Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes

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Most recently, Ghofrani et al. (14) reported the increase in exercise capacity in healthy subjects at high altitude after the intake of sildenafil, a PDE-5 inhibitor used for erectile dysfunction (7) and shown to be efficacious in the treatment of pulmonary arterial hypertension (12). This observation raised the possibility that the limitation of cardiac output at altitude could be related to an increase in pulmonary vascular resistance (PVR) and associated with right ventricular flow output limitation (14). However, sildenafil intake was also associated with higher exercise oxygen saturations (SO2) so that no definitive conclusions could be drawn as to whether the observed improvements in exercise capacity could be accounted for by improved cardiac output, arterial O2 content, or both (29).

We therefore got interested in revisiting the cardiovascular and exercise effects of acetazolamide, a carbonic anhydrase inhibitor of established efficacy in the treatment of acute mountain sickness (1). Acetazolamide decreases the renal reabsorption of bicarbonate and thereby induces a metabolic acidosis with increased ventilation and improved oxygenation (34). Interestingly, acetazolamide has been reported to inhibit hypoxic pulmonary vasoconstriction (HPV) in experimental animal preparations (2, 8, 17, 18) and, most recently, in humans (36). In the present study, we investigated the respective contributions of pulmonary vascular and gas exchange changes induced by acetazolamide intake on exercise capacity in normal volunteers at high altitude.

METHODS

Subjects. Fifteen lowlanders, 8 women and 7 men, aged from 16 to 61 years, mean 35 years, with a height of 169 ± 7 cm (mean ± SD) and a weight of 63 ± 12 kg, gave a written informed consent to the study, which was approved by the Ethical Committee of the Erasme University Hospital. For the 16-yr-old volunteer, informed written consent was also obtained from his parents. All the subjects were healthy and active, with an unremarkable previous history, and normal clinical examination, chest X-ray, and electrocardiogram.

Experimental design. Each subject underwent an echocardiographic examination in a semirecumbent position, at rest, and at a moderated level of exercise (pedaling without load) to increase cardiac output (Q), and an incremental maximum cycle ergometer cardiopulmonary exercise test (CPET), at sea level in Brussels, and 10 days after arrival on the Bolivian altiplano (3,700–4,700 m), before and after 24 h treatment with acetazolamide or a placebo on Huayna Potosi, at 4,700 m. Acetazolamide and placebo were administered double-blind and in a random sequence. Altitude shifted Ppa/Q plots to higher pressures and decreased maximum O2 consumption (V˙O2max). Acetazolamide had no effect on Ppa/Q plots but increased arterial O2 saturation at rest from 84 ± 0.06 to 1.05 ± 0.01). However, acetazolamide did not affect V˙O2max (from 31 ± 0.06 to 31 ± 0.05, P < 0.001). We conclude that acetazolamide does not affect maximum exercise capacity or pulmonary hemodynamics at high altitudes. Associated changes in the respiratory exchange ratio may be due to altered CO2 production kinetics.
Table 1. Effects of high altitude on hemodynamics and echocardiographic variables in normal subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normoxia</th>
<th>High Altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO2, %</td>
<td>98±1</td>
<td>85±5†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>59±8</td>
<td>71±11†</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td>91±9</td>
<td>96±10</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>4.6±0.9</td>
<td>5.2±0.8*</td>
</tr>
<tr>
<td>AT, ms</td>
<td>145±5</td>
<td>115±10†</td>
</tr>
<tr>
<td>TR, m/s</td>
<td>2.1±0.2</td>
<td>2.7±0.3†</td>
</tr>
</tbody>
</table>

Values are means ± SD. SO2, O2 saturation; HR, heart rate; Psa, mean systemic arterial pressure; Q, cardiac output; AT, pulmonary artery flow acceleration time; TR, maximum velocity of tricuspid regurgitation. *P < 0.05, †P < 0.001, high altitude compared with normoxia.

Fig. 1. Mean pulmonary artery pressure (Ppa) vs. cardiac index (Q) plots in normoxia (N), at high altitude at baseline without medication (HA bl) and after intake of acetazolamide (HA acz). Vertical and horizontal bars represent SE. Values of P are related to changes in mean Ppa. High altitude shifted Ppa/Q plots to higher pressures, and the intake of acetazolamide had no effect.

Table 2. Effects of high altitude on cardiopulmonary exercise variables in normal subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normoxia</th>
<th>High Altitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wmax, W</td>
<td>244±81</td>
<td>177±29‡</td>
</tr>
<tr>
<td>VO2max, ml·kg⁻¹·min⁻¹</td>
<td>41±10</td>
<td>31±5†</td>
</tr>
<tr>
<td>VE max, l/min</td>
<td>108±33</td>
<td>120±38</td>
</tr>
<tr>
<td>RER max</td>
<td>1.26±0.07</td>
<td>1.17±0.06*</td>
</tr>
<tr>
<td>HR max, beats/min</td>
<td>179±9</td>
<td>162±18*</td>
</tr>
<tr>
<td>O2 pulse, ml/beat</td>
<td>16±7</td>
<td>12±4*</td>
</tr>
<tr>
<td>VO2 at VT, ml·kg⁻¹·min⁻¹</td>
<td>29±10</td>
<td>21±4*</td>
</tr>
<tr>
<td>Exercise SO2, %</td>
<td>97±2</td>
<td>80±5‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. Wmax, maximum workload; VO2, O2 uptake; VO2max, maximum O2 uptake; VE max, maximum ventilation; RER max, maximum respiratory exchange ratio; HR max, maximum HR; VT, anaerobic threshold. *P < 0.05, †P < 0.01, ‡P < 0.001, high altitude compared with normoxia.
was associated with an increase in resting SO2 and V˙E but
ships with systolic Ppa calculated from TR (not shown).
(Fig. 2). There was no effect either on systolic Ppa/Q relationships with mean Ppa calculated from AT
mean Ppa/Q relationships with mean Ppa calculated from AT (Fig. 2). There was no
effect either on systolic Ppa/Q relationships with systolic Ppa
were shifted to higher pressures (Figs. 1 and 2). Altitude
decreases in HR, Q, and TR, while AT and SO2 decreased, and
V˙E/V˙CO2 increased. At the anaerobic threshold, V˙O2 was decreased (Table 2)
and V˙E/V˙CO2 at end exercise 50
Values are means 
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Effects of altitude. Altitude exposure was associated with increases in HR, Q, and TR, while AT and SO2 decreased, and
PsA remained unchanged (Table 1). The mean Ppa/Q plots were shifted to higher pressures (Figs. 1 and 2). Altitude
decreased V˙O2max, maximum workload, HR, O2 pulse, and RER. At the anaerobic threshold, V˙O2 was decreased (Table 2)
and V˙E/V˙CO2 increased.

Effects of acetazolamide. In the placebo group, an additional
day at 4,700 m was associated with unchanged resting SO2, V˙E,
HR, Q, AT, and TR (Table 3) and maximum workload, V˙O2,
V˙E, RER, HR, O2 pulse, SO2, V˙E/V˙CO2, or anaerobic threshold
workload, V˙O2, and HR (Table 4). Placebo had no effect on
mean Ppa/Q relationships with mean Ppa calculated from AT
(Fig. 2). There was no effect either on systolic Ppa/Q relationships with systolic Ppa calculated from TR (not shown).

In the acetazolamide group, an additional day at 4,700 m
was associated with an increase in resting SO2 and V˙E but
otherwise unchanged HR, Q, AT, and TR (Table 3). Acetazol-
amide increased workload, V˙O2, HR, and V˙E at the anaerobic
threshold but had no effect on V˙O2max or maximum workload,
HR, and O2 pulse, and increased maximum exercise SO2 and
V˙E/V˙CO2 (Table 4). Acetazolamide had no effect on Ppa/Q
plots with mean Ppa calculated from AT (Fig. 2). There was no
effect either on systolic Ppa/Q relationships with systolic Ppa
calculated from TR (not shown).

Table 3. Effects of acetazolamide or placebo on
hemodynamics and echocardiographic variables in normal
subjects at the altitude of 4,700 m

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL score</td>
<td>5 ± 4</td>
<td>2 ± 2*</td>
</tr>
<tr>
<td>SO2</td>
<td>88 ± 3</td>
<td>85 ± 4</td>
</tr>
<tr>
<td>V˙E</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>HR</td>
<td>70 ± 13</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Q</td>
<td>5 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>AT</td>
<td>111 ± 13</td>
<td>113 ± 7</td>
</tr>
<tr>
<td>TR</td>
<td>2.7 ± 0.2</td>
<td>2.8 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. LL score, Lake Louise score. *P < 0.05, placebo compared with baseline. †P < 0.05, acetazolamide compared with baseline.

Changes in workload and V˙O2 at the anaerobic threshold were correlated to the changes in resting SO2 induced by a placebo or acetazolamide (Fig. 3).

DISCUSSION

The present results suggest that the intake of acetazolamide at the upper limit of doses used for the treatment of AMS does not affect maximum aerobic exercise capacity or pulmonary hemodynamics at high altitudes.

Acetazolamide has been shown to be efficient in the prevention and the treatment of AMS (1). The drug inhibits carbonic anhydrase, an enzyme widely distributed in the body and concentrated in the proximal renal tube and erythrocytes. This causes metabolic acidosis and increases ventilation and arterial PO2 (34). The doses of acetazolamide effective in the treatment of AMS are thought to be below 5 mg·kg−1·day−1, but doses up to 10 mg·kg−1·day−1 are often used with satisfactory clinical results (1). Higher doses have more pronounced inhibition of red blood cell and tissue carbonic anhydrase, which leads to respiratory acidosis at the tissue level and further increases ventilation (34). The dose of acetazolamide used in the present study corresponded to an average of 11.5 mg/kg.

Table 4. Effects of acetazolamide and placebo on cardiopulmonary exercise variables in normal subjects at the altitude of 4,700 m

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Acetazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wmax, W</td>
<td>177 ± 20</td>
<td>166 ± 19</td>
</tr>
<tr>
<td>V˙O2max, ml·kg−1·min−1</td>
<td>31 ± 4</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>V˙E max, l/min</td>
<td>104 ± 22</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>RER max</td>
<td>1.14 ± 0.06</td>
<td>1.10 ± 0.07</td>
</tr>
<tr>
<td>HR max, beats/min</td>
<td>157 ± 22</td>
<td>162 ± 18</td>
</tr>
<tr>
<td>O2 pulse, ml·beat</td>
<td>12 ± 4</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Exercise SO2, %</td>
<td>80 ± 3</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>V˙E/V˙CO2 at end exercise</td>
<td>50 ± 8</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>Wmax at VT, W</td>
<td>105 ± 23</td>
<td>113 ± 36</td>
</tr>
<tr>
<td>V˙O2 at VT, ml·kg−1·min−1</td>
<td>22 ± 3</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>HR at VT, ml·beat</td>
<td>137 ± 24</td>
<td>148 ± 20</td>
</tr>
</tbody>
</table>

Values are means ± SD. VT, anaerobic threshold measure by V-slope method; V˙CO2, CO2 output. *P < 0.05, †P < 0.01, ‡P < 0.001, acetazolamide compared with baseline.

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most likely optimal to increase arterial oxygenation through enhanced metabolic acidosis-increased chemosensitivity (1).

In the present study, acetazolamide intake was associated with no changes in the Lake Louise AMS score. However, this effect was observed on average below the threshold score of 7 considered to be diagnostic of severe AMS (28). The absence of improvement of the AMS score after acetazolamide intake may be related to nonspecific side effects of the drug, which include dizziness, somnolence, asthenia, dyspnea, headache, nausea, vomiting, loss of appetite, and gastrointestinal discomfort (1).

Acetazolamide has been reported to inhibit HPV in experimental animal models (2, 8, 17, 18) and, more recently, in humans (36). The inhibition of HPV by acetazolamide has been shown to be independent of the inhibition of carbonic anhydrase or changes in intracellular pH or membrane potential but entirely explained by a specific inhibition of hypoxia-induced calcium responses (32). The inhibition of human HPV by acetazolamide was reported after the intake of 250 mg of the drug three times per day during 3 days and estimated by changes in TR in normal subjects exposed to isocapnic hypoxia (36). In the present study, the same dose of acetazolamide taken during 24 h did not reverse hypoxic pulmonary hypertension in subjects who had been acclimatized for 10 days at altitudes ~4,000 m before climbing to 4,700 m. A false-negative result appears unlikely, as pulmonary artery pressure was estimated using two independent Doppler measurements, respectively: the acceleration time of pulsed Doppler pulmonary flow waves (21) and the maximum velocity of continuous Doppler tricuspid regurgitation (41). Both methods have been shown to allow for satisfactory estimates of pulmonary artery pressures (26), with the advantage of a higher recovery rate of good quality signals for pulmonary flow waves in case of no or only mild pulmonary hypertension, as seen at high altitudes (22, 26). In addition, the measurements were repeated at exercise to refine the measurement of pulmonary vascular resistance by measurements of pressures at two different flows (25).

A possible explanation for the discrepancy between the present results and those reported by Teppema et al. (36) may be in the time course of hypoxia-induced pulmonary hypertension. Previous studies in normal subjects indicate that the reversibility of hypoxia-induced pulmonary hypertension with oxygen administration decreases rapidly over time, with no return to baseline already after a few hours, and marked loss of reversibility after only a few days at high altitudes (9, 15, 23). These observations are suggestive of early progression from hypoxic constriction to remodeling and explain the loss or decreased efficacy of acute vasodilating interventions. However, it would be interesting to see if higher doses of acetazolamide would be able to reverse established hypoxic pulmonary hypertension.

Acetazolamide in normoxic conditions has been reported either to decrease (10, 31) or to leave unchanged (33, 35) aerobic exercise capacity. Acetazolamide-induced decrease in exercise capacity has been explained by relative dehydration (3, 5) and muscle acidosis due to impaired buffer capacity (19). The effects of acetazolamide on hypoxic exercise capacity has been reported variably, with decreased (4, 13, 16), increased (24, 31), or unchanged VO2max and maximal workload (10, 33). These discrepant results are related to variable experimental conditions, dose regimens, altitude acclimatization, exercise mode, and degree of AMS during exercise testing. In better standardized exhaustive constant-work rate, one-leg knee-extension exercise compared with placebo, acetazolamide impaired endurance performance at sea level but not at altitude, which the authors explained by offsetting secondary effects of acidosis and increased arterial oxygenation (10).

In the present study, we tried to limit acetazolamide-induced dehydration by liberal and unlimited intake of fluid and food. HR and Q were unchanged compared with placebo-treated controls. However, we cannot exclude that isosmotic hypovolemia previously reported after intake of acetazolamide (4) could have affected our results. On the other hand, the finding of absence of effect of acetazolamide on maximum workload and VO2max is in keeping with previous work (10, 33). The maximum RER was decreased, which has also been previously reported (31). This could be explained by altered VCO2 kinetics, which could also have delayed the anaerobic threshold as measured by the V-slope method, even though there are data suggesting that the intake of the drug does not delay the appearance of lactic acid in the blood (30). We found a significant correlation between increased SO2 and anaerobic threshold VO2, but this is of uncertain causality.

In summary, acetazolamide at the upper doses recommended for the treatment of AMS does not affect pulmonary vascular resistance or maximum aerobic exercise capacity in subjects acclimatized to high altitude. Associated decrease in the RER may be due to altered VCO2 kinetics.

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REFERENCES


