Preliminary Communications

Plasma Ionized Calcium in Hypomagnesaemia*

The association of hypocalcaemia and hypomagnesaemia, both responding to magnesium but not to calcium supplements, has been reported in cattle (Smith, 1961), sheep (L’Estrange and Axford, 1964), and man (Fletcher et al., 1960; Petersen, 1963; Heaton and Fourman, 1963; Friedman et al., 1967).

Heaton and Fourman reported seven cases of hypocalcaemia and hypomagnesaemia in which both plasma calcium and magnesium rose when magnesium was given orally or intravenously. They suggested that magnesium deficiency interferes with the release of calcium from bone, and that correction of the deficiency increases the movement of calcium into the plasma. Jones and Fourman (1966) have shown that intravenous infusion of magnesium reduces total plasma calcium levels in normal people.

**Patients and Method**

The first patient was diagnosed in 1963 as having intestinal lymphangiectasia. She had had recurrent episodes of tetany associated with low plasma calcium levels for many years. Recently the tetany had proved refractory to intravenous calcium gluconate. Plasma magnesium was shown to be 0.5 mEq/l., and the tetany disappeared once intramuscular magnesium therapy was begun. A rise in total plasma calcium of 1.45 mEq/l. was noted after six days of magnesium therapy. Previous to magnesium therapy the serum alkaline phosphatase was 5 K.A. units, but rose to 20 K.A. units after magnesium. It remained at this level in the few days before the infusion. Blood urea was 38 mg./100 ml., serum phosphate 1.7 mEq/l., and there was no radiological evidence of metabolic bone disease.

The second patient was diagnosed in 1962 as having adult coeliac disease. In the past his episodes of tetany had been relieved by calcium supplements, but recently large doses of calcium intravenously had produced only temporary relief. It was then noted that his plasma magnesium level was 0.95 mEq/l. Blood urea was 21 mg./100 ml., serum phosphate 1.2 mEq/l., and there was no radiological evidence of bone disease.

Both patients had been treated with vitamin D for many years, but there was no response with respect to plasma calcium and magnesium levels.

During episodes of tetany both patients were given infusions of 50% magnesium sulphate in 5% dextrose lasting two hours. The first patient received 100 mEq of magnesium, and the second patient 70 mEq, given as 50% magnesium sulphate in 250 ml. of 5% dextrose over a period of two hours.

Blood samples were taken without venous stasis before infusion, then hourly for four hours, and at 6, 8, and 22 hours. At the times when blood samples were taken the patients were examined for latent tetany (Trousseau’s sign). Plasma magnesium was estimated by atomic absorption (Willis, 1960), total calcium by calcium oxalate precipitation (Kramer and Tisdall, 1921), ionized calcium by biological technique (McLean and Hastings, 1934), and serum phosphate and alkaline phosphatase by autoanlyser.

* Based on a paper presented at the Scientific Meeting of the Royal Australasian College of Physicians, Melbourne, on 12 October 1967.

**Results**

The plasma concentrations of magnesium, total and ionized calcium, and alkaline phosphatase immediately before, during, and after infusion are shown in the Table. In the first patient the plasma magnesium rose to a high level of 4.45 mEq/l. at two hours. Total calcium rose from 5.5 to 7 mEq/l. (normal 5–7 mEq/l.) and ionized calcium from 1.9 to 3.5 mEq/l. (normal 2.5–3.5 mEq/l.) at eight hours. Serum alkaline phosphatase rose from 20 to 40 K.A. units at six hours. Serum phosphate levels remained unchanged. In the second patient the plasma magnesium rose to 5.5 mEq/l. at two hours. Total calcium rose from 5.8 to 7.5 mEq/l. and ionized calcium from 1.7 to 3.5 mEq/l. at eight hours. Serum phosphate and phosphatase levels did not change.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Plasma Magnesium (mEq/l.)</th>
<th>Plasma Total Calcium (mEq/l.)</th>
<th>Plasma Ionized Calcium (mEq/l.)</th>
<th>Serum Alkaline Phosphatase (K.A. units)</th>
<th>Latent Tetany</th>
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<tbody>
<tr>
<td>Patient 1. 100 mEq magnesium</td>
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<td></td>
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<td>0</td>
<td>1.24</td>
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<tr>
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<td>7.2</td>
<td>3.5</td>
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<td>Patient 2. 75 mEq magnesium</td>
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In both patients Chrveste's and Trousseau's signs were positive before infusion, but were negative when the infusions had ended.

**Discussion**

The results of these two infusions show that intravenous magnesium permits mobilization of ionized calcium into the plasma in hypomagnesaemic individuals. The rise in plasma calcium levels in hypomagnesaemic patients given magnesium therapy seems to be accounted for by a rise in the ionized fraction. Though the source of the ionized calcium is not known it is probably derived from the exchangeable bone pool or intracellular sites—for example, muscle cells. It is unlikely that it comes from the protein-bound fraction, as this does not change significantly during the infusions.

Calcium and magnesium ions compete actively for intracellular sites in renal tubules (Samny et al., 1960), gastrointestinal mucosa (Alcock and MacIntyre, 1962), and other body tissues (Wallach et al., 1963), and mobilization of hypomagnesaemia may produce flushing of calcium ions from muscle cells through this competitive mechanism. We favour the suggestion of Heaton and Fourman (1965) that magnesium deficiency prevents liberation of calcium from bone. We would suggest that correction of the deficiency immediately allows the mobilization of ionized calcium from the exchangeable bone pool. The rise in serum alkaline phosphatase during the first infusion might suggest increased bone activity, though it is known that magnesium ions are activators of this enzyme throughout the body.
Neuman and Neuman (1957) have implied a process of ion exchange whereby calcium ions can enter the extracellular fluid only if the bone crystal takes up other cations—for example, Mg++. To maintain electroneutrality. In the presence of magnesium deficiency this exchange process may be inhibited. Correction of the deficiency would allow mobilization of calcium ions from bone.

The absence of a significant change in serum phosphate levels during these infusions suggests that the effect of magnesium in restoring normal plasma ionized calcium levels is not directly mediated through the parathyroid gland. However, it is possible that magnesium deficiency causes blunting of end-organ—for example, bone—responsiveness to parathyroid hormone.

The magnesium deficiency tetany syndrome in man has been described by Vallee et al. (1960). We would suggest that the tetany occurring in this syndrome is due to low plasma ionized calcium levels, despite apparently normal total calcium levels. The rise in plasma ionized calcium to normal levels during magnesium infusion explains why magnesium therapy will relieve tetany in these patients.

It would appear that the tetany seen with hypomagnesaemia is not attributable to magnesium directly but as a result of magnesium deficiency causing depression of ionized plasma calcium levels. Hypomagnesaemia without lowering of plasma ionized calcium levels has not been reported; this hypothesis awaits confirmation.

SUMMARY

Plasma levels of ionized calcium were measured before and after intravenous infusion of magnesium in two patients with tetany and hypomagnesaemia. The tetany reported in association with hypomagnesaemia seems to be a consequence of low plasma ionized calcium. The nature of the defect is uncertain, but evidence is consistent with inhibition of release of ionized calcium from the exchangeable bone pool as a result of magnesium deficiency.

We thank Dr. J. A. Owen, Director of Biochemistry, and his staff for invaluable advice and assistance, and Dr. T. E. Lowe and Dr. D. Coventry for permission to investigate the second patient. Plasma total and ionized calcium levels were measured by one of us (W. G. N.).

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REFERENCES


Medical Memoranda

Toxic Epidermal Necrolysis Caused by Skin Hypersensitivity to Monosulfiram


This paper records a peculiar and dangerous complication of treatment with the antiscabetic preparation monosulfiram, which caused an eruption that was diagnosed as toxic epidermal necrolysis of Lyell (1956), and made the patient very ill. Later, on patch-testing, she was found to have had a previously acquired skin hypersensitivity to one of the common rubber vulcanizing accelerators, tetramethylthiuram disulphide, a substance very similar in composition to monosulfiram.

CASE HISTORY

A housewife aged 47, a scabies contact, was admitted to hospital as an emergency case with a three-day history of a rash that had developed three and a half hours after applying diluted Tetmosol (monosulfiram) solution to her body below the neck. She had not taken any alcohol at this time. In 1940 she had consulted the late Dr. Henry MacCormac about rubber dermatitis on her hands which had developed while working in a munition factory. Since then she had been unable to wear certain rubber-containing garments, and after blowing up balloons at Christmas she got an itchy rash on her face. Examination showed that a diffuse erythema with considerable dermal oedema affected all of her body, though initially it was less severe on the face and neck.

On her admission the red areas were rapidly becoming covered by large numbers of small pustules which were coalescing to form lakes of subcorneal pus. The horny layer now started to desquamate and to be shed in vast sheets—the one below her right knee like a stocking in one piece. The pustules were distributed diffusely, and not in groups or in rings. Mucous membranes were unaffected. She had a fever and was severely ill. Toxic epidermal necrolysis was diagnosed as due perhaps to the methylpapa and hydrochlorothiazide with which her hypertension was being treated, or to a systemic effect of monosulfiram absorbed through the skin.

Investigations.—A cytoplast smear from the pustules showed a great quantity of polymorph neutrophils but no bacteria. No organisms were cultured. Blood counts: W.B.C. 20,000 (95% neutrophils, 4% eosinophils). Two weeks later: W.B.C. 8,900 (48% neutrophils, 15% eosinophils) (1,335 absolute count), 31% lymphocytes, 5% monocytes, 1% plasma cells). The following tests were normal: haemoglobin, urine (×3), blood culture, serological tests for syphilis, blood electrolytes, blood urea, random blood sugar, blood uric acid, liver function, serum vitamin B12, and serum folate.

The oedema increased noticeably for the first 10 days; she gained 20 lb. (9 kg) in weight and had oliguria. Later the jugular venous pulsation was raised to about 6 cm. and the liver became palpable. A large circulating blood volume from fluid retention and protein loss through the skin rather than cardiac failure was complicated. Chest x-ray examination (×3) showed no evidence of heart failure, and the E.C.G. sinus tachycardia only. The serum proteins totalled 5.0 g./100 ml, but they had risen to 6.3 g./100 ml two weeks later.