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Cis-diamminedichloroplatinum-induced Hypomagnesemia and Renal Magnesium Wasting

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Abstract—*Hypomagnesemia is a well-recognised complication of* cis-*diamminedichloroplatinum (DDP) treatment. We prospectively evlauated 50 patients with advanced malignant disease receiving DDP for the development of hypomagnesemia. Urinary magnesium excretion was measured in 24 patients. The mean serum magnesium fell from* 0.79 mmol/l *(normal* 0.7-1.1 mmol/l) *prior to therapy to* 0.55 mmol/l 3 months *after commencing DDP. All 50 patients had become hypomagnesemic by this time and 10% were symptomatic, requiring oral magnesium supplementation. At* 6 weeks *after commencing DDP only four patients had restricted urinary magnesium excretion to less than* 1.0 mmol/day. *The other patients clearly had inappropriately high levels of urinary magnesium excretion, suggesting that DDP may induce a renal tubular defect in magnesium conservation. Hypomagnesemia is a common complication of DDP therapy which in many patients is asymptomatic. Further, more detailed studies of renal magnesium handling are necessary to determine fully the effect of DDP on urinary magnesium excretion.*

INTRODUCTION

Cis-DIAMMINEDICHLOROPLATINUM (DDP) is an important chemotherapeutic agent with a spectrum of activity against a broad range of solid tumours [1]. Nephrotoxicity has been identified as the common dose-limiting factor [2]. Other toxicities include nausea, vomiting, myelosuppression and high-frequency hearing loss [3].

Renal magnesium wasting and hypermagnesemia have more recently been described with DDP therapy [4, 5]. However, the severity, incidence and mechanism of these side-effects have not been established. Symptoms of hypomagnesemia are nausea, vomiting, weakness, muscular irritability, twitching, convulsions and tetany. A significant proportion of patients with DDP-induced hypomagnesemia may be asymptomatic. Schilsky and Anderson recently suggested that DDP may induce a renal tubular defect resulting in impaired magnesium conservation and subsequently in significant magnesium deficiency [4]. Their study was too small to establish the overall incidence or severity of this complication. This study was designed to determine the incidence and severity of hypomagnesemia in patients receiving multiple courses of DDP, and additionally to evaluate renal magnesium conservation.

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MATERIALS AND METHODS

There were 30 male patients and 20 female patients in this study. The mean age was 54 yr, with a range of 27-83 yr. A wide variety of tumour types were treated with a DDP based regimen. The tumour types and corresponding DDP dosages are shown in Table 1.

RESULTS

The mean pretreatment serum magnesium level was 0.78 mmol/l, with a range of 0.67-0.97 mmol/l, the normal range being 0.70-1.1 mmol/l. Three weeks following the initiation of DDP therapy the mean serum magnesium had fallen to 0.69 mmol/l (range 0.40-0.86 mmol/l). At this time 16 patients (32%) were hypomagnesemic, but only one patient was symptomatic. Three months after the initiation of chemotherapy the mean serum magnesium had fallen further to 0.55 mmol/l (range 0.44-0.69 mmol/l). Figure 1 shows the steady decline in mean serum magnesium levels during this 3-month period. Patients receiving larger doses of DDP (80-100 mg/m^2) developed hypomagnesemia

Table 1. Tumour types and DDP dosages

Tumour	No. of patients	Dosage of DDP (mg/m²)	Other drugs
Small cell lung	15	80	VP16-213
Head and neck	8	50 or 100 (randomized trial)	methotrexate bleomycin
Ovary	7	50	chlorambucil
Testicular	5	100	vinblastine bleomycin
Adenocarcinoma of unknown primary	4	60	vinblastine bleomycin
Non-small cell lung	3	60	vinblastine bleomycin
Cervix	3	60	vinblastine bleomycin
Transitional cell carcinoma of bladder	2	80	methotrexate
Others (including neuroblastoma, lymphoma)	3	80	VM 26 or VP16-213

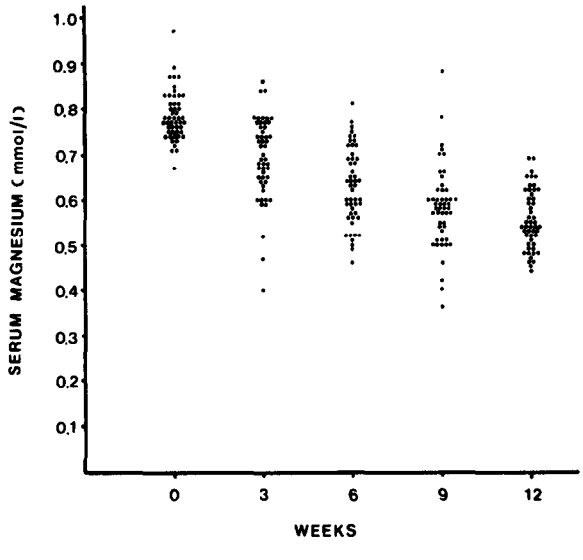

Fig. 1. Serum magnesium levels from commencement of DDP therapy.

Table 2. Rate of fall in serum magnesium according to dose of DDP

Weeks from treatment	No. of patients with serum magnesium <0.7 mmol/l: Low-dose DDP (50-60 mg/m²)	High-dose DDP (80-100 mg/m²)
3	11 (48%)	14 (52%)
6	15 (65%)	23 (85%)
9	18 (78%)	25 (92%)
12	23 (100%)	27 (100%)
Total No. of patients	23	27

somewhat more quickly than patients receiving lower doses of DDP (50-60 mg/m²). Table 2 shows the rate of fall of serum magnesium levels. Six weeks after commencing DDP 15 patients (65%) receiving lower dose DDP and 23 patients (85%) receiving higher dose DDP were hypomagnesemic. However, irrespective of the dose of DDP, no patient had a serum magnesium within the normal range 3 months after commencing therapy. In addition there were no other electrolyte, calcium of uric acid disturbances noted in any patient.

Five patients (10%) developed symptomatic hypomagnesemia. Symptoms reported included muscular weakness, tremulousness and dizziness. One patient had become profoundly hypomagnesemic (0.40 mmol/l) just 3 weeks after commencing therapy, presenting with marked tremulousness. The other symptomatic patients presented between 6 and 12 weeks after commencing DDP treatment. In all symptomatic patients the serum magnesium was less than 0.50 mmol/l and the symptoms resolved following the commencement of oral magnesium supplementation. A further 13 patients (26%) had serum magnesium levels less than 0.50 mmol/l but remained asymptomatic. Oral magnesium supplementation was commenced in eight of these patients. None of these patients were at any time hypocalcemic.

In 24 patients the mean pretreatment urinary magnesium level was found to be 2.8 mmol/day (range 1.0-4.24 mmol/day). In 12 patients the mean urinary magnesium 3 weeks after commencing therapy and prior to the second course of DDP was 2.62 mmol/day (range 0.91-4.3 mmol/day). The mean urinary magnesium prior to the third course of DDP was 1.99 mmol/day (range 1.0-4.1 mmol/day). In the other 12 patients the mean urinary magnesium level 3 weeks after commencing DDP and immediately following the second course of therapy was 1.94 mmol/day

(range 0.55-3.3 mmol/day) and following the third course of therapy was 1.69 mmol/day (range 0.46-3.6 mmol/day). These fluctuations in urinary magnesium levels are shown in Fig. 2.

Six weeks after commencing DDP, when 38 patients (76%) were hypomagnesemic, only four of the 24 patients evaluated for urinary magnesium excretion were conserving urinary magnesium levels to less than 1.0 mmol/day. Urinary magnesium excretion remained at a relatively high level (>1.0 mmol/day) in other patients despite the presence of hypomagnesemia.

DISCUSSION

The kidney is the major regulator of serum magnesium concentration. A number of factors are known to have a role in the control of renal magnesium handling. Sodium reabsorption is inhibited in proximal sites by saline infusion or osmotic diuresis and this is associated with a parallel inhibition of magnesium reabsorption [6]. Hypercalcemia inhibits magnesium reabsorption and this may be on the basis of competition for a common transport site [6]. Tubular transport of magnesium is also influenced by serum magnesium concentration and dietary magnesium deprivation reduces urinary magnesium excretion [6]. The normal kidney is able to restrict urinary magnesium losses to less than 0.5 mmol/day during periods of magnesium deficiency [7].

We found hypomagnesemia to be a very common complication of treatment with DDP. Although all patients became hypomagnesemic only 10% were symptomatic. However, a further 16% of patients were given oral magnesium supplementation when the serum magnesium had fallen to ≤0.5 mmol/l despite absence of symptoms. Had oral supplementation not been commenced then these patients may also have developed symptoms of hypomagnesemia. Despite sometimes profound hypomagnesemia we observed in most of our patients inappropriate levels of urinary magnesium excretion. The expected renal response to such low levels of serum magnesium should be increased reabsorption of magnesium and thus less urinary magnesium. Certainly four patients showed evidence of renal conservation of magnesium in the face of hypomagnesemia. However, these patients were the exception rather than the rule. There appeared to be no real difference in the degree of renal magnesium wasting between the pre- and post-treatment urine collections. These data suggest that the defect in renal magnesium conservation is not simply an acute effect of DDP, but is also observed at least 3 weeks after DDP administration.

It could be contended that the induction of an osmotic diuresis immediately prior to DDP therapy would inhibit renal magnesium reabsorption. This would account for the inappropriately high levels of urinary magnesium in patients who had post-treatment urinary collections. However, the same cannot be the case for the 12 patients who had urinary collection taken before each DDP treatment and before the pre-treatment osmotic diuresis was established. Yet the mean urinary magnesium excretion remained inappropriately high for the level of serum magnesium in these patients as well. In fact the mean urinary magnesium excretion was somewhat lower in the post-treatment collection than in the pre-treatment collection. It is thus

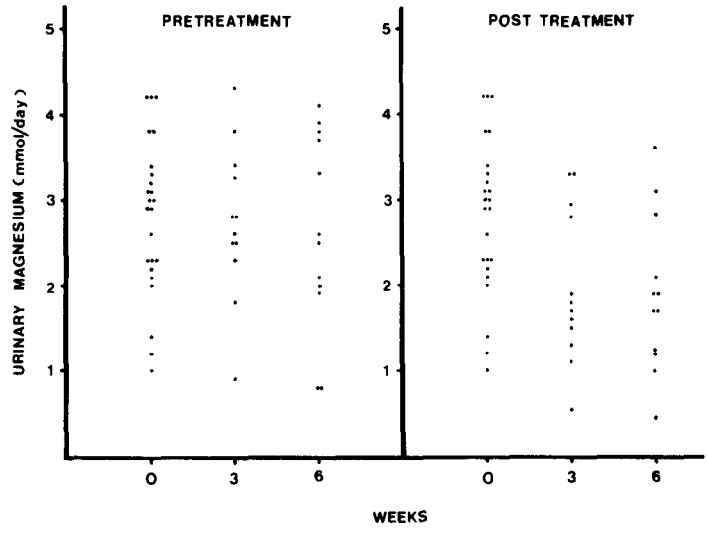

Fig. 2. Urinary magnesium excretion from commencement of DDP showing pre- and post-treatment urine collections. Note: *The 24 pre-treatment urinary magnesium values are shown at the beginning of each graph.*

unlikely that the osmotic diuresis had a significant influence on renal magnesium excretion.

Schilsky and Anderson have recently proposed that DDP induces a renal tubular defect in magnesium conservation [4]. The DDP-damaged renal tubule is unable to conserve magnesium and allows inappropriately large amounts of magnesium to be lost. This is an attractive hypothesis, but no other significant abnormalities of tubular function were observed in their patients. There was no evidence of potassium wasting in this group. We performed no other tests of tubular function on our series of patients. Some other support for their hypothesis comes from studies measuring renal tubular enzyme elevations in patients treated with DDP. Urinary betaglucuronidase activity (UBGA) is the measurement of such an enzyme. UBGA has been shown to be elevated in diseases with renal tubular disruption [8, 9]. Kuhn *et al.* have shown a marked rise in UBGA in patients after DDP therapy, suggesting tubular toxicity due to DDP [10]. Moreover, ultrastructural changes have been seen in the proximal tubules, distal tubules and collecting ducts in renal biopsies obtained from patients treated with DDP [11, 12]. However, identification of the site of DDP-induced renal damage causing renal magnesium wasting will require more accurate knowledge of renal magnesium handling and correlation with functional and ultrastructural changes in renal tubular cells.

There are to date no data on renal magnesium handling in patients with malignant disease not receiving chemotherapy. Such data would form the basis of a control group for comparison with patients receiving chemotherapy, in particular DDP. Clearly further studies are needed to correlate serum and urinary magnesium levels in conjunction with detailed evaluation of renal function in patients receiving DDP. Additionally, other factors which may influence renal magnesium excretion, such as dietary intake of magnesium, sodium and potassium, and other drug usage, would need to be considered. It was not the purpose of this early study to undertake such an extensive evaluation of urinary magnesium handling. However, our early data on urinary magnesium losses do seem to support the hypothesis of Schilsky and Anderson.

Hypomagnesemia is a more common complication of DDP therapy than has been originally thought. In our series of patients followed for 3 months 10% became symptomatic with hypomagnesemia, requiring oral magnesium supplementation. It is possible that with further observation more patients will develop symptoms of hypomagnesemia. The incidence and severity of hypomagnesemia in patients treated with DDP indicate a need for regular surveillance of magnesium levels in all patients receiving DDP, and further studies will be necessary to fully assess the effect of DDP on renal magnesium handling.

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