PAPER

Achieved serum magnesium concentrations and occurrence of delayed cerebral ischaemia and poor outcome in aneurysmal subarachnoid haemorrhage

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Background: Magnesium therapy probably reduces the frequency of delayed cerebral ischaemia (DCI) in subarachnoid haemorrhage (SAH) but uncertainty remains about the optimal serum magnesium concentration. We assessed the relationship between serum magnesium concentrations achieved with magnesium sulphate therapy 64 mmol/day and the occurrence of DCI and poor outcome in patients with SAH.

Methods: Differences in magnesium concentrations between patients with and without DCI and with and without poor outcome were calculated. Quartiles of last serum magnesium concentrations before the onset of DCI, or before the median day of DCI in patients without DCI, were related to the occurrence of DCI and poor outcome at 3 months using logistic regression.

Results: Compared with the lowest quartile of serum magnesium concentration (1.10–1.28 mmol/l), the risk of DCI was decreased in each of the higher three quartiles (adjusted odds ratio (OR) in each quartile 0.2; lower 95% CI 0.0 to 0.1; upper limit 0.8 to 0.9). The OR for poor outcome was 1.8 (95% CI 0.5 to 6.9) in the second quartile, 1.0 (95% CI 0.2 to 4.5) in the third quartile and 4.9 (95% CI 1.2 to 19.7) in the highest quartile.

Discussion: Magnesium sulphate 64 mmol/day results in a stable risk reduction of DCI over a broad range of achieved serum magnesium concentrations, and strict titration of the dosage therefore does not seem necessary. However, concentrations $\leqslant$1.28 mmol/l could decrease the effect on DCI while concentrations $\geqslant$1.62 might have a negative effect on clinical outcome.

Aneurysmal subarachnoid haemorrhage (SAH) has a poor prognosis: half of patients die and one out of every five survivors remains dependent.[1] In patients who survive the initial hours after the haemorrhage and undergo early aneurysm treatment, delayed cerebral ischaemia (DCI) is the most important cause of poor outcome. DCI occurs in approximately one-third of patients and develops mostly between the fourth and tenth day after SAH.[2 3]

Magnesium is a neuroprotective agent with a well established clinical profile, and is commonly used in obstetric medicine.[4 5] Hypomagnesaemia occurs in more than half of patients with SAH and is related to the occurrence of DCI.[6] Recently, we conducted a randomised, placebo controlled phase II trial with magnesium sulphate in patients with SAH.[7] Magnesium therapy reduced the occurrence of DCI by 34% (95% CI −14 to 62) and of poor outcome by 23% (95% CI −9 to 46). In this trial, magnesium sulphate was given in a standard dose of 64 mmol/day. With this dosage, 85% of patients had serum magnesium levels between 1.0 and 2.0 mmol/l.[8] Whether there is an optimal serum magnesium concentration within this range is unclear.

In this study, we assessed whether there is a relationship between achieved serum magnesium levels and the occurrence of DCI and poor outcome in patients with aneurysmal SAH treated with continuous magnesium sulphate infusion at a fixed dose.

METHODS

Patients

Patients were recruited from the MASH-1 study[7] and the MASH-2 study[9] (still ongoing and therefore not yet unblinded). Patients included in the study were those admitted between November 2000 and November 2005 to the University Medical Centre, Utrecht, the Netherlands, and when their mean serum magnesium concentration during treatment was $\geqslant$1.10 mmol/l. In MASH-1, all patients in the placebo group had mean values below 1.10 mmol/l whereas 97% of patients in the magnesium group had a mean magnesium >1.10 mmol/l. The remaining 3% did not receive magnesium therapy, and were not included in the current study. Serum magnesium concentrations were measured at admission and every other day during the study. When serum magnesium concentrations were not known before the occurrence of DCI, the patient was excluded from the study. The outcome raters of the MASH-2 study are masked for magnesium concentrations.

All patients started magnesium therapy 64 mmol/day or placebo within 4 days after SAH and continued medication for 20 days after SAH, or until discharge if this occurred before day 20. All patients were treated according to a standardised protocol that consisted of absolute bed rest until aneurysm treatment, administration of nimodipine, cessation of antihypertensive medication and intravenous administration of fluids with the aim of achieving normovolaemia. We recorded age, sex, clinical condition at admission using the World Federation of Neurological Surgeons Score,[10] and amount of cisternal and ventricular blood on the initial CT scan, as assessed by the Hijdra Score.[11] The Hijdra Score has a better interobserver agreement than the Fisher Score and, in contrast with the Fisher Score, is an independent prognosticator for DCI and clinical outcome.[12] DCI was defined as the occurrence of clinical features of DCI (gradually developed focal deficits,

Abbreviations: DCI, delayed cerebral ischaemia; SAH, subarachnoid haemorrhage

Table 1 Baseline patient characteristics and serum magnesium concentrations

	DCI		Poor outcome	
	Yes	No	Yes	No
No (%)	27 (17)	128 (83)	41 (26)	114 (74)
Age (y) (mean (SD))	57 (18)	56 (13)	64 (15)	53 (13)
Women (%)	19 (70)	83 (65)	30 (73)	72 (63)
WFNS Score 4–5 (%)	11 (40)	22 (17)	17 (42)	16 (14)
Hijdra Score cisterns (median (SD))	26 (4)	25 (9)	24 (8)	24 (8)
Hijdra Score ventricles (median (SD))	1 (3)	0 (3)	0 (2)	0 (2)
Time of start of study medication after SAH (h) (mean (SD))	28 (18)	32 (24)	32 (20)	31 (24)
Mg during treatment (mmol/l) (mean (SD))	1.48 (0.41)	1.46 (0.30)	1.63 (0.41)	1.40 (0.26)
Latest Mg before DCI/before median day of DCI (mmol/l) (mean (SD))	1.44 (0.55)	1.54 (0.54)	1.82 (0.84)	1.41 (0.33)

DCI, delayed cerebral ischaemia; SAH, subarachnoid haemorrhage; WFNS, World Federation of Neurological Surgeons.

decreased level of consciousness or both) confirmed by new hypodense lesions on CT compatible with the clinical features.

Clinical outcome was assessed 3 months after SAH using the modified Rankin Score by a rater blinded for serum magnesium concentrations.[13] Poor outcome was defined as a Rankin Score of ⩾4.

Data analysis

Mean magnesium levels were calculated for each patient during the whole treatment period. In patients with DCI, the last magnesium concentration before the onset of DCI was recorded. To compare concentrations in patients with DCI with those in patients without DCI, we calculated the median day of onset of DCI. In patients without DCI, the last magnesium concentration before this day was recorded and used for comparison.

Mean differences in magnesium concentrations were calculated between patients with and without DCI, and between patients with and without a poor outcome, and its precision was described with 95% CIs based on the Student's t test.

The relationship between serum magnesium concentrations and the occurrence of DCI was studied by means of logistic regression. To accommodate a possible non-linear relationship, values for the last serum magnesium concentrations before the onset of DCI (and the concentration on the comparable day in patients without DCI) were divided into quartiles. Odds ratios (ORs) were calculated for each of the three highest quartiles in comparison with the lowest quartile. Results were adjusted for age, World Federation of Neurological Surgeons Score at admission and amount of blood on the initial CT scan, as these are known predictors of DCI and poor outcome. All factors were introduced as continuous variables.

RESULTS

During the study period, 359 patients were included in the MASH studies in the University Medical Centre, Utrecht, of whom 165 had mean magnesium concentrations ⩾1.10 mmol/l. Ten patients were excluded because no serum magnesium levels were known before the onset of DCI. Thus 155 patients were included in this study.

Baseline characteristics of the patients are shown in table 1. Twenty-seven patients (17%) developed DCI between day 1 and day 21 (median day 8). Poor outcome occurred in 41 patients (26%). There were no statistically significant differences in the timing of the start of the study drug after SAH between patients with and without DCI or poor outcome. There were minimal non-significant differences between mean serum magnesium concentrations during treatment or the last serum magnesium concentration before DCI onset, in patients with and without DCI. Compared with patients with a good outcome, patients with a poor outcome had a higher mean serum magnesium concentration during treatment (mean difference 0.22 (95% CI 0.09 to 0.36)) and a higher last serum magnesium concentration before the onset of (median day of) DCI (mean difference 0.42 (95% CI 0.14 to 0.69) (table 1).

Compared with the lowest quartile of the last magnesium before the (median day of) onset of DCI, the risk of DCI was equally low for all higher quartiles, with adjusted ORs of 0.2 (lower 95% CI 0.0 to 0.1; upper limit 0.8 to 0.9). The adjusted ORs for the occurrence of poor outcome tended to be increased for the second (OR 1.8; 95% CI 0.5 to 7.0) and fourth (OR 4.9; 95% CI 1.2 to 19.7) quartiles but not for the third quartile (OR 1.0; 95% CI 0.2 to 4.5) (table 2).

Table 2 Odds ratios for the last magnesium concentration before delayed cerebral ischaemia, and occurrence of delayed cerebral ischaemia and poor outcome

	No events/ No at risk	Crude OR (95% CI)	Adjusted* OR (95% CI)
DCI			
1st quartile (⩾1.10 ⩽1.28 mmol/l)	13/41	Reference	Reference
2nd quartile (>1.28, ⩽1.40 mmol/l	4/38	0.3 (0.1–0.9)	0.2 (0.1–0.8)
3rd quartile (>1.40, ⩽1.62 mmol/l)	4/38	0.3 (0.1–0.9)	0.2 (0.0–0.8)
4th quartile (>1.62 mmol/l)	6/38	0.4 (0.1–1.2)	0.2 (0.1– 0.9)
Poor outcome			
1st quartile (⩾1.10 ⩽1.28 mmol/l)	6/41	Reference	Reference
2nd quartile (>1.28, ⩽1.40 mmol/l)	8/38	1.6 (0.5–5.0)	1.8 (0.5–6.9)
3rd quartile (>1.40, ⩽1.62 mmol/l)	7/38	1.3 (0.4–4.3)	1.0 (0.2–4.5)
4th quartile (>1.62 mmol/l)	20/38	6.5 (2.2–18.9)	4.9 (1.2–19.7)

DCI, delayed cerebral ischaemia.
*Adjusted for age, clinical condition at admission and amount of blood on the initial CT scan.

DISCUSSION

This study shows that there is no linear relationship between serum magnesium levels and risk reduction for DCI in patients with hypermagnesaemia, achieved with magnesium sulphate therapy. Patients with serum magnesium concentrations above the 25th percentile at the last measurement before the (median day of) onset of DCI had equally reduced risks for DCI compared with the lowest quartile. In contrast, no such relationship was observed for poor outcome; risks tended to be higher in patients with magnesium concentrations above the 75th percentile.

In animal models of stroke, evidence was found of a dose–response effect, with optimal serum magnesium concentrations of approximately 1.50 mmol/l.[14 15] Most human studies tried to achieve this concentration as soon as possible after stroke onset with different magnesium dosing strategies.[16] However, an important difference is that magnesium therapy in ischaemic stroke is started only after the stroke, while in SAH, magnesium therapy can be initiated before the onset of DCI.

We do not have an adequate explanation for the discrepant findings for DCI and poor outcome. Side effects of magnesium sulphate therapy, such as flushing, headache and nausea, are usually mild and transient and occur mostly at serum magnesium concentrations above 2 mmol/l. Severe side effects are described with concentrations of >3.5 mmol/l, and include respiratory paralysis and cardiac conduction alterations.[17 18] In a dose evaluation study in 94 patients with SAH allocated to treatment with 64 mmol/day magnesium sulphate in the MASH-1 study, only 3% developed minor side effects and none developed severe side effects.[8] Thus these side effects do not explain the possible higher risk of poor outcome with higher magnesium concentrations.

An increased rate of rebleeding with higher magnesium levels may be a possible explanation, but this was not the case in our data set. In another study in the same study population, we found a relationship between hypermagnesaemia and hypocalcaemia (unpublished data). Hypocalcaemia was associated with an increased risk of poor outcome. However, hypocalcaemia is an unlikely explanation for the discrepant findings for DCI and poor outcome in patients with high magnesium concentrations because in that study hypocalcaemia was not only associated with an increased risk of poor outcome but also with an increased risk of DCI. The higher risk of poor outcome in patients in the highest quartile might be a chance finding.

In eclampsia, serum magnesium concentrations of 1.8–3.0 mmol/l have been advocated for prevention of eclamptic convulsions,[18 19] which is substantially higher than the concentration we obtained after magnesium therapy of 64 mmol/day in SAH patients. However, the optimal magnesium dose and plasma concentration to prevent or treat eclampsia have never been assessed.[19] One study that compared actual serum magnesium concentration with patient outcome did not find an association between treatment failure and magnesium concentration.[20] A potentially important difference is that patients with eclampsia receive magnesium therapy for a short period while magnesium therapy in SAH can be maintained for as long as 21 days.

In this study, we assessed only CT proven cerebral ischaemia and not vasospasm. Mild forms of ischaemia could have been missed using this approach but it is unlikely that this underestimation was related to magnesium concentrations and would thus affect risk estimates. Moreover, all data were collected prospectively, and assessment of DCI and clinical outcome were performed by observers blinded to treatment allocation and serum magnesium concentrations.

In conclusion, we found no linear relationship between serum magnesium concentrations and the occurrence of DCI. Magnesium sulphate 64 mmol/day resulted in stable risk reduction of DCI over a broad range of serum magnesium concentrations, and titration of the dose therefore does not seem necessary.

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