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ORIGINAL RESEARCH

Prophylactic Acetaminophen or Ibuprofen Result in Equivalent Acute Mountain Sickness Incidence at High Altitude: A Prospective Randomized Trial

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Objective.—Recent trials have demonstrated the usefulness of ibuprofen in the prevention of acute mountain sickness (AMS), yet the proposed anti-inflammatory mechanism remains unconfirmed. Acetaminophen and ibuprofen were tested for AMS prevention. We hypothesized that a greater clinical effect would be seen from ibuprofen due to its anti-inflammatory effects compared with acetaminophen's mechanism of possible symptom reduction by predominantly mediating nociception in the brain.

Methods.—A double-blind, randomized trial was conducted testing acetaminophen vs ibuprofen for the prevention of AMS. A total of 332 non-Nepali participants were recruited at Pheriche (4371 m) and Dingboche (4410 m) on the Everest Base Camp trek. The participants were randomized to either acetaminophen 1000 mg or ibuprofen 600 mg 3 times a day until they reached Lobuche (4940 m), where they were reassessed. The primary outcome was AMS incidence measured by the Lake Louise Questionnaire score.

Results.—Data from 225 participants who met inclusion criteria were analyzed. Twenty-five participants (22.1%) in the acetaminophen group and 18 (16.1%) in the ibuprofen group developed AMS ($P = .235$). The combined AMS incidence was 19.1% (43 participants), 14 percentage points lower than the expected AMS incidence of untreated trekkers in prior studies at this location, suggesting that both interventions reduced the incidence of AMS.

Conclusions.—We found little evidence of any difference between acetaminophen and ibuprofen groups in AMS incidence. This suggests that AMS prevention may be multifactorial, affected by anti-inflammatory inhibition of the arachidonic-acid pathway as well as other analgesic mechanisms that mediate nociception. Additional study is needed.

Keywords: Nepal, altitude illness, Everest, prevention, drug trials, ibuprofen, acetaminophen

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Introduction

Increasing numbers of people are visiting elevations >2500 m around the globe. Individuals who ascend to high altitude and fail to acclimatize can experience

altitude illness, including acute mountain sickness (AMS), which is characterized by a constellation of symptoms: headache, fatigue, gastrointestinal upset, dizziness, and poor sleep.[1,2] These symptoms can be self-assessed and severity of illness standardized with the Lake Louise Questionnaire (LLQ).[3] A diagnosis of AMS is made when the LLQ is ≥ 3, in the presence of a headache. Along the trekking path to Everest Base Camp, the prevalence of AMS ranges from 25% to 53%.[4,5] AMS often is preceded by high-altitude headache (HAH), which is described as headache upon ascent to high altitude in the absence of any other AMS symptoms. Although timing of altitude illness is highly variable, it often presents within the first 24 hours of arrival to high altitude. If AMS is ignored, it can progress to dangerous and often fatal neurologic and/or pulmonary conditions, termed high-altitude cerebral edema (HACE) and high-altitude pulmonary edema. Left untreated, HACE can lead to death within 24 to 48 hours,[6] thus highlighting the importance of preventing AMS. The best prevention of altitude illness is a slow ascent.[7] However, proper acclimatization might be ignored or deemed impractical by mountain climbers, hikers, local pilgrims, rescue teams, or military operations.

Acetazolamide is a carbonic anhydrase inhibitor that is considered the gold standard for prophylaxis. It can help an individual acclimatize quicker and reduce the incidence of AMS.[7,8] Due to its side effects, potential for causing allergic reactions, and status as a prescription medication, alternative drugs for the prevention of AMS have been sought.

The exact mechanism that causes AMS still is not understood fully.[9] However, evidence points to a process in the central nervous system that increases expression of vascular endothelial growth factors, causing vasogenic edema in the brain and disruption of the blood–brain barrier.[10,11] Early cerebral inflammation due to hypobaric hypoxia also has been shown to trigger an inflammatory cascade, resulting in the formation of arachidonic acid metabolites (thromboxanes, prostacyclin, and prostaglandins) as well as serotonin, histamine, and nitric oxide and bradykinin.[12]

The proposed mechanism for ibuprofen in AMS prophylaxis is inhibition of cyclooxygenase at the rate-limiting step in the inflammatory cascade, reducing arachidonic acid metabolites. The efficacy of dexamethasone, a steroidal anti-inflammatory medication, in the prevention and treatment of AMS and HACE[9] provides a basis for the theory that the inflammatory pathway plays a major part in the pathogenesis and treatment of AMS. Three randomized, controlled trials have shown the usefulness of ibuprofen (600 mg 3 times a day [TID]) in the prevention of AMS.[13–15] The response in AMS prevention to nonsteroidal anti-inflammatory drugs and steroids provides indirect evidence for a causal relationship between inflammation and altitude illness. Two studies have proven the efficacy of ibuprofen in the treatment of HAH.[16,17] One of these studies[17] with a small sample size found acetaminophen to be as effective as ibuprofen in the treatment of HAH. However, we found no study in the literature that investigated the efficacy of acetaminophen in the prevention of AMS.

One must also consider that headaches in AMS are multifactorial, with various chemical and mechanical factors activating a final common pathway, activation of the trigeminovascular system. The role of drugs such as acetaminophen, which primarily provides analgesia (with little anti-inflammatory effect), is unclear in the prevention of AMS. Directly comparing acetaminophen to ibuprofen for the prevention of AMS would help in better understanding these relationships and potentially the underlying pathophysiology. Therefore, this study was designed as a double-blind, randomized, prospective clinical trial comparing ibuprofen (600 mg TID) and acetaminophen (1000 mg TID) in the prevention of AMS in non-Nepali trekkers in the Himalayas. We chose this dose based on precedent,[17] as well as effective pharmacologic dosing, avoiding maximum doses to minimize side effects.

Methods

A total of 332 non-Nepali volunteers aged 18 to 65 years were recruited at Pheriche (4371 m) and Dingboche (4410 m) along the Everest trekking route in the Khumbu region of Nepal. Subjects were recruited with flyers and door-to-door recruitment at the guesthouse hotels in which they stayed in Pheriche and Dingboche. Informed written consent was obtained, and participants were randomized to treatment group by a computer-generated program, prepared in advance, and held in a sealed envelope by an independent physician in the event of an emergency. Participants and researchers were blinded to the treatment group and group allocation. Each participant received 7 doses of visually matched capsules (Jolley's Compounding Pharmacy, Salt Lake City, UT) containing either ibuprofen 600 mg or acetaminophen 1000 mg. The medication dosing and frequency was chosen to approximate prior studies, maintain visual similarities and blinding, and provide effective dosing.

Participants were excluded if upon enrollment they met criteria for AMS diagnosis (LLQ ≥ 3 with headache), oxygen saturation (SpO_2) $<75\%$, or had spent >24 hours at altitudes >4500 m in the preceding 9 days. They must not have taken acetaminophen,