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Original Article

Acetazolamide pre-treatment before ascending to high altitudes: when to start?

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Abstract: Hypoxia is the main responsible factor initiating the symptoms of acute mountain sickness (AMS) in susceptible individuals. Measures that improve oxygenation and/or hasten acclimatization like pre-treatment with acetazolamide will prevent the development of AMS. We hypothesized that pre-treatment with acetazolamide the day before arrival at high altitude would elicit improved oxygenation compared to placebo not until the second day of high-altitude exposure. Fifteen study participants were randomly assigned in a double blind fashion to receive placebo or acetazolamide (2 × 125 mg) before (10 hours and 1 hour) exposure to high altitude (Monte Rosa plateau, 3480 m). Beside AMS scoring, heart rate, minute ventilation, and blood gas analyses were performed during rest and submaximal exercise at low altitude and on day 1, 2 and 3 at high altitude. From low altitude to day 1 at high altitude changes of pH (7.41 ± 0.01 vs. 7.48 ± 0.04) and HCO_3 (24.0 ± 0.46 vs. 24.6 ± 2.6 mmol/L) within the placebo group differed significantly from those within the acetazolamide group (7.41 ± 0.01 vs. 7.41 ± 0.02; 23.6 ± 0.38 vs. 20.7 ± 1.8 mmol/L) ($P < 0.05$). AMS incidence tended to be lower with acetazolamide ($P < 0.1$). From low altitude to day 2 at high altitude changes of paO_2 within the placebo group (75.3 ± 5.4 vs. 40.5 ± 3.4 mmHg) differed significantly from those within the acetazolamide group (76.5 ± 4.5 vs. 48.2 ± 4.9 mmHg) ($P < 0.05$). In conclusion, pre-treatment with low-dose acetazolamide on the day before ascending to high altitude tended to reduce AMS incidence on the first day at high altitude but improved oxygen availability to tissues not until the second day of exposure. Therefore, it is suggested that the beginning of pre-treatment with low-dose acetazolamide at least two days before arrival at high altitude, in contrast to usual recommendations, would be of greater beneficial effect on AMS development.

Keywords: Acute mountain sickness, prevention, low-dose acetazolamide, pre-treatment

Introduction

When ascending to high altitudes the decrease of barometric pressure is paralleled by a decreased partial pressure of inspired oxygen (PiO_2), a drop of alveolar pressure of oxygen (PAO_2) and of arterial oxygen pressure (PaO_2) resulting in diminished oxygen availability at the tissue level (hypoxia). Hypoxia is clearly the main responsible factor initiating the symptoms of acute mountain sickness (AMS) in susceptible individuals [1].

The prevalence of AMS depends on the absolute altitude reached and varies from about 10% on mountain huts in the Alps below 3,000 m [2, 3] to up to more than 80% at Mount Kilimanjaro (5,895 m) [4]. The symptoms of AMS include headache, anorexia or vomiting, dizziness, fatigue, and insomnia [5]. Although AMS is usually benign and self-limiting, the symptoms may affect well-being as well as motor and cognitive function [6, 7], and in some cases AMS can progress to potentially fatal conditions such as high altitude pulmonary or/and cerebral oedema [5, 8].

Increases in minute ventilation and cardiac output are acute physiological responses to the drop in PaO_2 which are partly counteracting the decrease in PiO_2 and the resulting hypoxia [5]. During the first days at high altitude, ventilatory acclimatization results in progressive hyperventilation and improved oxygenation [9]. Measures that improve oxygenation and/or hasten acclimatization like pre-treatment with acetazol-

Table 1. Baseline characteristics of the study participants

	Placebo group N = 7	Acetazolamide group N = 8
Age (yrs)	44.7 ± 8.6	43.6 ± 13.4
Height (cm)	170.7 ± 5.4	173.4 ± 4.2
Weight (kg)	64.5 ± 12.5	68.3 ± 8.4
Sex (male/female)	4/3	4/4
HR (b/min)	67.6 ± 9.0	69.3 ± 8.9
SpO_2 (%)	97.0 ± 1.0	97.1 ± 0.8

HR, Heart rate; SpO_2, arterial oxygen saturation by pulsoximetry.

amide will prevent the development of AMS [10-13]. Acetazolamide is a potent carbonic anhydrase inhibitor causing diuresis and renal bicarbonate loss, increasing minute ventilation and oxygenation by enhanced central chemoreceptor output, and improving sleep quality by attenuation of periodic breathing by inhibition of peripheral chemoreceptors [14]. Acetazolamide is the only medication approved by The US Food and Drug Administration (FDA) for AMS prevention and, therefore, the drug of choice for this purpose [15]. Most studies investigating prophylactic effects of acetazolamide on AMS started intake of acetazolamide at high altitude or the day before arrival at high altitude [16]. Also recent guidelines recommend a dose of 125 mg to 250 mg acetazolamide taken twice daily begun the day before arrival at high altitude [8, 10, 11]. However, an early study performed by Cain and Dunn demonstrated that effects of pre-treatment with acetazolamide prior to high-altitude exposure (simulated hypobaric hypoxia) peaked not before the second day at high altitude [17]. However, AMS symptoms usually manifest between 6 and 12 hours at high altitude [5, 18]. To our knowledge, there is no randomized controlled trial investigating the effects of pre-treatment with low-dose acetazolamide (2 × 125 mg) on ventilation and arterial blood gases during the first 3 days at real high altitude. Based on the findings by Cain and Dunn [17] we hypothesized that this kind of pre-treatment would elicit improved oxygenation compared to placebo not until the second day of high-altitude exposure. If true, the question would arise how to change pre-treatment modality with acetazolamide to achieve peak effects on the first day of altitude exposure.

Methods

Fifteen volunteers with a history of AMS were recruited for this study. Exclusion criteria were any type of acute or chronic illness, regular smoking (> 5 cigarettes per day), regular medications, and sojourns at an altitude > 2500 meters during the previous 4 weeks, age < 20 or > 60 years, pregnancy or lactation, and hemoglobin concentration < 12.0 g/dL. Written informed consent was obtained from each subject. The study was approved by the ethics committee of the Medical University of Innsbruck.

Study participants were randomly assigned in a double blind fashion to receive placebo or acetazolamide (for baseline characteristics see **Table 1**) before exposure to high altitude. After routine examination and submaximal exercise testing at low altitude (600 m), subjects were transported by car and cable car to high altitude for 3 days (Monte Rosa plateau, Italy, 3480 m). Subjects received two tablets (2 × 125 mg acetazolamide or placebo) to be taken 10 hours and 1 hour before arrival at high altitude. Tablets were administered by a person who was not involved in evaluations and the timely intake of tablets has been checked. During high-altitude exposure, resting measurements were conducted in the evening of the first, the second and the third day at high altitude. Resting measurements were performed after a 10-minute rest in a sitting position and included the determination of heart rate (chest belt, Polar, Finland), minute ventilation (K4, Cosmed, Italy), analysis of blood gases from the arterialized capillary blood (Opti1, Opti Medical, USA), and the evaluation of AMS symptoms according to the Lake-Louise-Score [19]. Subjects were considered to suffer from AMS when the score was ≥ 3 [19]. Subsequently, subjects exercised for 3 minutes by stepping 90 times up and down a 24 cm step, during which heart rate (chest belt, Polar, Finland), gas exchange (K4, Cosmed, Italy), and oxygen saturation (Onyx 9500 finger pulse oximeter, Nonin Medical Inc, USA) were continuously monitored [20]. Samples for blood gas analyses were taken immediately after stopping exercise. Participants had no physical activity during the first day of altitude exposure. On the second and third day, they climbed up to about 3800 meters within 2.5 to 3 hours at an individual perceived intensity of about 14 on the Borg Scale [21]. Nutrition and sleep were standardized during the study period.

Statistical analyses were conducted by PASW Statistics 18 (IBM, Austria). Normality in the distribution of data was tested by the

Table 2. Resting values of ventilation and blood gases at low (LA) and high altitude (HA) for the placebo and the acetazolamide group

	Placebo group				Acetazolamide group				ANOVA
	LA	HA1	HA2	HA3	LA	HA1	HA2	HA3	*P*
VE (L/min)	10.5 ± 2.9	13.2 ± 2.5	14.6 ± 2.5	16.1 ± 3.8	11.1 ± 2.3	14.1 ± 2.5	17.5 ± 3.3^{t}	16.0 ± 3.1	0.04
SpO_2 (%)	97.0 ± 1.0	86.9 ± 2.6	88.9 ± 3.9	89.0 ± 3.7	97.1 ± 0.8	87.4 ± 3.3	89.8 ± 2.9	89.8 ± 2.8	0.94
pH	7.41 ± 0.01	7.48 ± 0.04	7.46 ± 0.04	7.48 ± 0.04	7.41 ± 0.01	7.41 ± 0.02*	7.44 ± 0.03	7.48 ± 0.02	0.004
$PaCO_2$ (mmHg)	39.2 ± 0.82	34.2 ± 2.5	31.6 ± 1.8	28.8 ± 2.9	38.6 ± 1.6	33.6 ± 3.1	28.8 ± 3.1	27.6 ± 2.9	0.20
PaO_2 (mmHg)	75.3 ± 5.4	43.6 ± 2.1	40.5 ± 3.4	45.7 ± 3.8	76.5 ± 4.5	45.8 ± 3.6	48.2 ± 4.9*	47.3 ± 4.8	0.02
HCO_3 (mmol/L)	24.0 ± 0.46	24.6 ± 2.6	22.0 ± 1.8	20.9 ± 2.6	23.6 ± 0.38	20.7 ± 1.8*	19.0 ± 2.5^{t}	19.7 ± 1.6	0.02

VE, Minute ventilation; SpO_2, arterial oxygen saturation; PaO_2, arterial pressure of oxygen; $PaCO_2$, arterial pressure of carbon dioxide; HCO_3, arterial bicarbonate concentration. *Significantly different changes from low altitude (LA) compared to the placebo group. ^{t}Different changes from low altitude (LA) by trend when compared to the placebo group.

Table 3. Submaximal exercise responses at low (LA) and high altitude (HA) within the placebo and the acetazolamide group

	Placebo group				Acetazolamide group				ANOVA
	LA	HA1	HA2	HA3	LA	HA1	HA2	HA3	*P*
HR (b/min)	125 ± 12	144 ± 14	140 ± 12	140 ± 12	126 ± 14	141 ± 19	142 ± 14	139 ± 15	0.89
[La] (mmol/L)	2.9 ± 0.6	4.3 ± 0.9	4.0 ± 0.7	3.5 ± 1.0	3.0 ± 0.5	3.4 ± 0.4*	3.6 ± 1.0^{t}	3.2 ± 1.1	0.02
VE (L/min)	42.7 ± 7.8	64.2 ± 19.3	70.5 ± 19.2	73.6 ± 21.2	45.6 ± 6.7	64.7 ± 12.0	70.9 ± 8.8	68.8 ± 9.9	0.87
SpO_2 (%)	95.2 ± 1.5	74.9 ± 5.9	76.1 ± 4.1	74.4 ± 3.7	95.6 ± 1.6	74.5 ± 4.6	78.6 ± 4.7	78.4 ± 3.4	0.27
pH	7.37 ± 0.03	7.46 ± 0.04	7.47 ± 0.04	7.48 ± 0.04	7.39 ± 0.02	7.42 ± 0.02*	7.41 ± 0.05^{t}	7.46 ± 0.04	0.04
$PaCO_2$ (mmHg)	41.3 ± 3.2	33.1 ± 2.2	29.7 ± 3.0	27.9 ± 2.7	39.5 ± 3.1	33.2 ± 3.6	31.3 ± 3.3	27.9 ± 3.4	0.72
PaO_2 (mmHg)	78.2 ± 6.3	34.3 ± 5.4	34.4 ± 2.7	33.2 ± 2.6	76.2 ± 3.6	36.9 ± 2.6^{t}	36.2 ± 3.6^{t}	36.2 ± 2.7	*0.09*
HCO_3 (mmol/L)	23.4 ± 2.2	22.7 ± 3.0	21.3 ± 2.3	20.0 ± 2.5	23.5 ± 2.5	19.8 ± 2.8^{t}	19.1 ± 2.4	19.0 ± 2.6	*0.09*

HR, Heart rate; [La], lactate concentration; VE, minute ventilation; SpO_2, arterial oxygen saturation; PaO_2, arterial pressure of oxygen; $PaCO_2$, arterial pressure of carbon dioxide; HCO_3, arterial bicarbonate concentration. *Significantly different changes from low altitude (LA) compared to the placebo group. ^{t}Different changes from low altitude (LA) by trend when compared to the placebo group.

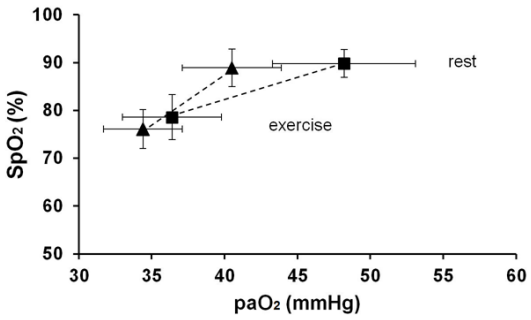

Figure 1. Relationship between SpO_2 and PaO_2 within the placebo and the acetazolamide group during rest and submaximal exercise on the second day at high altitude. Placebo group is represented by triangles and the acetazolamide group by squares.

Kolmogorov-Smirnov test. A mixed-design ANOVA was performed to analyze interaction effects (pre-treatment x time). T-tests with Bonferroni correction were used to evaluate different changes between groups from low altitude to the first, second and third day at high altitude. Spearman correlation analyses were used to test the relationship between AMS scores and physiological variables. A P value < 0.05 was considered to indicate statistical significance. Data are presented as mean ± SD.

Results

On day one of the altitude exposure AMS score was negatively related to PaO_2 (r = -0.720, P = 0.002) and positively to pH (r = 0.64, P = 0.01). A trend towards a reduced AMS incidence was found in the acetazolamide group where only 2 out of 8 suffered from AMS compared to 5 out of 7 within the placebo group (P = 0.07). During the first night or in the morning of the second day at high altitude, subjects suffering from AMS were treated with ibuprofen (600 mg). In the late afternoon of the second day at high altitude all participants were free of AMS. ANOVA revealed significant interaction effects between pre-treatment and time on resting values of minute ventilation, PaO_2, HCO_3, and pH (**Table 2**). From low altitude to day 1 at high altitude changes of pH (7.41 ± 0.01 vs. 7.48 ± 0.04) and HCO_3 (24.0 ± 0.46 vs. 24.6 ± 2.6 mmol/L) within the placebo group differed significantly from those within the acetazolamide group (7.41 ± 0.01 vs. 7.41 ± 0.02; 23.6 ± 0.38 vs. 20.7 ± 1.8 mmol/L) (P < 0.05). From low altitude to day 2 at high altitude changes of PaO_2 within the placebo group (75.3 ± 5.4 vs. 40.5 ± 3.4 mmHg) differed significantly from those within the acetazolamide group (76.5 ± 4.5 vs. 48.2 ± 4.9 mmHg) (P < 0.05). Moreover, a tendency of a larger increase in minute ventilation and a more pronounced decrease in HCO_3 within the acetazolamide group compared to the placebo group occurred from low altitude to day 2 at high altitude (P < 0.1) (**Table 2**).

ANOVA revealed significant interaction effects between pre-treatment and the duration of altitude exposure on blood lactate concentration and pH at submaximal exercise and a tendency of such interaction effects on PaO_2 and HCO_3 (**Table 3**). Blood lactate concentration and pH increased to a lower extent from low altitude to day 1 at high altitude within the acetazolamide group compared to the placebo group (P < 0.05). These changes still tended to be different between groups on day 2 at high altitude. The decrease of PaO_2 during submaximal exercise from low altitude to day 1 and day 2 at high altitude tended to be less pronounced within the acetazolamide group compared to the placebo group (P < 0.1). HCO_3 during submaximal exercise tended more to decrease from low altitude to day 1 at high altitude within the acetazolamide group when compared to the placebo group (P < 0.1) (**Table 3**). There were no different between-group changes from low altitude to day 3 at high altitude. **Figure 1** demonstrates the relationship between PaO_2 and SpO_2 at rest and during exercise on day 2 at high altitude.

Discussion

The presented findings demonstrate that pre-treatment with acetazolamide (2 × 125 mg) compared to placebo resulted in decreased resting HCO_3 and pH values (arterialized capillary blood) on the first day and increased PaO_2 values on the second day of subsequent high-altitude exposure (3,480 m). On the first day at high altitude these changes were accompanied by lower increases in blood lactate concentration during submaximal exercise when pre-treated with acetazolamide. Pre-treatment effects had disappeared on day 3 at high altitude. Since PaO_2 and pH values were correlated with AMS scores, acetazolamide pre-treatment might have inhibited AMS development by inducing relative metabolic acidosis and

improved oxygen availability. It cannot be excluded that sleep quality might also have contributed to the tendency of lower AMS incidence with acetazolamide [14]. The preventive effects on AMS would likely have been more pronounced with the use of a larger acetazolamide dose, i.e. 2 × 250 mg [22]. As hypothesized, after pre-treatment with acetazolamide, resting PaO_2 was highest on the second day at high altitude when AMS had already disappeared. Thus, the question arises whether an earlier beginning with pre-treatment would have more effectively prevented AMS development?

Acetazolamide is a potent carbonic anhydrase inhibitor causing renal bicarbonate excretion and metabolic acidosis [12]. In turn, metabolic acidosis diminishes the inhibitory effect of hypoxia-induced respiratory alkalosis, increases minute ventilation and improves PaO_2 (12, 14]. In the present study, pre-treatment with acetazolamide (2 × 125 mg) compared to placebo did not increase resting minute ventilation on the first day at high altitude but tended to enhance ventilation on the second day. This may partly be due to the relatively low dose of acetazolamide. However, a more important explanation may be provided by the observation that the hypoxic ventilatory response was suppressed by acute acetazolamide by inhibition of peripheral chemoreceptors [13]. Acetazolamide related changes of ventilation and blood gases on the second day at high altitude might most likely be attributed to the somewhat delayed effects on the lowering of pH in the cerebrospinal fluid subsequent to renal bicarbonate diuresis [14, 17]. In fact, this delayed response to acetazolamide pre-treatment has already been reported in the early study by Cain and Dunn [17].

The effects of acetazolamide on submaximal exercise were small but the lower concentrations of blood lactate were found on day 1 (trend on day 2) at high altitude. These findings are in line with those of Jonk et al. but these authors demonstrated improved arterial oxygenation during exercise, due to greater minute ventilation and more efficient pulmonary gas exchange which was not observed in our study [23]. Differences between both studies may partly be explained by different acetazolamide doses (2 × 125 mg vs. 3 × 250 mg). It seems likely that it was the lower alkalosis with acetazolamide in our study that impacted on muscle metabolism during short-term exercise at altitude [24]. In turn, lower production of lactic acid with acetazolamide pre-treatment might explain the smaller right shift of the oxygen-haemoglobin dissociation curve during exercise when compared to placebo (**Figure 1**).

The most important limitation that has to be addressed is the fact that AMS symptoms were treated with ibuprofen and have disappeared on the second day at high altitude. Thus, we can only speculate that the higher PaO_2 values found on the second day at high altitude after pre-treatment with acetazolamide would have more effectively prevented AMS development. This assumption however, is supported by the correlation between AMS scores and PaO_2 demonstrated on the first day at altitude. Additionally, although all subjects performed the same physical activity on day 2 and day 3 at altitude some differently modulating effects of exercise cannot be excluded.

In conclusion, pre-treatment with low-dose acetazolamide (2 × 125 mg) one day before ascent to high altitude tended to reduce AMS incidence and enhance tolerance to submaximal exercise on the first day at high altitude (3,480 m) but did not improve oxygen availability to tissues before the second day of exposure. Therefore, we suggest that the beginning of pre-treatment with low-dose acetazolamide at least two days before arrival at high altitude, in contrast to usual recommendations, would have greater beneficial effect on AMS development. However, this has to be confirmed by future studies.

Disclosure of conflict of interest

None.

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