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CLINICAL EXPERIENCE

The Case for Intravenous Magnesium Treatment of Arterial Disease in General Practice: Review of 34 Years of Experience

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Magnesium sulphate ($MgSO_4$) in a 50% solution was injected initially intramuscularly and later intravenously into patients with peripheral vascular disease (including gangrene, claudication, leg ulcers and thrombophlebitis), angina, acute myocardial infarction (AMI), non-haemorrhagic cerebral vascular disease and congestive cardiac failure. A powerful vasodilator effect with marked flushing was noted after intravenous (IV) injection of 4-12 mmol of magnesium (Mg) and excellent therapeutic results were noted in all forms of arterial disease. This technique of rapidly securing very high initial blood levels of $MgSO_4$ produces results in arterial disease which cannot be equalled by oral vasodilators of intramuscular (IM) or IV infusion therapy. It is suggested that the most important action of $MgSO_4$ in AMI is to open up collateral circulation and relieve ischaemia thus reducing infarct size and mortality rates. Prophylactic use of $MgSO_4$ and its effect on serum lipid, fibrinogen, urea and creatinine levels are discussed.

Keywords: intravenous magnesium sulphate injections, angina, acute myocardial infarction, non-haemorrhagic cerebral vascular disease, claudication, serum lipids, fibrinogen, congestive cardiac failure, early renal failure.

INTRODUCTION

Parenteral magnesium sulphate ($MgSO_4$) has been used [1, 2] in cardiovascular disease for the last 60 years. Initially, no satisfactory explanation of its mode of action emerged. To facilitate observation of its effects, $MgSO_4$ was given at first intramuscularly and then intravenously in my practice in 1958 [3] to patients with gangrene, leg ulcers, Raynaud's disease, chilblains and intermittent claudication. A powerful vasodilator action immediately became apparent; this action increased in potency with increased initial blood concentrations, as had been seen with arterial infusion of magnesium (Mg) in dogs [4]. Thus, maximum therapeutic effect was, if necessary, obtained by rapidly injecting 12 mmol of Mg; the intravenous (IV) route proved to be the method of choice.

This vasodilator therapy has been highly effective especially in coronary disease and non-haemorrhagic cerebrovascular disease (NHCVD) [3, 5-8] but has been ignored by hospital workers until the last few years. Mg has been demonstrated to be a calcium antagonist in vascular muscle [9], at post-ganglionic sympathetic nerve endings, in adrenal glands [10-12] and in blood clotting. The possibility of using drugs to dilate coronary collateral and peripheral vessels has been generally decried, but the conclusion that it can occur has been inescapable from consideration of patients with complete relief of severe angina and claudication for 10 years or more after full courses of $MgSO_4$. The relief of anginal pain in elderly patients for long periods in my practice drew attention to the possibility of improving the coronary circulation in patients with congestive cardiac failure (CCF) and a series of 30 patients is reported showing long-term improvement after six injections.

$MgSO_4$ injections have been shown to reduce the level of serum lipids [2, 3, 13, 14]. The results of further investigations are reported together with findings in the treatment of angina, acute myocardial infarction (AMI), CCF, NHCVD and peripheral vascular disease.

METHODS OF TREATMENT

Heparin was used initially with $MgSO_4$ to protect anginal patients against possible thrombosis [3, 5] during the short period of hypotension often following IV $MgSO_4$ injections. As Mg has an anticoagulant action [15] as well as a fibrinolytic action [13], the use of heparin was discontinued without any problems arising. However, in AMI, I now give 5000 units of IV heparin along with 8 mmol of Mg to make absolutely certain that the sudden hypotension seen in some patients does not lead to extension of the thrombus. Heparin appears to give good pain relief when used with $MgSO_4$ in AMI and a trial of $MgSO_4$ with and without heparin would be of interest.

Normally, in angina, the initial dose of $MgSO_4$ is 4 mmol given in an arm vein in about 10 seconds after 1 mmol has been given fairly slowly to accustom the patient to the intense feeling of warmth generated by IV Mg. If the patient is quite happy, the dose is often increased to 8 mmol given on a further five occasions either daily or weekly as is found convenient. In AMI, I give 7 mmol $MgSO_4$ with 5000 units of heparin in about 15 seconds after an initial 1 mmol has been given more slowly. Then, $MgSO_4$ (8 mmol) is given daily for 2-3 days, or for longer if chest pain recurs. A further course of three doses of 8 mmol is given after 2-3 weeks. In AMI, the dose is reduced to 1 mmol or less, repeated at 15-min intervals, if the blood pressure has fallen unduly (see later).

In NHCVD, I give a rest dose of 0.25 mmol before proceeding to administer 4 mmol $MgSO_4$. With careful selection of patients, I have never had any problems but feel the treatment of patients with NHCVD is ideally conducted in a hospital setting with the use of modern diagnostic techniques. Obviously, the use of $MgSO_4$ is completely contra-indicated in cerebral haemorrhage. In resistant cases of NHCVD, up to 12 mmol $MgSO_4$ have been injected in 20-30 seconds. The largest daily dose given has been 16 mmol $MgSO_4$. In angina, repeated courses of $MgSO_4$ are given if symptoms recur.

Side-effects have not been a serious problem. Occasionally, patients complain of headache and mild nausea and further injections are than given more slowly or, rarely, intramuscularly if the IV route is too upsetting. There is sometimes temporary hypotension and patients are asked to rest in the horizontal position for 5-10

min after injection. Patients with severe renal failure will need special care to avoid undue rises in serum Mg levels. Small and infrequent doses are indicated. Two patients after treatment with IV $MgSO_4$ and 5000 units of heparin have developed subcutaneous haemorrhages.

RESULTS

Angina

A total of 126 patients with proven angina have been treated with IV $MgSO_4$ and 116 have either been completely relieved of pain or markedly improved. Patients were considered improved if they used significantly less glyceryl trinitrate and could walk at least three times as far as previously at their normal pace. Most patients were given six IV injections of $MgSO_4$ with a total dose of between 24 and 48 mmol of Mg.

Case reports. A significant case [6] was that of a man of 56 who after a major infarction in 1958 had very severe angina which forced him to stop every 5 m when walking in cold weather. He improved considerably on intramuscular (IM) therapy but after a course of rapid bolus injections of 8 mmol of Mg remained completely free from angina until his death from carcinoma 8 years later. Subsequently, a number of similar patients were completely relieved of severe anginal pain for 10 years or longer by IV therapy.

A male patient of 44 had a massive infarction followed by severe angina in 1980. Angiogram revealed a huge ventricular aneurysm 'with a very poor prognosis'. After a course of $MgSO_4$, he dramatically improved and had a normal exercise test lasting 12.5 min. He had two further courses of $MgSO_4$ and had another normal exercise test in 1991 and is well at present.

Two other patients with post-infarction ventricular aneurysm also made excellent improvement. One had been offered a heart transplant but markedly increased his exercise tolerance and more than doubled his ejection fraction after weekly IV $MgSO_4$ and returned to a strenuous full-time job.

A patient of 66 had angina and claudication in the left leg with a history of infarction and an ECG showing right bundle branch block and ischaemic changes in the anterior and lateral leads. The dorsalis pedis was not palpable in his left foot. After repeated IV $MgSO_4$ courses, he is free from angina and claudication with a normal ECG and a strong pulse in his left dorsalis pedis.

Myocardial Infarction

In a series of 59 patients treated immediately with 8 mmol of IV Mg with or without heparin for AMI, chest pain was completely or markedly improved in 24 patients before analgesics were administered. Good recovery without any evidence of arrhythmias occurred in all 59 patients in whom AMI was confirmed by ECG and raised cardiac enzymes. The only patient with infarction and arrhythmia seen had, on initial examination, a rapid and irregular pulse of 160 plus with blood pressure of 45 systolic. After IV administration of 1 mmol of Mg, the blood pressure quickly improved to 120/80 and the pulse became regular with a rate of 120 and the patient made a good recovery with further IV therapy.

Cardiac Failure

In a series of 30 patients [6] with mild to moderate CCF but without anginal symptoms, treated with IV $MgSO_4$, 24 showed marked long-term improvement and at one year follow-up 20 patients had maintained their improved status. Of 13 similar patients previously reported [3], 11 were improved in varying degrees.

Case report. A woman with CCF and gross hepatic enlargement showed dramatic improvement in exercise tolerance and complete resolution of liver enlargement.

Cerebral Vascular Disease

Eighteen out of 34 patients [3, 5, 6, 8] with NHCVD showed marked improvement after IV $MgSO_4$, often with dramatic recovery of function, always occurring within 1-2 min of an injection.

Case reports. A man of 60 with severe paralysis of the left arm was able to move his arm with full power 1 min after IV injection of 8 mmol of Mg.

A woman of 73 was admitted on three occasions to the local GP hospital with complete hemiplegia and aphasia and on the third occasion was in status epilepticus. On each occasion, she made a full recovery and walked out of hospital after 4 days of IV $MgSO_4$ injections.

A female of 57 had gradual onset of marked weakness and loss of sensation in her left arm, hand, leg and foot. She attended a professorial medical clinic for 3 months without improvement. Treatment was begun with oral vasodilators which were ineffective and then IM therapy with $MgSO_4$ produced slight improvement. After rapid injection of 10 mmol of Mg, her symptoms completely resolved for 12 h and then relapsed but full recovery occurred after a short course of IV therapy. Her CCF was much improved concurrently. This patient reaffirmed the importance of rapid IV injection and also showed that full recovery is possible from a stroke even after a considerable period of time has elapsed. Presumable, partial ischaemia affected function without permanently damaging brain tissue.

A woman of 31 on oral contraceptives suffering from cerebral thrombosis presented with moderate right-sided hemiplegia, marked right-sided sensory loss, dysphasia and right homonymous hemianopia which were considered to be due to thrombosis of the left middle cerebral artery. After 3 weeks in hospital, she was discharged unimproved in any respect. After six injections each of 8 mmol of IV Mg given at intervals of 2 or 3 days, recovery was almost complete. Each stage of recovery was closely related to each injection with a marked initial response within 1.5 min followed by further improvement observed over a period of 2-3 h. Within 1.5 min of the first injection the patient reported 'tingling feelings' in the right arm and leg and demonstrated marked improvement in touch and pain sensation. The second and third injections secured an immediate increase in power and sensation in the right arm and leg, and the fourth a further increase, demonstrated dramatically by improved walking and recovery of her ability to feed and change her baby from that point without assistance from her husband. She remained well apart from minor partial seizures which have responded to IV $MgSO_4$ and Carbamazepine and Sodium Valproate. One patient with retinal vessel thrombosis, confirmed at a consultant clinic, made a complete recovery after treatment with $MgSO_4$.

Peripheral Vascular Disease

In a soft water area [3], 6 out of 7 patients with claudication were markedly improved by IV or IM $MgSO_4$. In a hard water area, 14 out of 25 patients with claudication showed marked improvement after IV $MgSO_4$, and of 8 patients with leg ulcers 5 healed quickly after failing to respond to all other measures over extended periods. One patient with spina bifida had a chronic trophic foot ulcer which completely healed in 4 weeks. Seventeen patients with superficial

thrombo-phlebitis were free of pain, tenderness and inflammation with only residual induration observable after 2 weeks of treatment, a further seven were fully recovered after 3-4 weeks of treatment with one patient unimproved. Four patients with deep vein thrombosis showed rapid improvement on IV $MgSO_4$ given in addition to anticoagulant therapy.

Case report. Two elderly men [3] with incipient gangrene and severe pain and swelling of heels and toes rapidly improved on regular IM doses of 4 mmol of Mg. After 18 months their feet were much warmer and free from pain and swelling.

Serum Lipids, Fibrinogen, Urea and Creatinine Levels

In a soft water area [3] $MgSO_4$ therapy of 12 patients with an average serum cholesterol level of 9.7 mmol 1^{-1} produced an average fall of 23% in 7 patients with no change in 5. In a hard water area, IV $MgSO_4$ of 36 patients with an average cholesterol level of 6.84 mmol 1^{-1} resulted in 23 patients showing a fall in cholesterol and 13 a rise, while 15 showed a rise in high-density lipoprotein and 21 a fall. Changes in triglyceride levels were equally divided. Forty patients showed a fall in fibrinogen levels and 8 patients showed a rise after $MgSO_4$ treatment with 4 patients unaffected. In 22 patients with early renal disease, serum creatinine and urea levels were reduced in 16 patients with a rise in 3 and no change in 3 others.

DISCUSSION

Angina and Claudication

Parenteral $MgSO_4$ was found to be effective in angina and in AMI by a number of early workers [16-18]. The best results were obtained with IV therapy. While Agranat [19] reported only 25 out of 50 patients with angina improved by IM therapy, Perlia [20] found 77 out of 79 patients improved after IV $MgSO_4$.

It has been noted [21] that calcium and magnesium were decreased in coronary arteries in soft water areas in males under 40 and decreases in older males may have been concealed by the presence of magnesium in atheromatous plaques. My impression is that results in claudication (6 out of 7) were significantly better in a soft water area [3] than in a hard water area (14 out of 25) and this may reflect a difference in arterial rigidity and capacity for dilation, which may also contribute to the reported varying results of Mg therapy in AMI.

I have previously reported [3] an experiment with intra-femoral injection of $MgSO_4$ in claudication which was only partly successful because of heat discomfort in the femoral artery. In view of the striking benefits noted with intra-arterial perfusion of thymoxamine in occlusive arterial disease of the lower limbs [22], further work seems indicated in a hospital setting with $MgSO_4$, as 2 patients treated recently by intra-femoral injections have had complete relief of claudication. As access to the femoral artery is difficult in patients with gross femoral artery disease, rapid injection of 6 ml of IV $MgSO_4$ may be almost as effective.

In a series of patients with angina [5], 3 patients failed to respond to $MgSO_4$ after relapsing and 2 of them died within 3 months. Another patient treated later died 4 months after unsuccessful treatment. In consequence, it was decided that in similar circumstances patients under 70 would be referred for urgent coronary arteriography in the belief that coronary disease in two or more vessels was present preventing any increase in collateral circulation, and since then this has been confirmed in almost every patient referred [6]. This finding supports the conclusion that the only explanation for the complete recovery of patients with severe angina after treatment for periods of 10 years or more must be that collateral circulation has been extensively opened up which obviously cannot occur if severe coronary disease is present. Mg therapy is therefore of value in indicating patients who need bypass grafts, and dilating collaterals with IV $MgSO_4$ before surgery may improve the run-off from grafts.

Myocardial Infarction and Arrhythmias

The absence of arrhythmias in 59 patients with AMI treated with IV $MgSO_4$ highlights the importance of early bolus therapy. Malkiel-Shapiro [16] reported the treatment of 64 patient with AMI with IM $MgSO_4$ with only one death. He also emphasized the importance of early treatment. Parsons [13] reported one death in 33 patients with AMI treated with IM $MgSO_4$.

In the prevention or treatment of arrhythmias after AMI, Mg acts in a variety of ways, the most important action being its vasodilating effects which improves the blood supply to ischaemic areas and reduces infarct size. Mg also has a direct depressant action on heart conductivity, an important role in potassium metabolism and a calcium-blocking action, which includes the prevention of catecholamine release from post-ganglionic sympathetic nerve endings and adrenal glands [10, 11, 23]. Seifter [24] has found that Mg, ATP and catecholamines form complexes which are much less potent than the original catecholamines. Both modes of action reduce the mobilization of free fatty acids by catecholamines [25]. Significantly more deaths from serious arrhythmias occur in AMI patients with high serum levels of free fatty acids [26]. Mg also has a fibrinolytic action [13], prolongs clotting time, delays peak thrombin time [15], slows down platelet clumping [27] and appears to reduce fibrinogen levels, all of which may prevent development or extension of an infarct. Significant Mg deficiency in heart muscle [28, 17, 29] after death from AMI has been well documented, as has the use of Mg salts to control arrhythmias [30, 31].

Recent trials of Mg infusion [32-34] in AMI have shown reduction of mortality rates ranging from one-third to two-thirds and some have shown reduction in arrhythmias. Rasmussen [32] believed the beneficial results of Mg infusion in AMI were due to its anti-arrhythmic action. In my view, this is much less important than the vasodilator action which opens collateral circulation and reduces myocardial damage. This is confirmed by Rasmussen's own results. Of 136 patients treated with Mg, only 56 actually developed an infarction compared with 74 in the placebo group.

In a recent trial [35], general practitioners gave Anistreptase to patients when first seen with suspected AMI and reduced the mortality rate by 50% compared with the 25% reduction usually achieved in hospital trials. If a similar approach were adopted with IV $MgSO_4$, the reduction in mortality rates could be considerably increased. The frequent relief of pain and the improved general condition of patients given $MgSO_4$ when first seen by myself suggests that myocardial ischaemia is relieved at a vitally important early stage. Some patients do not progress to AMI as shown later by normal enzyme levels while those who do have minimal myocardial damage.

In some patients with AMI, IV $MgSO_4$ can produce a fall in blood pressure which, if not excessive, may be more beneficial than harmful. In severe cardiogenic shock, the dosage of Mg has been reduced from 8 mmol to 1 mmol or even 0.20 mmol repeated at 15-min intervals with blood pressure monitoring until 4 mmol have been given [5]. Singh [36] has reported dramatic improvement in severe shock using an IV vasodilator. Further studies are required of $MgSO_4$ administration in cardiogenic shock. The patient reported with blood pressure of 45 systolic made a rapid recovery after 1 mmol of Mg was given.

Patients in high-risk categories for coronary disease would logically be in less danger during actual AMI if collateral circulation were previously maximized. High-risk patients in my practice are therefore offered a prophylactic course of $MgSO_4$, as are all patients after suffering myocardial infarction. Routine $MgSO_4$ therapy after AMI produces considerable improvement with respect to angina and exercise tolerance [3], and did so in all 7 post-infarction patients in one series of 30 patients with angina.

Cerebral Vascular Disease

Only 34 patients with NHCVD have been treated because of the importance of being certain of the diagnosis. Patients with hypertension and dramatic onset of symptoms have not been treated, as $MgSO_4$ is obviously contra-indicated in cerebral haemorrhage and consequently few cases have been treated. With modern methods of diagnosis, hospital patients with cerebral thrombosis, embolus or cerebral vascular insufficiency could easily be diagnosed and treated.

In view of the complete resolution of retinal vessel thrombosis in the only patient treated, it is interesting to note that Malkiel-Shapiro [2] reported marked improvement in 2 patients with hypertensive retinopathy following treatment with $MgSO_4$.

HEART DISEASE AND WATER SUPPLIES

In soft water areas, the heart muscle of people dying after accidents has been shown to have significantly lower concentrations of Mg [37] than similar samples from people in a hard water area. Serum Mg levels were similar in residents of hard and soft water areas [38] but Seelig has concluded that serum Mg levels are an unreliable indicator of Mg status [39]. The low level of Mg in heart muscle in soft water areas is significant when one considers the well-known fact of an increased incidence of sudden death from heart disease [40] in those areas; it has been suggested frequently that lack of Mg in soft drinking water [39] may be the vital factor concerned. I advise anginal patients in soft water areas to take at least one Mg hydroxide tablet daily and patients in hard water areas to do the same, or at least drink some unboiled water each day. As Mg balance may be very critically poised with modern diets [41], even small additions of Mg to the diet may be crucial in preventing Mg deficiency and hence the possible development of arrhythmias and sudden death during infarction.

Enough attention has not been paid to the higher incidence of heart disease and hypertension in the soft water areas of Scotland, Northern Ireland and Northern England. Morris [42] reported high negative correlations between cardiovascular disease and water hardness in England and Wales. Dyckner [43] and many others have demonstrated falls in blood pressure when Mg supplements were added to patients' diets. Stitt [44] found that there was a significantly higher level of blood pressure between the ages of 50 and 65 in residents of a soft water area as compared with those in a hard water area.

SERUM LIPIDS

Parsons [13] treated 50 patients with IM $MgSO_4$ of whom 39 showed a fall in cholesterol levels and 11 a rise; 32 exhibited a rise in fibrinolytic activity and 18 a fall, while 42 had a fall in plasmin inhibition and 8 a rise. There was no correlation between serum Mg and cholesterol levels. I found that Mg reduced serum fibrinogen in a majority of patients. Savenkov [45] found a fall in cholesterol levels in 29 out of 41 patients treated with Mg with no change in 9 and a rise in 3. However, epidemiological studies of hard and soft water cities report varying results in relating hardness of water supplies [39, 44, 46, 47] to serum cholesterol levels, nor as a clear pattern emerged from conflicting studies of serum Mg and cholesterol levels in healthy and atherosclerotic patients [39] and in racial groups with differing rates of heart disease [39, 48]. It may be that some patients have satisfactory Mg balance and so control their serum lipids more effectively through the calcium-blocking action of Mg in the adrenal glands and post ganglionic sympathetic nerve endings [10, 11], thus preventing the release of catecholamines which mobilize free fatty acids from adipose tissue [24]. Excessive mobilization may possible lead to increased body production of cholesterol and to higher serum levels. I found that Mg therapy appeared to lower serum cholesterol more effectively in a soft water area where total body Mg is more likely to be reduced.

In one study [44], non-smokers living in hard water areas were reported to have lower serum cholesterol levels than those in soft water areas, but smokers, ex-smokers, cigar and pipe smokers did not show any significant difference. Nicotine promotes catecholamine release in the adrenals and at sympathetic nerve endings [25] and appears to prevent the cholesterol-lowering effect noted in non-smokers which could possibly be mediated by higher Mg status [39] in residents of hard water areas.

CONCLUSION

The successful use of IV $MgSO_4$ as a powerful calcium-blocking vasodilator is described in angina, AMI, cardiac failure, NHCVD and peripheral vascular disease. IV $MgSO_4$ appears to relieve completely or markedly improve all patients with angina unless severe double or triple vessel disease is present. It is suggested that the powerful vasodilating action of $MgSO_4$ in coronary disease opens permanently collateral circulation in the heart. Routine early $MgSO_4$ therapy in AMI is doubly effective in that it appears to prevent arrhythmias as well as increasing collateral circulation, often with immediate relief of chest pain and reduction of infarct size. It also offers an effective treatment for NHCVD. Mg therapy has great therapeutic potential in arterial disease and has the prime advantages of being cheap and free from unwelcome side-effects.

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