CLINICAL RESEARCH STUDY

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Budesonide Versus Acetazolamide for Prevention of Acute Mountain Sickness

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ABSTRACT

BACKGROUND: Inhaled budesonide has been suggested as a novel prevention for acute mountain sickness. However, efficacy has not been compared with the standard acute mountain sickness prevention medication acetazolamide.

METHODS: This double-blind, randomized, placebo-controlled trial compared inhaled budesonide versus oral acetazolamide versus placebo, starting the morning of ascent from 1240 m (4100 ft) to 3810 m (12,570 ft) over 4 hours. The primary outcome was acute mountain sickness incidence (headache and Lake Louise Questionnaire ≥3 and another symptom).

RESULTS: A total of 103 participants were enrolled and completed the study; 33 (32%) received budesonide, 35 (34%) acetazolamide, and 35 (34%) placebo. Demographics were not different between the groups ($P > .09$). Acute mountain sickness prevalence was 73%, with severe acute mountain sickness of 47%. Fewer participants in the acetazolamide group (n = 15, 43%) developed acute mountain sickness compared with both budesonide (n = 24, 73%) (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.3-10.1) and placebo (n = 22, 63%) (OR 0.5, 95% CI 0.2-1.2). Severe acute mountain sickness was reduced with acetazolamide (n = 11, 31%) compared with both budesonide (n = 18, 55%) (OR 2.6, 95% CI 1-7.2) and placebo (n = 19, 54%) (OR 0.4, 95% CI 0.1-1), with a number needed to treat of 4.

CONCLUSION: Budesonide was ineffective for the prevention of acute mountain sickness, and acetazolamide was preventive of severe acute mountain sickness taken just before rapid ascent.

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KEYWORDS: Acetazolamide; Acute mountain sickness; Budesonide; High altitude; Prevention

INTRODUCTION

Acute mountain sickness is a distressing constellation of symptoms including headache, sleep disturbance, fatigue, dizziness, and gastrointestinal upset that commonly occurs in travelers ascending to altitudes above 2500 m (8250 ft).[1,2] Acute mountain sickness incidence varies according to altitude and ascent profile, with rates reported up to 25%-75% on rapid ascent[3-5] and symptom onset typically 6-12 hours after arrival to high altitude.[6] Although this illness is usually self-limiting, it can be debilitating when severe, and left unrecognized or untreated it may progress to potentially fatal high altitude cerebral edema.[6] Gradual ascent can prevent acute mountain sickness through acclimatization,[7,8] but this approach is often impractical or unfeasible for hikers, climbers, or in tactical operations, highlighting the need for effective prophylactic medications when rapid ascent is unavoidable.

Acetazolamide is a carbonic anhydrase inhibitor that is considered the standard agent for chemoprophylaxis of acute mountain sickness and is usually taken the night before

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ascent,[6,9] because this drug has decreased efficacy on rapid ascent.[10,11] Acetazolamide's mechanism of action in acute mountain sickness prevention is not completely clear and likely includes renal-induced metabolic acidosis, resulting in diuresis and enhanced respiratory drive. Budesonide is a novel drug for acute mountain sickness prevention, which was recently explored in 2 studies.[12,13] This inhaled steroid is commonly used to improve pulmonary function for acute and chronic reactive airway disease. Its concentrated action is in the lungs, with free plasma concentrations well below receptor saturation levels in the brain,[14] which raises the intriguing consideration of whether alveolar hypoxia may be responsible for the signaling pathways leading to acute mountain sickness—a condition considered to have a cerebral rather than pulmonary etiology.[6] Pulmonary inflammation as the pathogenic instigator of acute mountain sickness rather than its downstream "victim" would require a paradigm shift of both treatment and prevention of the illness. However, the results of the recent budesonide studies have not been reproduced and validated, nor has budesonide been directly compared with the standard acute mountain sickness prophylactic acetazolamide.

CLINICAL SIGNIFICANCE

- Inhaled budesonide was found to be ineffective for the prevention of acute mountain sickness.
- Day of ascent dosing of acetazolamide offered robust protection against severe acute mountain sickness.
- End tidal carbon dioxide was a better predictor of acute mountain sickness than peripheral oxygen saturation, with smaller increases in ventilation from low altitude associated with greater symptoms of acute mountain sickness.

The objective of this study was to evaluate inhaled budesonide and oral acetazolamide compared with placebo for their efficacy in prevention of acute mountain sickness, using a rapid ascent profile generalizable to the elevations and recreation patterns commonly found in the mountains of the United States and Europe.

MATERIALS AND METHODS

Study Design

This study was a prospective, double-blind, randomized, placebo-controlled trial of budesonide (AstraZeneca, Washington, Del) compared with acetazolamide versus an oral and inhaled visually identical placebo for the prevention of acute mountain sickness. The study was approved by the Stanford University School of Medicine and registered with Clinicaltrials.gov (NCT02604173).

Selection of Participants

We recruited a convenience sample of volunteers through a variety of e-mail lists with both local and national distribution, as well as posted advertisements in Northern and Southern California. Inclusion and exclusion criteria were presented for participants to self-screen for eligibility before enrollment. Eligible participants for this free study had to be healthy, reside at low altitude <1240 m (4100 ft), and be able to complete a moderately strenuous hike at high altitude. Exclusion criteria included participants younger than 18 years or older than 65 years; pregnant or thought to be pregnant; having lived or slept at altitudes >1240 m (4100 ft) in the past week; having taken diuretics, steroids, acetazolamide or nonsteroidal anti-inflammatory drugs the week before the study; allergy to acetazolamide, sulfa medication, or corticosteroids; or a hazardous condition that precluded the ability to hike to high altitude, including sickle cell anemia, severe asthma or chronic obstructive pulmonary disease, severe anemia, or severe coronary artery disease.

Participants' demographic variables were examined to assess selection bias. The study was conducted over the course of 4 weekends in August 2016 in the White Mountains of California. Participants were enrolled at the city of Bishop, Calif with signed informed consent.

Randomization

Randomization was by computer-generated random sequence with an allocation of 1:1:1, with the randomization code unavailable to administrators and participants.

Intervention

We randomized eligible participants in a double-blind fashion the morning of ascent to budesonide (180 μg twice daily [bid], dry powder inhaler; AstraZeneca) and lactulose placebo pill (oral [PO] bid); visually matched acetazolamide (125 mg PO bid; Advantage Pharmaceuticals, Rocklin, Calif) and indistinguishable empty inhaler bid; or inhaled and oral placebo (both bid). The participants were all instructed at time of inhalation regarding the correct method of inhaler use, with medications delivered by researchers to ensure proper inhalation technique to optimize adequate delivery of budesonide to the lungs. Prior studies demonstrated that study participants are unable to differentiate a medicated from a sham inhaler.[12,13]

Baseline data collected at 1240 m (4100 ft) in Bishop, Calif included demographic questionnaires, peripheral oxygen saturation (SpO_2, fingertip pulse oximetry; Nonin Medical Products, Minneapolis, Minn), and end tidal carbon dioxide ($EtCO_2$, Capnostream 20p bedside capnography monitor; Medtronic, Minneapolis, Minn). Participants took the first dose of study medication, then over the next 4 hours drove to a 0.8-km (0.5 mile) hike at 3424 m (11,300 ft), then drove to a staging area at 3545 m (11,700 ft), then hiked approximately 4.3 km (2.7 miles) to 3810 m (12,570 ft), where participants spent the night. The second dose of study medication was taken the evening after dinner, approximately 8 hours after starting ascent. Questionnaires, SpO_2, and $EtCO_2$ were recorded at high altitude the evening of and morning

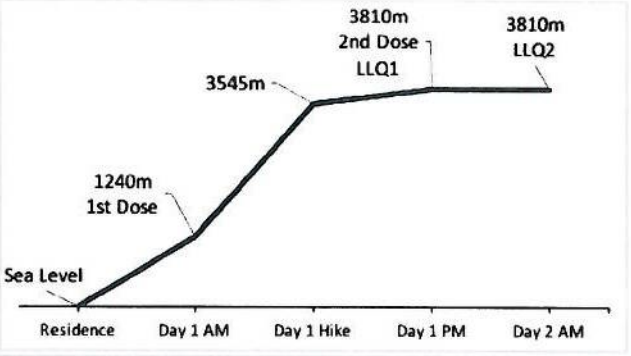

Figure 1 Ascent profile, medications, and examinations. LLQ = Lake Louise Questionnaire.

after ascent (**Figure 1**). If the participants requested treatment for acute mountain sickness symptoms, they provided end point data and then were treated with combinations of acetazolamide (250 mg PO), ondansetron (8 mg oral dissolving tablet), dexamethasone (4 mg PO), and/or supplemental oxygen (2 L/min). Once treated, no further measurements were gathered to not confound results.

Analysis

The primary outcome was incidence of acute mountain sickness as calculated on the Lake Louise Questionnaire (LLQ), a widely used and validated self-reported symptom-based questionnaire.[2] Presence of acute mountain sickness was defined by a LLQ score of ≥3 with the presence of a headache and one other symptom.[2] Secondary outcome measures included incidence of severe acute mountain sickness (LLQ ≥5), SpO_2, and $EtCO_2$. The LLQ was measured the evening of ascent and again the next morning; the values the morning after ascent (or at time of rescue medication) were used for acute mountain sickness analysis to ensure that the maximum amount of time was allotted for the symptoms of acute mountain sickness to declare themselves, and acute mountain sickness severity is typically highest the night after ascent.[9] Furthermore, an LLQ taken the evening of ascent would, by necessity, include the quality of sleep from the prior night at low altitude, and using a low altitude value for diagnosis of a high altitude illness would likely be less accurate.

Primary Data Analysis

Sample size was calculated on the basis of a native acute mountain sickness prevalence of 69% from a previous study with an identical ascent profile to the same elevations.[2] With a total sample size of 100 ($\alpha = .05$, 2-tailed test), the trial had 80% power to detect a significant difference defined a priori as a reduction in acute mountain sickness incidence by 26%. The study was a 2-sample comparison of drug versus placebo, with a 1-sided alternative hypothesis of drug to drug. All demographic variables were analyzed by Pearson's χ^2 tests, with analysis of variance used for weight, height, and age. Primary and secondary outcome measures of acute mountain sickness incidence and severity were analyzed using t tests, with acute mountain sickness peak LLQ by Welch 2-sample t tests. Lake Louise Questionnaire scores were analyzed by Wilcoxon rank sum test, with P values corrected for multiple comparisons by the Holm method. Logistic regression was used to examine multivariate factors for binary outcomes. Outcome measures $EtCO_2$ and SpO_2 were both evaluated for their ability to predict acute mountain sickness (LLQ score) using a Spearman correlation test. P values <.05 were considered significant, and 95% confidence intervals were used. All analysis was conducted using R software (R Foundation for Statistical Computing, Vienna) with standard statistics packages.[15]

RESULTS

One hundred three participants signed informed consent and were randomized to the medications; all participants completed the trial and were included in analysis (**Figure 2**). All the participants had similar baseline characteristics in the 3 treatment arms (**Table 1**). No participants required evacuation.

The total prevalence of acute mountain sickness was 73%. Those participants taking acetazolamide had an absolute reduction of acute mountain sickness by 30% compared with budesonide, and 20% less than those taking placebo (**Figure 3**), with a number needed to treat of 5. Severe acute mountain sickness (LLQ ≥5) was significantly reduced with acetazolamide compared with both budesonide and placebo, with a number needed to treat of 4. The average LLQ score was also significantly reduced in the acetazolamide versus budesonide groups (**Table 2**), with headache significantly less in those taking acetazolamide than budesonide (**Table 3**). We found no changes in significance between placebo and the 2 medication groups after adjusting for age, sex, ethnicity, history of altitude illness, and arrival route by multivariate logistic regression.

Those in the acetazolamide group had statistically significant lower heart rates and increased ventilation (**Table 4**). Combining all the treatment groups as a single cohort, smaller increases in ventilation from low altitude were associated with greater symptoms of acute mountain sickness, with $EtCO_2$ a better predictor of acute mountain sickness than SpO_2 ($r = -0.26$, $P = .01$ vs $r = -0.19$, $P = .05$) (**Figure 4**).

DISCUSSION

This study was the first to compare inhaled budesonide versus oral acetazolamide for the prevention of acute mountain sickness. We found that budesonide was not effective in reducing the incidence of acute mountain sickness; the odds of acute mountain sickness with budesonide were more than 3 times that of participants receiving prophylactic acetazolamide. Study participants taking budesonide were similar to those taking placebo in both the incidence of severe acute mountain sickness and average severity of symptoms.

Our study's findings differed from those that have recently found a benefit of budesonide in reducing acute

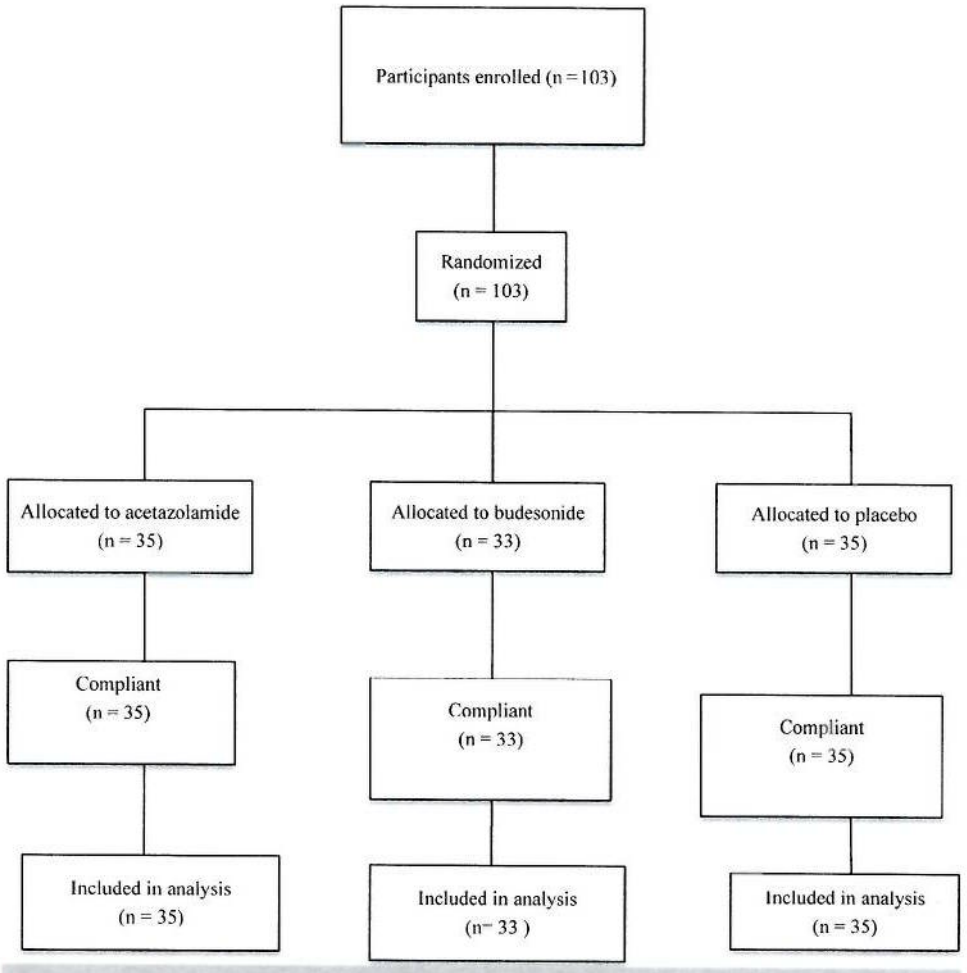

Figure 2 CONSORT participant flow diagram.

mountain sickness compared with placebo on ascent to high altitude.[12,13] Both of the prior budesonide studies had methodologic limitations; however, that need to be considered. The first study compared 3 drugs with placebo, and all were started 3 days before ascent to 3700 m (12,210 ft), which took 2.5 hours by airplane. They found that budesonide reduced acute mountain sickness by 25% and severe acute mountain sickness by 20% over placebo, but the study was not adequately powered for effect, thus limiting interpretation.[13] The second study compared budesonide with dexamethasone and placebo starting the day before a gradual ascent by car to 4200 m (13,869 ft) and then evaluated acute mountain sickness symptoms 3 to 4 days later.[12] They found a 30%-40% difference in acute mountain sickness compared with placebo, but the prolonged ascent profile and time between ascent to symptom measurement limits the generalizability of the findings to most mountain travelers. Although there were numerous demographic factors that may have contributed to the divergent outcomes between the studies, there were many similarities, including dosage of the study drug, size of the cohorts, and symptom measurement tools. Therefore, some benefit of budesonide for acute mountain sickness prevention should have been reproducible if the medication were a truly successful chemoprophylactic.

The action of corticosteroids in the lungs has been suggested to counteract the effects of hypoxia in numerous ways, including reducing pulmonary capillary leakage, stimulation of alveolar fluid reabsorption, inhibition of hypoxic pulmonary vasoconstriction, and stimulating ventilation.[16,17] The potential advantageous pulmonary effects of budesonide and lack of systemic side effects make this a conceptually and clinically attractive option for altitude illness prevention. However, the drug's ineffectiveness compared with both placebo and acetazolamide are such that budesonide should not be recommended for preventon of acute mountain sickness.

The study participants taking placebo were twice as likely to get acute mountain sickness compared with acetazolamide, and although not statistically significant, acetazolamide resulted in a 20%-30% absolute reduction in acute mountain sickness incidence over placebo and budesonide, which is clinically significant. Acetazolamide doubled the odds of preventing severe acute mountain sickness compared with placebo. It is more important and clinically relevant to prevent

Table 1 Participant Characteristics

Variable	Placebo (n = 35)	Acetazolamide (n = 35)	Budesonide (n = 33)	Difference between treatment groups (*P* value)
Female sex	21 (60)	12 (34.3)	15 (45.5)	.27
Age (y), mean (SD)	32 (7)	33 (9)	33 (10)	.68
Height (in), mean (SD)	67 (4.7)	69 (3.6)	69 (4.2)	.16
Weight (lb), mean (SD)	153 (24.2)	163 (26.2)	154 (27.4)	.21
Ethnicity				
White	23 (65.7)	24 (68.6)	24 (72.7)	.57
Asian	9 (25.7)	7 (20)	6 (18.2)	.73
Hispanic	3 (8.6)	2 (5.7)	3 (9.1)	.88
Other	0	2 (5.7)	0	.14
Home altitude				
Sea level	32 (91.4)	30 (85.7)	28 (84.9)	.67
0-455 m (1500 ft)	3 (8.6)	5 (14.3)	5 (15.2)	.74
Arrival route				
Tioga/Sonora	26 (72.2)	22 (61.1)	26 (76.5)	.81
S. California	7 (19.4)	12 (33.3)	6 (17.7)	.29
Lake Tahoe	1 (2.8)	1 (2.8)	1 (2.9)	.59
History of altitude illness	1 (2.9)	0 (0)	3 (9.1)	.81
Birth continent: N. America	25 (71.4)	26 (74.3)	24 (72.7)	.74

Values are number (percentage) unless otherwise noted.

severe acute mountain sickness than the milder form of the disease, because these debilitating symptoms are a more accurate indicator of true high altitude illness and found to be more specific than a lower LLQ score.[18,19]

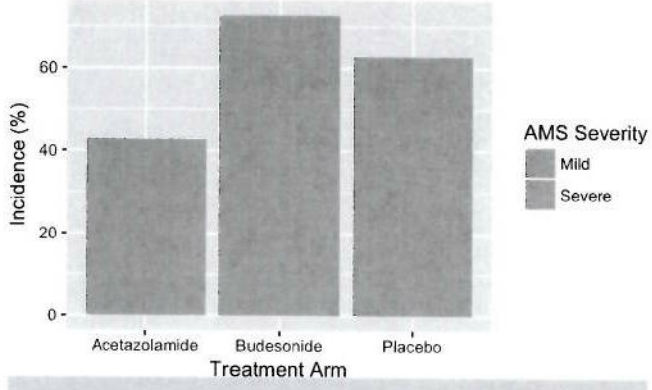

Figure 3 Acute mountain sickness incidence and severity by treatment. AMS = acute mountain sickness.

Although acetazolamide is commonly used as an acclimatization aid, it is traditionally started the day or evening before ascent to optimize time for its diuretic effect and compensatory respiratory changes.[6] This timing may be impractical when rapid ascent is necessary. Acetazolamide's effectiveness for acute mountain sickness prevention has an inverse relationship with rate of ascent to high altitude[20] and is attenuated during rapid ascent.[10,11,21,22] Alternatively, 2 studies have shown its protective effect despite rapid ascent to high altitudes.[23,24] The robust protective effect of acetazolamide on severe acute mountain sickness found in our study supports the drug's utility when taken the morning of ascent, and this was the first study to examine day of ascent dosing. This finding has the potential to increase its usage in those who rapidly ascend in the mountains, such as trekkers, skiers, climbers, and search and rescue or military missions.

Our study found that acetazolamide did not improve SpO_2 at altitude. This is contrary to some previous reports[25-27] and may be related to the drug being started on the day of ascent. However, because acetazolamide lowers the arterial pH and thus shifts the oxygen dissociation curve to the right, the SpO_2

Table 2 Acute Mountain Sickness Scores

Variable	Placebo (n = 35)	Acetazolamide (n = 35)	Budesonide (n = 33)	Acetazolamide vs Placebo, OR (95% CI)	Budesonide vs Placebo, OR (95% CI)	Budesonide vs Acetazolamide, OR (95% CI)
AMS incidence (%)	22 (63)	15 (43)	24 (73)	0.5 (0.2, 1.2)	1.6 (0.6, 4.5)	3.5 (1.3, 10.1)*
Severe AMS incidence (%)	19 (54)	11 (31)	18 (55)	0.4 (0.1, 1)*	1 (0.4, 2.7)	2.6 (1, 7.2)*
LLQ severity, mean (SD)	4.6 (3.5)	3.4 (3.1)	4.5 (2.6)	−1.1 (−2.4, 0.3)	0.5 (−0.9, 1.8)	−1.5 (−2.7, −0.4)*

AMS = acute mountain sickness; CI = confidence interval; LLQ = Lake Louise Questionnaire; OR = odds ratio.
*Statistically significant.

Table 3 Severity of LLQ Symptoms by Subgroup

Variable	Placebo, Mean (SD)	Acetazolamide, Mean (SD)	Budesonide, Mean (SD)	Acetazolamide vs Placebo, *P* value	Budesonide vs Placebo, *P* value	Acetazolamide vs Budesonide, *P* value
GI symptoms	0.47 (0.62)	0.26 (0.45)	0.52 (0.71)	.41	.89	.41
Headache	1.38 (1.07)	0.82 (0.83)	1.45 (0.94)	.06	.84	.02*
Dizziness	0.47 (0.76)	0.38 (0.7)	0.45 (0.56)	1	1	1
Poor sleep	1.47 (0.88)	1.24 (0.89)	1.45 (0.83)	.73	.87	.73
Fatigue	0.69 (0.82)	0.41 (0.66)	0.67 (0.78)	.4	.98	.4

GI = Gastrointestinal; LLQ = Lake Louise Questionnaire.
*Statistically significant.

for a given arterial PO_2 should be lower on acetazolamide. We did not measure arterial blood gases and cannot confirm that arterial PO_2 was higher in the acetazolamide group, although other studies have demonstrated this.[26,28] The relationship of SpO_2 to acute mountain sickness is unclear, and we found only a very weak correlation. Overall, values of SpO_2 in those with and without acute mountain sickness have so much overlap that SpO_2 is an inaccurate test for diagnosis of altitude illness or acute mountain sickness prediction.[26,28,31]

Alternatively, we found a significant increase in alveolar ventilation in the acetazolamide group measured by a decrease in $EtCO_2$. This is consistent with increased ventilation stemming from the bicarbonate diuresis that has been implicated as the primary acclimatization mechanism of acetazolamide.[32,33] Independent of treatment group, those with smaller increases in ventilation were more likely to be diagnosed with acute mountain sickness, which supports the ventilatory component of acclimatization. Future high altitude studies may want to explore $EtCO_2$ for more accurate

Table 4 Physiologic Variables by Subgroup

Variable	Placebo, Mean (SD)	Acetazolamide, Mean (SD)	Budesonide, Mean (SD)	Acetazolamide vs Placebo, *P* value	Budesonide vs Placebo, *P* value	Acetazolamide vs Budesonide, *P* value
RR	14.7 (6.1)	13.9 (4.4)	14.5 (5)	.59	.9	.64
HR	88.3 (14.8)	80.2 (13.6)	83.8 (14.7)	.02*	.22	.31
SpO_2	86.4 (5)	88.1 (3.8)	88.6 (4.1)	.12	.06	.6
$EtCO_2$	28.6 (3.3)	26.7 (3.1)	27.4 (2.6)	.01*	.1	.3

$EtCO_2$ = end tidal CO_2; GI = gastrointestinal; HR = heart rate; LLQ = Lake Louise Questionnaire; RR = respiratory rate; SpO_2 = peripheral oxygen saturation.
*Statistically significant.

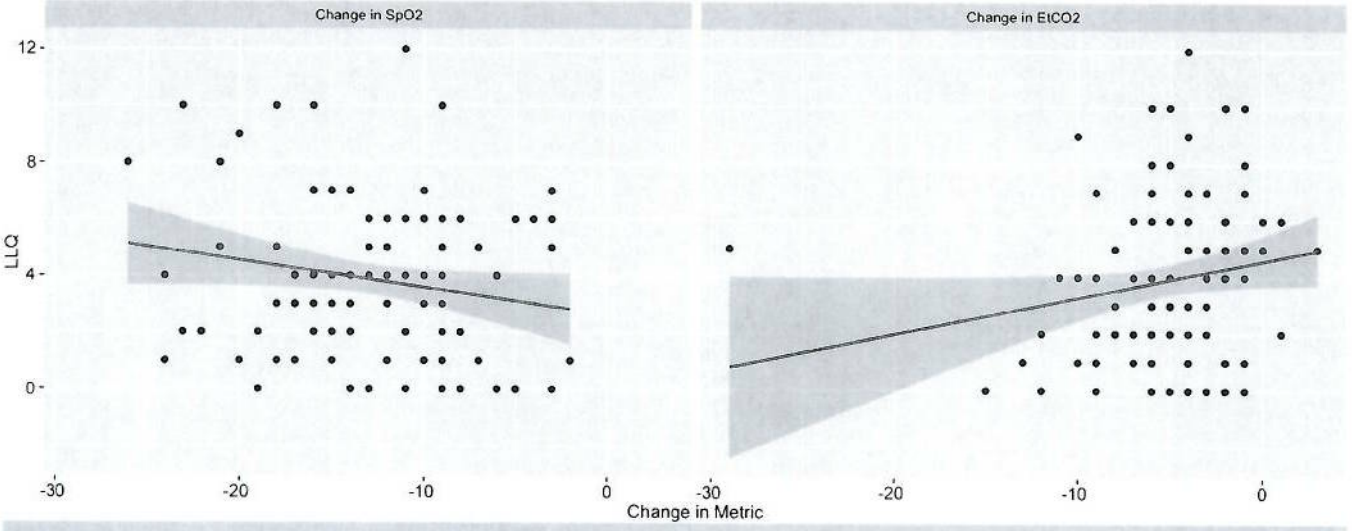

Figure 4 Correlation of changes from low altitude to high altitude in end tidal carbon dioxide and peripheral oxygen saturation with acute mountain sickness severity. $EtCO_2$ = end tidal CO_2; LLQ = Lake Louise Questionnaire; SpO_2 = peripheral oxygen saturation.

insight into pulmonary functional changes and drug responsiveness to the hypobaric hypoxic environment.

This study has some limitations. Our study started the participants' medication the morning of ascent. This differed from the prior budesonide studies that began chemoprophylaxis several days before ascent. The prolonged pretreatment strategy may have contributed to the previously observed efficacy, but the drug's short half-life and high receptor affinity make it less likely that a short antecedent treatment course attenuated the drug's protective effects. Additionally, a slightly lower dose of 180 μg was used (vs 200 μg in the previous budesonide studies), which may have been relevant to the observed lack of treatment effect. This study was conducted at altitudes commonly encountered by recreationists in North America and Europe. The setting was chosen to maximize generalizability, but caution should be exercised when extrapolating the results of acetazolamide's efficacy started the day of rapid ascent to higher altitudes than those specifically studied. We could not control for various factors, such as ambient temperature, wind speed, rate of ascent, liquid and caloric intake of the participants, or underlying physiological condition of the participants, that could potentially confound the study results and conclusions. The randomization was not stratified by sex, and the placebo arm had almost double the number of female participants; however, sex-related adaptions to high altitude have not been established and were unlikely a factor. The participants were self-selected and cannot necessarily be applied to other hiking populations because ascent rate, demographics, and final elevations may differ.

CONCLUSION

We found that budesonide was ineffective for prevention of acute mountain sickness compared with both placebo and acetazolamide. Budesonide should not be recommended for acute mountain sickness prevention. Acetazolamide decreased the incidence of severe acute mountain sickness when taken just before rapid ascent. The favorable effect from day-of medication dosing may be an advantage for time constrained ascents to high altitude.

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