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Both Tadalafil and Dexamethasone May Reduce the Incidence of High-Altitude Pulmonary Edema

A Randomized Trial

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Background: High-altitude pulmonary edema (HAPE) is caused by exaggerated hypoxic pulmonary vasoconstriction associated with decreased bioavailability of nitric oxide in the lungs and by impaired reabsorption of alveolar fluid.

Objective: To investigate whether dexamethasone or tadalafil reduces the incidence of HAPE and acute mountain sickness (AMS) in adults with a history of HAPE.

Design: Randomized, double-blind, placebo-controlled study performed in summer 2003.

Setting: Ascent from 490 m within 24 hours and stay for 2 nights at 4559 m.

Patients: 29 adults with previous HAPE.

Intervention: Prophylactic tadalafil (10 mg), dexamethasone (8 mg), or placebo twice daily during ascent and stay at 4559 m.

Measurements: Chest radiography was used to diagnose HAPE. A Lake Louise score greater than 4 defined AMS. Systolic pulmonary artery pressure was measured by using Doppler echocardiography, and nasal potentials were measured as a surrogate marker of alveolar sodium transport.

Results: Two participants who received tadalafil developed severe AMS on arrival at 4559 m and withdrew from the study; they did not have HAPE at that time. High-altitude pulmonary edema developed in 7 of 9 participants receiving placebo and 1 of the remaining 8 participants receiving tadalafil but in none of the 10 participants receiving dexamethasone ($P = 0.007$ for tadalafil vs. placebo; $P < 0.001$ for dexamethasone vs. placebo). Eight of 9 participants receiving placebo, 7 of 10 receiving tadalafil, and 3 of 10 receiving dexamethasone had AMS ($P = 1.0$ for tadalafil vs. placebo; $P = 0.020$ for dexamethasone vs. placebo). At high altitude, systolic pulmonary artery pressure increased less in participants receiving dexamethasone (16 mm Hg [95% CI, 9 to 23 mm Hg]) and tadalafil (13 mm Hg [CI, 6 to 20 mm Hg]) than in those receiving placebo (28 mm Hg [CI, 20 to 36 mm Hg]) ($P = 0.005$ for tadalafil vs. placebo; $P = 0.012$ for dexamethasone vs. placebo). No statistically significant difference between groups was found in change in nasal potentials and expression of leukocyte sodium transport protein messenger RNA.

Limitations: The study involved a small sample of adults with a history of HAPE.

Conclusions: Both dexamethasone and tadalafil decrease systolic pulmonary artery pressure and may reduce the incidence of HAPE in adults with a history of HAPE. Dexamethasone prophylaxis may also reduce the incidence of AMS in these adults.

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Rapid ascent to altitudes greater than 2500 m may cause acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE). In nonacclimatized mountaineers, the prevalences of AMS and HAPE at 4559 m are approximately 50% and 4%, respectively (1). Individual susceptibility, rate of ascent, and preexposure to high altitude are major, independent determinants of the prevalence of AMS (2). Acute mountain sickness is not a prerequisite for HAPE. Acetazolamide (3, 4) or dexamethasone (5, 6) prophylaxis can prevent AMS, whereas nifedipine prophylaxis can prevent HAPE (7). Whether acetazolamide or dexamethasone also prevents HAPE has not been studied.

Exaggerated hypoxic pulmonary vasoconstriction leading to elevated pulmonary capillary pressure (8) is the major pathophysiologic mechanism of HAPE. This elevated pulmonary capillary pressure may be caused by inhomogeneous hypoxic pulmonary vasoconstriction (9), which leads to areas that are subjected to high pressure and flow, consequent mechanical overdistention of pulmonary capillaries, and injury of the blood–gas barrier (10). This phenomenon causes extravasation of fluid, plasma proteins, and blood cells into the interstitial and alveolar spaces (11). Decreased bioavailability of nitric oxide might explain the elevated pulmonary artery pressure (12, 13). Therefore, phosphodiesterase-5 inhibitors are an attractive option to restore impaired effects of nitric oxide in persons susceptible to HAPE (14–16).

Constitutively impaired sodium and water transport in the lung has been thought to be an additional factor in the pathogenesis of HAPE (17, 18). Hypoxia also decreases water reabsorption from the alveolar space. Direct experi-

See also:

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Editors' Notes 498
Editorial comment. 550
Summary for Patients. I-28

Web-Only
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Context

Very few trials have evaluated ways to prevent high-altitude pulmonary edema (HAPE).

Contribution

In this double-blind trial, 29 adults with a history of HAPE were randomly assigned to receive prophylactic tadalafil, dexamethasone, or placebo during a 24-hour ascent and 2-day stay at 4559 m. Compared with placebo recipients, adults taking dexamethasone less often experienced acute mountain sickness and those taking either dexamethasone or tadalafil less often had HAPE.

Cautions

The trial involved a small number of selected adults who rapidly ascended to a high altitude.

Implications

Either tadalafil or dexamethasone might help prevent HAPE in mountaineers with a history of pulmonary edema.

—The Editors

mental evidence has been obtained from hypoxia-exposed rats (19), and indirect evidence derives from decreased sodium transport activity in cultured alveolar epithelial cells (20). Prophylactic inhalation of the β_2-adrenergic agonist salmeterol to stimulate alveolar sodium transport (17) decreased the incidence of HAPE in susceptible persons. However, other mechanisms of action may also contribute to the preventive effects of salmeterol, because β-adrenergics tighten the endothelial barrier and decrease pulmonary artery pressure (21).

Dexamethasone may be an alternative therapy to prevent HAPE because it stimulates alveolar sodium and water reabsorption (22); may enhance nitric oxide availability in pulmonary vessels (23, 24); and is effective against AMS (5, 6), which may develop despite use of nifedipine as prophylaxis against HAPE (25). However, HAPE has occurred in persons who received dexamethasone for AMS (26, 27). We sought to test whether prophylaxis with dexamethasone or tadalafil reduces the risk for HAPE in adults with a history of HAPE on rapid ascent to 4559 m.

Table 1. **Participant Characteristics**

Variable	Placebo Group	Tadalafil Group	Dexamethasone Group
Participants (women), *n*	9 (2)	10 (1)	10 (1)
Mean age (SD), *y*	41 (8)	46 (3)	44 (3)
Median previous episodes of high-altitude pulmonary edema (interquartile range), *n*	1 (1–3)	1 (1–2)	1 (1–2)

METHODS

Sample and Setting

Mountaineers with a history of HAPE were recruited through announcements in the journals of the Swiss Alpine Club and the German Alpine Club. Four women and 25 men with at least 1 documented episode of HAPE participated after providing written informed consent. **Table 1** shows the age and average number of HAPE episodes for each participant. No participant spent more than 4 nights above 2500 m within 30 days before ascent to the Capanna Regina Margherita, Italy (altitude, 4559 m).

Two to 4 weeks before the study at the Capanna Regina Margherita, baseline evaluations were performed in Zürich, Switzerland (altitude, 490 m). For ascent, participants traveled to Alagna, Italy (altitude, 1100 m), ascended to 3200 m by cable car, and continued by foot to the Capanna Gnifetti (altitude, 3600 m), where they spent 1 night. The journey from the cable car arrival station (3200 m) to the Capanna Gnifetti took about 1.5 hours. The next morning, the participants continued to the Capanna Regina Margherita (about 4 hours), where they spent 2 nights.

Figure 1 shows the study design. The institutional ethics boards of the University Hospital Zürich and University Hospital Heidelberg approved the study and its protocol, which was consistent with the principles of the Declaration of Helsinki.

Randomization and Interventions

Medication consisted of white gelatin capsules, identical in appearance, containing placebo; tadalafil, 10 mg (Cialis [Eli Lilly, Geneva, Switzerland]); or dexamethasone, 8 mg (Fortecortin [Merck, Dietikon, Switzerland]). Before the study, the pharmacist at the University Hospital Zürich packaged the medication into numbered bottles, which were assigned to individual participants according to a computer-generated list. Randomization was stratified by the number of previous episodes of HAPE (1 or $\geq$2) without blocking. Participants started taking the medication twice daily on the morning of the day before ascent to high altitude and continued intake until the end of the study.

Primary End Point and Assessment of HAPE and AMS

The primary end point was development of HAPE, which was assessed by clinical examination and chest radiography in each participant after the first and second nights at 4559 m or when HAPE or severe AMS occurred (**Figure 1**). Two physicians who were blinded to treatment assignment performed clinical examinations according to a predefined checklist in the mornings after the first and second night at 4559 m or when severe AMS or HAPE occurred. High-altitude pulmonary edema was clinically suspected at the appearance of dry cough, orthopnea, or pulmonary rales in at least 1 lung area. A posteroanterior thorax radiograph was then obtained by using a mobile unit (TRS [Siemens, Stockholm, Sweden]) at a fixed distance of 1.4 m at 95 kV and a charge of 3 to 6 mAs.

Radiographs were scored retrospectively by a second radiologist who was blinded to other study results. After the lung was divided into 4 quadrants, the following scores were assigned: 1 for a questionable infiltrate, 2 for interstitial edema in less than 50% of the quadrant area, 3 for interstitial edema on 50% or more of the quadrant area, and 4 for alveolar edema. A radiograph showing interstitial or alveolar edema (score >1) in at least 1 quadrant (28) confirmed the diagnosis of HAPE.

The severity of AMS was evaluated by clinical examination and was quantified by using the Lake Louise scoring protocol (29). Each participant answered the first 5 questions of the protocol that asked about the severity of headache, gastrointestinal symptoms, fatigue, lightheadedness or dizziness, and insomnia. A score of 0 to 3 points (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms) was assigned for each item. In clinical examination, a score of 0 (normal) to 4 points was given for mental status (for which 4 points indicated coma) and ataxia (for which 4 points indicated inability to stand on the heel-to-toe walking test). A score of 1 was given for peripheral edema in 1 location, and a score of 2 was given for edema in more than 1 location. The sum of all points yielded the Lake Louise score (maximum score, 25 points). A Lake Louise score greater than 4 defined AMS (30).

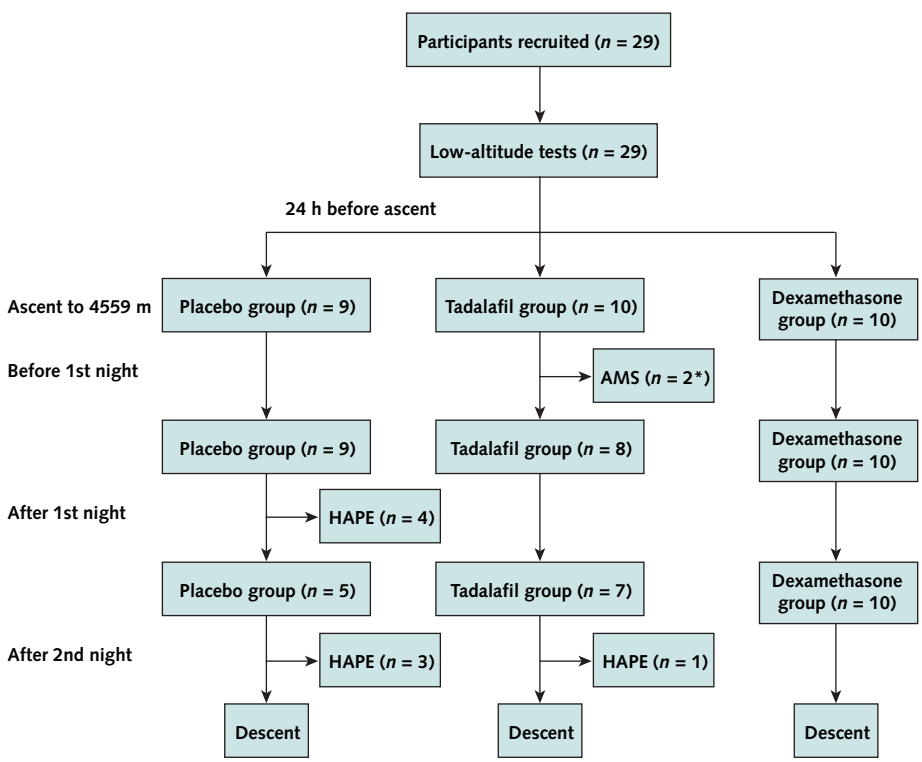
To assess possible side effects of the study medications, we separately evaluated the Lake Louise score question that asked for information on headache severity and the degree of insomnia, and we measured blood glucose levels in addition to vital signs. To test for adherence, participants were requested to document medication intake and investigators counted the remaining capsules at each visit. Blood and urine samples were collected to measure cortisol and tadalafil, respectively.

Treatment of HAPE and AMS consisted of nifedipine for HAPE, dexamethasone for AMS, and supplemental oxygen for both disorders. Participants who required treatment were withdrawn from the study.

Echocardiography and Measurement of Cardiac Output

Doppler echocardiography was performed by using an integrated color Doppler system with a 4.0-MHz transducer (Aplio 80 [Toshiba-Medical Systems, Oetwil am See, Switzerland]) while participants were lying in a semisupine, left-lateral position. Systolic pulmonary artery pressure was calculated from the pressure gradient across the

Figure 1. **Flow diagram of the study.**



Twenty-nine participants were recruited and underwent prealtitude tests, after which they were randomly assigned to treatment groups. *Two participants in the tadalafil group were withdrawn from the study early because they required treatment for severe acute mountain sickness (*AMS*) with oxygen and dexamethasone before the first night at 4559 m, but high-altitude pulmonary edema (*HAPE*) was not diagnosed at the time of withdrawal. However, the duration of exposure to 4559 m may not have been long enough to develop HAPE.

Table 2. **Incidence of High-Altitude Pulmonary Edema and Acute Mountain Sickness***

Variable	Placebo Group, *n/n (%)*	Tadalafil Group, *n/n (%)*	Dexamethasone Group, *n/n (%)*	Difference (95% CI), *percentage points*					
				Tadalafil Group versus Placebo Group	*P* Value	Dexamethasone Group versus Placebo Group	*P* Value	Dexamethasone Group versus Tadalafil Group	*P* Value
Incidence of HAPE	7/9 (78)	1/8 (13)	0/10 (0)	65 (30 to 100)	0.007	78 (51 to 100)	<0.001	13 (−10 to 35)	0.25
Incidence of acute mountain sickness	8/9 (89)	8/10 (80)	3/10 (30)	9 (−23 to 41)	1.0	59 (24 to 94)	0.020	50 (12 to 88)	0.038
Assumption for 2 tadalafil group participants									
Best case									
0 of 2 with HAPE	7/9 (78)	1/10 (10)	0/10 (0)	68 (35 to 100)	0.003			10 (−9 to 29)	0.31
1 of 2 with HAPE		2/10 (20)		58 (21 to 95)	0.012			20 (−5 to 45)	0.14
Worst case: 2 of 2 with HAPE		3/10 (30)		48 (8 to 87)	0.037			30 (2 to 58)	0.06

* HAPE = high-altitude pulmonary edema.

tricuspid valve and measured with continuous-wave Doppler echocardiography by using the modified Bernoulli equation and an estimated right atrial pressure of 7 mm Hg (8). Color flow imaging was used for alignment. The recordings were stored on magneto-optical disk for evaluation by 2 investigators who were blinded to all other data. Averages of at least 3 cardiac cycles were used. Cardiac output was measured by using beat-to-beat stroke volume measurement with impedance cardiography (Task Force Monitor [CNSystems, Graz, Austria]).

Nasal Potential Measurements

Differences in nasal potentials were determined as described elsewhere (18). In brief, each participant was seated in a chair with his or her head on a headrest. An umbilical vessel catheter (Sherwood Medical, Tullamore, Ireland) connected to the measuring electrode (DRIREF [World Precision Instruments, Berlin, Germany]) was placed on the nasal mucosa for superfusion of the inferior turbinate (31). An intravenous infusion line connected to the reference electrode was placed into an antecubital vein and perfused with Ringer solution. The potential difference was measured by using a high-impedance millivolt meter and was recorded on a computer. The total nasal potential was measured during superfusion (100 μL/min) with Ringer solution. Sodium transport through the epithelial sodium channels was assessed as the change in potential after intranasal administration of amiloride (100 μM).

Blood and Urine Assays

Arterial blood samples were obtained from the radial artery and were analyzed by using a blood gas analyzer (ABL 5 [Radiometer, Copenhagen, Denmark]). Blood to obtain serum and plasma was collected from antecubital veins. For later preparation of total RNA, buffy coat was washed twice with a medium containing 155 mM of ammonium chloride, 10 mM of potassium carbonate, and 0.1 mM of EDTA (pH, 7.4) to remove erythrocytes; was dissolved in 1.5 mL of Trifast reagent (peqLab, Erlangen, Germany); and was stored frozen in liquid nitrogen. Real-time polymerase chain reaction was used to measure messenger RNA expression (Lightcycler [Roche Diagnostics, Mannheim, Germany]) by using established primers (32); 28S ribosomal RNA was used as the internal standard. Concentrations of monocyte chemoattractant protein-1 and cyclic guanosine monophosphate in urine were measured by using radioimmunoassay (Immunotech, Marseille, France). Sensitive C-reactive protein in plasma was measured by using chemiluminescence (Roche Diagnostics, Basel, Switzerland). Glucose and cortisol in blood and creatinine in urine were measured by using routine laboratory techniques. Plasma tadalafil was measured by using high-performance liquid chromatography.

Statistical Analysis

We based the original estimate of sample size on an assumed incidence of HAPE of 70% in the placebo group and 10% in the treatment group, on the basis of results from studies of nifedipine (7). To achieve 80% power with a type I error (2-sided) of 0.05, we would have needed 18 participants per arm (54 total). We were not able to recruit 54 participants and decided to perform the study after 29 participants had been enrolled.

Participants were withdrawn from the study at the time of diagnosis of HAPE ($n = 8$), when AMS required treatment with dexamethasone and oxygen ($n = 2$), or after the second night at high altitude (**Figure 1**). Two participants receiving tadalafil had to be withdrawn from the study a few hours after arrival at 4559 m because of severe AMS, as diagnosed by clinical examination. A chest radiograph and an arterial sample for blood gas analysis were obtained to exclude HAPE. Because the time of exposure to an altitude of 4559 m in these 2 participants was probably not long enough to develop HAPE, we evaluated the best-case (neither participants with HAPE) and worst-case (both participants with HAPE) scenarios to estimate the treatment efficacy of tadalafil (**Table 2**).

Kaplan–Meier curves for the time to development of HAPE during the time (hours) spent at 4559 m were de-

termined and compared by treatment group, using the log-rank test. Results are shown as mean values with 95% CIs or medians with interquartile ranges, as appropriate. For normally distributed variables, 1-way analysis of variance was used to determine whether an overall difference in high- versus low-altitude changes was present. Pairwise treatment comparisons were made by using the Fisher protected least-significant-difference procedure. For variables that were not normally distributed, changes were compared by using the Kruskal–Wallis test and the Mann–Whitney test. A P value less than 0.05 was considered statistically significant. Statistical analyses were performed by using the StatView software package (Abacus Concepts, Berkeley, California) (33).

Role of the Funding Sources

The funding sources did not influence the study design; the collection, analysis, or interpretation of the data; or the writing of the manuscript and its submission for publication.

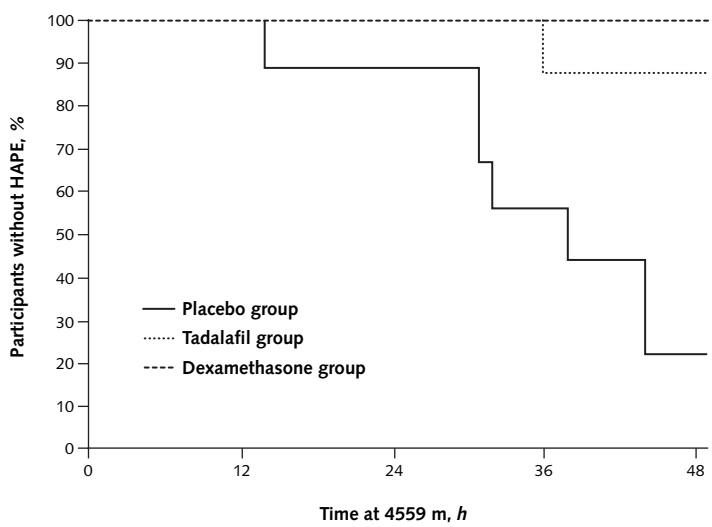
RESULTS

Occurrence of HAPE and AMS

In the tadalafil group, 2 participants developed severe AMS on the evening of arrival at 4559 m and were withdrawn from the study. At that time, they had AMS scores of 13 and 8 points, radiographic scores of 0 and 1 point (0 = no HAPE), heart rates of 96 and 116 beats/min, Pa_{O_2} of 39 and 30 mm Hg, and Pa_{CO_2} of 28 and 31 mm Hg. High-altitude pulmonary edema developed in 7 of 9 participants receiving placebo and 1 of the remaining 8 participants receiving tadalafil but in none of 10 participants receiving dexamethasone (**Table 2**). Four of 10 participants receiving placebo and 1 of 8 participants receiving tadalafil were prematurely withdrawn from the study because of HAPE during day 2 (**Figure 1**). The percentage of participants without HAPE who remained in the study during the stay at 4559 m decreased fastest in the placebo group ($P = 0.001$ for placebo vs. tadalafil; $P < 0.001$ for placebo vs. dexamethasone [log-rank tests]), whereas there was no difference between the dexamethasone and tadalafil groups ($P = 0.26$ [log-rank test]) (**Figure 2**). Acute mountain sickness was diagnosed in 8 of 9 participants receiving placebo, 8 of 10 participants receiving tadalafil, and 3 of 10 participants receiving dexamethasone (**Table 2**). All participants with HAPE also had AMS. The average Lake Louise score of AMS was higher in the placebo and tadalafil groups than in the dexamethasone group (**Table 3**). The headache score did not differ between the placebo and tadalafil groups but was significantly lower in the dexamethasone group. Insomnia was moderate and did not differ among groups (**Table 3**).

The median radiographic score in the placebo group was 5 (interquartile range, 1.7 to 6.2). The radiographic score in the participant who developed HAPE in the

Figure 2. **Proportion of participants without high-altitude pulmonary edema (*HAPE*) during their stay at high altitude.**



Participants without HAPE, *n*					
Placebo group	9	9	8	5	2
Tadalafil group	10	8	8	7	7
Dexamethasone group	10	10	10	10	10

Development of HAPE during time spent at 4559 m necessitated withdrawal from the study. The 2 participants in the tadalafil group who were withdrawn from the study because of severe acute mountain sickness a few hours after arrival at 4559 m were treated as censored observations at the time of withdrawal. $P = 0.001$ for placebo versus tadalafil, $P < 0.001$ for placebo versus dexamethasone, and $P > 0.2$ for dexamethasone versus tadalafil (log-rank test). The data below the figure indicate the number of participants who remained in the study.

Table 3. **Acute Mountain Sickness Scores at High Altitude**

Variable	Median Lake Louise Score (Interquartile Range)			*P* Value*		
	Placebo Group	Tadalafil Group	Dexamethasone Group	Tadalafil Group versus Placebo Group	Dexamethasone Group versus Placebo Group	Dexamethasone Group versus Tadalafil Group
Acute mountain sickness	7.0 (6.0–10.2)	6.5 (2.0–7.0)	2.5 (1.0–5.0)	0.31	0.005	0.07
Headache†	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.5 (0.0–1.0)	1.0	0.002	0.002
Insomnia†‡	2.0 (2.0–2.5)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	–	–	–

* Mann–Whitney test.
† The subset of questions of the Lake Louise score asking for headache and insomnia was used to assess possible adverse treatment effects; hence, they were analyzed separately.
‡ Pairwise treatment comparisons were not done because the overall *P* values were greater than 0.05.

tadalafil group was 11, whereas it was 0 in all participants receiving dexamethasone and in the 8 tadalafil recipients who were not withdrawn from the study.

Medication intake protocols indicated that all participants took the assigned drug. Tadalafil was detected in the urine of all participants in this group. Endogenous cortisol blood levels were below the detection limit only in the dexamethasone group.

Hemodynamic and Arterial Blood Gas Findings

At 4559 m, systolic pulmonary artery pressure was increased in all groups. The increase was significantly smaller in participants receiving tadalafil and dexamethasone than in those receiving placebo (**Table 4**, **Figure 3**). Upon ascent to 4559 m, the heart rate had increased significantly in the participants receiving tadalafil and placebo but not in those receiving dexamethasone. Systolic blood pressure and cardiac output did not differ between groups at both altitudes (**Table 4**).

At high altitude, the mean Pa_{O_2} was lowest in the placebo group but was significantly higher in the tadalafil and dexamethasone groups. The change in Pa_{CO_2} between high and low altitude did not differ between treatment groups (**Table 4**).

Sodium Transport

Changes in the total, amiloride-inhibitable, and amiloride-insensitive nasal potentials (**Table 5**) upon ascent to 4559 m did not differ among groups. In all groups, expression of messenger RNA of the α_1 subunit of Na^+,K^+-ATPase decreased and the β subunit of the epithelial sodium channel in leukocytes increased significantly; these changes did not statistically differ among groups (**Table 5**).

Other Measurements

Compared with values at low altitude, urinary levels of cyclic guanosine monophosphate were increased in the tadalafil and dexamethasone groups but not in the placebo group on the first morning at 4559 m (**Table 6**). However, the change in values after ascent did not statistically differ among groups.

Table 4. **Hemodynamic and Arterial Blood Gas Values at Low and High Altitude**

Variable	Placebo Group (n = 9)		Tadalafil Group (n = 10)*		Dexamethasone Group (n = 10)		*P* Value†
	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	
Heart rate, min^{-1}	61 (8)	26 (12 to 40)	61 (12)	28 (14 to 42)	59 (10)	−4 (−3 to 11)	<0.001
Systolic blood pressure, *mm Hg*	132 (12)	−4 (−4 to 12)	134 (15)	−3 (−14 to 19)	133 (12)	−3 (−12 to 6)	0.63
Diastolic blood pressure, *mm Hg*	81 (6)	−3 (0 to 5)	87 (9)	9 (1 to 17)	82 (9)	1 (−5 to 3)	0.024
Cardiac output, $L \cdot min^{-1}$	5.13 (0.89)	0.02 (−0.9 to 0.8)	5.12 (1.52)	−0.02 (−1.2 to 1.3)	5.24 (0.66)	0.1 (−1.5 to 1.2)	0.98
Systolic pulmonary artery pressure, *mm Hg*	29 (4)	28 (20 to 36)	28 (7)	13 (6 to 20)	24 (4)	16 (9 to 23)	0.009
Pa_{O_2}, *mm Hg*	90 (10)	−60 (−52 to −71)	84 (7)	−46 (−35 to −49)	88 (10)	−40 (−30 to −46)	<0.001
Pa_{CO_2}, *mm Hg*	40 (2)	−11 (−9 to −13)	39 (2)	−11 (−8 to −13)	41 (3)	−12 (−10 to −14)	0.30

* Data on systolic pulmonary artery pressure and cardiac output are missing for 2 of the 10 participants because they were given dexamethasone for severe acute mountain sickness without high-altitude pulmonary edema a few hours after arrival at 4559 m.
† *P* values refer to the overall comparison of the difference between values obtained at 4559 m and those obtained at 490 m (placebo vs. tadalafil vs. dexamethasone).
‡ Change in values observed on the morning after the first night spent at 4559 m.

Exposure to high altitude increased the C-reactive protein level in participants receiving tadalafil and placebo but not in those receiving dexamethasone. Dexamethasone, but not placebo or tadalafil, tended to decrease the monocyte chemoattractant protein-1 level after exposure to 4559 m (**Table 6**). Upon ascent, the blood glucose level increased in participants receiving tadalafil and dexamethasone but not in those receiving placebo (**Table 6**); the difference in this value from baseline levels was significant in the dexamethasone group.

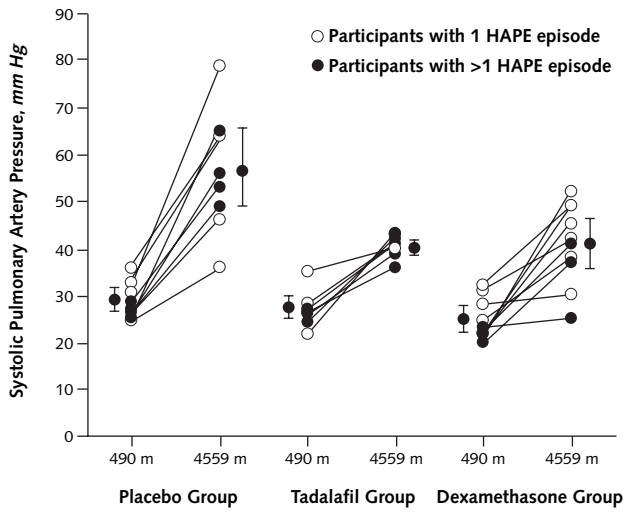
DISCUSSION

When treatment was given 24 hours before rapid ascent to 4559 m, both tadalafil and dexamethasone reduced the incidence of HAPE after arrival at high altitude in persons with 1 or more previous episodes of HAPE. Moreover, dexamethasone prevented the excessive increase in systolic pulmonary artery pressure; its vasodilatory effect was comparable to that of the selective pulmonary vasodilator tadalafil (a phosphodiesterase-5 inhibitor). Dexamethasone, but not tadalafil, decreased the incidence of AMS in these HAPE-susceptible adults.

Although drugs are frequently used to prevent high-altitude illness, the primary recommendation to decrease its incidence is to perform progressive acclimatization with an ascent rate of 300 m to 600 m daily (34–36). Prophylaxis with acetazolamide is generally recommended to prevent AMS in susceptible persons (3, 4, 34, 35), although dexamethasone (5, 6) has also been proven effective. The main reason for recommendation of acetazolamide is the potential side effects of glucocorticoids (37). For prophylaxis against HAPE, nifedipine is recommended (34–36) on the basis of a single randomized, placebo-controlled trial in persons susceptible to HAPE (7) and favorable results obtained in patients with HAPE (38). Because only a minority of patients with HAPE do not have AMS (28) and because nifedipine does not prevent AMS (25), acetazolamide is frequently combined with nifedipine for prophylaxis against AMS in persons susceptible to HAPE. Whether acetazolamide also prevents HAPE is not yet known. Recent results in rats (39) and dogs (40) suggest that this could be the case.

Our results obtained with tadalafil are very similar to those seen with the nonselective vasodilator nifedipine (7). In fact, if we trust the best-case scenario, only 1 of 10 participants receiving tadalafil developed HAPE, which is exactly the same ratio as that in the study of nifedipine. Even under the assumption of the worst-case scenario, tadalafil would still be better than placebo. Phosphodiesterase-5 inhibitors may be preferred to nifedipine because they have been shown to improve gas exchange even in participants who are not susceptible to HAPE (16), an effect that was not found with nifedipine (25). Furthermore, evidence indicates that the endothelial nitric oxide synthase–nitric oxide–cyclic guanosine monophosphate axis is crucial for regulation of pulmonary vascular tone at high altitude (16, 41). In hypoxia, persons susceptible to HAPE have a lower concentration of nitric oxide in exhaled air (12, 13) and lower levels of nitrites and nitrates in bronchoalveolar lavage fluid (11) than do resistant persons. Therefore, counteracting impaired nitric oxide–mediated pulmonary vasorelaxation with use of phosphodiesterase-5 inhibitors appears to directly interfere with a possible cause of susceptibility to HAPE.

Figure 3. **Increase in systolic pulmonary artery pressure upon ascent to 4559 m.**



Only 8 participants were evaluated in the tadalafil group; 2 were withdrawn from the study early because of severe acute mountain sickness. Values are presented as the mean (95% CI) systolic pulmonary artery pressure at 490 m and 4559 m. *P* values are shown in Table 3. HAPE = high-altitude pulmonary edema.

The preventive effect of dexamethasone on HAPE in our study was surprising, because it contrasts with 2 anecdotal reports of HAPE during or after use of dexamethasone to treat AMS (26, 27). In the 2 patients from those reports, dexamethasone was taken after the onset of severe AMS, whereas in our study, dexamethasone was taken preventively (that is, intake began 24 hours before the ascent). Thus, the effectiveness of dexamethasone in preventing HAPE appears to depend critically on prolonged intake, which might indicate effects requiring stimulation of gene expression. Recent studies point to a possible explanation for the significant vasodilator effect of dexamethasone in our study. They indicate that dexamethasone improves endothelial dysfunction in cultured pulmonary arteries, stimulates the production of cyclic guanosine monophosphate in hypoxia (24), and increases the activity of nitric oxide synthase and the nitrate–nitrite concentration (42). These results are in line with the increased urinary level of cyclic guanosine monophosphate in our dexamethasone-treated participants (**Table 6**). They might also suggest that dexamethasone prevents HAPE by improvement of cyclic

Table 5. **Change in Nasal Potentials and Expression of Sodium Transporters in Leukocytes**

Variable	Placebo Group (n = 9)		Tadalafil Group (n = 8)*		Dexamethasone Group (n = 10)		*P* Value†
	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Mean (95% CI) Change after Ascent to 4559 m‡	
Nasal potential, *mV*							
Total	−20 (27.8)	–8.8 (–1.7 to –15.9)	–14.6 (17.3)	2.9 (0.6 to –6.4)	–16.9 (21.9)	–4.8 (–1.8 to –8.8)	0.191
Amiloride inhibitable	8.7 (5.9)	–4.1 (0.9 to –9.1)	5.9 (1.6)	–0.9 (2.2 to –4.0)	6.5 (5.6)	–1.9 (1.3 to –5.1)	0.42
Amiloride insensitive	–11.3 (5.9)	–4.3 (0.1 to –8.7)	–8.4 (2.6)	–1.9 (1.6 to –5.4)	–10.4 (3.1)	–2.9 (–1.3 to –4.5)	0.49
Sodium transporter messenger RNA, *pg/ng 28S ribosomal RNA*							
α_1 subunit of Na^+,K^+-ATPase	34.3 (1.1)	–1.8 (–1.2 to –2.4)	34.6 (1.1)	–1.7 (–0.5 to –2.9)	34.7 (1.1)	–1.5 (–0.5 to –2.4)	0.91
β_1 subunit of the epithelial sodium channel	42 (32)	85 (29 to 141)	32 (42)	50 (–17 to 117)	35 (56)	47 (–9 to 102)	0.45

* Two of the 10 participants were withdrawn from the study because they were given dexamethasone for severe acute mountain sickness without high-altitude pulmonary edema a few hours after arrival at 4559 m.
† Overall *P* values refer to the change after ascent to 4559 m from 490 m (placebo vs. tadalafil vs. dexamethasone).
‡ Change in values observed on the morning after the first night spent at 4559 m.

guanosine monophosphate–mediated pulmonary vasodilation.

We cannot exclude that further actions of dexamethasone contributed to the prevention of HAPE. Dexamethasone may favorably modulate increased sympathetic activity associated with HAPE (43). The lower heart rate in the dexamethasone group and experimental evidence from hypobaric hypoxia (44) and normoxia (45) support this possibility. At high altitude, dexamethasone prevented increase in the C-reactive protein level and tended to decrease the monocyte chemoattractant protein-1 level. This finding suggests that dexamethasone might tighten pulmonary vessels (46), possibly by preventing an inflammatory response to hypoxia (47) and inhibiting vascular endothelial growth factor–induced angiogenesis (48). Thus, dexamethasone might prevent interstitial edema and improve arterial oxygenation, an idea that is in line with the findings of another study (49).

Enhanced alveolar fluid clearance (17, 22) might be another mechanism that could improve gas exchange upon dexamethasone treatment. However, we found no evidence for stimulation of sodium transport with dexamethasone therapy, which did not prevent hypoxic inhibition of nasal potentials, a proposed surrogate marker of alveolar sodium

Table 6. **Laboratory Variables in Blood and Morning Urine**

Variable	Placebo Group (n = 9)		Tadalafil Group (n = 8)*		Dexamethasone Group (n = 10)		*P* Value†
	Mean (SD) Results at 490 m	Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Change after Ascent to 4559 m‡	Mean (SD) Results at 490 m	Change after Ascent to 4559 m‡	
Blood glucose level							
mmol/L	5.8 (1.0)	0.4 (–0.4 to 1.1)§	5.8 (0.7)	0.9 (0.2 to 1.7)§	5.3 (0.3)	1.6 (1.0 to 2.2)§	0.019
mg/dL	104 (18)	7 (–6 to 20)§	105 (13)	17 (3 to 31)§	95 (6)	29 (19 to 39)§	0.019
C-reactive protein level, *mg/L*	1.8 (2.8)	4.6 (1.5 to 6.1)‖	1.4 (1.1)	8.0 (5.1 to 12.6)‖	1.1 (1.2)	0.1 (–0.7 to 0.4)‖	<0.001
Urinary monocyte chemoattractant protein-1 level, *ng/L*	19.3 (2.9)	0.9 (–1.3 to 3.1)‖	21.2 (3.7)	1.6 (–3.3 to 5.3)‖	20.0 (2.5)	–3.0 (–0.7 to –0.7)‖	0.065
Urinary cyclic guanosine monophosphate, *nmol/mol creatinine*	60 (10)	21 (19 to 54)‖	40 (15)	36 (27 to 39)‖	34 (15)	40 (25 to 67)‖	0.32

* Two of the 10 participants were withdrawn from the study because they were given dexamethasone for severe acute mountain sickness without high-altitude pulmonary edema a few hours after arrival at 4559 m.
† Overall *P* values refer to the change after ascent to 4559 m from 490 m (placebo vs. tadalafil vs. dexamethasone).
‡ Change in values observed on the morning after the first night spent at 4559 m.
§ Mean (95% CI).
‖Median (interquartile range).

reabsorption (50). In addition, dexamethasone did not prevent the decrease in expression of the α_1 subunit of Na^+,K^+-ATPase in leukocytes and did not alter messenger RNA expression of the β-subunit of epithelial sodium channels. The expression of these 2 transport proteins is typically upregulated by dexamethasone in the lung (22). Thus, our results allow no conclusion on a contribution of inhibited sodium transport in HAPE or its modulation by the treatment.

Whereas treatment with dexamethasone, as expected (3, 4), considerably decreased the incidence of AMS, treatment with tadalafil did not. In fact, 2 of the participants receiving tadalafil had to be withdrawn from the study prematurely on the evening of the arrival day at 4559 m because of severe AMS. This unfavorable effect has also been reported with use of sildenafil (15), which suggests that phosphodiesterase-5 inhibitors may exacerbate AMS in some susceptible persons. A known side effect of phosphodiesterase-5 inhibitors is headache. However, the headache score did not differ between participants receiving tadalafil and those receiving placebo, which is in line with findings of a previous study (16). We also found that use of tadalafil was not associated with systemic hypotension, as demonstrated elsewhere for nifedipine (7, 25). However, because the number of persons receiving tadalafil was small, further trials are required to test whether tadalafil is a good alternative to nifedipine for prophylaxis against HAPE in susceptible adults without AMS, which are approximately 20% to 30% of all persons with HAPE (28).

Taken together, the results from studies of nifedipine and from our study indicate that in persons susceptible to HAPE, prophylaxis with vasodilators decreases the incidence of HAPE but is ineffective against AMS (25). Although acetazolamide therapy is the standard of care for prevention of AMS (34, 35), dexamethasone may be the ideal prophylaxis to reduce the risk for HAPE and AMS in HAPE-susceptible persons who must ascend rapidly to high altitude. Side effects associated with the use of dexamethasone during short exposure to high altitude may be hyperglycemia, insomnia, and systemic hypertension. In our study, dexamethasone at a dosage of 8 mg twice daily increased blood glucose levels more than did placebo. This unfavorable effect of dexamethasone upon acute exposure to hypoxia has been reported elsewhere (37). Use of dexamethasone did not affect sleep quality and blood pressure. Another potential side effect of prolonged use of dexamethasone at a high dose might be an increased risk for infection. We did not conduct a formal assessment for adverse drug effects. A general recommendation for use of dexamethasone in prophylaxis against HAPE and AMS in adults who are susceptible to HAPE cannot be made on the basis of our findings because of the limited number of highly selected participants, the participants' short exposure to high altitude, the single-center nature of this study, and the lack of assessment of adverse side effects. Further studies are needed to determine the minimal effective dose and to test whether inhaled glucocorticoids are equally effective.

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