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doi: 10.1152/japplphysiol.00180.2007

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

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1Laboratory of Physiology, Faculty of Medicine, Free University of Brussels, Brussels; 2Department of Cardiology, Erasme University Hospital, Brussels, Belgium; 3Laboratory of Physiology, University of Bordeaux 2, Bordeaux, France; 4Department of Pneumology, St. Elisabeth Hospital, Namur, Belgium; and 5Laboratory of Physiology, Institute of Sports and Physiotherapy, Free University of Brussels, Belgium

Submitted 12 February 2007; accepted in final form 28 June 2007

Faoro V, Huez S, Giltaire S, Pavelescu A, van Osta A, Moraine J-J, Guenard H, Martinot J-B, Naeije R. Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes. J Appl Physiol 103: 1161–1165, 2007. First published July 5, 2007; doi:10.1152/japplphysiol.00180.2007.—Aerobic exercise capacity is decreased at altitude because of combined decreases in arterial oxygenation and in cardiac output. Hypoxia pulmonary vasoconstriction could limit cardiac output in hypoxia. We tested the hypothesis that acetazolamide could improve exercise capacity at altitude by an increased arterial oxygenation and an inhibition of hypoxic pulmonary vasoconstriction. Resting and exercise pulmonary artery pressure (Ppa) and flow (Q) (Doppler echocardiography) and exercise capacity (cardiopulmonary exercise test) were determined at sea level, 10 days after the arrival on the Bolivian altiplano, at Huayna Potosi (4,700 m), and again after the intake of 250 mg acetazolamide vs. a placebo three times a day for 24 h. 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 (V̇O2max). Acetazolamide had no effect on Ppa/Q plots but increased arterial O2 saturation at rest from 84 to 87% (P < 0.05) and at exercise from 79 to 83% (P < 0.05, and O2 consumption at the anaerobic threshold (V̇O2anaer) from 21 ± 5 to 25 ± 5 ml·min⁻¹·kg⁻¹ (P < 0.01). However, acetazolamide did not affect V̇O2max (from 31 ± 6 to 29 ± 7 ml·kg⁻¹·min⁻¹), and the maximum respiratory exchange ratio decreased from 1.2 ± 0.06 to 1.05 ± 0.03 (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.

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-year-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 moderate 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...
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, \( O_2 \) 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.

double-blind and in a random sequence. The dose of acetazolamide was 250 mg three times per day for 24 h. This dose had been decided on the basis of the upper range of doses recommended for the treatment of acute mountain sickness (AMS) (1). The subjects were requested to drink 1.5 liters of water within the hour preceding the echocardiographic examination to optimize the Doppler signals.

Clinical measurements. Systemic arterial pressure (Psa) was measured by sphygmomanometer, with mean pressure calculated as diastolic pressure + one-third pulse pressure. A three-lead ECG was used to measure heart rate (HR). SO2 was measured by pulse oximetry (Konica Minolta Pulsox-3i; Konica Minolta Sensing, Osaka, Japan), which was tested and calibrated following the manufacturer’s recommendations. Particular attention was paid to quality of the signal, especially during exercise, as it is known that accuracy and precision of pulse oximetry at exercise may be decreased by local perfusion (40). The presence of AMS was assessed by use of the Lake Louise consensus scoring system (28), which was obtained just before echocardiographic examination.

Echocardiography. Echocardiography was performed using a portable ultrasound system equipped with a 2.5-MHz probe (Cypress, Acuson/Siemens, Erlangen, Germany). Recordings were stored on optical disks and analyzed by two independent cardiologists experienced in echocardiography and blinded to the study. Q was estimated from left ventricular outflow tract cross-sectional area and continuous Doppler velocity-time integral measurements. Mean pulmonary artery pressure (Ppa) was calculated from the pulsed Doppler pulmonary artery flow acceleration time (AT) (21). Systolic Ppa was estimated on the basis of the upper range of doses recommended for the treatment of acute mountain sickness (AMS) (1). The subjects were randomized and in a random sequence. The dose of acetazolamide had no effect.

CPET. The CPET was performed in an erect position on an electronically braked cycle ergometer (Monark, Ergomedic 818 E, Vansbro, Sweden) with breath-by-breath measurements, through a tightly fitted facial mask, of ventilation (\( V_1 \)), \( O_2 \) uptake (\( V_{O_2} \)), and \( CO_2 \) output (\( V_{CO_2} \)) using a Cardiopulmonary Exercise System (Oxycon Mobile, Jaeger, Hoechberg, Germany). After 3-min warmup at 0 W, the work rate was increased by 15–30 W according to previous CPET and predicted decrease by ~35% at high altitude so that the test would last for 10–12 min (38). Maximum \( V_{O_2} \) (\( V_{O_2\text{max}} \)) was defined as the \( V_{O_2} \) measured during the last 20 s of peak exercise. The respiratory exchange ratio (RER) was calculated as \( V_{CO_2}/V_{O_2} \), and \( O_2 \) pulse as \( V_{O_2}/HR \). The ventilatory equivalents for \( CO_2 \) (\( Ve/V_{CO_2} \)) were calculated by dividing \( V_{CO_2} \) by \( V_{O_2} \). The anaerobic threshold was estimated by the V-slope method (38).

Statistics. Results are presented as means ± SE. The statistical analysis consisted in a two-way ANOVA. When the F-ratio of the ANOVA reached a P < 0.05 critical value, paired or unpaired modified Student’s t-tests were applied as indicated to compare specific situations (39). Correlations were calculated by linear regression analysis.

RESULTS

Altitude exposure was well tolerated by the participants of the study, with minimal and transient increases in Lake Louise scores in La Paz. The day after arrival at the Potosí (4,700 m), the Lake Louise scores were increased to 4.5 ± 3, to decrease again 24 h later to 2.1 ± 2 in the placebo-treated subjects and to 3.0 ± 3 in the acetazolamide-treated group.

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>( V_{O_2\text{max}}, \text{ ml.kg}^{-1}\cdot\text{min}^{-1} )</td>
<td>41±10</td>
<td>31±5†</td>
</tr>
<tr>
<td>( V_{E\text{ max}}, \text{ 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>( O_2 ) pulse, \text{ ml/beat}</td>
<td>16±7</td>
<td>12±4*</td>
</tr>
<tr>
<td>( V_{O_2} ) at VT, \text{ ml.kg}^{-1}\cdot\text{min}^{-1} )</td>
<td>29±10</td>
<td>21±4*</td>
</tr>
<tr>
<td>Exercise ( SO_2, % )</td>
<td>97±2</td>
<td>80±5§</td>
</tr>
</tbody>
</table>

Values are means ± SD. Wmax, maximum workload; \( V_{O_2} \), \( O_2 \) uptake; \( V_{O_2\text{max}} \), maximum \( O_2 \) uptake; \( V_{E\text{ max}} \), 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.

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 a placebo (HA pl). Vertical and horizontal bars represent SE. Values of P are related to changes in mean Ppa (NS indicates no differences). High altitude shifted Ppa/Q plots to higher pressures, and the intake of a placebo had no effect.

Fig. 2. Mean Ppa vs. Q plots in normoxia, in high altitude 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.
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 exposure was associated with higher VO2max, workload, HR, O2 pulse, and RER. At the anaerobic threshold, VO2 was decreased (Table 2) and VE/VO2 increased.

Effects of acetazolamide. In the placebo group, an additional day at 4,700 m was associated with unchanged resting So2, Ve, HR, Q, AT, and TR (Table 3) and maximum workload, VO2, Ve, RER, HR, O2 pulse, So2, Ve/VO2, or anaerobic threshold workload, VO2, and TR (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 Ve but otherwise unchanged HR, Q, AT, and TR (Table 3). Acetazolamide increased workload, VO2, Ve, and HR at the anaerobic threshold but had no effect on VO2max or maximum workload, HR, and O2 pulse, and increased maximum exercise So2 and Ve/VO2 (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).

Changes in workload and VO2 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,
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 acetazolamide was reported after the intake of 250 mg of the drug three times per day during 3 days and estimated 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 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 VO2 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 VO2 kinetics.

ACKNOWLEDGMENTS

The technical assistance of Stéphane Demol (Erasme Hospital, Brussels, Belgium) and Stéphane Denison (St. Elisabeth Hospital, Namur, Belgium) was greatly appreciated.

We also thank M. Martiot from Medisoft (Dinant, Belgium) for help. Dr. M. Ajata from the Dept. of Pneumology, Santa Cruz de la Sierra, Bolivia, provided administrative and technical assistance in the preparation of the experiments.

We thank Siemens, Erlangen, Germany, for the loan of the portable Acuson echocardiographic device.

REFERENCES


