

REVIEW

Magnesium in stroke treatment

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Magnesium is involved in multiple physiological processes that may be relevant to cerebral ischaemia, including antagonism of glutamate release, NMDA receptor blockade, calcium channel antagonism, and maintenance of cerebral blood flow. Systemically administered magnesium at doses that double physiological serum concentration significantly reduces infarct volume in animal models of stroke, with a window of up to six hours after onset and favourable dose-response characteristics when compared with previously tested neuroprotective agents. Small clinical trials have reported benefit, but results are not statistically significant in systematic review. A large ongoing trial (IMAGES) will report in 2003-4 and further trials are planned.

For 15 years, neuroprotective agents have promised to add to the limited therapeutic armamentarium for acute ischaemic stroke, but have as yet delivered nothing. Despite major reductions in infarct volume in animal models of focal cerebral ischaemia by drugs that embrace a multitude of mechanisms of action, a succession of clinical trials in acute stroke have failed to translate histological animal effects into clinical improvement.¹ The bones of abandoned drug development programmes have been thoroughly picked over in a bid to find reasons for these failures, and a mixture of inadequate animal data, poorly established pharmacokinetics, dose limiting tolerability problems, and overoptimistic trial design have variously been proposed as culpable.²⁻⁴ Magnesium sulphate is currently undergoing clinical trials in acute stroke: will this be the compound to break the mould and finally confirm the neuroprotection hypothesis?

GENERAL PROPERTIES OF MAGNESIUM

Magnesium ions have a physiological role in multiple processes pertinent to ischaemia. In the brain, magnesium is predominantly complexed with adenosine triphosphate (ATP), and is an important cofactor in cellular energy metabolism and protein synthesis.⁵ Brain magnesium concentrations are regulated by active blood-brain barrier transport that maintains cerebrospinal fluid concentrations higher than those in serum (typically 1.1 mmol/l compared to 0.8 mmol/l).⁶ Cerebrospinal fluid magnesium concentration increases by 20%–25% after typical intravenous or intramuscular treatment regimens both in animals and in humans, and peaks around four

hours after parenteral administration.⁷⁻⁸ Magnesium concentration is selectively increased in regions of pathology in animals, including focal ischaemia⁹ and seizures.⁷ Intracellular free magnesium concentrations increase in ischaemic stroke, presumably largely through dissociation from ATP.¹⁰

Magnesium generally antagonises calcium in biological systems,¹¹ for example relaxing vascular smooth muscle and inhibiting calcium mediated activation of intracellular enzymes. Therapeutic uses of magnesium principally include obstetric use to prevent seizures in pre-eclampsia/eclampsia,¹²⁻¹³ and use in cardiology to prevent dysrhythmias. Wider cardiological application as a possible cytoprotective agent in acute myocardial infarction was suggested by meta-analysis¹⁴ and a moderate sized trial,¹⁵ but seemingly refuted in a very large open study, the fourth international study of infarct survival (ISIS-4).¹⁶ The possible failure of ISIS-4 to test magnesium in a biologically relevant manner has led to continued debate and further trials in myocardial infarction.¹⁷⁻¹⁸

Magnesium is an attractive therapeutic agent: it is inexpensive, widely available, and intravenous or intramuscular administration yields predictable serum concentrations. Therapeutic effects are observed in pre-eclampsia at serum concentrations 2–3 times physiological (1.6–2.4 mmol/l).¹⁹ Magnesium is normally excreted by the kidneys with a half life of four hours or less, and adverse effects generally arise only in patients with significant renal impairment or in situations of iatrogenic overdose. Overdose can be detected clinically by loss of deep tendon reflexes (occurring at concentrations of 3.5 mmol/l and greater), and administration of calcium gluconate generally avoids significant problems. In rare cases, where serum concentrations are 5 mmol/l or greater, more profound neuromuscular block may necessitate temporary ventilatory support.²⁰ Since conduction is slowed throughout the heart, symptomatic bradyarrhythmias may arise in individuals with heart block, but if used correctly, the risk of this even in patients with acute myocardial infarction in ISIS-4 was only 0.3%. The reasonably wide therapeutic index for mag-

nesium contrasts with many synthetic neuroprotective agents which have been associated with

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Abbreviations: ATP, adenosine triphosphate; FAST-MAG, Field Administration of Stroke Treatment-Magnesium (trial); IMAGES, Intravenous Magnesium Efficacy in Stroke (trial); ISIS-4, fourth international study of infarct survival; MRI, magnetic resonance imaging; NMDA, N-methyl D-aspartate; rtPA, recombinant tissue plasminogen activator

Table 1 Animal models of focal cerebral ischaemia and magnesium treatment

Study	Year	Model	Magnesium regimen	Infarct volume
Izumi et al ³⁶	1991	Permanent MCAO in Fischer-344 rats	1 mmol/kg before and 1 hour after ischaemia intraperitoneal MgCl ₂	–26% (–44% if euglycaemia maintained with insulin)
Sjostrom and Wester ⁹	1995	Wistar rats	2 mmol/kg IV MgCl ₂	Not reported
Marinov et al ³⁴	1996	Reversible MCAO for 1.5 or 2 hours in Sprague-Dawley rats	30 or 90 mg/kg intra-arterial MgSO ₄	–60%
Schmid-Elsaesser et al ³⁷	1999	Transient MCAO for 1.5 hours in Sprague-Dawley rats	1 mmol/kg MgCl ₂ pretreatment and at reperfusion	–25% (significant cortical infarct volume reduction but non-significant total infarct volume reduction)
Yang et al ⁵⁵	2000	Thromboembolic MCAO in rats	90 mg/kg IV MgSO ₄ 2, 6, or 8 hours after onset of ischaemia	–61%

IV, intravenous; MCAO, middle cerebral artery occlusion; MgCl₂, magnesium chloride; MgSO₄, magnesium sulphate.

major central nervous system side effects including psychotomimetic potential, sedation and hallucinations, as well as dose limiting cardiovascular effects.^{21–22} However, since magnesium is, in practice, likely to be prepared by local pharmacies, care must be taken over the chemistry. Confusion has arisen from magnesium dosing by weight rather than using SI units, since magnesium sulphate exists either as a heptahydrated or anhydrous salt, with molecular weights of 246 and 120 respectively, and there is therefore a risk that double or half of the intended dose may be prepared.²³

POTENTIAL MECHANISMS OF ACTION

There are numerous possible modes of action for magnesium in protecting neurones and glia from ischaemic damage. Reduction of cerebral infarct volume by magnesium may be consequent to effects on cerebral blood flow, or primarily neuronal actions, or more probably through a combination of these effects.

After middle cerebral artery occlusion, a core region where blood flow falls below around 10 ml/100 g/min (corresponding to the end arterial middle cerebral artery supply) rapidly necroses. The surrounding region of ischaemia, where collateral flow supports blood flows of 10–20 ml/100 g/min is known as the ischaemic penumbra.^{24–25} The metabolic and neurochemical consequences of ischaemia set in chain a complex range of processes that, unless interrupted by reperfusion or (at least experimentally) by neuroprotective drugs, will result in the death of the penumbra. These processes include excessive release of neurotransmitters, particularly glutamate, excessive activation of post-synaptic glutamate receptors (including the *N*-methyl *D*-aspartate (NMDA) receptor), excessive sodium and calcium ion entry to cells via ligand and voltage gated channels, and activation of calcium dependent intracellular enzyme systems, that lead to free radical production, membrane lipid breakdown, proteolysis, upregulation of specific genes, and the initiation of both apoptosis and an inflammatory response.

In experimental systems, magnesium antagonises many of these processes. Magnesium ions are antiexcitotoxic through inhibition of ischaemia-induced glutamate release,²⁶ and through antagonist properties at the NMDA receptor ion channel,^{27–29} where magnesium ions provide a physiological voltage dependent block.³⁰ Magnesium antagonises calcium entry via voltage gated channels of all types, enhances mitochondrial buffering of excessive calcium,³¹ and may prevent depletion of ATP.³² Intracellular magnesium concentrations in experimental systems are sufficiently high to antagonise a number of voltage gated ion channels including calcium, sodium and potassium,²⁹ all implicated in cerebral ischaemia. Despite doubts about brain penetrance by systemically administered magnesium based on its pharmacokinetics, animal evidence that intravenous, intramuscular, oral, or intraperitoneal magnesium ameliorates direct excitotoxic brain injury induced by injection of NMDA,³³ prevents NMDA

induced seizures,^{34–35} increases free brain magnesium after head trauma,³⁶ modifies NMDA receptor binding characteristics,³⁷ and supports a potential neuronal mechanism of action in ischaemia.

In addition to the neuronal effects, magnesium also has a number of vascular effects that may be pertinent, particularly antagonism of vasoconstrictive mediators (for example endothelin-1),^{38–40} enhanced cerebral blood flow⁴¹—presumably consequent to vasodilatation of cerebral blood vessels⁴²—and increased cardiac output.^{43–44} Magnesium concentrations within the usual “therapeutic range” prolong bleeding time,⁴⁵ but no clinical consequences of this have been noted, even in ISIS-4 where concomitant thrombolysis and aspirin were frequently used.

ANIMAL MODELS

In vivo, magnesium ameliorates histological damage in models of global forebrain ischaemia, focal head injury, subarachnoid haemorrhage, and spinal cord ischaemia.^{46–50} It improves behavioural or functional outcomes after head injury or spinal cord ischaemia,^{36–48} prevents seizures provoked by various chemical or electrical stimuli,^{7–34–51–52} and antagonises a range of vasoconstrictive mediators that may be relevant to focal brain ischaemia.^{38–40} In vitro, magnesium prevents anoxic axonal injury.⁵³

The most relevant model for human stroke is temporary or permanent middle cerebral artery occlusion, usually in rats. Magnesium has been tested in different models, by different investigators, and in different laboratories. This diversity of models and laboratories was a key recommendation in attempts to improve neuroprotective drug development.²

Results are summarised in table 1. Magnesium sulphate consistently reduces cerebral infarct volume after middle cerebral artery occlusion, with evidence of a dose response effect⁴⁴ within readily achieved serum levels, and a prolonged time window of up to six hours after onset of ischaemia,⁵⁵ which is highly favourable for a neuroprotective drug. Rat serum levels of 1.49 mmol/l after a 90 mg/kg intra-arterial dose are associated with up to 60% infarct volume reduction, and retain efficacy when administration is delayed for six hours after onset of ischaemia.^{54–55} The same dose has antiexcitotoxic activity in a rat seizure model. Average infarct volume reductions in rats range from 25% to 61%. Hyperglycaemia in rodents given magnesium chloride attenuates neuroprotection,⁵⁶ but this has not been reported in humans and has not been seen in animals given magnesium sulphate. There is evidence of improved functional outcome and reduced mortality⁵⁴ in magnesium treated animals.

HUMAN TRIALS

A systematic review of neuroprotective agents modulating glutamate action disclosed six randomised, controlled trials of magnesium in stroke, including 716 participants. Unfortunately, data are available for five trials of only 206 patients,^{58–62}

Box 1: Key features of the IMAGES trial

- Time window <12 hours after stroke onset.
- Inclusions: stroke with limb weakness.
- Exclusions: coma, renal impairment, pregnancy.
- Placebo or intravenous magnesium sulphate: 16 mmol loading infusion, then 65 mmol over 24 hours.
- Central randomisation via minimisation algorithm to ensure balance of prognostic factors.
- Outcome data (Barthel index and modified Rankin scale) at 30 and 90 days.
- Primary outcome: proportion of patients dead or dependent at 90 days.
- 80% power to detect 5.5% absolute difference in death or dependence, also has 80% power to detect a 7% absolute difference in outcome for patients treated within six hours of stroke.
- Magnetic resonance imaging (MRI) substudy to detect 25% difference in proportion of patients with infarct expansion between pretreatment diffusion weighted MRI and 90 day T2 weighted MRI.

and only four report data suitable for formal meta-analysis.⁶³ All trials have reported reduction in the end point of death or dependence, but small numbers mean that this finding lacks statistical significance, and results must be interpreted with caution: stroke is highly heterogeneous and minor baseline differences in characteristics may explain the apparent outcome effect. Systematic review of four trials yields an odds ratio for poor outcome (death or dependence at 3–6 month follow up) of 0.67 (95% confidence interval 0.35 to 1.26), with an absolute reduction of 8% (95% confidence interval 24% decrease to 7% increase).^{58–61 64} Greater neurological improvement over 30 days after stroke in the magnesium group was reported in the trial of Lampl and colleagues,⁶² but outcomes are not presented in a manner amenable to inclusion in meta-analysis. There are uncertainties about the randomisation, control and blinding procedures in the largest trial, which has reported only unconventional outcome measures of uncertain relevance to stroke (mini-mental state examination and limb power on the Medical Research Council scale).⁶⁵ A small open trial (Field Administration of Stroke Treatment-Magnesium, FAST-MAG) confirms the feasibility of pre-hospital magnesium administration by paramedics with appropriate training in diagnosis of acute stroke, and a full scale trial of treatment initiated within two hours of stroke onset is planned.⁶⁶

Most clinical trials have administered magnesium as an intravenous loading infusion, usually over 15 minutes, followed by a maintenance infusion over 24 hours or longer. Serum levels, where reported, have been predominantly within the therapeutic range suggested by animal models (mean serum concentration 1.55 mmol/l in two trials). Higher loading doses ensure that the majority of patients achieve presumed therapeutic levels rapidly.⁶⁰ A minor reduction in diastolic blood pressure at 24 hours has been reported, but no significant haemodynamic sequelae have been described.

The results of these small trials are encouraging, and have informed the sample size calculations for a large ongoing trial, the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial.⁶⁷ IMAGES is a multicentre study involving over 130 centres worldwide, and has now recruited over 2200 participants within 12 hours of stroke onset. Results are expected in 2003. Key features of the IMAGES trial design are described in box 1.

Viewed from the perspective gained from a decade of failed neuroprotective studies in stroke, the design of IMAGES may be criticised. In particular, the time window of 12 hours after stroke onset must now be regarded as optimistic, despite both favourable animal data for magnesium compared with many other drugs, and trends toward benefit for another neuroprotective drug with extended time window, citicoline.⁶⁸ However,

the sample size planned for IMAGES is larger than for any other individual neuroprotective trial to date, and the *a priori* assumption of around one third of patients being treated within the first six hours has been exceeded. Academic levels of funding—investigators receive about 1%–2% of the amount provided by commercially sponsored acute stroke trials per patient entered in IMAGES—have necessitated the participation of many small stroke centres, and many countries not usually involved in acute stroke trials, with potentially greater generalisability of results. Co-administration of recombinant tissue plasminogen activator (rtPA) is allowed, and IMAGES may therefore provide useful data in an area hitherto not extensively studied. There are clear theoretical advantages in combination therapy, with the possibilities that neuroprotective drugs may extend tissue viability and enhance the benefit or extend the time window for thrombolysis, and conversely, that reperfusion may enhance drug delivery and benefit from neuroprotection. Animal data support this view.^{69 70} A substudy using magnetic resonance imaging (MRI) parameters to assess treatment effect (MR-IMAGES) aims to recruit 150 patients and again may provide further insight. MRI studies with other neuroprotective agents reinforce the belief that MRI lesion volume provides a viable biomarker for activity.⁶⁸ Finally, the FAST-MAG trial should provide the most rigorous test of neuroprotection ever undertaken with its protocol for pre-hospital treatment.

CONCLUSIONS

Magnesium is a promising neuroprotective agent. The preclinical profile is superior to many previously investigated compounds, and is robust in the hands of different investigators. Clinical experience is extensive in other therapeutic areas and the pharmacokinetics and safety profile of magnesium are already widely known. Large academically funded clinical trials in acute ischaemic stroke are ongoing after favourable trends in small trials. The IMAGES trial and its MRI substudy are expected to report in 2003, and the FAST-MAG programme thereafter may provide the most rigorous test of any neuroprotective agent yet undertaken.

QUESTIONS (TRUE (T)/FALSE (F)); ANSWERS AT END OF REFERENCES)**Q1. Concerning magnesium physiology:**

- (A) Cerebrospinal fluid magnesium concentration is in equilibrium with that in serum
- (B) Brain magnesium is predominantly in the free, ionised form
- (C) Magnesium is excreted renally
- (D) Hypermagnesaemia is associated with slowed cardiac conduction
- (E) Depression of deep tendon reflexes occurs with hypermagnesaemia

Q2. Neuroprotective agents for stroke treatment:

- (A) Have a well established role
- (B) Are contraindicated in patients given rtPA
- (C) Are thought to prevent cell death in the infarct core
- (D) May limit expansion of lesions on MRI
- (E) Share a common mechanism of action

Q3. Possible neuroprotective actions of magnesium include:

- (A) Inhibition of glutamate release
- (B) L-type calcium channel block
- (C) NMDA receptor activation
- (D) Antiaggregatory effects on platelets

(E) AMPA receptor antagonism

Q4. Concerning magnesium in animal models of stroke:

- (A) Infarct volume is reduced if treatment is delayed by up to six hours
- (B) The chloride salt is less effective than the sulphate
- (C) Hyperglycaemia may be induced
- (D) Neuroprotection is evident only at doses that cause neuromuscular blockade
- (E) Is only effective if the blood-brain barrier has broken down

Q5. Clinical trials of magnesium have demonstrated:

- (A) Unequivocal benefit in acute myocardial infarction
- (B) Superiority to other agents in prevention of eclamptic seizures
- (C) Reduced risk of death or dependence after stroke
- (D) Increased risk of bleeding
- (E) Benefit in subarachnoid haemorrhage and head injury

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ANSWERS

Q1. (A) F, (B) F, (C) T, (D) T, (E) T; Q2. (A) F, (B) F, (C) F, (D) T, (E) F; Q3. (A) T, (B) T, (C) F, (D) F, (E) F; Q4. (A) T, (B) T, (C) T, (D) F, (E) F; Q5. (A) F, (B) T, (C) T (but not quite significant!), (D) F, (E) F.

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