

Acetazolamide Fails to Decrease Pulmonary Artery Pressure at High Altitude in Partially Acclimatized Humans

Buddha Basnyat,^{1,2} Jenny Hargrove,³ Peter S. Holck,⁴ Soni Srivastav,² Kshitiz Alekh,² Laxmi V. Ghimire,² Kaushal Pandey,² Anna Griffiths,² Ravi Shankar,² Komal Kaul,² Asmita Paudyal,² David Stasiuk,² Rose Basnyat,² Christopher Davis,² Andrew Southard,² Cathleen Robinson,² Thomas Shandley,² Dan W. Johnson,² Ken Zafren,^{2,5} Sarah Williams,⁵ Eric A. Weiss,⁵ Jeremy J. Farrar,⁶ and Erik R. Swenson⁷

Abstract

Buddha Basnyat, Jenny Hargrove, Peter S. Holck, Soni Srivastav, Kshitiz Alekh, Laxmi V. Ghimire, Kaushal Pandey, Anna Griffiths, Ravi Shankar, Komal Kaul, Asmita Paudyal, David Stasiuk, Rose Basnyat, Christopher Davis, Andrew Southard, Cathleen Robinson, Thomas Shandley, Dan W. Johnson, Ken Zafren, Sarah Williams, Eric A. Weiss, Jeremy J. Farrar, and Erik R. Swenson. Acetazolamide fails to decrease pulmonary artery pressure at high altitude in partially acclimatized humans. *High Alt. Med. Biol.* 9:209–216, 2008.—In this randomized, double-blind placebo controlled trial our objectives were to determine if acetazolamide is capable of preventing high altitude pulmonary edema (HAPE) in trekkers traveling between 4250 m (Pheriche)\4350 m (Dingboche) and 5000 m (Lobuje) in Nepal; to determine if acetazolamide decreases pulmonary artery systolic pressures (PASP) at high altitude; and to determine if there is an association with PASP and signs and symptoms of HAPE. Participants received either acetazolamide 250 mg PO BID or placebo at Pheriche\Dingboche and were reassessed in Lobuje. The Lake Louise Consensus Criteria were used for the diagnosis of HAPE, and cardiac ultrasonography was used to measure the velocity of tricuspid regurgitation and estimate PASP. Complete measurements were performed on 339 of the 364 subjects (164 in the placebo group, 175 in the acetazolamide group). No cases of HAPE were observed in either study group nor were differences in the signs and symptoms of HAPE found between the two groups. Mean PASP values did not differ significantly between the acetazolamide and placebo groups (31.3 and 32.6 mmHg, respectively). An increasing number of signs and symptoms of HAPE was associated with elevated PASP ($p < 0.01$). The efficacy of acetazolamide against acute mountain sickness, however, was significant with a 21.9% incidence in the placebo group compared to 10.2 % in the acetazolamide group ($p < 0.01$). Given the lack of cases of HAPE in either group, we can draw no conclusions about the efficacy of acetazolamide in preventing HAPE, but the absence of effect on PASP suggests that any effect may be minor possibly owing to partial acclimatization during the trek up to 4200 m.

Key words: altitude illness, high altitude pulmonary edema, Nepal, Himalayas.

Introduction

HIGH ALTITUDE PULMONARY EDEMA (HAPE) is a life-threatening illness seen in high altitude sojourners including skiers, trekkers, mountain climbers, pilgrims to sacred high altitude sites, soldiers, and porters (Basnyat and Murdoch, 2003). Although many drugs including nifedipine (Bartsch et al., 1991), tadalafil, dexamethasone (Maggiolini et al.,

2006), and salmeterol (Sartori et al., 2002) have been used effectively in the prevention of HAPE, surprisingly acetazolamide, a “tried and tested” drug in the prevention and treatment of acute mountain sickness (AMS) has not been studied in the field for the prevention of HAPE. Because exaggerated hypoxic pulmonary vasoconstriction (HPV) is a crucial pathogenetic factor in HAPE (Bartsch, 2005), any drug that decreases HPV may be helpful in preventing or ameliorat-

¹Nepal International Clinic, Kathmandu, Nepal. ²Himalayan Rescue Association, Kathmandu, Nepal. ³Institute for Altitude Medicine, Telluride, Colorado. ⁴University of Hawaii, John A Burns School of Medicine, Honolulu, Hawaii. ⁵Stanford University Medical Center, Stanford, California. ⁶Oxford University Clinical Research Unit, The Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam. ⁷University of Washington, Seattle, WA.

ing HAPE. Recently there have been several animal (Deem et al., 2000; Hohne et al., 2007; Berg et al., 2004) and one human (Teppema et al., 2007) laboratory investigations that have shown that acetazolamide can decrease HPV. Hence, we hypothesized that acetazolamide could prevent HAPE in human sojourners to high altitude. Indeed, we felt that acetazolamide would be an ideal, single inexpensive drug with minimal side effects, already proven useful in acute mountain sickness (AMS), and high altitude cerebral edema (HACE), to prevent all the three forms of acute altitude sickness (AMS, HAPE and HACE). Interestingly, researchers (Swenson, 2006), (Hohne et al., 2007) have shown that HPV reduction by acetazolamide is not mediated by carbonic anhydrase (CA) inhibition but rather by a non-CA dependent inhibition of pulmonary vascular smooth muscle calcium release from the sarcoplasmic reticulum. The decrease in HPV may also, in part be due to the enhanced hyperventilation and increased oxygen saturation caused by the inhibition of renal, vascular endothelial and chemoreceptor CA (Basnyat and Murdoch, 2003; Swenson and Teppema, 2007)

We had three specific objectives in our study: (1) to determine if oral acetazolamide as compared to placebo is capable of preventing HAPE in trekkers traveling between 4250 m\4350 m and 5000 m in Nepal; (2) to determine if oral acetazolamide decreases pulmonary artery systolic pressures (PASP) at high altitude; (3) to determine if there is an association between PASP and signs and symptoms of HAPE.

Materials and Methods

Study selection

Inclusion criteria. Healthy subjects between the ages of 18 and 65, male or female, non-Nepali, without AMS or any concurrent illness, and not already taking acetazolamide or any other drug for the prevention of altitude illness were enrolled by study administrators at the villages of Pheriche/Dingboche.

Exclusion criteria. Individuals not meeting inclusion criteria, including mild AMS (more than one mild symptom on the Lake Louise Questionnaire) or significantly depressed oxygen saturation (<75%) were excluded. Other exclusions were: females known to be pregnant or unable to exclude the possibility of being pregnant, or having missed menses by over 7 days; individuals with a known drug allergy to acetazolamide or other sulfa drugs; individuals who had spent 24 hours at an altitude of 4500 m or higher within the last 9 days; anyone known to have taken any of the following in the last 2 days: acetazolamide, steroids (dexamethasone, prednisone), theophylline, or diuretics; individuals who had a known intracranial space-occupying lesion or a history of elevated intracranial pressure (i.e., tumors, hydrocephalus, etc.).

Subjects meeting the inclusion criteria and having no exclusions gave informed written consent to the study, which was approved by the Nepal Health Research Council and the Oxford Tropical Research Ethics Committee.

Intervention

This was a prospective two-armed, double-blind, randomized, placebo-controlled trial. Computer generated randomization of commercial pharmaceutical grade acetazo-

lamide and placebo were carried out by Deurali Janata Pharmaceuticals (Kathmandu, Nepal). After consent was obtained, participants received a four days supply of either acetazolamide 250 mg bid or visually identical appearing placebo tablets bid. Trekkers were enrolled, study demographics were collected and baseline measurements were done at Pheriche (4250 m) or Dingboche (4350 m). The participants were reassessed after their arrival at the endpoint in Lobuje (5000 m). The reassessment took place at least 36 hours to a maximum of 96 hours (4 days) after beginning the study drug so that all subjects were still taking acetazolamide or placebo at the end-point. Assessments and measurements made in these areas prior to and after ascension included the Lake Louise Questionnaire, oxygen saturation via pulse oximetry (Nonin Medical Products Inc., Minneapolis, MN) blood pressure, heart and pulse rate monitoring, and stethoscopic lung examination. Doppler echocardiography (Sonosite Micromaxx, Bothell, Washington with a P17 transducer, 1–5 MHz) to measure PASP by analysis of the tricuspid valve regurgitant flow (Allemann et al., 2000) was carried out only at the endpoint at Lobuje.

Primary outcomes

1. Evaluation for HAPE was made by upper-level medical students or doctors after the study participants rested for a minimum of 15 minutes. Diagnosis of a participant with or without AMS (LLQ ≥ 3 with headache and at least one other symptom) was made only if two of the following signs and two of the following symptoms were present as suggested in the Lake Louise consensus committee (Roach et al., 1993)
 - Symptoms: chest tightness, cough, dyspnea at rest, markedly decreased exercise performance (LLQ fatigue score of 3)
 - Signs: central cyanosis, pulmonary crackles, tachycardia (heart rate >110 per min), tachypnea (respiratory rate >25 per min)
2. Doppler echocardiography was performed by 2 professional echocardiographers after the subjects rested for 15 minutes at Lobuje. Cutoff criteria for HAPE was a measurement of pulmonary artery systolic pressure of 48 mmHg or greater using transtricuspid pressures with normal left ventricular wall motion and function (Allemann et al., 2000). The echocardiographer was blinded and did not have any data on the participant. After tricuspid valve regurgitation was localized with Doppler flow imaging, the peak flow velocity of the tricuspid valve regurgitant jet was measured with a continuous wave Doppler. All reported values represented the highest peak of 3 transtricuspid pressure measurements. The tricuspid valve gradient was calculated using a modified Bernoulli equation (Allemann et al., 2000). PASP was estimated after adding the clinically determined mean jugular venous pressure.

Secondary outcomes

1. Pulse oxygen saturation of $< 70\%$ in subjects meeting HAPE diagnosis.
2. The change in PASP from 4250 m\4350 m to 5000 m was compared between placebo and acetazolamide groups,

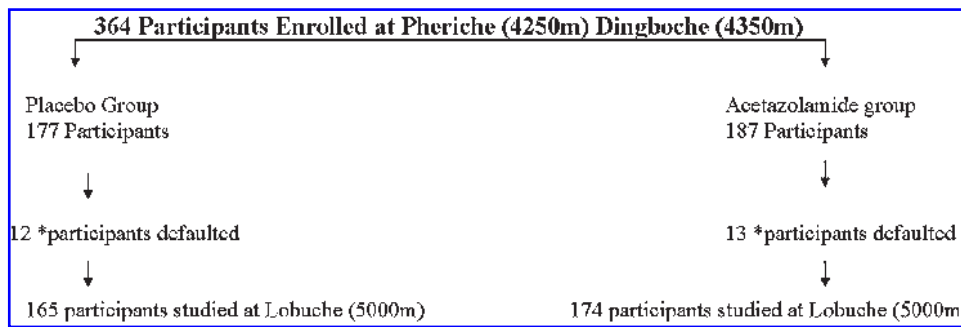


FIG. 1. Flow chart of participants in study. *Dropped out or disqualified for stopping study drugs or taking non-study acetazolamide.

and sign and symptoms of HAPE were examined for association with PASP value.

- Incidence of AMS, HAPE, and HACE in this cohort of people ascending from 4250 m\4350m to 5000 m in the Khumbu region was determined.

Study monitoring. Study investigators were available at both Pheriche\Dingboche and Lobuche. Three sealed master lists of the randomization code were held by the manufacturer, an independent clinician at the Nepal International Clinic in Katmandu, and an independent clinician at the aid post in Pheriche. The code was only to be opened during the trial by an independent clinician who was not a study author when there was concern of allergic reaction or any other adverse event that would require knowledge of the patient's medication history. The primary investigators held monthly teleconference to discuss progress of the trial. All serious adverse events were reported to the Data Safety Monitoring Board (DSMB) within 7 days.

Sample size. The chosen sample size was based on the incidence of HAPE at > 4000m which we hypothesized to be 4%, a figure based upon personal experience in the region (BB) and a 2.5% incidence reported by Hackett and Rennie (1976). To detect a difference in HAPE incidence of 4% in the placebo arm to 0% in the acetazolamide arm with 80% power and $\alpha = 0.05$ (standard parameters), we estimated we would need to recruit 192 volunteers in each arm. However as the date of the study drew near we felt that given the worsening political situation in Nepal we would not be able to recruit these numbers, and we decided to study as many as were feasible.

Statistical methods. We utilized simple univariate comparisons to examine risk factors for binary outcomes. Odds ratios and confidence intervals (asymptotic or Fisher's exact test) were used to estimate associations of categorical variables. Means of continuous outcomes (PASP) were compared using *t* tests, wilcoxon rank tests, with multivariate linear regression models fit to estimate effects adjusted for potential covariates. All *p* values less than 0.05 were considered significant. All analysis was conducted using R 2.5.0 (R Development Core Team, 2007).

Adverse events. The risks associated with this clinical trial were limited to the adverse effects (Basnyat et al., 2006) of

the study drug acetazolamide (paresthesias, polyuria, dyspepsia, metallic-like taste changes). Allergic reactions are extremely rare; however, all participants were provided access to medical care for at least 24 hours after taking the drug. This research team had a well-established safety record working with trekkers in the Everest region, with three studies (Basnyat et al., 2003; Basnyat et al., 2006; Gertsch et al., 2004) since 2002 using similar design protocols under the auspices of the Nepal Health Research Council. Only 2 people out of a total of 1065 trial participants had an adverse event (mild rash from acetazolamide) necessitating care.

Timeline. The study was performed during October and November, 2006.

Results

The flow chart (Fig. 1) outlines the number of participants and drop outs in the study. Complete measurements were performed on 339 of the 364 participants enrolled. None of the dropouts had HAPE. The demographic characteristics (Table 1) of participants in each arm were similar, which was collected at the study start point (Pheriche\Dingboche).

Mean PASP values (at Lobuche) did not differ significantly between the acetazolamide and placebo groups (31.3 and 32.6 mmHg respectively, Fig. 2). Although 26 people had PASP > 48 mmHg at 4900 m, there were no cases of HAPE in either study group, and there were no differences in the number of signs and symptoms that comprise HAPE (Roach et al., 1993) between the two groups. Doppler readings due to poor or unidentifiable tricuspid valve regurgitation could not be documented in 97 individuals, but in 242 participants measurements were clearly ascertainable. In the 97 participants where a reading could not be taken, we presumed this to be normal PASP (25 mmHg) if left ventricular function was normal. There was no difference in the PASP between acetazolamide or placebo groups even when these 97 participants were excluded from the analysis.

Table 2 lists the covariates in the multivariate model. In this table the outcome (dependent variable) is continuous PASP value. All independent variables are listed, with continuous variables, age and nights spent in ascent. The remaining variables being categorical are self-explanatory as far as dichotomization (for example sex, male or female). Evident are differences in PASP value by gender (increased in women), and increased PASP values with increasing age.

After adjusting for age and sex, more signs and symptoms

TABLE 1. DESCRIPTIVE STATISTICS BY TREATMENT GROUP

	Acetazolamide (N = 187)	Placebo (N = 177)	Combined (N = 364)	p-value*
Sex				
F	42.2% (79)	32.2% (57)	37.4% (136)	0.05
M	57.8% (108)	67.8% (120)	62.6% (228)	
Age (years)	37.9 ± 12.5	39.4 ± 12.1	38.6 ± 12.3	0.16
Arrival Mode				
walk (Jiri**)	10.7% (20)	10.7% (19)	10.7% (39)	0.99
flight (Lukla)	89.3% (167)	89.3% (158)	89.3% (325)	
Residence				
Dingboche	50.8% (95)	57.6% (102)	54.1% (197)	0.19
Pheriche	49.2% (92)	42.4% (75)	45.9% (167)	
Nights spent since Lukla	4.91 ± 1.25	4.96 ± 1.14	4.94 ± 1.20	0.43
Medicines taken Day of Enrollment				
No	98.40% (184)	100% (177)	99.18% (361)	0.25
Yes	1.60% (3)	0% (0)	0.82% (3)	
Lake Louise score zero				
Yes	63.6% (119)	60.5% (107)	62.1% (226)	0.53
No	36.4% (68)	39.5% (70)	37.9% (138)	
Chest tightness				
No	98.40% (184)	97.2% (172)	97.80% (356)	0.49
Yes	1.60% (3)	2.82% (5)	2.20% (8)	
Cough				
No	81.8% (153)	80.8% (143)	81.3% (296)	0.8
Yes	18.2% (34)	19.2% (34)	18.7% (68)	
Pulse Oximetry (SpO ₂ %)	86.45 ± 3.39	85.91 ± 4.08	86.19 ± 3.75	0.21
Weight (kg)	71.9 ± 13.8	71.9 ± 2.3	71.9 ± 13.0	0.86
Heart Rate (per minute)	82.6 ± 12.0	82.5 ± 12.0	82.6 ± 12.0	0.91
Respiratory Rate (per minute)	17.27 ± 3.07	17.0 ± 3.24	17.13 ± 3.15	0.23
Shortness of Breath				
No	98.40% (184)	99.4% (176)	98.90% (360)	0.62
Yes	1.60% (3)	0.6% (1)	1.10% (4)	
Fatigue				
No	94.65% (177)	97.7% (173)	96.15% (350)	0.17
Yes	5.35% (10)	2.3% (4)	3.85% (14)	

*Chi-square or Fishers Exact tests of Null Hypothesis: no difference between acetazolamide and placebo groups.

**Where the trekking starts (1900 m) if not flying into Lukla (2860 m).

suggested higher PASP values, (Fig. 3). On average each additional sign and symptom resulted in an increase of 1.6 mmHg in PASP ($P < 0.01$), a finding which persisted after adjustment in a multivariate analysis for other potential PASP influences. In addition those with 3 or more sign and symptoms have a PASP value about 8 mmHg higher ($P < 0.01$) than those without any sign and symptoms. In fact (data not shown), when the participants with poor quality Doppler are excluded, the PASP is even higher by 12 mmHg for those with 3 or more sign and symptoms. Analysis of individual signs and symptoms of HAPE indicate that crackles (average increase of 5.6 in PASP value, $p = .02$), and cough (average increase of 2.7 in PASP value, $p = .03$) were the most significant determinates of elevated PASP value. Finally, Fig. 4 illustrates an inverse correlation between oxygen saturation and PASP ($p < 0.01$).

AMS developed in 21.9% of people in the placebo group compared to 10.2% in the acetazolamide group ($p < 0.01$). No patient was diagnosed with HACE.

Discussion

In this large field study of trekkers in the Himalayas climbing between the altitudes of 4250 m \ 4350 m and 5000 m, we observed no cases of readily diagnosed HAPE. This does not rule out an incidence of very mild disease, because we did document signs and symptoms consistent with HAPE in some subjects. By the Lake Louise consensus criteria, however, no trekker met the mandatory threshold for diagnosis. Hence our first objective which was to determine if oral acetazolamide might prevent HAPE in trekkers traveling between 4250 m \ 4350 m and 5000 m in Nepal could not be ad-

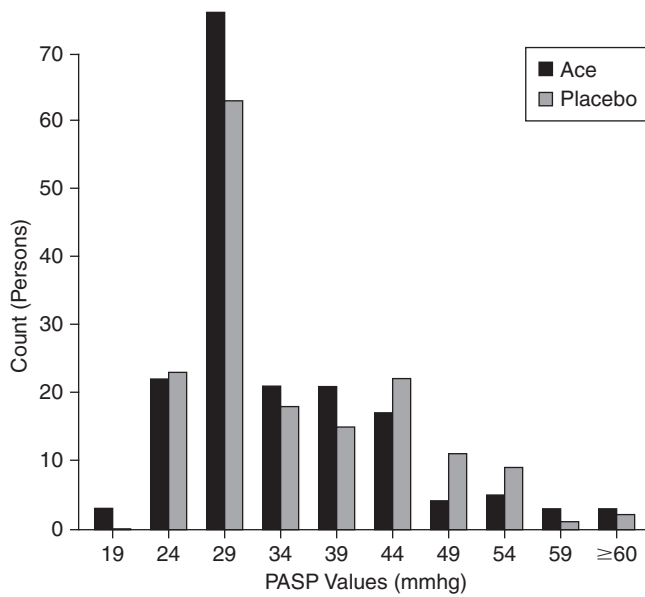


FIG. 2. Pulmonary artery systolic pressure (PASP) distribution value by treatment group.

dressed. However, the second objective, which was to determine if oral acetazolamide could reduce PASP at high altitudes, revealed that it did not lower the PAP elevation observed at these altitudes in trekkers. Because increased PAP is considered a key causal factor in HAPE, our negative results with acetazolamide on PASP suggest that acetazolamide at this dosing will not prevent HAPE under the trekking conditions of our study: 2–4 days between 4250 m\4350 m and 5000 m wherein some element of pre-acclimatization may have transpired in the several days by foot that it took subjects to reach the recruitment and start point.

Other explanations that might be offered to explain the lack of effect of acetazolamide on PAP and the signs and symptoms of HAPE include possible failure of sufficient drug absorption. This is effectively, however, ruled out by the 50% reduction in AMS we noted in the acetazolamide group, an efficacy routinely observed at these doses in other studies by our group in this region (Basnyat et al., 2003; Bas-

nyat et al., 2006; Gertsch et al., 2006). Another possibility is that the dosing of acetazolamide, while sufficient to alter AMS incidence by virtue of carbonic anhydrase inhibition (Swenson, 1998) may need to be higher to affect hypoxic pulmonary vascular resistance. In two animal studies acetazolamide appears to act on HPV by a mechanism independent of CA inhibition (Hohne et al., 2007), Shimoda et al., 2007), because other structurally dissimilar potent CA inhibitors fail to inhibit HPV. A minor methyl substitution on the sulfonamide group of acetazolamide, sufficient to abolish its ability to inhibit carbonic anhydrase, does not diminish its effect on HPV.

Another plausible explanation for the lack of efficacy of acetazolamide on PAP is that the effectiveness of acetazolamide to reduce HPV and PAP at high altitude may be limited to only a short duration of time upon ascent to high altitude; i.e., in the earliest phase of HPV. The phenomenon of HPV has several phases and reaches its fullest expression over the course of many days. In humans, as in animals, there is a rapid rise in PA pressure over 5 to 10 minutes with inspired hypoxia (Morell et al., 1995), which progressively, but more slowly, increases in the next 2 to 24 hours (Talbot et al., 2005). Beyond this time frame, there is very little human investigation, but studies in cattle and rats reveal further progressive pulmonary hypertension that displays less and less acute vasodilation with normal or hyperoxic inspired PO₂. Therefore it may be that the early mechanism(s) of HPV, which are sensitive to acetazolamide, become less important with time in determining pulmonary vascular resistance.

In support of the idea that acetazolamide may only be effective in a one to two day time frame, Faoro and colleagues (2007) recently found no changes in PASP at 4700 m in the Bolivian Altiplano in a double blind randomized trial of acetazolamide (250 mg tid for one day) after 10 days at that altitude. It is possible that in the Bolivian study, the pulmonary vasculature had already undergone considerable adaptation and remodeling by ten days such that it no longer was responsive to the anti-hypertensive effects of acetazolamide observed in laboratory studies of acute hypoxia over 0.5 to 8 hours (Deem et al., 2000; Hohne et al., 2004; Berg et al., 2004; Teppema et al., 2007). Likewise, our subjects may have already undergone some of this transition to a more 'remodeled' and less responsive state in their several days trek

TABLE 2. MULTIVARIATE MODEL OF PASP (PULMONARY ARTERY SYSTOLIC PRESSURE) VALUE

	Estimate	Standard error	p-value
Lake Louise score	0.34	0.37	0.35
Treatment = Placebo	0.17	1.04	0.86
Age	0.22	0.04	<0.01
Sex = Male	-3.77	1.04	<0.01
Nights spent in Ascent	-1.73	0.94	0.06
1 Sign/Symptom	0.69	1.09	0.52
2 Signs/Symptoms	0.32	1.59	0.83
3 or more Signs/Symptoms	7.87	2.43	<0.01
Oxygen saturation	-0.31	0.11	<0.01

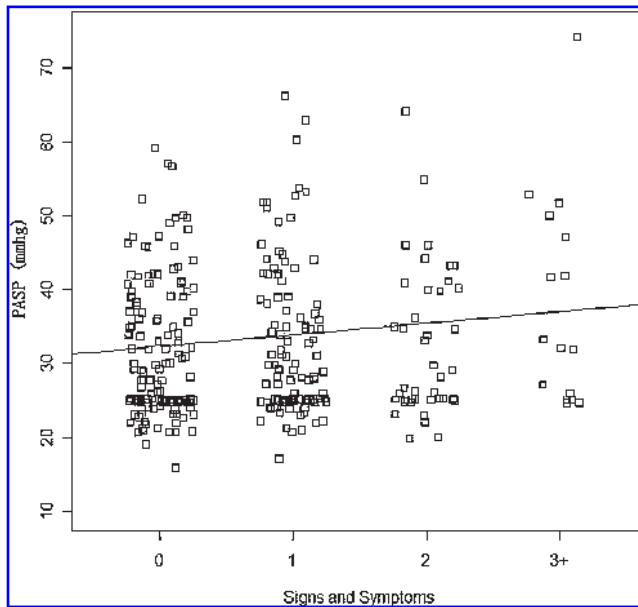


FIG. 3. Pulmonary artery systolic pressure (PASP) vs. number of signs and symptoms. (The correlation was significant, $p < 0.01$).

up to the start point of 4250 m or 4350 m (Stenmark et al., 1999). The further, approximate 700 m altitude gain after this may have been too little new acute-on-chronic hypoxia to be affected by acetazolamide. Thus at this point it is fair to conclude that either acetazolamide may not be effective except in the course of a 1–2 day acute ascent to high altitude from sea level or that higher dosing will be needed. Answers to these questions must await direct investigation.

The third objective was to determine if an association existed between PASP and signs and symptoms of HAPE. Although each additional sign and symptom correlated with a statistically significant 1.6 mmHg increase of PASP and participants with 3 or more signs and symptoms had 8 mmHg higher PASP values than those with no sign or symptoms, we are unsure of the clinical significance of this pressure difference. Crackles and cough were the signs and symptoms most correlated to the PASP values. Biochemical correlation has been noted by Swenson and colleagues (2002) who showed that increased bronchoalveolar lavage red blood cells and albumin concentrations had a clear correlation when plotted against PASP at 4559 m in bona fide HAPE cases. The concept of subclinical or preclinical HAPE has been put forward by some high altitude investigators (Cremona et al., 2002) and we postulate that perhaps some of our participants at the higher end of the correlation (Fig. 3) were developing subclinical HAPE.

The fact that 26 participants had a PASP ≥ 48 mm Hg (a value consistent with pulmonary hypertension) and yet did not develop HAPE suggests that HPV, central though its role may be in the causation of HAPE, may require other factors to incite HAPE. For example the concept that HAPE patients may have impaired alveolar epithelial clearance of sodium and water (Sartori et al., 2002) may be relevant here. Another mechanism that may work in tandem with pulmonary hypertension to bring on HAPE may be inflammatory changes in the pulmonary vasculature initiated by respiratory tract

infections (Durmowicz et al., 1997). Thus while it may be plausible that these 26 participants who may be HAPE susceptible (Basnyat and Murdoch, 2003) either simply did not develop HAPE on this occasion or that their several day trek into the start point may have initiated enough protective remodeling and strengthening of the pulmonary microvasculature to avoid alveolar edema (Tozzi et al., 1989; Meyrick and Reid, 1980). Finally the difference between the baseline and endpoint of the study which was about 700 m may have been too small to induce HAPE.

Although we have not seen this reported in a field survey of this nature, an inverse correlation between oxygen saturation and PASP (Fig. 4) is not surprising given that hypoxia is the most potent stimulus for pulmonary vasoconstriction. Older people and women were more susceptible to increased PASP in our study, although the impression is that HAPE is more common in men and younger people.

Limitations of the study: Although right heart catheterization would have more accurately measured the PA pressures, this would have been very impractical in such a large study performed under field conditions. Studies have shown that Doppler derived estimates of PASP at high altitude are accurate (Allemann et al., 2000) and serve well in this capacity, although this is operator dependent and the systolic pulmonary artery pressure may differ up to 15 mmHg. An important and relevant point that needs to be addressed is that many participants had inadequate tricuspid regurgitation to reliably estimate PASP. We arbitrarily decided to include even those 97 participants with no recordable PASP and assign them normal pressures. We felt that excluding these participants without detectable tricuspid regurgitation may introduce a strong bias and that in practice if an inadequate tricuspid jet was present it is likely that the PASP is < 30 (John Irving, personal communication). However, as men-

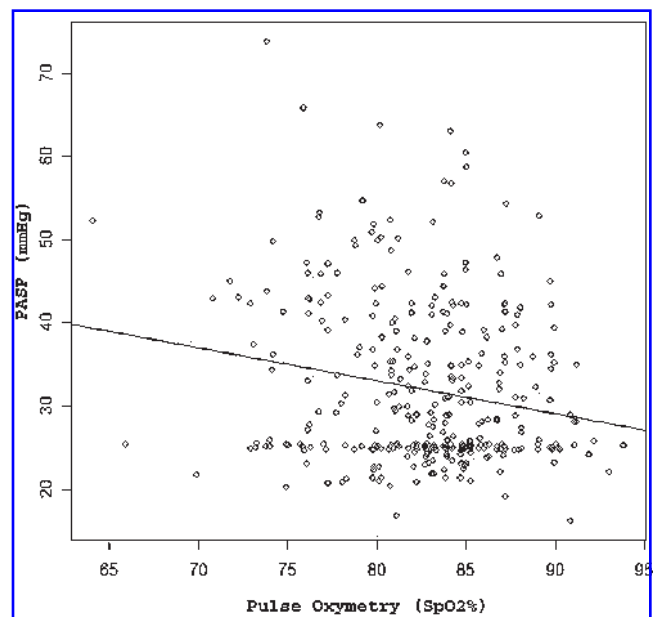


FIG. 4. Pulmonary artery systolic pressure (PASP) vs. oxygen saturation (SpO2 %). (The inverse correlation was significant, $p < 0.01$).

tioned above, we separated out the data of the 242 subjects with ascertainable Doppler readings, and still found no PASP differences between those who took acetazolamide and placebo. In addition, we also compared the participants with only > 30 mmHG PASP in the two groups, but there was still no difference.

Finally we had expected a higher incidence of HAPE based on personal (BB) assessment (4%) and 2.5% incidence reported by Hackett and Rennie (1976); but the ongoing unrest in Nepal that has decreased tourism here and the fact that many trekkers were already taking acetazolamide which excluded them from the study prevented us from enrolling more people in the study. Retrospectively given the fact that we did not have any HAPE patients, there were clear limitations of our endpoints.

Our study was unable to show as hypothesized that acetazolamide decreases HAPE by reducing HPV. However, a definitive answer may require studying HAPE-susceptible persons in a placebo-controlled study and taking them up to high altitude more rapidly for measurements of PASP and more 'gold standard' diagnosis of HAPE as has been done in the past (Bartsch et al., 1991; Swenson et al., 2002; Maggiorini et al., 2006; Sartori et al., 2002) We now know that our region, while useful for studies of AMS, does not lend itself to studying drug interventions in HAPE in the general population of trekkers who gradually ascend to the Everest base camp or Kalapattar and may have a low risk of developing HAPE.

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Disclosures

The authors have no conflicts of interest or financial ties to disclose.

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Address reprint requests to:
Buddha Basnyat
Nepal International Clinic,
Lal Durbar,
GPO Box 3596,
Kathmandu, Nepal

E-mail: Rishibas@wlink.com.np

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