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Hypomagnesemia– A Toxicity of Platinum Co-Ordination Compounds

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Abstract
Hypomagnesemia is a know side effect of platinum coordination complexes (cisplatin, carboplatin and oxaliplatin) which have revolutionised the treatment of many human cancers.
The objective of the study was to determine association of hypomagnesemia with platinum based chemotherapy and to study the association of hypomagnesemia with hypocalcemia and hypomagnesemia with hypokalemia. 70 newly diagnosed cancer patients who were put on combination chemotherapy were evaluated for various electrolyte abnormalities during chemotherapy and were subsequently followed at six monthly intervals for a period of 18 months to ascertain any improvrment or persistence of dyselectrolytemias.we found that among the 70 patients studied, 42 patients received a cisplatin based chemotherapy; 7 received carboplatin based chemotherapy and 21 received oxaliplatin based chemotherapy. Cisplatin was the most nephrotoxic among the three with hypomagnesemia occurring in 87.5% of cases. Serum magnesium fell sequentially from pre-treatment value from 0.9±0.2mg/dl to 0.61±0.17 mg/dl at sixth cycle. Hypomagnesia persisted in 23 of 35 patients at follow up. Hypocalcemia and hypokalemia both occurred in the presence of hypomagnesemia. Hypokalemia occurred more frequently than hypocalcemia in cisplatin group. Electrolyte abnormalities were less common with carboplatin and oxaliplatin.
Our study indicated that hypomagnesemia occurs sequentially and commonly with platinum based chemotherapy despite corrective measures. A strong association ($p<0.05$) is seen between hypomagnesemia with hypocalcemia and hypomagnesemia with hypokalemia. There is persistence of electrolyte disturbances even after discontinuation of chemotherapy which makes continous monitoring and replacement mandatory.
Keywords: *Hypomagnesemia, cisplatin, monitoring.*

Introduction

Magnesium is predominantly an intracellular ion and is necessary for a host of physiological functions besides being an important cofactor in many intracellular enzymatic reactions. Plasma levels of magnesium depend upon renal tubular reabsorption of filtered ion, although 25-65%of dietary magnesium is intestinally absorbed. [1,2] .
Hypomagnesemia due to platinum co-ordination compounds, of which Cisplatin is the prototype was demonstrated as early as 1979 by Schilsky and Anderson.[3] This was confirmed by

subsequent studies and the mechanism is primarily attributed to renal magnesium wasting and / or reduced intestinal absorption. Studies have confirmed that renal magnesium wasting occurs in 90% of patients receiving platinum based chemotherapy and persists for years after discontinuation of chemotherapy.[4] Our study and its persistence for eighteen months on follow up. However, we went a step further to demonstrate the association between hypomagnesemia and other electrolytes i.e. potassium and calcium.

Materials and Methods

The study was done on 70 new cancer patients who had not received any chemotherapy previously. They were put on platinum containing chemotherapy after ensuring normal creatinine clearance > 80 ml/min as estimated by Cockraft-Gault formula(CG) [(140-age)body weight/72 x sr. creatinine (x0.85 for females)]. Complete clinical, biochemical and investigational data was reviewed before institution of chemotherapy. Informed verbal consent was obtained from each patient . 42 of 70 patients received cisplatin based combination chemotherapy. Cisplatin was used as a combination therapy with 5 Flouro- uracil in 13 patients, with etoposide in 9 patients, with taxol in 7 patients and with gemcitabine in 5 patients while adriamycin, cyclophosphamide and decarbazine were used in combination with cisplatin in a single patient only. External beam radiotherapy in combination with cisplatin were employed in 5 patients only. 21 patients with colorectal cancers received oxaliplatin along with 5 flourouracil(5-FU) and calcium leucovorin (CLV) while 7 patients received carboplatin based chemotherapy.

Methods of administration

The cisplatin dose per course ranged from 50-100mg/sq.m given as a continous infusion in 5% dextrose over 2-3 hours followed by infusion of 100ml of 20% mannitol over 30 min. Prehydration and premedication in the form of 500 ml of 0.9%NS with 24 mgs of metaclopromide and 16 mgs of dexamethasone was given over 1-2 hours. Posthydration was given along with potassium and magnesium supplements in all patients in the form of 500ml of 0.9% NS with 21 meq. of KCl and 1gm of MgSo4 over 3-4 hours. Potassium and magnesium supplements were given in all patients. Carboplatin was administered as a continous infusion in 5% dextrose over ½ - 1 hour with prehydration same as for cisplatin but without posthydration. Oxaliplatin was given as a continous infision in 5% dextrose over 3 hours preceded by premedication in the form of anti-emetics. This was followed by CLV infusion over 4 hours followed 2 hours later by 5FU intravenous push.

All patients received a standard evaluation before each course, including a history and physical examination, complete blood counts, serum electrolytes, biochemical screening battery including serum calcium, serum potassium and serum magnesium levels. After completion of 6 courses of chemotherapy, all investigations were repeated at 6 monthly intervals at 6, 12 and 18 months.

None of the patients received diuretics or nephrotoxic drugs or analgesics during the study period. All patients were normotensives, non-diabetic and had sterile urine. All had a thorough examination including urography and renography to identify any obstruction of urinary collecting duct.

Serum calcium and serum magnesium were estimated by standard procedures followed routinely in our clinical biochemistry laboratory. Potassium levels were measured on IL-Synthesis 45 analyser using ion selection method.

Statistical Method:

Data was described as averages and percentages. The intergroup comparison was done by students T test and Manwhitnui U test. The overall variables were analysed by analysis of variance (ANOVA) and Kruskalwallis test.

Results

Among the 70 patients studied, 48 were males and 22 were females. 42 patients (27 males and 15 females) received a cisplatin based chemotherapy; 7 patients (3 males and 4 females) received carboplatin based chemotherapy and 21 patients (18 males and 3 females) received oxaliplatin based chemotherapy.(Table 1)

21 patients with colorectal carcinoma were placed on oxaliplatin based chemotherapy; 4 patients with ovarian carcinoma, 2 with bronchogenic carcinoma and 1 with urothelial tumor were placed on carboplatin based chemotherapy while the rest of 42 patients of which 19 had bronchogenic carcinoma, 11 had gastro-intestinal tumor,4 had ovarian carcinoma, 3had head and neck cancer, 3 had pancreatic cancer and one each with GB mass and urothelial tumor were on cisplatin based combination regimen.

All the patients were subjected to 6 cycles of chemotherapy after every 3-4 weeks with investigations being done one day prior to each cycle to assess the effect of previous cycle on various parameters. The patients were followed six monthly for a total of 18 months. 2 patients on cisplatin based chemotherapy lost follow up during the study period. 1 patient on carboplatin based chemotherapy died after completing 6 cycles while 2 patients on oxaliplatin based chemotherapy died at followup.(Table 2)

There was a sequential fall in the serum magnesium, calcium and poatassium levels during therapy and hypomagnesemia persisted during followup. Hypomagnesemia (normal range was taken as 0.8-1.2mg/dl) was more common and more severe with cisplatin than with carboplatin and oxaliplatin. Intergroup comparison and overall comparison was significant after the institution of chemotherapy with a< 0.05 after third cycle and b< 0.05 and F< 0.05 after second and third cycle onwards respectively.

87.5% patients on cisplatin developed hypomagnesemia at sixth cycle and hypomagnesemia persisted in 80-85% patients at followup. In carboplatin group, hypomagnesemia was seen in 14.3% cases at sixth cycle and persisted in 16.7% cases on follow up. In oxaliplatin group, 25% patients developed hypomagnesemia and persisted in 15 % on followup. Table:3

When the association between hypomagnesemia and other electrolytes was assessed, it was found that there was a significant relation (p <0.05) between hypomagnesemia , hypokalemia and hypocalcemia after institution of chemotherapy. Tables 4

After first course of chemotherapy, 17 (23.4%) had hypomagnesemia. Out of these 17 patients , hypokalemia was seen in 7 patients(p=0.024) and hypocalcemia in 3 patients (p=0.501). Similarly after second cycle, hypomagnesemia was seen in 22 (31.4%) patients; out of which only 4 had hypokalemia (p=0.332) and 2 had hypocalcemia (p= 0.865). Table 4a.

After third cycle of chemotherapy, hypomagnesemia occurred in 32 (46.4%) patients. 14 among these had associated hypokalemia (p=0.090) and 7 had hypocalcemia (p=0.044). Table 4b. A similar trend was observed after fourth, fifth and sixth cycles. Tables 4dc , 4d and 4e. The association was statistically significant with <0.05. With falling magnesium, calcium and potassium also decreased.

At follow up after six, twelve and eighteen months, there was persistence of hypomagnesemia. 32(48.5%) patients persisted at six months with hypomagnesemia. 7 among these had hypokalemia (p=0.017) and 16 had hypocalcemia (p=0.00). Table 4f. A similar trend was seen after twelve and eighteen months with significant association. Table g and table h

Hypokalemia and hypocalcemia thus occurred in the presence of hypomagnesemia and persisted even on follow up despite discontinuation of chemotherapy. A significant relationship was thus found to exist between hypomagnesemia and other electrolytes especially potassium and calcium.

Table 1

Chemotherapy Regimen							
	Cisplatin		Carboplatin		Oxaliplatin		
Gender	n	%	N	%	N	%	p value
Male	27	64.3	3	42.9	18	85.7	
Female	15	35.7	4	57.1	3	14.3	0.071

Table 2

		CISPLATIN		CARBOPLATIN		OXALIPLATIN	
Final Outcome	Surviving	40	95.2	6	85.7	19	90.5
	Died			1	14.3	2	9.5
	Lost to Follow Up	2	4.8				

Table 3 Hypomagnesemia During Treatment and Follow Up in the Studied Patients

	Cisplatin		Carboplatin		Oxaliplatin		Total		p value			
Hypomagnesemia	n	%	n	%	n	%	n	%	a	b	c	Overall
2nd Cycle	15	35.7	2	28.6	0	0.0	17	24.3	0.716	0.002	0.013	0.008
3rd Cycle	19	45.2	2	28.6	1	4.8	22	31.4	0.414	0.001	0.083	0.005
4th Cycle	28	68.3	1	14.3	3	14.3	32	46.4	0.008	0.000	1.000	0.000
5th Cycle	32	80.0	2	28.6	4	19.0	38	55.9	0.005	0.000	0.602	0.000
6th Cycle	35	87.5	1	14.3	5	25.0	41	61.2	0.000	0.000	0.565	0.000
6 month Follow Up	28	70.0	1	16.7	3	15.0	32	48.5	0.001	0.000	0.677	0.000
12 month Follow Up	25	62.5	1	16.7	3	15.0	29	43.9	0.001	0.000	0.677	0.001
18 month Follow Up	23	57.5	1	16.7	3	15.8	27	41.5	0.000	0.000	0.636	0.005

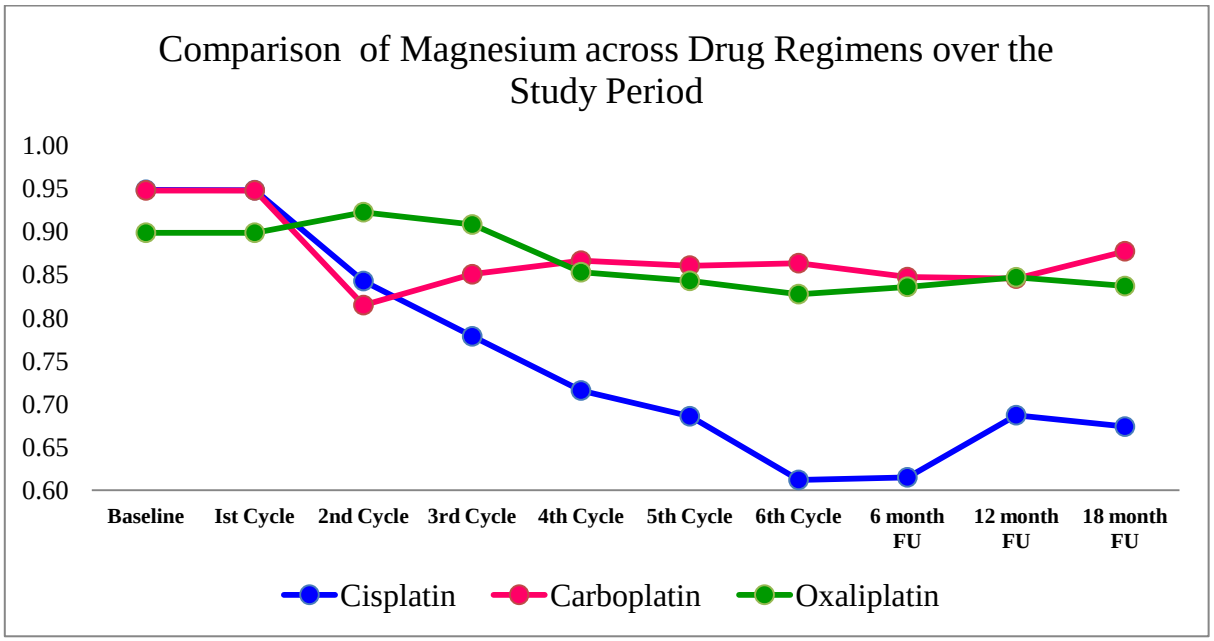

Table 4a

2nd Cycle Magnesium in relation with Potassium, and Corrected Calcium					
	Normal		Abnormal		
	n	%	n	%	p value
Hypokalemia	8	15.1	7	41.2	0.024
Hypocalcemia	6	11.3	3	17.6	0.501

Table 4 b

3rd Cycle Magnesium in relation with Potassium and Corrected Calcium					
	Normal		Abnormal		
	N	%	n	%	p value
Hypokalemia	14	29.2	4	18.2	0.332
Hypocalcemia	5	10.4	2	9.1	0.865

Table: 4c

4^{th} cycle magnesium in relation with potassium and corrected calcium					
	Normal		Abnormal		
	n	%	n	%	p value
Hypokalemia	9	24.3	14	43.8	0.090
Hypocalcemia	0	0.0	7	21.9	0.003

Table: 4d

5th Cycle Magnesium in relation with Potassium andCorrected Calcium					
	Normal		Abnormal		
	n	%	n	%	p value
Hypokalemia	7	23.3	23	60.5	0.002
Hypocalcemia	0	0.0	7	18.4	0.014

Table: 4e

6th Cycle Magnesium in relation with Potassiumand Corrected Calcium.					
	Normal		Abnormal		
	n	%	n	%	p value
Hypokalemia	7	26.9	28	68.3	0.001
Hypocalcemia	0	0.0	8	19.5	0.017

Table: 4f

6 month Follow Up Magnesium in relation with Potassium, and Corrected Calcium.					
	Normal		Abnormal		
	N	%	n	%	p value
Hypokalemia	1	2.9	7	21.9	0.017
Hypocalcemia	6	17.6	16	50.0	0.000

Table: 4g

12 month Follow Up Magnesium in relation with Potassium and Corrected Calcium.					
	Normal		Abnormal		
	N	%	n	%	p value
Hypokalemia	3	8.1	4	13.8	0.46
Hypocalcemia	8	21.6	13	44.8	0.046

Table: 4h

18 month Follow Up Magnesium in relation with Potassium, Corrected Calcium, Creatinine and ARF					
	Normal		Abnormal		
	n	%	n	%	p value
Hypokalemia	1	2.6	3	11.1	0.164
Hypocalcemia	8	21.1	12	44.4	0.046

Discussion

Platinum co-ordination compounds are anti-neoplastic agents used in variety of solid tumors and have become an integral part of chemotherapeutic regimens. Renal toxicity in the form of decrease in creatinine clearance and hypomagnesemia is a known and accepted sideeffect of platinum based chemotherapy. Studies have demonstrated hypomagnesemia occurring in as many as 90% of patients on cisplatin despite the corrective measures. The mechanism of renal toxicity is multifactorial. It has been attributed to reduced renal perfusion and tubular concentrating defect whereas, morphologically necrosis of terminal portion of proximal tubule and apoptosis of distal nephron characterise its effect on cell fate.[5,6] The renal toxicity is cumulative and was demonstrated in our study which was done on 70 newly diagnosed cancer patients. Hypomagnesemia (< 0.8/dl) was seen in 87.5% patients on cisplatin chemotherapy, 28.6% patients on carboplatin chemotherapy and 25% patients on oxaliplatin chemotherapy despite magnesium replacement in our study. These results are consistent with those obtained by Schilsky and Anderson who found hypomagnesemia in 21 of 37 patients and found persistence of hypomagnesemia in 50% patients as long as 20 months after cisplatinum was discontinued[7]. In our study, hypomagnesemia persisted in 61.5% patients at 18 months after stopping cisplatinum. The incidence of hypomagnesemia increased with cumulative cisplatin [4] which was also seen in our study. In a study by Stewal AF , Keating T et al , cisplatin induced hypomagnesemia was seen in 53-88% and hypocalcemia was seen in 5.8%.[8]. In another study by Lycer H et al hypomagnesemia was seen in 90% patients if corrective measures are not given.[9]

Hypomagnesemia does not occur frequently with carboplatin(10-15%)[10, 11]. Higher incidence in our study was due to small sample size of the studied patients in carboplatin group. A close association have been found with oxaliplatin induced hypomagnesemia and peripheral nephropathy.[12]

A close association between hypomagnesemia and hypokalemia and between hypomagnesemia and hypocalcemia.[13, 14] was seen in our study ($p < 0.05$) thereby confirming findings of earlier studies . Hypocalcemia and hypokalemia occur in the presence of hypomagnesemia. It is imperative to mention here that dyselectrolytemia occur despite replacement before and during chemotherapy. There was persistence of electrolyte disturbances at follow up despite discontinuation of chemotherapy. Renal electrolyte disturbances frequently occur with platinum based chemotherapy despite corrective measures and as such should be regularly monitored in patients on chemotherapy and supplemented accordingly.

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