Possible pharmacological actions of magnesium in acute myocardial infarction

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Introduction

Seven randomised clinical trials in a total of over 1,300 patients have examined the effects of intravenous magnesium salts (chloride or sulphate) given early after acute myocardial infarction. Five of them (Abraham *et al.*, 1987; Ceremuzynski *et al.*, 1989; Rasmussen *et al.*, 1986, 1987, 1988a; Schechter *et al.*, 1990; Smith *et al.*, 1986) reported a reduction in mortality, in frequency of arrhythmias or both in those patients who received magnesium. Two (Feldstedt *et al.*, 1988; Morton *et al.*, 1984) were negative; the first of these included only 76 patients. Rasmussen *et al.* (1986, 1988a) randomised 273 patients with suspected acute myocardial infarction to receive 62 mmol magnesium chloride or saline over 48 h. Significantly fewer patients had infarction confirmed in the magnesium group and mortality at 1 year was 32% in the placebo group and 20% in the magnesium group ($P < 0.02$). Although none of the trials had sufficient statistical power to be conclusive, collectively they strongly suggest a beneficial effect of intravenous magnesium and this interpretation is supported by a formal meta-analysis of all the available data (Teo *et al.*, 1990). A further trial with a sample size of 2,500 patients, due to be completed in early 1992, is described in a later section.

Magnesium antagonises the effects of calcium in a range of important cellular processes and many of its cardiovascular effects can be described as those of 'Nature's physiological calcium blocker' (Altura *et al.*, 1987; Iseri & French 1984). In addition magnesium is important for the function of many key enzymes, including adenylate cyclase (Bockaert *et al.*, 1984). The maintenance of free intracellular magnesium concentration ($[Mg^{2+}]_i$) within narrow limits suggests that the cation has a regulatory role (Maguire, 1984; White & Hartzell, 1989). Developments in ^{31}P nuclear magnetic resonance spectroscopy and in fluorescence spectrophotometry for the measurement of $[Mg^{2+}]_i$ are rapidly expanding our understanding of basic mechanisms and it is opportune to draw together the clinical and laboratory data which might have relevance to the therapeutic use of magnesium in myocardial infarction.

This paper reviews the pharmacological effects on the cardiovascular system which occur when serum magnesium concentration is raised above the physiological range (0.7–0.95 mM), and considers how the clinical course of acute myocardial infarction might be modified in consequence.

Haemodynamic effects

When magnesium is given intravenously as a slow bolus or short infusion in sufficient amount (typically 8–16 mmol) to raise serum $[Mg^{2+}]$ about twofold, flushing and a sensation of cutaneous warmth occur. Peripheral resistance falls by 20–35% with a compensatory rise of around 25% in cardiac index. A slight fall in blood pressure and rise in heart rate may be seen and the rate-pressure product is unaltered. The haemodynamic response is similar in normal subjects and untreated hypertensives (Mroczek *et al.*, 1977; Nadler *et al.*, 1987; Rasmussen *et al.*, 1988b) and in men with coronary artery disease (Borschat *et al.*, 1988). Nadler *et al.* (1987) infused 25 mmol $MgSO_4$ over 3 h in normal subjects and observed a mean fall of 10 mm Hg in systolic and diastolic blood pressure, a 22% increase in renal blood flow and a 60% increase in urinary excretion of 6-keto-PGF $_{1\alpha}$, the stable metabolite of prostacyclin. Pre-treatment with either ibuprofen or indomethacin abolished both the rise in 6-keto-PGF $_{1\alpha}$ output and the blood pressure changes in response to infused magnesium. Two other observations support this evidence that prostacyclin mediates, at least in part, the haemodynamic effects of infused magnesium. Firstly, infusions of prostacyclin and of magnesium elicit closely similar responses (Bergman *et al.*, 1981). Secondly, concentrations of magnesium producing a haemodynamic effect *in vivo* stimulate the release of prostacyclin from human endothelial cells *in vitro* (Briel *et al.*, 1987; Watson *et al.*, 1986).

Other mechanisms regulating vascular tone may also be modified by magnesium, however. Gold *et al.* (1990) have shown that magnesium competes with calcium to inhibit both the production of endothelium-derived relaxing factor (EDRF) and the contraction of vascular smooth muscle in canine pulmonary artery. Recent evidence identifies EDRF as nitric oxide (Palmer *et al.*, 1987) or a labile nitrosylated compound (Myers *et al.*, 1990) which requires calcium for its synthesis in (or perhaps release by) vascular endothelium. External magnesium is also required for endothelium dependent relaxation to occur in canine coronary arteries (Altura & Altura, 1987).

Altura *et al.* (1987) have summarised a large body of work showing that magnesium inhibits basal, myogenic and hormone-induced contraction of vascular smooth muscle. Antagonism by magnesium of vascular calcium flux is seen at leak, voltage-operated and receptor-operated calcium channels and appears to occur in all

vascular beds, in contrast to the organic calcium channel blockers such as the dihydropyridines and verapamil which show some vascular selectivity. The vasodilator action of magnesium has been shown to be competitively inhibited by calcium in man by forearm plethysmography (Fujita *et al.*, 1990).

In summary, the haemodynamic response to infused magnesium is characterised by afterload reduction and a secondary rise in cardiac output without a significant increase in cardiac work. Evidence exists for both a direct vasodilator action of magnesium on arteriolar smooth muscle and an endothelium-mediated vasodilatation by prostacyclin release; the role of EDRF is not yet clear.

Mg²⁺ and the coronary circulation

Segmental coronary artery spasm can frequently be demonstrated angiographically in patients with recent myocardial infarction and may be a trigger to acute thrombotic occlusion (Maseri *et al.*, 1978, 1990; Oliva & Breckenridge 1977). Magnesium competes with calcium to inhibit contractility of coronary arteries, as with other vascular smooth muscle (Altura *et al.*, 1987). Extracellular magnesium is necessary for endothelium-dependent relaxation of coronary arteries (Altura & Altura, 1987) and *in vitro* the withdrawal of magnesium both increases coronary artery tone and potentiates the contractile response to angiotensin, 5-HT, noradrenaline, acetylcholine and potassium (Turlapaty & Altura, 1980).

Several lines of evidence indicate that pharmacological concentrations of magnesium can relieve spasm in human coronary arteries. Kimura *et al.* (1989) used as a model coronary arteries obtained at autopsy and studied at a mean of 2.6 h after death. On exposure to prostaglandin F_{2α}, arterial segments generated tonic contraction which was inhibited by 1–2 mM magnesium. The inhibition seen with magnesium was more marked than with therapeutic concentrations of diltiazem and comparable with that observed with glyceryl trinitrate. Periodic contraction also occurred in the preparations, which was inhibited by magnesium only at concentration of 4 mM and above though the peak tension generated was reduced at 2 mM magnesium and above.

The second line of evidence is provided by patients with variant angina, in whom myocardial ischaemia occurs episodically at rest or on exercise as a result of coronary spasm. Although serum [Mg²⁺] is normal, Goto *et al.* (1990) have reported that magnesium depletion can be demonstrated in these patients by a significantly increased magnesium retention relative to controls following an intravenous magnesium load (60 ± 5% vs 36 ± 3%, *P* < 0.001). In a separate placebo-controlled study intravenous magnesium sulphate (0.27 mmol kg⁻¹ body weight) suppressed exercise-induced vasospastic angina in patients with the variant form but was without therapeutic effect in patients with stable effort angina due to fixed coronary stenoses (Kugiyama *et al.*, 1988).

Finally, the release of prostacyclin stimulated by magnesium infusion (Nadler *et al.*, 1987) is likely to have qualitatively similar effects to those described in patients with coronary artery disease when prostacyclin was

infused (Bergman *et al.*, 1981). These included a reduction in coronary vascular resistance, increase in coronary blood flow at rest, and reduced myocardial lactate production and increased time to angina during rapid atrial pacing.

The available data therefore indicate that magnesium is a coronary vasodilator at pharmacological concentrations which can safely be achieved in man. This property may be of particular value in the prevention and relief of coronary spasm associated with acute myocardial infarction.

Electrophysiological and antiarrhythmic effects of magnesium

Clinical reports of the successful treatment of cardiac arrhythmias with magnesium salts began to appear in the literature nearly 50 years ago (Boyd & Sherf, 1943) but it is only in the last three years that the necessary electrophysiological studies have been carried out to shed light on these empirical observations. Three aspects need to be considered: the effect of magnesium on normal electrophysiology, its ability to modify abnormal rhythms of diverse aetiologies, and its possible influence on arrhythmogenesis in acutely ischaemic myocardium.

The electrophysiological effects of a doubling of serum [Mg²⁺] in man have been studied in detail by several groups (Kulick *et al.*, 1988; Rasmussen & Thomsen 1989; Rogiers *et al.*, 1989; Sager *et al.*, 1990). The only consistent finding has been slowing of conduction through the atrioventricular (AV) node with a significant prolongation of the AH (atrium-His) interval. This has also been reported to occur in the isolated perfused guinea-pig heart (Stark *et al.*, 1988) and in dogs (Haverkamp *et al.*, 1988) and resembles the effect of organic calcium antagonists on the slow calcium current which mediates conduction through the upper AV node. A small increase in AV nodal refractory period has been observed in some studies but not in others. Sinus node function and QT interval are unchanged (Kulick *et al.*, 1988; Rasmussen & Thomsen, 1989; Rogiers *et al.*, 1989).

It might be anticipated that magnesium would be effective in the treatment of re-entrant supraventricular tachycardias (SVT) conducted through the AV node. Wesley *et al.* (1989) terminated supraventricular tachycardia in eight of ten patients by doubling serum [Mg²⁺] with one or two rapid (10 s) boluses of magnesium sulphate. Sager *et al.* (1990) gave a 10 min bolus and an infusion of magnesium sulphate and confirmed that doubling serum [Mg²⁺] increased the tachycardia cycle length in this arrhythmia but termination occurred in only two of eleven patients; in these, termination appeared to be due to transient ventricular ectopy rather than any slowing of AV conduction. The inducibility of re-entrant SVT was unaffected by hypermagnesaemia. Etienne *et al.* (1988) likewise restored sinus rhythm with intravenous magnesium (12 mmol over 3 min) in only three of 12 patients with SVT, though significant lengthening of the cardiac cycle was confirmed.

Magnesium sulphate infusion, given with potassium supplements, terminated multifocal atrial tachycardia in seven of eight patients treated (Iseri *et al.*, 1985). All had

clinically significant cardiorespiratory disease and were receiving theophylline and/or digoxin. Three had low magnesium and potassium levels prior to treatment. The same group (Allen *et al.*, 1989; Iseri *et al.*, 1989) has also described the termination of monomorphic ventricular tachycardia with bolus magnesium sulphate, an effect independent of prior serum $[Mg^{2+}]$.

Intravenous magnesium is highly effective in terminating torsades de pointes, a distinctive form of ventricular tachycardia with a constantly changing electrical axis and the potential to trigger ventricular fibrillation. Torsades de pointes occurs in the setting of congenital or acquired QT prolongation and is a toxic effect of a range of drugs which can increase the QT interval: tricyclic antidepressants, phenothiazines, class 1 and class 3 antiarrhythmic agents and others. The therapeutic use of magnesium was suggested by the earlier observation that profound hypomagnesaemia can cause the long QT syndrome. However, the efficacy of intravenous magnesium in terminating torsades de pointes appears to be independent of the initiating cause and not to be mediated by correction of an underlying magnesium depletion or by shortening of the QT interval (Tzivoni *et al.*, 1988). Indeed, the presumption that hypomagnesaemia or magnesium depletion in themselves are arrhythmogenic has been disputed (Surawicz, 1989).

It has been proposed that the long QT syndrome and torsades de pointes result from early afterdepolarisations, for which an experimental model can be produced by the injection of caesium chloride. In dogs, caesium chloride induced early afterdepolarisations (detectable with contact electrodes recording the monophasic action potential) and increased the QT interval; sustained monomorphic ventricular tachycardia, torsades de pointes or ventricular fibrillation almost invariably followed. Infusion of magnesium significantly reduced the amplitude of afterdepolarisations and the proportion of animals developing sustained ventricular arrhythmias in response to caesium chloride (Bailie *et al.*, 1988). Another model for the long QT syndrome utilised the effect of quinidine (a class 1 antiarrhythmic) on canine Purkinje fibres *in vitro* (Davidenko *et al.*, 1989). Action potential duration, early afterdepolarizations and triggered activity were recorded with intracellular microelectrodes. Increasing $[Mg^{2+}]_o$ to 3 mM completely suppressed triggered activity in all preparations even in the presence of low $[K^+]_o$ and slow stimulation rates, without significantly reducing action potential duration. Early afterpotentials were only partially suppressed even at 5 mM $[Mg^{2+}]_o$.

Of particular relevance to the present review is the effectiveness of magnesium in preventing arrhythmias arising in acutely ischaemic myocardium. There is empirical evidence for this both from randomized clinical trials in patients with acute myocardial infarction (Abraham *et al.*, 1987; Ceremuzynski *et al.*, 1989; Rasmussen *et al.*, 1987; Schechter *et al.*, 1990; Smith *et al.*, 1986) and from experimental models of myocardial ischaemia (Barros *et al.*, 1988; Crampton & Clark, 1983; Haverkamp *et al.*, 1988). How do arrhythmias develop in acute ischaemia, and how might magnesium inhibit them? Three possible mechanisms need to be considered: re-entrant rhythms around infarcted myocardium; automaticity (abnormal pacemaker activity) resulting from spontaneous phase 4 depolarization; and the generation

of afterpotentials by activation of the slow calcium channel in partially depolarized cells.

The effect of magnesium on afterpotentials has already been discussed in the context of long QT syndromes. The development and persistence of a re-entrant circuit depend critically on conduction velocity and the presence of unidirectional block. With the possible exception of re-entrant pathways including the AV node (see above), pharmacological modification by magnesium is unlikely since neither conduction velocity nor refractory period of myocardium appear to be altered by magnesium concentrations attainable *in vivo* (Kulick *et al.*, 1988; Sager *et al.*, 1990).

Hasegawa *et al.* (1989) have studied the effect of extracellular $[Mg^{2+}]$ on catecholamine-induced abnormal pacemaker activity in guinea-pig ventricular myocytes partially depolarized by 27 mM potassium. The model is likely to be representative of myocardium in the peri-infarct ischaemic zone after acute coronary occlusion. The threshold concentrations of isoprenaline required to induce depolarization and automaticity rose significantly as external $[Mg^{2+}]$ was increased in the range 1–4 mM. Under conditions of partial depolarization the slow calcium channel is activated and calcium current (I_{Ca}) can contribute to automaticity (see Fleckenstein, 1983 for review); I_{Ca} is rapidly blocked by external magnesium (Hartzell & White, 1989). The data of Hasegawa *et al.* (1989) suggest that receptor-mediated calcium channel activation is also susceptible to magnesium inhibition.

Internal magnesium may have an important role in the voltage-dependent inactivation of I_{Ca} (Hartzell & White, 1989), which was demonstrated in frog isolated ventricular myocytes using the patch-clamp technique and internal perfusion to vary $[Mg^{2+}]_i$ in the range 0.3–3 mM. Inhibition of calcium channel activity by $[Mg^{2+}]_i$ has also been reported in guinea pig ventricular myocytes, though the mechanism differs in that it is independent of ligand-mediated phosphorylation (Agus *et al.*, 1989). At present, however, little is known about the control of $[Mg^{2+}]_i$. It is apparent that $[Mg^{2+}]_i$ or a functionally important subcellular pool of it is regulated by β -adrenoceptor agonists via a pathway which is not cAMP-dependent (Maguire, 1984; Romani & Scarpa, 1990). Maguire (1984) has argued that $[Mg^{2+}]_i$ has a physiological role in the regulation of adenylate cyclase activation by β -adrenoceptor agonists, and thus of adrenergic responsiveness, using data from S49 lymphoma cells. It is not yet known what effect a supraphysiological serum $[Mg^{2+}]$ has on myocardial free $[Mg^{2+}]_i$.

In summary, therefore, elevation of serum magnesium to 1.5–2.0 mM has little effect on normal cardiac electrophysiology but has been reported to reduce the frequency of clinically significant arrhythmias early after acute myocardial infarction in several controlled trials. Laboratory studies suggest that magnesium may have an anti-arrhythmic action by suppressing automaticity in partially depolarized cells and that inhibition of calcium current is likely to contribute to this effect. Prevention of lethal arrhythmias is unlikely to account for the reported reduction of early post-infarction mortality by infused magnesium since life-threatening primary arrhythmias are normally rapidly rectified within the coronary care unit. If confirmed, however, prevention of serious

arrhythmias by magnesium might be of great value in the pre-admission care of the coronary patient.

Protection of ischaemic myocardium

When myocardial cells become ischaemic, a cascade of adverse metabolic changes is triggered (Figure 1). As aerobic metabolism declines, cellular ATP is depleted to the detriment of active membrane ionic transport and other energy-dependent processes. Anaerobic metabolism generates lactate, resulting in intracellular acidosis. $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$ increase and cell swelling occurs. Increased calcium uptake into mitochondria further inhibits ATP synthesis while the contracture caused by elevated $[\text{Ca}^{2+}]_i$ accelerates ATP hydrolysis. As a large fraction of intracellular ATP is in the form of its magnesium salt, cellular $[\text{Mg}^{2+}]$ depletion accompanies the fall in ATP. Paradoxically, restoration of perfusion may accelerate the destructive process by exacerbation of calcium overload. The generation of oxygen free radicals and the activation of phospholipases during reperfusion contribute to membrane disruption. Recent research has emphasised the central role of calcium overload in ischaemic myocardial death, shed light on the factors which cause it and suggested the possibility of cytoprotective strategies based on calcium antagonism (Boddeke *et al.*, 1989; Tani, 1990; Tani & Neely, 1989).

There are several known mechanisms whereby magnesium might provide cellular protection during ischaemia. These include the inhibition of calcium influx across the sarcolemma (Agus *et al.*, 1989; White & Hartzell 1988), reduction of mitochondrial calcium overload (Favaron & Bernardi, 1985; Ferrari *et al.*, 1986) and conservation of intracellular ATP as MgATP (Hearse, 1977). There is also direct experimental evidence that some protection of myocardium can be achieved by raising extracellular $[\text{Mg}^{2+}]$ to supraphysiological levels during ischaemic arrest. Hearse *et al.* (1978) showed using the perfused rat heart that the speed and extent of recovery of pump function after 30 min of ischaemia at 37° C were increased as $[\text{Mg}^{2+}]$ in the perfusate was increased over the range 0–15 mM.

Pernot *et al.* (1981) used ^{31}P nuclear magnetic resonance to measure changes in intracellular ATP, creatine phosphate and inorganic phosphate in the isolated working rat heart during 1 h of cardioplegic arrest at 4° C. The recovery of aortic flow after reperfusion was measured

Figure 1 Proposed mechanisms and consequences of cytosolic calcium overload in ischaemic myocardium.

and the effects of altering perfusate concentrations of magnesium, calcium and potassium were examined. The best preservation of high energy phosphates and the most rapid recovery of pump function were achieved with a 13 mM magnesium, 0.25 mM calcium perfusate, but the design of the experiments did not allow the separate effect of $[\text{Mg}^{2+}]$ to be quantified. In a more recent ^{31}P -NMR study, Borchgrevink *et al.* (1989) confirmed a protective effect of increased extracellular $[\text{Mg}^{2+}]$ during reperfusion of the post-ischaemic rat heart, as assessed by rate of recovery of ATP and creatine phosphate, correction of intracellular pH and recovery of pump function.

In a rabbit model, Ferrari *et al.* (1986) showed that reperfusion injury in the presence of 1.5 mM calcium could be modified by 15 mM magnesium in the perfusate; mitochondrial calcium overload was reduced, oxidative phosphorylation by mitochondria was preserved and there was some recovery of tissue ATP. However, gain in tissue calcium was not prevented and this was associated with impaired diastolic relaxation. These two abnormalities could be partially prevented by the combination of 15 mM magnesium and 0.75 mM calcium in the perfusate, though at the cost of severe depression of post-reperfusion pump function.

Thus there is some experimental evidence that magnesium can protect myocardium against ischaemic injury under certain conditions. Before a therapeutically useful cellular protection can be inferred, however, several important issues have to be resolved. Firstly, several of the experiments cited have used concentrations of magnesium unattainable in man though the data of Hearse *et al.* (1978) suggest some benefit in the 1–2 mM range of magnesium (Figure 2). Secondly, protection against ischaemia appears to vary greatly between species (marked in rat and guinea pig, slight in rabbit) and may only occur if a strong negative inotropic effect is produced which reduces ATP consumption during ischaemia (Bersohn *et al.*, 1982; Shine, 1979). The explanation for the species difference may lie in the differing contributions of sarcolemmal calcium flux and calcium release from sarcoplasmic reticulum in electrical-mechanical

Figure 2 The effect of infusate $[\text{Mg}^{2+}]$ on the recovery of aortic flow in the rat heart (expressed as % of pre-ischaemic control) measured 30 min after the end of a 30 min period of ischaemia at 37° C. (Means $\pm$ s.e. mean). Data from Hearse *et al.* (1978).

coupling. Thirdly, clinical trials of several organic calcium antagonists after acute myocardial infarction have given mixed results, despite demonstrable protection of ischaemic myocardium by such agents in laboratory models. Early intravenous verapamil followed by oral verapamil for 6 months had no significant effect on mortality or re-infarction rate (Danish Study Group, 1984). A late intervention trial of oral verapamil, started in the second week after infarction, reduced mortality and re-infarction only in patients who had had no evidence of heart failure in the coronary care unit (Danish Study Group, 1990). Diltiazem and nifedipine have not proved beneficial in secondary prevention (Muller *et al.*, 1984; Multicentre Diltiazem Postinfarction Trial Research Group 1988) though oral diltiazem may reduce risk of early reinfarction after non-Q-wave infarction (Gibson *et al.*, 1986). The apparent discrepancy between experimental and clinical studies of myocardial protection by the organic calcium antagonists might be explained by the need for the drug to be delivered to the jeopardised myocardium before reperfusion injury can occur. In addition, adverse haemodynamic effects of the available organic calcium antagonists may outweigh any myocardial protection they confer (Boddeke *et al.*, 1989).

If, however, calcium overload mainly occurs at the time of reperfusion there may be benefit in raising serum $[Mg^{2+}]$ before giving a thrombolytic drug to restore patency of the infarct-related coronary artery. The trials of organic calcium antagonist drugs pre-dated the introduction of thrombolytic therapy into routine use. It is feasible to raise serum $[Mg^{2+}]$ quickly before thrombolysis and the value of doing so is currently being tested in a large clinical trial described below.

Anti-platelet effects of magnesium

Much of the work done on anti-platelet drugs in ischaemic heart disease has been concerned with primary or secondary prevention by long-term treatment. Only recently has it been clearly established that aspirin reduces early mortality after myocardial infarction when it is given in the acute phase of the illness (ISIS-2 1988). Its effectiveness is attributed to platelet inhibition by the irreversible acetylation of cyclooxygenase resulting in blockade of thromboxane synthesis. Current understanding of the pathogenesis of coronary occlusion gives an important role to platelet activation at sites of rupture of atheromatous plaques resulting from a dynamic interplay of thromboxane and other aggregatory influences with the anti-aggregatory effect of prostacyclin released from the endothelium.

Calcium plays an important part in platelet activation and under certain experimental conditions magnesium can be shown to inhibit platelet function (Adams & Mitchell, 1979; Baudouin-Legros *et al.*, 1986). The organic calcium antagonists have little inhibitory action on platelets, however (Walley *et al.*, 1989a,b), and it is unlikely that magnesium will have a direct anti-platelet effect at clinically attainable concentrations.

A potentially important indirect effect is suggested by the evidence that magnesium stimulates the release of prostacyclin from human vascular endothelium *in vitro*

(Briel *et al.*, 1987), potentiates the inhibitory action of human endothelial cells on platelet aggregation (Watson *et al.*, 1986) and increases the production of prostacyclin in human volunteers infused with intravenous magnesium (Nadler *et al.*, 1987). The anti-aggregatory activity of human endothelium is substantially augmented by magnesium in the clinically attainable range of 1–3 mM, even after repetitive thrombin stimulation of the endothelial cells which normally enhances platelet adherence. Serum from women being treated with magnesium sulphate for pre-eclampsia stimulated prostacyclin production by human endothelial cells 2–5 fold relative to pre-treatment serum from the same individuals (Watson *et al.*, 1986). This evidence that magnesium modulates the interaction between human platelets, endothelium and thrombin in the direction of reduced platelet adhesion and aggregation is of particular interest in relation to unstable coronary artery disease.

Summary and prospect

To assess the therapeutic potential of intravenous magnesium in acute myocardial infarction, judgements have to be made of the quality and consistency of the available trials and also of the external evidence for a biologically plausible mechanism of protection. A detailed critique of the seven published trials is outside the scope of this review, which is mainly concerned with the cardiovascular pharmacology of magnesium, but several general points can be made.

Firstly, the trials offer broad support for a reduction in early mortality and serious arrhythmias in patients receiving magnesium but lack the statistical power individually or collectively to be definitive. Whereas one study (Rasmussen *et al.*, 1987) reported a reduction in the incidence of supraventricular arrhythmias, in others the reduction was in ventricular arrhythmias (Abraham *et al.*, 1987; Ceremuzynski *et al.*, 1989; Smith *et al.*, 1986) or neither (Feldstedt *et al.*, 1988; Morton *et al.*, 1984; Schechter *et al.*, 1990). One study observed a reduced rate of confirmation of myocardial infarction in the group given magnesium whereas the others did not; this observation could be interpreted either as evidence of a therapeutic effect or of chance failure of randomization to achieve comparability of the treatment groups. Such ambiguities and apparent inconsistencies are predictable when small studies are compared.

Secondly, several of the trials used infusion regimens which would have achieved only a slow increase in serum $[Mg^{2+}]$. As the greatest opportunity for myocardial protection and prevention of arrhythmias occurs early after the onset of symptoms of infarction, the protocols may not have given the best opportunity to demonstrate a therapeutic effect.

Thirdly, the possible value of magnesium during thrombolysis-induced reperfusion has not yet been examined but deserves particular study for reasons set out above.

To resolve these issues, a larger study (the Leicester Intravenous Magnesium Intervention Trial, LIMIT) was started by the author and co-workers in 1987 and is due to be completed in early 1992. Consenting patients

Figure 3 Power curves for the primary end-point of 28 day mortality in the Leicester Intravenous Magnesium Intervention Trial. Calculations were based on the following assumptions: an expected 28 day mortality of 15% in patients with confirmed acute myocardial infarction (AMI), reduced to 12.5% in those suitable for thrombolysis and aspirin; zero 28 day mortality in patients in whom AMI is not confirmed; confirmation of AMI in 60% of patients randomized; two-sided significance testing with $\alpha = 0.05$. A study size of 2,500 was chosen.

admitted to the coronary care unit of Leicester Royal Infirmary with suspected acute myocardial infarction are randomized to receive either a bolus of magnesium sulphate 8 mmol intravenously over 5 min followed by a constant infusion of 65 mmol over 24 h, or equal volumes of saline. In the magnesium group, serum $[Mg^{2+}]$ is raised to around 1.6 mM by the bolus and held at that level during the infusion, declining exponentially to reach the normal range 24 h after the end of the infusion. All trial patients receive standard medical treatment, including thrombolysis if there are no contra-indications. The primary trial end-point is 28 day mortality on an intention-to-treat basis. Arrhythmia frequency and long term survival will also be analysed, with stratification to compare effects with and without concurrent thrombolysis. Interim one-sided analyses to detect any adverse effect of magnesium are conducted by an independent statistician as a safeguard; this has little effect on overall study power (DeMets & Ware, 1980). The planned study size of 2500 (1500 with confirmed myocardial

infarction) gives the power curve shown in Figure 3. Enrolment reached 1800 patients in February 1991.

The review presented here highlights five aspects of the cardiovascular pharmacology of magnesium which might contribute to a therapeutic benefit in myocardial infarction. The afterload reduction produced by intravenous magnesium would tend to improve output from a damaged left ventricle without increasing myocardial oxygen consumption. However, it is necessary to confirm that the haemodynamic response seen in healthy subjects and patients with stable ischaemic heart disease can be extrapolated to patients with acute myocardial infarction. This is being addressed using a Doppler technique for cardiac output in a sub-study of LIMIT.

Platelet aggregation and coronary artery spasm are now known to be important elements in the pathogenesis of unstable angina and coronary occlusion. The evidence reviewed here for coronary vasodilation by magnesium, in conjunction with the reported stimulation of prostacyclin release and enhancement of endothelial platelet inhibition in man, are therefore of great interest. On the other hand, it is possible that a prostaglandin-mediated effect of parenteral magnesium could be blocked by concurrent use of non-steroidal inflammatory drugs. This can be tested further in human studies.

Additional data are also needed on the question of an antiarrhythmic effect of magnesium in ischaemic myocardium. These could be acquired from a more detailed analysis of the type and frequency of rhythm disturbances arising in post-infarct patients randomized to magnesium or placebo treatment.

The least satisfactory area of those reviewed concerns the possible cellular protective action of magnesium against ischaemia. Newer methods such as fluorescence spectrophotometry are now available to explore the mechanisms and consequences of calcium overload. If satisfactory laboratory models of myocardial ischaemia can be developed, they will offer scope to examine the effects of varying extracellular $[Mg^{2+}]$ on calcium overload and the associated functional disturbances of mitochondria, contractile elements and sarcoplasmic reticulum. Spectrophotometric measurement of free $[Mg^{2+}]_i$ is also made possible by the availability of magnesium-specific fluorescent intracellular probes.

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References

- Abraham, A. S., Rosenmann, D., Kramer, M., Balkin, J., Zion, M., Farbstein, H. & Eylath, U. (1987). Magnesium in the prevention of lethal arrhythmias in acute myocardial infarction. *Arch. int. Med.*, **147**, 753–755.
- Adams, J. H. & Mitchell, J. R. A. (1979). The effect of agents which modify platelet behaviour and of magnesium ions on thrombus formation *in vivo*. *Thromb. Haemost.*, **42**, 603–610.
- Agus, Z. S., Kelepouris, E., Dukes, I. & Morad, M. (1989). Cytosolic magnesium modulates calcium channel activity in mammalian ventricular cells. *Am. J. Physiol.*, **256**, C452–C455.
- Allen, B. J., Brodsky, M. A., Capparelli, E. V., Luckett, C. R. & Iseri, L. T. (1989). Magnesium sulfate therapy for sustained monomorphic ventricular tachycardia. *Am. J. Cardiol.*, **64**, 1202–1204.
- Altura, B. M. & Altura, B. T. (1978). Magnesium and vascular tone and reactivity. *Blood Vessels*, **15**, 5–16.
- Altura, B. M., Altura, B. T., Carella, A., Gebrewold, A., Murakawa, T. & Nishio, A. (1987). Mg^{2+} - Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can. J. Physiol. Pharmacol.*, **65**, 729–745.

- Altura, B. T. & Altura, B. M. (1987). Endothelium-dependent relaxation in coronary arteries requires magnesium ions. *Br. J. Pharmacol.*, **91**, 449–451.
- Bailie, D. S., Inoue, H., Kaseda, S., Ben-David, J. & Zipes, D. P. (1988). Magnesium suppression of early after-depolarizations and ventricular tachyarrhythmias induced by cesium in dogs. *Circulation*, **77**, 1395–1402.
- Barros, L. F. M., Da-Luz, P. L., Silveira, M. C., Chagas, A. C. P. & Pileggi, F. (1988). Ventricular fibrillation in acute experimental myocardial ischaemia: protection by magnesium sulfate. *Braz. J. med. biol. Res.*, **21**, 791–799.
- Baudouin-Legros, M., Dard, B. & Guicheney, P. (1986). Hyperreactivity of platelets from spontaneously hypertensive rats. Role of external magnesium. *Hypertension*, **8**, 694–699.
- Bergman, G., Daly, K., Atkinson, L., Rothman, M., Richardson, P. J., Jackson, G. & Jewett, D. E. (1981). Prostacyclin: haemodynamic and metabolic effects in patients with coronary artery disease. *Lancet*, **i**, 569–572.
- Bersohn, M. M., Shine, K. I. & Serman, W. D. (1982). Effect of increased magnesium on recovery from ischemia in rat and rabbit hearts. *Am. J. Physiol.*, **242**, H89–H93.
- Bockaert, J., Cantau, B. & Sebben-Perez, M. (1984). Hormonal inhibition of adenylate cyclase. A crucial role for Mg^{2+} . *Mol. Pharmacol.*, **26**, 180–186.
- Boddeke, E., Hugtenburg, J., Jap, W., Heynis, J. & van Zweiten, P. (1989). New anti-ischaemic drugs: cytoprotective action with no primary haemodynamic effects. *Trends pharmac. Sci.*, **10**, 397–400.
- Borchgrevink, P. C., Bergan, A. S., Bakoy, O. E. & Jynge, P. (1989). Magnesium and reperfusion of ischemic rat heart as assessed by ^{31}P -NMR. *Am. J. Physiol.*, **256**, H195–204.
- Borschat, J., Gilard, M., Etienne, Y., Roriz, R., Blanc, J. J., Penher, P. & Morvan, C. H. U. (1988). Haemodynamic effects of magnesium sulphate in men. *Eur. Heart J.*, **9**, 228.
- Boyd, L. J. & Scherf, D. (1943). Magnesium sulfate in paroxysmal tachycardia. *Am. J. med. Sci.*, **206**, 43–48.
- Briel, R. C., Lippert, T. H. & Zahradnik, H. P. (1987). Veränderungen von Blutgerinnung, Thrombozytenfunktion und vaskulärer Prostazyklinsynthese durch Magnesium-sulfat. *Geburtsh. u. Frauenheilk.*, **47**, 332–336.
- Ceremuzynski, L., Jurgiel, R., Kulakowski, P. & Gebalska, J. (1989). Threatening arrhythmias in acute myocardial infarction are prevented by intravenous magnesium sulphate. *Am. Heart J.*, **118**, 1333–1334.
- Crampton, R. S. & Clark, C. W. (1983). Varying extracellular $[Mg^{2+}]$ alters ischaemic and reperfusion tachyarrhythmias. *Circulation*, **68**, III–146.
- Danish Study Group on Verapamil in Myocardial Infarction (1984). Verapamil in myocardial infarction. *Eur. Heart J.*, **5**, 516–528.
- Danish Study Group on Verapamil in Myocardial Infarction (1990). Effect of verapamil on mortality and major events after acute myocardial infarction (The Danish Verapamil Infarction Trial II—DAVIT II). *Am. J. Cardiol.*, **66**, 779–785.
- Davidenko, J. M., Cohen, L., Goodrow, R. & Antzelevitch, C. (1989). Quinidine-induced action potential prolongation, early afterdepolarizations and triggered activity in canine Purkinje fibers. *Circulation*, **79**, 674–686.
- DeMets, D. L. & Ware, J. H. (1980). Group sequential methods for clinical trials with a one-sided hypothesis. *Biometrika*, **67**, 191–199.
- Etienne, Y., Blanc, J. J., Bosch, J., Le Potier, J., Jobic, Y., Le Grand, O. & Penher, P. (1988). Effets antiarythmiques du sulfate de magnésium intraveineux dans les tachycardies supraventriculaires paroxystiques. *Ann. Cardiol. Angeiol.*, **37**, 535–538.
- Favaron, M. & Bernardi, P. (1985). Tissue-specific modulation of the mitochondrial calcium uniporter by magnesium ions. *FEBS Letters*, **183**, 260–264.
- Feldstedt, M., Bouchelouche, P., Svenningsen, A., Boesgaard, S., Brooks, L., Aldershvile, J., Skagen, K., Godtfredsen, J. & Lech, Y. (1988). Failing effect of magnesium substitution in acute myocardial infarction. *Eur. Heart J.*, **9**, 226.
- Ferrari, R., Albertini, A., Curello, S., Ceconi, C., Di Lisa, F., Raddino, R. & Visioli, O. (1986). Myocardial recovery during post-ischaemic reperfusion: effects of nifedipine, calcium and magnesium. *J. mol. cell. Cardiol.*, **18**, 487–498.
- Fleckenstein, A. (1983). *Calcium antagonism in heart and smooth muscle*, pp 186–208. New York: Wiley.
- Fujita, T., Ito, Y., Ando, K., Noda, H. & Ogata, E. (1990). Attenuated vasodilator responses to Mg^{2+} in young patients with borderline hypertension. *Circulation*, **82**, 384–393.
- Gibson, R. S., Boden, W. E., Theroux, P., Strauss, H. D., Pratt, C. M., Gheorghade, M., Capone, R. J., Crawford, M. H., Schlant, R. C., Kleiger, R. E., Young, P. M., Schechtman, K., Perryman, M. B., Roberts, R. & the Diltiazem Reinfarction Study Group (1986). Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. *New Engl. J. Med.*, **315**, 423–429.
- Gold, M. E., Buga, G. M., Wood, K. S., Byrns, R. E., Chaudhuri, G. & Ignarro, L. J. (1990). Antagonistic modulatory roles of magnesium and calcium on release of endothelium-derived relaxing factor and smooth muscle tone. *Circulation Res.*, **66**, 355–366.
- Goto, K., Yasue, H., Okumura, K., Matsuyama, K., Kugiyama, K., Miyagi, H. & Higashi, T. (1990). Magnesium deficiency detected by intravenous loading test in variant angina pectoris. *Am. J. Cardiol.*, **65**, 709–712.
- Hartzell, H. C. & White, R. E. (1989). Effects of magnesium on inactivation of the voltage-gated calcium current in cardiac myocytes. *J. gen. Physiol.*, **94**, 745–767.
- Hasegawa, J., Matsumoto, T., Takami, T., Fujimoto, Y., Kotake, H. & Mashiba, H. (1989). Suppression of catecholamine-induced abnormal pacemaker activities by magnesium ion in guinea pig cardiac muscle cells. *Magnesium*, **8**, 94–99.
- Haverkamp, W., Hindricks, G., Keteller, T., Allberty, D., Wiethold, D. & Gulker, H. (1988). Prophylactic antiarrhythmic and antifibrillatory effects of intravenous magnesium sulphate during acute myocardial ischaemia. *Eur. Heart J.*, **9**, 228.
- Hearse, D. J. (1977). Reperfusion of the ischaemic myocardium. *J. mol. cell. Cardiol.*, **9**, 605–616.
- Hearse, D. J., Stewart, D. A. & Braimbridge, M. V. (1978). Myocardial protection during ischaemic cardiac arrest: the importance of magnesium in cardioplegic solutions. *J. Thoracic. cardiovasc. Surg.*, **75**, 877–885.
- Iseri, L. T., Allen, B. J. & Brodsky, M. A. (1989). Magnesium therapy of cardiac arrhythmias in critical-care medicine. *Magnesium*, **8**, 299–306.
- Iseri, L. T., Fairshier, R. D., Hardemann, J. L. & Brodsky, M. A. (1985). Magnesium and potassium therapy in multifocal atrial tachycardia. *Am. Heart J.*, **110**, 789–794.
- Iseri, L. T. & French, J. H. (1984). Magnesium: Nature's physiological calcium blocker. *Am. Heart J.*, **108**, 188–193.
- ISIS-2 Collaborative Group (1988). A randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet*, **ii**, 349–360.
- Kimura, T., Yasue, H., Sakaino, N., Rokutanda, M., Jougasaki, M. & Araki, H. (1989). Effects of magnesium on the tone of isolated human coronary arteries. *Circulation*, **79**, 1118–1124.
- Kugiyama, K., Yasue, H., Okumura, K., Goto, K., Minoda, K., Miyagi, H., Matsuyama, K., Kojima, A., Koga, Y. & Takahashi, M. (1988). Suppression of exercise-induced angina by magnesium sulphate in patients with variant angina. *J. Am. Coll. Cardiol.*, **12**, 1177–1183.
- Kulick, D. L., Hong, R., Ryzen, E., Rude, R. K., Rubin, J. N., Elkayam, U., Rahimtoola, S. H. & Bhandari, A. K. (1988).

- Electrophysiological effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. *Am. Heart J.*, **115**, 367–373.
- Maguire, M. E. (1984). Hormone-sensitive magnesium transport and magnesium regulation of adenylate cyclase. *Trends pharmac. Sci.*, **5**, 73–77.
- Maseri, A., Davies, G., Hackett, D. & Kaski, J. C. (1990). Coronary artery spasm and vasoconstriction. The case for a distinction. *Circulation*, **81**, 1983–1991.
- Maseri, A., L'Abbate, A., Baroldi, G., Chierchia, S., Marzilli, M., Ballestra, A. M., Severi, S., Parodi, O., Biagini, A., Distanti, A. & Pesola, A. (1978). Coronary vasospasm as a possible cause of myocardial infarction. *New Engl. J. Med.*, **299**, 1271–1277.
- Morton, B. C., Nair, R. C., Smith, F. M., McKibbin, T. G. & Poznanski, W. J. (1984). Magnesium therapy in acute myocardial infarction—a double-blind study. *Magnesium*, **3**, 346–352.
- Mroczek, W. J., Lee, W. R. & Davidov, M. E. (1977). Effect of magnesium sulfate on cardiovascular hemodynamics. *Angiology*, **28**, 720–724.
- Muller, J. E., Morrison, J., Stone, P., Rude, R. E., Rosner, B., Roberts, R., Pearle, D. L., Turi, Z. G., Schneider, J. F., Serfas, D. H., Tate, C., Scheiner, E., Sobel, B. E., Hennekens, C. H. & Braunwald, E. (1984). Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. *Circulation*, **69**, 740–747.
- Multicentre Diltiazem Postinfarction Trial Research Group (1988). The effect of diltiazem on mortality and reinfarction after myocardial infarction. *New Engl. J. Med.*, **319**, 385–392.
- Myers, P. R., Minor, R. L., Guerra, R., Bates, J. N. & Harrison, D. G. (1990). Vasorelaxant properties of the endothelium-derived relaxing factor more closely resemble S-nitrosocysteine than nitric oxide. *Nature*, **345**, 161–163.
- Nadler, J. L., Goodson, S. & Rude, R. (1987). Evidence that prostacyclin mediates the vascular action of magnesium in humans. *Hypertension*, **9**, 379–383.
- Oliva, P. B. & Breckenridge, J. C. (1977). Arteriographic evidence of coronary artery spasm in acute myocardial infarction. *Circulation*, **56**, 366–374.
- Palmer, R. M. J., Ferrige, A. G. & Moncada, S. (1987). Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature*, **327**, 524–526.
- Palmer, R. M. J., Ashton, D. S. & Moncada, S. (1988). Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature*, **333**, 664–666.
- Pernot, A. C., Ingwall, J. S., Menasche, P., Grousset, C., Bercot, M., Mollet, M., Piwnica, A. & Fossel, E. T. (1981). Limitations of potassium cardioplegia during cardiac ischaemic arrest: a phosphorus-31 nuclear magnetic resonance study. *Ann. Thoracic Surg.*, **32**, 536–545.
- Rasmussen, H. S. & Thomsen, P. E. B. (1989). The electrophysiological effects of intravenous magnesium on human sinus node, atrioventricular node, atrium and ventricle. *Clin. Cardiol.*, **12**, 85–90.
- Rasmussen, H. S., Gronbaek, M., Cintin, C., Balslov, S., Norregard, P. & McNair, P. (1988a). One-year death rate in 270 patients with suspected acute myocardial infarction, initially treated with intravenous magnesium or placebo. *Clin. Cardiol.*, **11**, 377–381.
- Rasmussen, H. S., McNair, P., Norregard, P., Backer, V., Lindeneq, O. & Balslev, S. (1986). Intravenous magnesium in acute myocardial infarction. *Lancet*, **i**, 234–236.
- Rasmussen, H. S., Suenson, M., McNair, P., Norregard, P. & Balslev, S. (1987). Magnesium infusion reduces the incidence of arrhythmias in acute myocardial infarction. A double-blind placebo-controlled study. *Clin. Cardiol.*, **10**, 351–356.
- Rasmussen, H. S., Videbaek, R., Melchior, T., Aurup, P., Cintin, C. & Pedersen, N. T. (1988b). Myocardial contractility and performance capacity after magnesium infusions in young healthy persons: a double-blind, placebo-controlled, cross-over study. *Clin. Cardiol.*, **11**, 541–545.
- Rogiers, P., Vermeier, W., Kesteloot, H. & Stroobandt, R. (1989). Effect of the infusion of magnesium sulphate during atrial pacing on ECG intervals, serum electrolytes and blood pressure. *Am. Heart J.*, **117**, 1278–1283.
- Romani, A. & Scarpa, A. (1990). Hormonal control of magnesium transport in the heart. *Nature*, **346**, 841–844.
- Sager, P. T., Widerhorn, J., Petersoen, R., Leon, C., Ryzen, E., Rude, R., Rahimtoola, S. H. & Bhandari, A. K. (1990). Prospective evaluation of parenteral magnesium sulfate in the treatment of patients with reentrant AV supraventricular tachycardia. *Am. Heart J.*, **119**, 308–316.
- Schechter, M., Hod, H., Marks, N., Kaplinsky, E., Behar, S. & Rabinowitz, B. (1990). Beneficial effect of magnesium sulfate in acute myocardial infarction. *Am. J. Cardiol.*, **66**, 271–274.
- Shine, K. I. (1979). Myocardial effects of magnesium. *Am. J. Physiol.*, **237**, H413–H423.
- Smith, L. F., Heagerty, A. M., Bing, R. F. & Barnett, D. B. (1986). Intravenous infusion of magnesium sulphate after acute myocardial infarction: effects on arrhythmias and mortality. *Int. J. Cardiol.*, **12**, 175–180.
- Stark, G., Stark, U., Pilger, E., Hoening, K., Bertuch, H. & Tritthart, H. A. (1988). Changes of cardiac pacemaker activity and conduction velocity during hypermagnesaemia. *Wien med. Wochenschr.*, **138**, 379–381.
- Surawicz, B. (1989). Is hypomagnesaemia or magnesium deficiency arrhythmogenic? *J. Am. Coll. Cardiol.*, **14**, 1093–1096.
- Tani, M. (1990). Mechanisms of Ca^{2+} overload in reperfused ischemic myocardium. *Ann. Rev. Physiol.*, **52**, 543–559.
- Tani, M., Neely, J. (1989). Role of intracellular Na^{+} in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. *Circulation Res.*, **65**, 1045–1056.
- Teo, K., Held, P., Collins, R. & Yusuf, S. (1990). Effect of intravenous magnesium on mortality in myocardial infarction. *Circulation*, **82**, III–393.
- Turlapaty, P. D. M. V. & Altura, B. M. (1980). Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science*, **208**, 198–200.
- Tzivoni, D., Banai, S., Schuger, C., Benhorin, J., Keren, A., Gottlieb, S. & Stern, S. (1988). Treatment of torsade de pointes with magnesium sulphate. *Circulation*, **77**, 392–397.
- Walley, T. J., Woods, K. L. & Barnett, D. B. (1989a). Effects of calcium channel blockers on *in vitro* platelet function in whole blood using single platelet counting. *Thrombosis and Haemostasis*, **61**, 137–139.
- Walley, T. J., Woods, K. L. & Barnett, D. B. (1989b). The effects of intravenous and oral nifedipine on *ex vivo* platelet function. *Eur. J. Clin. Pharmacol.*, **37**, 449–452.
- Watson, K. V., Moldow, C. F., Ogburn, P. L. & Jacob, H. S. (1986). Magnesium sulfate: Rationale for its use in pre-eclampsia. *Proc. Nat. Acad. Sci. USA*, **83**, 1075–1078.
- Wesley, R. C., Haines, D. E., Lerman, B. B., DiMarco, J. P. & Crampton, R. S. (1989). Effect of intravenous magnesium sulphate on supraventricular tachycardia. *Am. J. Cardiol.*, **63**, 1129–1131.
- White, R. E. & Hartzell, H. C. (1988). Effects of intracellular free magnesium on calcium current in isolated cardiac myocytes. *Science*, **239**, 778–780.
- White, R. E. & Hartzell, H. C. (1989). Magnesium ions in cardiac function. Regulator of ion channels and second messengers. *Biochem. Pharmacol.*, **38**, 859–867.

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