

Amiloride for the treatment of cisplatin-induced hypomagnesemia

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ABSTRACT

Hypomagnesemia secondary to cisplatin-induced nephrotoxicity is caused by a tubular defect that results in renal loss of magnesium.

The objective was to evaluate the effect of amiloride in patients with cisplatin-induced hypomagnesemia. To this end, we included nine cancer patients who were evaluated sequentially in three stages: without corrective treatment, with magnesium supplementation, and with combined treatment of magnesium plus amiloride.

Magnesium supplementation increased serum magnesium levels compared with no treatment (1.22 ± 0.07 vs. 1.01 ± 0.13 mg/dl; $p < 0.01$), without reducing urinary magnesium excretion. The addition of amiloride produced a further increase in serum magnesium levels (1.38 ± 0.17 mg/dl; $p < 0.05$) and was associated with a significant decrease in magnesium excretion and fractional magnesium excretion ($p < 0.01$). No episodes of hyperkalemia were observed.

Amiloride reduced hypermagnesuria and increased serum magnesium levels in patients with cisplatin-induced nephrotoxicity.

Keywords: *magnesium deficiency; cisplatin; amiloride; toxicity; kidney disease.*

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INTRODUCTION

Cisplatin is one of the most widely used chemotherapeutic agents; however, it is associated with numerous adverse effects, among which hypomagnesemia with increased fractional magnesium excretion (FEMg) is common.¹⁻³ For hypomagnesemia that is not corrected by magnesium (Mg^{2+}), the addition of amiloride (a distal diuretic)—by reducing intratubular sodium reabsorption—decreases the intracellular negative potential, reduces potassium and proton secretion, promotes the intratubular influx of Mg^{2+} through the TRPM6 channel, and reduces magnesuria.^{4,5} Furthermore, blocking the epithelial sodium channel (ENaC) alters the membrane potential of distal tubule cells and increases the electrical gradient, allowing Mg^{2+} to enter via the TRPM6 magnesium channel.^{6,7}

We hypothesize that amiloride reduces urinary Mg^{2+} loss, thereby increasing its serum concentration. The objective was to evaluate the effect of amiloride in pediatric patients with hypomagnesemia secondary to cisplatin-induced nephrotoxicity.

POPULATION AND METHODS

We present a retrospective case series with intra-individual comparison, treated between January 2024 and May 2026, including 9 patients with cancer and persistent hypomagnesemia, defined as a serum Mg^{2+} concentration below 1.7 mg/dl associated with hypermagnesuria, as determined by an FEMg greater than 4%.⁸ All patients had persistent hypomagnesemia despite treatment with Mg^{2+} supplements for a period of at least 1 week before enrollment.

Patients with a glomerular filtration rate (GFR) of 90 mL/min/1.73 m² or higher were included. Exclusion criteria included serum potassium levels greater than 5.5 mEq/L, chronic kidney disease, persistent gastrointestinal disorders, and hereditary tubulopathies (e.g., Gitelman syndrome, Bartter syndrome).

Each patient served as their own control, as they were evaluated sequentially in three stages:

- Without corrective treatment.
- With Mg^{2+} salt supplementation.
- With combination therapy using Mg^{2+} and amiloride, indicated in cases of persistent hypomagnesemia.

We monitored serum magnesium levels, urinary magnesium excretion, and FEMg.

Statistical analysis was performed using paired

t-tests and the Wilcoxon test. A p -value <0.05 was considered statistically significant.

Ethical considerations

The protocol was approved by the Teaching and Research Committee of the Hospital General de Niños Ricardo Gutiérrez.

RESULTS

Fifty-two patients received cisplatin and hydration with 0.9% saline solution (3000 mL/m²/day), initiated 6 hours before treatment, along with an oral supplement of Mg^{2+} gluconate (3 g/m²/day). The cumulative dose of cisplatin was 550 ± 145 mg/m² (range: 400-720), administered as a continuous infusion, and calculated as the sum of the administered doses. The mean number of cycles was 4.7 ± 1.4 (range: 2-6).

Twenty-one patients developed hypomagnesemia with hypermagnesuria and were prescribed 25% Mg^{2+} sulfate orally at an initial dose of 200 mg/kg/day of Mg^{2+} sulfate (range: 186-208), with no changes to its formulation, or 20 mg/kg/day of elemental Mg^{2+} (range: 18.3-20.5), in 3 daily doses.

Finally, 9 of these 21 children—three girls and six boys—with a mean age of 5.5 years (range: 4.3-10.1), whose diagnoses were one hepatoblastoma, one medulloblastoma, two neuroblastomas, three osteosarcomas, one germ cell tumor, and one acute lymphoblastic leukemia (multiple relapse), due to an insufficient response to supplementation, were also given amiloride at a mean dose of 0.36 mg/kg/day (SD: 0.05), which was prescribed upon reaching the maximum tolerated dose of Mg^{2+} or due to diarrhea ($n = 3$), vomiting ($n = 4$), and/or unscheduled discontinuation ($n = 2$).

Adherence was good, and all participants completed the treatment without any adverse effects. The results of the three sequential phases were as follows:

- The mean serum Mg^{2+} concentration without treatment was 1.01 ± 0.13 mg/dl (95% CI: 0.91-1.11); with Mg^{2+} supplementation, it was 1.22 ± 0.07 mg/dl (95% CI: 1.17-1.27); and with the addition of amiloride, it was 1.38 ± 0.17 mg/dl (95% CI: 1.25-1.51).
- The mean magnesium excretion without treatment was 6.30 ± 0.48 mg/kg/day (95% CI: 5.93-6.67); with Mg^{2+} supplementation, it was 6.42 ± 0.46 mg/kg/day (95% CI: 6.07-6.78); and with amiloride, it was 1.89 ± 0.27 mg/kg/day (95% CI: 1.68-2.10).

- The FEMg without treatment was $5.37 \pm 0.69\%$ (95% CI: 4.83-5.90); with oral Mg^{2+} , it was $5.71 \pm 0.72\%$ (95% CI: 5.16-6.27); and with the addition of amiloride, it was $3.90 \pm 0.17\%$ (95% CI: 3.77-4.03).

Compared with the untreated period, Mg^{2+} supplementation increased serum magnesium levels by 0.21 mg/dl (95% CI: 0.14-0.28; $p = 0.00013$ by paired t-test and $p = 0.0078$ by the Wilcoxon test).

Amiloride resulted in an additional increase of 0.16 mg/dl (95% CI: 0.03-0.28; $p = 0.023$ and $p = 0.043$, respectively).

The comparison between no treatment and combination therapy showed the greatest increase in serum magnesium levels, with a mean difference of 0.37 mg/dl (95% CI: 0.21-0.52; $p = 0.00057$ and $p = 0.0078$, respectively); however, even with the reduction in hypomagnesemia, the 9 children continued to have serum Mg^{2+} levels below 1.7 mg/dl until the end of the study (Table 1).

Magnesuria did not decrease with supplementation alone; in fact, a mean increase of 0.12 mg/kg/day was observed compared with the untreated period (95% CI: 0.01-0.24), as determined by a paired t-test ($p = 0.038$) and Wilcoxon test ($p = 0.063$). In contrast, the addition of amiloride significantly reduced FEMg

compared with supplementation alone, the mean decrease was 4.53 mg/kg/day (95% CI: -4.95--4.12; $p = 6.3 \times 10^{-9}$ and $p = 0.0039$, respectively), whereas for the untreated period it was 4.41 mg/kg/day (95% CI: -4.85--3.97; $p = 1.4 \times 10^{-8}$ and $p = 0.0039$, respectively).

FEMg also did not improve with oral supplementation. A mean increase of 0.34% was observed compared with the untreated period (95% CI: 0.10-0.59; $p = 0.012$ and $p = 0.023$, respectively). In contrast, the addition of amiloride significantly reduced this parameter: the mean difference was -1.81% compared with magnesium treatment (95% CI: -2.30--1.32; $p = 0.000027$ and $p = 0.0039$, respectively) and by -1.47% compared with the untreated period (95% CI: -1.94--0.99; $p = 0.00010$ and $p = 0.0039$, respectively) (Table 1 and Figure 1).

Three patients reported sporadic episodes of muscle cramps, with no other clinical manifestations attributable to hypomagnesemia.

During treatment with amiloride, the mean potassium concentration was 4.6 mEq/L (range: 3.9-5.1), with no cases of hyperkalemia reported, and the mean GFR was 96 ml/min/1.73 m² (range: 91-112).

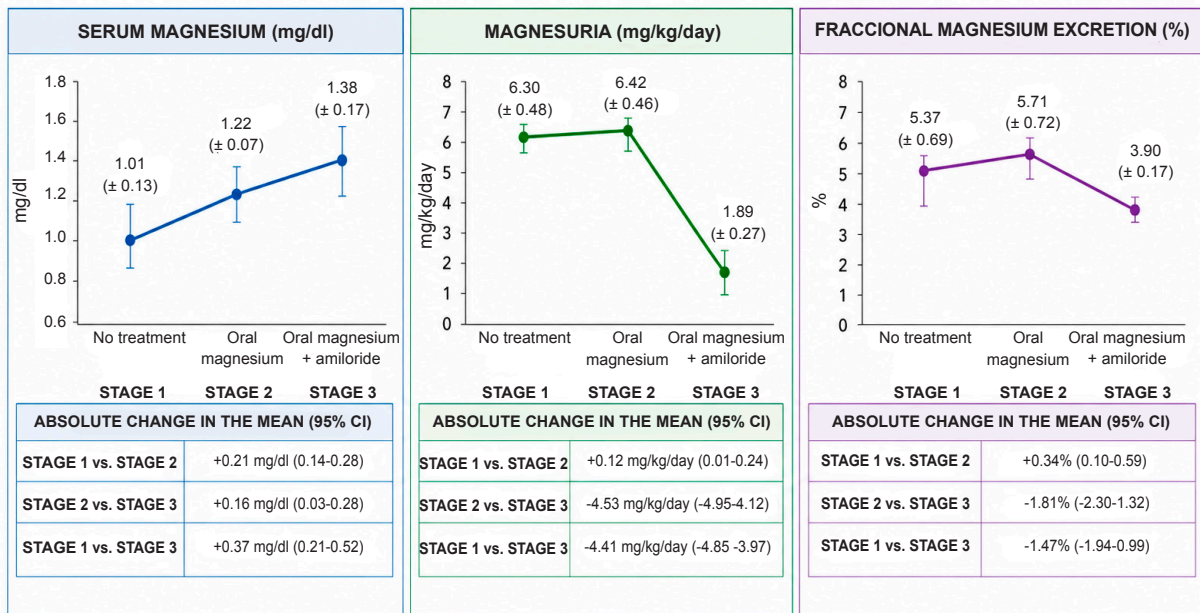
The time between the diagnosis of hypomagnesemia and initiation of Mg^{2+} supplementation was 13 days after the start

TABLE 1. Variation in serum and urinary magnesium levels according to the treatment received by each patient

Patient	Magnesium level (mg/dl)			Magnesuria (mg/kg/day)			Fractional Mg excretion (%)		
	No treatment	Oral elemental Mg	Oral elemental Mg + amiloride	No treatment	Oral elemental Mg	Oral elemental Mg + amiloride	No treatment	Oral elemental Mg	Oral elemental Mg + amiloride
1	1	1.2	1.3	5.5	5.7	2.2	4.4	4.8	3.9
2	1.1	1.3	1.5	6.3	6.4	1.9	4.8	4.7	3.8
3	0.9	1.1	1.4	6.1	6.5	1.8	5.2	5.1	3.7
4	0.9	1.2	1.4	6.9	7.1	2.1	5.9	6.2	4
5	1	1.3	1.5	6.3	6.5	1.7	5.5	6.1	4.2
6	1	1.2	1.6	5.9	6.4	1.9	4.7	5.5	3.8
7	1.3	1.3	1.4	6.4	6.3	1.3	5.9	6.4	3.9
8	0.9	1.2	1.3	6.2	6.2	2.1	6.6	6.7	4.1
9	1	1.2	1	7.1	7.1	2	5.3	5.9	3.7
Mean	1.01	1.22	1.38	6.30	6.42	1.89	5.37	5.71	3.90
(95% CI)	(0.91-1.11)	(1.17-1.27)	(1.25-1.51)	(5.93-6.67)	(6.07-6.78)	(1.68-2.10)	(4.83-5.90)	(5.16-6.26)	(3.77-4.03)
		$p < 0.01$			$p < 0.01$			$p < 0.01$	

The results are expressed as means and 95 %confidence intervals (95% CI).

The lower limit of the reference range for serum magnesium concentration was set at 1.7 mg/dl, and the upper limit of the reference range for FEMg was set at 4%.

FIGURE 1. Changes in serum magnesium, urinary magnesium excretion, and fractional magnesium excretion throughout the three stages of treatment

CI: confidence interval.

Data are expressed as mean (± SD).

of cisplatin treatment (range: 11-15). The time from initiation of amiloride administration to the maximum recovery of serum magnesium levels was 13 days (range: 11-15). The mean duration of magnesium and amiloride administration following completion of the cisplatin regimen was 26 days (range: 18-33).

The mean duration of nephrological follow-up for each patient was 96 days (range: 42-115).

DISCUSSION

Hypomagnesemia is a common complication of cisplatin-induced nephrotoxicity, resulting from acquired distal tubulopathy. It can affect up to 90% of exposed patients.

Although renal impairment may persist for months or even years,⁹⁻¹¹ we did not evaluate the recovery time for tubulopathy, but rather the initial therapeutic response. In this regard, we observed in our series that the addition of amiloride to supplemental Mg^{2+} therapy partially increased the serum concentration of this cation, without normalizing it, and was accompanied by a simultaneous decrease in magnesuria and hypomagnesemia. This biochemical change occurred 13 days after initiating amiloride treatment and involved a partial, early recovery of serum magnesium levels, without completely

preventing renal loss. We speculate that these changes are related to the diuretic blockade of the $ENaC$,^{12,13} and to its action on the $TRPM6$ channel.^{14,15}

The study's main strength lies in its intra-individual design, which reduces inter-individual variability. On the other hand, among the limitations, we note the small sample size, the non-randomized design, and the possibility of spontaneous recovery of serum magnesium levels, which could not be assessed due to the limited follow-up period. However, these results provide a foundation for future prospective studies.

CONCLUSION

During the study period, adding amiloride to Mg^{2+} therapy reduced magnesuria and increased serum Mg^{2+} concentrations in patients with cisplatin-induced nephrotoxicity. ■

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