Inhaled budesonide does not improve incidence and severity of acute mountain sickness

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Background and Goal of the Study

Recent data suggest that the lung may play a crucial role in the pathophysiology of AMS [1]. In that study inhaled budesonide (200 µg twice/day) was as effective as oral dexamethasone (4 mg twice/day) in reducing the incidence of AMS after passive and slow ascent (within 6 days to 3900 m) when compared with placebo. This finding raised the possibility that pathogenic signals released from the hypoxic lung are conveyed to the brain, ultimately causing AMS [2]. However, the study was performed in a low-risk setting, where the likelihood for developing clinically relevant AMS was low as mirrored by the low Lake Louise score of ~3.4 in the placebo group, indicating only mild AMS.

The present study investigated whether prophylactic inhalation of budesonide can prevent AMS in a high-risk setting, consisting of a rapid ascent (<20 h) from 1130 to 4559 m. Budesonide was inhaled at doses of 200 and 800 µg twice/day and compared with a placebo. A possible role of the lung in the pathophysiology of AMS was assessed by blood gas measurements.

Methods

The study was approved by the Ethical Committee Salzburg, Austria, and by the Ethical Committee of the University of Torino, Italy, and was registered at ClinicalTrials.gov (NCT02811016).

The study was conducted as a prospective, randomized, double-blind and placebo-controlled trial, with group stratification according to gender, age and physical fitness. 51 subjects were randomized to receive placebo, or 200 or 800 µg of budesonide twice/day. Inhalation started 1 day prior to ascending from 1130 m to 4559 m within ~20 hours (Figure 1). Individuals were considered AMS-positive with a Lake Louise score (LLS) ≥5 and an AMS-C score ≥0.70 to at least one time point during the stay at 4559 m. Plasma and 24h-urine concentrations of cortisol were measured to evaluate potential systemic effects of inhaled budesonide. Oxygenation was assessed by capillary blood gas analysis and pulmonary artery systolic pressure (PASP) by transthoracic echocardiography. Lung function was evaluated by measuring the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC).

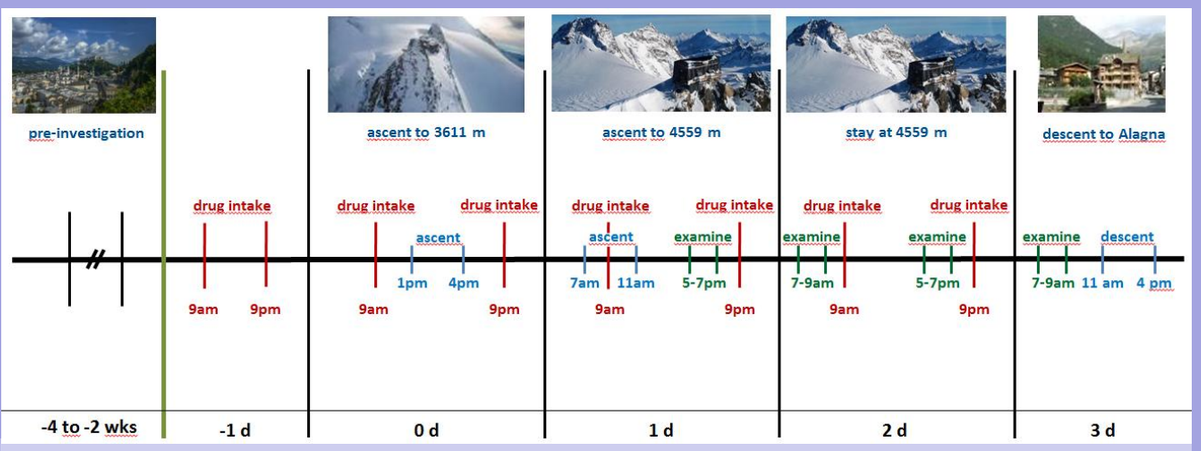

Figure 1. Schematic illustration of the study design. Subjects travelled to Alagna (1130 m), Valsesia, Italy, and ascended in groups of 10 accompanied by licensed mountain guides to 4559 m within ~20 h. The ascent consisted of transport by cable car to 3275 m, and a 90-minutes climb to 3611 m (Capanna Giovanni Gnifetti), where the subjects spent one night. On the next morning subjects performed a 4-5 h climb to 4559 m (Capanna Regina Margherita, Monte Rosa).

References:

1) Zheng CR et al. Am J Med 2014: 127(10): 1001-1009.
2) Swenson ER. Am J Med 2014: 127(10): 899-900.

Results and Discussion

Ascent to high-altitude decreased SpO_2 from 97±1% at low-altitude to 80±7%, and capillary PO_2 from 84±7 to 47±5 mmHg (P<0.001; mean±SD) and was significantly lower in the AMS-positive than in healthy individuals in the placebo and 200 µg budesonide group. Capillary PO_2 was, however, not different between those with and without AMS in the 800 µg group. At high-altitude a decreased $AaDO_2$ and PCO_2 were observed (both P<0.001, not shown) without a significant difference between the study groups. An inverse correlation was observed between PASP and both SpO_2 (R=-0.56; P<0.001) and PO_2 (R=-0.58; P<0.001). Ascent to high-altitude increased AMS scores, with no significant difference in the incidence (Table 1) and severity (Figure 2) between the study groups.

TABLE 1

Hours at 4559m	placebo	budesonide 200 µg	budesonide 800 µg	P-value
7 h	29% (5/17)	38% (6/16)	47% (8/17)	0.777
20 h	44% (7/16)	50% (8/16)	63% (10/16)	0.834
32 h	40% (6/15)	38% (6/16)	25% (4/16)	0.795
44 h	36% (5/14)	31% (5/16)	50% (8/16)	0.761
Overall incidence	53% (9/17)	56% (9/16)	76% (13/17)	0.768

Table 1. Incidence of AMS after arrival at 4559 m. The total number of subjects per group decreased over time due to drop-outs caused by severe AMS and treatment with oxygen and acetazolamide. The overall incidence reflects subjects that were AMS-positive to at least one time point.

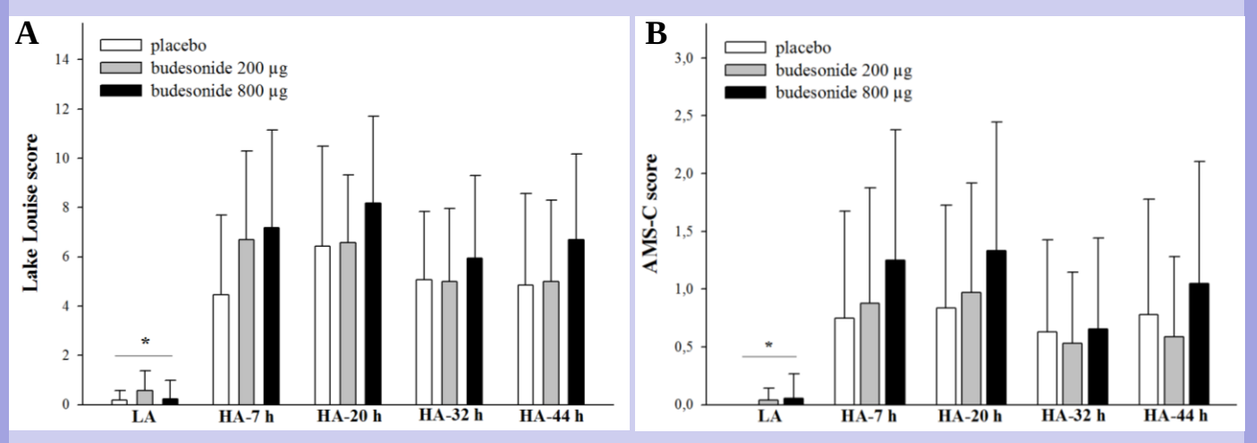

Figure 2. Severity of AMS as indicated by the Lake Louise score (2A), and the AMS-C score of the Environmental Symptoms Questionnaire Cerebral scoring system (2B).
* P<0.001 versus high-altitude.

Also the plasma concentration of cortisol and ACTH, as well as of free cortisol in 24-h urine samples, did not differ between the three study groups. FVC and FEV_1 were in the normal range at low altitude, and values were decreased slightly at high-altitude. There were no differences among the three study groups at any time-point. Ascent to high-altitude increased PASP about 2-fold (P<0.001). The degree of high-altitude induced pulmonary hypertension was not affected by inhalation of budesonide (P=0.288).

Conclusion

This study demonstrates that inhalation of budesonide has no beneficial effect on the incidence and severity of AMS after rapid ascent to 4559 m. Therefore, prophylactic inhalation of budesonide cannot be recommended for the prevention of AMS. Our results further indicate that budesonide inhalation might not be effective in the prevention of high-altitude pulmonary edema.

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