BRIEF REPORT

No evidence of cerebral oedema in severe acute mountain sickness

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In a randomized, double-blind cross-over study 10 subjects were exposed to a simulated altitude of 4500 m for 10 h after administration of placebo, acetozolamide (250 mg bid) or theophylline (250 mg bid). T2-weighted magnetic resonances images (MRI) and diffusion weighted MRI were obtained directly after exposure to altitude under hypoxic conditions. Although eight of 10 subjects had moderate to severe acute mountain sickness (AMS), we found no evidence of cerebral oedema, irrespective of the medication taken. Almost all subjects showed a decrease in inner cerebrospinal fluid (iCSF) volumes (placebo −10.3%, $P = 0.02$; acetazolamide −13.2%, $P = 0.008$, theophylline −12.2%, n.s.). There was no correlation between AMS symptoms and fluid shift. However, we found a significantly positive correlation of large (>10 ml) iCSF volume and more severe AMS after administration of placebo ($r = 0.76$, $P = 0.01$). Moderate to severe AMS after high altitude exposure for 10 h is associated with a decreased iCSF-volume independent of AMS severity or medication without signs of cerebral oedema. □*High altitude, acute mountain sickness, cerebral oedema, diffusion weighted imaging*

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Introduction

Acute mountain sickness (AMS) occurs frequently when people reach high altitudes too fast. Typical symptoms are moderate to severe headache, nausea, anorexia, vomiting, dizziness and sleep disturbances (1). Key factor leading to AMS is the increasingly hypoxic environment due to a lower atmospheric pressure at higher altitudes. The symptoms of AMS can be mild, although headache and at least one of the symptoms mentioned above are required to confirm the diagnosis. The symptoms usually start 6–8 h after arrival at high altitude. If the subjects are exposed to severe hypoxia rapidly, the symptoms can increase dramatically. When hypoxaemia persists, some subjects may develop high altitude cerebral oedema (HACE), a life – threatening condition which is considered to be the final stage of severe AMS in the current literature (1).

The pathophysiology of AMS still remains unclear, although recent data have provided some evidence that the increasing hypoxia when travelling to high altitude leads to an increase in blood–brain-barrier permeability. This is followed by vasogenic oedema in severe AMS and subsequently results in high altitude cerebral oedema (HACE) (2, 3). However, at present there are only indirect measurements available to support this hypothesis (4).

We therefore investigated the presence of cerebral oedema in severe AMS with diffusion weighted magnetic resonance imaging. Changes of inner cerebrospinal fluid volumes were evaluated as an indicator of brain swelling.

Methods

Subjects and medication

Ten healthy, nonsmoking male volunteers (mean age 24.8 years, BMI < 24 kg/m^2) agreed to participate in the study. The study protocol was approved by the local ethics committee. The data were obtained in the context of a larger study to investigate the effects of acetazolamide and theophylline vs. placebo in severe AMS. The design of this prospective cross-over study was randomized, double-blind, placebo controlled, with an interval of two weeks between each of the three chamber sessions. Ten subjects each were randomly allocated to 250 mg oral slow release theophylline (Euphylong; Byk Gulden, Konstanz, Germany), or 250 mg acetazolamide (Diamox; Lederle, Muenster, Germany) or placebo (matched tablets) twice daily, starting three days prior to the chamber session and ending in the evening after each exposure to the simulated altitude.

Altitude simulation

The study was performed in a decompression chamber in Munich (Starmed 2200, Inc. Haux, Karlsbad, Germany). The chamber was decompressed for a total of 10 hours to reach a simulated altitude of 4500 m (14 850 ft), this altitude was reached within 15 min. All subjects entered and left the chamber in 20 min intervals. After 10 hours, the subjects were brought to the nearby located magnetic resonance imaging unit (MRI) within five minutes, wearing a closed face mask which delivered a 12% FiO_2 gas mixture (O_2/NO_2) to guarantee a hypoxic environment equivalent to an altitude of 4500 m until the end of the imaging process.

Study parameters

The Lake Louise Self Assessment Questionaire (LLSS) and the Environmental Susceptibility Questionaire (ESQ) were used to assess symptoms of AMS at 0, 3, 6 and 9 h (5, 6). Two subscores were calculated according to the provided equations to select between cerebral (ESQ-C-scores) and respiratory (ESQ-R-scores) symptoms. AMS was defined as an ESQ-C score > 0.5 or a LLSS of more than 3. Arterialized capillary blood was collected at 0, 3, 6 and 9 h to measure PaO_2, $PaCO_2$ and pH (ABL 5, Radiometer Inc., Copenhagen, Denmark). Theophylline serum levels were measured in the morning of the study day before administration of the medication (enzyme immunoassay CEDIA® Theophylline II; Boehringer Mannheim, Indianapolis, IN, USA).

Magnetic resonance imaging

Images were acquired on a 1.5 Tesla whole-body scanner with a maximum gradient strength of 25 mT/m, using a standard head coil (Magnetom Vision, Siemens, Erlangen, Germany). T2 weighted turbo-spin-echo sequences (T2w, TR 3500 ms, TE 112 ms) were aquired in axial orientation, covering the whole brain and cerebellum. For better evaluation of the corpus callosum additional parasagittal and coronar images were recorded. A fluid attenuated inversion recovery sequence (FLAIR, TR 900 ms, TE 110 ms, TI 2200 ms) and diffusion weighted images (DWI, single-shot echo-planar imaging, TR 10 s, TE 93 ms, b = 0 and b = 1000 s/mm^2) were recorded, matching the slice geometry of axial T2 images (19 slices, 5 mm slice thickness, field of view 220 mm). Evaluation of diffusion weighted images was based on visual inspection by two different observers, unaware of the medication taken. Volumetry of inner cerebrospinal fluid spaces (iCSF) was done by manual segmentation of the lateral ventricles and the third ventricle. To correct partial volume effects, segmentation was combined with a treshholding technique to select only liquor equivalent pixel values in T2w images.

Data analysis

Data were analysed using SPSS Software (release 10.0, SPSS Inc., Chicago, IL, USA). The Wilcoxon-test with exact procedures was used to compare the effects of the study medication on AMS-scores and iCSF-volumes. Correlation between volumetry variables and AMS-symptoms were calculated with the Spearman correlation coefficient. A P-value of < 0.05 was regarded statistically significant. Values are expressed as median and range.

Results

Although eight of 10 subjects treated with placebo experienced severe AMS symptoms such as headache, nausea and vomiting (median LLSS score 6.0, range 1–10; median ESQ-C score 1.3, range 0.16–2.5) after 10 hours of pronounced hypoxia, we found no evidence of abnormalities in diffusion weighted imaging and no increased signals in T2w or FLAIR images (Figs 1 and 2). These negative findings in MR imaging remained unchanged in all subjects after

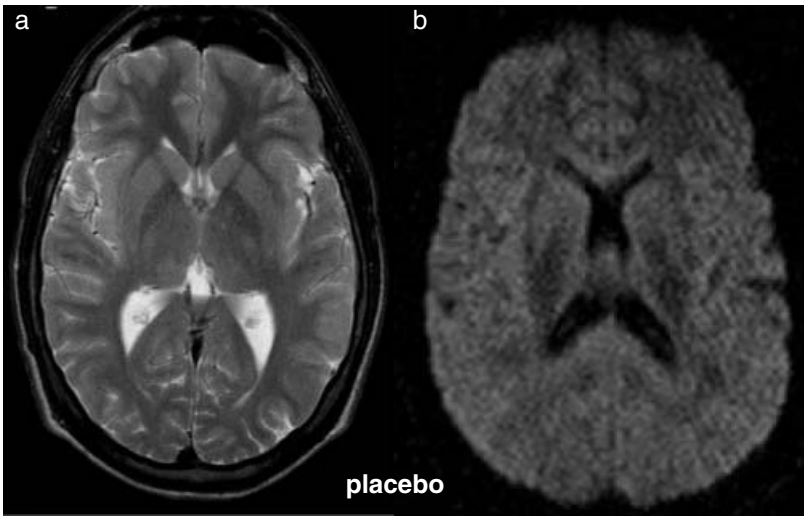

Figure 1 T2 weighted (a) and diffusion weighted (b) magnetic resonance imaging in subject no. 3 with very severe AMS (with placebo, AMS-score 10, see Table 1) without abnormal increase in signal intensity.

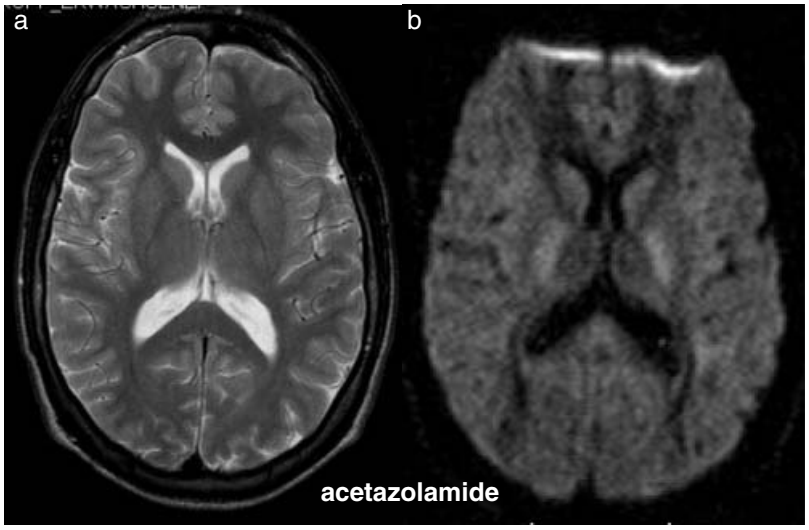

Figure 2 T2 weighted (a) and diffusion weighted (b) magnetic resonance imaging in the same subject (no. 3, with acetazolamide, see Table 1) with only mild symptoms of AMS without abnormal increase in signal intensity.

administration of acetazolamide or theophylline (interobserver reliability 100%).

Volumetry of the inner cerebrospinal fluid shift revealed large interindividual differences (Table 1). Ten hours of severe hypoxaemia led to a significant reduction of inner cerebrospinal fluid volume in subjects taking either placebo or acetazolamide (median change placebo –10.3%, range –35.8% –0%, $P = 0.002$; median change acetazolamide –13.2%, range –19.5% –0%, $P = 0.008$)((Figs 3 and 4). In the theophylline group, we found an increase in iCSF volume in four subjects and a decrease in six subjects (median change theophylline –12.2%, range –36.6% to 6.7%, $P = 0.08$). There was no significant correlation between AMS symptom scores and absolute or relative change in inner cerebrospinal fluid volumes. However, we found a significant relationship between larger inner cerebrospinal volumes (>10 ml) at normoxia and higher AMS symptoms scores with placebo (Spearman's $\rho = 0.76$, $P = 0.01$). This relationship disappeared when subjects were on acetazolamide or theophylline.

Compared to placebo, both treatments reduced significantly the risk of developing AMS –

Table 1 Variables of all 10 subjects at the end of a 10 hour stay at a simulated altitude of 4500 m with either placebo, acetazolamide or theophylline

	Subject no.										
Parameter	1	2	3	4	5	6	7	8	9	10	Median
PO_2											
placebo	40	30	36	41	36	43	40	33	36	39	37.5
acetazolamide	44	36	47	46	45	47	41	41	45	45	45.0
theophylline	43	36	38	40	37	42	40	36	30	37	37.5
PCO_2											
placebo	33	35	33	29	34	27	37	34	30	29	33.0
acetazolamide	28	35	29	29	30	25	29	30	33	28	29.0
theophylline	44	30	32	32	33	32	30	35	33	30	32.0
AMS score											
placebo	6	7	10	1	6	8	5	2	5	6	6.0
acetazolamide	2	6	3	2	2	1	3	2	3	2	2.0
theophylline	5	8	6	5	3	5	2	2	5	3	5.0
Headache											
placebo	++	++	+++	+	++	+++	++	+	+++	++	
acetazolamide	–	++	+	–	+	–	–	+	+++	+	
theophylline	+	+++	+++	+	+	++	–	+	++	++	
Inner cerebrospinal fluid volume (ml) normoxia	10.3	30.9	23.5	9.5	12.4	36.6	12.4	7.1	5.6	9.0	11.3
% volume change											
placebo	–13	–19	0	–0,5	–1	–5	–36	–12	–9	–34	–10.3
acetazolamide	–11	–14	0	–13	–13	†	–15	–16	–8	–20	–13.2
theophylline	–8	–37	+1	+6	+7	–16	–20	+5	–21	–20	–12.2

No abnormal MRT findings before entering the study, median theophylline serum level 7.7 µg/ml. The given PO_2 – values and PCO_2 – values (mmHg) were measured after 9 h of hypoxia. Symbols denote severity of headache (– = no headache, + = light headache, + + = medium headache, + + + = severe headache). The AMS-scoring system is described in the methods section. †Data on subject 6 are missing due to technical reasons.

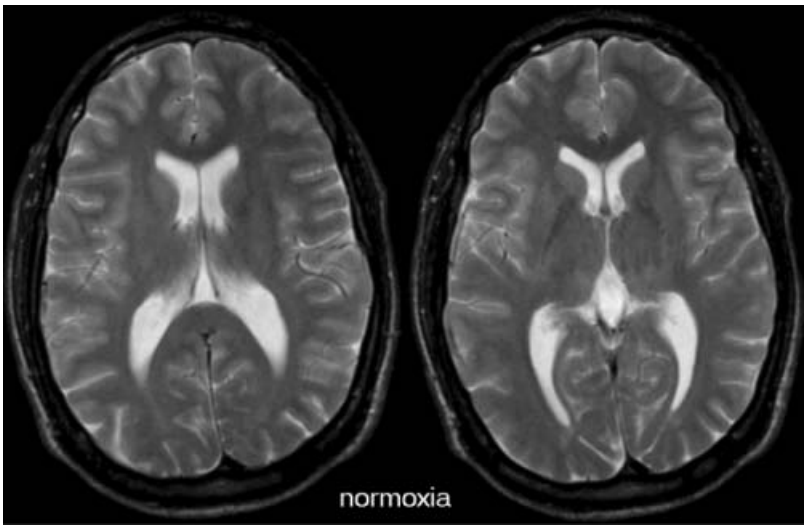

Figure 3 Two axial layers of T2 weighted magnetic resonance imaging in subject no. 2 (see Table 1) under normoxic conditions. Note the larger inner cerebrospinal fluid volume.

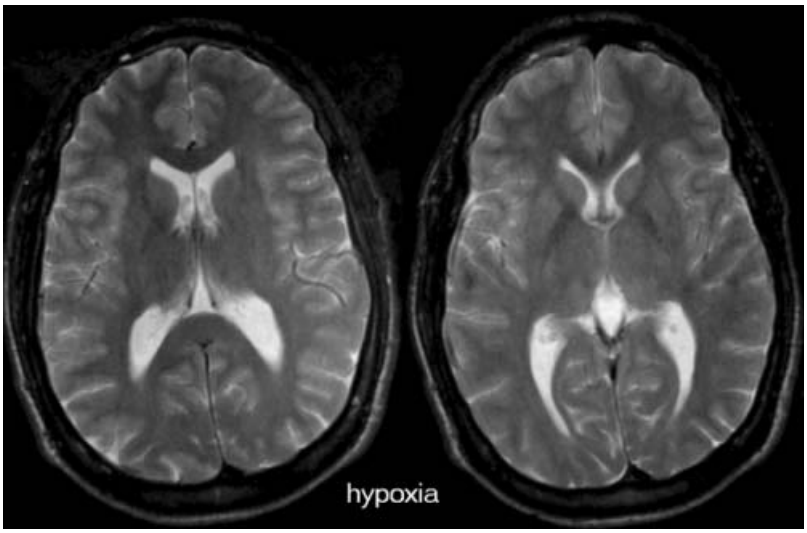

Figure 4 Two axial layers of T2 weighted magnetic resonance imaging in the same subject (no. 2 with placebo, see Table 1) after 10 h of exposure to a simulated altitude of 4500 m with severe AMS. Note the reduction in inner cerebrospinal fluid without changes in signal intensity in the cerebral tissue.

symptoms in our subjects (placebo vs. acetazolamide $P = 0.008$; placebo vs. theophylline $P = 0.023$). However, the effect of theophylline was less pronounced and significantly smaller compared to the administration of acetazolamide (acetazolamide vs. theophylline $P = 0.016$).

Discussion

This is the first study to report on diffusion weighted magnetic resonance imaging in subjects with severe AMS. All subjects did not show any evidence of hypoxaemia-induced cerebral oedema, neither of cytotoxic nor vasogenic origin. However, there was a significant reduction of inner cerebrospinal fluid volume during prolonged severe hypoxaemia indicating moderate swelling of the brain.

When planning the study, we expected to find morphologic changes in MRI in subjects with severe AMS, as hypothesized by several authors (2, 3, 7). This hypothesis was based on findings in severe AMS and HACE. Hackett et al. (3) found an increased T2 signal intensity in seven of nine subjects with HACE, particularly in the corpus callosum. Levine et al. (7) reported diffuse low density on brain computer tomography scans of the sickest of five subjects with AMS, however, the measurements were performed only 48 h after the onset of the symptoms. The most convincing evidence was the report from Matsuzawa et al. (2) showing increased T2 signal intensity in the white matter in the sickest four of seven subjects with AMS after 24 h of altitude exposure. With these findings in mind we expected to see changes in MR imaging when our subjects were taking placebo compared to the administration of acetazolamide or theophylline.

Acetazolamide is the standard drug used as a prophylaxis for AMS (1). It is a strong respiratory stimulant due to its inhibition of carbonic anhydrase. It has been shown to increase ventilation and PaO_2 during daytime and sleep at high altitude, thereby reducing AMS (8, 9). This drug should therefore be able to reduce the degree of hypoxic oedema by improving brain oxygenation.

In a previous study, we were able to demonstrate that theophylline reduces the severity of AMS without improving oxygenation (10). We therefore hypothesized that a decreased microvascular permeability induced by theophylline may account for the better performance observed in our subjects taking theophylline after acute exposure to high altitude (11).

Both hypotheses were not supported by the findings of this study. There was no evidence of increased T2 signals or impaired diffusion during repetitive measurements in the same subjects with different degrees of AMS. All subjects with placebo or acetazolamide showed a reduction of inner cerebrospinal fluid, an indicator of increased brain volume. This can be attributed to the increase in cerebral blood flow and cerebral blood volume, found in hypoxia (12). The recently published study of Morocz et al. (13) supports our findings. The authors could not detect any increase in T2 signal

with a new imaging technique after more than 32 h of altitude exposure in nine subjects. However, they found an increase in brain volume in all subjects, irrespective of their symptoms.

According to the Monro-Kellie hypothesis (as modified by Weeds; 14) which states that the sum of the volume of the brain plus CSF plus intracranial blood remains constant, the depletion of iCSF volume indicates an increase of brain volume and/or intracranial blood volume. As we found no evidence of cerebral oedema in our study, one possible mechanism could be the increase of cerebral blood volume. It can be speculated that the increase in cerebral blood flow (12) results in a dilatation of cerebral vessels which can then be stretched or displaced. The combination of these mechanical and additional chemical stimuli (e.g. NO release, which is released by hypoxia) (15) will then trigger headache and nausea by activation of the trigeminovascular system as a common pathway. This could explain the effect of different agents such as dexamethason, anti-inflammatory drugs, and acetazolamide in the prophylaxis and treatment of AMS symptoms, reflecting multiple components of the AMS pathophysiology.

Whether the increase of iCSF in four of our subjects during treatment with theophylline is due to cerebral vasoconstriction (16) with a reduced amount of hypoxic cerebral vasodilatation (and therefore less AMS symptoms) remains uncertain, as one of these subjects experienced severe headache (similar to placebo) after 10 hours of hypoxia. Nevertheless, this demonstrates the lack of correlation between changes of iCSF volumes and AMS symptoms in our study.

We conclude that simulated exposure to high altitude reduces iCSF-volume independent of AMS severity or medication. We found no evidence of vasogenic oedema in moderate to severe AMS as previously hypothesized. Future studies including measurements of cerebral blood volume in humans may contribute to further elucidation of AMS pathophysiology.

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