ORIGINAL RESEARCH

Prospective Double-Blinded Randomized Field-Based Clinical Trial of Metoclopramide and Ibuprofen for the Treatment of High Altitude Headache and Acute Mountain Sickness

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Introduction—High altitude headache (HAH) and acute mountain sickness (AMS) are common pathologies at high altitudes. There are similarities between AMS and migraine headaches, with nausea being a common symptom. Several studies have shown ibuprofen can be effective for AMS prophylaxis, but few have addressed treatment. Metoclopramide is commonly administered for migraine headaches but has not been evaluated for HAH or AMS. We aimed to evaluate metoclopramide and ibuprofen for treatment of HAH and AMS.

Methods—We performed a prospective, double-blinded, randomized, field-based clinical trial of metoclopramide and ibuprofen for the treatment of HAH and AMS in 47 adult subjects in the Mount Everest region of Nepal. Subjects received either 400 mg ibuprofen or 10 mg metoclopramide in a 1-time dose. Lake Louise Score (LLS) and visual analog scale of symptoms were measured before and at 30, 60, and 120 min after treatment.

Results—Subjects in both the metoclopramide and ibuprofen arms reported reduced headache severity and nausea compared to pretreatment values at 120 min. The ibuprofen group reported 22 mm reduction in headache and 6 mm reduction in nausea on a 100 mm visual analog scale at 120 min. The metoclopramide group reported 23 mm reduction in headache and 14 mm reduction in nausea. The ibuprofen group reported an average 3.5-point decrease on LLS, whereas the metoclopramide group reported an average 2.0-point decrease on LLS at 120 min.

Conclusions—Metoclopramide and ibuprofen may be effective alternative treatment options in HAH and AMS, especially for those patients who additionally report nausea.

Keywords: high altitude illness, hypobaric hypoxia, Nepal Himalayas

Introduction

Approximately 30 to 50% of people exposed to high altitude develop symptoms of acute mountain sickness

(AMS) and 1 to 2% develop life-threatening high altitude cerebral edema (HACE) and high altitude pulmonary edema (HACE and HAPE).¹ High altitude headache (HAH) affects up to 80% of persons who ascend above 3000 m.²

From most mild to severe, HAH, AMS, and HACE can be considered a spectrum of clinical syndromes related to exposure to the hypobaric hypoxia of high altitude. HAH has a variable and nonspecific presentation, defined by the International Headache Society as developing within 24 h of ascent to 2500 m, resolving within 8 h of descent, and having at least 2 of the following features: bilateral,

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frontal/frontotemporal, dull or pressing quality; mild to moderate severity; or aggravated by exertion, movement, straining, coughing, or bending. Patients can present with HAH in isolation or as a part of AMS defined by the Lake Louise Score (LLS) (Table 1),³ including symptoms of nausea/vomiting, fatigue/lassitude, dizziness, or insomnia. Mild AMS may be the result of HAH leading to systemic symptoms, whereas severe AMS and HACE may have evidence of edema on neuroimaging, particularly in the splenium of the corpus callosum, as well as microhemorrhages. Progression from AMS to HACE can occur between 0.5 to 3 d. Physical examination findings are not usually present until a patient develops HACE, which can present with altered mental status, papilledema, retinal hemorrhages, or ataxia. Case reports also describe focal neurologic findings such as weakness and cranial nerve palsies; however, this should broaden the differential because HACE is not commonly associated with focal deficits. The risk of developing these conditions is not reliably predictable and is multifactorial, dependent on the rate of ascent, duration and degree of exposure, and genetic predisposition. The mechanism and pathophysiology of AMS are debated but are thought to involve hypoxia-induced increased cerebral blood volume leading to increased intracranial pressure along with disruption of the blood-brain barrier, in turn leading to vasogenic edema in mild presentations and the addition of cytotoxic edema in severe cases.

Acetazolamide is a carbonic anhydrase inhibitor commonly used to aid acclimatization and prevent and treat mild to moderate AMS.⁴ It is generally well tolerated, although some patients may not be able to use it due to side effects (commonly paresthesia and taste disturbances), medication interactions, or allergy, including low-risk sulfonamide cross-reactivity. If a patient cannot use acetazolamide, an alternative agent may be considered. Because HAH and AMS share features with migraines and tension headaches, similar therapeutics may be efficacious.

Ibuprofen is a cyclo-oxygenase inhibitor that decreases production of inflammatory prostaglandins and in turn

decreases activation of the cerebral nociception pathway. Several studies have evaluated ibuprofen in preventing HAH and AMS. Prophylactic ibuprofen decreased the incidence of AMS and HAH in certain groups in both the ASCENT⁵ and the HEAT⁶ trials. In a separate study, prophylactic ibuprofen decreased AMS incidence and severity compared to placebo,⁷ but with equal incidence when compared to acetazolamide. A recent meta-analysis concluded that AMS occurred in 27% of subjects taking nonsteroidal anti-inflammatory drugs prophylactically compared to 44% taking placebo.⁸ Ibuprofen may also have benefit for treatment of HAH and AMS, but it is less well studied. In a single study of 74 subjects, ibuprofen was found to be as effective as acetaminophen in relieving HAH.⁹

Several similarities exist between AMS and migraine headaches, with nausea commonly associated with both. Metoclopramide is proposed to antagonize central and peripheral dopamine receptors that block stimulation of the medullary chemoreceptor trigger zone and has been shown to be effective for migraine headache.¹⁰ To our knowledge, metoclopramide has not previously been studied for the relief of HAH and AMS. This study aims to evaluate and compare ibuprofen and metoclopramide for treating HAH and AMS.

Methods

This study was approved by the Massachusetts General Hospital institutional review board (protocol #2010P002837) and the Nepal Health Research Council (Reg no. 16/2012). The clinical trial identifier number is [NCT01522326](#). Written, informed consent was obtained from all subjects.

We performed a prospective, double-blinded, randomized, field-based clinical trial of metoclopramide and ibuprofen for the treatment of HAH and AMS. Subjects were enrolled by convenience sample of trekkers in the Khumbu Valley of Nepal via the typical route to Mount Everest Base Camp. Enrollment took place during the trekking seasons

Table 1. Comparison of high altitude headache and acute mountain sickness definitions

<i>High altitude headache</i>	<i>Acute mountain sickness</i>
Headache with onset within 24 h of ascent and resolution within 8 h of descent with at least 2 of the following:	High altitude headache at an altitude above 2500 m plus at least 1 of the following:
<ul style="list-style-type: none"> •Bilateral •Frontal or frontotemporal •Dull or pressing pain •Mild to moderate intensity •Aggravated by exertion, straining, or coughing 	<ul style="list-style-type: none"> •Nausea or vomiting •Fatigue or general weakness •Dizziness or lightheadedness •Sleep disturbance^a
Defined by the International Headache Society	Defined by the Lake Louise Conference Consensus Group

^a Although included at the time of this data collection, sleep disturbance was removed from the Lake Louise Score in 2018.

of March to May 2013 and March to April 2015. No members of the research team were available to enroll patients during the 2104 season. Subjects were recruited from tea houses in Pheriche (4280 m) and Dingboche (4358 m), the Himalayan Rescue Association clinic in Pheriche, and posted signage. Potential subjects included patients seeking care at the clinic, interested persons who followed posted signage about the study or heard about the study at the daily altitude lecture, or trekkers at local tea houses approached by research staff during nightly rounds. To be included, subjects were required to have symptoms at the time of enrollment. Eligibility criteria included (1) increase in altitude of >300 m in the last 24 h and (2) presence of headache plus 1 other symptom (including nausea, vomiting, fatigue, weakness, lightheadedness, or difficulty sleeping). Patients with HACE/HAPE, prior chronic headaches, and allergies to ibuprofen or metoclopramide were excluded. Subjects were asked report other medications they were taking but were not excluded based on medications, aside from those who had taken ibuprofen or metoclopramide within 6 h of the study start. A few subjects had taken acetazolamide during their trek, but the majority had not. Subjects were asked to refrain from taking additional medications during the 120 min of the study.

Subjects were randomized to a 1-time oral dose of either 10 mg metoclopramide or 400 mg ibuprofen in blinded blister packaging. Subjects and study staff were blinded to the assigned group. Medications were assigned by random number generator and labeled by an independent assistant before arrival in Nepal. Onsite research staff had the ability to break the blinding in case of emergency, but this was never required. Vital signs, LLS, and visual analog scale (VAS) for headache and nausea were assessed immediately before medication administration and at 30, 60, and 120 min.

Mean age, resting heart rate, resting respiratory rate, oxygen saturation, and initial LLS were compared to verify no significant differences were present between the treatment groups at baseline (Table 1). For subsequent data points at 30, 60, and 120 min (Figures 1 and 2), values were calculated as change from the subject's own baseline value at time 0. Because significant variability is found in individuals' high altitude response, each subject could serve as his or her own control.

Several subjects ($n=10$) did not complete the entire LLS at 120 min but did complete the VAS. Sleep quality was the most commonly omitted question ($n=8$), with the remainder ($n=2$) leaving the LLS section blank. In these cases of sleep quality, it was assumed to be unchanged from the initial values because subjects were not expected to sleep during the 120 min of the study. When the entire LLS section was blank, these numbers were omitted from analysis; however, VAS scores were included.

Results were analyzed by univariate comparisons (signed-rank tests) and logistic regression, with Wilcoxon rank sum $P<0.05$ considered significant.

Results

We enrolled 47 adult subjects from Pheriche (4280 m) and Dingboche (4358 m). There were no significant differences between the metoclopramide and ibuprofen groups with respect to age, sex, heart rate, respiratory rate, oxygen saturation, or initial LLS (Table 2).

Subjects in both the ibuprofen and metoclopramide groups reported decreased headache on the 100 mm VAS compared to their initial headache at all time points (Figure 1A). For ibuprofen, headache VAS decreased 6 mm at 30 min (95% CI: 2–10), 13 mm at 60 min (95% CI: 8–19), and 22 mm at 120 min (95% CI: 15–29). For metoclopramide, headache VAS decreased 4 mm at 30 min (95% CI: 1–7), 13 mm at 60 min (95% CI: 6–21), and 23 mm at 120 min (95% CI: 16–29). Subjects in both ibuprofen and metoclopramide groups reported decreased nausea on the 100 mm VAS compared to their initial nausea at 120 min. Decreased nausea in the ibuprofen group only reached statistical significance at 120 min, but decreased nausea reported in the metoclopramide group reached statistical significance at all 3 time points (Figure 1B). For ibuprofen, nausea VAS decreased 1 mm at 30 min (95% CI: 0–3), 4 mm at 60 min (95% CI: 0–7), and 6 mm at 120 min (95% CI: 1–11). For metoclopramide, nausea VAS decreased 5 mm at 30 min (95% CI: 1–9), 8 mm at 60 min (95% CI: 2–14), and 14 mm at 120 min (95% CI: 7–21).

No significant difference was found between ibuprofen and metoclopramide groups in the reported degree of headache relief at any time point on the VAS ($P=0.13$ at 30 min, $P=0.74$ at 60 min, and $P=0.53$ at 120 min). No significant difference was found between ibuprofen and metoclopramide groups in degree of nausea relief on the VAS at 30 min ($P=0.2$) or 60 min ($P=0.24$). At 120 min, subjects in the metoclopramide group reported significantly less nausea on the VAS than did subjects in the ibuprofen group ($P=0.03$) (Figure 1B).

Subjects in both ibuprofen and metoclopramide groups had decreased LLS at 120 min compared to initial scores. Subjects in the ibuprofen group reported a decrease of 3.5 points (95% CI: 2.8–4.3) on the total LLS at 120 min. Subjects in the metoclopramide group reported a decrease of 2.0 points (95% CI: 1.15–2.9) on the total LLS at 120 min. Looking at individual components of the LLS, the ibuprofen group reported a significant decrease in headache (ibuprofen 1.3 [95% CI: 1.0–1.6] vs metoclopramide 0.8 [95% CI: 0.5–1.14]), dizziness (ibuprofen 0.5 [95% CI: 0.3–0.7] vs metoclopramide 0.2 [95% CI: 0–0.9]), and

Figure 1. A, Decrease in headache after treatment. Ibuprofen and metoclopramide are both effective at reducing headache severity at 30, 60, and 120 min compared to baseline headache ($P < 0.05$; CI=95% confidence interval). B, Decrease in nausea after treatment. Both ibuprofen and metoclopramide decreased nausea on the 100 mm visual analog scale compared to initial nausea at 120 min. Ibuprofen only reached statistical significance at 120 min, but metoclopramide reached statistical significance at all 3 time points (30, 60, and 120 min) ($P < 0.05$; CI=95% confidence interval).

total LLS when compared to metoclopramide at 120 min ($P < 0.05$). There were no statistically significant differences in the other symptoms (Figure 2).

Discussion

Patients visiting or living in high altitudes may present during an acute illness or before travel to discuss strategies to prevent or treat future effects of high altitude exposure. Syndromes can range from HAH to HACE or HAPE, with descent as the definitive treatment. However, immediate descent is not always feasible or necessary in milder cases, and gradual ascent and pharmacotherapy are useful strategies to aid acclimatization.

In our study, both metoclopramide and ibuprofen were effective in reducing HAH severity compared to pretreatment headache. Metoclopramide had the additional benefit of reducing nausea to a greater degree than ibuprofen. Both medications reduced overall symptoms of AMS. These results agree with the growing body of evidence that ibuprofen may help prevent and alleviate AMS and HAH symptoms. Unlike previous studies that used ibuprofen prophylactically for AMS, here we show ibuprofen to be useful for the treatment of AMS and HAH. In addition, to our knowledge, metoclopramide has not been previously studied for the relief of HAH and AMS. These results show that metoclopramide can decrease both headache and nausea at high altitude.

Figure 2. Improvement in LLS after treatment. When the LLS system was used, there was a statistically significant decrease in headache and total LLS from baseline with both ibuprofen and metoclopramide ($P < 0.05$). In addition, ibuprofen was more effective than metoclopramide at decreasing headache, dizziness, and total LLS ($P < 0.05$). LLS, Lake Louise Score; N/V, nausea/vomiting.

There was a difference in the scoring between VAS and LLS. Although both treatments decreased headache and total LLS, ibuprofen outperformed metoclopramide in relief of headache, dizziness, and total LLS. One disadvantage of LLS is that it is reported only in integers of 0 to 3, whereas the VAS can detect smaller increments of change. In this study, few subjects reported significant levels of symptoms (at most 0 or 1) other than headache on the LLS. This finding supports ongoing debate about whether HAH leads to associated systemic symptoms that then meet criteria for AMS and whether treatment is simply resolving the headache, which is central to diagnosis, or addressing an underlying mechanism of a distinct entity. This draws parallels to migraine headaches such that patients find relief from treating the headache through a variety of pharmacologic mechanisms and not only through the nociception pathway. In addition, several subjects did not complete the entire LLS at both time points. This may in part explain the discrepancy between the VAS and the LLS.

Recently, there has been some debate on the inclusion of particular symptoms as a part of AMS, namely sleep disturbance, because this may be mediated by a different mechanism.^{11,12} Subjects did not sleep during the 2 h of

the study, so these reported values should not have changed, yet a few subjects reported an improvement in the prior night's sleep, implying a possible recall bias introduced by the improvement of their symptoms. In addition, several subjects ($n=10$) omitted the sleep question. Since the time of this data collection, sleep has been eliminated as a part of the LLS.

Several limitations of this study exist. First, we had a smaller sample size than our goal, largely due to the 2015 earthquake that ended the season. In addition, no placebo control was included, and the symptoms of mild altitude illness improve as an individual acclimatizes. However, it is the consensus of the authors, who have considerable experience treating patients at high altitude, that most untreated individuals experience these improvements over a much longer time frame (6–24 h) than the 2 h seen in this study. Lastly, these interventions were not tested against or in combination with acetazolamide, which has strong evidence supporting its use in preventing and treating AMS. The sample size was not large enough to analyze the subset of subjects that had taken additional medications in addition to the study medications during their trek. However, as with any therapy, some patients do not respond to acetazolamide and still develop altitude illness. This study supports the use of alternative agents that can be considered if acetazolamide is contraindicated or if symptomatic relief is needed in addition to that with acetazolamide.

Although the results here are promising, additional larger studies are needed. Future studies would ideally be larger scale, address mechanism, and evaluate the potential synergistic effect of taking metoclopramide and ibuprofen together.

Conclusions

Both metoclopramide and ibuprofen were effective at reducing HAH and AMS symptoms, including headache and nausea. Metoclopramide had the additional benefit of reducing nausea to a greater degree than ibuprofen and may be an alternative treatment option, particularly for those with associated nausea.

Table 2. Study demographics

	Subjects (n)	Age (y) (mean±SD)	Percent male ^a	Heart rate (beats·min ⁻¹)	Respiratory rate (breaths·min ⁻¹)	O ₂ saturation (%)	Lake Louise Score
Ibuprofen	24	33.7±10.4	67	87±16	18±3	84±4%	5.8±2.4
Metoclopramide	23	35.3±11.2	61	82±18	18±1	85±4%	5.0±1.4
All	47	34.5±10.7	64	85±17	18±3	84±4%	5.4±2.0

No statistically significant differences were found between metoclopramide and ibuprofen groups with respect to age, sex, heart rate, respiratory rate, oxygen saturation, or initial Lake Louise Score. Data collected at rest.

^a Two subjects in metoclopramide group did not report sex.

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