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Clinical Article

Magnesium therapy after aneurysmal subarachnoid haemorrhage a dose-finding study for long term treatment

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Summary

Background. Magnesium is a neuroprotective agent which might prevent or reverse delayed cerebral ischemia (DCI) after aneurysmal subarachnoid haemorrhage (SAH). Although the dosage for short-term magnesium therapy is well established, there is lack of knowledge on the dosage for extended use of magnesium. Our aim was to find a dosage schedule of magnesium sulphate to maintain a serum magnesium level of 1.0–2.0 mmol/L for 14 days to cover the period of DCI.

Methods. We prospectively studied 14 patients admitted within 48 hours after aneurysmal subarachnoid haemorrhage (SAH) to our hospital. Magnesium sulphate was administrated intravenously for 14 days, using 3 different dosage schedules. Group A ($n = 3$) received a bolus injection of 16 mmol magnesium sulphate followed by a continuous infusion of 16 mmol/dayly; group B ($n = 6$) a continuous infusion of 30 mmol/dayly; and group C ($n = 5$) a continuous infusion of 64 mmol/dayly. Serum magnesium was measured at least every two days and all patients were under continuous observation during magnesium treatment. Renal magnesium excretion was measured only in group C.

Findings. In treatment group A the mean serum magnesium level during treatment was 1.03 ± 0.14 (range 0.82–1.34) mmol/L, in group B 1.10 ± 0.15 (range 0.87–1.43) mmol/L, and in group C 1.38 ± 0.18 (range 1.11–1.98) mmol/L. The renal magnesium excretion in group C was equal to the administrated doses within 48 hours after treatment had started. All patients in group A reported a flushing sensation during the bolus injection; no other side effects were noted.

Interpretation. With a continuous intravenous dosage of 64 mmol/L per day, serum magnesium levels maintained within the range of 1.0–2.0 mmol/L for 14 days.

Keywords: Subarachnoid haemorrhage; magnesium; delayed cerebral ischemia; therapy.

Introduction

Delayed cerebral ischemia (DCI) occurs in approximately 30% of patients with subarachnoid haemorrhage (SAH) from rupture of an intracranial aneurysm and is an important cause of poor outcome [14]. Because DCI usually occurs 4 to 10 days after the haemorrhage [4], neuroprotective treatment can be started before the onset of ischemia, but must be administered for an extended period of time.

Magnesium is a neuroprotective agent that is readily available, inexpensive, and has a well-established clinical profile in obstetrical and cardiovascular practice [2, 7, 9, 10]. [2, 7, 10] Although dosage for short-term magnesium therapy is well established, there is lack of knowledge on the dosage for extended use of magnesium. *Because normal serum magnesium levels are between 0.7–1.0 mmol/L, and signs of hypermagnesaemia can occur from levels of 2.0 mmol/L onwards*, our aim was to find a dosage schedule of magnesium sulphate to maintain a serum magnesium level within the range of 1.0–2.0 mmol/L for 14 days to cover the onset period of delayed cerebral ischemia.

Patients and methods

We prospectively studied 14 patients admitted within 48 hours after aneurysmal subarachnoid haemorrhage (SAH) to the Academic Medical Centre Amsterdam and the University Medical Centre Utrecht. The diagnosis of SAH was made by the presence of extravasated blood in the basal cisterns on CT; the aneurysm was confirmed by conventional or CT-angiography. Exclusion criteria were renal failure (serum creatinin > 150 μmol/L), age below 18 y, no informed consent or imminent death. The clinical condition on admission was assessed by the World Federation of Neurological Surgeons (WFNS) scale, a 5 point scale based on the Glasgow Coma Scale and the presence or absence of focal deficits [1].

Table 1. *Patient data and outcome events*

Group	Sex	Age	WFNS	Loc	Treatm	Day	DCI	Rebleed	GOS	[mg]s	Range
A	F	46	2	ACA	clip	1	yes	no	4	.90	.82–1.18
A	M	52	2	ACA	clip	1	no	no	5	.71	.93–1.34
A	F	35	2	ACI	clip	1	no	no	4	.71	.97–1.20
B	F	73	3	MCA	coil	3	yes	yes	1	.84	1.21–1.28
B	F	39	4	BA	coil	3	no	yes	5	.81	.80–1.18
B	F	77	1	MCA	clip	9	yes	yes	4	.95	1.14–1.43
B	F	62	2	BA	coil	3	no	no	5	.65	.87–1.24
B	M	47	4	ACA	–	–	no	yes	1	.83	1.01–1.10
B	M	52	1	ACA	clip	10	no	no	5	.89	1.08–1.37
C	M	61	2	ACA	clip	17	no	no	4	.79	1.20–1.54
C	F	45	1	ACA	clip	3	no	no	5	.70	1.14–1.56
C	F	66	1	ACA	clip	3	no	no	5	.75	1.24–1.58
C	F	49	4	ACP	clip	9	no	yes	5	.81	1.11–1.76
C	M	67	1	ACA	clip	2	no	no	5	.86	1.21–1.98

ACA Anterior communicating artery; *MCA* middle cerebral artery; *BA* basilar artery, *PCA* posterior communicating artery; *DCI* delayed cerebral ischemia; [Mg]s, baseline serum magnesium in mmol/L; range, serum magnesium range during 14 days of magnesium therapy.

Magnesium sulphate was administrated intravenously for 14 days, started within 48 hours after SAH, using 3 different dosage schedules. Although infusion rates of 1–2 g/h are common in obstetrical practice, this dosage regime would most probably lead to side effects in the long term. Since long-term treatment with magnesium has not been described before, our first aim was to administer a reasonably safe dosage. Group A (n = 3) received a bolus injection of 16 mmol magnesium sulphate followed by a continuous infusion of 16 mmol/dayly, which is adapted from cardiology practice where magnesium is used in this dosage for treatment of torsade de points. Group B (n = 6) received a doubling of dosage regime A, but without the bolus injection, thus a continuous infusion of 30 mmol/dayly. Group C (n = 5) was given a continuous infusion of 64 mmol/dayly, which dosage regime was adapted from the IMAGES-trial [11] for acute stroke. Normal serum magnesium is between 0.7–1.0 mmol/L. The aim of the magnesium treatment was to obtain a serum magnesium level above 1.0 mmol/L but below 2.0 mmol/L. With serum magnesium levels above 2.0 mmol/L signs of hypermagnesemia like nausea, headache and muscle weakness can occur.

Serum magnesium was routinely measured at admission and at least every two days during the 14 days of magnesium therapy. In group C, urine magnesium was measured daily as well. During the 14 days of magnesium therapy special attention was given to detect possible side effects. All patients were kept under close observation for at least two weeks of their hospitalisation, with continuous monitoring of blood pressure, heart rate, ECG, and arterial oxygen saturation. Patients were treated according to a standardised protocol which consisted of absolute bedrest until treatment of the aneurysm, oral nimodipine, intravenous administration of fluid aiming at normovolemia, and refraining from antihypertensive medication.

We recorded side effects of magnesium, occurrence of DCI and rebleeding, and outcome according to the Glasgow Outcome Scale (GOS).

The difference between serum magnesium on admission and during treatment within one of the dose regimes was assessed by the independent-samples T test. Mean values are given with standard deviation. No data analyses were done on the outcome events or the differences in serum magnesium between groups.

Table 2. *Serum and urine magnesium (mean values)*

Group	Baseline $[Mg]_{serum}$ (mmol/L)	Treatment $[Mg]_{serum}$ (mmol/L)	Range (mmol/L)	$[Mg]_{urine}$ volume (mmol)
A	0.77	1.03 ± 0.14 (+34%)	0.82–1.34	
B	0.83	1.10 ± 0.15 (+56%)	0.87–1.43	
C	0.78	1.38 ± 0.18 (+77%)	1.11–1.98	63 ± 19

Results

Patient characteristics are shown in Table 1. Serum magnesium levels within the groups are shown in Table 2 and Fig. 1. In treatment group A the mean serum magnesium increased with 34% to 1.03 ± 0.14 mmol/L; in treatment group B with 56% to 1.10 ± 0.15 mmol/L; and in group C with 77% to 1.38 ± 0.18 mmol/L. The magnesium concentration ranged between 0.82–1.34 mmol/L in group A, between 0.87–1.43 mmol/L in group B, and between 1.11–1.98 mmol/L in group C.

In all patients in group A the level of serum magnesium peaked on day 1 (1.34 mmol/L), after which it slowly decreased to values below 1.0 mmol/L. In group B (maximum 1.43 mmol/L) as well as in group C (maximum 1.98 mmol/L), the maximum level was reached between day 1 and 5 (median day 3) after start of treatment. In group B, levels gradually decreased after day 5, and sometimes dropped below 1.0 mmol/L. In group C levels remained reasonably stable after

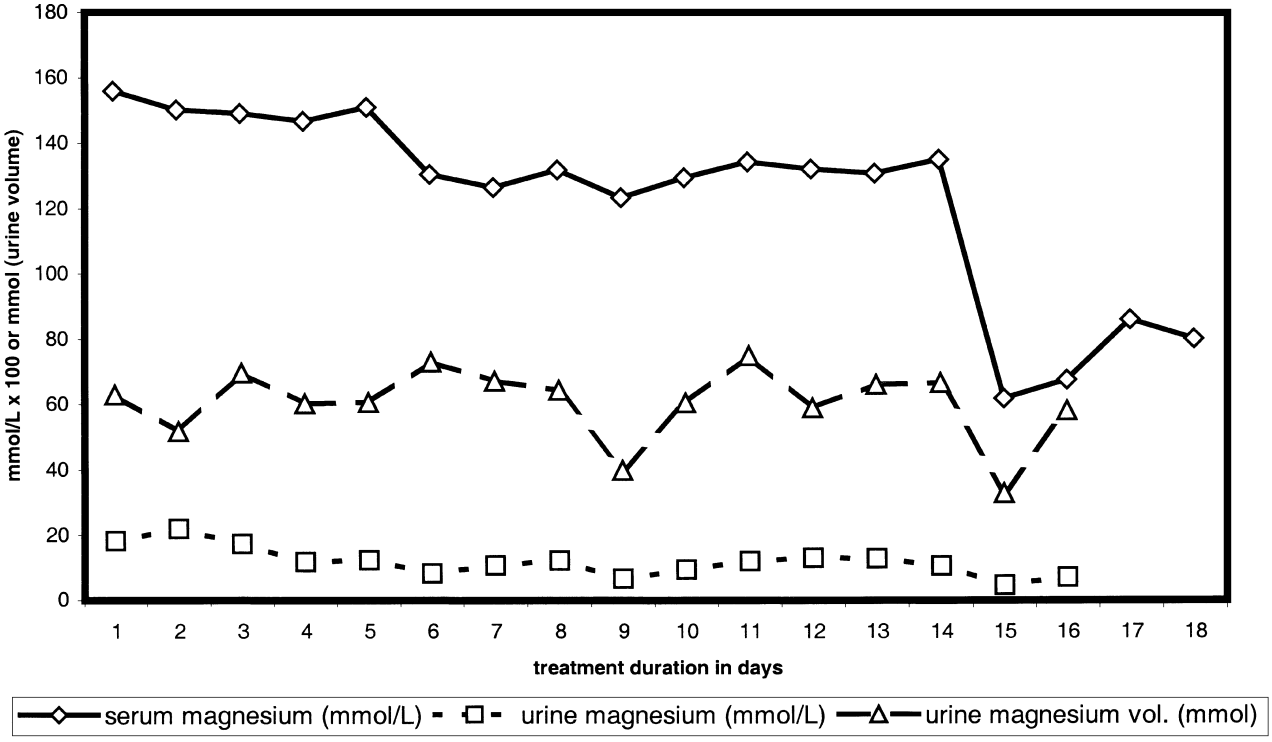

Fig. 1. Magnesium in urine and serum during 14 days of treatment with 64 mmol/d (mean values)

an initial decline and remained always above 1.0 mmol/L (Fig); the lowest value measured was 1.11 mmol/L, on day 8, the highest was 1.98 mmol/L, on day 5.

Urine magnesium levels were only measured in group C (Fig. 1). On the first day of urine sampling after starting magnesium treatment, the mean magnesium volume in the urine was 63 mmol/24 h, and thus approximately equals the treatment amount. The renal excretion of magnesium remained stable during the whole treatment period, with a mean of 63 ± 19 mmol/24 h and with a concentration of 13 ± 7.0 mmol/L (strongly depended on the fluid intake and any diuresis).

Outcome events

All patients in group A experienced a flushing sensation in their head and face immediately after the bolus injection, but without any changes in blood pressure. No other side effects were noted. In the other treatment groups also no side effects were noted.

Table one shows that three of the 14 patients developed delayed cerebral ischemia and five patients had a rebleeding. In three patients rebleeding had occurred before the start of the magnesium treatment. Two patients eventually died from rebleeding or a combination of rebleeding and DCI. One patient had a poor outcome three months after the haemorrhage. In treatment group C, none of the patients had DCI, one patient had a rebleeding during magnesium treatment and all patients achieved a favourable outcome after 3 months.

Discussion

Our aim of maintaining a serum magnesium level between 1.0 and 2.0 mmol/L for 14 days was achieved only with a dosage of 64 mmol magnesium sulphate per day using continuous infusion. In a series of patients with subarachnoid haemorrhage but no magnesium supplementation, serum magnesium levels were low and in more than half the patients even below the lower limit for normal at some point in the initial two weeks after the haemorrhage [15]. The increased concentrations of magnesium found in this study are therefore an effect of the magnesium therapy.

The increased concentration with 64 mmol/dayly supplementation was maintained despite the rapid increase of the renal magnesium excretion, which

reached values equal to the administered dosage within 48 hours after treatment. Although we did not measure renal excretion in the other treatment groups, this increased excretion of magnesium might well be the cause of the failure to maintain adequate levels in those groups; if this is true, dosages higher than 64 mmol/dayly may lead to concentrations above 2.0 mmol/L and should therefore not be given. Because the effect of 64 mmol/dayly was homogeneous in our group of 5 patients, we did not expand this group. Nevertheless, we advise paying close attention to signs of hypermagnesaemia or to serum-magnesium concentration if this dosage is used in clinical practice.

Magnesium administration is the first line strategy in eclampsia. In eclampsia the dosage is a bolus infusion of 16 mmol followed by a continuous administration of 4–8 mmol/hour, which aims at a serum magnesium value between 2.0–4.0 mmol/L, but magnesium administration is continued for only 48 hours. Because of the increased risk of overdosing and inherent side effects, serum magnesium levels need close monitoring with such a dose regime. Close monitoring and possible dose-adjusting, make the strategy less feasible, and impractical for a double-blind randomised placebo-controlled trial. Studies on magnesium-sulphate in subarachnoid haemorrhage are scarce and we do not know of other dose-escalating studies for fixed dose supplementation. Two studies adjusted dosages to reach and maintain pre-specified levels. A first study aimed at serum magnesium levels between 2.0 and 2.5 mmol/L or at doubling of the baseline serum magnesium level. This goal was reached in 8 out of 10 patients with a initial bolus infusion of 20 mmol magnesium sulphate followed by a mean infusion rate of 84.7 mmol/d and frequent dose adjustments [3]. In another study, with the aim to maintain serum magnesium levels between 1.6 and 2.3 mmol/L, an initial bolus of 24 mmol magnesium sulphate followed by an initial continuous infusion of 8 mmol/h with frequent dosage adjustments was used resulted in a mean serum magnesium level of 1.9 mmol/L, using a mean dosage schedule of 6 ± 1.88 mmol/h (144 mmol/d) [16]. In the only report on magnesium sulphate as a fixed continuous infusion, a dose of 48 mmol/d in 10 patients with aneurysmal subarachnoid haemorrhage was used, which resulted in a serum magnesium level of 1.2 mmol/L [8]. These results confirm our finding that levels above normal can be maintained for longer periods with fixed dosages of intravenous magnesium-sulphate.

A strategy without a bolus injection obviates the risk of side effects from a bolus injection. During bolus injection, a flushing sensation is often felt, as in all our patients who were given a bolus injection. Also, when a bolus injection is given in seconds, a potentially fatal neuromuscular blockade can occur. Apart from effects from rapid infusion, side effects of magnesium are rare but do exist. Nausea and headache can occur with serum magnesium levels as low as 1.8 mmol/L, but mostly occur in the 2.0–2.5 mmol/L range. Other, more serious side effects occur only at levels higher than 2.0 mmol/L. Bradycardia and hypotension can occur with serum magnesium levels between 2.2–3.1. Bradypnea with oxygen saturation below 85% can occur in serum magnesium levels of 3.1 mmol/L [5]. Magnesium can prolong the effect of muscle relaxants used during anaesthesia, but this did not lead to any complication during or after surgery in our study [6].

In two patients rebleeding occurred after magnesium treatment had started, one in group B and one in group C. This is not higher than expected, but given the reports on the platelet inhibiting effect of magnesium [12, 13], close surveillance of the proportion of patients with rebleeding or postoperative haemorrhage is needed in future studies on magnesium therapy after subarachnoid haemorrhage.

Conclusion

Serum magnesium levels of 1.0–2.0 mmol/L can easily be maintained using a dosage schedule of 64 mmol a day without any side effects. This study was not designed for assessment of the effects of magnesium administration on the development of DCI or on final outcome. To assess the efficacy of magnesium therapy, large randomised clinical trials are needed. We are presently running a randomised, placebo-controlled, double-blind trial which studies the effect of magnesium on the occurrence of delayed cerebral ischemia after subarachnoid haemorrhage using a dose of 64 mmol magnesium sulphate (or saline as a placebo) a day.

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Comment

The article concerns the use of magnesium therapy in patients with subarachnoidal haemorrhage (SAH). Its aim, however, is not to evaluate the actual effectiveness of this therapy modality in preventing delayed cerebral ischemia (DCI). Instead, it aims at establishing an ideal doage to keep serum magnesium levels between 1.0 and 2.0 mnol/l. Taking this objective into consideration, we can consider that the study achieved its purpose.

Ideally, a dosage finding study should be based on clinical effectiveness and side effects, rather than on a theoretical ideal serum level. The ideal dose would be the one in which maximum therapeutical effect is achieved with minimal side effects. If an effective and non-toxic dose (with a respective serum level) is found, then it can be taken as a true treatment parameter.

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