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Efficacy of Low-dose Acetazolamide (125 mg BID) for the Prophylaxis of Acute Mountain Sickness: A Prospective, Double-blind, Randomized, Placebo-controlled Trial

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ABSTRACT

Basnyat, Buddha, Jeffrey H. Gertsch, E. William Johnson, Franco Castro-Marin, Yoshio Inoue, and Clement Yeh. Efficacy of low-dose acetazolamide (125 mg BID) for the prophylaxis of acute mountain sickness: a prospective, double-blind, randomized, placebo-controlled trial. *High Alt Med Biol* 4:45–52, 2003.—The objective of this study was to determine the efficacy of low-dose acetazolamide (125 mg twice daily) for the prevention of acute mountain sickness (AMS). The design was a prospective, double-blind, randomized, placebo-controlled trial in the Mt. Everest region of Nepal between Pheriche (4243 m), the study enrollment site, and Lobuje (4937 m), the study endpoint. The participants were 197 healthy male and female trekkers of diverse background, and they were evaluated with the Lake Louise Acute Mountain Sickness Scoring System and pulse oximetry. The main outcome measures were incidence and severity of AMS as judged by the Lake Louise Questionnaire score at Lobuje. Of the 197 participants enrolled, 155 returned their data sheets at Lobuje. In the treatment group there was a statistically significant reduction in incidence of AMS (placebo group, 24.7%, 20 out of 81 subjects; acetazolamide group, 12.2%, 9 out of 74 subjects). Prophylaxis with acetazolamide conferred a 50.6% relative risk reduction, and the number needed to treat in order to prevent one instance of AMS was 8. Of those with AMS, 30% in the placebo group (6 of 20) versus 0% in the acetazolamide group (0 of 9) experienced a more severe degree of AMS as defined by a Lake Louise Questionnaire score of 5 or greater ($p = 0.14$). Secondary outcome measures associated with statistically significant findings favoring the treatment group included decrease in headache and a greater increase in final oxygen saturation at Lobuje. We concluded that acetazolamide 125 mg twice daily was effective in decreasing the incidence of AMS in this Himalayan trekking population.

Key Words: altitude sickness; Himalayas; prevention; trekkers; randomized; placebo-controlled; double blind

INTRODUCTION

ACUTE MOUNTAIN SICKNESS (AMS) is a syndrome of headache, nausea, dizziness, sleeplessness, and fatigue that affects travelers ascending above 2000 m. Although itself a benign malady, AMS can easily progress to often fatal high altitude pulmonary edema (HAPE)

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and/or high altitude cerebral edema (HACE) (Basnyat, 2001; Hackett and Roach, 2001). The best method of AMS prevention remains a slow, conservative ascent to altitude, with minimal physical exertion in order to acclimatize. However, this is sometimes impractical, such as with AMS-susceptible persons attempting to go to high altitude and rescue or military endeavors. It therefore becomes important to take additional prophylactic measures to reduce the incidence of AMS in these at-risk groups, thereby also decreasing the incidence of HAPE and HACE.

Acetazolamide is a carbonic anhydrase inhibitor that acts as a diuretic and induces mild metabolic acidosis with a concomitant reflex hyperventilation. Acetazolamide is the most studied and current "gold standard" pharmacologic intervention for altitude sickness; however, the optimum prophylactic dose of this medication has not been well established (Reid et al., 1994; Basnyat, 2001). While most studies using acetazolamide as AMS prophylaxis employed 500 mg per day (Grissom et al., 1992) or higher, only one anecdotal report with nine subjects has employed a lower dose of 250 mg per day in an attempt to find the lowest possible dose (Mayer, 1995). In 2000, a controversial meta-analysis authored by Dumont et al. stated that 750 mg of acetazolamide was the ideal dose, and a lesser dosage was not effective for the prevention of AMS (Dumont et al., 2000). Many prominent altitude researchers have criticized Dumont's analysis and suggest that this dosage is unnecessarily high and causes excessive side effects that may lead to poor compliance (Hackett, 2001; Severinghaus, 2001). Additionally, Dumont's conclusions are contrary to our own observation in the heavily traveled Nepal Himalayas, where for over a decade our regimen of 125 mg BID has been clinically effective in preventing AMS among trekkers. However, this has not yet been adequately demonstrated in a rigorous clinical trial. This study was designed to verify our hypothesis that a prophylactic regimen of acetazolamide 125 mg BID will effectively prevent AMS in Himalayan trekkers. A lower dosage of acetazolamide for prevention of AMS with concomitant fewer side effects (paresthesias, polyuria, occasional nausea and vomiting, drowsiness, and rarely blurring of vision, Hardman et al., 2001) is certainly preferable if effective; hence the clinical importance for this study.

METHODS

Protocol

This study was designed as a prospective randomized, double-blind, placebo-controlled trial. The study took place between November 1 and 22, 2001, along the popular trekking route to Mount Everest in the Nepal Himalaya. It was conducted under the auspices of the Himalayan Rescue Association and the Nepal International Clinic and was approved by the Nepal Health Research Council. Study administrators were unpaid upper-level medical students. Preliminary estimates suggested that at minimum 60 subjects per group would be needed in order to resolve a statistically significant difference between treatment and placebo groups based on a published AMS attack rate of 57% at 4950 m (Murdoch, 1995).

Instruments

The Lake Louise Acute Mountain Sickness Scoring System is a well-validated discipline standard for field evaluation of AMS (Bartsch et al, 1993; Roach et al., 1993; Maggiorini et al., 1998). AMS in a high altitude setting is defined as headache plus at least one of the following symptoms: nausea, fatigue, dizziness, or difficulty sleeping. HACE and HAPE have also been quantified previously by their clinical findings (Roach et al., 1993). Oxygen saturation is roughly correlated with illness and was measured using a pulse oximeter (Nonin Medical Products Inc., Minneapolis, MN). The measurement was carried out with the person at rest in the evening.

Outcome measures. The main outcome measures were incidence and severity of AMS as judged by the Lake Louise Questionnaire score at Lobuje (4937 m), the study endpoint. Secondary outcome variables included (1) the presence or absence of high altitude headache; (2) diagnosis of HAPE or HACE; (3) pulse oximetry differential between Pheriche (4243 m), the study enrollment site, and Lobuje (4937 m), the study endpoint (Figs. 1 and 2); (4) acute

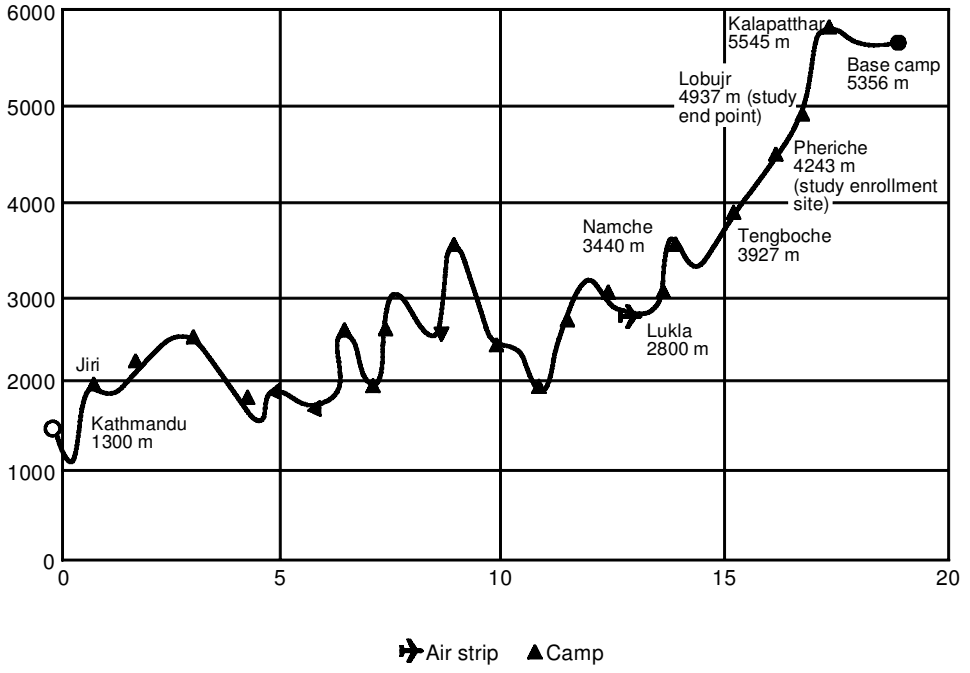

FIG. 1. Days on trek to the Everest base camp.

symptoms suggestive of infection at 4937 m (sore throat, cough, sinusitis, diarrhea); (5) incidence of paresthesias; and (6) missed capsules.

Assignment

Participants included 197 trekkers, who received no incentives and gave full consent before participation. Inclusion criteria specified healthy non-Nepali male and female trekkers of greater than 18 years of age traveling between the villages of Pheriche and Lobuje. Potential subjects were excluded if they (1) already had a diagnosis of AMS, HACE, or HAPE; (2) had been on a high altitude trek 2 weeks prior to this trek; (3) were not trekking directly to Lobuje; (4) had taken acetazolamide or *Ginkgo biloba* in the week prior to presentation; or (5) had diabetes, serious heart or pulmonary disease, or a sulfa allergy.

Masking

This study was conducted as a double-blind trial. Acetazolamide and study capsules were visually indistinguishable, and neither study administrators nor participants knew the identity of any of the study capsules. With the complaint of paresthesias typical for acetazolamide users, there was concern that administrators may become unblinded. To prevent this, subjects were asked to fill in data on side effects last, and their data sheet was promptly sequestered from investigators. Random allocation occurred on site, with each container taken out and assigned to the next person before that person was identified in order to remove bias. Randomization code was drawn up by a neutral party and was securely kept in Kathmandu, completely unavailable to the study administrators.

Participant flow and follow-up

Trekkers newly arrived at Pheriche were enrolled (Fig. 2) on a daily basis, answering questions concerning demographics and rate of ascent from Lukla (2000 m) (see Table 1). Participants filled out the Lake Louise Questionnaire, had pulse oximetry readings taken, and were then randomized in a double-blind fashion to either acetazolamide 125 mg or visually matched placebo twice daily. Participants were then allowed to continue on their trek without any influence of study administrators. On their ascent from Pheriche, some subjects stopped overnight at a lodge at 4595 m (Thukla) for one night, but all were expected to arrive at 4937 m (Lobuje) for data collection (rate of ascent from Pheriche, Lake Louise

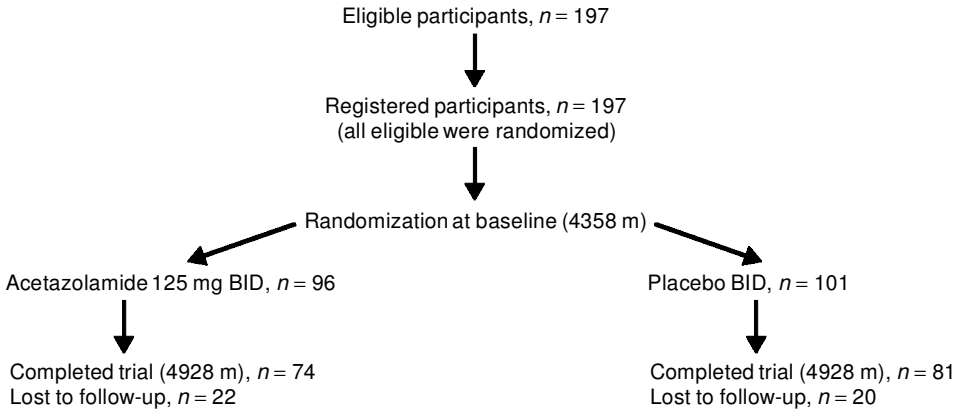

FIG. 2. Flow chart of study participants.

Questionnaire score, symptoms of other acute illness, pulse oximetry, and side effects). The study was complete at this point and the data were used to identify participants with acute illness, who could then be treated and/or evacuated as necessary. The capsules were taken for 2 to 3 days in total before the final evaluation in Lobuje.

Analysis

Likelihood ratio tests or Fisher's exact test were used to compare categorical variables. *T*-tests were used to compare means of continuous variables, and in all cases p values of less than 0.05 were considered significant.

RESULTS

Of the 197 participants enrolled in the study, 155 completed the study questionnaire at Lobuje (4937 m), with 42 lost to follow-up. All persons whose data were collected at Lobuje were analyzed in the group to which they were assigned originally. For those lost to follow-up,

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY GROUP

	Study participants		*Placebo group*		*Acetazolamide group*		
Variables	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Sig. (p)*[a]
Total cohort (155 of 197)	155	100	81	52.3	74	47.7	
Gender:							
Male	104	67.1	56	69.1	48	64.9	0.572
Female	51	32.9	25	30.9	26	35.1	
Mean age	34.8 ± 11.7	Range 18–70	33.9 ± 11.4		35.8 ± 12.1		0.318
Trek start point:[b]							
2000 m	71	45.8	35	43.2	36	48.6	0.497
2800 m	84	54.2	46	56.8	38	51.4	
Ascent rate from Lukla (2800 m) to Pheriche (4243 m) (no. of nights)	4.3 ± 1.1	Range 3–6	4.5 ± 0.9		4.1 ± 1.2		0.075
Nights at Pheriche (4243 m)	1.9 ± 0.5	Range 1–3	1.9 ± 0.5		1.8 ± 0.6		0.24
Night at Thukla (4595 m):[c]							
No	124	80.0	64	79.0	60	81.1	0.747
Yes	31	20.0	17	21.0	14	18.9	
O_2 sat at Pheriche (4243 m)	86.9 ± 3.9	Range 74–95	86.9 ± 4		86.9 ± 3.9		0.927
Lost to follow-up	42	21.3	22	21.4	20	21.3	0.989

[a]Denotes $p < 0.05$, statistical significance.

[b]Jiri is the start point at 2000 m, and the Lukla airport is at ~2800 m. Everyone coming from Jiri had to trek through Lukla.

[c]This is an optional intermediate stop on the way to Lobuje (4937 m).

few data are available; however, they were spread almost evenly between the treatment and placebo groups (22 and 20 respectively, $p = 0.99$) and were an equal percentage of their respective cohorts (21.3%). At Pheriche the groups were well matched (Table 1), including those lost to follow-up, and this was considered evidence of appropriate blinding.

The outcome profile of subjects who completed the study ($n = 155$) is summarized in Table 2. Analysis for the primary outcome variables revealed that in the treatment group there was a statistically significant reduction in incidence of AMS. Prophylaxis with acetazolamide conferred a 50.6% relative risk reduction, and the number needed to treat in order to prevent one instance of AMS was 8. There were 30% in the placebo group (6 of 20) versus 0% in the acetazolamide group (0 of 9) that experienced a more severe degree of AMS as defined by a Lake Louise Questionnaire score of 5 or greater ($p = 0.14$). Several secondary outcome measures in Tables 2 through 4 were associated with statistically significant findings favoring the treatment group, including the presence of headache, final oxygen saturation at Lobuje, and the absolute change in oxygen saturation. Subjects in the treatment group were more likely to miss taking capsules and to experience paresthesias. Furthermore, subjects with paresthesias were more likely to miss taking study capsules: 8 of 39 subjects with paresthesias (20.5%) versus 9 of 116 subjects without paresthesias (7.8%, $p = 0.04$). There was no significant difference between groups in the incidence of nonaltitude-related illness, after arriving at Lobuje. There were no cases of HACE or HAPE in either study group, and no identifiable cases of allergic reaction to acetazolamide.

DISCUSSION

Key findings of the study

Acetazolamide 125 mg twice daily was statistically effective in (1) halving the incidence of AMS, (2) decreasing the incidence of high altitude headache, and (3) improving oxygenation. The strong trend of reduced severity of illness in the treatment group probably does not

Table 2. Outcome Profile

	Study participants		*Placebo group*		*Acetazolamide group*		
Variables	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Sig. (p)*[a]
Total cohort (155 of 197)	155	100	81	100	74	100	
Headache:[b]							
No or 0	98	63.2	43	53.1	55	74.3	0.006
Yes	57	36.8	38	46.9	19	25.7	
(Lake Louise Score)							
1	47	30.3	30	37.0	17	23.0	
2	8	5.2	6	7.4	2	2.7	0.022
3	2	1.3	2	2.5	0	0.0	
AMS diagnosis:[c]							
No	126	81.3	61	75.3	65	87.8	0.043
Yes	29	18.7	20	24.7	9	12.2	
Final O_2 sat at Lobuje (4937 m) ($n = 154$)	81.9 ± 4.9	Range 60–93	81 ± 5.5		82.8 ± 4.1		0.023
O_2 sat change ($n = 153$)	−5 ± 4.8	Range −18–16	−5.9 ± 5.3		−4.1 ± 4		0.023
Missed capsules:							
No	138	89	78	96.3	60	81.10	0.002
Yes	17	11.0	3	3.7	14	18.90	
Paresthesias:							
No	116	74.8	78	96.3	38	51.40	<0.001
Yes	39	25.2	3	3.7	36	48.60	

[a]Denotes $p < 0.05$, statistical significance.
[b]1 denotes mild, 2 moderate, and 3 severe headache.
[c]Defined as headache plus at least one other symptom.

Table 3. Potential Modifiers of Outcome—Symptoms of Potential Infection at Lobuje (4937 m)

	Study participants		*Placebo group*		*Acetazolamide group*		
Variables	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Sig. (p)*
Overall symptoms suggestive of infection:							
No	92	59.4	46	56.8	46	62.2	0.496
Yes	63	40.6	35	43.2	28	37.8	
Diarrhea:[a]							
No	145	93.5	73	90.1	72	97.3	0.101
Yes	10	6.5	8	9.9	2	2.7	
Sore throat:							
No	127	81.9	63	77.8	64	86.5	0.156
Yes	28	18.1	18	22.2	10	13.5	
Cough:							
No	121	78.1	64	79.0	57	77.0	0.765
Yes	34	21.9	17	21.0	17	23.0	
Sinusitis:[b]							
No	145	93.5	75	92.6	70	94.6	0.748
Yes	10	6.5	6	7.4	4	5.4	

[a]Loose motion at least 3 times per day in the last 2 days.
[b]Nasal congestion with facial pain.

reach statistical significance, because the numbers were not large enough to effectively substantiate the effect. However, the treatment effect of 50% reduction in AMS was similar to that found in other studies, and the treatment group exhibited classic features consistent with a robust clinical effect due to acetazolamide therapy (improved oxygenation and the presence of paresthesias) (Hackett et al., 1976). Furthermore, one other indicator suggests that acetazolamide may have been even more efficacious than the study was able to show: The treatment group also had a greater degree of medication noncompliance as measured by missed capsules; had they taken all their medications they may have fared even better. The higher rate of paresthesias in the treatment group compared to placebo was expected and is probably related to the overall rate of missed capsules. This association most likely represents medication noncompliance as a result of the bothersome side effect of the paresthesias associated with acetazolamide. The overall rate of AMS in this study population was 18.7%, a lower value than that found in previous studies (Hackett et al., 1976). Five points are noteworthy. First, since the vast majority of trekkers do not take acetazolamide as a matter of course, the true incidence of AMS is most likely closer to the rate of 24.7% found in the placebo group. Second, a psychobehavioral cause may be found in the fact that the subjects were recruited at Pheriche after the daily Himalayan Rescue Association informational sessions on altitude sickness, possibly selecting for a more conservative group that were aware of the health risks of altitude and methods of risk reduction. Third, we sampled on the evening of the arrival to Lobuje instead of on the next day when the rates may have been higher. Fourth, since we did not enroll people at Pheriche who had AMS, this certainly influenced the incidence of AMS higher up at Lobuje. Finally, it is true that in recent years the overall incidence of AMS has declined in trekkers who are assessed at Pheriche on their way up (Basnyat et al., 1999; Dubowitz and Miller, 2001).

Limitations of the study

First, a significant number of participants (21%) were lost to follow-up, and the outcome among these subjects may have affected the significance of our findings. Three points minimize this difficulty: (1) subjects in either group were equally likely to drop out of the study, (2) this degree of attrition is consistent with previous studies, and (3) this degree of attrition is not unexpected in a wilderness setting, with no incentive for subjects to follow up at the ren-

TABLE 4. RISK FACTORS FOR ACUTE MOUNTAIN SICKNESS

	AMS No		*AMS Yes*		
Variable	*No.*	*%*	*No.*	*%*	*Sig. (p)*[a]
Total cohort	126	100	29	100	
Gender:					
Female	41	32.5	10	34.5	0.841
Male	85	67.5	19	65.5	
Mean age	35 ± 11.8		34.1 ± 11.6		0.702
Trek start point:[b]					
2000 m	59	46.8	12	41.4	0.595
2800 m	67	53.2	17	58.6	
Ascent rate from Lukla (2800 m) to Pheriche (4243 m) (no. of nights)	4.3 ± 1.2		4.2 ± 0.5		0.692
Nights at Pheriche	1.9 ± 0.5		1.8 ± 0.6		0.31
Night at Thukla (4595 m):[c]					
No	100	79.4	24	82.8	0.676
Yes	26	20.6	5	17.2	
Medications (self-report):					
No	87	69.0	17	58.6	0.288
Yes	39	31.0	12	41.4	
O_2 sat at Pheriche (4358 m)	87.3 ± 3.9		85.4 ± 4		0.026
Final O_2 sat at Lobuje (4937 m)	82.7 ± 4.4		78.2 ± 5.6		<0.001
Overall symptoms suggestive of acute infection (4937 m):					
No	76	60.3	16	55.2	0.612
Yes	50	39.7	13	44.8	
1. Diarrhea:					
No	120	95.2	25	86.2	0.092
Yes	6	4.8	4	13.8	
2. Sore throat:					
No	104	82.5	23	79.3	0.688
Yes	22	17.5	6	20.7	
3. Cough:					
No	98	77.8	23	79.3	0.856
Yes	28	22.2	6	20.7	
4. Sinusitis:					
No	117	92.9	28	96.6	0.689
Yes	9	7.1	1	3.4	
Missed capsules:					
No	113	89.7	25	86.2	0.527
Yes	13	10.3	4	13.8	
Paresthesias:					
No	94	74.6	21	72.4	0.74
Yes	31	24.6	8	27.6	

[a]Denotes $p < 0.05$, statistical significance.
[b]Jiri is the start point at 2000 m, and the Lukla airport is at ~2800 m.
[c]This is an intermediate stop (Thukla 4595 m) on the way to (Lobuje 4937 m).

dezvous point in Lobuje (Hackett et al., 1976; Murdoch, 1995). Another limitation of this study is that, with the complaint of paresthesias that is typical for acetazolamide usage, blinding may have been compromised both for the subject and the investigator. However, the method of blinding minimized the impact of this specific difficulty. Finally, the choice of starting point of the study is unusually high since many subjects will suffer from AMS below this altitude, and hence it does make comparison with other studies difficult. However, from our previous anecdotal experience we knew that many people become ill in Lobuje with AMS as compared with Pheriche or any other part of this Everest trek and, in addition, the "logistics" of this sector were very attractive for us. However, we would submit that, if anything, this study showed that even these "hardy" individuals were protected from AMS,

which is in keeping with the efficacy of low-dose acetazolamide.

CONCLUSIONS

Acetazolamide 125 mg twice daily was significantly efficacious in decreasing the incidence of AMS in this Himalayan trekking population. The results of this study thus clearly refute Dumont's conclusion that acetazolamide 750 mg is the minimum prophylactic dose. We believe these results are generalizable to many trekking scenarios because of the number and variety of participants involved. Further research with acetazolamide (i.e., an RCT with different acetazolamide dosing arms) to find the optimal balance of efficacy versus side effects would be a significant next step to build on these findings.

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