Magnesium for the prevention and treatment of acute mountain sickness

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ABSTRACT

Magnesium is a physiological N-methyl-D-aspartate (NMDA) antagonist. The NMDA receptor may be involved in the pathogenesis of acute mountain sickness (AMS). In the present study, healthy subjects were randomized to receive either 400 mg of oral magnesium citrate (16 mmol) or matching placebo every 8 h for 5 days (prevention trial). Subjects then climbed to 4559 m in approx. 24 h and stayed there for 48 h. A Lake Louise Score < 3 at any time was defined as the absence of AMS, whereas a score > 6 (with ataxia, headache and nausea) was defined as a prevention failure. In a subsequent trial (treatment trial), subjects with a Lake Louise Score > 6 (with ataxia, headache and/or nausea) were randomized to receive either 4 g of intravenous magnesium sulphate (16 mmol) or matching placebo. A decrease in the score > 50 % within 60 min was regarded as a treatment success. Dichotomous data were analysed using relative risk (RR) or odds ratio (OR), and continuous data using Student’s t test or Wilcoxon’s rank-sum test. In the prevention trial, data from 61 subjects (30 receiving magnesium and 31 placebo) were analysed. With oral magnesium, 20 % of subjects had no AMS compared with 16.1 % in the placebo group [RR (95 % CI), 1.2 (0.4–3.6); where CI is confidence interval]. With magnesium, 40 % were prevention failures compared with 35.5 % in the placebo group [RR (95 % CI), 1.13 (0.59–2.15)]. The mean time to failure and severity of AMS was similar between the two groups. With magnesium, 38.2 % had loose stools compared with 11.8 % in placebo group [RR (95 % CI), 3.25 (1.18–8.97)]. In the treatment trial, 12 subjects received magnesium and 13 received the placebo. With intravenous magnesium, 25 % were regarded as treatment successes compared with none in the placebo group [OR (95 % CI), 9.71 (0.91–103.4)]. With magnesium, mean (± S.D.) scores decreased from 11.6 ± 1.7 before treatment to 9.0 ± 3.5 after treatment (P = 0.009); scores remained unchanged in the placebo group. With magnesium, 75 % of subjects experienced a transient flushing compared with 7.7 % in the placebo group [RR (95 % CI), 0.05 (0.01–0.25)]. In conclusion, oral magnesium does not prevent AMS. In subjects with established AMS, intravenous magnesium reduces the severity of symptoms to some extent, but this effect is of no clinical importance.

INTRODUCTION

In theory, magnesium could be useful for neuroprotection. Magnesium inhibits calcium entry into the cell via a non-competitive blockade of the N-methyl-D-aspartate (NMDA) receptor [1,2]. Magnesium is also a physiological calcium antagonist at different voltage-gated channels [3]. Indeed, in vitro experiments [4]...
and animal models of hypoxic, ischaemic and traumatic brain injury have suggested a brain-protecting effect of magnesium [5–7]. In humans, there is also some evidence that magnesium may be involved in brain protection; for instance, magnesium is clearly anticonvulsive in eclamptic women [8–10]. Low-birth weight infants of mothers who received magnesium supplementation during labour are at a lower risk of cerebral palsy [11]. Finally, magnesium supplementation has been shown to have beneficial effects in patients suffering from stroke [12–14], and is under evaluation in a large clinical trial for use in both traumatic brain injury [15] and stroke [16].

Acute mountain sickness (AMS) is a potentially lethal illness that affects the brain and occurs at high altitude [17]. The incidence varies from 15 % to more than 70 %, depending on speed of ascent and individual susceptibility [18]. Although the pathophysiology of AMS is not fully understood [19], mechanisms are thought to include hypoxia-related increases in cerebral blood flow and permeability of the blood–brain barrier leading to brain swelling [19,20]. In analogy to the molecular and cellular events that are initiated during ischaemia and anoxia [21,22] and based on models of hypobaric hypoxia [23–28], NMDA receptor activation with subsequent calcium influx into the cell is plausible. Thus magnesium may be a useful alternative to current pharmacological strategies to prevent AMS. Acetazolamide and dexamethasone, for instance, are both efficacious in the prevention and treatment of AMS; however, both are not universally effective and both have adverse effects [18]. In a small observational study, oral supplementation with magnesium citrate (48 mmol·day⁻¹) reduced AMS symptoms in volunteers who had a positive history of AMS and who were rapidly ascending to 4000 m [29].

In the present study, we set out to test formally the usefulness of magnesium in the prevention and treatment of AMS, and to study its effect on cerebral blood flow. In the first of two papers, we report the results of two randomized trials that were conducted under field conditions in healthy volunteers ascending to high altitude. The aim of these trials was to test efficacy and adverse effects of magnesium in the control of AMS. The effect of magnesium and exposure to high altitude on blood flow velocity in the middle cerebral artery in the same volunteers is reported in the accompanying paper [30].

METHODS

Subjects

We conducted two randomized, placebo-controlled, double-blind trials, a prevention trial and a treatment trial. The Institutional Research Advisory Board and the Ethical Committee approved both protocols. Subjects were invited to take part in the prevention trial and, if prevention failed, in the subsequent treatment trial. Subjects gave written informed consent for both trials independently and were briefed and underwent a medical examination before entering the trials. Professional mountaineering guides ensured safety of all participants from the start of ascent to the end of descent. At high altitude, there was permanent professional medical surveillance. The Geneva University Hospital Pharmacy was responsible for randomization (table of random numbers) and preparation of the study drugs.

Prevention trial

Subjects and allocation

Healthy adults were recruited via our Internet page (http://www.hcuge.ch/anesthesie/montagne/margh2001.htm) and by word of mouth. Exclusion criteria were residency above 600 m, a stay above 2000 m, medication, including vitamins or magnesium, during the last 3 months and cardiac, pulmonary, neurological, renal, hepatic or psychiatric disease.

Subjects were divided according to history of previous AMS and were then separately randomized to receive magnesium citrate tablets or matching placebo. Tablets of identical size, colour and taste were taken every 8 h; the daily dose of magnesium citrate was 1.2 g (48 mmol of magnesium). This dose corresponded to the maximum oral dose that did not induce unacceptable adverse gastrointestinal effects in a previous uncontrolled pilot study [29]. Prophylaxis was started 3 days prior to ascent and was continued throughout the study until the start of descent. Subjects and investigators were blinded to the assigned treatment. As an indicator of compliance and magnesium absorption, urine samples were collected at altitude and analysed for magnesium concentrations. In addition, subjects completed a standardized questionnaire daily on adverse effects.

Study design

On day 1, subjects travelled in groups of two to five to Staffal in the Italian Alps (1130 m), ascended by cable car to an altitude of 3200 m and climbed to the Capanna Mantova at 3420 m, where they spent the first night. On day 2, they climbed to the Capanna Regina Margherita on the Swiss–Italian border (4559 m). Arrival time for all subjects was planned to be around noon. After a stay for 48 h at the Capanna Regina Margherita, subjects descended back to the valley on the morning of day 4. Throughout the study, food and drink intake was ad libitum, but alcohol was not allowed. Measurements were taken immediately after arrival at the Capanna Regina Margherita (noon, day 2), and then every 12 h (08:00 and 20:00 hours). The last measurements were taken in the morning of day 4 before descent.
To quantify AMS we used the Lake Louise Score [31,32], an eight item questionnaire, that is based on symptoms (gastrointestinal, headache, insomnia, weakness/fatigue and dizziness/drowsiness) and clinical assessment (change in mental status, ataxia and peripheral oedema). The minimum score is 0 and the maximal score is 25. There were two pre-hoc decisions. First, a Lake Louise Score <3 during the entire study period was considered as an absence of AMS, and thus as a prevention success. Secondly, a Lake Louise Score >6 with a headache score >2 and/or a gastrointestinal score >2 and/or an ataxia score >2 was considered a prevention failure. Prevention failures were documented as such and removed from the prevention trial. If these subjects had consented to take part in the treatment trial, they were randomized further. If not, they received conventional rescue medication (oxygen by face mask, 4 mg of dexamethasone intravenously and 500 mg of acetazolamide orally). If there was no improvement, despite rescue medication, they were evacuated by helicopter. Subjects who complained of a headache only without further AMS symptoms received oral acetaminophen (0.5–1 g every 6 h) upon request. These subjects were not considered as prevention failures. The total dose of acetaminophen was recorded. No other drugs were allowed during the study period. At each medical assessment, non-invasive blood pressure, heart rate and transcutaneous arterial oxygen saturation were recorded, and the subjects were asked for any adverse effects.

Endpoints
The primary efficacy endpoint was the number of prevention successes. Secondary efficacy endpoints were the number of prevention failures, delay until prevention failure and the maximum Lake Louise Scores at any time during the study period.

Treatment trial
Subjects and allocation
Subjects who participated in the treatment trial originated from two cohorts. First, there were subjects from the prevention trial who had consented to take part in the treatment trial providing prevention failed. Their group assignment from the prevention trial remained concealed. Secondly, we recruited volunteers at the Capanna Regina Margherita who had not taken part in the prevention trial, but who had a Lake Louise Score >6 with a headache score >2 and/or a gastrointestinal score >2 and/or an ataxia score >2. For these subjects, exclusion criteria and briefing were as for the prevention trial, and they all gave written informed consent.

Study design
Subjects were randomized to an intravenous infusion of 4 g of magnesium sulphate (16 mmol) or matching placebo. Study drugs were provided in identical, numbered 20 ml ampoules. Ampoules were opened consecutively, drawn into bags of 100 ml of physiological saline and infused over 30 min. Non-invasive blood pressure, heart rate and transcutaneous arterial oxygen saturation were monitored from the start of the infusion to 90 min after the end of the infusion. If the treatment failed, or if the volunteers wished so, they received the same rescue medication as for prevention failures. From the start of the infusion until 30 min after the end of the infusion, adverse effects, both spontaneously reported and actively asked for, were recorded.

Endpoints
The primary efficacy endpoint was the number of subjects who had a drop in the Lake Louise Score >50% at 60 min after the start of the treatment (i.e. 30 min after the end of the infusion); this was defined as a treatment success. Secondary efficacy endpoints were the number of subjects who had a drop in the Lake Louise Score >25% and whether or not there was a significant decrease in the score after treatment compared with before the start of the treatment.

Statistics
Prevention trial
We expected an incidence of Lake Louise Score >3 with placebo (i.e. the baseline risk of AMS) of approx. 75% [18]. A >25% risk reduction with magnesium compared with placebo was considered relevant. Thus 31 subjects/group were needed to detect a significant difference in the rates of AMS between oral magnesium and placebo. To account for dropouts we randomized 70 subjects.

Treatment trial
We expected a 95% failure rate with placebo and considered a >50% improvement of symptoms with intravenous magnesium as relevant. Thus 12 subjects/group were needed to detect a significant difference between intravenous magnesium and placebo.

For continuous variables, we used Student’s t test or Wilcoxon’s rank-sum test. For dichotomous data, we calculated relative risk (RR) or odds ratio (OR) when there were zero cells, with 95% confidence intervals (CI). In the prevention trial, comparison between groups with respect to the proportions of subjects that were not prevention failures, as a function of time, was done with a log-rank test on Kaplan–Meier estimates; information on dropouts was censured. All P values were based on two-tailed tests of significance, except for the measurements of urine magnesium, where values were expected to be higher in the magnesium group and, thus, a one-tailed test was used.
Table 1  Flow of randomized subjects in the prevention and treatment trials

<table>
<thead>
<tr>
<th>Study group</th>
<th>Placebo (n)</th>
<th>Magnesium (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention trial</td>
<td>35</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>Ill before starting</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Drop out for logistic reasons</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Drop out due to physical exhaustion</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Efficacy data prevention trial</td>
<td>31</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>Treatment trial</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Included from prevention trial having received oral placebo</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Included from prevention trial having received oral magnesium</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Recruited at high altitude</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Efficacy data treatment trial</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

RESULTS

Prevention trial (oral magnesium citrate compared with placebo)

Characteristics of subjects

Of the subjects recruited to the study, there were nine dropouts that were unrelated to the study drug (Table 1). One subject (placebo) fell ill before starting the trial and did not turn up; he was not considered for any analysis. Five subjects (two in the placebo group and three in the magnesium group) had to return from the Capanna Mantova (3420 m) in the morning of day 2 due to bad weather conditions. One subject in the magnesium group abandoned due to physical exhaustion on day 2 before reaching the Capanna Regina Margherita. She was evacuated by helicopter and accompanied by two colleagues (one placebo and one in the magnesium group). None of these eight subjects had experienced symptoms of AMS and they were considered for the adverse-effect analysis only.

Data from 61 subjects (31 placebo and 30 magnesium subjects) were included in the efficacy analysis. There were 29 females and 32 males, the mean (± S.D.) age was 35.3 ± 8.5 years. Twenty subjects had a history of AMS (10 in the magnesium group and 10 placebo). The average duration of ascent from 1130 m (Staffal) to 4559 m (Capanna Regina Margherita) was 24 ± 2 h; thus the average rate of ascent was about 140 m/h. All subjects reported to have taken their tablets according to the protocol. Urine samples were obtained from 27 magnesium and 26 placebo subjects, and magnesium concentrations were significantly higher in the experimental group (4.17 ± 2.87 compared with 3.71 ± 3.38 mmol litre⁻¹ respectively; P < 0.05).

Efficacy of oral magnesium in the prophylaxis of AMS

There was no difference between the two groups in the number of prevention successes and failures, Lake Louise Scores at drop out, time to prevention failure and maximum scores at any time point (Table 2). Similarly, there was no difference in the proportion of subjects without AMS (Figure 1). When subjects with a history of AMS were analysed separately, there was still equivalence (results not shown). Incidence and severity of three isolated AMS symptoms, headache, insomnia and ataxia, were not different between groups (Table 3). Acetaminophen consumption was not significantly different between groups; with magnesium, 18 subjects (60 %) asked for acetaminophen (median dose/subject = 2250 mg, range = 1000–6000 mg) compared with 14 subjects in the placebo group (45 %; median dose per subject = 1250 mg, range = 500–4000 mg).

Table 2  Efficacy data for the prevention trial

<table>
<thead>
<tr>
<th>Study group</th>
<th>Placebo (n = 31)</th>
<th>Magnesium (n = 30)</th>
<th>RR (95 %CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention success*</td>
<td>5 (16.1)</td>
<td>6 (20.0)</td>
<td>1.24 (0.42–3.63)</td>
<td></td>
</tr>
<tr>
<td>Prevention failure†</td>
<td>11 (35.5)</td>
<td>12 (40.0)</td>
<td>1.13 (0.59–2.15)</td>
<td></td>
</tr>
<tr>
<td>Maximum Lake Louise score at any time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>5 (16.1)</td>
<td>6 (20.0)</td>
<td>1.24 (0.43–3.63)</td>
<td></td>
</tr>
<tr>
<td>4–5</td>
<td>9 (29.0)</td>
<td>9 (30.0)</td>
<td>1.03 (0.48–2.24)</td>
<td></td>
</tr>
<tr>
<td>&gt; 6</td>
<td>17 (55.0)</td>
<td>15 (50.0)</td>
<td>0.91 (0.56–1.47)</td>
<td></td>
</tr>
<tr>
<td>Lake Louise Score at drop out</td>
<td>11.3 ± 2</td>
<td>11.5 ± 3</td>
<td></td>
<td>0.975</td>
</tr>
<tr>
<td>Delay to prevention failure (h)</td>
<td>33.0 ± 8.2</td>
<td>39.1 ± 10.2</td>
<td></td>
<td>0.406</td>
</tr>
<tr>
<td>Maximum Lake Louise Score at any time</td>
<td>7.4 ± 3.6</td>
<td>7.4 ± 4.4</td>
<td></td>
<td>0.839</td>
</tr>
</tbody>
</table>
Figure 1  Effect of oral magnesium citrate supplementation on AMS in the prevention trial
Kaplan–Meier curves showing the effect on AMS in subjects receiving oral magnesium citrate (solid line) or placebo (dotted line) during the time course of the prevention trial. There was no significant difference between subjects receiving magnesium or placebo ($P = 0.97$ as determined by the log-rank test).

Table 3  Symptoms, according to the Lake Louise Score, of headache, ataxia and insomnia in placebo and magnesium groups in the prevention trial

<table>
<thead>
<tr>
<th>Study group</th>
<th>Placebo ($n = 31$)</th>
<th>Magnesium ($n = 30$)</th>
<th>RR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2 pm</td>
<td>$1.1 \pm 0.9$</td>
<td>$1.2 \pm 1.0$</td>
<td>$0.682$</td>
<td></td>
</tr>
<tr>
<td>Day 3 am</td>
<td>$1.1 \pm 0.9$</td>
<td>$1.0 \pm 1.1$</td>
<td>$1.000$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 0 at any time ($n$)</td>
<td>$4 (12.9)$</td>
<td>$5 (14.7)$</td>
<td>$1.29 (0.38–4.35)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 1 at any time ($n$)</td>
<td>$5 (16.1)$</td>
<td>$4 (13.3)$</td>
<td>$0.83 (0.25–2.79)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 2 at any time ($n$)</td>
<td>$11 (35.5)$</td>
<td>$11 (33.3)$</td>
<td>$1.03 (0.53–2.02)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 3 at any time ($n$)</td>
<td>$11 (39.0)$</td>
<td>$10 (33.3)$</td>
<td>$0.94 (0.47–1.88)$</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3 am</td>
<td>$1.4 \pm 0.8$</td>
<td>$1.4 \pm 1.0$</td>
<td>$1.000$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 0 at any time ($n$)</td>
<td>$1 (3.2)$</td>
<td>$5 (16.7)$</td>
<td>$5.17 (0.64–41.7)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 1 at any time ($n$)</td>
<td>$10 (32.3)$</td>
<td>$5 (16.7)$</td>
<td>$0.52 (0.20–1.33)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 2 at any time ($n$)</td>
<td>$16 (51.6)$</td>
<td>$14 (46.7)$</td>
<td>$0.90 (0.54–1.51)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with score 3 at any time</td>
<td>$4 (12.9)$</td>
<td>$6 (20.0)$</td>
<td>$1.55 (0.49–4.95)$</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2 pm</td>
<td>$0.2 \pm 0.4$</td>
<td>$0.3 \pm 0.6$</td>
<td>$0.391$</td>
<td></td>
</tr>
<tr>
<td>Day 3 am</td>
<td>$0.3 \pm 0.5$</td>
<td>$0.3 \pm 0.5$</td>
<td>$1.000$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 0 at any time ($n$)</td>
<td>$11 (35.5)$</td>
<td>$12 (40.0)$</td>
<td>$1.13 (0.59–2.15)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 1 at any time ($n$)</td>
<td>$17 (54.8)$</td>
<td>$14 (46.7)$</td>
<td>$0.85 (0.52–1.40)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 2 at any time ($n$)</td>
<td>$3 (9.7)$</td>
<td>$3 (10.0)$</td>
<td>$1.03 (0.23–4.72)$</td>
<td></td>
</tr>
<tr>
<td>Subjects with a score of 3 at any time ($n$)</td>
<td>$0 (0)$</td>
<td>$1 (3.3)$</td>
<td>$0.14 (0.00–6.82)^*$</td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects

One subject, who had to return early due to bad weather conditions, lost her adverse effect questionnaire and, thus, data on adverse effects from 34 subjects in each group were analysed. With oral magnesium, 13 subjects (38.2 %) had loose stools compared with four (11.8 %) subjects in the placebo group (RR (95% CI), 3.25 (1.18–8.97)). There was no difference between the groups in the occurrence of any of the other adverse effects.

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Treatment of AMS (intravenous magnesium sulphate compared with placebo)

Characteristics of subjects
Twenty-five subjects were randomized and, of these, 20 were failures from the prevention trial (nine had received oral magnesium and 11 placebo) and five were recruited in the Capanna Regina Margherita. Twelve subjects received intravenous magnesium and 13 received the placebo (Table 1).

Efficacy of intravenous magnesium on the treatment of AMS
A > 50 % decrease in the Lake Louise Score (i.e. a treatment success) was found in three out of 12 (25 %) subjects who had received intravenous magnesium, but none of the 13 subjects who had received the placebo [OR (95 % CI), 9.71 (0.91–103.4)]. All three successes had previously taken part in the prevention trial (two had received oral magnesium and one received the placebo).

A > 25 % decrease in the Lake Louise Score was found in seven out of 12 (58.3 %) subjects who had received intravenous magnesium and in two out of 13 (15.4 %) of those who had received placebo [RR (95 % CI) 3.79 (0.97–14.8)].

Before treatment commenced, groups had similar Lake Louise Scores (Figure 2). With intravenous magnesium sulphate, the mean (± S.D.) Lake Louise Score decreased from 11.6 ± 1.7 before treatment to 9.0 ± 3.5 after treatment (P = 0.009). With placebo, average scores remained unchanged (P = 0.866). At 60 min, 10 out of 12 (83.3 %) subjects who had received intravenous magnesium and all of those who had received intravenous placebo asked for rescue medication [RR (95 % CI) 0.83 (0.65–1.07)]. Two subjects receiving magnesium asked for rescue medication at 90 min. One subject in the placebo group who did not obtain satisfactory relief, despite rescue medication, was evacuated by helicopter 3 h later and recovered completely after arrival in the valley.

Adverse effects
With intravenous magnesium, nine out of 12 (75 %) subjects had a transient flush compared with one of 13 (7.7 %) subjects who had received placebo [RR (95 % CI) 0.05 (0.01–0.25)]. During the infusion and up to 90 min thereafter, arterial blood pressure, heart rate and oxygen saturation did not significantly change in either group.

DISCUSSION
In the present study, we tested in field conditions the efficacy of magnesium for the prevention and treatment of AMS. There were two main results: firstly, oral magnesium citrate did not prevent AMS; and secondly, in subjects with overt AMS, a single intravenous infusion of magnesium sulphate attenuated symptoms to some extent.

The rationale of our prevention trial was to start oral magnesium supplementation before the onset of AMS. It has been pointed out repeatedly in clinical studies on cerebral ischaemia that the inevitable time window between ischaemic lesion and commencement of the pharmacological intervention to prevent further neurological damage is a major problem [33,34]. Our hypothesis was that, with the onset of AMS, the permeability of the blood–brain barrier would increase [19,35]. Magnesium would then cross the barrier, act as an antagonist at the NMDA receptor and reduce calcium entry. However, oral magnesium supplementation had no impact on the development of AMS or any effect on headache.

There are several explanations for these negative findings. It may be that oral magnesium supplementation was insufficient to lead to an adequate increase of magnesium in the brain and, thus, to an effective modulation of
the NMDA receptor. Two explanations arise: the dosage of oral magnesium was too low (or alternatively the time of supplementation was too short) or the ingested magnesium did not reach the target tissue, i.e. the brain. We have chosen magnesium citrate, since it is well absorbed [36], and the dosage we were using was at least twice that used in studies demonstrating efficacy of oral magnesium in other settings [37–39]. However, urine magnesium excretion was significantly increased and a significant number of subjects had loose stools, suggesting the availability of whole body magnesium was indeed increased in the experimental group. It also indicates that it would be unrealistic to test an even higher dose of oral magnesium. The second issue concerns the transfer of magnesium across the blood–brain barrier. We did not measure cerebrospinal fluid magnesium concentrations before and after prophyllaxis. Thus we do not know if the absorbed magnesium eventually crossed the volunteers’ blood–brain barrier. Parenterally administered magnesium has been shown to cross the blood–brain barrier in conditions where the barrier was likely to be damaged, such as in parturients with pre-eclampsia or in patients undergoing brain surgery [40,41]. We assumed that this would also be the case in subjects suffering from AMS [35,42]. However, we do not know what magnesium blood concentration is needed to lead to an increased amount of magnesium in brain tissue. In addition, we do not know if this hypothetical magnesium blood concentration could be achieved with an oral magnesium substitution. At least some effect on headache would have been expected, since magnesium has been demonstrated to be efficacious in the treatment of headache in a randomized trial [37]. Also, magnesium and the NMDA receptor are thought to be involved in the modulation of pain [43].

The lack of efficacy of oral magnesium may be due to our specific study design. Both incidence and severity of AMS have been shown to be dependent on the rate of ascent, and the efficacy of drugs that are used to prevent AMS is directly related to this baseline risk [18]. Thus it is important to know the underlying risk. If the risk is low, prophylaxis will not have the scope to show improvement compared with no intervention. If the risk is extremely high, the efficacy of an only marginally beneficial prophylaxis may remain masked. In our present study, the average rate of ascent was approx. 140 m/h, suggesting a setting with a high underlying risk. Indeed, in the placebo group, only 13 % of the subjects were free of AMS throughout the study period according to our preset criteria (Lake Louise Score < 3). It cannot be ruled out, therefore, that there was some minimal beneficial effect of magnesium and that this effect was hidden by this high baseline risk.

Finally, the mechanisms underlying the development of AMS may be completely independent of the NMDA receptor and, thus, of magnesium. In animal models, it has been shown that the NMDA receptor was involved in the pathophysiology of hypobaric hypoxic convulsions [23]. In mice with hypoxic preconditioning, blockage of NMDA receptors had been shown to be beneficial [26]. Thus it would appear unlikely that the NMDA receptor does not play some role in the complex pathophysiology of AMS. In humans, however, there are no data on NMDA involvement in AMS, and the role of the NMDA receptor in AMS remains hypothetical. It is interesting to note in this context that magnesium has been shown to be efficacious in the treatment of eclampsia [10], despite a lack of a biological basis that would explain this beneficial effect.

The question remains as to why intravenous magnesium showed some efficacy in the treatment of AMS. A treatment success (fall in Lake Louise Score > 50 %) was found in three subjects in the magnesium group, but the difference between magnesium and placebo groups was not significant. A > 25 % decrease in the Lake Louise Score was found in nine subjects, seven in the magnesium group and two in the placebo group. This difference was on the borderline of being significant. With magnesium, the scores decreased significantly compared with the scores before treatment was started; however, this was not the case in the placebo group. Even though this degree of effectiveness was irrelevant from a clinical point of view, it suggests a potential role of magnesium in the pathophysiology of AMS. We have chosen the dose of intravenous magnesium (16 mmol) according to acute stroke studies [13,16]. Higher doses or a prolonged administration of magnesium (as in the treatment of pre-eclamptic women) [8] may have improved outcome further. The majority of the subjects reported a flush sensation during the intravenous infusion. Thus, although our study design was double-blind, it is possible that this typical magnesium-related adverse effect may have introduced some degree of observer bias and a placebo effect. On the other hand, the inclusion of 11 subjects that had received oral magnesium in the prevention trial (and in whom prevention failed) may have biased the treatment trial against a true treatment effect.

In conclusion, we found that oral magnesium citrate did not prevent AMS. In subjects with AMS, a single intravenous infusion of magnesium sulphate reduced symptoms to some extent, but this effect was not relevant from a clinical point of view. However, we do not know if treatment with higher doses of intravenous magnesium would have improved the outcome further. It remains possible that magnesium is involved in the pathophysiology of AMS.

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