Thorax (1972), **27**, 212.

Magnesium in patients undergoing open-heart surgery

M. P. HOLDEN, M. I. IONESCU, and G. H. WOOLER

Department of Cardiothoracic Surgery, The General Infirmary at Leeds, Leeds, Yorkshire

Measurements of serum and urinary magnesium levels were made together with the other electrolytes, haematocrit, pH, and albumin in patients comprising two groups—one group of 50 patients undergoing heart valve replacement, and the other, 30 patients undergoing non-perfusion thoracic operations.

Low serum magnesium levels were found in some patients admitted to hospital who were or had recently been in congestive heart failure. All patients were found to have low serum magnesium levels postoperatively, but to a greater degree and for a longer period following open-heart surgery. The latter group exhibited hypomagnesuria postoperatively.

The literature is reviewed in an attempt to explain the reasons for the changes in the magnesium levels.

It is concluded that the changes observed in this limited study warrant further detailed investigation including the use of a double blind trial for assessing the therapeutic value of administering magnesium salts to patients undergoing open-heart surgery.

It is standard practice to measure sodium, potassium, and urea in the blood, and occasionally in the urine, before and after major surgical procedures. This is especially so during open-heart surgery. There is much interest currently in the level of serum potassium in view of its known effects on myocardial function when its concentrations are outside the physiological range (Lockey, Longmore, Ross, and Sturridge, 1966). Attempts are diligently made to maintain normal serum potassium levels with large doses of oral and intravenous potassium salts pre- and postoperatively.

Calcium and magnesium ions are quantitatively the third and fourth most important cations in the body. The effects of calcium on myocardial function are generally known. It is involved in the physiochemical process of contraction and relaxations of the myofibrils (Heilbrunn and Wiercinski, 1947). However, the effects of magnesium are little known and little attention is paid to its estimation clinically. This is surprising considering its importance in so many metabolic pathways, especially those of oxidation and energy transfer. It is an essential co-factor in over 95 metabolic reactions in which inorganic phosphate is involved (Schroeder, Nason, and Tipton, 1969).

With regard to the disturbances of myocardial metabolism during anoxic arrest, ventricular fibrillation, and coronary perfusion (Moffit, Maher, and Kirklin, 1965; Moffit, Rosevear, and McGoon, 1969) and the known reciprocal function of Ca^{++} ions in sarcomere contraction, we decided to investigate the possibility of serum and urinary magnesium changes in patients undergoing open-heart surgery. While appreciating that only 1% of total body magnesium exists in the extracellular fluid, we accepted Wacker and Parisi's (1968) statement that measurement of serum magnesium is the quickest, simplest, and most effective first approach to the evaluation of magnesium deficiency states. If the clinical situation is suggestive of magnesium deficiency and the serum values are normal, then erythrocyte magnesium and 24-hour urinary excretion of magnesium should be measured. If the latter two are normal then magnesium deficiency is unlikely. Skeletal muscle gives the most reliable index of body magnesium (Lim, Jacob, Dong, and Khoo, 1969). Hypomagnesaemia can occur when cellular magnesium is normal, and cellular depletion can exist in the presence of normal serum levels. If in the presence of normal pH, hydration, and electrolyte balance a 24-hour specimen of urine contains less than 25·0 mg, then depletion probably exists (Henzel, De Weese, and Ridenbour, 1967).

An attempt was made to correlate changes in serum magnesium levels and known postperfusion problems such as cardiac arrhythmia, cerebral dysfunction, and poor peripheral blood circulation.

To ascertain if the possible changes in serum and urinary magnesium were part of the metabolic response to trauma or due solely to the effects of total body perfusion, using the 'Pemco' heart-lung machine, we carried out the same measurements on a similar number of closed cardiac patients and non-cardiac thoracic patients undergoing operation.

MATERIAL AND METHODS

The measurements were made on (group 1) 50 patients (38 female, 12 male) randomly selected and undergoing valve replacement during 1969 and (group 2) three patients having closed mitral valvotomy and 30 patients undergoing non-cardiac operations such as lung resections and all types of oesophageal surgery. The age range in the open-heart group was 25 years to 55 years (mean 40 years) and in the other group 27 years to 70 years (mean 45 years). Blood samples were taken from a vein without stasis and on each occasion the following estimations were performed: Na, K, Cl, CO_2, urea, pH, Ca, Mg, albumin, haematocrit. At the same time part of a 24-hour collection of urine was analysed for Na, K, Cl, urea, Ca, Mg, pH, and specific gravity. The electrolytes were all measured in order to correlate their changes with those of the magnesium. The haematocrit was measured to make any dilutional corrections. Albumin was determined because magnesium exists in two parts in the plasma, diffusible and non-diffusible (Watchorn and McCance, 1932). The non-diffusible part is bound to serum protein, mainly albumin. The diffusible magnesium represents 60 to 85% of total serum magnesium content.

However, it is debatable whether diffusible magnesium is affected by the level of proteins in the serum (Aikawa, 1963a). Changes in pH of blood affect protein-bound unfilterable magnesium (MacIntyre, 1968).

Patients came into hospital one week before the operation was to be performed, and the first samples were taken to form a base line. Samples were repeated on the morning of the operation, six hours after operation, on the first, third, and seventh postoperative days and, finally, the day of discharge, which varied from 16 to 40 days (average 22 days). Due to the large number of samples necessary it was not possible to obtain them during every operation. Therefore, 10 patients undergoing open-heart procedures and 10 patients undergoing closed cardiac and non-cardiac operations were randomly selected for additional sampling at the following times: at the beginning of operation; after half an hour of perfusion (in open-heart cases); and at the end of the operation.

Patients were randomly selected, but those who had an elevated blood urea before operation were not included in this series, because it is recognized that hypermagnesaemia occurs in renal failure (Aikawa, 1963b) even in the presence of magnesium depletion (Lim and Khoo, 1969).

The magnesium levels were determined by atomic absorption spectrophotometry and during the period, the laboratory analysed specimens containing known amounts of magnesium, and this showed that there was no systematic drift in the accuracy or precision.

The results are expressed in milligrammes per 100 millilitres (mg%) for serum levels. Care should be taken when comparing the findings of various authors due to the fact that the atomic weight of magnesium is 24 with a valency of 2. The results expressed in milligrammes per cent (mg%) or in milliequivalents per litre (mEq/litre) are often similar numerically.

The urine results are expressed in milligrammes per 24 hours and additionally in milligrammes per cent where many samples were sent during a given 24-hour period. The laboratory normal range for serum magnesium is 1·8–2·2 mg%. The lower limit of urine magnesium excretion per 24 hours is set at 25 mg.

RESULTS

All samples were taken without stasis and with the pH in the normal range except for those obtained during perfusion in the open-heart group when the range of pH of the blood was 7·31–7·49.

Conveniently, the haematocrit and serum albumin levels were all within physiological limits in the samples examined.

The results are presented in Tables I to VI and in Figures 1 and 2.

Low serum magnesium levels were found in patients admitted to hospital who had been or who still were in congestive heart failure and receiving diuretic therapy. It was not possible to assess the effect of diuretics because both congestive heart failure and diuretics are known to be separately associated with lowered serum magnesium levels, and all the patients on diuretics had been in congestive heart failure.

Low serum magnesium levels were found in all patients postoperatively, but in the open-heart group this occurred during perfusion and lasted for three days and the levels were lower than those found in the group 2 patients. There appeared to be decreased excretion of magnesium in the urine of the open-heart patients during the first two postoperative days.

Figure 1 shows that there is a greater percentage change in mean serum levels of magnesium than there is for calcium or potassium during and after open-heart surgery. This could be a misleading graph in that there were individual changes (both rise and fall) for potassium and, to a lesser extent, calcium, on occasion to dangerous levels.

No definite relationship could be found between the lowered serum magnesium levels and the problems of cardiac arrhythmia, poor peripheral perfusion, and neurological problems in the postoperative period. It would have been necessary to give the patients magnesium therapy and to examine a larger group of patients to assist in making any definite conclusions. This work is taking place and will be published.

Figure 2 demonstrates histographically the levels of serum magnesium obtained in the 50 open-heart patients (group 1) on the first postoperative days.

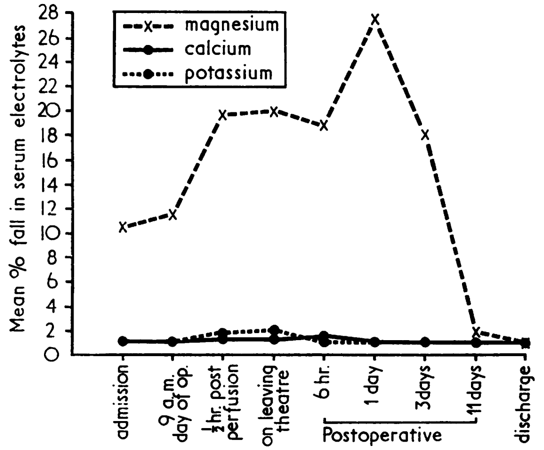

FIG. 1. *Mean percentage fall of serum magnesium, calcium, and potassium levels at various stages of the investigation.*

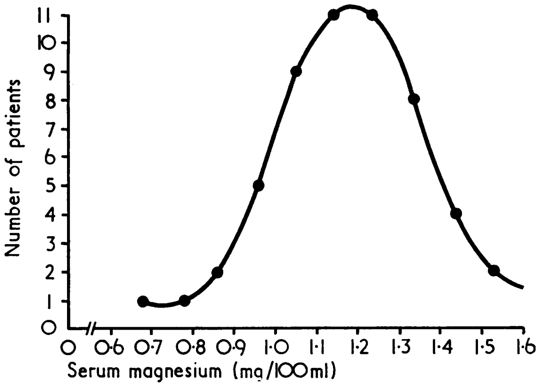

FIG. 2. *Relationship between the number of patients and the range of serum magnesium levels on the first postoperative day.*

DISCUSSION

LOW SERUM MAGNESIUM LEVELS IN PATIENTS ON ADMISSION TO HOSPITAL—EFFECTS OF DIURETICS AND CONGESTIVE HEART FAILURE Only a small number of patients had low serum magnesium levels on admission to hospital in the open-heart group (group 1) (Tables I and V) and they were almost all (6=66%) in the group for mitral valve replacement. Only one patient had a low serum magnesium in the control group (group 2). He had advanced carcinoma of the oesophagus with a long history of dysphagia producing malnutrition (age 69 years).

The patients in the group for mitral valve replacement who had low serum magnesium levels on admission had been in varying degrees of congestive heart failure and were on diuretics. Both these factors have an effect on serum magnesium levels. In a small series, Lazzara *et al.* (1965) showed that there was a greater excretion of magnesium than potassium in the urine of patients with congestive heart failure than in the urine of a control group. Seller, Ramirez, Brest, and Moyer (1966) found serum and erythrocyte magnesium levels to be significantly lower in patients with congestive heart failure than in a control group. In view of the serum sodium also being lower he postulated a dilution factor to be the cause. Hyponatraemia was not seen preoperatively in this study, and postoperatively it never coincided with hypomagnesaemia.

TABLE I

SERUM AND URINARY MAGNESIUM VALUES IN 10 FULLY INVESTIGATED PATIENTS UNDERGOING OPEN-HEART SURGERY

Collection Time of Samples	Mean Serum Mg (mg%)	% Decrease from Normal Serum Mg	Mean Urinary Mg (mg%)	Mean Urinary Mg (mg/24 hr)
Admission day	1·62	10	5	63
Morning of operation	1·60	11	3·6	—
Start of perfusion	1·57	15	4·7	—
½ hour of perfusion	1·32	20	5·4	—
End of operation	1·32	20	8·0	—
6 hr after operation	1·33	19	6·0	—
1st postop. day	1.25	30	2·9	28
3rd postop. day	1·46	18	2·4	30
7th postop. day	1·70	5·5	5·1	60
Day of discharge from hospital	1·78	1	4·9	65

TABLE II

SERUM AND URINARY MAGNESIUM VALUES IN 50 *PARTIALLY* INVESTIGATED PATIENTS UNDERGOING OPEN-HEART SURGERY (GROUP 1)

Collection Time of Samples	Mean Serum Mg (mg%)	Mean Urinary Mg (mg/24 hr)
Admission day	1·65	60
Morning of operation	1·64	—
Start of perfusion	1·60	—
½ hour of perfusion	1·30	—
End of operation	1·31	—
6 hr after operation	1·34	—
1st postop. day	1·22	27
3rd postop. day	1·40	31
7th postop. day	1·70	55
Day of discharge from hospital	1·81	60

TABLE III

SERUM AND URINARY MAGNESIUM LEVELS IN PATIENTS PARTIALLY INVESTIGATED IN NON-OPEN-HEART GROUP (30 NON-CARDIAC PATIENTS AND 3 CLOSED MITRAL VALVOTOMIES—GROUP 2)

Collection Time of Samples	Mean Serum Mg (mg%)	Mean Urinary Mg (mg/24 hr)
Admission day	1·84	50
Morning of operation	1·74	49
Start of operation	—	—
½ hour of operation	—	—
End of operation	—	—
6 hr after operation	1·6	—
1st postop. day	1·31	55
3rd postop. day	1·49	51
7th postop. day	1·7	50
Day of discharge from hospital	1·85	45

TABLE IV

SERUM AND URINARY MAGNESIUM LEVELS IN 10 PATIENTS FULLY INVESTIGATED IN NON-OPEN-HEART GROUP

Collection Time of Samples	Mean Serum Mg (mg%)	Mean Urinary Mg (mg/24 hr)
Admission day	1·83	50
Morning of operation	1·74	49
Start of operation	1·72	—
½ hour of operation	1·70	—
End of operation	1·71	—
6 hr after operation	1·6	—
1st postop. day	1·30	54
3rd postop. day	1·49	51
7th postop. day	1·7	51
Day of discharge from hospital	1·84	45

The effects of diuretics on serum magnesium are well documented. Martin, Mehl, and Wertman (1952) demonstrated hypomagnesaemia following administration of mercurial diuretics, and Smith, Hammarsten, and Eliel (1960) had similar results using the thiazides. However, Seller *et al.* (1966) found that hydrochlorthiazide did not greatly exacerbate the already existing hypomagnesaemia in patients with congestive heart failure. Frusemide (Holden, 1969) and ethacrynic acid (Hanze and Seyberth, 1967) increase the renal excretion of magnesium and calcium. Hanze also found that trimaterene increased the excretion of calcium but conserved magnesium. Smith, Kyriakopoulos, Mock, and Hammarsten (1959) and Hills, Parsons, Rosenthal, and Webster (1955) produced hypermagnesuria with various diuretic agents. Ingestion of large amounts of glucose also increases the urinary excretion of magnesium (Lindeman, Adler, Yiengst, and Beard, 1967) presumably by virtue of the osmotic diuretic effect of the glucose. Jackson and Meier (1968) confirmed this in patients with diabetes mellitus, especially those who are poorly controlled, with resultant ketosis. These patients have marked hypomagnesaemia. The effects of mannitol are not documented, but it seems reasonable to assume that it will produce increased magnesuria by the same osmotic diuretic mechanism. Magnesium salts in themselves have an osmotic diuretic effect when administered intravenously. None of our patients in this investigation had diabetes mellitus as revealed by urine testing on the ward and by blood sugar estimations.

A reduced magnesium intake will play a small part in lowering serum magnesium levels in these patients, who often have poor appetites due to anxiety and depression at the thought of impending major surgery, and from their poor physical condition due to congestive heart failure, or due

TABLE V

NUMBER OF PATIENTS UNDERGOING VARIOUS TYPES OF VALVE REPLACEMENTS WHO HAD CHANGES IN SERUM MAGNESIUM LEVELS

	Site of Valve for Replacement				
	Aortic	Mitral	Tricuspid	Mixed	Totals
Total no. of patients operated upon	10	37	1	2	50 (100%)
No. of patients admitted with low serum magnesium	1	6	1	1	9 (18%)
No. of patients with low serum magnesium 6 hr after operation	10	37	1	2	50 (100%)
No. of patients with low serum magnesium for 3 days postop.	(7)[1]	(32)[2]	1	(1)[3]	(41) (100% of patients still alive)
No. of patients with low serum magnesium on discharge from hospital	0	1	0	0	1 (2%)

[1] (7) = 10 minus 3 postoperative deaths
[2] (32) = 37 minus 5 postoperative deaths
[3] (1) = 2 minus 1 postoperative death

TABLE VI

RELATIONSHIP BETWEEN LOW SERUM MAGNESIUM LEVELS AND CONGESTIVE HEART FAILURE (CHF) AT TIME OF ADMISSION TO HOSPITAL

	Site of Valve for Replacement				
	Aortic	Mitral	Tricuspid	Aortic and Mitral	Totals
Total no. of patients operated upon	10	37	1	2	50 (100%)
No. of patients admitted with low serum magnesium	1	6	1	1	9 (18%)
No. of patients admitted with low serum magnesium without CHF	0	1	0	0	1 (2%)
No. of patients admitted with low serum magnesium with CHF	0	5	1	1	7 (14%)
No. of patients admitted with low serum magnesium on diuretics	0	5	1	1	7 (14%)
No. of patients admitted with normal serum magnesium but with CHF	1	0	0	1	2 (4%)

to anorexia and nausea produced by the many oral drugs they are taking.

Some of the patients for valve replacement had poor renal function as judged by creatinine clearance studies (9 patients=19%) but unless there is gross renal disease this should not affect magnesium excretion or balance. Steele, Wen, Evenson, and Rieselbach (1968) comment that the chronically diseased kidney has the capacity 'to maintain a normal absolute rate of magnesium excretion per nephron' until advanced disease supervenes and then hypermagnesaemia is likely to result (Lim *et al.*, 1969).

CHANGES IN SERUM AND URINARY MAGNESIUM LEVELS DURING OPERATION—EFFECT OF CITRATED BLOOD, EXCHANGE TRANSFUSION, AND HAEMOLYSIS A decrease in serum magnesium may be due to the following factors. The priming of the heart-lung machine is achieved in most centres with a solution containing varying proportions of citrated blood. We used a 50% dilution with all patients during this period. During the operation the blood volume is maintained with varying amounts of citrated blood and a flow rate of 3 litres/m^2/min is obtained in most patients. The total amount of citrated blood that is used during one valve replacement operation varies from 5 pints normally to 10 pints in exceptional cases. By the end of the operation fresh blood is usually available. Bajpai, Sugden, Stern, and Denton (1967) found that citrated blood in neonatal exchange transfusions produced decreasing levels of ionized magnesium in the patient's serum. (Citric acid forms a weakly dissociated salt with divalent cations such as Ca^{++} and Mg^{++}.) Measuring the serum magnesium for the subsequent three days, he found that it returned to normal spontaneously in all the patients examined. This may have been due to the release of Mg^{++} ions as the citrate part of the salt is metabolized, or due to release of protein-bound magnesium, or even a shift of intracellular magnesium to the extracellular fluid space.

It is possible that a high flow perfusion may greatly increase the urinary excretion with a subsequent increase in urinary loss of magnesium, especially in centres where mannitol is routinely added to the priming fluid. Table I shows an increased urinary magnesium (mg%) towards the end of operation but this had no direct relationship to perfusion flow rate. It is well recognized that the serum haemoglobin levels increase during perfusion, depending on the length of operation, the type of materials in the pump system (a Pemco heart-lung machine with a Kay-Cross disc oxygenator was used during this period), and the care with which the blood is sucked from the pericardium. This increase in plasma haemoglobin is an indication of the amount of haemolysis occurring. Thus, if haemolysis occurs it follows that the magnesium content of the erythrocyte, which is much higher than the serum, will be discharged into the circulating plasma.

Therefore, this rise may partially or completely counteract the reduction due to the citrate and the partial exchange transfusion.

POSTOPERATIVE CHANGES IN SERUM AND URINARY MAGNESIUM LEVELS—ADDITIONAL EFFECTS OF HAEMORRHAGIC HYPOTENSION AND MYOCARDIAL ISCHAEMIA In spite of increased tissue catabolism and possible acidosis (due to low cardiac output producing anaerobic metabolism) producing a shift of intracellular magnesium to the extracellular fluid space (Martin and Jones, 1961) which occurs postoperatively, the serum magnesium levels fall to their lowest point on the first postoperative day and remain so for at least three days (Tables I and IV). This confirms the findings of Sawyer *et al.* (1970) and Heaton (1964). Heaton also showed that normally the postoperative urinary magnesium increases, but if the dietary intake has been reduced preoperatively there will be a diminished magnesuria postoperatively.

The possible factors responsible for the postoperative hypomagnesaemia will be in part the same as those in the operative period. They are the use of citrated blood and the resulting exchange transfusion. Obviously time taken in theatre to produce haemostasis and thus reduce postoperative bleeding will limit these two factors, and the use of fresh blood will help also to prevent a further fall in serum magnesium.

Postoperative hypotension due to low cardiac output or low blood volume may play a part in lowering serum magnesium levels as shown by the observation on dogs by Cánepa and Gómez-Poviña (1965) that haemorrhagic hypotension markedly decreased myocardial magnesium and sodium but increased potassium content. Anaesthesia without haemorrhagic hypotension did not change the potassium but decreased to a lesser extent the magnesium and sodium. Cummings (1960) noted similar changes in infarcted areas of dog myocardium following coronary occlusion. Figure 1 shows a much greater overall change in serum magnesium as opposed to calcium and potassium.

We did not take myocardial biopsies to assay magnesium levels because specimens from the control group were not available.

The effect of myocardial infarction or ischaemia during the operation or afterwards is difficult to assess. Hughes and Tonks (1965) found reduced serum magnesium in all male patients presenting with myocardial infarction, but only in one-third of the females. However, Murnaghan *et al.* (1969) found elevated magnesium levels in patients with coronary artery disease.

Table I shows a reduction of total urinary loss of magnesium and decreased urinary magnesium concentrations in the open-heart group, beginning 12 hours after the operation, but not in the non-open-heart group (Tables III and IV), in agreement with the findings of Sawyer *et al.* (1970). They also noted that the more severe the surgical procedure, the greater was the retention of magnesium by the kidneys. Walker, Fleming, and Stewart (1968) had conflicting results in that they observed an increased excretion of magnesium and nitrogen in the urine for six days. They assumed that this was due to release of magnesium from damaged cells. These differences seem to depend on the degree of surgical trauma and also on the preoperative magnesium intake, as demonstrated by Heaton (1964) and Heaton and Parsons (1961). They were able to produce a positive magnesium balance by feeding large amounts of oral magnesium (just insufficient to produce purgation). This diet also produced a positive nitrogen balance.

Patients suffering from major burns were found to have hypomagnesaemia, 55% with symptoms (Broughton, Anderson, and Bowden, 1968). The hypomagnesaemia is presumably due to hypotension, loss of plasma, and reduced magnesium intake subsequently, and additional surgical trauma. These three factors are very common during and after open-heart operations.

By the time of discharge 98% of the patients undergoing valve replacement had normal serum magnesium even though 90% of them had received diuretics during the postoperative period.

The biological effects of magnesium on the heart, blood vessels, and nerve cell membranes, its importance in acetylcholine release, and the electron microscopic appearances of the myocardium in magnesium deficiency will be discussed elsewhere when the results of magnesium therapy in patients undergoing open-heart surgery are published.

CONCLUSIONS

A limited investigation such as this carried out on a relatively small number of patients may produce results which must be treated with caution. However, the results show these abnormalities:

1. Patients with valvular heart disease who had been in congestive heart failure and on diuretics were more likely to be admitted with lowered serum magnesium than were those who had not been in heart failure (Table VI).

2. Most patients with valvular heart disease who had undergone valve replacement on perfusion had lowered serum magnesium levels for the first three postoperative days with diminished excretion of magnesium in the urine (Table I).

3. All patients who had undergone major surgery had a lowered serum magnesium on the first postoperative day (Table IV). This suggests that the reduction in serum magnesium in the open-heart group is in part due to the metabolic response to trauma.

4. Abnormalities in serum and urinary levels of magnesium had all disappeared spontaneously (except in one case) by the time the patients were

discharged from hospital although 90% of them were receiving diuretic therapy.

We wish to thank Dr. Brian Payne, senior lecturer in the Department of Chemical Pathology at Leeds General Infirmary, for helping to plan the investigations and for supervising the laboratory estimations, Dr. Christopher Fleming for taking most of the samples, and Sisters Elizabeth Loach and Mary Poole and their respective staffs.

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