ORIGINAL RESEARCH

Prospective, Double-Blind, Randomized, Placebo-Controlled Comparison of Acetazolamide Versus Ibuprofen for Prophylaxis Against High Altitude Headache: The Headache Evaluation at Altitude Trial (HEAT)

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Objective.—High altitude headache (HAH) is the most common neurological complaint at altitude and the defining component of acute mountain sickness (AMS). However, there is a paucity of literature concerning its prevention. Toward this end, we initiated a prospective, double-blind, randomized, placebo-controlled trial in the Nepal Himalaya designed to compare the effectiveness of ibuprofen and acetazolamide for the prevention of HAH.

Methods.—Three hundred forty-three healthy western trekkers were recruited at altitudes of 4280 m and 4358 m and assigned to receive ibuprofen 600 mg, acetazolamide 85 mg, or placebo 3 times daily before continued ascent to 4928 m. Outcome measures included headache incidence and severity, AMS incidence and severity on the Lake Louise AMS Questionnaire (LLQ), and visual analog scale (VAS).

Results.—Two hundred sixty-five of 343 subjects completed the trial. HAH incidence was similar when treated with acetazolamide (27.1%) or ibuprofen (27.5%; $P = .95$), and both agents were significantly more effective than placebo (45.3%; $P = .01$). AMS incidence was similar when treated with acetazolamide (18.8%) or ibuprofen (13.7%; $P = .34$), and both agents were significantly more effective than placebo (28.6%; $P = .03$). In fully compliant participants, moderate or severe headache incidence was similar when treated with acetazolamide (3.8%) or ibuprofen (4.7%; $P = .79$), and both agents were significantly more effective than placebo (13.5%; $P = .03$).

Conclusions.—Ibuprofen and acetazolamide were similarly effective in preventing HAH. Ibuprofen was similar to acetazolamide in preventing symptoms of AMS, an interesting finding that implies a potentially new approach to prevention of cerebral forms of acute altitude illness.

Key words: altitude, headache, ibuprofen, acetazolamide, acute mountain sickness, high altitude headache

Introduction

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Headache ranks among the most common complaints at altitude, with an incidence of 25% at 1920–2956 m to between 47% and 62% at 4928 m.^{1–4} Diagnostic criteria have been proposed for altitude-associated headaches

(termed high altitude headache or HAH) by researchers and expert panels; however, HAH is sufficiently variable in presentation that altitude researchers mainly define HAH by the setting under which it occurs.⁵⁻⁷

HAH frequently occurs as a benign isolated ailment but is also considered a sentinel symptom in the development of acute mountain sickness (AMS). HAH is the requisite cornerstone symptom of AMS, defined at altitudes above 2500 m by the presence of headache and at least 1 other symptom of anorexia, fatigue, insomnia, or dizziness. If unrecognized or left untreated, advanced AMS may progress to its end-stage expression as high altitude cerebral edema. The diagnosis of high altitude cerebral edema comes with significant mortality, highlighting the practical importance of preventing HAH and AMS at an early stage.⁸⁻¹⁰

Ibuprofen is a widely available over-the-counter, non-steroidal anti-inflammatory drug (NSAID) commonly used for treatment of HAH. Ibuprofen via cyclo-oxygenase inhibition prevents the production of prostaglandins and the inflammatory cascade, chemical irritants known to sensitize meningeovascular receptors that mediate nociception.¹⁰⁻¹⁴ Multiple studies show the NSAID aspirin to be an effective prophylactic agent against HAH as well.¹⁵⁻¹⁷ Several studies put forth conflicting data with respect to NSAIDs' ability to prevent AMS. Two small studies have suggested that the related NSAIDs naproxen and calcium carbasalate are ineffective for prevention of AMS, whereas a preliminary observational report suggests a protective effect.¹⁸⁻²⁰

Acetazolamide is a diuretic and carbonic anhydrase inhibitor used as the standard prophylactic agent against AMS, and has been documented to prevent headache at altitude as well.^{2-4,21} Acetazolamide's multifactorial mechanism of prevention for altitude sickness includes renally induced metabolic acidosis resulting in diuresis and enhanced ventilation, improvements in sleep quality from modulation of carotid body activity, and inhibition of cerebrospinal fluid production.^{22,23} While intuitive that acetazolamide would prevent headaches at altitude, it has seen limited study for HAH prevention specifically.¹⁶

This study was designed to compare the effect of the NSAID ibuprofen with acetazolamide for prevention of HAH and AMS, as well as to better establish clinical standards for HAH prevention.

Methods

This study was designed as a prospective, double-blind, randomized, placebo-controlled trial. Enrollment took place between October and November 2005 along the approach trail to Mount Everest in the Nepali Himalaya. The study was conducted in accordance with the Decla-

ration of Helsinki,²⁴ and under the auspices of the Himalayan Rescue Association. Ethical approval was provided by the Stanford University School of Medicine Institutional Review Board and the Nepal Health Research Council.

Participants and Outcome Measures

Trekkers completed questionnaires after giving signed informed consent. Inclusion criteria specified healthy non-Nepali males and females 18 to 65 years of age traveling directly between the baseline villages of Pheriche or Dingboche (4280 m and 4358 m, respectively) and the endpoint in Lobuje (4928 m). Potential participants were excluded if they had any headache, diagnosis of AMS, signs or symptoms of a substantial acute infection, had slept above 4500 m, or had taken any NSAIDs or acetazolamide within 1 day or 3 days prior to enrollment, respectively.

The predetermined primary outcome measure was presence of headache incidence at the study endpoint as calculated on the Lake Louise AMS Questionnaire (LLQ), a validated field standard for diagnosis of AMS, which includes a question on headache presence and severity.^{25,26}

A predetermined secondary endpoint included evaluation of headache severity by Visual Analog Scale (VAS).^{27,28} Other secondary measures included pulse oximetry (Nonin Medical Products, Minneapolis, MN), as well as AMS incidence and severity as measured by the LLQ. Demographics, ascent profile, compliance, and side effects data were collected to adjust for potential confounders.

Study Design

Commercial pharmaceutical grade acetazolamide and ibuprofen were packed in visually identical capsules by Deurali-Janta Pharmaceuticals (Kathmandu, Nepal). Study medications were randomized via computer-generated code. Participants were sought out on a daily basis in all baseline village hotels and sequentially enrolled in order to minimize selection bias.

All trekkers newly arrived at the baseline altitude were screened daily. Interviewers gathered demographics, ascent profile data, LLQ, VAS, and pulse oximetry. All trekkers were given information on methods for reducing the risk of AMS, thereby meeting the minimum standard of care. They were then randomized in a double-blind fashion to receive 3 times daily dosing of placebo, ibuprofen 600 mg, acetazolamide 85 mg (total daily dose of 255 mg to approximate a cumulative 250 mg daily dose given for AMS prophylaxis). Participants took a mini-

num of 3 doses at the baseline altitude before proceeding on their trek.

On their ascent from baseline, a minority of participants stopped overnight at a lodge at 4595 m, but all were expected to arrive at the endpoint altitude for data collection. VAS and LLQ scores were self-reported the night of arrival and the morning after arrival, at which point the study was complete. Endpoint data collection represents morning-after-arrival data (unless missing, then replaced with night-before data) in order to emphasize specificity in the diagnosis of HAH and AMS.

In order to minimize morbidity from high altitude illness, participants were discouraged, but not actively prevented, from using unblinded analgesics or acetazolamide. In the event of a severe illness that might be attributable to altitude or a reaction to medications, administrators were at the baseline and endpoint sites with appropriate steroid medication available.

Statistical Analysis

Power calculations suggested target sample sizes of 200 participants per treatment group and 100 in the placebo group. This was calculated to be sufficient to identify a statistically significant difference (at 80% power) between treatment and placebo, based on published HAH incidence of 50% at the study endpoint.^{2,4} Because the efficacy of acetazolamide relative to placebo has previously been established at identical altitudes and to permit improved power to detect differences between treatment groups, the relative number of participants allotted to the placebo group was reduced.

Intent-to-treat analyses, univariate comparisons (Pearson chi-square, Fisher exact tests, *t* tests), and logistic regression were used to examine multivariate risk factors for binary outcomes. *P* values less than .05 were considered significant. All analyses were conducted using R 2.6.0 software.²⁹

Results

A total of 343 healthy trekkers were enrolled and compared at baseline with 265 subjects presenting at the endpoint to provide data (78 subjects or 22.7% lost to follow-up, see Figure). An intent-to-treat analysis per protocol was used to evaluate the data, with 48 participants deviating from the proscribed protocol (see Table 1 and Figure).

While strict blinding and randomization methodology were incorporated, univariate comparisons of groups at baseline suggests that participants in the ibuprofen group were more likely to ascend slowly and sleep at the slightly higher baseline village of Dingboche (see Table

Figure. HEAT study flow chart.

1), characteristics that could potentially provide a protective effect against altitude. As such, we included ascent rate and baseline village variables in our multivariate models to adjust for any potential effects. Neither variable approached significance in multivariate models (data not shown).

There were no major adverse events reported throughout the trial (ie, drug reactions, gastrointestinal bleeding, or life-threatening altitude sickness). Ibuprofen was not associated with a higher incidence of gastrointestinal upset or nausea after multiple statistical evaluations were performed.

Intent-to-Treat Analysis

Intent-to-treat data analysis revealed several key findings (see Table 2). For the primary endpoint, there was no significant difference between treatments in preventing HAH incidence (acetazolamide 27.1%, ibuprofen 27.5%; *P* = .95). Combining treatment groups revealed a decrease in HAH incidence when compared to placebo at 45.3% (*P* = .01), resulting in a number needed to treat of 5.5. Headache severity was not significantly reduced either between treatments or compared to placebo by several measures (see below). The combined treatment groups were efficacious in prevention of AMS incidence (acetazolamide 18.8%, ibuprofen 13.7%, placebo 28.6%, *P* = .03), resulting in a number needed to treat of 8.1. Participants taking placebo had a greater oxygen desaturation on ascent than those in the treatment arms (*P* = .03).

Secondary Analysis

Analysis with fully compliant participants (defined as those who took all study medications and did not take off-study

Table 1. Baseline characteristics of the completed study group

Variables	Study participants		Placebo group		Acetazolamide group		Ibuprofen group		P
Cohort at endpoint (of 343) ^a	265		65	24.5%	97	36.6%	103	38.9%	
Male gender	187	71.1%	47	72.3%	65	67.7%	75	73.5%	.64
Mean age	38.3	± 11.8	39.2	± 12.1	39.1	± 12.0	37	± 11.4	.36
Trekkers starting from 2800 m ^b	228	86.7%	55	84.6%	83	85.6%	90	89.1%	.65
Nights to ascend to baseline	3.4	± .9	3.3	± .87	3.3	± 1.0	3.7	± .9	.01
Enrolled at 4358 m ^c	151	58.5%	30	46.9%	52	55.3%	69	69.0%	.01
History of altitude illness	7	2.6%	3	4.6%	2	2.1%	2	1.9%	.55
Positive LLQ score ^d	21	7.0%	7	9.2%	9	8.1%	5	4.5%	.40
Enrollment Sao ₂	86.0	± 4.1	86.1	± 4.8	86.4	± 3.7	85.5	± 3.9	.25
Lost-to-follow up	78	22.7%	24	27.0%	28	22.4%	26	2.2%	.52

Values are number and percent or mean ± SD.

^a Endpoint cohort consists of participants enrolled at baseline and followed up at endpoint (n = 265).

^b The Lukla airport is at ~2800 m, and trekkers starting from Jiri (2000 m) pass through Lukla.

^c Enrollment occurred in the villages of Dingboche (4358 m) and Pheriche (4280 m).

^d Participants were allowed to have 1 mild (LLQ = 1) non-headache symptom on the LLQ to prevent self-selection bias.

medications) revealed several effects not observed in the intent-to-treat evaluation (see Table 3). HAH severity measured by LLQ as moderate or severe had a more frequent incidence in the placebo group as compared to either treatment (acetazolamide n = 3 [3.8%], ibuprofen n = 4 [4.7%], placebo n = 7 [13.5%]; $P = .03$). This finding correlated well on the VAS for acetazolamide, while ibuprofen notably was similar to placebo (acetazolamide 2.5 cm, ibuprofen 6.0 cm, placebo 5.9 cm; $P = .04$). Upon further analysis of VAS headache scores, 3 of the ibuprofen participants recorded outlier VAS scores that were much higher than any values in the acetazolamide group. In small sample sizes outlier scores may bias the results, caution in drawing conclusions based on VAS scores with wide discrepancy in individual values seems prudent.

Multivariate logistic regression analysis was utilized to assess the association of treatment and probability of HAH or AMS incidence as defined by LLQ score. After adjusting for potential baseline confounders (mode of arrival, time spent on ascent to baseline, baseline village altitude, compliance status, age, and sex), no significant difference was found between the treatments for probability of HAH or AMS. However, treatment overall was estimated to reduce the likelihood of development of HAH and AMS compared to placebo (HAH $P = .01$, AMS $P = .02$), and results did not vary when excluding noncompliant individuals rather than adjusting for compliance status (data not shown).

Discussion

This study represents the largest interventional clinical trial for HAH prevention and establishes 2 important

findings. First, acetazolamide and ibuprofen were both shown to be effective in preventing incidence and severity of HAH. Second, ibuprofen performed as well as acetazolamide in the prevention of AMS.

These study data have been externally corroborated in two aspects. First, the protective effect of ibuprofen in development of HAH was found to be roughly similar to the effect of the NSAID aspirin observed in prior smaller studies.^{15–17} Interestingly, acetazolamide was found to be as effective in preventing a pain syndrome (HAH) as the nonsteroidal analgesic ibuprofen. This is not to suggest that acetazolamide is an analgesic; rather it suggests the likelihood that acetazolamide is effectively mitigating the pathophysiologic processes leading to headache pain at altitude.

The secondary finding that ibuprofen performed as well as acetazolamide in the prevention of AMS is novel and will require confirmation. Indirect support of ibuprofen for AMS prophylaxis is implied from multiple studies with either dexamethasone or NSAIDs showing a protective effect against AMS, suggesting that inhibition of the inflammatory cascade may play a significant role in both drug effects.^{9,20,21,30,31}

The secondary finding that an approximation of low dose acetazolamide (255 mg/d) prevents AMS incidence represents the largest trial to date corroborating prior studies.^{2,3,32} This low dose of acetazolamide was found to exhibit a robust and predictable clinical effect.

Theory and Mechanism

Headache pain in normoxic conditions is thought to originate from activation of the trigeminovascular sys-

Table 2. Main outcome profile (intent-to-treat)

Variables	Study participants	Acetazolamide			Ibuprofen group		Acetazolamide vs ibuprofen (P)		Significance treatment vs placebo (P)	
		Placebo group	Acetazolamide group	Ibuprofen group	Ibuprofen group	Acetazolamide vs ibuprofen (P)	Ibuprofen group	Acetazolamide vs ibuprofen (P)	Significance treatment vs placebo (P)	Significance treatment vs placebo (P)
Endpoint cohort	265	65	97	103						
Headache incidence	83	29	26	28	27.5%			.95		.01
Severe headache incidence ^a	18	7	6	5	4.9%			.68		.14
AMS incidence ^b	50	18	18	14	18.8%			.34		.03
Severe AMS incidence ^c	17	4	7	6	7.3%			.69		.95
Endpoint Sao ₂ (%)	81.8	81.0	82.6	81.7	± 4.2			.22		.09
Sao ₂ decrease from baseline	-4.3	-5.4	-3.9	-3.9	± 4.1			.99		.03
Headache VAS	5.0	5.6	4.1	5.3	± 1.08			.46		.58
Participants who broke protocol ^d	48	12	18	18	18.5%			.84		.94

Values are number and percent or mean ± SD. AMS, acute mountain sickness; VAS, visual analogue scale; LLQ, Lake Louise Questionnaire.

^a Severe headache incidence as determined by a value of 2 or greater (of 0–3) on the LLQ question: “Do you have a headache?”

^b AMS defined as LLQ score of 3 or greater, requiring headache plus 1 or more symptoms.

^c Severe AMS incidence as determined by a LLQ score of 5 or greater.

^d Participants who broke protocol were defined as those taking a medication conflicting with their assigned treatment group (crossovers) or missed 2 or more doses.

tem by mechanical and/or chemical inflammatory mediators; similar theorized mechanisms of HAH pathophysiology are applied to the action of agents presently studied.^{11–13} An oxygen-starved brain at altitude will swell with blood and create traction on the meninges, potentially irritating mechanoreceptors therein.¹³ Cerebral blood flow has been shown to increase by 26% upon acute exposure to high altitude, and an increase in cerebral blood volume can be inferred.³³ This increase in cerebral blood flow is also likely to be associated with distended cerebrovasculature, as observed in transcranial Doppler studies at altitude.³⁴

Hypobaric hypoxemia is associated with production of inflammatory mediators known to sensitize meningeovascular nociceptors and/or mediate vasodilation.^{11,12,35–37} The inflammatory mediator’s role has also been implied by multiple studies using steroids and/or NSAIDs to prevent and treat headaches in the context of AMS and/or high altitude cerebral edema.^{9,20,21,30,31,35,36} However, current evidence suggesting a role for inflammation in the pathophysiology for cerebral forms of acute altitude illness is scant.

Postulated HAH pathophysiology intersects with proposed mechanism of action for both of the study drugs. The basic mechanisms for acetazolamide have already been discussed above. Chemoprophylaxis with the NSAID ibuprofen may be theorized to address HAH pathophysiology by blunting the inflammatory cascade. The implication is that prevention of arachidonic acid metabolism, nociceptor irritation, and vascular endothelial breakdown suggest reasonable mechanisms whereby pain perception and increased cerebral blood flow and edema (leading to downstream events) may be attenuated.^{11,12,30,38}

Caution is warranted in interpretation of ibuprofen’s efficacy against HAH and AMS. Mechanisms have been discussed that tentatively suggest a means whereby ibuprofen may antagonize the pathophysiology of HAH and AMS. Alternatively, ibuprofen as a simple analgesic may transiently mask painful symptoms of altitude sickness without truly preventing illness. While one quantitative measure in this trial (oxygen saturation) may suggest true protection, this question awaits further careful research of physiologic parameters.

Limitations of the Study

There are several limitations to application of these data in clinical practice. First, participants had already been exposed to significant altitudes for several days prior to baseline enrollment (4280 or 4358 m), a comparatively low-risk setting that could introduce selection bias and limit comparison with other studies.³² This study in-

Table 3. Main outcome profile excluding those who broke protocol^a

Variables	Study participants	Placebo group	Acetazolamide group	Ibuprofen group	Acetazolamide vs ibuprofen (P)	Significance treatment vs placebo (P)
Endpoint cohort	217	53	79	85		
Headache incidence	68	31.6%	18	25	29.4%	.01
Severe headache incidence ^b	14	6.5%	3	4	4.7%	.03
AMS incidence ^c	41	19.2%	12	13	15.3%	.01
Severe AMS incidence ^d	13	6.1%	5	5	5.9%	.95
Endpoint SaO ₂ (%)	82.0	± 4.0	82.6	± 3.5	± 4.2	.25
SaO ₂ decrease from baseline	4.4	± 3.8	4.1	± 3.4	± 4	.12
Headache visual analog scale (VAS)	4.7	± 1.09	2.5	± .55	± 13.8	.34

Values are number and percent or mean ± SD. AMS, acute mountain sickness; LLQ, Lake Louise Questionnaire.

^a Participants who broke protocol were defined as those taking a medication conflicting with their treatment group (crossovers) or those who missed 2 or more doses.

^b Severe headache incidence as determined by a value of 2 or greater (of 0-3) on LLQ question: "Do you have a headache?"

^c AMS defined as LLQ score of 3 or greater, requiring headache plus 1 or more symptoms.

^d Severe AMS incidence as determined by a LLQ score of 5 or greater.

volved a diverse population in typical trekking conditions; these results cannot necessarily be applied to other high altitude trekking environments where ascent rate, demographics, and final elevation may differ. Second, just over a fifth of enrollees were lost to follow-up. Participants in all groups were equally likely to drop out of the study, and some attrition is expected (and similar to prior studies) given the realities of conducting a clinical trial in a wilderness setting. While an intent-to-treat analysis was intended to minimize this bias, it seems plausible that the overall incidence of HAH may be underestimated by these study results. Third, increased sample sizes would permit more power to identify small differences between the treatments, should they exist. This study employed an adequate sample size to detect with 95% certainty differences between treatments as small as 12% based on our reasonable prestudy assumptions.

Conclusions

In summary, these findings are in agreement with prior studies and support the clinical effectiveness of both ibuprofen and acetazolamide in the prevention of HAH. Either medication can be recommended for prophylaxis at altitude, with the inference that acetazolamide may prevent more severe headaches.

The clinical efficacy of low-dose acetazolamide (~250 mg/d) in the prevention of AMS has been reconfirmed. Ibuprofen was also found to be well tolerated and effective against symptoms of AMS. This is an interesting finding that implies the possibility of a new prophylactic agent against AMS. Ibuprofen is a commonly used and well-tolerated NSAID that could conceivably be used as an alternative to acetazolamide in those susceptible to HAH/AMS and who struggle with a sulfonamide allergy or acetazolamide side effects. However, at present, the widespread use of ibuprofen for HAH and AMS prophylaxis is only cautiously recommended until further research is conducted.

Competing Financial Interests

No authors received funding or reimbursement for this study from commercial interests.

Council

This study was conducted under the auspices of the Himalayan Rescue Association and received ethical approval from the Stanford University School of Medicine IRB and the Nepal Health Research Council.

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