Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions

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Garske, Luke A., Michael G. Brown, and Stephen C. Morrison. Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions. J Appl Physiol 94: 991–996, 2003. First published October 4, 2002; 10.1152/japplphysiol.00746.2001.—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 O\textsubscript{2} 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 p\textsubscript{H} was lower and P\textsubscript{CO\textsubscript{2}} 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

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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 P\textsubscript{CO\textsubscript{2}} (P\textsubscript{aco}), 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 O\textsubscript{2} consumption (V\textsubscript{O\textsubscript{2}}; V\textsubscript{O\textsubscript{2 max}}) 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.

Acz has been reported to have varying effects on exercise capacity and ventilation under hypoxic conditions. Schoene et al. (27) found no difference in maximal power but significantly increased V\textsubscript{O\textsubscript{2 max}} on Acz at an inspired O\textsubscript{2} fraction (Fi\textsubscript{O\textsubscript{2}}) of 0.118 under normobaric conditions, which was associated with modest increases in ventilation and O\textsubscript{2} saturation measured from pulse oximetry (Sp\textsubscript{O\textsubscript{2}}) during exercise. Increased arterial and capillary P\textsubscript{O\textsubscript{2}} leading to increased O\textsubscript{2} delivery may have accounted for these findings, although these parameters were not successfully measured (27). In contrast, Stager et al. (30) found no effect on maximal power, V\textsubscript{O\textsubscript{2 max}}, ventilation, or Sp\textsubscript{O\textsubscript{2}} when studied under conditions of hypobaric hypoxia with barometric pressure of 446 mmHg. Also, using simulated altitude, McElhan et al. (22) found a reduced time to exhaustion at 90% V\textsubscript{O\textsubscript{2 max}} on Acz. At a higher altitude, acclimatized mountain climbers demonstrated modest increases in ventilation, but no difference in Sp\textsubscript{O\textsubscript{2}}, and a trend to reduced exercise capacity (13). Potential mechanisms for reduced exercise capacity include the effect of acidosis on muscle function, dehydration due to diuretic effect, and increased dyspnea due to stimulation of ventilation.

Although there may be some inconsistency in the reported effect of Acz on ventilation and arterial O\textsubscript{2} saturation during exercise, there is clear evidence of increased ventilatory drive at rest, as evidenced by the finding of increased hypercapnic ventilatory response (HCVR) (1, 33, 36). Hypoxic ventilatory response (HVR) was not increased (1, 36), although this conclusion was based on measurement of HVR without Acz at baseline P\textsubscript{CO\textsubscript{2}}, whereas HVR after Acz was measured at the new lower resting P\textsubscript{CO\textsubscript{2}} (hypocapnic HVR). Hypocapnia attenuates HVR (29), thus possibly offsetting any augmentation due to the drug itself. Any consideration of the impact of hypoxic ventilatory drive in explaining the effect of Acz in preventing acute mountain sickness would, therefore, need to eliminate the effects of CO\textsubscript{2} by holding P\textsubscript{CO\textsubscript{2}} at the same level with and without Acz (eucapnic HVR). Eucapnic HVR on...
ACETAZOLAMIDE REDUCES HYPOXIC EXERCISE CAPACITY

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 (CD-3A, Applied Electrochemistry, Pittsburgh, PA). Subsequently, two HVR runs were performed in a modification of the technique described by Rebuck and Campbell (24) using room air as the filling gas for a 6-liter rebreathing bag. End-tidal CO2 concentration was maintained at the resting level by using manually varied flow through a CO2-absorbing bypass circuit. SpO2 was measured by using a pulse oximeter (Radiometer, Copenhagen, Denmark). Ventilation was measured with a rotating-vane ventilation monitor (PK Morgan, Chatham, UK). Borg category ratio scale scores (0–10) for dyspnea recorded each 30 s and cessation at 4 min were measured over 5 min by using an infrared CO2 analyzer (CD-3A, Applied Electrochemistry) and infrared CO2 analyzer (CSA1, Applied Electrochemistry). End-tidal CO2 was measured on 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 leg fatigue (4) were recorded. Near completion of exercise, a repeat arterialized CBG (peak CBG) was sampled. Exercise capacity was taken as the highest increment that the subject maintained for at least 30 s. At the completion of exercise, subjects were asked to describe the predominant limiting symptom.

Statistics. Normally distributed variables were compared by using paired 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-
Acetazolamide reduces hypoxic exercise capacity

Table 2. Comparison of peak exercise values

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Acetazolamide</th>
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<tbody>
<tr>
<td>Maximum power, W</td>
<td>225 ± 40</td>
<td>203 ± 38*</td>
</tr>
<tr>
<td>( \dot{V}O_2_{max} ), l/min</td>
<td>2.98 ± 0.38</td>
<td>2.73 ± 0.39*</td>
</tr>
<tr>
<td>( \dot{V}CO_2_{max} ), 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>78.5 ± 5.2</td>
<td>77.3 ± 4.9</td>
</tr>
<tr>
<td>Ventilation, l/min (%)</td>
<td>128.3 ± 8.6</td>
<td>124.8 ± 7.8</td>
</tr>
<tr>
<td>( \dot{V}CO_2_{max} ), l/min</td>
<td>3.4 ± 0.7</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>Borg score dyspnea</td>
<td>7 (5–10)</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. \( \dot{V}O_2_{max} \), maximal \( O_2 \) consumption; \( \dot{V}CO_2_{max} \), maximal \( CO_2 \) production; HR, heart rate; MVV, maximum voluntary ventilation calculated as \( 35 \times \) forced expiratory volume in 1 s. Acetazolamide vs. placebo: *\( P < 0.01 \); †\( P < 0.05 \).

Table 3. Comparison at same power

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2 ), l/min</td>
<td>2.75 ± 0.50</td>
<td>2.73 ± 0.39</td>
</tr>
<tr>
<td>( \dot{V}CO_2 ), 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>( \dot{V}CO_2_{max} ), l/min</td>
<td>3.4 ± 0.7</td>
<td>3.2 ± 0.6</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>10 (8–10)</td>
<td>10 (8–10)</td>
</tr>
</tbody>
</table>

Values are means ± SD; Borg score values are medians with ranges in parentheses. \( \dot{V}O_2 \), \( O_2 \) consumption; \( \dot{V}CO_2 \), \( CO_2 \) production. Acetazolamide vs. placebo: *\( P < 0.05 \); †\( P < 0.02 \); ‡\( P < 0.001 \).

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). \( F_{O_2} \) 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. 

Fig. 2. Plot of Borg score for dyspnea vs. ventilation during hypercapnic ventilatory response measurement in subject 6.
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 ventilatory 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 increment at which placebo peak CBG was sampled. As shown previously (27), we showed reduced CO2 production 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 subjects.

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 exercise (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 breathing 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 breathing 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 additional factor limiting exercise, no increase in dyspnea was observed. A further potential mechanism for increased 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 benefit of Acz in reducing acute mountain sickness during 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 altitude. A previous study at 4,846 m showed better exercise performance at altitude in acclimatized subjects 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 prolonged hypoxia at altitude include high-altitude pulmonary edema (11). Acz reduces hypoxic pulmonary vasoconstriction, which may prevent high-altitude pulmonary 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>Placebo</th>
<th>Acetazolamide</th>
<th>Placebo</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>
</tr>
<tr>
<td>PaO2, Torr</td>
<td>38.4 ± 2.1</td>
<td>34.2 ± 2.1*</td>
<td>32.9 ± 2.8</td>
</tr>
<tr>
<td>PaCO2, Torr</td>
<td>49.5 ± 4.3</td>
<td>54.4 ± 3.4*</td>
<td>46.6 ± 5.9</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>87.4 ± 3.2</td>
<td>89.1 ± 3.2</td>
<td>80.9 ± 4.5</td>
</tr>
<tr>
<td>Base excess</td>
<td>+1.4 ± 1.1</td>
<td>-5.9 ± 0.9*</td>
<td>-6.6 ± 3.2</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>
</tr>
</tbody>
</table>

Values are means ± SD. ABG, arterial blood gas; CBG, capillary blood gas; PaCO2, arterial PCO2; PaO2, arterial PO2; 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 PCO2 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