are no studies of exercise performance in this group. Conventionally, Az usage at altitude is perceived as having few consequential side effects, which are limited to taste disturbance and paraesthesia. However, there are concerns about the optimal dosage, which is currently recommended as 125 mg twice daily. Our data provide evidence that this may not be appropriate under all circumstances. The optimum therapeutic dose of Az may have to be individualised for the prophylaxis of AMS.⁷ Higher dosing schedules may provide additional benefits by reducing the risk of AMS, but this could be offset by reduced exercise performance. Studies of doses as low as 125 mg per day in older people are required with assessments of AMS scores, peripheral oxygen saturations, exercise performance and accompanied by measurement of blood concentrations of Az to fully address this question. Nevertheless, our results are consistent with the current recommendations on the dose of Az used for prophylaxis of AMS and indicate that Az would not enhance exercise performance if taken by healthy individuals at altitude and, indeed, might have the opposite effect at maximum effort.

Limitations

We acknowledge that a $\text{VO}_{2\text{max}}$ test is only one measure of performance, and other determinants of exercise performance and capacity at high altitude, such as endurance, may be relevant in this context. Further our study contained only 20 individuals, so was relatively low-powered statistically, particularly for older participants. We used a matched-paired design to address this low power issue. While an alternative crossover study would improve this further, such a design is difficult to achieve in the field. In common with most reported studies, blood concentrations of Az were not measured, which could have provided direct evidence of an age effect. Since Az is a mild diuretic, dehydration may have contributed to reductions in exercise performance in this group. In a carefully controlled hypobaric chamber study, in which a reduction of 4% body weight was achieved, resulted in 8% reduction in maximum exercise performance.³³ We did not measure hydration status, but we do not believe

our subjects were dehydrated to that extent, as they had free access to fluids. Hydration would be worth assessing in future studies of exercise at high-altitude exercise. Further work is required to establish more clearly the effect of Az on exercise performance and the possible effects of age and perhaps gender.³⁴

CONCLUSION

During an alpine ascent to 4559 m over 5 days, Az 500 mg daily reduced maximum exercise capacity, particularly in older people. Compared with individuals on placebo, those on Az had reduced O_2 uptake and CO_2 production at P_{max} . The greater effect of Az on exercise performance in older people may have reflected relative overdosage due to age-related reduction in renal clearance. While Az has value in preventing AMS, age-appropriate dosage may be necessary to compensate for age-related changes in Az clearance.

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Competing interests None declared.

Ethics approval The study was approved by Chichester University Research Ethics Committee (protocol number: 1314_42) and was performed according to the Declaration of Helsinki. All individuals provided signed informed consent.

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