The Effects of a 5-Lipoxygenase Inhibitor on Acute Mountain Sickness and Urinary Leukotriene E₄ After Ascent to High Altitude*

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Background: Elevated urine and blood leukotriene levels have been reported after ascent to high altitude in association with acute mountain sickness (AMS) and high-altitude pulmonary edema. Zileuton is an inhibitor of the enzyme 5-lipoxygenase that catalyzes conversion of arachidonic acid to leukotrienes.

Study objectives and design: The objectives of this randomized, double-blind, placebo-controlled clinical trial were to determine whether zileuton (600 mg po qid) is effective prophylaxis for AMS, and to measure the effect of ascent to high altitude and zileuton on urinary leukotriene E₄ levels.

Setting and participants: The study group consisted of volunteers from among climbers on the West Buttress of Mt. McKinley (Denali), Alaska. After baseline urine samples at sea level, subjects flew by airplane to 2,300 m, and then ascended to the 4,200-m camp in 5 to 10 days.

Measurements and results: Using an enzyme immunoassay, urinary leukotriene E₄ was found to decrease after ascent to high altitude in both the zileuton and placebo groups. Urinary leukotriene E₄ in the zileuton group (n = 9) decreased from 67 ± 35 pg/mg creatinine at sea level to 33 ± 22 pg/mg creatinine at high altitude (p = 0.003) [mean ± SD]. Urinary leukotriene E₄ in the placebo group (n = 9) decreased from 97 ± 82 pg/mg creatinine at sea level to 44 ± 21 pg/mg creatinine at high altitude (p = 0.045). One subject in the zileuton group and three subjects in the placebo group met Lake Louise criteria for AMS after arriving at 4,200 m (p = 0.257).

Conclusions: Elevated leukotrienes are not associated with ascent to high altitude. In subjects with AMS, urinary leukotrienes were not elevated, suggesting that leukotrienes may not be a component of the pathophysiology of AMS. The low incidence of AMS and the small sample size in this study prevented determination of whether zileuton is effective prophylaxis for AMS.

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Key words: acute mountain sickness; high altitude; urinary leukotriene E₄; zileuton

Abbreviations: AMS = acute mountain sickness; HAPE = high-altitude pulmonary edema; SpO₂ = pulse oximetric saturation

Acutemountain sickness (AMS) is a neurologic syndrome that occurs in unacclimatized persons after acute ascent to altitudes > 2,000 m. Headache is the prominent feature and is associated with one or more nonspecific symptoms of anorexia, nausea, vomiting, fatigue, weakness, dizziness, lightheadedness, or difficulty sleeping. The pathophysiology of AMS involves neurohumoral and hemodynamic responses that occur in the brain, lungs, and peripheral tissues, resulting in fluid retention, overperfusion of microvascular beds, and extravasation of fluid into the extravascular space.¹

Leukotrienes, lipoxygenase products of arachidonic acid, are inflammatory mediators that can contribute to increased endothelial cell permeability and have been implicated in the pathophysiology of AMS.²–⁵ Leukotriene E₄, a stable metabolite excreted in the urine, was increased in eight subjects after a 4-day ascent to 4,300 m and was associated with symptoms of AMS.² Blood leukotriene B₄ levels

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were increased in persons rapidly transported to 4,350 m and corresponded to the time course and clinical severity of AMS. Inhibition of cysteinyl leukotriene receptors with montelukast transiently improved symptoms of AMS after ascent to 4,300 m in a hypobaric chamber. Previous studies also suggest that leukotrienes may contribute to increased capillary permeability in the lung in high-altitude pulmonary edema (HAPE), a form of non-cardiogenic pulmonary edema that occurs after acute ascent to high altitude. Increased urinary leukotriene E4 levels, and increased BAL fluid leukotriene B4 levels were reported in established cases of HAPE. Other studies, however, show that increased leukotriene synthesis may be a result of established high-altitude illness, rather than an etiologic factor. Leukotrienes in urine and BAL fluid were not increased early in the course of HAPE. Thus, previous studies have contradictory findings regarding the role of leukotrienes in high-altitude illness, and the regulation of leukotriene metabolism after ascent to high altitude is not precisely established.

We designed a study to determine if leukotrienes have a causal role in the pathophysiology of AMS. We hypothesized that inflammation in AMS is caused in part by inappropriate synthesis of the proinflammatory leukotrienes, and that blocking synthesis of leukotrienes would prevent AMS. To test this hypothesis, we conducted a randomized, double-blind, placebo-controlled clinical trial evaluating the effectiveness of an inhibitor of 5-lipoxygenase, zileuton, in the prevention of AMS. The objectives of this study were as follows: (1) to determine whether zileuton is effective prophylaxis for AMS, (2) to examine the effect of ascent to altitude on urinary leukotriene levels, and (3) to correlate urinary leukotriene E4 levels with the presence and severity of AMS.

**Materials and Methods**

This study took place during the May to June climbing season in 1998 on Mt. McKinley (Denali; elevation: 6,195 m) in Alaska. The study group consisted of volunteers from among climbers in Talkeetna, AK (elevation, 200 m; referred to as sea level in the text) preparing for an expedition on the West Buttress route of Denali. Climbers learned of the study when they checked in at the National Park Service ranger station in Talkeetna. Climbers volunteering for the study were interviewed about their medical history, history of high-altitude illness, allergies, and medications. Climbers were excluded from the study if they were < 18 years of age; if they had chronic heart, lung, liver, or kidney disease; if they were receiving any medication known to be metabolized by the cytochrome P450 enzyme; or if they were using dexamethasone or acetazolamide for prophylaxis of AMS. Climbers volunteering for the study who met inclusion criteria were randomized in a double-blind fashion to either zileuton, 600 mg po qid, or placebo starting 1 day prior to beginning their ascent. Zileuton or placebo drug packets for 10 days of study drug therapy were prepared prior to initiation of the study by an independent pharmacist in groups of four (two placebo and two zileuton packets) to permit block randomization. The procedures used in this human research study were in accordance with the Helsinki Declaration. The University of Utah Institutional Review Board approved this study, and written informed consent was provided by volunteers.

Baseline measurements in Talkeetna included pulse oximetric saturation (SpO2). Baseline urine samples were obtained in Talkeetna, frozen at –20°C, and stored until shipment to the University of Utah for analysis. From Talkeetna, subjects flew by bush plane with their expedition to 2,300 m, and then ascended to 4,200 m in 5 to 10 days. When subjects arrived at the 4,200 m camp on the West Buttress, they checked in with a study investigator at the National Park Service 4,200-m medical camp. A second urine sample was obtained on the day of arrival at 4,200 m, and SpO2 was measured. Symptoms of AMS were assessed at 4,200 m using the Lake Louise AMS score. A score of ≥ 3 on the Lake Louise AMS self-report questionnaire was used to indicate AMS. This ended the subject’s participation in the study.

Urine samples stored in sterile containers and frozen at –20°C were transported to the University of Utah for analysis. An immunoaffinity resin for purification of urinary leukotriene E4 was performed using a commercially available cysteinyl-leukotriene affinity sorbent (Cayman Chemical; Ann Arbor, MI). Urinary leukotriene E4 levels are expressed as picograms per milligram of creatinine.

Comparisons of measured parameters between the zileuton and placebo groups were made using an unpaired t test. Comparisons of measured parameters at sea level vs high altitude in the zileuton and placebo groups were made using a paired t test. The number of subjects with AMS in the zileuton and placebo groups was compared using a χ2 test. Spearman rank order correlation was used to determine correlation between high-altitude urinary leukotriene E4 and high-altitude SpO2. AMS score, and number of days for ascent to 4,200 m. Statistical software (Statistica, 1999 edition; StatSoft; Tulsa, OK) was used for all statistical analysis. p < 0.05 was considered statistically significant. Data are reported as mean ± SD.

**Results**

Nineteen subjects entered the study. One male subject randomized to the placebo group discontinued the study due to inconvenience of the qid dosing of the study drug. The rest of the subjects were compliant with all dosing of the study drug. Therefore, a total of 18 subjects are included in the data analysis. Nine subjects were randomized to zileuton (one woman and eight men; mean age, 37 ± 10 years), and nine subjects were randomized to placebo (one woman and eight men; mean age, 33 ± 5 years; p = 0.27) [Fig 1, 2]. In the zileuton group, the mean ascent rate from sea level to 4,200 m was 8.9 days (range, 5 to 10 days); in the placebo group, the mean ascent rate was 7.3 days (range, 5 to 10 days; p = 0.12). In the placebo group, there was a significant correlation between urinary leukotriene E4 levels at high altitude and the number of days of ascent from sea level to 4,200 m (p = 0.02), but not in the zileuton group (p = 0.79) [Fig 3].
One subject in the zileuton group and three subjects in the placebo group met Lake Louise criteria for AMS on, or shortly after, arriving at 4,200 m (p = 0.257). Two subjects in the zileuton group had Lake Louise AMS scores > 2 but did not have a headache, which is required for the diagnosis of AMS. One subject was ill with an upper respiratory infection and had an AMS score of 5, and another subject had an AMS score of 3 but denied any headache. Mean AMS scores at 4,200 m were 1.7 ± 0.02 in the zileuton group and 1.7 ± 2.1 in the placebo group (p = 1.0). All subjects in whom AMS developed had decreased urinary leukotriene E₄ levels after ascent to high altitude (Fig 2). In the zileuton group, SpO₂ significantly decreased from 97 ± 3% at sea level to 87 ± 1% at high altitude (p < 0.001). In the placebo group, SpO₂ also significantly decreased from 98 ± 1% at sea level to...
87 ± 5% at high altitude (p = 0.001). SpO₂ at high altitude was not different between the zileuton and placebo groups (p = 0.87). Urinary leukotriene E₄ levels significantly decreased from sea level to high altitude in both groups (Fig 1). Urinary leukotriene E₄ in the zileuton group decreased from 67 ± 35 pg/mg creatinine at sea level to 33 ± 22 pg/mg creatinine at high altitude (p = 0.003). Urinary leukotriene E₄ in the placebo group decreased from 97 ± 82 pg/mg creatinine at sea level to 44 ± 21 pg/mg creatinine at high altitude (p = 0.045). Urinary leukotriene E₄ levels were not significantly different between zileuton and placebo at sea level (p = 0.33) or at high altitude (p = 0.30). Urinary leukotriene E₄ levels at high altitude did not significantly correlate with AMS score (p = 0.27 for placebo, and p = 0.49 for zileuton) or SpO₂ (p = 0.64 for placebo, and p = 0.60 for zileuton).

**DISCUSSION**

Our study demonstrates that urinary leukotrienes are not increased after ascent to high altitude or in association with AMS. Our data instead show that urinary leukotrienes decrease after rapid ascent from sea level to 2,300 m, followed by gradual ascent from 2,300 to 4,200 m. A decrease in urinary leukotriene E₄ after ascent to high altitude might be expected in the zileuton group in our study because zileuton inhibits the enzyme 5-lipoxygenase and leukotriene synthesis. In prior studies, treatment with zileuton has decreased urine leukotriene E₄ levels in both healthy persons and patients with asthma. In the placebo group in our study, eight of nine subjects had a decrease in urine leukotriene E₄, and the mean urine leukotriene E₄ level significantly decreased after ascent to high altitude. AMS developed in three subjects in the placebo group, and all had a decrease in urine leukotriene E₄ after ascent to high altitude. This suggests that leukotrienes are not causally related to the pathophysiology of AMS.

In our study, the dosage of zileuton at 600 mg qid did not completely inhibit urinary leukotriene E₄. This raises the question whether a higher dose of zileuton may have been more effective in preventing AMS. We used the maximum recommended dose of zileuton, which should have shown a beneficial clinical result in preventing AMS if leukotrienes play a role in AMS. The dose of zileuton used in our study has been shown to be effective in both short and long-term treatment of asthma, and clinical efficacy of zileuton in asthma is observed with a reduction, but not total elimination, of urinary leukotriene E₄ levels. One dose of zileuton, 800 mg, reduces urinary excretion of leukotriene E₄ by 50% and reduces the acute asthmatic response to inhaled allergen. A 4-week course of zileuton, 600 mg qid, decreased urinary leukotrienes and improved lung function.
function in asthmatic patients,\textsuperscript{13} and a 2-day course of zileuton, 600 mg qid, ameliorated exercise-induced asthma.\textsuperscript{19}

Our study failed to show efficacy of zileuton for prophylaxis of AMS. In view of the significant decrease in urinary leukotrienes in the placebo group after ascent to high altitude, in retrospect we would not expect an inhibitor of leukotriene synthesis to prevent AMS. We recognize that incidence of AMS in our placebo group was not high enough to preclude a type II statistical error. A larger study with more subjects is required to conclusively demonstrate that zileuton is not effective for AMS prophylaxis. We suggest, however, that our findings of a decrease in urinary leukotriene \( E_4 \) after ascent to high altitude makes efficacy of zileuton for prevention of AMS unlikely.

Our findings are in contrast to those of Roach and colleagues\textsuperscript{2} in two respects. First, Roach and colleagues\textsuperscript{2} observed a significant increase in urine leukotriene \( E_4 \) in eight subjects after graded rapid ascent from sea level to 4,300 m. Second, Roach and colleagues\textsuperscript{2} observed a significant correlation between symptoms of AMS and urinary leukotriene \( E_4 \) levels, although this was due to the influence of data from one subject. AMS developed in only three of eight subjects after ascent from 1,830 to 4,300 m. The ascent profile in their study included rapid passive ascent from sea level to 1,830 m, and then after a 3-day stay at 1,830 m, rapid passive ascent to 4,300 m. Urinary leukotriene \( E_4 \) levels were measured at sea level, 1,830 m, and 4,300 m. Their data show that three of eight subjects had decreased urinary leukotriene \( E_4 \) levels after rapid ascent from sea level to 1,830 m, and two of eight subjects had decreased urinary leukotriene \( E_4 \) levels after rapid ascent from 1,830 to 4,300 m. Mean increase in urinary leukotriene \( E_4 \) level was not significant after ascent from sea level to 1,830 m, but was significant after ascent from 1,830 to 4,300 m. The difference in findings between the study by Roach and colleagues\textsuperscript{2} and our study might be attributed to rate of ascent and hypoxic stress. The subjects in our study rapidly ascended from sea level to 2,300 m and then had a gradual active ascent over 5 to 10 days from 2,300 to 4,200 m. The subjects in the study by Roach and colleagues\textsuperscript{2} had rapid passive ascent from 1,830 to 4,300 m. The subjects in our study had more time for acclimatization, which is reflected in a higher mean \( \text{SpO}_2 \) of 87\% after arrival at 4,200 m, as compared to the subjects in the study by Roach and colleagues,\textsuperscript{2} in whom mean \( \text{SpO}_2 \) was 82\% after arrival at 4,300 m. Rapid ascent with greater hypoxic stress may have resulted in increased leukotriene synthesis in the study by Roach and colleagues.\textsuperscript{2}

Richalet and colleagues\textsuperscript{3} measured plasma leukotriene \( B_4 \) and \( C_4 \) after rapid ascent to 4,350 m. The enzyme 5 lipooxygenase acts on arachidonic acid to form an unstable intermediate, leukotriene \( A_4 \), which may be converted to leukotriene \( B_4 \), a powerful chemotaxin. Leukotriene \( A_4 \) may also be converted to the cysteinyl leukotrienes, \( C_4, D_4, \) and \( E_4 \), which cause bronchoconstriction, airway edema, mucous secretion, and increased capillary permeability. Richalet and colleagues\textsuperscript{3} found that plasma leukotriene \( B_4 \) was significantly increased after rapid ascent to high altitude, but that the cysteinyl leukotriene \( C_4 \) was unchanged. We did not measure leukotriene \( B_4 \) in our study, but we did measure a metabolite of the cysteinyl leukotriene \( C_4 \), urinary leukotriene \( E_4 \). If it is assumed that urinary leukotriene \( E_4 \) levels reflect plasma leukotriene \( C_4 \) levels, then our findings are consistent with those of Richalet and colleagues,\textsuperscript{3} in that neither study showed an increase in the cysteinyl leukotrienes (plasma leukotriene \( C_4 \) or urinary leukotriene \( E_4 \) after ascent to high altitude.

Muza and colleagues\textsuperscript{5} studied the cysteinyl leukotriene receptor blocker montelukast for prevention of AMS after ascent to 4,300 m for 24 h in a hypobaric chamber. Although montelukast improved AMS symptoms after 11 h, it was no different than placebo after 20 h. Similar to the results of our study, Muza and colleagues\textsuperscript{5} found no increase in urinary leukotriene \( E_4 \) after ascent to altitude and no correlation with symptoms of AMS.

The findings in our study are also consistent with those of Bartsch and colleagues,\textsuperscript{9} who studied seven HAPE-susceptible subjects and five control subjects during a 20-h stay in a hypobaric chamber after a 4-h ascent from 450 to 4,000 m. In both groups, there was no significant increase in urinary leukotrienes, and there was no significant correlation between urinary leukotrienes and maximum AMS score or \( \text{SpO}_2 \). In a field portion of their study, urinary leukotrienes were not increased in subjects with HAPE compared to values obtained prior to HAPE at high altitude and during 2 control days at low altitude. These findings are consistent with those from a study by Swenson and colleagues,\textsuperscript{8} in which there was no increase in leukotriene \( B_4 \) levels in BAL fluid after ascent from 490 to 4,559 m in control subjects or in HAPE-susceptible subjects in whom HAPE did or did not develop at high altitude.

We do not believe that other factors influenced urinary leukotriene \( E_4 \) levels in our study, such as urine creatinine after ascent to high altitude or exercise. Although plasma creatinine increases after ascent to high altitude due to body water reduction, urine creatinine remains unchanged.\textsuperscript{20} This is important to our measurements of urinary leukotriene \( E_4 \) because it is normalized to milligrams of creatinine in urine. Exercise does not increase urinary leuko-
triene E₄ levels in healthy or asthmatic persons, although agents that block 5 lipoxygenase can decrease urinary leukotriene E₄ after exercise as compared to control subjects.

We conclude that climbing to high altitude using a gradual ascent profile is associated with a decrease in urinary leukotrienes. Urinary leukotriene levels were not effected by ingestion of zileuton and did not correlate with symptoms of AMS. These data suggest that leukotrienes are not critical to the pathogenesis of AMS.

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