Inhaled budesonide does not prevent acute mountain sickness after rapid ascent to 4559 m

To the Editor:

Recent studies showed that inhaled budesonide (200 µg twice per day) reduced the incidence of acute mountain sickness (AMS) after passive ascent to 3700 and 3900 m [1, 2]. These findings raised the possibility that mediators released from the hypoxic lung transmit signals to the brain which contribute to the cerebral processes leading to AMS [3]. Because neither of these studies reflect alpine-style climbing, the present study was performed to test whether inhalation of budesonide at two different doses (200 and 800 µg twice per day) prior to active and rapid ascent (<20 h) to 4559 m prevents AMS in this high-risk setting.

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ethical Committee Salzburg, Austria, the Ethical Committee of the University of Torino, Italy, and the Austrian Competent Authority, Vienna. The trial was registered at ClinicalTrials.gov (NCT02811016) and conducted as a prospective, randomised, double-blind and placebo-controlled study, with group stratification according to gender, age and physical fitness.

After written informed consent was obtained, 50 healthy, non-acclimatised lowlanders were included in the study. Subjects were randomly assigned to receiving 200 µg budesonide twice per day (B200, n=16), 800 µg budesonide twice per day (B800, n=17) or lactose-monohydrate (placebo, n=17). Subjects were instructed in the correct use of the single-dosed capsules in the inhaler (Cyclohaler®, PB Pharma, Meerbusch, Germany). Complete emptying of the capsules was visually verified. Inhalations were performed at 07:00 h and 19:00 h, starting 1 day prior to ascent and continued until the end of the study. At high altitude, all inhalations were performed under supervision to ensure correct inhalation technique.

Baseline measurements were performed at an altitude of 423 m (Salzburg, Austria). Two to four weeks later, subjects ascended from 1130 m (Alagna, Italy) to 4559 m within ~20 h. The ascent consisted of transport by cable car to 3275 m, a 90-min climb to 3611 m (Capanna Gnifetti), where they spent the night, and a 4–5 h climb to 4559 m (Capanna Regina Margherita, Monte Rosa). Tests were performed 7, 20, 32 and 44 h after arrival at 4559 m.

AMS was evaluated using the Lake Louise score (cumulative self-report plus clinical scores) and the AMS-C score of the abbreviated version of the Environmental Symptoms Questionnaire [4, 5]. Individuals were considered AMS-positive when they had a Lake Louise score ⩾5 in combination with an AMS-C score ⩾0.70 points [6].

Oxygen saturation (S_{pO_2}) was measured by pulse oximetry (Covidien Nellcor, Mansfield, USA). Blood gas analysis was performed on capillary blood (Siemens, RapidPoint 500, Germany). Adrenocorticotropic hormone (ACTH) and cortisol were measured in venous blood samples. Cortisol was also measured in 24 h-urine.

The primary end-point of the study was the occurrence of AMS. In previous studies, budesonide reduced AMS by between 60% and 75% [1, 2]. Sample-size estimation based on an effect size of 0.5, an α-error of 0.05, and a power (1-β error probability) of 0.80 yielded a total sample size of 44 for the three study groups. Differences in incidence of AMS were analysed by Chi-squared test. Differences in AMS severity were analysed by two-way-repeated-measures-ANOVA and pairwise multiple comparisons using the

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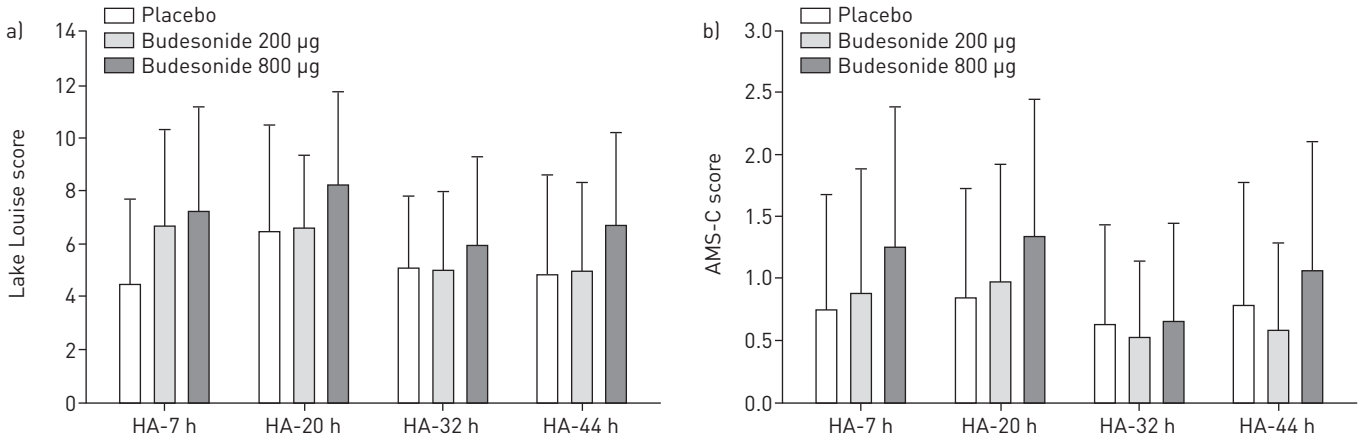

FIGURE 1 Severity of acute mountain sickness (AMS) as indicated by the Lake Louise score (a), and the AMS-C score of the Environmental Symptoms Questionnaire Cerebral scoring system (b). HA: high altitude (4559 m). Data are presented as mean±SD.

Student–Newman-Keuls test. Data are presented as mean±SD. A $p \leqslant 0.05$ (two-sided) was considered significant.

The baseline values were not different between study groups. Ascent to high altitude significantly increased AMS scores ($p<0.001$) without significant intergroup differences (figures 1a and b). There was also no significant difference in the incidence of AMS (overall incidence: 53%, 56% and 76% for the placebo, B200 and B800 groups, respectively, $p=0.768$). Owing to severe AMS, one subject in the B800 and three subjects in the placebo group were treated with oxygen, acetazolamide, and oral dexamethasone after 9, 10, 21 or 35 h at 4559 m. Data collection was terminated thereafter. Results from the blood gas analyses and hormone measurements are shown in table 1.

This study shows that inhalation of budesonide at 200 and 800 µg twice per day reduced neither the incidence nor the severity of AMS in this high-risk setting of fast ascent to 4559 m within ~20 h, which is in contrast to the protective effect of budesonide inhalation (200 µg twice per day) during passive ascent to 3700 m [2] and 3900 m [1].

The incidence of AMS in the placebo group of our study is in accordance with previous studies [7–9]. The criterion we used for diagnosing AMS (Lake Louise score ⩾5 points in combination with an AMS-C score ⩾0.70 points) has a sensitivity and specificity of ~80–90% for identifying those who feel sick or those who have to reduce activity at an altitude of 4559 m [10]. Even analysing potential budesonide effects based on a Lake Louise score ⩾3, which the two previous studies [1, 2] had used to detect mild AMS, shows that budesonide inhalation was ineffective in preventing AMS at 4559 m. Applying this criterion to our study, the incidence of AMS in subjects with headache was 88%, 81% and 100% for the placebo, B200 and B800 groups, respectively.

Although in the two previous studies, the medication protocols were slightly different from ours, this does not explain the different outcomes. Indeed, in all studies, inhalation was started before ascent. Budesonide was administered at a dosage of 200 µg twice per day for 3 [2] and 4 [1] days in the previous studies, while in our study budesonide was administered at 200 and 800 µg twice per day for 4 days. Therefore, it is unlikely that in the present study, the dose and duration of medication were insufficient to reproduce the protective effect of budesonide from AMS. It is noteworthy, however, that in the two previous studies, measurements were performed 2 days after the last inhalation, while in our study inhalation was continued until all measurements were completed.

The results for S_{pO_2}, capillary P_{O_2} and P_{CO_2} (table 1) demonstrate that budesonide, independent of dosing, had no significant effects on gas exchange and ventilation compared to placebo. Subjects with AMS, compared to those without AMS, had on average slightly lower S_{pO_2} and capillary P_{O_2} values in the placebo and B200 but not in the B800 group (data not shown). These findings are in agreement with many previous studies reporting lower oxygenation in subjects with AMS [11–14]. In summary, our data indicate that inhalation of budesonide does not have a significant effect on pulmonary gas exchange.

Budesonide was given at 200 µg twice per day in order to match the dose of the two previous studies [1, 2]; the 800 µg twice per day dose was chosen to achieve maximum efficacy. Plasma levels of ACTH and cortisol as well as the urinary excretion of cortisol over 24 h were not different between study groups (table 1)

TABLE 1 Blood gas analysis and hormone levels at low and high altitude

	LA	HA-7 h	HA-20 h	HA-32 h	HA-44 h	p-value (t)	p-value (group)	p-value (x group)
S_{pO_2} %								
Placebo	97±1	79±7	82±6	81±10	83±7			
B200	97±1	77±8	81±8	79±9	82±9	<0.001	0.467	0.657
B800	98±1	75±7	80±5	80±6	80±6			
Capillary P_{O_2} mmHg								
Placebo	84±7	46±4	48±5	47±6	49±5			
B200	85±8	47±5	48±5	48±6	50±6	<0.001	0.072	0.885
B800	82±6	43±4	48±3	47±4	46±3			
Capillary P_{CO_2} mmHg								
Placebo	35±3	27±2	26±2	27±2	25±2			
B200	34±3	28±3	26±2	27±2	25±2	<0.001	0.710	0.484
B800	36±3	28±3	27±2	27±2	26±2			
Plasma ACTH pg·mL^{-1}								
Placebo	14.8±7.2	15.1±12.0	24.8±14.2	17.1±12.5	26.8±16.2			
B200	20.5±10.6	21.1±25.7	37.7±26.9	15.0±8.5	30.7±11.9	<0.001	0.276	0.647
B800	20.8±17.0	28.0±30.4	29.3±18.5	18.8±28.9	31.7±19.5			
Plasma cortisol ng·mL^{-1}								
Placebo	136±50	118±83	201±64	122±69	173±32			
B200	148±62	122±74	221±76	96±71	176±56	<0.001	0.944	0.578
B800	140±55	150±105	220±52	92±67	175±55			
Urine cortisol µg per 24 h								
Placebo	43.3±15.7				73.6±52.0			
B200	47.2±14.0				64.4±24.4	<0.001	0.958	0.667
B800	47.6±25.2				67.9±48.7			

Data are presented as mean±SD from all individuals in each treatment group, with and without acute mountain sickness. p-value (t) refers to p-value for differences over time; p-value (group) refers to p-value for differences between groups; and p-value (x group) refers to p-value for degree of interaction between factor A (time) and B (group). Oxygen saturation (S_{pO_2}), as well as capillary oxygen tension (P_{O_2}) and carbon dioxide tension (P_{CO_2}), were decreased at high altitude (p<0.001) without a significant difference between the groups. Concentrations of cortisol and adrenocorticotropic hormone (ACTH) in plasma, as well as of free cortisol in 24-h urine samples, were increased at 4559 m but not significantly different between the groups. LA: low altitude (423 m, Salzburg, Austria); HA: high altitude (4559 m); B200 and B800: budesonide inhalation at 200 µg and 800 µg twice per day.

and demonstrate that even the higher dose of 2×800 µg budesonide per day did not supress the hypothalamic–pituitary–adrenal axis and thus had no systemic effects [15].

In conclusion, this study shows that inhalation of budesonide has no beneficial effect on the incidence and severity of AMS after active, rapid ascent to 4559 m. Therefore, prophylactic inhalation of budesonide cannot be recommended for the prevention of AMS in a high-risk setting of alpine climbing to high altitudes. Moreover, our study does not support the hypothesis that pulmonary signalling, which might be locally suppressed by inhaled budesonide, contributes to the pathophysiology of AMS.

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