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Short Communication

Prophylaxis Against Hypomagnesaemia Induced by *cis*-Platinum Combination Chemotherapy

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Summary. *Hypomagnesaemia is recognised as a feature of the renal tubular defect produced by cis-platinum therapy for cancer. It may be sufficiently severe to cause tetany and grand mal fits. Attempts to correct established hypomagnesaemia whilst continuing cis-platinum therapy have not proved satisfactory. We have therefore investigated the prophylactic addition of 3 g magnesium sulphate to the high-dose platinum regimen with which metastatic malignant teratoma is treated in this unit. Serum magnesium levels have been measured in eight patients treated in this way and compared with those recorded for eight matched patients previously treated without routine magnesium supplements. Magnesium levels fell into the range frequently associated with clinical manifestation in five of the eight unsupplemented patients and only one of those given magnesium prophylactically. Mean serum magnesium levels were significantly higher in the supplemented group when compared using the paired t-test ($P < 0.01$). Routine supplementation with intravenous magnesium sulphate is a simple and effective way of preventing symptomatic hypomagnesaemia associated with cis-platinum therapy.*

Introduction

cis-Platinum (*cis*-diamminedichloroplatinum; Neoplatin) is a chemotherapeutic agent of proven value in the treatment of malignant teratomas and certain other tumours. Since its introduction in the mid-1970s its wide range of toxic effects has become apparent [17]. These include nausea and vomiting, myelosuppression, ototoxicity, peripheral neuropathy, and nephropathy.

Platinum-induced renal magnesium wasting [12] may lead to hypomagnesaemia, manifest as muscular twitching, tetany, and generalised convulsions [9]. Nystagmus and dysphagia have also been described [7]. Furthermore, hypomagnesaemia can lead to hypocalcaemia by causing parathyroid gland dysfunction [14] or end-organ refractoriness to the effects of parathormone [3].

We have encountered various difficulties with oral and parenteral replacement therapy in established hypomagnesaemia. It was therefore decided that all patients undergoing treatment with high-dose *cis*-platinum should receive routine IV magnesium supplements. In this paper we attempt to assess, retrospectively, the value of this manoeuvre by analysis of serum magnesium and calcium levels.

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Patients and Methods

Patients with metastatic malignant teratoma were treated as described by Newlands et al. [11]. Platinum was given at a dose of 120 mg/m^2 with hydration and mannitol diuresis. The other agents were vincristine, methotrexate, bleomycin, VP 16–213, actinomycin-D, and cyclophosphamide. The total number of platinum-containing courses received by each patient was related to the extent and responsiveness of their disease.

Patients treated since 6. 3. 1981 have received routine IV magnesium supplements as a prophylactic measure. Magnesium sulphate 1 g (providing 4 mmol magnesium) was added to each of the first 3 l of fluid in the *cis*-platinum hydration regimen, as shown in Table 1.

The last consecutive patients completing treatment without routine magnesium supplements prior to that date were compared with consecutive patients treated subsequently with supplementation. Patients with abnormal renal function, as judged by serum urea and creatinine levels, were excluded, as were patients who had had previous chemotherapy at other hospitals.

The two groups were matched for age, sex, and number of high-dose *cis*-platinum courses. There were six men and two women in each group, with a mean age of 31 years (range 18–63). The duration of chemotherapy ranged from 2 to 12 months, with a mean of 6.6 months in the unsupplemented group and 5.6 months in the supplemented group. Each patient received between two and eight (median 3) *cis*-platinum-containing courses.

Table 1. *cis*-Platinum hydration with magnesium sulphate supplements

	125 ml 10% mannitol IV stat
Hour 1	1 l N/saline with 1 g KCl and 1 g $MgSO_4$ IV 100 ml 10% mannitol IV
Hour 2	1 l dextrose 5% with 1 g KCl and 1 g $MgSO_4$ IV 100 ml 10% mannitol IV
Hour 3	1 l N/saline with 1 g KCl and 1 g $MgSO_4$ IV 100 ml 10% mannitol IV
	cis-Platinum 120 mg/m^2 IV stat
Hour 4	1 l dextrose 5% with 1 g KCl IV 100 ml 10% mannitol IV
Hour 5	1 l N/saline with 1 g KCl IV 100 ml 10% mannitol IV
Hour 6	1 l dextrose 5% with 1 g KCl IV 100 ml 10% mannitol IV

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Table 2. Serum magnesium and calcium levels in patients with malignant testicular or ovarian teratoma

Unsupplemented				Routinely Supplemented			
Patient	Serum Mg levels (mmol/l)		Mean serum calcium (mmol/l)	Patient	Serum Mg levels (mmol/l)		Mean serum calcium (mmol/l)
	Mean	Lowest			Mean	Lowest	
1	0.60 (7)	0.40	2.29	9	0.75 (4)	0.70	2.31
2	0.50 (2)	0.50	2.33	10	0.72 (4)	0.60	2.38
3*	0.36 (10)	0.20	2.03	11*[1]	0.72 (5)	0.70	2.41
4	0.50 (4)	0.40	2.36	12	0.78 (5)	0.70	2.29
5*	0.50 (1)	0.50	2.43	13*	0.62 (5)	0.40	2.27
6	0.72 (7)	0.60	2.29	14	0.78 (6)	0.70	2.28
7	0.70 (2)	0.70	2.29	15	0.78 (5)	0.70	2.27
8	0.70 (2)	0.60	2.34	16	0.73 (3)	0.70	2.39

* Female patients
*[1] Mixed mesodermal tumour of ovary
() = number of samples
Normal ranges: magnesium: 0.68–0.96 mmol/l; calcium: 2.20–2.65 mmol/l

Blood samples for calcium assay were taken twice weekly during treatment. Samples for magnesium estimation were obtained 10–28 days after *cis*-platinum administration. Additional samples were taken when clinical features suggested hypomagnesaemia.

Magnesium analyses were performed by atomic absorption spectrophotometry [16] on a Hilger and Watts Atomspek Mark 3 or Pye Unicam SP 1900. Calcium assays were performed colorimetrically on an autoanalyser (Technicon AA II*).

Results

Table 2 shows that serum magnesium levels in the unsupplemented group were more frequently below the normal range and particularly below 0.5 mmol/l, when clinical manifestations of hypomagnesaemia are likely [18].

A mean magnesium level was obtained for each patient. These were analysed by the paired *t*-test, which showed the results in the routinely supplemented group to be significantly higher than in the unsupplemented patients ($P < 0.01$).

Calcium levels were within the normal range except in one patient (patient 3), in whom severe protracted hypomagnesaemia was associated with significant hypocalcaemia.

Analysis by paired *t*-test fails to show any difference in calcium levels between the two groups ($P > 0.5$).

Discussion

A normal diet provides 10–20 mmol magnesium daily, one third of which is absorbed [15]. The total body content is 21–28 g (about 1,000 mmol), half being in bone and the rest in muscle, liver, soft tissues, and erythrocytes. Magnesium is transported in serum bound to plasma proteins, and 95% of filtered magnesium is actively reabsorbed in the proximal and distal tubules and loop of Henle [1]. In the presence of low magnesium intake, renal excretion is less than 0.5 mmol/24 h [15]. Thus intake and output are well balanced and the daily requirement for magnesium is very low.

Cytotoxic chemotherapy may cause hypomagnesaemia in a number of ways. Anorexia, nausea, and vomiting reduce magnesium intake. Volume expansion, frusemide, and mannitol affect renal handling of magnesium [4, 10] and methotrexate-induced tubular toxicity [2] may increase magnesium loss. Disturbance of magnesium metabolism rarely complicates the use of other cytotoxics, though it has recently been described during treatment with adriamycin and cytarabine [5].

Hypomagnesaemia is particularly associated with *cis*-platinum, a known nephrotoxin. Focal acute tubular necrosis [6] is accompanied by rising urea and creatinine levels and is ameliorated by mannitol diuresis [8]. Gross deterioration in renal function may be preceded by syndromes of tubular dysfunction, of which hypomagnesaemia is an example. Schilsky and Anderson noted hypomagnesaemia during *cis*-platinum therapy and demonstrated inappropriate urinary magnesium loss in the presence of low serum levels [12].

Since 1975 we have treated over 150 patients with malignant germ cell tumours with high-dose (120 mg/m^2) *cis*-platinum therapy. Before the association with hypomagnesaemia was known, one patient had an unexplained epileptic fit and several developed tetany in the absence of hypocalcaemia. Following the recognition of *cis*-platinum-induced hypomagnesaemia, all patients developing these symptoms have had serum magnesium levels measured. Overall, less than 5% have become symptomatic, but the incidence was rising with the use of increasing doses of *cis*-platinum. Latterly total doses of 360–1,320 mg/m^2 have been used to obtain complete remission in patients with large-volume metastatic teratoma, especially those referred to us after failing on prior chemotherapy. Magnesium data are available in 21 of 29 patients with metastatic teratoma who underwent treatment in this unit between March 1980 and March 1981. Seven patients (33.3%) had consistently normal serum magnesium levels; 14 (66.7%) were hypomagnesaemic at some time during treatment, 10 (47.6%) being asymptomatic and four (19.1%) being affected by tetany and muscle twitching (3 patients) or fits (1 patient). These symptoms are unpleasant for the patients and those developing fits require further investigation to exclude the presence of cerebral metastases.

We have tried various approaches to this problem. Oral magnesium hydroxide and chloride mixtures cause unacceptable nausea and diarrhoea. Magnesium glycerophosphate tablets (1 g provides 95 mg magnesium) are better tolerated, but even these cause gastrointestinal upset in doses sufficient to restore normal serum levels in a hypomagnesaemic patient.

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Hypomagnesaemia is rapidly corrected by IV magnesium sulphate. Where hypocalcaemia coexists we note a simultaneous rise in serum calcium levels. However, this improvement is often short-lived, presumably because of persistent renal magnesium leak and failure to correct the intracellular deficit [9]. Thus we have seen fits occur in established hypomagnesaemia despite the prior instigation of parenteral replacement therapy.

The results presented here suggest that symptomatic hypomagnesaemia may be effectively avoided by giving magnesium prophylactically. Our data are, however, derived from samples whose timing was imprecisely related to therapy. We may have failed to detect nadir serum magnesium levels. A prospective study, with samples timed in relation to *cis*-platinum and magnesium administration, might clarify this point.

We have now routinely administered parenteral magnesium sulphate to over 35 patients with germ cell tumours, and there have been no further manifestations of hypomagnesaemia. Neither has there been any toxicity from the measure itself, with none of the serum magnesium levels exceeding the normal range. (Muscle relaxation is reportedly marked over 2 mmol/l [13] and a further rise may lead to paralysis.)

Although this is a retrospective study of small numbers of patients we believe we have demonstrated the value of this simple prophylactic measure.

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