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Original Research

OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASES

Patients With Obstructive Sleep Apnea Syndrome Benefit From Acetazolamide During an Altitude Sojourn

A Randomized, Placebo-Controlled, Double-Blind Trial

Yvonne Nussbaumer-Ochsner, MD; Tsogyal D. Latshang, MD; Silvia Ulrich, MD; Malcolm Kohler, MD; Robert Thurnheer, MD, FCCP; and Konrad E. Bloch, MD, FCCP

Background: **Many patients with obstructive sleep apnea syndrome (OSA) are unable or unwilling to use continuous positive airway pressure (CPAP) therapy when traveling to the mountains for work or recreation even though they risk pronounced hypoxemia and exacerbation of sleep apnea. Because the treatment of OSA at altitude has not been established, we tested the hypothesis that acetazolamide improves hypoxemia, sleep, and breathing disturbances in otherwise untreated patients with OSA at altitude.**

Methods: **Forty-five patients with OSA on long-term CPAP, median age 64 years, living at < 600 m underwent a placebo-controlled, double-blind, crossover trial randomized for the sequence of drug and altitude exposure (490 m, 1,860 m, and 2,590 m). Patients spent two 3-day periods at altitude and a 2-week wash-out period at < 600 m. At altitude, patients discontinued CPAP and received acetazolamide 2 × 250 mg daily or placebo. Polysomnography, vigilance, and symptoms were evaluated.**

Results: **At 490 m, off CPAP, median nocturnal oxygen saturation was 93%, and the apnea/hypopnea index was 51.2/h. On placebo at 1,860 m and 2,590 m, the corresponding values were 89% and 85% and 63.6/h and 86.2/h, respectively ($P < .01$ vs 490 m, both instances). On acetazolamide at 1,860 m and 2,590 m, oxygen saturation was higher (91% and 88%) and apnea/hypopnea indices were lower (48.0/h and 61.4/h) than on placebo ($P < .01$ all instances). Acetazolamide reduced nocturnal transcutaneous P_{CO_2}, improved sleep efficiency and subjective insomnia, and prevented excessive BP elevations at altitude.**

Conclusions: **In patients with OSA discontinuing CPAP during an altitude sojourn, acetazolamide improves oxygenation, breathing disturbances, and sleep quality by stimulating ventilation. Therefore, patients with OSA may benefit from acetazolamide at altitude if CPAP therapy is not feasible.**

Trial registry: **ClinicalTrials.gov; No.: NCT00714740; URL: www.clinicaltrials.gov**

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Abbreviations: AHI = apnea/hypopnea index; CPAP = continuous positive airway pressure; EMG = electromyogram; NREM = nonrapid eye movement; OSA = obstructive sleep apnea; OSLER = Oxford sleep resistance test; PB = barometric pressure; Pet_{CO_2} = end-tidal P_{CO_2}; Ptc_{CO_2} = transcutaneous P_{CO_2}; REM = rapid eye movement; Sp_{O_2} = oxygen saturation

Continuous positive airway pressure (CPAP) is currently the most effective therapy for the obstructive sleep apnea syndrome (OSA). It improves breathing disturbances, sleep quality, and daytime symptoms. Traveling to altitude for work and recreational activities is quite popular, but carrying a CPAP device is inconvenient, and electric power is not always available. Certain patients with OSA, therefore, discontinue CPAP during altitude sojourns, not being aware of the undesirable health effects of untreated sleep apnea under hypoxic conditions. Recently,[1] we showed that patients with OSA discontinuing CPAP during a stay in the Swiss mountains (at 1,860 m and 2,590 m) experienced an exacerbation of sleep-related breathing disturbances because of frequent central apneas/hypopneas, pronounced hypoxemia, impaired driving simulator performance, and elevated BP. Because CPAP may not provide optimal control of

central sleep apnea and because an alternative treatment of sleep apnea during altitude sojourns would be desirable, we evaluated whether acetazolamide, a carbonic anhydrase inhibitor, might be effective in this specific setting. Acetazolamide improves high-altitude periodic breathing and acute mountain sickness in healthy subjects,[2,3] and mitigates Cheyne-Stokes breathing in patients with heart failure.[4] Because patients with OSA have central apnea predominantly at altitude,[1] we reasoned that acetazolamide might improve their sleep-related breathing disturbances in this setting. We, therefore, performed a randomized, double-blind, placebo-controlled, crossover trial evaluating the hypothesis that acetazolamide alone improves nocturnal hypoxemia and reduces sleep and breathing disturbances in patients with OSA residing at low altitude and discontinuing CPAP during a temporary altitude sojourn.

Materials and Methods

Design Overview

We performed a randomized, placebo-controlled, double-blind, crossover trial to evaluate the effect of acetazolamide on nocturnal breathing, sleep, and daytime performance in patients with untreated OSA at altitude. The trial comprised two altitude sojourns of 3 days each, separated by a 2-week washout period spent at < 600 m (Fig 1). In the 3 nights before and during the altitude sojourns, patients discontinued CPAP, but used it during washout. Patients were not allowed to drive a car or operate heavy machinery during the study period.

Setting and Participants

The study was performed in Zurich (490 m [1,608 ft]; barometric pressure [PB], 717 torr) and two locations in the Swiss Alps, Davos Schatzalp, 1,860 m (6,103 ft; PB, 607 torr) and Davos Jakobshorn, 2,590 m (8,498 ft; PB, 554 torr). Patients with OSA, 20 to 80 years old, both genders, living at an altitude of < 600 m on long-term CPAP were invited to participate. A prior diagnosis of OSA based on excessive sleepiness and an apnea/hypopnea index (AHI) > 20/h before initiation of CPAP had to be documented. Study inclusion required > 15 oxygen desaturations/h (> 3% dips) during an ambulatory pulse oximetry performed during the last of four nights of CPAP withdrawal allowing sleep-disordered breathing to return to untreated level.[5,6] Baseline polysomnography at Zurich had to show an AHI > 10/h with predominantly obstructive events. Exclusion criteria comprised unstable cardiovascular disease, any lung disease, renal failure, any disease thought to interfere with sleep quality, chronic rhinitis, previous upper airway surgery, and medication interfering with ventilation or sleep (acetazolamide, benzodiazepines, opioids, aspirin > 100 mg/d). Alcohol and more than one cup of coffee in the morning were not allowed during the study period. Patients were advised to continue their regular medications; patients with diabetes monitored their glucose levels as usual. The study was approved by the Cantonal Ethics Committee (EK-1522). Subjects gave written informed consent.

Randomization and Interventions

During altitude sojourns, patients took acetazolamide (2 × 250 mg daily) or identical-looking placebo capsules according to a randomized, double-blind, crossover design balanced for the order of medication. Medication was dispensed and labeled with a code that was not disclosed to patients and investigators until the conclusion of data analysis. A balanced design with regard to the order of altitude exposure was obtained by randomly assigning patients to four parallel groups with permuted sequences of stays at the different altitudes (Fig 1).

Outcomes

Polysomnography, including standard derivations, diaphragmatic surface electromyogram (EMG),[7] capnography of expired air, and transcutaneous P_{CO_2} (Ptc_{CO_2}),[8,9] was performed and scored as described previously[1] (e-Appendix 1). Briefly, obstructive apneas were differentiated from central apneas/hypopneas by means of nasal pressure swings, calibrated respiratory inductive plethysmography, and diaphragmatic surface EMG recordings. Obstructive apneas/hypopneas were identified by rib cage and abdominal asynchrony and persistent or increasing diaphragmatic EMG activity. Central apneas/hypopneas were identified by absent rib cage-abdominal asynchrony, no signs of inspiratory flow limitations (no flattening of nasal pressure contour), and reduced or absent diaphragmatic EMG activity.

Morning examinations comprised BP, pulse oximetry, and body weight. Vigilance was evaluated by the Oxford sleep resistance (OSLER) test during a 40-min session between 9:00 AM and 10:00 AM.[10] The time until seven successive responses to a light signal were missed (sleep resistance time) and the mean number of missed responses per minute were recorded.[11] Acute mountain sickness was assessed by the Environmental Symptoms Questionnaire cerebral score.[12] It consists of 11 questions evaluating symptoms of acute mountain sickness, rated from 0 (not at all) to 5 (extreme). A score > 0.7 of the weighted sum of responses is considered clinically relevant acute mountain sickness. Perceived insomnia was evaluated by asking patients to estimate the time spent awake during the night. Sleepiness was assessed by the Karolinska Sleepiness Scale.[13] Patients rated side effects of the study drug, such as paresthesias, unpleasant taste, or polyuria, on a scale from 0 to 3 (0 = absent to 3 = severe, forcing discontinuation of medication), and indicated any other side effects.

Statistics

Data are summarized as medians (quartiles) to account for nonnormal data distribution. The effects of acetazolamide vs placebo

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were evaluated by Wilcoxon matched pairs tests applying a Bonferroni correction and by computing mean differences with 95% CIs. The effects of altitude were evaluated by Friedman analysis of variance. Statistical significance was assumed at $P < .05$.

Primary outcomes were the AHI and nocturnal oxygen saturation (Spo_2). Minimally important differences were assumed as 10 events/h (SD, 20/h) and 2% (SD, 4%),[1] respectively, corresponding to moderate effect sizes of 0.5 in these outcomes.[14] Assuming a minimal number of 44 patients, the study was powered with 80% to detect minimally important differences in primary outcomes (α 0.05).

Results

Of 75 patients who applied for study participation, 49 met the inclusion criteria and were randomized (Fig 2). One patient had to withdraw from the study after the first night at 2,590 m because of an acute peripheral vestibulopathy. Data from three patients had to be excluded after study completion according to the predefined criteria, because baseline polysomnography at Zurich revealed an obstructive AHI < 10/h in two patients and predominant central sleep apnea in one patient. Data from 45 patients were available for analysis (Table 1).

Sleep Studies

Results of sleep studies are summarized in Table 2. Baseline studies of CPAP at 490 m revealed that

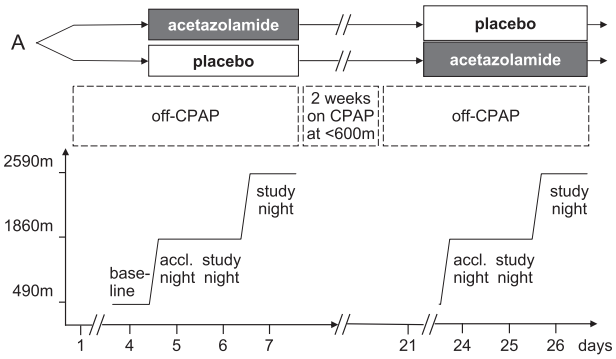

Figure 1. Study design. Patients underwent two altitude sojourns of 3 days each during which they were treated with acetazolamide and placebo according to a crossover design. CPAP was discontinued 3 days before and during study periods and resumed during a 2-week washout period in between. To control for a potential order effect of altitude exposure, patients were additionally randomized to four different study sequences A to D. Patients assigned to sequence A (shown here) stopped CPAP on day 1, underwent baseline evaluation on day 4 in Zurich and traveled to Davos, 1,860 m, on day 5 for acclimatization. On days 6 and 7, patients underwent studies at 1,860 m and 2,590 m. They resumed CPAP for the following 2 weeks at < 600 m. On day 21, patients stopped CPAP again and entered the second study period. Patients randomized to sequence B underwent a similar protocol but the order of stay at 1,860 m and 2,590 m on days 6 and 7 and 25 and 26 was reversed. Sequences C and D were similar to A and B except that baseline evaluations were performed after the two altitude stays, another 2-week washout period at < 600 m, and 3 nights off CPAP. accl. = acclimatization; CPAP = continuous positive airway pressure.

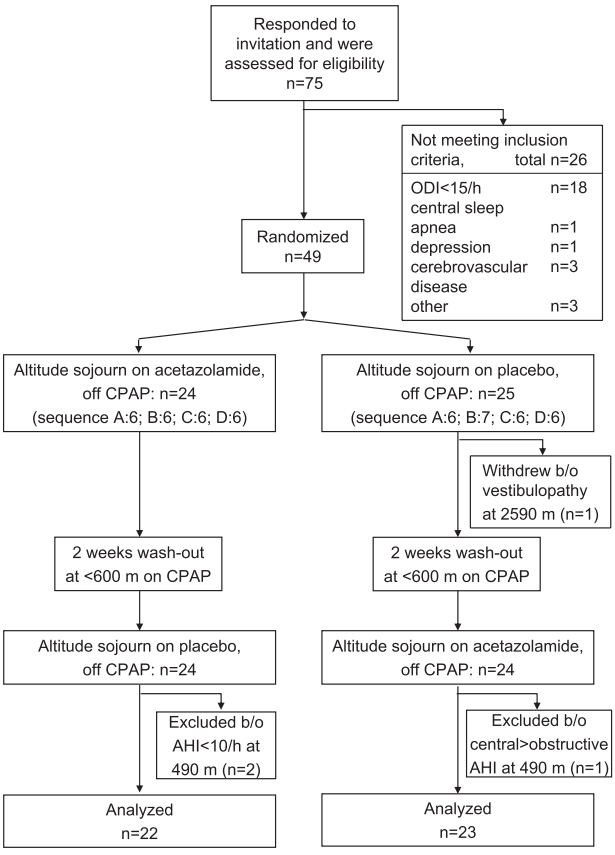

Figure 2. Patient flow. Of 75 eligible patients, 49 could be randomized. Twenty-four were treated first with acetazolamide and second with placebo; 25 were treated first with placebo and second with acetazolamide. Within the two groups, patients were randomized to sequences of altitude exposure A to D with corresponding numbers of patients indicated. Data from a total number of 45 patients (22 and 23) were included into the analysis. AHI = apnea/hypopnea index; b/o = because of; ODI = oxygen desaturation index. See Figure 1 legend for expansion of other abbreviations.

patients had severe OSA. According to the inclusion criteria, central apneas/hypopneas (ie, the total absence of any movement of the chest/abdomen wall) were observed only occasionally. At 1,860 m and 2,590 m on placebo, the total AHI increased significantly to medians of 124% and 168% of the value at 490 m, respectively, which was mainly related to an increase in central events (Fig 3, Table 2). Acetazolamide prevented the increase in total AHI at 1,860 m and alleviated the increase at 2,590 m. This was mainly related to a reduction in central AHI in nonrapid eye movement (NREM) sleep (e-Table 1). Compared with 490 m, Spo_2 was significantly reduced at 1,860 m and even more so at 2,590 m on placebo. On acetazolamide, Spo_2 was significantly higher at the corresponding altitude (Table 2). Hypoxemia was most pronounced during rapid eye movement (REM) sleep (e-Table 1). $PtcCO_2$ was progressively reduced with increasing altitude, in particular during studies

Table 1—*Patient Characteristics*

Characteristic	No. (%)
No. patients, M (F)	42 (3)
Age, median (quartiles), y	64 (58, 66)
BMI, median (quartiles), kg/m^2	31.7 (28.0, 36.1)
Comorbidities	
Arterial hypertension	31 (69)
Hypercholesterolemia	13 (29)
Diabetes mellitus	6 (13)
Time on CPAP therapy, median (quartiles), mo	28 (5, 70)
Concurrent medication	27 (60)
Antihypertensive medication[a]	13 (29)
Diuretics	13 (29)
Lipid-lowering therapy	13 (29)
Sulfonylureas	2 (4)
Insulin	1 (2)

Data from 45 patients were available for analysis. CPAP = continuous positive airway pressure; F = female; M = male.
[a]Includes angiotensin converting enzyme-inhibitor/angiotensin-II antagonist, β-blocker, and calcium channel blocker.

on acetazolamide (Table 1), with lowest values at 2,590 m on acetazolamide during NREM sleep (e-Table 1). Multiple logistic regression analysis with quartiles of the AHI and oxygen desaturation index as dependent and sequence A to D (Figs 1, 2), altitude, and type of drug as independent variables, respectively, did not reveal any order effect (data not shown).

To evaluate potential mechanisms involved in the reduction of central apneas/hypopneas by acetazolamide, apnea thresholds and CO_2 reserves were determined during NREM sleep. This was feasible in 17 patients at 1,860 m and in 16 patients at 2,590 m in whom central apneas/hypopneas occurred even on acetazolamide. Patients included and not included in this analysis did not differ with regard to the baseline AHI, Spo_2, and $PtcCO_2$, respectively. Acetazolamide resulted in a parallel reduction of the eupneic end-tidal Pco_2 ($PetCO_2$) and the Pco_2 apnea threshold (Fig 4, Table 3). Therefore, the CO_2 reserve was similar on acetazolamide and placebo. The cycle time of central events was longer on acetazolamide than on placebo at 1,860 m and 2,590 m, whereas the circulation time was unchanged by acetazolamide.

At 1,860 m and 2,590 m, sleep quality was significantly better on acetazolamide than on placebo, as reflected in a longer total sleep time, greater sleep efficiency, and a lower arousal index. Slow-wave sleep was reduced at 2,590 m compared with 490 m, independent of whether patients were on placebo or acetazolamide (Table 2).

Daytime Evaluation

The Karolinska sleepiness scale indicated that patients felt moderately sleepy in the morning (Table 4). They did not report more than very mild symptoms of acute mountain sickness. However, their BP and weight were significantly elevated at altitude, and this was prevented by acetazolamide (Table 4). Subjective sleep quality was improved by acetazolamide compared with placebo, as reflected in a reduced time that patients estimated to have spent awake during nights. OSLER tests did not reveal differences between tests at 490 m, 1,860 m, and 2,590 m, respectively, and there was no effect of acetazolamide. Table 5 summarizes the effects of acetazolamide in terms of mean differences in various outcomes.

The most commonly reported side effects of acetazolamide were paresthesias and unpleasant taste (Table 4). Side effects were generally mild to moderate

Table 2—*Sleep Studies*

Variable	Zurich (490 m)	Davos Schatzalp (1,860 m)		Davos Jakobshorn (2,590 m)		*P* Value (ANOVA)
		Placebo	Acetazolamide	Placebo	Acetazolamide	
Total sleep time, min	321 (257, 363)	372[a] (319, 420)	418[a,b] (358, 444)	344[a] (277, 423)	398[a,b] (355, 437)	$<10^{-5}$
Sleep efficiency, %	78 (59, 85)	72 (64, 81)	81[a,b] (70, 86)	66[a] (51, 81)	77[b] (67, 85)	$<10^{-3}$
NREM 1 + 2, %	86 (74, 92)	80 (74, 88)	84 (72, 92)	85[c] (79, 93)	88[a,c] (81, 93)	$<10^{-2}$
NREM 3 + 4, %	6 (1, 15)	6 (2, 16)	8 (1, 14)	4[a,c] (0, 8)	3[a,c] (0, 10)	$<10^{-5}$
REM, %	8 (4, 13)	12 (7, 15)	8[b] (3, 14)	9 (2, 17)	8 (4, 12)	.14
Arousal index, 1/h	44.9 (38.9, 68.0)	52.8 (40.7, 73.4)	47.3[b] (34.7, 61.6)	72.7[a,c] (55.2, 84.8)	54.9[a,b,c] (41.1, 83.1)	$<10^{-5}$
Spo_2, %	93 (92, 94)	89[a] (88, 91)	91[a,b] (89, 93)	85[a,c] (83, 88)	88[a,b,c] (85, 89)	$<10^{-5}$
$PtcCO_2$, mm Hg	50 (49, 50)	44[a] (42, 46)	39[a,b] (36, 43)	38[a,c] (35, 39)	36[a,b,c] (33, 39)	$<10^{-5}$
Total AHI, 1/h	51.2 (42.4, 72.2)	63.6[a] (53.6, 85.9)	48[b] (30.3, 62.4)	86.2[a,c] (67.2, 103.1)	61.4[a,b,c] (50.3, 83.8)	$<10^{-5}$
Obstructive AHI, 1/h	49.4 (41.4, 67.6)	42.5 (26.4, 72.2)	39.0[a] (20.5, 51.5)	55.5 (34.0, 75.0)	52.3[c] (34.9, 75.2)	$<10^{-5}$
Central AHI, 1/h	1.6 (0.5, 3.2)	16.2[a] (8.3, 24.7)	8.7[a,b] (4.4, 13.2)	23.4[a,c] (14.0, 44.5)	5.8[a,b] (1.2, 15.4)	$<10^{-5}$
Heart rate, 1/min	65 (61, 69)	67[a] (60, 74)	68[a] (61, 74)	66 (59, 70)	69[a] (61, 73)	<.025

Data from 45 patients were available for analysis. Data are presented as median (quartiles). AHI = apnea/hypopnea index; ANOVA = analysis of variance; NREM = nonrapid eye movement; $PtcCO_2$ = transcutaneous CO_2 pressure; REM = rapid eye movement; Spo_2 = oxygen saturation.
[a]$P < .05$ m vs 490 m.
[b]$P < .05$ vs placebo at same altitude.
[c]$P < .05$ m vs 1,860 m within treatment.

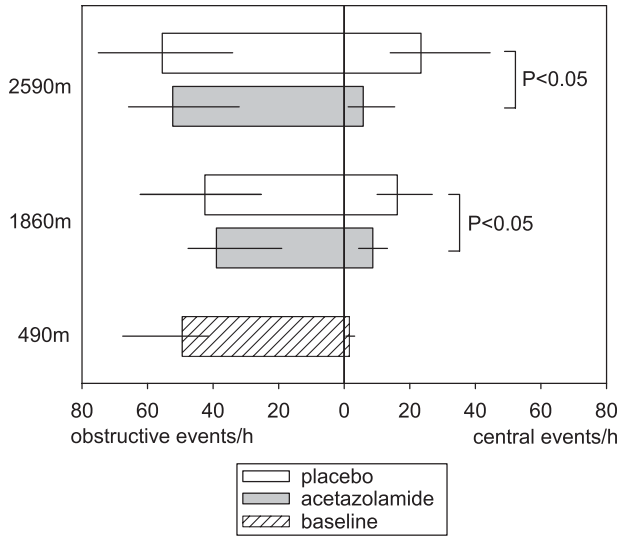

FIGURE 3. Effect of acetazolamide and altitude on obstructive and central apneas/hypopneas during CPAP discontinuation. The total length of each horizontal bar represents the total AHI (ie, the sum of obstructive and central events per hour). Quartile ranges are indicated by the horizontal lines. At altitude, the bars are shifted to the right, toward more central events. Acetazolamide significantly reduced central events at both altitudes. See Figure 1 and 2 legends for expansion of abbreviations.

and, with one exception, none of the patients had to interrupt therapy or withdraw from the study. One patient suffered from heart burn while on acetazolamide at 1,860 m but recovered after treatment with antacids and continued the study. Another patient suffered from disturbing vertigo at 2,590 m while on placebo. His Spo_2 at this time was 92%. Symptoms resolved spontaneously within a few hours. No specific cause of the vertigo was identified.

DISCUSSION

We evaluated the effect of acetazolamide on sleep and breathing disturbances in patients with OSA discontinuing CPAP therapy during a temporary stay at moderate altitude. Our randomized, double-blind, placebo-controlled trial revealed a significantly improved nocturnal Spo_2 related to an increase in ventilation and a decrease in the AHI by acetazolamide mainly because of a reduction of central events. Because the drug alleviated sleep-related breathing disturbances, improved subjective insomnia, and prevented an excessive rise in BP, it may be beneficial in patients with OSA when CPAP cannot be used during mountain travel.

Acetazolamide has been used to treat high-altitude periodic breathing in healthy subjects,[3,16,17] central sleep apnea/Cheyne-Stokes respiration in heart failure patients,[4] and central sleep apnea in patients with idiopathic respiratory control instability.[18] In patients with OSA at low altitude, acetazolamide reduced breathing disturbances only marginally[19] and even converted mixed to obstructive apneas in some patients.[20] To our knowledge, the current study is the first that specifically evaluates the treatment of patients with OSA at altitude by acetazolamide. The drug improved Spo_2 and sleep-related breathing disturbances at 1,860 m and 2,590 m to a clinically relevant degree considering the favorable effects on subjective and objective sleep quality and on altitude-related rises in BP and weight (Tables 2-5). However, in accordance with the cited studies,[19,20] obstructive apneas/hypopneas were not affected by the treatment. As observed in our previous study in patients with OSA,[1] the increase in total AHI at altitude was almost entirely related to the emergence of central events during NREM sleep, whereas central apneas/hypopneas occurred only rarely during REM sleep (e-Table 1). This was consistent with a greater increase in hypoxic and hypercapnic ventilatory drive in NREM compared with REM sleep at altitude.[21] Correspondingly, acetazolamide exerted its action predominantly on central events during NREM sleep.

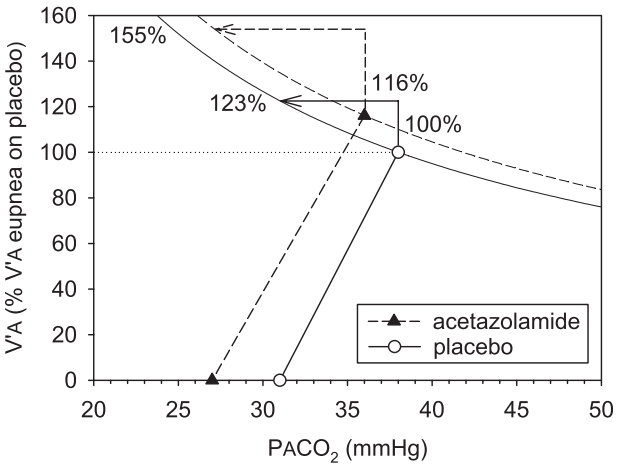

FIGURE 4. Mechanisms of central apnea reduction by acetazolamide based on data obtained at 2,590 m (Table 3) according to Dempsey et al.[15] The diagram illustrates the hyperbolic relationship between V′A and $PACO_2$. Median eupneic end-tidal PCO_2 ($PetCO_2$) on placebo (37 mm Hg) was taken as the surrogate of eupneic $PACO_2$, with corresponding V′A defined as 100%; $PetCO_2$ of 31 mm Hg at V′A = 0 is the apnea threshold. Assuming an increase in metabolic rate on acetazolamide (by an arbitrary amount of 10%) related to hyperventilation, a second metabolic hyperbola was constructed (dashed line). The corresponding eupneic $PetCO_2$ (35 mm Hg) and apnea threshold $PetCO_2$ (27 mm Hg) are also shown. Driving $PetCO_2$ from the eupneic level to the apnea threshold requires a greater ventilatory overshoot on acetazolamide (increase in V′A from 116% to 155%) than on placebo (from 100% to 123%). This is because the eupneic $PetCO_2$ on acetazolamide is positioned more to the left to a steeper position on the metabolic hyperbola, whereas the CO_2 reserve (difference between eupneic and apneic $PetCO_2$) is similar to that on placebo. The slope of the lines connecting the apnea threshold to the corresponding eupneic $PetCO_2$ reflects the ventilatory sensitivity to CO_2 below eupnea, which is similar on acetazolamide and on placebo. V′A = alveolar ventilation.

Table 3—*Mechanisms of Acetazolamide Action*

Variable	Davos Schatzalp (1,860 m; n = 17)		Davos Jakobshorn (2,590 m; n = 16)	
	Placebo	Acetazolamide	Placebo	Acetazolamide
Eupneic $PetCO_2$, mm Hg	37 (43, 39)	36 (33, 36)	38 (35, 40)	36[a] (34, 38)
Apnea threshold, mm Hg	31 (29, 32)	28[b] (26, 29)	31 (27, 34)	27[a,b] (25, 29)
CO_2 reserve, mm Hg	7 (6, 8)	8 (6, 9)	7 (6, 9)	8 (6, 11)
SpO_2 baseline, %	94 (92, 95)	95 (93, 96)	92 (89, 93)	93[b] (92, 94)
Average event SpO_2 nadir, %	85 (82, 88)	87 (83, 88)	80 (76, 84)	85 (79, 87)
Cycle time, s	23 (28, 40)	38[b] (36, 44)	27 (26, 32)	32[a,b] (30, 36)
Circulation time, s	29 (25, 38)	33 (29, 37)	31 (28, 34)	32 (27, 38)

Data are presented as median (quartiles). $PetCO_2$ = end-tidal PCO_2. See Table 2 legend for expansion of other abbreviations.
[a]$P < .05$ overall effect, both altitudes vs placebo.
[b]$P < .05$ vs placebo within altitude.

In a previous study in 10 healthy mountaineers, acetazolamide, 2×250 mg daily, started 3 days before ascent to 3,454 m, prevented high-altitude periodic breathing nearly completely (ie, the residual AHI was 2.5/h vs 16.2/h on placebo).[3] In an uncontrolled study in 11 patients with idiopathic central sleep apnea (baseline AHI, 25.5/h), acetazolamide, 250 mg before sleep, reduced the AHI in the first night to 13.8/h, and after 1 month of continuous treatment to 6.6/h.[18] It could be argued that central apneas/hypopneas might have been more completely eliminated in the current study if we had administered acetazolamide to the patients before ascent, permitting more time to induce a metabolic acidosis.

By which mechanisms does acetazolamide exert its stabilizing effect on ventilation? As a carbonic anhydrase inhibitor, the drug promotes renal bicarbonate excretion, thus counteracting the hypoxia-induced respiratory alkalosis.[22] The resulting reduction in pH stimulates ventilation and augments the hypercapnic ventilatory response.[23,24] Hyperventilation dampens periodic breathing by moving the $PaCO_2$ on the isometabolic hyperbola to a steeper portion so that a larger overshoot in ventilation is required to reduce the $PaCO_2$ by a given amount (Fig 4). Thus, the plant gain of the respiratory control system is reduced. Moreover, hypocapnia mitigates an exaggerated increase in hypoxic ventilatory sensitivity through

Table 4—*Daytime Evaluation*

Variable	Zurich (490 m)	Davos Schatzalp (1,860 m)		Davos Jakobshorn (2,590 m)		*P* Value (ANOVA)
		Placebo	Acetazolamide	Placebo	Acetazolamide	
BP systolic, mm Hg	135 (128, 151)	140 (129, 146)	133[a,b] (122, 138)	144 (132, 151)	134[a] (125, 146)	$< 10^{-3}$
BP diastolic, mm Hg	86 (80, 97)	88 (81, 93)	85[b] (77, 89)	90 (81, 95)	85 (81, 92)	$< 10^{-2}$
BP mean, mm Hg	104 (96, 114)	103 (96, 111)	98[a,b] (94, 106)	107 (100, 114)	102[a] (97, 107)	$< 10^{-2}$
Heart rate, 1/min	68 (61, 76)	70 (61, 78)	70 (63, 80)	74[b,c] (62, 85)	75[b] (62, 82)	$< 10^{-3}$
Weight, kg	93.1 (84.2, 104.4)	94.3[b] (83.8, 103.8)	93.3[a] (83.3, 103.8)	94.2[b] (83.8, 104.2)	93.0[a] (82.6, 103.4)	$< 10^{-5}$
OSLER time, min	40.0 (40.0, 40.0)	40.0 (40.0, 40.0)	40.0 (40.0, 40.0)	40.0 (40.0, 40.0)	40.0 (40.0, 40.0)	NS
OSLER missed stimuli, 1/s	0.18 (0.03, 0.93)	0.18 (0.00, 0.96)	0.28 (0.03, 0.95)	0.15 (0.00, 0.65)	0.13 (0.00, 1.27)	NS
AMSc	0 (0, 1)	0 (0, 0.4)	0 (0, 0.5)	0 (0, 0.5)	0 (0, 0.8)	NS
Karolinska sleepiness scale[c]	3 (3, 4)	3[b] (2, 4)	3[b] (3, 4)	3 (2, 5)	3 (3, 4)	$< 10^{-2}$
Subjective insomnia, time spent awake, min	60 (18, 120)	45 (10, 90)	30[b] (10, 80)	75[b] (30, 165)	58[a] (15, 90)	< .05
Side effects,[d] No. (%)						
Unpleasant taste	…	0 (0)	10 (22)[e]	1 (2)	8 (18)[e]	…
Paresthesias	…	1 (2)	1 (24)[e]	1 (2)	5 (11)	…
Polyuria	…	3 (7)	5 (11)	6 (12)	3 (7)	…
Heartburn	…	0 (0)	1 (2)	0 (0)	0 (0)	…

Data from 45 patients were available for analysis. Data are presented as median (quartiles). AMSc = acute mountain sickness cerebral score; NS = not significant; OSLER = Oxford sleep resistance test. See Table 2 legend for expansion of other abbreviations.
[a]$P < .05$ vs placebo at same altitude.
[b]$P < .05$ m vs 490 m.
[c]The Karolinska sleepiness scale ranges from 1 (very awake) to 9 (very tired).
[d]0 = absent; 1 = mild, not disturbing; 2 = moderate, somewhat disturbing; 3 = severe, forcing discontinuation of medication. With the exception of one patient with severe heartburn, no other side effects were rated as severe.
[e]$P < .05$ vs prevalence on placebo, χ^2 test.

Table 5—*Treatment Effects of Acetazolamide*

Variable	Davos Schatzalp (1,860 m)	Davos Jakobshorn (2,590 m)
Total sleep time, min	43.6 (23.1 to 64)	47.4 (20.5 to 74.4)
Sleep efficiency, %	6 (2 to 9)	9 (5 to 13)
Arousal index, 1/h	−8 (−12.5 to −3.4)	−9.8 (−17.6 to −2.2)
Spo_2, %	2 (1 to 2)	2 (1 to 2)
$Ptco_2$, mm Hg	−4 (−6 to −3)	−1[a] (−3 to 0)
Total AHI, 1/h	−18.2 (−24.8 to −11.6)	−21.4 (−27.2 to −15.5)
Obstructive AHI, 1/h	−7.7 (−13.9 to −1.6)	−0.3 (−6.7 to 6)
Central AHI, 1/h	−10.4 (−15.4 to −5.5)	−21[a] (−27.8 to −14.2)
Mean arterial BP, mm Hg	−7 (−7 to −2)	−5 (−8 to −1)
Weight, kg	−0.8 (−1.2 to −0.5)	−1.1[a] (−1.4 to −0.7)
AMSc	0.4 (−0.1 to 0.8)	−0.4[a] (−1.1 to 0.3)
Subjective time spent awake, min	−26 (−50 to −2)	−45 (−75 to −14)

Data are presented as mean difference (95% CI) for values on acetazolamide minus corresponding values on placebo. See Table 2 and 4 legends for expansion of abbreviations

[a]$P < .05$ mean difference 2,590 m vs 1,860 m.

interaction at the chemoreceptor[24,25] and because of the reduced loop gain that results from the higher Spo_2 associated with hyperventilation.[26] Our observations in sleeping patients with OSA extend recent data obtained in awake healthy volunteers,[24] suggesting that acetazolamide reduces the apnea threshold $Petco_2$ in parallel with the eupneic $Petco_2$ while preserving the CO_2 reserve (Fig 4, Table 3). Because a major increase in ventilatory sensitivity to CO_2 would have reduced the CO_2 reserve, our data suggest that acetazolamide induced only a moderate increase in the ventilatory sensitivity to CO_2, which may have contributed to breathing stability. The longer cycle time of periodic breathing on acetazolamide may be related to the higher baseline Spo_2 allowing more time for the Spo_2 to fall to its nadir, which was similar to that on placebo (Table 3).

Acetazolamide significantly improved sleep quality as reflected by the total sleep time, the sleep efficiency, and the arousal index (Table 2). Correspondingly, patients perceived a reduced amount of insomnia while on acetazolamide (Table 4). However, the drug had no significant effects on objective vigilance assessed by the OSLER test, which revealed a high sleep resistance time in all conditions (Table 4), possibly related to the short CPAP withdrawal time that did not result in a measurable relapse of sleepiness. Correspondingly, subjective sleepiness was only moderate and was not altered by acetazolamide. OSA is associated with systemic hypertension at low altitude.[27] The prevention of an excessive rise of BP and body weight with acetazolamide (Table 4) favors its use during hypoxic exposure at altitude, considering the increased risk of cardiovascular stress in OSA even at low altitude. Acetazolamide was generally well tolerated, and the side effects consisted mostly of unpleasant taste and paresthesias of mild to moderate intensity (Table 4). Nevertheless, patients should be informed about potential undesirable effects. We consider acetazolamide as an unlikely cause of the heartburn in one patient because reported GI side effects include mainly unpleasant taste, nausea/vomiting, and diarrhea.

In summary, the current trial evaluating OSA treatment at altitude confirms that acetazolamide improves oxygenation, nocturnal breathing, and sleep quality, and prevents excessive BP rises at altitude. Even though the number of residual breathing disturbances was considerable, acetazolamide is superior to no therapy at all for patients with OSA at altitude if CPAP therapy is not feasible. Whether CPAP alone or CPAP combined with acetazolamide optimally controls breathing disturbances in patients with OSA at altitude has to be evaluated in future studies.

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Dr Nussbaumer-Ochsner: contributed to designing the study, collecting the data, analyzing the data, and writing the manuscript.
Dr Latshang: contributed to designing the study, collecting the data, analyzing the data, and revising the manuscript.
Dr Ulrich: contributed to collecting the data, analyzing the data, and revising the manuscript.
Dr Kohler: contributed to designing the study, analyzing the data, and revising the manuscript.
Dr Thurnheer: contributed to designing the study, analyzing the data, and revising the manuscript.
Dr Bloch: contributed to designing the study, collecting the data, analyzing the data, and writing the manuscript.
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Patients With Obstructive Sleep Apnea Syndrome Benefit From Acetazolamide During an Altitude Sojourn

A Randomized, Placebo-Controlled, Double-Blind Trial

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e-Appendix 1.

Sleep study analysis

Sleep stages and arousals were scored according to [1,2]. Apneas/hypopneas were defined as a reduction of the inductive plethysmographic sum signal or the nasal pressure swings to <50% of the preceding 2 min baseline during ≥10 s [3-5]. Transient reductions in breathing amplitude to <50% baseline for 5-10 s were also scored as apneas/hypopneas if they occurred as part of a periodic breathing pattern with hyperventilation alternating with central apneas/hypopneas for at least three consecutive cycles [6]. Obstructive apneas/hypopneas were identified by rib cage and abdominal asynchrony and persistent or increasing diaphragmatic EMG activity. Central apneas/hypopneas were identified by absent rib cage-abdominal asynchrony, no signs of inspiratory flow limitations (no flattening of nasal pressure contour) and reduced or absent diaphragmatic EMG activity. Mixed apneas/hypopneas that showed some characteristics suggesting upper airway obstruction were classified as obstructive events. The apnea/hypopnea index and the oxygen desaturation index (>3% dips) were computed as the number of events per hour of sleep.

Determination of the apnea threshold for PCO_2 and the CO_2 reserve

Recordings were reviewed on the computer screen to identify series of at least 3-5 consecutive central apnea-hyperpnea cycles during NREM sleep. The apnea threshold for PCO_2 was defined as the end-tidal PCO_2 ($PetCO_2$) of the last breath before a central apnea occurred. The CO_2 reserve was defined as the difference between the eupneic $PetCO_2$ and the apnea threshold [7-9]. The cycle time of central apnea-hyperpnea was measured from the beginning of one to the following hyperpenic phase of a periodic breathing cycle. The lung-to-finger circulation time was measured on the nasal pressure or inductive plethysmographic sum signal from the resumption of ventilation after an apnea to the corresponding rapid rise in oxygen saturation [8,9]. The SpO_2 nadir represents the mean lowest SpO_2 during the analysed apneas/hypopneas (average event SpO_2 nadir).

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e-Table 1. Stage specific effects of acetazolamide on breathing during sleep

		Zurich 490m	Davos Schatzalp 1860 m		Davos Jakobshorn 2590 m		
			Placebo	Aceta-zolamide	Placebo	Aceta-zolamide	P ANOVA
SpO_2, %	NREM	92‡ (92;94)	89†‡ (87;90)	91*†‡ (88;92)	84¶†‡ (82;88)	88*¶†‡ (85;89)	$<10^{-5}$
	REM	92 (89;94)	87† (81;90)	90*† (86;92)	82¶† (80;86)	85¶† (79;88)	$<10^{-5}$
$PtcCO_2$, mmHg	NREM	50 (49;50)	45†‡ (42;46)	40*†‡ (37;44)	39¶†‡ (36;42)	36*¶†‡ (34;38)	$<10^{-5}$
	REM	50 (50;50)	47† (43;49)	42*† (37;46)	40†¶ (38;43)	38*¶† (34;40)	$<10^{-5}$
Obstructive AHI, 1/h	NREM	49.4‡ (41.4;67.6)	43.6 (29.1;72.8)	35.9*† (14.3;54)	56¶ (33.2;75.2)	54.2¶‡ (33.2;75.2)	$<10^{-4}$
	REM	39.3 (12.6;62.5)	39.1 (10.6;60.9)	32.5 (11.7;51.5)	47.5 (29.5;74.1)	47.4 (11.8;67.8)	<0.05
Central AHI, 1/h	NREM	1.6‡ (0.6;3.4)	16.1†‡ (8.9;27.8)	8.1*† (4.1;13.5)	26.2¶†‡ (13.5;47.2)	6*†‡ (1.2;16.2)	$<10^{-5}$
	REM	0 (0;0)	9† (2.9;19.1)	4.4† (0;12.5)	10.5† (1.2;17.5)	0*† (0;6.3)	$<10^{-5}$

n=45; medians (quartiles); * P<0.05 vs. Placebo at corresponding altitude and sleep stage; ¶ P<0.05 vs. 1860 m within treatment. † P<0.05 vs. 490 m; ‡ P<0.05 vs. REM; SpO_2= oxygen saturation; $PtcCO_2$= transcutaneous carbon dioxide pressure; # includes wakefulness. P = probability of overall effect of altitude by Friedman ANOVA.