Hypocalcaemia may reduce the beneficial effect of magnesium treatment in aneurysmal subarachnoid haemorrhage

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Abstract. To assess whether magnesium treatment in patients with subarachnoid haemorrhage (SAH) is associated with hypocalcaemia and whether hypocalcaemia in these patients is associated with an increased risk of delayed cerebral ischemia (DCI) and poor outcome. All 137 patients randomized in the clinically controlled “Magnesium in Aneurysmal Subarachnoid Haemorrhage” trial were included. The relationship between mean serum magnesium and mean serum calcium during treatment was assessed with linear regression. The relationship between hypocalcaemia (serum calcium < 2.0 mmol/L) during treatment and the occurrence of DCI and poor outcome was studied with the Cox proportional hazards method and logistic regression, respectively. There was a statistically significant inverse relation between elevated serum magnesium and mean serum calcium during treatment was assessed with linear regression. The relationship between hypocalcaemia (serum calcium < 2.0 mmol/L) during treatment and the occurrence of DCI and poor outcome was studied with the Cox proportional hazards method and logistic regression, respectively. There was a statistically significant inverse relation between elevated serum magnesium and hypocalcaemia (B = -0.27; 95% CI -0.33 to -0.20; p < 0.001). Patients with hypocalcaemia during study treatment had an increased frequency of DCI (HR 2.1; 95% CI, 1.0 to 4.3), and an increased risk for poor outcome (OR 2.9; 95% CI, 1.4 to 6.4), but this effect attenuated in the multivariable analysis (OR 1.9; 95% CI, 0.8 to 4.7). In conclusion, prolonged elevated serum magnesium is associated with hypocalcaemia. Hypocalcaemia is associated with an increased risk of DCI and poor outcome and may therefore reduce the potential beneficial effect of magnesium treatment in SAH.

Key words: magnesium, calcium, subarachnoid haemorrhage, brain ischemia

Subarachnoid haemorrhage (SAH) caused by rupture of an intracranial aneurysm has a poor prognosis. Approximately half the patients die and one third remain dependent on help for activities of daily life. Delayed cerebral ischemia (DCI) is the most important cause of poor outcome in patients who survive the initial period after the haemorrhage [1].

Magnesium is a neuroprotective agent with a well established clinical profile. Putative modes of action in subarachnoid haemorrhage are its calcium antagonistic properties and dilatation of intracranial arteries [2, 3]. In a recently conducted placebo controlled clinical trial, magnesium therapy reduced the occurrence of DCI by 34% (95% Confidence Interval (95% CI) 14 to 62) and of poor outcome by 23% (95% CI 9 to 46) [4]. In this trial, magnesium sulphate was given in a standard dosage of 64 mmol daily for 14 to 18 days. With this dosage, 85% of patients had serum magnesium levels between 1.0 and 2.0 mmol/L [5].
Magnesium treatment may not be without risk as hypermagnesaemia may lead to a decrease in serum calcium [6, 7]. Hypocalcaemia is associated with increased case fatality in critically ill patients admitted to the intensive care unit with a wide variety of diagnoses [8-10]. Thus, the beneficial effect of magnesium treatment may be offset by low calcium levels. In the current study we assessed whether extended magnesium therapy results in hypocalcaemia and if so, whether hypocalcaemia is related to DCI and subsequent poor outcome after SAH.

Patients and methods
We included all 137 patients with aneurysmal SAH who were randomized in our hospital from November 2000 until October 2004 for the multicentre “Magnesium in Aneurysmal Subarachnoid Haemorrhage” (MASH) trials. Since January 2004 fifty-two patients have been recruited from the phase III MASH-2 study (still ongoing and therefore not yet deblinded). The outcome raters of the MASH-2 study are masked for the magnesium concentrations. Patients were either treated with magnesium or placebo; magnesium was administrated in a daily intravenous dosage of 64 mmol, placebo consisted of 50 mL of normal saline. A loading dose was not used.

Serum magnesium and serum calcium were measured on admission and every other day up to a maximum of 21 days after SAH onset. Mean serum magnesium and calcium values during study treatment were calculated for each patient. To assess the course of serum magnesium and serum calcium during magnesium treatment we also calculated daily mean values for each day of treatment.

Hypermagnesaemia was defined as mean serum magnesium above 1.0 mmol/L during the study period. Although hypocalcaemia in our hospital is defined as serum calcium levels below 2.2 mmol/L, we defined hypocalcaemia as serum calcium levels below 2.0 mmol/L as 96% of the patients with SAH had a mean serum calcium level below 2.2 mmol/L.

The clinical condition on admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale [11]. A dichotomy was made between good neurological condition (WFNS scale I, II or III) and poor neurological condition (WFNS scale IV or V) on admission.

We assessed the amount of cisternal and ventricular blood on the initial CT scan according to the method described by Hijdra et al. [12]. The sum scores of blood in the cisterns (range, 0-12) and ventricles (range, 0-12) were dichotomised at their median value.

We quantified the size of the frontal horns by means of the bicaudate index (BCI). To calculate age-adjusted relative sizes, the BCIs were divided by the corresponding upper limit per age group [13]. Hydrocephalus was defined as an age-adjusted relative BCI greater than 1.

DCI was defined as the occurrence of a new spontaneous hypodense lesion as revealed by a CT scan compatible with clinical features of DCI (gradually developed focal deficits, decreased level of consciousness, or both). We assessed outcome 3 months after SAH in a telephone interview by means of the modified Rankin scale; poor outcome (death or dependence) was defined as a modified Rankin score of 4 or worse [14].

All patients were under continuous observation for at least 2 weeks of their hospitalization, and they were treated according to a standardized protocol that consisted of absolute bed rest until aneurysm treatment, oral nimodipine, cessation of antihypertensive medication, and intravenous administration of fluid with the aim of normovolemia.

Statistical analysis
The relationship between serum magnesium and serum calcium was assessed with linear regression analysis during study treatment only. The regression coefficient (B) has to be interpreted as the amount of change in serum calcium in mmol/L for an increase of serum magnesium with 1.0 mmol/L.

The relationship between hypocalcaemia during treatment and the occurrence of DCI was studied with the Cox proportional hazards model, which yields a crude hazard ratio (HR). In subsequent multivariable analysis we assessed the extent to which adjusted HRs differed from the crude HR.

The relationship between hypocalcaemia during treatment and poor outcome after 3 months was studied with the logistic regression model, yielding crude odds ratios (OR). In a subsequent multivariable analysis, we assessed the extent to which adjusted ORs differed from the crude OR.

Results
Baseline characteristics of the 137 included patients are shown in table 1. The median interval between SAH and start study treatment was 26 hours. Fifty-nine (43%) of the patients had mean serum calcium below 2.0 mmol/L during study treatment. This percentage was considerably higher (67%) in the
70 patients with hypermagnesaemia during study treatment. Figure 1 shows the course of the daily means for magnesium and calcium levels for this group of patients. The nadir of hypocalcaemia is reached after 4 days of treatment; thereafter calcium levels start to increase but remain below normal during the initial 8 days of treatment. Only after the 8th day of treatment are calcium levels in the normal range, despite continuation of the magnesium treatment.

There was a statistically significant relationship between mean serum magnesium and calcium concentrations during study treatment. An increase of serum magnesium with 1.0 mmol/L, led to a decrease

<table>
<thead>
<tr>
<th></th>
<th>Normocalcaemia (≥ 2.0 mmol/L)</th>
<th>Hypocalcaemia (&lt; 2.0 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (total 137)</strong></td>
<td>78</td>
<td>50</td>
</tr>
<tr>
<td><strong>Hypermagnesaemia (&gt; 1.0 mmol/L)</strong></td>
<td>23 (29 %)</td>
<td>47 (80 %)</td>
</tr>
<tr>
<td><strong>Mean age ± SD (years)</strong></td>
<td>55 ± 13</td>
<td>61 ± 15</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>50 (64 %)</td>
<td>38 (64 %)</td>
</tr>
<tr>
<td><strong>WFNS score IV-V</strong></td>
<td>15 (19 %)</td>
<td>12 (20 %)</td>
</tr>
<tr>
<td><strong>Cisternal blood sum score &gt; median (26)</strong></td>
<td>33 (42 %)</td>
<td>31 (53 %)</td>
</tr>
<tr>
<td><strong>Ventricular blood sum score &gt; median (1)</strong></td>
<td>23 (29 %)</td>
<td>25 (42 %)</td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
<td>24 (31 %)</td>
<td>25 (42 %)</td>
</tr>
<tr>
<td><strong>Delayed cerebral ischaemia</strong></td>
<td>13 (17 %)</td>
<td>19 (32 %)</td>
</tr>
<tr>
<td><strong>Poor outcome (Rankin ≥ 4)</strong></td>
<td>14 (18 %)</td>
<td>24 (41 %)</td>
</tr>
</tbody>
</table>

Figure 1. Daily means for serum magnesium and calcium levels in patients (n = 70) with hypermagnesaemia during study treatment.
of serum calcium with 0.27 mmol/L (B = -0.27; 95% CI, -0.33 to -0.20; p < 0.001) (figure 2).

Patients with hypocalcaemia had a statistically significant increase in the occurrence of DCI (34% versus 17%) compared with patients with normal calcium levels during study treatment (HR 2.1; 95% CI, 1.0 to 4.3). There was also an increased risk for poor outcome (42% versus 17%) in patients with hypocalcaemia (OR 2.9; 95% CI, 1.4 to 6.4), but this relationship was no longer statistically significant in the multivariable analysis (OR 1.9; 95% CI, 0.8 to 4.7). The results are summarized in table 2.

Discussion

The results of this study indicate that prolonged elevated serum magnesium during magnesium treatment leads to hypocalcaemia. Hypocalcaemia is in turn associated with a more than two-fold risk of DCI and an increased risk for poor outcome, although hypocalcaemia was not found to be an independent risk factor after multivariable analyses.

Ionized calcium levels are probably more accurate for assessing calcium homeostasis than total serum calcium levels, mainly because approximately 50% of all calcium is bound to proteins, mostly albumin [15-17]. Unfortunately we had insufficient data on ionized calcium and albumin to perform additional analyses.

We calculated mean serum calcium based on measurements during the entire treatment period. In patients with DCI, ischemia theoretically might have decreased serum calcium levels in which case our findings about the causal relationship between hypocalcaemia and DCI may not be correct. Additional analyses, however, showed that serum calcium did not decrease after the occurrence of DCI and results remained essentially the same when mean serum calcium levels until the occurrence of DCI were used.

Calcium is required for many intra- and extracellular processes, such as muscle contraction, including the vascular musculature, hormone release, nerve conduction, enzyme activation, blood coagulation and bone structure. In addition, calcium plays an
important role in the ischemic cascade and is a mediator of cell death [15, 18-21]. Important factors in maintaining calcium homeostasis include parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D), and magnesium [22].

Hypocalcaemia is very common in critically ill patients (60-90%) and associated with an increased case fatality. The reason why hypocalcaemia is related to DCI and poor outcome is uncertain. It may be an epiphenomenon of low vitamin D levels, elevated PTH levels in response to hypocalcaemia, or an increase in inflammatory cytokines. However, there may be a causal relation as hypocalcaemia could lead to impaired cardiovascular performance and subsequent hypotension, which may reduce cerebral perfusion [8-10, 23].

Since hypocalcaemia may be related to the occurrence of DCI and poor outcome, it might be worthwhile considering calcium supplementation in SAH patients on a regimen aiming for hypermagnesaemia. However, before supplementing calcium is implemented as a routine, the effects of supplementing should be studied carefully. Supplementing calcium might, for instance, reduce magnesium concentrations and thereby counteract the beneficial effect of magnesium treatment. Moreover, administration of intravenous calcium will lead to a greater availability of calcium and therefore may enhance the risk of an increase of intracellular calcium concentrations, which in turn may lead to cell death.

Finally, the evidence for the benefit of magnesium treatment in SAH still has to be confirmed in on-going phase III trials [24].

**Table 2. Relationship of hypocalcaemia to the occurrence of delayed cerebral ischemia and poor outcome.**

<table>
<thead>
<tr>
<th>Hypocalcaemia during treatment</th>
<th>Delayed cerebral ischaemia Hazard ratio (95% CI)</th>
<th>Poor outcome Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude</strong></td>
<td>2.1 (1.0 - 4.3)</td>
<td>2.9 (1.4 - 6.4)</td>
</tr>
<tr>
<td><strong>Adjusted for single variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>2.0 (1.0 - 4.2)</td>
<td>2.2 (0.9 - 4.9)</td>
</tr>
<tr>
<td>Gender</td>
<td>2.1 (1.0 - 4.3)</td>
<td>2.9 (1.4 - 6.4)</td>
</tr>
<tr>
<td>WFNS score IV-V</td>
<td>2.1 (1.0 - 4.2)</td>
<td>3.1 (1.4 - 7.0)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2.1 (1.0 - 4.2)</td>
<td>3.0 (1.3 - 6.6)</td>
</tr>
<tr>
<td>Cisternal blood</td>
<td>2.0 (1.0 - 4.1)</td>
<td>2.9 (1.3 - 6.3)</td>
</tr>
<tr>
<td>Ventricular blood</td>
<td>2.0 (1.0 - 4.1)</td>
<td>2.7 (1.2 - 5.8)</td>
</tr>
</tbody>
</table>

**Multivariable analysis**

- adjusted for age, WFNS score, and ventricular blood.
- *b because in bivariable analyses no influence of co-variables was found, multivariable analysis was not performed.

**Conclusion**

Magnesium treatment in subarachnoid hemorrhage may not be without risk as it leads to hypocalcaemia which is associated with delayed cerebral ischemia and poor outcome. Hypocalcaemia may therefore reduce the potential beneficial effect of magnesium treatment in subarachnoid hemorrhage.

**Acknowledgments**

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**References**


