Pharmacology in Emergency Medicine

INHALED BUDESONIDE PREVENTS ACUTE MOUNTAIN SICKNESS IN YOUNG CHINESE MEN

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Abstract—Background: Oral glucocorticoids can prevent acute mountain sickness (AMS). Whether inhaled budesonide (BUD) can prevent AMS remains unknown. Objective: Our aim was to investigate the effectiveness of BUD in AMS prevention. Methods: Eighty subjects were randomly assigned to receive budesonide (BUD, inhaled), procaterol tablet (PT), budesonide/formoterol (BUD/FM, inhaled), or placebo tablet (n = 20 in each group). Subjects were treated for 3 days before ascending from 500 m to 3700 m within 2.5 h by air. Lake Louise AMS questionnaire, blood pressure, heart rate, and oxygen saturation (SpO2) were examined at 20, 72, and 120 h after high-altitude exposure. Pulmonary function was measured at 20 h after exposure. Results: Compared with placebo, BUD significantly reduced the incidence of AMS (70% vs. 25% at 20 h, p < 0.05; both 10% vs. 5% at 72 and 120 h, both p > 0.05) without side effects. The relative risk was 0.357, and the risk difference was 0.45. Mean SpO2 was higher in BUD, BUD/FM, and PT groups than in the placebo group at 20 h (p < 0.05). SpO2 in all 80 subjects dropped after ascent (98.1% to 88.12%, p < 0.01) and increased gradually, but it was still lower at 120 h than at baseline (92.04% vs. 98.1%, p < 0.01). Pulmonary function did not differ among the four groups at 20 h. Conclusion: BUD can prevent AMS without side effects. The alleviation of AMS may be related to increased blood oxygen levels rather than pulmonary function. © 2015 Elsevier Inc.

Keywords—budesonide; hypoxia; inhaled; prevention; altitude sickness; acute mountain sickness

INTRODUCTION

Acute mountain sickness (AMS) is the most common form of illness after acute exposure to high altitude (HA). The Lake Louise Consensus Group defines AMS as headache with one or more of the following symptoms: gastrointestinal symptoms (e.g., poor appetite, nausea, or vomiting), fatigue/weakness, dizziness/ligtheadness or difficulty in sleeping (1). The symptoms usually occur within 6 to 12 h after arrival at HA and are usually alleviated spontaneously during the next 48 to 72 h (2). AMS occurs in 50% to 85% of unacclimatized individuals at 4500 to 5500 m. Although rarely serious, these
unpleasant symptoms affect life quality and work ability of people ascending to HA. AMS may even deteriorate to high-altitude cerebral edema (HACE), which can be life-threatening.

Gradual staged ascent is an effective approach to prevent AMS, but it is not always practical (3). Certain people need to ascend rapidly to HA, including those involved in military action, disaster relief, and helicopter operation. Prophylactic therapy with acetazolamide has been shown to reduce the incidence and severity of AMS (4,5). The lowest effective dosage is 250 mg/day (6). Dexamethasone (DXM), an oral glucocorticoid, is also effective in AMS prevention (7). These two drugs are recommended for AMS and HACE prevention by the Wilderness Medical Society (3). Acetazolamide prophylaxis is relatively safe; minor side effects include polyuria and paresthesia in hands and feet (5). Acetazolamide may not be sufficient to prevent AMS during excessively rapid ascents, however (8). Oral DXM may cause multiple systemic side effects, such as gastrointestinal bleeding, interference with blood glucose levels, and impairment of the function of the hypothalamo-pituitary-adrenal (HPA) hormone axis (9–11). Some of these side effects may result in long-term damage (12). Therefore, the Committee to Advise on Tropical Medicine and Travel recommends restricting the use of DXM to the treatment of AMS or for prophylaxis in intolerant persons or those allergic to acetazolamide (13). DXM should not be used for prophylaxis in the pediatric population, according to the consensus of the Wilderness Medical Society (3).

Inhaled budesonide (BUD), a glucocorticoid with few systemic side effects, has been demonstrated to be effective and safe in asthma treatment for both adults and children. Its effects on the HPA axis are limited (14,15). An inhaled \( \beta_2 \)-adrenergic agonist was shown to prevent high-altitude pulmonary edema (HAPE) in a previous study (16). The mechanisms under this protective action may be related to increased transport of cross-epidermal sodium ions in alveolar epithelial cells (16). Inhaled salmeterol (125 \( \mu \)g twice daily [b.i.d]) is a third-line choice for the prevention of HAPE, but is not used to prevent AMS (2). It is still unclear whether inhaled \( \beta_2 \)-adrenergic agonists have prophylactic efficacy against AMS. Both BUD and budesonide/fomoterol (BUD/FM) improve pulmonary function of asthma patients (17). The vital capacity (VC) and forced expiratory volume in 1 s (FEV1) are often reduced after HA exposure (18). Therefore, BUD and \( \beta_2 \)-adrenergic agonists may prevent AMS through a mechanism that affects pulmonary function. To evaluate whether BUD, procaterol (PT, an oral \( \beta_2 \)-receptor agonist), or BUD/FM prevent AMS, we designed an open randomized controlled trial in which these agents were compared to placebo in healthy subjects ascending from 500 m to 3700 m by air. We hypothesized that one or more of the three drugs would prevent AMS.

MATERIALS AND METHODS

Subjects

The 80 healthy young, male, lowland residents in this trial were recruited in Chengdu, China between June 4 and June 16, 2012. Inclusion criteria were residence at or below 500 m, healthy, and 18 to 35 years of age. Potential participants were excluded if they had HA (> 2500 m) exposure history in the past year or organic diseases such as congenital heart disease, dysrhythmia, liver or kidney dysfunction, or psychological or neurological disorders. Subjects who agreed to participate in this study were familiarized with the purpose and process of the study and signed written informed consent forms before the trial. This study was approved by the Ethics Committee of Xinqiao Hospital, the Second Clinic Medical College of Third Military Medical University (Trial registration: Chinese Clinical Trial Registry, ChiCTR-PRC-12002748).

Study Protocol

The study protocol is illustrated schematically in Figure 1. Structured case report form questionnaires were used to record demographic data (age, height, weight, and smoking and drinking history), medical history (overall health and HA exposure history in the past year), physiological data (blood pressure [BP], heart rate [HR] and pulse oxygen saturation [SpO2]) and symptoms related to AMS (headache, gastrointestinal symptoms, fatigue/weakness, dizziness/lightheadedness and difficulty in sleeping). Pulmonary function outcomes were also recorded. Demographic data were collected during recruitment. Baseline examinations were performed at 500 m about 6 days before ascent to HA; these included measurement of BP, HR, and SpO2.

Subjects were randomly assigned to four groups (n = 20), by a physician who did not participate in later parts of the study, using a computer-generated random number list. Group A received BUD (AstraZeneca AB, Södertälje, Sweden), 100 \( \mu \)g per inhalation, two inhalations b.i.d.. Group B was given PT (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), 25 \( \mu \)g b.i.d. Group C received BUD/FM (AstraZeneca AB), 160 \( \mu \)g BUD/4.5 \( \mu \)g FM per inhalation, one inhalation, b.i.d. Group D was given placebo tablets, one tablet, b.i.d. The physician who made group assignments prepared one medicine box for each subject. The physician then gave these boxes to other researchers and kept the blinding code. The subjects were fully informed and knew that they could be assigned to any of four groups and that one group would take a placebo.
The subjects began to take their drugs 3 days before ascending. A medical team was responsible for monitoring subjects for adverse reactions related to the investigational drugs. The subjects were also encouraged to report to the investigators or the medical team if they had any adverse symptoms. Each subject was instructed in the correct use of the medication, especially use of inhalants. After each dose of medication, the subjects’ boxes were stored by the medical team.

Subjects were taken to 3700 m (Lhasa, Tibet, China) from 500 m (Chengdu, Sichuan, China) in a 2.5-h trip by air on June 23 or June 24, 2012. The treatment was not continued after arrival. Lake Louis AMS questionnaire, HR, and SpO2 were examined at 20, 72, and 120 h after arrival at HA. Pulmonary function test was performed at 20 h after exposure.

Primary and Secondary Outcomes

Primary outcome measure was symptoms of AMS at 20, 72, and 120 h after arrival at 3700 m altitude. Secondary outcome measures were HAPE or HACE.

AMS Score Questionnaire

AMS was diagnosed by the Lake Louise Scoring system, which includes five self-reported symptoms: headache, gastrointestinal symptoms, fatigue/weakness, dizziness/lightheadedness, and difficulty in sleeping (1). Each symptom was scored on a scale from 0 to 3, with 0 indicating none and 1, 2, and 3 indicating mild, moderate, and severe, respectively. AMS was defined if headache was present and the total score for all symptoms was 3 or more. AMS with a total score of 3 to 4 was defined as mild AMS, whereas severe AMS was indicated by a total score of 5 or more.

BP, HR, and SpO2

BP was obtained using electronic sphygmomanometers (OMRON HEM-6200; OMRON Healthcare Ltd.; Kyoto, Japan). HR and SpO2 were measured using pulse oximeters (Nonin Onyx® 9550; Nonin Medical, Inc.; Plymouth, MA). BP, HR, and SpO2 were measured three times after the subjects had rested in a quiet environment for 15 min or more. The mean is reported.

Pulmonary Function Evaluation

VC and FEV1 were measured with a portable spirometer (Minato AS-507; Minato Medical Science Co., Ltd.; Osaka, Japan).

Statistical Analyses

Shapiro-Wilk tests were used to assess normal distribution of quantitative data. Normally distributed variables were expressed as means ± standard deviations (SD),
whereas the non-normally distributed variables were expressed as medians (interquartile ranges). The quantitative data of subjects who developed AMS (AMS+) and those who remained free of AMS (AMS−) during HA exposure were compared using independent t-tests or Mann-Whitney tests, as appropriate. The qualitative comparison between AMS+ and AMS− groups was made by χ² tests or Fisher’s exact tests, as appropriate. One-way analyses of variance were used for the comparisons of quantitative data among the four groups, assuming normal distribution of data and homogeneity of variances. If significant differences were observed, Student-Newman-Keuls tests were used for comparisons between each two groups. χ² tests were applied for the comparisons of qualitative data among the four groups. Pearson or Spearman correlation analyses were utilized for correlation analyses, as appropriate. All tests were two-tailed. Differences were considered statistically significant if p < 0.05. The statistical analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC) by a blinded professional statistics company (TJ-Elite Statistical Service Center; Chongqing, China).

RESULTS

Baseline Data

There were no significant differences in baseline measurements among the four groups. These measurements included age, height, weight, body mass index, smoking and drinking history, systolic and diastolic BP, HR, and SpO₂ (p > 0.05) (Table 1).

### Table 1. Baseline Subject Data

<table>
<thead>
<tr>
<th>Age (years), mean ± SD</th>
<th>Budesonide</th>
<th>Procatrol</th>
<th>Budesonide/formoterol</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>21.85 ± 3.23</td>
<td>20.30 ± 2.03</td>
<td>20.60 ± 2.76</td>
<td>21.65 ± 3.31</td>
<td>0.246</td>
</tr>
<tr>
<td>Height (cm), mean ± SD</td>
<td>61.15 ± 7.55</td>
<td>62.35 ± 5.96</td>
<td>63.30 ± 4.46</td>
<td>64.65 ± 8.38</td>
<td>0.416</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>170.70 ± 3.97</td>
<td>172.20 ± 5.27</td>
<td>171.05 ± 4.38</td>
<td>170.20 ± 4.42</td>
<td>0.554</td>
</tr>
<tr>
<td>Smoking (yes/no), n</td>
<td>20.98 ± 2.21</td>
<td>21.00 ± 1.44</td>
<td>21.64 ± 1.49</td>
<td>22.15 ± 2.94</td>
<td>0.243</td>
</tr>
<tr>
<td>Drinking (yes/no), n</td>
<td>16/4</td>
<td>13/7</td>
<td>18/2</td>
<td>16/4</td>
<td>0.283</td>
</tr>
<tr>
<td>SBP (mmHg), mean ± SD</td>
<td>116.00 ± 11.40</td>
<td>114.10 ± 8.53</td>
<td>114.50 ± 8.00</td>
<td>115.35 ± 9.40</td>
<td>0.929</td>
</tr>
<tr>
<td>DBP (mmHg), mean ± SD</td>
<td>73.90 ± 9.17</td>
<td>70.60 ± 5.66</td>
<td>73.00 ± 6.82</td>
<td>69.75 ± 8.33</td>
<td>0.274</td>
</tr>
<tr>
<td>HR (bpm), mean ± SD</td>
<td>64.65 ± 9.31</td>
<td>67.00 ± 8.78</td>
<td>70.40 ± 12.14</td>
<td>66.25 ± 9.52</td>
<td>0.327</td>
</tr>
<tr>
<td>SpO₂ (%), mean ± SD</td>
<td>98.40 ± 1.14</td>
<td>98.00 ± 0.73</td>
<td>98.20 ± 0.89</td>
<td>97.80 ± 0.89</td>
<td>0.208</td>
</tr>
</tbody>
</table>

BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; SD = standard deviation; SBP = systolic blood pressure; SpO₂ = pulse oxygen saturation.

Baseline data among four groups were compared using one-way analysis of variance, Student-Newman-Keuls, cross-table methods, and χ² test.

One subject did not answer question on drinking history.

AMS Incidence and Severity

AMS incidence at 20 h after exposure to HA was significantly different among the four groups (Figure 2A). Compared with placebo, BUD effectively prevented AMS: 25% of subjects treated with BUD were diagnosed with AMS vs. 70% of those given placebo (p < 0.01). The relative risk was 0.357 and the risk difference was 0.45. The number of cases with severe AMS was also lower in the BUD group than in the placebo group, but the difference was not significant (5% vs. 25%; p > 0.05). The differences in AMS incidence in the PT and BUD/FM groups compared with placebo did not reach significance (in both treatment groups 50% were diagnosed with AMS vs. 70% in the placebo group; p > 0.05).

There were no statistically significant differences in AMS incidences at 72 and 120 h among the four groups (Figures 2B and C; p > 0.05). Also, there was no statistically significant difference in AMS incidence between the BUD and placebo groups at 72 or 120 h (5% vs. 10%; p > 0.05, respectively). AMS incidence in all four groups declined at 72 h compared to 20 h (from 25% to 5% in BUD; p = 0.0507; from 70% to 10% in the placebo group; p < 0.05; from 50% to 30% in PT and BUD/FM; p > 0.05; Figure 3). AMS incidence rates in the placebo and BUD groups were stable from 72 to 120 h. Subjects in the PT and BUD/FM groups appeared to have higher AMS incidence rates compared to placebo at 72 h (both 30% vs. 10% in placebo) and 120 h (both 20% vs. 10% in placebo), but these differences did not reach statistical significance (p > 0.05; Figure 3).

Side Effects

The subjects in all four groups tolerated all treatments without obvious side effects.

SpO₂, BP, and HR

The mean SpO₂ of all 80 subjects dropped from 98.1% ± 0.94% to 88.12% ± 2.47% with acute exposure to HA...
(level at 500 m before ascent vs. 20 h after ascent; \( p < 0.001 \)) and then went up gradually to 92.04\% ± 2.72\% as the exposure to HA continued (Figure 4). It did not return to the level before ascent at 120 h (\( p < 0.001 \)). HR increased to 84.61 ± 10.63 bpm from 67.08 ± 10.06 bpm at 20 h after ascent (\( p < 0.001 \)). There were no differences in HR from 20 h to 120 h (\( p > 0.05 \)) (Figure 4).

SpO2 was higher, on average, in each of the treatment groups than in the placebo group at 20 h (88.90\% ± 2.17\%, 88.55\% ± 2.56\%, 89.67\% ± 1.73\% for BUD, PT, and BUD/FM, respectively, vs. 86.2\% ± 1.85\% for placebo; \( p < 0.05 \)). The same phenomenon was observed at 72 h (\( p < 0.05 \)), but not at 120 h (\( p > 0.05 \); Figure 5).

HR was elevated in all subjects at high altitude. HRs at 20 h after exposure were 78.85 ± 11.31 bpm, 86.60 ± 7.52 bpm, 84.78 ± 7.33 bpm, and 88.30 ± 12.01 bpm in BUD, PT, BUD/FM, and placebo groups, respectively (Figure 6). There were no significant differences in HR among the four groups at 72 and 120 h (\( p > 0.05 \)).

In the BUD group, SpO2 negatively correlated with AMS score (\( R = -0.45, p = 0.0489 \)); no other vital signs were correlated to AMS score. AMS+ subjects had a greater reduction in SpO2 compared to AMS− subjects at 20 h (\( \Delta\text{SpO}_2 = \text{SpO}_2 \text{ at HA} - \text{SpO}_2 \text{ at 500 m} \): -11.00 ± 2.83\% vs. -8.47\% ± 1.81\%; \( p < 0.05 \)). In the PT and BUD/FM groups, there were no correlations between SpO2 and AMS scores. The increase in HR and reduction in SpO2 did not differ between AMS+ and AMS− subjects (\( \Delta\text{HR} = \text{HR at HA} - \text{HR at 500 m}, \Delta\text{SpO}_2 \) as mentioned above; \( p > 0.05 \), respectively).

There were no significant differences in systolic BP among the four groups at HA. There were also no significant differences in diastolic BP (DBP) among the four groups at 20 h after exposure. However, the DBPs of BUD and placebo subjects were, on average, lower than those of the BUD/FM and PT groups, with significance at 72 and 120 h (\( p < 0.05 \), Figure 7).
Pulmonary Function

In pulmonary function tests, there were no significant differences in VC (Figure 8) or FEV1 (Figure 9) among the four groups at 20 h after exposure to HA. Further analyses also showed no differences between subjects with and without AMS in each group (Figure 9).

DISCUSSION

In this study, we compared BUD, PT, BUD/FM, and placebo for the prevention of AMS at an altitude of 3700 m
after ascension from 500 m. BUD inhalation (200 µg b.i.d.) for 3 days before ascent significantly reduced the incidence of AMS compared to placebo. BUD treatment caused no side effects during the follow-up period of the trial.

Prophylactic DXM has been demonstrated to reduce the incidence and severity of AMS (7,19–22). In addition, oral administration of DXM has shown preventive and therapeutic effects on HAPE (23). However, oral or injected forms of DXM may cause systemic adverse reactions, and sudden withdrawal of DXM may cause an AMS relapse (9–12,20). In contrast, long-term administration of inhaled glucocorticoids results in few adverse reactions (14). Although recent studies show that the use of inhaled glucocorticoids for 4 to 6 years can hinder growth and development of children, these side effects are limited to long-term administration (>3 years) (24). Inhaled glucocorticoids were well tolerated by subjects in our study, with no adverse reactions reported during the trial.

Our study showed that the prophylactic use of BUD (200 µg b.i.d.) for 3 days in advance of high-altitude exposure significantly reduced the incidence of AMS caused by acute exposure to HA. Importantly, this therapy might also decrease the incidence of severe AMS. The beneficial effects of BUD lasted at least 20 h after HA exposure and had no influence on the acclimatization of the body to HA. The subjects in BUD group were well acclimated at 72 h, with only 5% of subjects experiencing mild AMS at that time point.

The BUD group had higher SpO2 than the placebo group, indicating that BUD may attenuate the reduction in SpO2 observed after exposure to HA. A previous study demonstrated that the use of glucocorticoids reduced water exudation from the alveolar epithium under hypoxic conditions (25). In addition, inhaled corticosteroids maintain the integrity of airway epithelia under acute hypoxia (26). Therefore, inhalation of BUD may activate the glucocorticoid α-receptors and produce anti-inflammatory effects within the alveolar epithelium. These effects may antagonize negative effects of hypobaric hypoxic environments and decrease anoxia within the body.

The mechanisms of AMS remain unclear. Hypoxia and damage of the blood–brain barrier may contribute to AMS (27–29). BUD is absorbed into the blood mainly through the lungs, so we hypothesize that BUD prevents AMS through two effects: a local effect, which improves the function of alveolar epithelia, reduces the release of inflammatory mediators, and maintains the integrity of airway epithelia, thus increasing SpO2; and a general effect that protects the blood–brain barrier.

It is controversial whether SpO2 is an appropriate predictor of AMS (30–33). In our study, subjects with AMS who had been treated with BUD had a greater reduction in SpO2 than those treated subjects who were not diagnosed with AMS. This indicates that the reduction in AMS incidence is likely to be achieved by the maintenance of SpO2 by BUD. This also suggests that subjects may have a higher incidence of AMS if they have used BUD, but still have low SpO2 or high ΔSpO2 early after exposure to HA. In other words, SpO2 of subjects who have used BUD may predict AMS.

All three drugs used in this trial may dilate bronchi and improve pulmonary ventilation, so we expected that there would be differences between treated groups and placebo in pulmonary function tests. However, no differences were observed in VC or FEV1 among the four groups or between AMS+ and AMS− subjects. Thus, these drugs
do not appear to increase SpO₂ by enhancing pulmonary function. For patients with asthma, treatment with BUD/FM improves pulmonary function more than BUD alone (17,34). However, we found no significant difference in pulmonary function between BUD/FM and BUD groups in these healthy young male subjects. Our sample number is small, therefore, minor differences in pulmonary function may not have been found.

In this trial, BUD prevented AMS and BUD/FM did not. One reason for this inconsistency may be that the dose of BUD given to subjects in the BUD/FM group was lower than the dose given the BUD group (320 μg vs. 400 μg). Another possible explanation is that adding a β₂-adrenergic agonist antagonized the prophylactic effects of inhaled glucocorticoid.

AMS incidences in the PT and BUD/FM groups appeared to be even higher than placebo at 72 and 120 h, although the differences were not significant. We also found that PT and BUD/FM groups had higher DBP than subjects given placebo at 72 and 120 h. It has been reported that higher DBP is correlated to higher AMS severity and lower SpO₂ (35,36). PT and BUD/FM groups also had a nonsignificant trend toward higher HR than placebo at 72 and 120 h. So one possible explanation is that β₂-receptor agonist may increase HR, which increases oxygen consumption and aggravates hypoxia, causing adverse effects on acclimatization to HA.

Limitations

Our study had several limitations. We initially intended to design a double-blind trial. However, the PT and placebo groups used oral tablets, and the BUD and BUD/FM groups used inhalants. So subjects might assume that they were given a different drug than those in another group, although they could not know specifically what drug they were taking. The researchers might also have noted this difference, although an independent physician randomized subjects to treatment groups. Due to this limitation, this study is referred to as an open trial. Our subjects were healthy young men, so our results cannot be extended to other ages or to females. In addition, the dose of BUD contained in the BUD/FM group (160 μg b.i.d.) was not the same as in the BUD group (200 μg b.i.d.) due to the commercially available formulations we used.

CONCLUSIONS

By studying the effects of three drugs commonly used in the clinic, we found that inhaled BUD (200 μg b.i.d.) was effective for the prevention of AMS. Inhaled BUD is convenient for use, has few side effects, and deserves further study as a prophylactic for AMS. The reduction in the incidence of AMS may be related to increased SpO₂ rather than alterations in pulmonary function. The tested β₂-receptor agonists did not prevent AMS and appeared to have unfavorable influence on high-altitude acclimatization.

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REFERENCES

ARTICLE SUMMARY

1. Why is this topic important?
   Current methods for prevention of acute mountain sickness (AMS) are insufficient. More effective and safe drugs are needed.

2. What does this study attempt to show?
   Our study sought to determine the efficacy and the safety of inhaled budesonide for AMS prevention.

3. What are the key findings?
   We found that inhaled budesonide can prevent AMS without side effects. The alleviation of AMS may be related to increased blood oxygen levels rather than an impact on pulmonary function.

4. How is patient care impacted?
   Rescue or military personnel who must rapidly ascend to high altitudes may use inhaled budesonide as an effective and safe alternative for prevention of AMS.