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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 Louis AMS questionnaire, blood pressure, heart rate, and oxygen saturation (SpO_2) 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 SpO_2 was higher in BUD, BUD/FM, and PT groups than in the placebo group at 20 h ($p < 0.05$). SpO_2 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/lightheadedness 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

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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 β_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 μg 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 β_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 β-adrenergic agonists may prevent AMS through a mechanism that affects pulmonary function. To evaluate whether BUD, procaterol (PT, an oral β_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 [SpO_2]) 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 SpO_2.

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 μg per inhalation, two inhalations b.i.d.. Group B was given PT (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), 25 μg b.i.d. Group C received BUD/FM (AstraZeneca AB), 160 μg BUD/4.5 μg 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.