ORIGINAL RESEARCH

Reduced Acetazolamide Dosing in Countering Altitude Illness: A Comparison of 62.5 vs 125 mg (the RADICAL Trial)

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Introduction—North American guidelines propose 125 mg acetazolamide twice daily as the recommended prophylactic dose to prevent acute mountain sickness (AMS). To our knowledge, a dose lower than 125 mg twice daily has not been studied.

Methods—We conducted a prospective, double-blind, randomized, noninferiority trial of trekkers to Everest Base Camp in Nepal. Participants received the reduced dose of 62.5 mg twice daily or the standard dose of 125 mg twice daily. Primary outcome was incidence of AMS, and secondary outcomes were severity of AMS and side effects in each group.

Results—Seventy-three participants had sufficient data to be included in the analysis. Overall incidence of AMS was 21 of 38 (55.3%) in reduced-dose and 21 of 35 (60.0%) in standard-dose recipients. The daily incidence rate of AMS was 6.7% (95% CI 2.5–10.9) for each individual in the reduced-dose group and 8.9% (95% CI 4.5–13.3) in the standard-dose group. Overall severity of participants' Lake Louise Score was 1.014 in the reduced-dose group and 0.966 in the standard-dose group (95% CI 0.885–1.144). Side effects were similar between the groups.

Conclusions—The reduced dose of acetazolamide at 62.5 mg twice daily was noninferior to the currently recommended dose of 125 mg twice daily for the prevention of AMS. Low incidence of AMS in the study population may have limited the ability to differentiate the treatment effects. Further research with more participants with greater rates of AMS would further elucidate this reduced dosage for preventing altitude illness.

Keywords: high altitude, Diamox, prophylaxis, Nepal, Denali, Alaska

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Introduction

Acute mountain sickness (AMS) refers to a constellation of symptoms after acute ascent to high altitude, with the cardinal symptom of headache. Traditionally, AMS is defined as the presence of headache plus 1 or more of the following: gastrointestinal symptoms, insomnia, dizziness/lightheadedness, and fatigue/weakness.¹ Insomnia was removed from the criteria in 2018 because sleep disturbances are thought to be attributable simply to hypoxia

of high altitude rather than true AMS.² Symptoms can occur as early as 1 h after ascent but typically present within the first 6 to 10 h.³ Approximately 10 to 25% of unacclimatized individuals ascending above 2500 m will experience mild AMS.⁴ The incidence can be 50 to 85% in those ascending to 4500 to 5500 m, especially at relatively fast ascent rates.^{4–8} At any high-altitude elevation, AMS symptoms can be incapacitating and lead to safety concerns.^{4,9–12} The severity of AMS increases with speed of ascent and increasing altitude.¹²

The common strategy for preventing altitude illness is gradual ascent, which allows time for acclimatization.¹³ This includes ascending an average of less than 500 m per day at altitudes above 3000 m with a rest day every 3 to 4 d, during which one sleeps at the same altitude.¹³ Given the time constraints associated with expeditions or the speed necessary for some rescue operations and military assignments, slow ascent is not always possible. In these cases, pharmacologic prophylaxis may be warranted. Individuals with a history of AMS while ascending at a reasonable profile and those with moderate or high risk for developing AMS should also consider pharmacologic prophylaxis.¹³ Acetazolamide is the standard agent of choice for medical prophylaxis against high-altitude illness.¹³

The main mechanism of acetazolamide is via inhibition of the carbonic anhydrase enzyme. At higher doses, both renal and red blood cell carbonic anhydrase is inhibited. At doses of 250 to 500 mg daily, renal carbonic anhydrase is preferentially inhibited because of the concentration of the drug at this site, leading to a bicarbonate diuresis and mild metabolic acidosis.^{14–16} During ascent to high altitude, ventilation is stimulated by lower oxygen partial pressure as a result of stimulation of hypoxia-sensitive peripheral chemoreceptors. This response is limited by the fall in arterial partial pressure of carbon dioxide and development of respiratory alkalosis. The mild metabolic acidosis produced by acetazolamide allows for an increase in this ventilatory response, thereby speeding acclimatization.^{15,16}

The use of acetazolamide for prevention of AMS has become more widespread among tourists to high-altitude areas of Nepal. One series of studies found that acetazolamide use in trekkers in the Annapurna region increased from less than 2% in 1986 to 12% in 1998.^{17,18} When a similar study was repeated in 2010, the incidence of self-medication with acetazolamide was 44% among those surveyed.¹⁹ A survey-based study of climbers on Everest expeditions between 1963 and 2015 indicated that medications were used during 43% of climbs. The majority of these data were collected after 2000, with acetazolamide noted to be the most commonly used medication.²⁰ In Europe, anonymously collected urine from male climbers

on Mont Blanc tested positive for acetazolamide in 21% of samples,²¹ indicating that acetazolamide use is prevalent in European high-altitude areas as well.

Six meta-analyses to date have reviewed the literature on acetazolamide.^{22–27} The most recently published meta-analysis²⁷ established that doses of 750 mg, 500 mg, and 250 mg per day are all effective with numbers needed to treat of 3, 7, and 6, respectively. This same analysis concluded that acetazolamide 250 mg·d⁻¹ is the lowest effective dose to prevent AMS above 3000 m. As of 2014, the current North American guidelines parallel this meta-analysis and recommend acetazolamide 125 mg twice daily for prophylaxis of altitude illness.¹³

Although acetazolamide speeds acclimatization and helps prevent high-altitude illness,²⁸ side effects may deter use. Multiple studies have demonstrated increased side effects with higher doses of acetazolamide.^{8,26,29} In particular, the incidence of paresthesia seems substantially higher in those taking 750 mg daily compared with those taking lower doses.²⁹ Altered sensation of taste, especially with respect to carbonated beverages, has also been found to be more common at higher doses.²⁹ Acetazolamide is a mild diuretic, which is its intended effect in certain medical treatments. However, when used for acclimatization, frequent urination is considered a negative side effect, potentially leading to interruption of daytime activities and disrupted sleep. Other side effects include headache, nausea, and rash.^{3,26} These side effects can lead to safety concerns at altitude.

To our knowledge, a dose lower than 125 mg twice daily has not been studied. Anecdotally, high-altitude mountaineers use these lower doses with reported beneficial effects. In addition, pharmacological data suggest that lower doses may be as effective as the standard dose on these AMS prophylactic mechanisms. Our primary objective was to compare the incidence of AMS between reduced-dose acetazolamide and standard-dose acetazolamide. Secondary objectives were to measure AMS severity and side effects. We hypothesized that a lower dose of acetazolamide of 62.5 mg twice daily would be as effective as 125 mg twice daily in preventing AMS and would result in fewer side effects.

Methods

PARTICIPANTS AND LOCATIONS

After receiving approval from the Nepal Health Research Council, the US National Park Service institutional review board, and the University of Utah institutional review board, we conducted a randomized, double-blinded, non-inferiority trial in Nepal and Alaska between March 2012 and March 2016. We subsequently chose to include only those participants from Nepal for analysis; the 2 cohorts

with different latitudes, technical and exertion efforts, and ascent rates could have interjected bias into the study. We chose a noninferiority design because many doses of acetazolamide, including the 125 mg twice-daily regimen, have been shown to be effective and safe in other placebo-controlled trials. The noninferiority design allowed us to compare the 2 treatment groups directly without inserting a placebo arm into the study.

We recruited participants who were planning to trek to Everest Base Camp in Nepal. Recruitment was during the spring (March–May) and fall (September–November) trekking seasons. Recruitment was performed 1) via flyers posted online and at hotels and 2) by a research assistant or coinvestigator who approached trekking or climbing groups in Kathmandu. A research assistant or coinvestigator obtained informed consent, and enrollment took place in Kathmandu, Nepal (1400 m, 4593 ft). Participants ascended on their own itinerary.

Inclusion criteria were age ≥ 18 y and no history of low potassium, low sodium, kidney disease or dysfunction, liver disease or dysfunction or cirrhosis, suprarenal gland failure or dysfunction, hyperchloremic acidosis, or angle-closure glaucoma. Participants were excluded if they had experienced any reaction to sulfa drugs or acetazolamide at any point in time, were planning to take aspirin > 325 mg·d⁻¹ on the trek or climb, were pregnant or lactating, or planned to take additional acetazolamide or any medications that were known to potentially prevent AMS (dexamethasone, ginkgo biloba, nifedipine, sildenafil). Two studies that examined ibuprofen to prevent AMS^{30,31} were published after our study commenced, and therefore planned ibuprofen use was not specifically an exclusion criterion. Participants did record whether they took a “pain reliever” during the study, and ibuprofen use was controlled for in the statistical methods as a potential confounder.

COLLECTION OF DEMOGRAPHIC INFORMATION

Participants completed a health questionnaire that included the following: age, sex, height, weight, chronic medical problems, medications, history of altitude illness (AMS, high-altitude cerebral edema, high-altitude pulmonary edema, high-altitude headache), altitude at which they currently live, and altitude from which they were traveling. Participants were then weighed on an accurately calibrated scale (Healthometer Digital Scale; Jarden-Newell, Hoboken, NJ) and wore only base layers without shoes or boots.

STUDY MEDICATION

Medications were formulated and randomized by the University of Utah investigational drug services. Participants received a bottle of 24 capsules (12 d of

medications) of either acetazolamide 62.5 mg or 125 mg that were identical in appearance and packaging. Participants were instructed to start taking acetazolamide on the morning before they flew into the mountains. They were instructed to take 1 pill in the morning (approximately 0800) and 1 pill in the evening (approximately 2000). Participants were instructed to take the study medication until they completed the 12-d course, their booklet was completed, or they reached their maximum altitude before descending. Everest Base Camp was not a specific endpoint for the study. Participants were instructed to avoid taking any nonprescribed additional medications while taking acetazolamide. If participants used these medications, they were instructed to record it in their booklet.

QUESTIONNAIRE

Participants completed 2 short questionnaires each day at approximately 0800 and approximately 2000. The questionnaires included 1) the Lake Louise Score (LLS)¹ to evaluate for AMS and 2) side effect questionnaire. The side effect questionnaire included the following questions: “In the past 12 h, have you experienced the following symptoms: Tingling of toes? Tingling of fingers? Increase in urination? Taste change of beverages?” This questionnaire has not been validated. Symptoms were self-reported and rated on a 5-point scale:

- 0—None
- 1—Very mild, barely noticeable
- 2—Mild, noticeably present but not bothersome
- 3—Moderate, present most of the day, mildly bothersome
- 4—Moderately severe, constantly aware and interrupted normal activities
- 5—Severe, incapacitating

Study medication compliance was self-recorded by the question: “In the past 12 h I took my acetazolamide as instructed, Yes/No.” Participants recorded whether they ingested any additional medications or supplements in the past 12 h: pain reliever, sleep medication, multivitamin, or supplement. Coinvestigators or research assistants collected booklets at the end of the trek in Kathmandu. If this was not possible, booklets were mailed to the primary investigator.

OUTCOMES

The primary outcome was incidence of AMS. Secondary outcomes were continuous LLS and self-recorded side effect scores. Both the number and severity of side effect scores were analyzed.

STATISTICAL METHODS

Sample size

For the primary incidence analyses, a noninferiority design was used in which a sample size calculation found that 73 participants (36.3 in each group) were required to have 80% power in a 1-sided test of significance at $\alpha = 0.05$, allowing for a 20% noninferiority margin. This is based on the incidence of mild or severe AMS from an article that assessed acetazolamide for the prevention of AMS.⁸ In that article, AMS was experienced by 13.6% of the acetazolamide group receiving the standard dose. We enrolled an additional 30% of participants to account for dropouts, those with an insufficient attained altitude, and those with insufficient data for analysis. Power calculations were performed using nQuery version 7.0 (Statistical Solutions Ltd, Cork, Ireland).

Analysis

Analyses for incidence of AMS used the Wilcoxon rank-sum test for differences in the number of days until the event and Kaplan-Meier analysis with the log-rank test. Daily incidence rates were computed using life table analysis to calculate the incidence rate on each day and mean values; 95% confidence intervals were determined from those data. The 2 trial arms had to be within 20% incidence of AMS to be noninferior at a level of $P < 0.05$.

Evaluation of continuous LLS was performed by comparing the point estimates and confidence intervals in a repeated measures mixed linear model. Although the mean LLS result for the reduced dose was expected to have no difference from the mean for the standard dose,

to be noninferior at $P < 0.05$, the LLS result for the reduced dose had to be within +1.1 of the mean for the standard dose. The analyses were performed with SPSS version 23.0 (IBM SPSS Statistics, Chicago, IL). The study was operated under clinical trials identifier NCT01993667 in clinicaltrials.gov.

Results

PARTICIPANTS AND ASCENT

A total of 130 participants were enrolled in the study, 96 from Nepal and 34 from Alaska. For the reasons noted previously, the Alaska participants were not included in the analysis. Participant details used for analysis are described in Table 1. All demographic variables were well matched between treatment arms. Figure 1 shows the enrollment and participant flow. Participants were excluded from the analysis if they did not meet the following criteria: 1) did not ascend higher than 3000 m (9843 ft); 2) had <25% compliance in taking the medication twice daily (slight variation on hours was acceptable; this threshold identified a small number of severe outliers in both arms of the study); and 3) had >25% missing data points in LLS and side effect questionnaire. The compliance rates were 78.6% in the standard-dose and 71.7% in the reduced-dose groups ($P = 0.21$). Seventy-three participants from Nepal met these criteria and satisfied the sample size requirements.

The average altitude reached was 5020 ± 420 m in the reduced-dose group and 5515 ± 332 m in the standard-dose group ($P = 0.60$). The ascent rate was 524 ± 232 m·d⁻¹ in the reduced-dose group and 488 ± 224 m·d⁻¹ in the standard-dose group ($P = 0.50$).

Table 1. Baseline characteristics of the study population

Characteristic	Overall	Standard dose	Reduced dose	P value
Age (y)	45.3±13.4	46.2±13.3	44.6±13.5	0.61
Sex (female)	35.6%	33.3%	37.8%	0.69
Height (m)	1.74±0.10	1.75±0.08	1.73±0.11	0.28
Weight (kg)	76.1±13.6	76.4±11.1	75.9±15.8	0.89
Altitude of residence (m)	632±804	582±719	682±887	0.62
Altitude traveling from (m)	745±803	766±724	726±892	0.85
History of AMS	10.1%	8.6%	11.8%	0.66
Taken acetazolamide previously	27.5%	31.4%	23.5%	0.46
History of HACE	1.4%	0.0%	2.9%	0.31
History of HAPE	2.9%	2.9%	2.9%	0.98
History of HAH	11.6%	14.3%	8.8%	0.48
History of aspirin use	18.8%	12.1%	15.4%	0.46
History of sulfa drugs	46.2%	46.9%	45.5%	0.91
Baseline Lake Louise Score $\geq 1^a$	36.1%	40.0%	32.4%	0.50

AMS, acute mountain sickness; HACE, high altitude cerebral edema; HAPE, high altitude pulmonary edema; HAH, high altitude headache.

^a Maximum LLS at baseline was 4.

Figure 1. Participant enrollment and flow during stages of study.

INCIDENCE OF ACUTE MOUNTAIN SICKNESS

The time to AMS was a median of 6.0 d (interquartile range 3.0–8.5) for the reduced dose and 4.5 d (interquartile range 2.5–7.75) for standard dose ($P=0.32$). [Figure 2](#) displays the incidence data in an incidence curve (1 minus the AMS-free survival).

Overall incidence of mild or severe AMS was 21 of 38 (55.3%) in reduced-dose and 21 of 35 (60.0%) in standard-dose recipients ($P=0.47$ and $P<0.05$, respectively, for noninferiority). The daily incidence rate of mild or severe AMS for each individual was 6.7% (95% CI 2.5–10.9) in the reduced-dose group and 8.9% (95% CI 4.5–13.3) in the standard-dose group. For just severe AMS, the daily incidence rate for each individual was 2.9% (95% CI 1.0–4.9) in the reduced-dose group and 1.7 (95% CI 0.2–3.1) for the standard-dose group.

LAKE LOUISE SCORE SEVERITY

The mean LLS for the reduced-dose group was 1.014, and mean LLS for the standard-dose group was 0.966 (95% CI 0.885–1.144). For the reduced 62.5 mg dose to be inferior, the LLS for that dose would have to be above 2.066. See [Figure 3](#) for the overall severity results. After adjusting for ibuprofen use, reduced-dose acetazolamide was not different from standard dose, with a mean LLS score of 1.14 in reduced-dose and 1.07 in standard-dose treatment when ibuprofen is included in the model (CI 0.91–1.23, $P<0.05$; thus demonstrating noninferiority). Those using ibuprofen had a mean LLS score of 1.55, and those not using it had 0.94, which was highly significantly different ($P=0.001$).

SIDE EFFECTS

Frequency and severity of side effects were similar in both groups, with urination ($P=0.15$), beverage taste change ($P=0.36$), toe tingling ($P=0.28$), and finger tingling ($P=0.28$) all nonsignificant.

Discussion

In our study of healthy trekkers and climbers ascending to high altitude, the reduced 62.5 mg twice-daily acetazolamide dose was noninferior to the current recommended dose of 125 mg twice daily for prevention of AMS within the 20% noninferiority margin. These results support our hypothesis on primary outcome and demonstrate the possibility of using a lower acetazolamide dose than previously recommended.

The prophylaxis of altitude illness with the lowest effective dose of acetazolamide has been a topic of attention in mountain medicine for many years. Acetazolamide dosing was discussed in the literature as early as the 1960s when acetazolamide was established as safe and effective in the prevention of AMS.³² Since then, numerous studies have examined acetazolamide at varying doses, and 6 meta-analyses have attempted to define the ideal dose. A meta-analysis by Dumont et al in 2000²³ reported that acetazolamide 750 mg·d⁻¹ was more efficacious than placebo (NNT 2-3) but that acetazolamide 500 mg·d⁻¹ was not significantly different from placebo (NNT 7). They concluded that lower doses were likely not effective and not recommended. Since that publication, however, many trials have examined 250 mg·d⁻¹ compared with placebo and noted this dose to be effective.

Figure 2. Incidence of the first mild or severe acute mountain sickness diagnosis in the standard- and reduced-dose groups across the study period. Nonevent participants with fewer than the full 12 d of follow-up are indicated as censored in the analysis at the time of their last reported Lake Louise Score.

The most recently published review on acetazolamide for preventing AMS²⁷ notes 250 mg·d⁻¹ as the lowest effective dose with supportive clinical evidence.

Lower doses have pharmacological evidence. A study of acetazolamide in critically ill patients indicated that substantial bicarbonate diuresis occurs at doses as low as 1 mg·kg⁻¹ intravenously, providing support for the lower doses examined in our study.¹⁴ When higher doses of acetazolamide were administered, a minimal increase in excretion of water and bicarbonate was observed above 2.5 to 5 mg of acetazolamide per kg,¹⁴ indicating that the bicarbonate diuresis may be maximized at such doses.

Our study found similar side effects with both doses and thus failed to support one of our secondary hypotheses. Although our study did not demonstrate fewer and less significant side effects with the reduced dose, evidence from other studies suggests that this should have been the case. Previous studies have established an increase in paresthesia at higher doses of acetazolamide.²⁹

Some of the side effects of acetazolamide seem to be weight based. Perhaps the 62.5 mg and 125 mg twice-daily doses are equivalent in both their ability to prevent AMS and in their side effect profile. Alternatively, our methods may not have been robust enough to detect differences. The side effect profile was based entirely on self-reported and subjective information, which may not have detected differences that may have existed. Environmental and logistical challenges in Nepal did not make it possible to design the study to precisely measure urine output and to conduct structured interviews; these actions would have more objectively quantified the side effect profiles in question.

Participants' use of ibuprofen correlated with higher LLS. We interpret this to mean that that ibuprofen was taken to treat symptoms experienced by these individuals with higher scores (eg, headache) rather than taken with the intent to prevent AMS. The ability of ibuprofen to potentially prevent AMS was likely not known to most of the study participants because of the publication times

Figure 3. Mean Lake Louise Scores for 62.5 mg and 125 mg twice-daily doses at each point in the study period (reduced dose = 62.5 mg twice daily, standard dose = 125 mg twice daily).

of those studies. Our results neither support nor contradict ibuprofen's ability to prevent AMS.

The ascent rates in our study (reduced-dose group: $524 \pm 232 \text{ m} \cdot \text{d}^{-1}$, standard-dose group: $488 \pm 224 \text{ m} \cdot \text{d}^{-1}$) were sufficient to cause AMS and would fall into a low or moderate risk category as described by Luks et al.¹³ Kayser et al defines an ascent to high altitude with transport as high risk (eg, a flight to Lukla or Denali Base Camp), even if ascent thereafter is performed by trekking or climbing.²⁵ Therefore, we believe that our study population was exposed to high-altitude ascent profiles sufficient to cause AMS.

Underlying AMS incidence may be a factor in any study that does not employ a placebo arm. Hackett et al in 1976¹⁰ reported an overall incidence of AMS of 52.5% along this same Nepal trekking route, with AMS occurring 60% in those who flew to Lukla. Another study by Gertsch et al³¹ published in 2012 on the same Nepal trekking route reported a 40% incidence of AMS in the placebo group. Basnyat et al²⁹ reported a 51% incidence of AMS in 2006 in their placebo group along the same Nepal

trekking route. Local educational campaigns and more widely published altitude illness prevention guidelines have likely helped decrease the rate of AMS in Nepal since these studies were completed. A more recent study published in 2015 measuring AMS prevention and sleep characteristics as 1-point measurements at 4530 m or 4371 m along the Nepal trekking route noted AMS incidence of 17%, indeed lower than the preceding values.³³ A placebo arm would have helped determine underlying AMS incidence. However, some high altitude scholars have called for cessation of placebo arms in acetazolamide prophylaxis trials because the benefit over placebo has been well established.³⁴ We conclude that medication effect was contributing to low daily AMS incidence rather than simple acclimatization, but we acknowledge that without underlying AMS rates or a placebo arm we cannot conclude this with absolute certainty.

Our overall AMS incidence was higher than many other published rates among individuals taking acetazolamide. We enrolled and started in Kathmandu and obtained 2 LLS measurements per day during ascent.

Many participants had minor AMS that arose and then resolved by the next LLS assessment 12 h later, and most participants had an LLS of 0 across the majority of the study period of 12 d. On any given day, a mix of different participants had an LLS ≥ 3 , which then dropped below 3 by the next measuring period, thereby resolving the AMS. Because the daily incidence and mean LLS severity was low, we attribute our high overall incidence to the number of measurements over the study period rather than inefficacy of the medication.

Current guidelines¹³ recommend that acetazolamide be taken before ascent to altitude when used for prophylaxis against AMS. Previous studies examining acetazolamide doses of 250 mg·d⁻¹ have, however, recruited participants after ascent to altitude, with some enrollment occurring above 3000 m.^{29,35,36} Initiating AMS prophylactic medications at these altitudes may not be generalizable to most trekking or climbing populations. By recruiting participants at low altitude, we paralleled current guidelines and aimed to represent typical prophylactic use of acetazolamide in trekking and climbing populations. This approach is, to our knowledge, the first to employ this prophylaxis strategy in a high-altitude research study. Although we cannot definitively explain the overall low LLS severity in our study, starting medical prophylaxis at low altitude (vs after partial acclimatization during ascent) may have provided additional AMS protection throughout the trek or climb.

Although recruiting and enrolling at low altitude may parallel current practices, we found recruiting in Kathmandu and Talkeetna challenging, perhaps more challenging than when trekkers or climbers were already in the mountains. Denali climbers in Talkeetna were anxiously preparing for their climb, and research was not their main priority (even if it meant a chance for better acclimatization). Recruiting in Kathmandu usually required our research team to identify trekking groups before groups arrived in Nepal, which added another layer of separation between the study team and potential participants. After travel to the mountains, though, the number of dropouts in our study, despite early enrollment and the longitudinal course, was sufficiently low that we can recommend this study design in the future. Research teams studying altitude prevention in the future may wish to match their protocols to the medical prophylactic strategies typically employed by climbers and trekkers and to continue to seek recruitment strategies to support these methodologies.

LIMITATIONS

Participants ascended at their own pace, and many in our study did not ascend extremely high or fast, which may

have masked a difference between AMS incidence rates. If climbers and trekkers proceeded with a slow and cautious ascent rate, then AMS rates would be low and potentially confound medication effect with that of simple acclimatization. In addition, the overall incidence of AMS is likely decreasing in the Khumbu area of Nepal because of greater education about altitude illness. A placebo arm would have helped determine the role of these potential confounders.

We conclude that medication effect was contributing to AMS incidence rather than simple acclimatization or low native AMS rates, but we acknowledge that our methods could not exclude a falsely significant finding. The 20% noninferiority threshold margin in the setting of an unknown rate of AMS (but which has been recently reported as lower than 20% in these parts of the Khumbu) would have led to treatments having a statistically significant lack of difference between them and an erroneous conclusion that the reduced-dose acetazolamide was noninferior to standard-dose acetazolamide.

Participants did not have a uniform rate of ascent, and this could have interjected an underlying bias into hypoxic stress of participants. We do not believe that the different trekking seasons in Nepal had barometric implications that affected rates of AMS. Geographical areas usually have slight seasonal variations in pressure. In Nepal, seasonal variations of pressure are more apparent during monsoon/nonmonsoon times. We anticipate little seasonal variation during the spring and fall enrollment periods.

The study was powered for incidence and severity and based on data that came from a different population at a different elevation, latitude, and rate of ascent. Incidence of AMS in the van Patot study⁸ for standard-dose acetazolamide was 14%, which could have biased the sample size calculation.

We did not ask specifically about perioral paresthesia in the side effect profiles, which may have decreased the reporting of side effects. Side effects were self-reported rather than objectively measured.

Conclusions

Reduced-dose acetazolamide 62.5 mg twice daily was noninferior to the current standard dose of 125 mg twice daily for the prevention of AMS in our study. These results indicate that trekkers and climbers with ascent profiles similar to those in our study may be able to use a lower dose of acetazolamide than has previously been recommended to prevent AMS. Although the difference in incidence of AMS between the reduced dose and standard dosing of acetazolamide was not inferior, the daily incidence was low. The very low daily incidence of

AMS without a placebo arm to fully appreciate the native rates of disease may have resulted in a false finding that the reduced dose of acetazolamide was no worse (ie, noninferior) than low-dose acetazolamide. We expected to see a decrease in side effects experienced by the reduced-dose group, but this was not demonstrated by our data. Further study is required with larger numbers of participants to confirm the efficacy of this dose for prophylaxis of AMS at these altitudes. Investigation into the most efficacious dose of acetazolamide should continue to be pursued, and further research will be required to definitively establish ideal dosing.

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