Theophylline improves acute mountain sickness


ABSTRACT: A randomized two-part study was conducted in order to determine the efficacy of theophylline in the treatment of acute mountain sickness during fast ascent to altitudes >2,500 m.

Fourteen healthy male subjects participated in a randomized single-blind placebo-controlled crossover study carried out in a decompression chamber (simulated altitude 4,500 m). A second randomized single-blind, placebo-controlled study was conducted at a high-altitude research laboratory (3,454 m) and included 21 healthy male subjects. The study medication was either 375 mg oral slow-release theophylline (250 mg if <70 kg) or a matched placebo tablet taken twice daily. The acute mountain sickness score (AMSS) was assessed three times a day, beginning 18 h prior to altitude exposure and continuing for 18 h after altitude exposure. In addition, measurements of respiratory frequency, pulse rate, oxygen saturation and arterial blood gas levels were performed.

Acute mountain sickness was significantly reduced by theophylline during the decompression chamber study (mean±SD 1.2±0.9) with placebo versus 3.6±0.8 with theophylline; p=0.03). During the high-altitude study, subjects with theophylline showed a significantly lower AMSS on arrival and after 18 h at altitude (0.6 versus 2.3, p=0.03). Oxygenation was improved in both parts of the study.

In conclusion, oral slow-release theophylline improves acute mountain sickness.


Acute mountain sickness (AMS) is a frequent medical disorder in travellers who rapidly ascend to altitudes >2,500 m [1]. When altitudes >4,000 m are reached within hours, only few do not have at least mild symptoms. The symptoms of mild AMS include headache, dizziness, fatigue, gastrointestinal symptoms and sleep disturbance. During prolonged stay at high altitude, symptoms improve usually within 24–48 h.

The pathogenesis of AMS is not fully understood, but it is generally agreed that the main underlying cause is hypoxia, which initiates the pathogenetic processes leading to AMS. Hypoxia is thought to cause water retention or a shift of water from intracellular to extracellular compartments [2], increase microvascular permeability [3] and increase cerebral blood flow [4]. All of these factors may contribute to AMS, although the role of enhanced cerebral blood flow remains controversial [5].

AMS is normally best prevented by ascending slowly to high altitude. However, when rapid ascent is necessary (i.e. during rescue operations or passive transportation to high altitude), medical prophylaxis may be indicated. Acetazolamide at a dose of 250 mg twice daily and dexamethasone at doses of >4 mg twice daily have been reported effective in the preventive treatment of AMS [6, 7].

The effects of theophylline on AMS have not been studied, although its pharmacological profile would seem to predispose this substance to the treatment of AMS. The multiple pharmacological effects of theophylline (a phosphodiesterase inhibitor) are well characterized, and comprise a decrease in cerebral blood flow [8], suppression of microvascular permeability in the brain and lungs [9], a bronchodilating effect [10], central respiratory stimulation [11], a decrease in pulmonary arterial pressure [12], inhibition of inflammatory mediators [13], a reduction in periodic breathing [14], improved diaphragmatic contractility [15], and induction of mild diuresis.

The purpose of this randomized single-blind study was to examine the effects of oral slow-release theophylline on AMS and blood oxygenation in a group of healthy male subjects during fast ascent to altitudes >3,500 m during an investigation carried out in a decompression chamber and during an excursion to the Jungfraujoch (Switzerland).

Materials and methods

Study population

All subjects gave informed consent to participation in the study, and the study protocol was approved by the local ethics committee. They were selected from a group of healthy mountaineers. Exclusion criteria for both studies were 1) female sex, to avoid a possible sex difference in susceptibility to AMS [16, 2) smoking, 3) noncompliance with the study protocol 4) previous pulmonary disease, and 5) concomitant medication. The criteria for entering
the study were: 1) normal weight (body mass index (BMI) <25), and 2) a medical history of constant good health. There were no significant differences in both studies regarding mean±SD age (29±8 yrs in the decompression chamber study versus 29±8 yrs in the high-altitude study) and BMI (21±3 in the decompression chamber study versus 21±2 in the high-altitude study).

Study design

The first part of the study (decompression chamber study) was performed in a decompression chamber at the medical institute of the air force near Munich (Fürstenfeldbruck, Germany). The crossover study had a randomized single-blind placebo-controlled design, with an interval of 3 weeks between the two chamber sessions. The chamber was decompressed for a total of 7 h to reach a simulated altitude of 4,500 m (14,850 ft); this altitude was reached within 30 min. Fourteen subjects were randomly allocated to placebo or study medication and were transported by rail within 3 h to the Jungfraujoch and stayed there for ≥36 h without physical exercise.

Study medication

For the decompression chamber study, subjects were randomly allocated to placebo or study medication and started taking the tablets 3 days before entering the chamber. The study medication was 375 mg oral slow-release theophylline taken twice daily (Euphylong; Byk Gulden, Constance, Germany) or 250 mg twice daily for subjects weighing <70 kg or matched placebo tablets twice daily. The study medication was stopped immediately after the experiment. After a 3-week interval, the medication was cross-changed and started 3 days before the second measurements were performed.

In the high-altitude study, subjects were randomly allocated to placebo or study medication, starting 3 days before the journey to Jungfraujoch, at the same doses as used in the decompression chamber study. Theophylline intake was stopped 12 h after arrival at altitude in order to investigate possible rebound effects.

Measurements

In both studies, all subjects completed a diary card recording symptoms included in the acute mountain sickness score (AMSS, Lake Louise version [17]) three times a day, beginning 18 h before and continuing for 18 h after altitude exposure. In the decompression chamber study, AMSS was additionally measured at 0, 210 and 420 min of exposure to hypobaric hypoxia. The questions related to the following symptoms: headache, gastrointestinal symptoms, fatigue/weakness and dizziness/light-headedness. The item "difficulty sleeping" was included during the high-altitude study. As not much activity was possible during the decompression chamber study, the question "reduction of activities" was not included in the questionnaire. Each symptom was scored from 0 (none) to 3 (severe). The overall score was then calculated by addition of each individual parameter score.

In both studies, measurements of respiratory frequency, pulse rate and oxygen saturation were performed by means of pulse oximetry (OXY3; Radiometer, Copenhagen, Denmark). For technical reasons, arterial blood gas levels could only be measured in eight subjects during the decompression chamber study and transcutaneous oxygen (PtCO2) and carbon dioxide tension (Ptc,CO2) (ABL 5 and TC3; Radiometer) only in nine subjects during the high-altitude study.

Samples for serum theophylline level determination were taken 6 h after the last intake of medication, the samples were processed immediately and frozen at -20°C until assayed. Measurement of theophylline levels was performed using an enzyme immunoassay technique (CEDIA® Theophylline II; Boehringer Mannheim, Indianapolis, IN, USA).

Data analysis

Data were analysed using SPSS software (release 8.0; SPSS, Inc. Chicago, IL, USA). Independent (high-altitude study) and paired (decompression chamber study) t-tests were used to compare blood gas parameters, respiratory frequency, pulse rate and serum theophylline levels; analysis of variance procedures and the Bonferroni post hoc test were used to compare time-dependent effects. The Wilcoxon signed-rank test with exact procedures (decompression chamber study) and the Mann-Whitney U-test with exact procedures (high-altitude study) were used to compare overall treatment effects on the AMSS and treatment effects at different time intervals. A p-values of <0.05 was regarded as significant.

Results

The mean serum theophylline levels were 40.5±28.3 μmol/L in the decompression chamber study and 51.6±4.4 μmol/L in the high-altitude study. Theophylline dosing was generally well tolerated, apart from in four subjects who suffered tachycardia and difficulty sleeping. Subjects experiencing side-effects reduced their theophylline intake and demonstrated lower serum theophylline levels. In the decompression chamber study, four subjects reduced their intake of theophylline tablets due to sleeplessness and tachycardia, and one subject suffered from tremors. In the presence of theophylline side-effects, low serum theophylline levels (as low as 18.9 μmol/L) were accepted as effective in these individuals.

The two study groups participating in the decompression chamber study did not differ in baseline mean arterial oxygen saturation (Sao2), PtcCO2, and PtcCO2 respiratory frequencies and pulse rates. Statistically significant differences in pulse rate and Sao2 could be demonstrated at 210 min (table 1). Slow-release theophylline given during exposure to acute hypobaric hypoxia resulted in a marked improvement in the AMSS as compared to that found in subjects taking matched placebo (table 2).

During the high-altitude study, both study groups did not differ significantly on arrival and after 36 h in their cardiopulmonary parameters (table 3). The placebo-treated
and 12 h after arrival at Jungfraujoch. Pants slept between 12 and 18 h but none slept between 0
not be reliably assessed at 6-h intervals as most partici-
versus "was omitted from analysis (mean rank placebo 13.2
could be observed, when the symptom "difficulty sleep-
up to 36 h), Data are presented as mean±SD. Theo: theophylline; P: placebo; S
exposure to hypobaric hypoxia [23]. Furthermore, theophy-
lane is able to improve central respiratory drive and,
therefore, to stimulate a blunted hypoxic ventilatory res-
response in AMS-susceptible subjects [24]. This is supported
by the present data, which show that the respiratory fre-
cuency was higher in subjects on theophylline compared to
the placebo group, although these data did not reach
statistical significance. As this increase in ventilation and,
therefore, in oxygenation was not pronounced in the
treatment group, this seems not to be the main mechanism
of action in reducing AMS. By contrast, acetazolamide is

tude study, a slight rebound of AMS (mainly headache)
was found.

Decreased microvascular permeability may be another
beneficial effect of theophylline, accounting for the better
performance observed in the subjects taking theophylline
after acute exposure to high altitude [20]. Hypoxia induces
microvascular permeability within the pulmonary vessels
[21], an effect which is probably also present in cerebral
vessels. In this context, theophylline and dexamethasone
could act in an additive way in the prevention of AMS.

Additional mechanisms may explain the beneficial eff-
ects of oral-slow release theophylline on the development
of AMS. Among them, dose-dependent bronchodilatation
leads to improvement of ventilatory patterns and reduces
trapped air. In patients with chronic obstructive pulmonary
disease, theophylline was shown to improve oxygenation
as well as the forced expiratory volume in one second [15,
22]. Similar effects can be expected in subjects acutely
exposed to hypobaric hypoxia [23]. Furthermore, theophy-
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The two parts of the study showed independently that
oral slow-release theophylline improves AMS, when sub-
jects are exposed to acute hypobaric hypoxia.

The mechanisms leading to the development of AMS are
not yet clear, but it has been shown that increasing cerebral
oedema and increased cerebral blood flow are associated
with this condition [2, 4, 5]. Owing to these changes, head-
ache is the leading symptom of AMS, which was confir-
méd in the present study. Theophylline reduces cerebral
blood flow, probably by acting directly through inhibition
of endothelial factors (e.g. adenosine) [18], although the
exact cellular mechanisms of theophylline action remain
evasive [19]. This effect could be beneficial in the preven-
tion and treatment of patients with AMS. In the present
subjects, theophylline was able to reduce the development
of headache during both parts of the study. Interestingly,
after stopping intake of theophylline during the high-alti-

Table 1. – Comparison of cardiopulmonary parameters
during the decompression chamber study in subjects
taking theophylline or placebo

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Subjects</th>
<th>Theo</th>
<th>P</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S_O₂ %</td>
<td>Baseline</td>
<td>14</td>
<td>97±2</td>
<td>97±2</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>210 min</td>
<td>14</td>
<td>84±4</td>
<td>81±5</td>
<td>0.01</td>
</tr>
<tr>
<td>P_tc,O₂ kPa</td>
<td>Baseline</td>
<td>8</td>
<td>11±0.9</td>
<td>11±0.9</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>300 min</td>
<td>8</td>
<td>6±0.9</td>
<td>6±0.4</td>
<td>0.31</td>
</tr>
<tr>
<td>P_tc,O₂ kPa</td>
<td>Baseline</td>
<td>8</td>
<td>5±0.3</td>
<td>5±0.4</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>300 min</td>
<td>8</td>
<td>4±0.6</td>
<td>5±0.3</td>
<td>0.47</td>
</tr>
<tr>
<td>(R) breath⁻⁻¹ min⁻¹</td>
<td>Baseline</td>
<td>14</td>
<td>15±2</td>
<td>13±3</td>
<td>0.18</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>Baseline</td>
<td>14</td>
<td>74±7</td>
<td>71±8</td>
<td>0.47</td>
</tr>
<tr>
<td>beats⁻⁻¹ min⁻¹</td>
<td>Baseline</td>
<td>210 min</td>
<td>14</td>
<td>16±5</td>
<td>15±5</td>
</tr>
<tr>
<td></td>
<td>210 min</td>
<td>14</td>
<td>86±15</td>
<td>81±12</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. Theo: theophylline; P: placebo; S\_O₂: arterial oxygen saturation; P\_tc,O₂: transcutaneous oxygen tension; P\_tc,O₂: transcutaneous carbon dioxide tension; \(R\): respiratory frequency.

Discussion

The two parts of the study showed independently that
oral slow-release theophylline improves AMS, when sub-
jects are exposed to acute hypobaric hypoxia.

The mechanisms leading to the development of AMS are
not yet clear, but it has been shown that increasing cerebral
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tion and treatment of patients with AMS. In the present
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Table 2. – Reduction in acute mountain sickness score
(AMSS) with theophylline during the decompression
chamber study

<table>
<thead>
<tr>
<th>Group</th>
<th>Time-point</th>
<th>Subjects</th>
<th>Theophylline</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14</td>
<td>14</td>
<td>1.4±1.5</td>
<td>1.4±1.0</td>
<td>0.78</td>
</tr>
<tr>
<td>210 min</td>
<td>14</td>
<td>14</td>
<td>1.2±0.9</td>
<td>3.6±0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>420 min</td>
<td>14</td>
<td>14</td>
<td>2.6±2.2</td>
<td>4.1±2.3</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.
thought to be a strong respiratory stimulant due to its inhibition of carbonic anhydrase. It has been shown to increase ventilation and arterial oxygen tension during daytime.

Other mechanisms of action of theophylline under discussion are the reduction in pulmonary arterial tension and improvement in right and left ventricular ejection fraction. This might also be an additional beneficial effect of theophylline. Whether theophylline could be used to reduce the incidence of high-altitude pulmonary oedema remains to be studied.

Currently there are two other substances which may be effective in the prevention and treatment of AMS: acetazolamide and dexamethasone [6, 26, 28]. Therefore, the question arises as to whether there is a need for additional medication. However, both acetazolamide and dexamethasone have a number of side-effects, limiting their widespread applicability. Theophylline could be a safe alternative for subjects with contra-indications for acetazolamide or dexamethasone. Its safety was a matter of concern for a long time, but, recently, it has been accepted as being a safe and well-tolerated drug [19]. The side-effects are dose-dependent and, in most cases, preventable by slow increase of the dose. In the small group of healthy mountaineers, mild side-effects were noted. Thus, the uncontrolled use of theophylline by the general public on high-altitude treks is undesirable. However, in subjects with asthma or mild chronic obstructive pulmonary disease, theophylline might be superior to acetazolamide [27].

In conclusion, the present data show that oral slow-release theophylline is an effective treatment for acute mountain sickness. However, it should be kept in mind that the use of drugs for the prevention of acute mountain sickness should be limited to circumstances in which rapid ascent to high altitude is unavoidable. It should not replace slow but physiological adaptation to hypobaric hypoxia.

References


21. Schoene RB, Swenson ER, Pizzo CJ, et al. The lung at...


