Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions

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Acetazolamide (ACZ) is an enzyme widely distributed in the body and concentrated in the proximal renal tubule and erythrocytes. It is effective in preventing acute mountain sickness (3, 10). In low dose (<5 mg/kg), ACZ inhibits renal CA, causing a modest metabolic acidosis, which increases ventilation at rest (32), thereby increasing arterial Po2 (PaO2), which simulates acclimatization (28, 31). At peak exercise, arterialized capillary pH was lower and Po2 higher on ACZ (P < 0.01). Ventilation was 118.6 ± 20.0 l/min at the maximal power on ACZ and 102.4 ± 20.7 l/min at the same power on placebo (P < 0.02), and Borg score for leg fatigue was increased on ACZ (P < 0.02), with no difference in Borg score for dyspnea. Hypercapnic ventilatory response on ACZ was greater (P < 0.02), whereas hypoxic ventilatory response was unchanged. During hypoxic exercise, ACZ reduced exercise capacity associated with increased perception of leg fatigue. Despite increased ventilation, dyspnea was not increased.

control of breathing; hypoxia; acidosis

ACETAZOLAMIDE (ACZ) INHIBITS carbonic anhydrase (CA), an enzyme widely distributed in the body and concentrated in the proximal renal tubule and erythrocytes. It is effective in preventing acute mountain sickness (3, 10). In low dose (<5 mg/kg), ACZ inhibits renal CA, causing a modest metabolic acidosis, which increases ventilation at rest (32), thereby increasing arterial Po2 (PaO2), which simulates acclimatization (28, 31). At higher doses (7–12 mg/kg), inhibition of red cell and tissue CA leads to respiratory acidosis at the tissue level, which also increases ventilation (32). ACZ under normoxic conditions is associated with a mild (<10%) reduction in exercise capacity (27, 30) associated with lower maximal O2 consumption (VO2; VO2max) and respiratory exchange ratio but increased ventilation (6, 27). As dexamethasone appears equally efficacious in preventing acute mountain sickness (10) without known acute effects on exercise performance, it is of importance to define the effect of ACZ on exercise performance at altitude, given the strenuous nature of exertion in mountaineering.

Acetazolamide (ACZ) is used at altitude to prevent acute mountain sickness, but its effect on exercise capacity under hypoxic conditions is uncertain. Nine healthy men completed this double-blind, randomized, crossover study. All subjects underwent incremental exercise to exhaustion with an inspired O2 fraction of 0.13, hypoxic ventilatory responses, and hypercapnic ventilatory responses after ACZ (500 mg twice daily for 5 doses) and placebo. Maximum power of 203 ± 38 (SD) W on ACZ was less than the placebo value of 225 ± 40 W (P < 0.01). At peak exercise, arterialized capillary pH was lower and Po2 higher on ACZ (P < 0.01). Ventilation was 118.6 ± 20.0 l/min at the maximal power on ACZ and 102.4 ± 20.7 l/min at the same power on placebo (P < 0.02), and Borg score for leg fatigue was increased on ACZ (P < 0.02), with no difference in Borg score for dyspnea. Hypercapnic ventilatory response on ACZ was greater (P < 0.02), whereas hypoxic ventilatory response was unchanged. During hypoxic exercise, ACZ reduced exercise capacity associated with increased perception of leg fatigue. Despite increased ventilation, dyspnea was not increased.

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Acz has been reported to be unchanged (12) or increased (1, 36). Our primary aim was to define the effect of Acz on exercise capacity in healthy subjects under hypoxic conditions. Second, we sought to determine which of the proposed mechanisms is likely to explain any observed effect. Third, we wished to explore further the issue of dyspnea in the context of the reported effects of Acz on ventilatory drive. We, therefore, measured HCVR and HVR in the same set of subjects, in an effort to explore the links between drive and exertional dyspnea.

**METHODS**

*Subjects.* Eleven healthy, nonsmoking, male subjects were enrolled in the study, which had the approval of the institutional research ethics committee. Each subject had normal examination and spirometry before commencement and was weighed at the start of each visit. Subjects were studied on three occasions, with the first study as a familiarization study on no medication. Each visit involved measurement of HVR and HCVR followed by maximal incremental exercise at FIO2 of 0.13 at sea level. After the familiarization study, subjects were randomized in concealed fashion to receive either Acz (500 mg twice daily for 2½ days, including the morning of the study) or placebo capsules before the second study 1 wk later. After a 2-wk washout, subjects crossed over to be treated for a further 2½ days with the alternative drug before the third visit. Subjects and investigators were blinded to randomization status, although subjects were aware of potential side effects of Acz. Subjects were told that the effect of Acz on hypoxic exercise was not certain and that there were sound physiological reasons to expect changes in either direction.

*Ventilatory response.* Resting end-tidal CO2 concentration was measured over 5 min by using an infrared CO2 analyzer (901-MK2, PK Morgan). In addition to all gas analyzer outputs, inspired ventilation and ear oximetry were recorded continuously on a multichannel chart recorder (TA2000, Gould, Cleveland, OH). After a 5-min rest period, an arterial blood-gas (ABG) sample was obtained by radial artery puncture (rest ABG) and analyzed in a blood-gas analyzer (ABL 520, Radiometer). This was followed by an arterialized capillary blood-gas (CBG) sample collected in two to three capillary tubes from a small incision in an earlobe vasodilated with nicotinic acid ointment (rest CBG). Incremental exercise was performed (10) on a calibrated, mechanically braked cycle ergometer (Monark Exercise AB, Varberg, Sweden) with 1-min increments fixed for each subject, calculated to achieve an exercise time of ~10 min (7). The increment was determined by dividing the predicted (normoxic) maximum exercise capacity by 10 and then multiplying by a further correction factor of 0.75 to allow for reduction in exercise capacity at altitude with a similar level of hypoxia (28). In practice, each subject had a calculated increment of either 17 or 20 W. Each minute, heart rate, ECG, and Borg category ratio scale scores for dyspnea and fatigue (4) were recorded each 30 s after 1 min, with each pair of scores being compared by using the t-test. Nonparametric variables were compared by using Wilcoxon’s matched-pairs signed-ranks test. Limiting symptoms were compared by using the χ² test. Variables are presented as means ± SD, unless otherwise stated. All statistics were performed by using SPSS statistical package, and P < 0.05 was required to reject the null hypothesis.

**RESULTS**

Two subjects withdrew from the study (one developed viral symptoms and mild neutropenia on the study drug; another withdrew for personal reasons). This left nine subjects with age of 27.9 ± 2.9 yr, height of 178.4 ± 5.0 cm, and baseline hypoxic exercise capacity of 219 ± 36 W, which was 88 ± 14% of predicted normoxic exercise capacity (18).

*Ventilatory studies.* See Table 1. In two subjects, HCVR could not be measured adequately due to pre-
syncope and bag emptying, respectively. In the remaining seven subjects, Acz was associated with a 32% increase in HCVR slope and a significant left shift in x-intercept (Fig. 1). In contrast, HVR was not significantly affected by Acz under hypocapnic or eucapnic conditions.

The Borg score for dyspnea was plotted in relation to corresponding ventilation during HCVR. The Borg score for dyspnea at a ventilation of 60 l/min was median 6 (range 3–8) on placebo and median 4 (range 2–6) on Acz (P = 0.03) (Fig. 2).

Exercise. Exercise capacity on Acz was reduced by a mean of 10%, with eight of nine subjects having reduced maximum power and the remaining subject able to maintain the same maximum power (see Table 2). FIO₂ was similar, being 0.1292 ± 0.0017 for placebo and 0.1288 ± 0.0024 for Acz. Weight on Acz was 78.1 ± 12.0 kg, which was < 78.5 ± 12.1 kg on placebo (P < 0.05). All nine subjects reported leg fatigue as the predominant limiting symptom on placebo. On Acz, one subject reported combined dyspnea and leg fatigue, with the remainder all citing leg fatigue as the predominant limiting symptom on Acz (P = 0.30). To adjust for the confounding effect of achieved exercise capacity, Table 3 compares results at the maximum power on Acz with results at the same power increment (submaximal in eight of the nine subjects) on placebo. Although Borg category ratio scale scores for leg fatigue were equivalent when compared at peak exercise, when compared at the same power, the median Borg score on Acz was 10, corresponding to the descriptor “very, very heavy,” compared with the median placebo Borg score of 8, corresponding between descriptors “very heavy” and “very, very heavy” (P < 0.02).

Adequate arterialized capillary samples were obtained. Resting ABG Po₂ was 50.9 ± 4.4 Torr, com-

### Table 2. Comparison of peak exercise values

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
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<tbody>
<tr>
<td>Maximum power, W</td>
<td>225 ± 40</td>
<td>203 ± 38*</td>
</tr>
<tr>
<td>VO₂max, l/min</td>
<td>2.98 ± 0.38</td>
<td>2.73 ± 0.39*</td>
</tr>
<tr>
<td>VCO₂max, l/min</td>
<td>3.31 ± 0.35</td>
<td>2.76 ± 0.42*</td>
</tr>
<tr>
<td>Duration of exercise, mins</td>
<td>11.54 ± 1.29</td>
<td>10.43 ± 1.29*</td>
</tr>
<tr>
<td>HR, beats/min (%)</td>
<td>179.0 ± 12.5 (98.3)</td>
<td>170.3 ± 12.8 (93.5)</td>
</tr>
<tr>
<td>Ventilation, l/min (%MVV)</td>
<td>123.7 ± 18.2 (77.8)</td>
<td>118.5 ± 20.0 (74.7)</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>79.0 ± 4.2</td>
<td>82.7 ± 4.3†</td>
</tr>
<tr>
<td>End-tidal PCO₂, Torr</td>
<td>26.9 ± 3.4</td>
<td>23.8 ± 2.4*</td>
</tr>
<tr>
<td>Borg score dyspnea</td>
<td>9 (7–10)</td>
<td>7 (4–10)</td>
</tr>
<tr>
<td>Borg score leg fatigue</td>
<td>10 (7–10)</td>
<td>10 (8–10)</td>
</tr>
</tbody>
</table>

Values are means ± SD; Borg score values are medians with ranges in parentheses. VO₂max, maximal O₂ consumption; VCO₂max, maximal CO₂ production; HR, heart rate; MVV, maximum voluntary ventilation calculated as 35 × forced expiratory volume in 1 s. Acetazolamide vs. placebo: *P < 0.01; †P < 0.05.

### Table 3. Comparison at same power

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, l/min</td>
<td>2.75 ± 0.50</td>
<td>2.73 ± 0.39</td>
</tr>
<tr>
<td>VCO₂, l/min</td>
<td>3.03 ± 0.49</td>
<td>2.76 ± 0.42*</td>
</tr>
<tr>
<td>HR, beats/min (%)</td>
<td>174.3 ± 11.4</td>
<td>170.3 ± 12.8</td>
</tr>
<tr>
<td>Ventilation, l/min</td>
<td>102.4 ± 20.7</td>
<td>118.6 ± 20.0†</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>79.7 ± 4.6</td>
<td>82.7 ± 4.3*</td>
</tr>
<tr>
<td>End-tidal PCO₂, Torr</td>
<td>30.4 ± 3.2</td>
<td>23.8 ± 2.4†</td>
</tr>
<tr>
<td>Borg score dyspnea</td>
<td>7 (5–9)</td>
<td>7 (4–10)</td>
</tr>
<tr>
<td>Borg score leg fatigue</td>
<td>8 (7–10)</td>
<td>10 (8–10)</td>
</tr>
</tbody>
</table>

Values are means ± SD; Borg score values are medians with ranges in parentheses. Values at maximal power at acetazolamide visit are compared with values at same power (generally one or two increments before maximal) at placebo visit. VO₂, O₂ consumption; VCO₂, CO₂ production. Acetazolamide vs. placebo: *P < 0.05; †P < 0.02; ‡P < 0.001.
pared with resting CBG PO2 of 50.9 ± 4.3 Torr. The
time of collection of peak CBG on Acz was 9 min 49 s ±
1 min 16 s, which was less than the time on placebo of
10 min 32 s ± 1 min 11 s (P = 0.01), due to the reduced
exercise capacity (Table 4).

**DISCUSSION**

We found a 10% reduction in exercise capacity under
hypoxic conditions on Acz. There was increased venti-
latory effort on Acz, but the predominant limiting
symptom was the perception of leg fatigue. Leg fatigue
was the same at maximum exercise, despite the lower
maximum power on Acz, and leg fatigue was increased
on Acz when compared at the same power, indicating
that Acz is associated with increased perception of leg
fatigue during maximal exercise.

The increased leg muscle fatigue on Acz may be due
to the effect of acidosis within muscle cells. Acidosis
decreases endurance time during exercise and inhibits
glycolytic enzymes, especially phosphofructokinase
(19). We have shown reduced arterialized capillary pH
at near-peak exercise on Acz. This reduction would
have been greater still if it had been possible to allow
for the confounding effect of the higher power incre-
ment at which placebo peak CBG was sampled. As
shown previously (27), we showed reduced CO2 produc-
tion during incremental exercise, which reflects slowed
CO2 production kinetics with CA inhibition (25). CA
inhibition without metabolic acidosis causes slower
recovery of muscle pH after progressive exercise (21).
Therefore, impaired CO2 elimination is also likely to
have contributed to decreased muscle pH in our sub-
jects.

Diuretic effects of CA inhibition may also impair
exercise. Acz decreases body weight by 2% within 24 h
(30), which may be associated with impaired stroke
volume, thermoregulation, and ability to maintain ex-
ercise (6). We observed a 0.5% reduction in weight on
Acz, suggesting very mild dehydration, but, because
maximal heart rate was lower on Acz, this is unlikely
to be the limiting factor to exercise.

An additional potential mechanism of increased leg
fatigue is the likely effect of increased work of breath-
ing associated with increased ventilation to reduce O2
delivery to working muscles. Blood flow and VO2 to the
respiratory muscles approximate 14–16% of total blood
flow and VO2 during maximal exercise (15). During
heavy exercise, additional increases in work of breath-
ning cause vasoconstriction in locomotor muscles (14),
which can impair exercise performance (16). Although
increased work of breathing might also have been
expected to increase perception of dyspnea as an addi-
tional factor limiting exercise, no increase in dyspnea
was observed. A further potential mechanism for in-
creased perception of leg fatigue is the reported effect
of CA inhibition to impair neural input to muscle (5)
and impair muscle function (20).

The reduction in hypoxic exercise capacity on Acz
contrasts with studies under sea-level and hypobaric
hypoxia, in which no significant limitation of maximum
exercise was seen (13, 27, 30). This may be attributed
to the higher dose of Acz used in our study, which is at
the upper limits of the usual clinical dosing. At doses of
7–12 mg/kg (as in this study), significant inhibition of
red cell and tissue CA may develop (32) and lead to
inefficient CO2 transport during exercise.

An alternative explanation is that previous studies
have used higher power increments of up to 50 W,
which may have reduced their sensitivity for detecting
the relatively small change in exercise capacity found
in our study.

These results do not detract from the proven ben-
efit of Acz in reducing acute mountain sickness dur-
ing rapid ascent (3). Although exercise capacity was
reduced under conditions of acute hypoxia at sea
level, the difference is relatively small and would not
necessarily occur with longer term exposure to alti-
tude. A previous study at 4,846 m showed better exer-
cise performance at altitude in acclimatized sub-
jects on Acz, with less weight and muscle loss (2).
Additional factors are likely to influence exercise
performance in acclimatized subjects at altitude,
such as higher ventilatory drive with higher PaO2
and polycythemia, which could increase O2 delivery
to tissues. Additional consequences of more pro-
longed hypoxia at altitude include high-altitude pul-
monary edema (11). Acz reduces hypoxic pulmonary
vasoconstriction, which may prevent high-altitude pul-
monary edema (9). The modest detrimental effect
on exercise capacity of Acz in the relatively high dose
used in our study needs to be weighed against its
proven benefits by those undertaking high-intensity
exercise at altitude.

**Table 4. Resting and exercise blood gas data**

<table>
<thead>
<tr>
<th></th>
<th>Rest ABG</th>
<th>Acetazolamide</th>
<th>Peak ABG</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.430 ± 0.013</td>
<td>7.350 ± 0.021*</td>
<td>7.346 ± 0.038</td>
<td>7.296 ± 0.017*</td>
</tr>
<tr>
<td>PaCO2, Torr</td>
<td>49.5 ± 4.3</td>
<td>54.4 ± 3.4*</td>
<td>48.6 ± 5.9</td>
<td>50.2 ± 5.5*</td>
</tr>
<tr>
<td>PaO2, Torr</td>
<td>87.4 ± 3.2</td>
<td>89.1 ± 3.2</td>
<td>80.9 ± 4.5</td>
<td>83.4 ± 4.4</td>
</tr>
<tr>
<td>Base excess</td>
<td>+3.0 ± 1.1</td>
<td>−5.9 ± 0.9*</td>
<td>−6.6 ± 3.2</td>
<td>−10.2 ± 1.1*</td>
</tr>
<tr>
<td>Bicarbonate, mmol/l</td>
<td>25.1 ± 1.3</td>
<td>18.3 ± 0.8*</td>
<td>16.5 ± 2.1</td>
<td>14.9 ± 1.1†</td>
</tr>
</tbody>
</table>

Values are means ± SD. ABG, arterial blood gas; CBG, capillary blood gas; PaCO2, arterial; PaO2, arterial; Sao2, arterial or arterialized capillary O2 saturation. Acetazolamide vs. placebo: *P < 0.01; †P < 0.05.
The similar peak CBG PCO₂ appears to contrast with the demonstration that Acz stimulates ventilation during exercise compared with placebo at the same power. However, inhibition of red cell CA is associated with blood-gas disequilibrium, such that the PCO₂ measured at equilibrium in the blood-gas analyzer is higher than the P CO₂ in disequilibrium within the arterial circulation (8, 34).

Acz did not increase dyspnea during exercise, which was unexpected given the increase in ventilation. We speculate that this intriguing finding, together with our demonstration of reduced dyspnea during HCVR, indicates that stimulating ventilatory drive does not come at the cost of worsening breathlessness during exercise, an observation of considerable clinical utility. It is possible that impaired neural input to respiratory muscle caused by Acz (5) may alter the perception of dyspnea.

The increase in HCVR on Acz is attributable to metabolic acidosis (33). By comparison, there was little effect on HVR. Metabolic acidosis increases HVR (33), but this is offset by direct suppression of peripheral chemoreceptors by CA inhibition (17, 26, 35). Previous studies have found significant decreases in hypocapnic HVR and unchanged or increased eucapnic HVR on Acz (1, 12, 33, 36). However, even if there is a real increase in eucapnic HVR on Acz, this would be of doubtful importance in practice, because high-altitude acclimatization is known to be accompanied by marked hypocapnia (37).

In summary, the increase in resting ventilatory drive due to Acz is associated with increased ventilatory response to hypercapnia, but not hypoxia. Acz continues to stimulate ventilation during maximal exercise at a PaCO₂ of 0.13, with associated increases in PaO₂ and arterial O₂ saturation. There is no increase in dyspnea during exercise on Acz, despite the increase in ventilation. Exercise capacity is reduced in association with an increased perception of leg effort.

We gratefully acknowledge the voluntary participation of all 11 subjects, the assistance of A. Brake and V. Copas (laboratory technicians), and the helpful advice of Dr. R. Bowman (thoracic physician).

REFERENCES