




Inhaled budesonide for acute mountain sickness

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Inhaled corticosteroids are ineffective for the treatment of acute mountain sickness
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In the present issue of the *European Respiratory Journal*, BERGER *et al.* [1] report the lack of efficacy of inhaled budesonide for the prevention of acute mountain sickness (AMS). This small well-designed study was undertaken to verify or refute the provocative finding of robust protection with budesonide against AMS reported by Chinese colleagues in 2014 [2] and 2015 [3]. In the presently reported study, 50 healthy volunteers were randomly assigned to inhale twice daily budesonide 200 µg, budesonide 800 µg or a placebo 1 day prior and during climbing in less than 48 h to an altitude of 4559 m. Such a rapid active ascent is known to be associated with a more than 50% incidence of AMS symptomatology [4]. Accordingly, AMS indeed occurred in 53% of the subjects in the placebo group, and in 56% and 76% of the subjects assigned to the 200 µg and 800 µg budesonide groups, respectively. Between group differences were not significant. Clearly, inhaled budesonide did not prevent acute mountain sickness.

This study raises two interesting questions: 1) why should a treatment targeted to the lungs be effective in AMS, which is not known as a respiratory disease, and 2) could the study by BERGER *et al.* [1] contradicting two previous randomised controlled trials be falsely negative?

AMS is a syndrome experienced within 6–12 h after reaching altitudes generally higher than 2500 m [4] It manifests as lassitude, malaise, headache, nausea, dizziness and poor sleep in various combinations. The condition is generally benign and self-limited, but may be complicated in a small proportion of cases by progression to clinically symptomatic cerebral and/or lung oedema. The cause of AMS is not exactly known. Imaging and clinical evidence favours an element of hypoxia-induced vasogenic cerebral oedema. Accordingly, drugs used for the treatment of vasogenic cerebral oedema, such as acetazolamide or high dose corticosteroids, initially introduced for the prevention of AMS [5, 6], have been repeatedly confirmed by randomised controlled trials to be effective for both the prevention and treatment of the condition [7].

Even though AMS is not *per se* a respiratory problem, altitude exposure is associated with alterations in lung function such as decreases in lung volumes, diffusing capacity and arterial oxygenation. These alterations are most often very mild, but may worsen in subjects suffering from AMS, and sometimes evolve to so-called high-altitude pulmonary oedema (HAPE) [8]. There is thus a spectrum of lung function changes, all likely related to an increase in lung water due to increased pulmonary capillary pressure in the context of hypoxic pulmonary vasoconstriction and secondary inflammatory changes [9, 10]. It is interesting that high dose corticosteroids in the form of dexamethasone 8 mg twice a day prevent both AMS and HAPE altogether in susceptible climbers, and that these beneficial effects are related to

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decreased pulmonary vascular pressures and a sympatholytic effect [11], underscoring the striking similarity between HAPE and neurogenic pulmonary oedema.

ZHENG *et al.* [2] hypothesised a possible reversal of this brain–lung axis at high altitude, and surmised that the previously reported efficacy of dexamethasone could be due to direct pulmonary effects such as decreased inflammation, enhanced sodium reabsorption from the alveolar space and increased surfactant secretion, which in some way protected the brain. The concept that events in the lung can lead to changes in the brain either by release into the circulation of inflammatory or vasoactive mediators or by afferent neural signalling has some support in the acute airway and lung injury literature [12, 13]. For instance, sensing of hypoxia or reaction to local hypoxia in the airways by oxygen-sensitive neuro-epithelial bodies leads to the release of neurotransmitters [14] that may be relayed to the brain *via* afferent neural pathways. Whether deposition of high concentrations of budesonide or other corticosteroids act in this fashion to dampen signalling *via* neural mechanisms or by suppression of signalling by hypoxic lung macrophages *via* release of cytokines, as suggested by CHAO *et al.* [15], remains unresolved.

Accordingly, with this as background, ZHENG *et al.* [2] had randomised 138 healthy volunteers to budesonide 200 µg twice daily, dexamethasone 4 mg twice daily or placebo before and during a passive ascent by automobile to 3900 m. Both budesonide and dexamethasone significantly decreased the incidence of AMS, from 60% to 23% and 31%, respectively. Both the budesonide and dexamethasone groups had higher pulse oximetry oxygen saturations and lower heart rates. Forced vital capacity was higher and quality of sleep was better in the budesonide-treated subjects. These results were confirmed by a subsequent study from the same group on 80 volunteers randomised to inhaled budesonide, oral procaterol, inhaled budesonide/formoterol or placebo [3]. In that study, the authors attributed the improvement of AMS in budesonide-treated subjects to the central effects of improved oxygenation. This could be possible, although the budesonide-related improvement in oxygen saturation at high altitude was only a few percentage points higher and above 90%, therefore probably too small to be of physiological relevance.

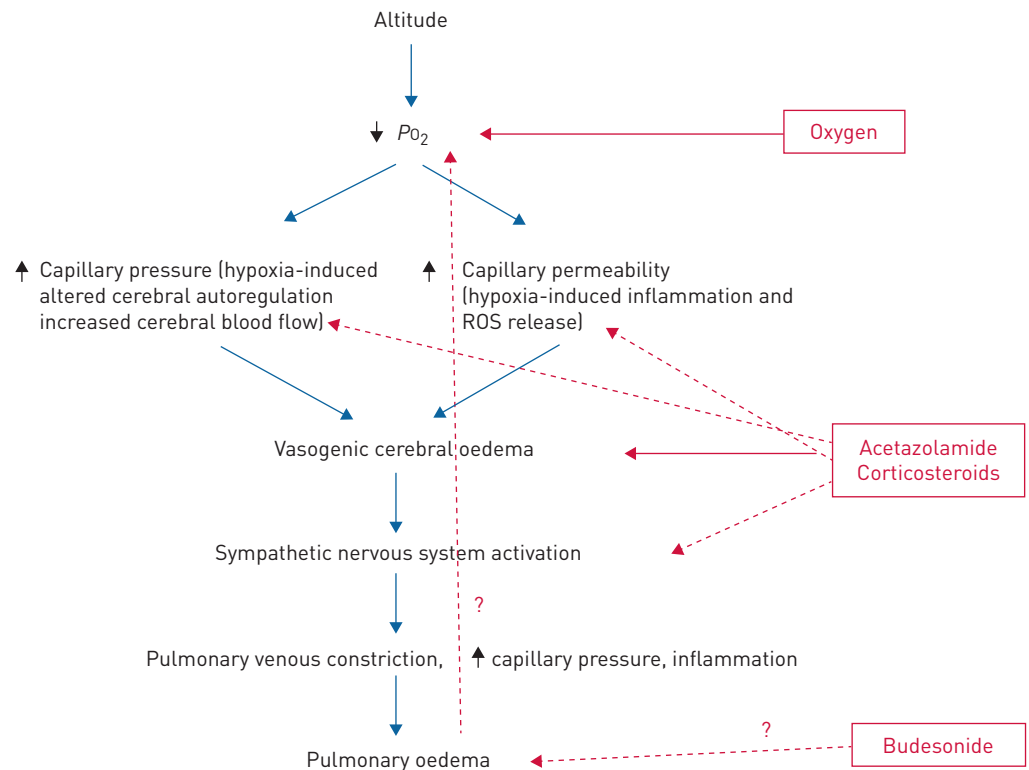


FIGURE 1 Schematic representation of the current understanding of acute mountain sickness and its cerebral and pulmonary complications. Established and hypothetical (stippled lines, question marks) therapeutic interventions are shown in red. Hypobaric hypoxia causes vasogenic cerebral oedema and hydrostatic pulmonary oedema. Brain and lung oedemas are worsened by inflammatory reactions and release of reactive oxygen species. Efficient treatments aim at improved oxygenation and relief of cerebral oedema. Relief of inflammation may limit the functional consequences of cerebral and pulmonary capillary leak. P_{O_2} : oxygen tension; ROS: reactive oxygen species.

Plasma levels of budesonide reached after inhalation of the drug are obviously very low and unlikely to saturate glucocorticoid receptors in the brain [8]. Accordingly, inhaled budesonide up to 800 µg did not affect urinary excretion of cortisol or plasma levels of cortisol or adrenocorticotrophic hormone in the study by BERGER *et al.* [1], thus ruling out any systemic effects including those on the brain. Only much higher doses of corticosteroids are effective in improving vasogenic brain oedema [4].

How these results might fit into the current pathophysiological understanding of AMS and its neurological or pulmonary complications is summarised in figure 1. Thus hypoxia causes cerebral oedema because of altered auto-regulation of cerebral perfusion which can lead to increased cerebral capillary filtration pressure, which then may be aggravated by secondary inflammatory reaction and release of reactive oxygen species. Cerebral oedema also causes sympathetic nervous system activation, which added to hypoxic pulmonary vasoconstriction increases pulmonary arterial and venous resistance and pulmonary capillary pressure. As in the brain, this pulmonary hydrostatic-type oedema is soon aggravated by an inflammatory reaction and release of reactive oxygen species. Pulmonary oedema impairs gas exchange, which worsens hypoxaemia and associated cerebral capillary filtration. Oxygen interrupts this vicious circle by a direct effect on the brain. Acetazolamide acts similarly by an increase in oxygen tension arising from its known ventilatory stimulation, improves auto-regulation of cerebral blood flow by associated hypocapnia along with a series of other *in vitro* demonstrated biological effects of yet unclear relevance [6]. High dose corticosteroids restore the integrity of the brain blood barrier through still incompletely understood genomic and non-genomic effects resulting in decreased activation of inflammatory pathways, inhibition of reactive oxygen species formation and decreased sympathetic nervous system tone. Inhaled budesonide could hypothetically mitigate AMS by an anti-inflammatory effect limited to the lungs, resulting in decreased capillary leak and improvement in arterial oxygen tension, and so limiting the hypoxaemic effects of altitude exposure. However, there is no evidence other than two trials of inhaled budesonide reported by the same authors to support this possibility, and it now appears that the results of these trials are not reproducible.

How can we explain contrasting results of randomised controlled trials? One first needs to exclude methodological problems. The studies by BERGER *et al.* [1], ZHENG *et al.* [2] and CHEN *et al.* [3] all were small, which could be a cause of type II or type I errors. However, sample sizes were adequate given the predictable high incidence of AMS in their experimental conditions, particularly in the study by BERGER *et al.* [1] with its active ascent to a higher altitude than in the Chinese studies. These studies were mono-centric, thus exposed to false signals generated in relation to hidden biases or unrecognised confounders, but otherwise there were no apparent methodological insufficiencies in trial conduct or design. Another possibly better explanation is in the difference between statistical significance and scientific truth.

A p-value measures whether an observed result can be attributed to chance, but it cannot answer a researcher's real question: what are the odds that a hypothesis is correct [16]. The odds depend on the strength of the result and the plausibility of the hypothesis tested. A $p < 0.05$ has 89% chance of indicating no real effect if the odds are 19 to 1 against, 29% if 1 to 1 odds and 96% if 9 to 1 odds. A $p < 0.01$ increases the likelihood of a real effect, yet in debatable plausibility, uncertainty remains. ZHENG *et al.* [2] reported on p values of 0.0006 and 0.0071, but many variables were measured. The authors invoked a Benferroni correction for multiple comparisons, but did not clearly explain how they applied it. A reasonable guess is that the reported p-values were overly optimistic, and in reality closer to 0.05. However, even a higher level of significance does not definitely prove a low-plausibility hypothesis [16].

What can be done in case of doubt generated by opposing results of apparently perfect trials? Repetition by an independent team of investigators and in a different setting. In this regard, a study performed in North America of equivalent size with a fast active ascent to 4344 m using 200 µg budesonide that also included a positive acetazolamide comparator arm was reported most recently by LIPMAN *et al.* [17] as being negative as well. Findings that cannot be reproduced by independent scientists in separate environments provide the strongest argument that significant results, however dramatic, do not necessarily prove that a hypothesis is correct [16].

AMS, along with its cerebral and pulmonary manifestations, remains incompletely understood. There is no experimental model of the condition to test specific hypothesis in controlled conditions, so that optimal use of all available clinical tools, including drug trials, will be essential to further progress. In this respect, Berger, Zheng, Chen, Lipman and their colleagues have to be congratulated for designing the best possible rigorous trials in difficult environmental conditions. The budesonide trials appear not to have led to a leap forward in better understanding the medical complications of high altitude exposure, but provide nevertheless important data to keep in mind for future studies on the pathophysiology and treatment of medical complications of high altitude exposure.

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