Dose Optimization of Intravenous Magnesium Sulfate After Acute Stroke
Keith W. Muir, MD, MRCP; Kennedy R. Lees, MD, FRCP

Background and Purpose—Parenterally administered MgSO₄ is neuroprotective in standard animal models of focal cerebral ischemia and in many other paradigms of brain injury. Previous small clinical trials in stroke patients have explored the safety and tolerability of different infusion regimens. This study was undertaken to optimize the regimen for a multicenter trial.

Methods—Within 24 hours of the onset of clinically diagnosed stroke, patients were randomized to receive placebo or one of three intravenous MgSO₄ infusions: a loading infusion of 8, 12, or 16 mmol, followed by 65 mmol over 24 hours. Cardiovascular parameters, serum magnesium concentrations, and blood glucose concentrations were determined. Outcome at 30 and 90 days was recorded.

Results—Twenty-five patients were recruited and treated at a mean time of 20 hours after stroke. No tolerability problems were identified. No effects of magnesium on heart rate, blood pressure, or blood glucose were evident. Serum magnesium concentrations rose to target levels most rapidly in the highest loading infusion group and were maintained in all groups for at least 24 hours.

Conclusions—MgSO₄ infusions that rapidly elevate the serum magnesium concentration to potentially therapeutic levels are well tolerated and have no major hemodynamic effects in patients with acute stroke. The 16-mmol loading infusion achieved target serum concentrations most rapidly and has been chosen for further trials. (Stroke. 1998;29:918-923.)

Key Words: clinical trials □ randomized controlled trials □ neuroprotection □ magnesium

Magnesium is neuroprotective in many preclinical models of ischemic and excitotoxic brain injury.¹–⁵ Unlike the great majority of other neuroprotective agents, there is extensive clinical experience with magnesium, largely in preeclampsia/eclampsia and MI, which confirm its safety and tolerability. There are a number of possible mechanisms by which magnesium may act, including increased regional cerebral blood flow to ischemic brain areas,⁶ nonspecific antagonism of all subtypes of voltage-sensitive calcium channel,⁷ noncompetitive blockade of the NMDA subclass of glutamate receptor,⁸–¹⁴ glutamate release inhibition,¹⁵–¹⁷ enhanced recovery of cellular energy metabolism after ischemia,¹⁸,¹⁹ and enhanced mitochondrial calcium buffering.²⁰

Previous small clinical trials of MgSO₄ in acute stroke have been undertaken,¹²,²² without evidence of undesirable neurological or cardiovascular effects. A large, multicenter international trial of MgSO₄ is now underway. Previous studies have used dosing schedules based on trials in acute MI or have aimed empirically to elevate serum magnesium concentration to double that of the physiological level. Serum concentrations of 1.49 mmol/L and above have been neuroprotective in preclinical models of focal cerebral ischemia, and the doubling of serum concentrations is known to be efficacious in the prophylaxis and treatment of seizures in preeclamptic and eclamptic women and is therefore a reasonable goal for optimization of dosing in the absence of any useful clinical markers in small pilot trials.

Because doubling of the serum magnesium concentration was achieved only after 24 hours of infusion in a previous pilot trial,²¹ this study was undertaken to optimize the intravenous infusion regime for further trials. This study therefore compared three different loading infusions (given over 15 minutes) with identical maintenance infusions against placebo. The primary end point was the doubling of the serum magnesium concentration after the loading infusion.

Subjects and Methods
The study was approved by the local hospital ethics committee. Written informed consent was obtained from all patients or from their next of kin. The study was a randomized, double-blind, placebo-controlled, parallel group study. All infusions were prepared by the study pharmacist in the hospital sterile pharmacy unit. Patients were randomized to three regimens of MgSO₄ or identical volumes of placebo (normal saline). The three regimens were loading infusions of 8, 12, or 16 mmol MgSO₄ in 100 mL normal saline given over 15 minutes, with all bolus infusions followed by 65 mmol MgSO₄ in 100 mL normal saline over 24 hours. Randomization of 6 subjects per group was planned.

All patients presenting within 24 hours of a clinically diagnosed acute stroke were eligible. Pregnancy, coma, or known renal failure (serum creatinine concentration of >200 µmol/L) were exclusions. All patients were examined neurologically at baseline, and their stroke type was classified according to Oxfordshire Community Stroke Project criteria.²³ Functional outcome was assessed by the Barthel activities of daily living score²⁴ and the modified Rankin index²⁵,²⁶ of disability on days 30 and 90 after stroke.

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Blood pressure and heart rate were performed semiautomatically by oscillometric recorders (Marquette). Blood was withdrawn from indwelling venous cannulas for serum magnesium concentrations at baseline; after the end of the bolus infusion (15 minutes); and at 12, 24, and 48 hours from the start of the maintenance infusion. The primary end point of the study was serum magnesium concentration, with the goal being elevation to double baseline levels by the end of the loading infusion.

Cardiovascular data, serum magnesium concentrations, and blood glucose were compared by repeated-measures ANOVA with Scheffé multiple pairwise comparisons. Baseline data were compared by 1-way ANOVA for parametric variables and \( \chi^2 \) tests for proportions. Outcome assessment was compared by the Kruskal-Wallis test and by \( \chi^2 \) tests (Statistica software, Statsoft Inc).

Results

A total of 25 subjects were recruited. All completed the study protocol. Numbers and demographic characteristics are detailed in Table 1. The overall median time-to-treatment was 19.25 hours. The cause of stroke demonstrated on CT scan was cerebral infarction in 21 subjects and primary intracerebral hemorrhage in 2; in 1 case (clinically posterior circulation stroke) the CT scan was normal.

There were no differences in systolic (\( P = 0.86 \)), diastolic (\( P = 0.70 \)), or mean arterial pressure (\( P = 0.92 \)) between any groups (Figure 1). A trend for lower blood pressure in the highest dosage group at the end of the bolus infusion was not significant. Heart rate similarly did not differ between groups (Figure 2; \( P = 0.68 \)). Hypotension that was sufficiently pronounced to be recorded by the investigators as a medical event (although asymptomatic) was reported in 1 subject who received placebo (Table 2).

Serum magnesium concentration (Figure 3) was not significantly different between groups at baseline, but it was significantly elevated by both bolus and maintenance infusions (\( P < 0.0001 \)). Multiple between-groups comparisons showed no significant elevation of magnesium concentration by the lowest dosage group (8+65 mmol) until 24 hours after initiation of infusion. Both the 12+65-mmol and 16+65-mmol groups caused significant increase in serum magnesium concentration from 15 minutes to 24 hours after the start of infusion. Serum concentrations in all groups were not significantly different from

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<th>TABLE 1. Demography and Stroke Characteristics of Treatment Groups</th>
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OCSP indicates Oxford Community Stroke Project; TACS, total anterior circulation stroke; PACS, partial anterior circulation stroke; POCs, posterior circulation stroke; and LACS, lacunar stroke.

Analysis by 1-way ANOVA* and Kruskal-Wallis ANOVA by ranks†; all other analyses by \( \chi^2 \) test.
placebo by 48 hours. Serum magnesium $>190\%$ of baseline was achieved by 15 minutes in none of the patients in the placebo and 8-mmol groups, 3 in the 12-mmol group, and 5 of 6 in the 16-mmol group. Serum concentrations of at least the minimum reported in the literature to be neuroprotective in preclinical studies ($1.49 \text{ mmol/L}$) were achieved during the course of the infusion in no placebo patients, 5 of 6 patients in the 8-mmol group, 4 of 6 in the 12-mmol group, and all patients in the 16-mmol group.

Baseline blood glucose concentrations and those obtained 24 to 36 hours later did not differ among groups (Figure 4). No dose related effect was found ($P=0.90$, ANOVA). The higher blood glucose in the highest dosage group was attributable to 1 diabetic individual with elevated baseline glucose (15 mmol/L) that rose further during treatment. When data for this individual were excluded, no differences between groups could be found.

No significant differences in outcome were found, regardless of the method of assessment (Table 3; Figures 5 and 6).

**Discussion**

Significant neuroprotective effects of parenteral magnesium salts have been shown in several animal models of cerebral ischemia, including permanent MCAO in the rat, global ischemia by four-vessel occlusion in the rat, direct intrastriatal NMDA injection, and focal fluid percussion injury. There are several potential mechanisms of neuroprotection, which include noncompetitive NMDA receptor blockade, enhanced regional cerebral blood flow to areas of focal ischemia, antagonism of voltage-gated calcium ion channels, and more favorable recovery of cellular energy metabolism after restoration of perfusion. In addition, magnesium infusions have improved neurological recovery after MCAO; have been neuroprotective in spinal cord ischemia and isolated white matter anoxia; and have shown potent anticonstrictor effects against relevant mediators, including endothelin-1, angiotensin II, prostaglandin F$_2$ alpha, and excitatory amino acids. Systemic infusion of magnesium reversed basilar artery vasoconstriction in a rat model of subarachnoid hemorrhage.

Although in several animal studies the doses of magnesium have been sufficiently large to produce profound blockade of neuromuscular junctions causing apnea, in many studies the concentrations known to be achievable in humans have resulted in significant pharmacological effects. Anticonstrictor effects were seen at plasma concentrations of 2.4 to 2.7 mmol/L, restoration of cerebral blood flow after permanent MCAO to baseline levels with concentrations of 3.21 mmol/L, and reduction of histological infarct volume in an intraluminal suture MCAO plus reperfusion model was seen with plasma levels of 1.49 mmol/L. Brain and cerebrospinal fluid magnesium concentrations are raised significantly after intravenous administration, especially when the blood-brain barrier is compromised by ischemia.
MgSO₄ has been used extensively in clinical trials in MI and also in preeclampsia/eclampsia. The safety, tolerability, and familiarity of magnesium in therapeutic settings offer considerable advantages over many drugs presently in development.

Support for the rationale of doubling serum magnesium concentration for therapeutic effects in humans is derived from the use of MgSO₄ for seizure prevention in preeclampsia and eclampsia. 37,38 Previously empirical use of magnesium salts as both prophylaxis and treatment of eclamptic seizures has now been supported by two randomized, controlled trials that found MgSO₄ to be superior to both diazepam and phenytoin for control of established eclamptic seizures 37 and more effective than phenytoin as seizure prophylaxis in preeclampsia. 38 In preeclampsia, intravenously administered magnesium sulfate increases cerebrospinal fluid magnesium concentration significantly. 39 Transcranial Doppler studies show flow velocity changes consistent with vasodilatation of the maternal and maternal/fetal circulations 40,41 in pregnancy-induced hypertension and preeclampsia. The doses of MgSO₄ typically given are from 5 to 6 g acutely (approximately 20 to 24 mmol). When reported, serum magnesium concentration after such doses has been approximately 2 to 3 times the physiological (eg, 2.28 mmol/L). 39

LIMIT-2 42,43 used a regimen of 8 mmol MgSO₄ over 5 minutes followed by 65 mmol over 24 hours. Mean serum magnesium concentration after maintenance infusion in LIMIT-2 was 1.55 mmol/L; in a previous trial in acute stroke using an identical regimen, the maximum concentration was 1.38 mmol/L after 24 hours. Again, in the current study, the 8-mmol bolus did not significantly raise serum magnesium concentrations until 24 hours after the start of infusion. Both of the other regimens successfully raised the serum concentration, neither with any significant systemic hemodynamic effects detectable within the limitations of the study design: the 16-mmol bolus doubled the serum concentration within 15 minutes (to a mean of 1.67 mmol/L, rising to a mean of 1.91 mmol/L after 24 hours) and appears therefore to be optimal for further trials. All patients in this group had serum levels above the minimum reported neuroprotective concentration in the literature, and 5 of 6 had doubled serum concentrations within 15 minutes. This dosage closely matches that used in Swedish studies, 22 in which 15 mmol infused over 20 minutes followed by 4 mmol/h for up to 5 days produced serum concentrations of 1.5 to 2.5 mmol/L with no significant hemodynamic effects.

Adverse events are uncommon with magnesium infusion regimens. The largest single demonstration of safety and tolerability was ISIS-4, 44 in which 29 011 patients with acute MI received MgSO₄ intravenously as 8 mmol over 15 minutes followed by 72 mmol over 24 hours. The incidence of both flushing and bradycardia was significantly greater than among control patients, but in both instances was less than 1%; a slight excess of significant hypotension, cardiac failure, and cardiogenic shock was also reported (excess risk between 3 and 12 per 1000 patients, depending on side effect). The ISIS-4 trial was an open, factorial design, and thus there is the possibility of reporting bias for adverse events previously associated with magnesium in the treatment arm; furthermore, a significant proportion of patients given magnesium also received streptokinase, captopril, or oral nitrates, all capable of of exaggerating the tendency to hypotension. Although in our study few cardiovascular recordings were

![Figure 4. Blood glucose concentrations by group before (Pre Infusion) and after (Post Infusion) treatment period (P<0.90 by ANOVA).](http://stroke.ahajournals.org/)
undertaken, the time points included the those of peak magnesium concentration (end of loading and maintenance doses), when maximum hemodynamic effect may be anticipated. The long time window (24 hours) in this study may disguise an effect on cardiovascular parameters that occurs only in the more acute phase of stroke; while this cannot be excluded, the absence of major excess risk of hypotension in ISIS-4, LIMIT-2, or trials in preeclampsia, in which patients are likely to be at greater risk than acute stroke patients of cardiovascular lability, is of some reassurance. Nevertheless, cardiovascular effects of magnesium infusion in acute stroke cannot be excluded by this study.

The therapeutic index of magnesium in pregnancy appears to be large (probably much more so than for other neuroprotective drugs). Serum concentrations of 4 to 6 mmol/L are necessary before symptomatic inhibition of neuromuscular transmission (clinically manifested as loss of deep tendon reflexes) is encountered, although caution is necessary in patients with renal impairment whose magnesium excretion may be diminished.

Some investigators have found neuroprotective effects in rodent models of cerebral ischemia to be counteracted by a hyperglycemic effect of magnesium.45,46 This appears to result from impaired endogenous insulin release from pancreatic islet cells, and it has been seen especially in rat models involving intraperitoneal administration of magnesium chloride. When normoglycemia has been maintained by insulin infusion, magnesium demonstrates significant neuroprotective effects in standard paradigms of cerebral ischemia.4 It has been proposed that the hyperglycemic effects may not be seen with all magnesium salts,1 because different vascular effects are seen with chloride and sulfate salts.47 No evidence of hyperglycemia has been found in human studies to date. Blood glucose levels were unchanged after magnesium infusions in a previous study21 and were similarly unaffected in this trial. No reports of hyperglycemia resulting from magnesium have come from ISIS-4 or other large trials in other indications.

This study was not powered to detect differences in clinical outcome, and efficacy cannot be inferred from the results. Despite the small numbers, however, there was a trend toward favorable outcome in magnesium-treated patients. This is consistent with previous observations.21 This study confirms that rapid elevation of serum magnesium concentration to double the physiological level is well tolerated by patients with acute stroke and that undesirable cardiovascular or biochemical effects are unlikely with such a regimen.

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