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Serum potassium, calcium and magnesium in patients receiving ESHAP chemotherapy for relapsed lymphomas

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ABSTRACT Etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) is one of the mostly widely used chemotherapy regimens for patients with relapsed lymphomas. Cisplatin administration is commonly associated with electrolyte imbalance. Careful monitoring of renal function and serum electrolytes is therefore essential in this setting.

Aims: To review the practice of electrolyte monitoring – potassium (K), calcium (Ca) and magnesium (Mg) – in patients receiving ESHAP and the frequency and severity of abnormalities and their management.

Methods: Twenty-one consecutive patients received ESHAP. The medical records of 16 patients were retrievable and reviewed retrospectively. Results of serum K, Ca and Mg were collected prior to and after cycles 1, 2 and 3 of ESHAP, if measured.

Results: Serum K levels prior to every cycle did not show any noticeable change. The means were 4.42, 4.34 and 4.43 mmol/l before cycles 1, 2 and 3, respectively. In one patient hypokalaemia was severe, refractory and symptomatic when preceded by hypomagnesaemia. Serum-adjusted calcium levels showed only minimal reduction. The means were 2.46, 2.40 and 2.38 mmol/l before cycles 1, 2 and 3 respectively. Mean serum Mg levels prior to every cycle showed progressive reduction; 0.84, 0.75 and 0.67 mmol/l before cycles 1, 2 and 3, respectively. This was associated with a progressive increase in the amount of required Mg supplementation. Serum K, Ca and Mg was measured prior to 100%, 67% and 35% of administered cycles, respectively.

Conclusion: In patients receiving ESHAP, hypokalaemia can occasionally be seen, especially if preceded by hypomagnesaemia. Mild cumulative hypocalcaemia is recognised. Hypomagnesaemia is a progressive complication and physicians need be aware of its importance.

KEYWORDS Cisplatin, ESHAP, hypocalcaemia, hypokalaemia, hypomagnesaemia

DECLARATION OF INTERESTS No conflict of interests declared.

INTRODUCTION

Etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) is one of the mostly widely used chemotherapy regimens for patients with relapsed lymphomas. The response rate in the first relapse is about 70%, with half of responders achieving complete response.[1,2] Cisplatin is a particularly effective anti-lymphoma agent in this regimen. The response rate is halved if cisplatin is omitted from the regimen.[2]

Renal toxicity is a common and dose-limiting toxicity of cisplatin. One of the recognised mechanisms of toxicity is renal tubular damage. This is thought to explain the chemical and/or clinical electrolyte imbalance seen. However, recent research indicates that magnesium loss associated with cisplatin treatment may be the result of lowered intestinal absorption.[3] Profound hypomagnesaemia, hypokalaemia and hypocalcaemia have been reported in patients on cisplatin therapy.[4,5]

Careful monitoring of renal function and serum electrolytes is therefore essential during the administration of cisplatin.[6]

We performed a retrospective review to audit the practice of electrolyte monitoring – potassium (K), calcium (Ca) and magnesium (Mg) – in patients having ESHAP chemotherapy, and documented the frequency and severity of abnormalities and their management.

PATIENTS AND METHODS

Twenty-one consecutive patients started ESHAP in one calendar year (January–December 2002) for salvage treatment of relapsed lymphomas in a single cancer centre. The regimen comprises etoposide 40 mg/m^2 on days 1–4, methylprednisolone 500 mg on days 1–5, cytarabine 2 g/m^2 on day 5 and cisplatin 25 mg/m^2 on days 1–4 (repeated every three weeks). Five patients were excluded from this analysis. The records for three of these patients were not

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retrievable, one patient died shortly after cycle 1 (cause of death not related to electrolyte imbalance) and one patient had the first cycle at another facility.

The medical and electronic records of 16 patients were retrievable, reviewed retrospectively and are the subject of this report. We restricted the analysis to the first three cycles of ESHAP. The baseline electrolytes level was that prior to cycle 1. Electrolyte values on day 1 of subsequent cycles were also collected. Some patients had serum electrolyte measurements between cycles if they had hospital visits for any reason other than administration of chemotherapy. Values at these visits were also captured and labelled as interim levels. The lowest values of K, Ca and Mg in any patient were also captured to reflect the extreme picture and were labelled nadir levels.

Standards for the audit were:
1. Patients on ESHAP had serum electrolytes monitored before every cycle. For the purpose of this audit these included K, adjusted Ca and Mg.
2. Mg supplementation should be administered if pre-treatment serum level is less than 0.7 mmol/l.

The approval of the hospital's audit department was obtained before data collection. All patients' identifying information was removed from the data prior to review.

This is an observational, retrospective report where no sample frame was specified nor comparator group presented. Statistical comparison was made to isolated baseline measures only and neither type 2 statistical error nor regression-to-mean effects can be ruled out.

RESULTS

Sixteen patients had one or more cycles of ESHAP. Fifteen had two or more, while 12 had three cycles. In total there were 43 episodes of chemotherapy. The baseline serum urea and creatinine, diuretic use, total cisplatin dose per cycle and regimen dose modification are illustrated in Table 1.

Potassium

Mean serum K levels prior to every cycle did not show any noticeable change. The means were 4.42, 4.34 and 4.43 mmol/l before cycles 1, 2 and 3, respectively. The interim and lowest K levels also did not show any change (Figure 1). This is reflected in only a minimum requirement for K supplementation (Figure 2). However, one patient with low baseline K level (2.8) was admitted 15 days after the third cycle with convulsions and hypokalaemia (2.5). This was preceded by a very low Mg level (0.23 mmol/l). The patient required a large amount of Mg (192 mmol) and K supplementation of 790 mmol over 17 days (Figure 2). Serum K was measured prior to all 43 administered cycles.

TABLE 1 Baseline serum urea and creatinine, diuretic use, total cisplatin dose per cycle and regimen dose modification

	Cycle 1	Cycle 2	Cycle 3
Number of patients	16	15	12
Dose reduction	2 patients (20%, 50%)	2 patients (20% x 2)	3 patients (20% x 3)
Mean cisplatin dose per cycle	175 mg	175.5 mg	157.7 mg
Oral diuretics			
Frusemide	2	0	0
Bendrofluazide	1	1	0
Other	1	1	1
Mean serum urea Normal (2–6.2 mmol/l)	4.74	3.99	4.62
Mean serum creatinine Normal (62–120 umol/l)	78.7	75.1	76.2
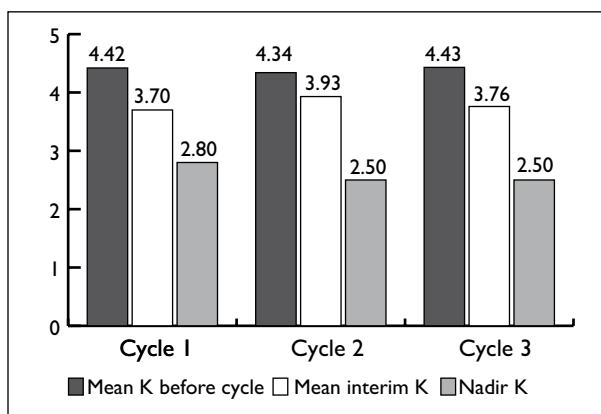
FIGURE 1 Pre-treatment, interim and nadir K levels (mmol/l)
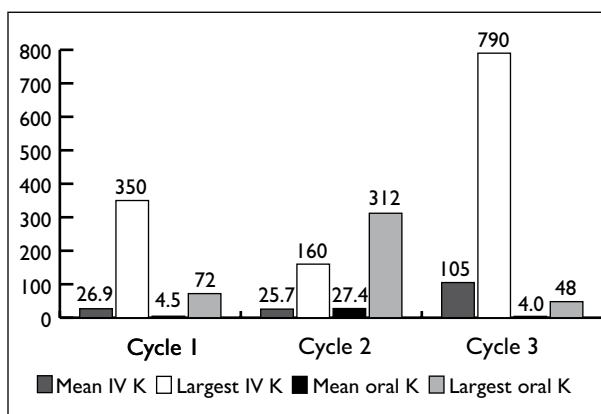
FIGURE 2 Administered K supplementation (mmol) after each ESHAP cycle

Calcium

Mean serum albumin-adjusted calcium levels showed only minimal reduction over sequential cycles. The means were 2.46, 2.40 and 2.38 mmol/L before cycles 1, 2 and 3, respectively. The interim levels did not show any relevant changes (Figure 3). Overall, there was only a minimum requirement for Ca supplementation. The
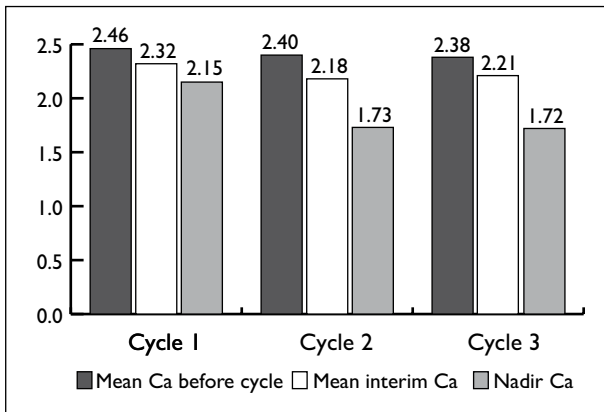
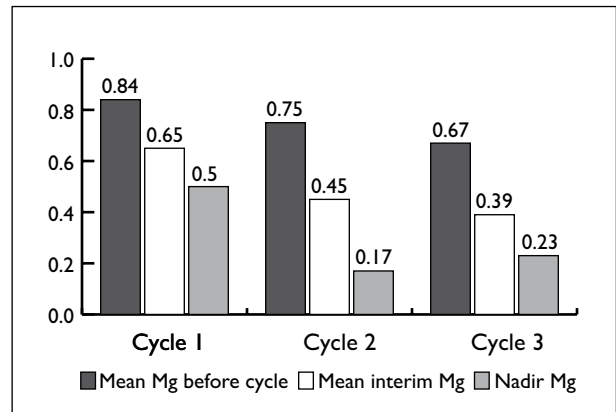**FIGURE 3** Pre-treatment, interim and nadir Ca levels (mmol/l)

FIGURE 4 Administered Ca supplementation (mmol) after each ESHAP cycle

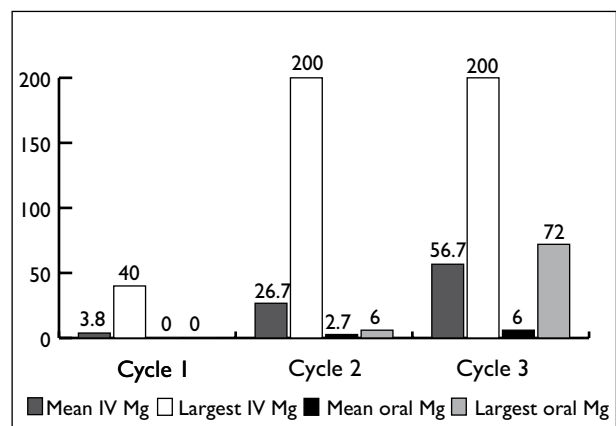**FIGURE 5** Pre-treatment, interim and nadir Mg levels (mmol/l)

FIGURE 6 Administered Mg supplementation (mmol) after each ESHAP cycle

lowest baseline Ca level in one patient was 2.15, i.e. below normal range (2.2–2.6 mmol/l) and fell further (Figure 3). This patient required a relatively large amount of Ca supplementation after the second and third cycles of chemotherapy (Figure 4). Serum Ca was measured prior to 29/43 (67%) of the administered cycles.

Magnesium

Mean serum Mg levels prior to every cycle showed sequential reduction. The means were 0.84, 0.75 and 0.67 mmol/l before cycles 1, 2 and 3, respectively. The interim levels showed obvious progressive decline (Figure 5). The lowest levels were very low: 0.5, 0.17 and 0.23 mmol/l after cycles 1, 2 and 3, respectively. There was a progressive increase in the amount of required Mg supplementation (Figure 6). The interim serum Mg was subnormal (less than 0.7 mmol/l) in 21 episodes. Magnesium replacement was administered in 12/21 (57.1%). Serum Mg was measured prior to 15/43 (35%) of the administered cycles.

DISCUSSION

Cisplatin is an effective component of the ESHAP regimen. The most common side effects associated with this agent include nausea and vomiting, nephrotoxicity (glomerular and tubular), ototoxicity, neuropathy and myelosuppression. The nephrotoxicity of cisplatin almost led to its abandonment, until research proved that diuresis and aggressive hydration significantly ameliorated the development of renal failure.[7,8]

Proposed mechanisms for cisplatin renal toxicity range from definitive histological changes found in the proximal convoluted tubules to physiological and biochemical alterations involving a decrease in mitochondrial respiratory function, enzymatic activity in the respiratory chain and glutathione peroxidase and effects on cellular calcium homeostasis.[9,10] Our retrospective review was conducted in an audit format to address the primary questions related to electrolytes changes and the practice of electrolyte monitoring. We did not collect data that would enable us to formally assess kidney function.

In cisplatin-treated patients creatinine clearance, a measure of kidney function, decreases as serum creatinine increases.[11] There is evidence that renal cortical platinum accumulation is significantly associated with increase in serum creatinine.[12] The mean serum creatinine values were stable and well within the normal range throughout the audit period (Table 1). This may be explained by

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patients receiving adequate hydration. On days 1–5, etoposide was administered as an intravenous infusion in 500 ml 0.9% normal saline (N/Sal) over one hour, methylprednisolone in 100 ml N/Sal over 30 minutes and cisplatin in 1,000 ml N/Sal over 11 hours. Concurrently, 2,000 ml N/Sal was infused over 22 hours.

The small sample size, lack of detailed renal function studies and non-randomised nature of this observational report precludes firm conclusions on the role and impact of drug-induced renal injury.

While a renal injury following cisplatin doses such as those used in this sample would be predicted, we could not characterise the impact of this on renal function in detail due to the retrospective nature of the observations and design of this study.

In a study of 35 adult patients who exhibited profound hypomagnesaemia, hypokalaemia, and hypocalcaemia on their admission, the most common causes of the syndrome were alcoholism and cisplatin administration.[4]

Overall, in our series serum K and Ca levels showed only minimum changes after cisplatin administration. Magnesium plays an important role in the maintenance of intracellular K. Concomitant Mg deficiency in K-depleted patients ranged from 38% to 42%. In one of our patients, and as also shown in previous reports in the literature, hypokalaemia was severe and refractory when preceded by hypomagnesaemia.[13] It is recommended that serum Mg is routinely assessed, and that until serum Mg is measured consideration should be given to treating hypokalaemic patients with both Mg and K.[14]

There are some reports in the literature of hypokalaemia in cisplatin-treated patients, and in some reports it has been associated with paralysis.[15] Glucocorticoids, including methylprednisolone, can cause hypokalaemia. It is interesting that our patients showed only minimal changes in K serum levels. One explanation is the routine and frequent measurement of serum K (100% in our patients), which may have led to the detection of early minor serum K changes that were effectively managed early with low doses of K supplements. The second explanation is that the study was not powered to detect important differences.

Hypocalcaemia is a recognised phenomenon in cisplatin-treated patients. However, it is not as common as changes in Mg levels. In a prospective study of 17 patients receiving chemotherapy with cisplatin, hypomagnesaemia was found in 53% to 88% of patients, depending on the definition of hypomagnesaemia. Hypocalcaemia occurred in only one patient (5.8%).[16] In a study of K and Mg metabolism after repeated cisplatin treatments in rats it was found that cisplatin treatment exerted a negative effect on total K balance, although the difference between cisplatin-treated and control rats was not significant at the end of the follow-up.[3]

Serum Mg levels showed an obvious and progressive decline in our patients. This finding is supported by similar reports in the literature. Hypomagnesaemia in cisplatin-treated patients was reported with or without renal failure. Gomez Campdera et al. reported a 15-year-old female who developed acute renal failure following two courses of cisplatin. The main features were symptomatic hypomagnesaemia, hypocalcaemia and hypokalaemia, which were adjusted after administering intravenous magnesium. Renal failure persisted for several months.[17] Other patient series report hypomagnesaemia in up to 88% of patients receiving cisplatin.[14,18,19] Hypomagnesaemia can be life-threatening; for example, Bashir et al. report a patient with cisplatin-induced hypomagnesaemia who suffered brief asystole.[20]

The degree of hypomagnesaemia is related to the cumulative cisplatin dose. The incidence following cisplatin 50 mg/m² in combination with vincristine, cyclophosphamide, lomustine and doxorubicin for the treatment of lung cancer was 41% (11 of 27 patients) after the first cycle, 86% (12 of 14 patients) after the fifth cycle and 100% (two of two patients) following the sixth cycle of chemotherapy.[21] Our results also show the cumulative effect of cisplatin on serum magnesium level. In our patients the baseline, interim and nadir levels showed progressive decline and the amount of magnesium supplementation progressively increased.

Hypomagnesaemia can result from decreased intake (starvation, alcoholism and prolonged postoperative state), decreased gastrointestinal absorption, diarrhoea and increased urinary losses. Severe deficiency usually requires a combination of these factors.[22] Persistent vomiting may contribute to Mg deficiency. In this retrospective sample we did not document accurate data on the prevalence or severity of vomiting. Severe and/or persistent chemotherapy-induced vomiting is less common with the regular use of effective modern anti-emetic drugs. Our patients received 3 mg of intravenous granisetron daily prior to starting chemotherapy on days 1–5. On discharge they were instructed to use 4 mg oral dexamethasone twice a day regularly for two days and 10–20 mg domperidone every six hours if they felt nauseous. On this principle we believe it is unlikely that short-term chemotherapy-induced vomiting generated significant Mg depletion in this sample of patients.

Cisplatin is the cytotoxic drug most commonly implicated in electrolyte imbalance. However, caution is needed in interpreting the cause of these imbalances, especially when using multi-drug chemotherapy regimens, diuretics, antimicrobials and other nephrotoxic drugs. Our patients received other cytotoxic agents (in ESHAP), although these are not known to significantly affect serum

electrolyte levels. The effect of systemic short pulses of high-dose steroids on serum Mg is not well defined. Data on longer-term use at smaller doses are conflicting. In renal transplant patients on steroids and other immunosuppressive therapies, cyclosporine but not steroids or azathioprine was associated with hypomagnesaemia.[23] In patients with chronic obstructive airway diseases, a significant negative correlation between serum Mg and the length (24 months) of oral steroid therapy was observed.[24] Diuretic use was infrequent and kidney function was satisfactory. This suggests that the electrolyte change in our patients was highly likely to be due to cisplatin. While intravenous (IV) Mg replacement was used, the net impact on renal clearance (loss) of Mg was not documented.

The standard replacement treatment of hypo-magnesaemia is via the IV route. We primarily used IV Mg replacement. Oral Mg glycerophosphate was used in cases of mild hypomagnesaemia and as short-term maintenance after IV supplementation (unlicensed indication but widely accepted).

We did not investigate the mechanism of Mg loss in our patients. However, it is now thought that Mg loss associated with cisplatin treatment is mainly the result of lowered intestinal absorption and not, as previously suspected, of increased renal elimination. Lajer et al. investigated changes in renal and intestinal homeostasis of Mg and K during repeated cisplatin treatments in rats.[3] Cisplatin exerted a significant negative effect on total Mg balance. This effect was cumulative. The observed difference was mainly due to the difference in Mg balance between the treatment day and the following two to three days. The urinary excretion of Mg did not differ significantly between the two groups at the end of the follow-up. A significant decrease was observed in intestinal absorption in treated rats compared with control rats at the end of the follow-up. Lowered intestinal absorption accounted for 90% of the difference in total Mg balance between the two groups as compared to renal loss.[3] The authors suggest that Mg metabolism is subject to predictable changes and that knowledge of these changes can be used in planning supplementation. Thus, the experimental observations support IV supplementation on the day of treatment and two to three days after treatment, followed by oral supple-mentation. Other possible prophylactic measures include the use of nephro-protectants such as amifostine.[25]

CONCLUSION

This evaluation shows that hypokalaemia and hypo-calcaemia are uncommon but recognised in patients receiving ESHAP. Hypokalaemia can be symptomatic and require prolonged admission, especially if associated with hypomagnesaemia. Physicians are aware of the importance of measuring serum K in these patients. However, hypomagnesaemia is a progressive complication of cisplatin administration and physicians need be aware of its importance and that of measuring serum Mg.

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