Premedication with intravenous magnesium has a protective effect against cisplatin-induced nephrotoxicity

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Abstract

Purpose Magnesium supplementation is an effective protective method against cisplatin-induced nephrotoxicity (CIN); however, there are few reports regarding the mechanism of its nephroprotective effect. The aim of this study was to determine whether premedication with intravenous magnesium prevents CIN and to determine the relationship between its nephroprotective effect and serum magnesium level.

Methods Fifty-eight patients with head and neck cancer who received cisplatin, docetaxel, and 5-fluorouracil (DCF) were retrospectively investigated. Grade 2 or more serum creatinine elevation was defined as CIN. The incidence of CIN was compared between a magnesium sulfate (20 mEq, 2.46 g) premedication group and a non-magnesium group during the first cycle and in all cycles.

Results CIN did not occur in any patients receiving magnesium premedication but did occur in 5 of 29 patients during the first cycle and in 6 patients during all subsequent cycles in patients who did not receive magnesium premedication. Furthermore, the variation of creatinine clearance was significantly worse in the non-magnesium group than in the magnesium premedication group from baseline. There was no difference in adverse effects or response rate between the two groups. Univariate analysis

suggested that magnesium premedication significantly reduced the risk of CIN. On the other hand, serum magnesium depletion was seen in both groups to equal degrees despite supplementation.

Conclusion Intravenous magnesium premedication has a protective effect on cisplatin-induced nephrotoxicity without the influence on the serum magnesium level. Magnesium premedication is a simple nephroprotective method that does not influence other adverse effects or rate of response to chemotherapy.

Keywords Cisplatin · Nephrotoxicity · Magnesium · Hypomagnesemia · Prevention

Introduction

Cisplatin is a widely used chemotherapeutic agent for lung, gastric, head and neck, ovarian, and urological malignancies [1]. However, it also has strong adverse effects such as nausea and vomiting, nephrotoxicity, neurotoxicity, and ototoxicity. Nephrotoxicity is one of the major and most serious toxicities caused by cisplatin and is known to be its dose-limiting toxicity [1]. Cisplatin-induced nephrotoxicity (CIN) occurs in 30–40 % of patients receiving cisplatin and is recognized to be cumulative, dose related, and usually reversible [2, 3]. It has been suggested that CIN is caused by cisplatin-induced direct cytotoxic damage, especially at the S3 segment of the proximal tubule located in the outer medulla and at the thick ascending limb of the loop of Henle [4]. The mechanisms of CIN are thought to be DNA damage, oxidative stress, mitochondrial dysfunction, inhibition of protein synthesis, and involvement of the tumor necrosis factor (TNF) family [5–7]. Hydration is used very commonly and while effective, it does not completely prevent CIN.

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Magnesium is the second most common intracellular cation in the human body [8]. It has been reported that magnesium works as a cofactor for approximately 300 cellular enzymes concerning cellular energy metabolism involving ATP, muscle Na^+/K^+ -pump activity, calcium channel activity, stabilization of membrane structures, and RNA/DNA polymerase [8–12]. Hypomagnesemia, which is defined as a serum magnesium level of less than 1.8 mg/dL [13], occurs in almost 90 % of patients receiving cisplatin chemotherapy [14]. It has been suggested that damage of renal tubular cells and $\text{Ca}^{2+}/\text{Mg}^{2+}$ -sensing receptors cause cisplatin-induced hypomagnesemia and hypocalcemia [14, 15]. Results of some studies have suggested that there is a correlation between prevention of CIN and administration of magnesium with cisplatin treatment [3, 16, 17]. It has also been reported that intravenous magnesium supplementation (magnesium sulfate, 3 g before each cisplatin administration) or oral magnesium supplementation (magnesium pidolate, 2 g every 8 h from days 2 to 21 of each cisplatin course) partially compensated for cisplatin-induced magnesium loss [18]. Although convenient, oral magnesium supplementation is not without adverse events consisting of mild gastrointestinal symptoms such as emesis and diarrhea. Intravenous administration is a simple and reliable administration route that is well tolerated in most patient populations.

The aim of this study was to evaluate the effect of intravenous magnesium premedication alone on the incidence of CIN, its safety, and its effect on the anti-tumor outcomes of a chemotherapy regimen containing cisplatin. We also sought to determine the relationship between its nephroprotective effect and serum magnesium level.

Patients and methods

Patients

Fifty-eight patients with head and neck cancer who received a cisplatin, docetaxel, and 5-fluorouracil (DCF) regimen as induction chemotherapy before chemoradiotherapy were enrolled in this retrospective study. Cisplatin and docetaxel at doses of 75 mg/m² were administered on day 1, and 750 mg/m² of 5-fluorouracil was administered on days 1–5. We introduced intravenous magnesium premedication to the DCF regimen in February 2012. The patients were divided into two groups: a control group that included a non-magnesium premedication DCF regimen from June 2010 to January 2012 and a magnesium group with an intravenous magnesium premedication DCF regimen from February 2012 to February 2015.

The present study was approved by the Institutional Review Board of the Hokkaido University Hospital and also carried out in accordance with the Declaration of Helsinki.

Treatment methods

Magnesium sulfate at a dose of 20 mEq (2.46 g) was diluted with normal saline solution and administered for 30 min before cisplatin administration in the magnesium group. On the same day, hydration with a total volume of 2500 mL (pre-cisplatin, 1500 mL; post-cisplatin, 1000 mL) was performed and 300 mL of 20 % mannitol was administered. On days 2–7, 1000–1500 mL of fluid for hydration was intravenously administered. Palonosetron (0.75 mg on day 1); dexamethasone (9.9 mg on day 1, 6.6 mg on days 2–5); and aprepitant (125 mg on day 1, 80 mg on days 2–5) were administered for prophylactic antiemetic therapy. There was no difference in treatment other than magnesium premedication between the two groups.

Evaluation of CIN

All toxicities were graded in accordance with the Common Terminology Criteria for Adverse Events, version 4.0. Renal function was evaluated on the basis of changes in the serum creatinine (SCr) level measured by an enzymatic method and creatinine clearance (CrCl) from each baseline level. In this study, CIN was defined to be grade 2 or more of SCr elevation from baseline. CrCl was calculated using Cockcroft-Gault formula.

Assessment of DCF response

The rate of response to DCF was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Statistical analysis

We hypothesized that the incidence of CIN would reach 30–40 % in the control group, and 5 % in the magnesium group. A required sample size was calculated to be 27–43 subjects per group to achieve 80 % power with an alpha error of 5 %. Twenty-nine patients were analyzed in each group.

The differences in baseline clinical characteristics between the magnesium premedication group and control group were assessed using Fisher's exact probability test for categorical outcome variables and the Mann-Whitney *U* test for continuous parameters. Differences in variation of SCr and serum magnesium levels and CrCl between the two groups and differences in the degree of severity of adverse effects between the two groups were assessed using the Mann-Whitney *U* test. Univariate analysis was performed using Fisher's exact probability test in order to identify independent risk or preventive factors against

CIN. Differences were considered to be statistically significant when the *P* value was less than 0.05.

Results

Patient characteristics

The baseline patient characteristics are shown in Table 1. Although body surface area (BSA) tended to be larger in the non-magnesium control group, there were no significant differences regarding gender, age, performance status (PS), BSA, serum albumin (Alb), hemoglobin (Hb), serum magnesium, SCr, comorbidities of hypertension and diabetes mellitus, and co-administration of non-steroid anti-inflammatory drugs (NSAIDs) between the two groups. Approximately 90 % of the enrolled patients were males.

Comparison of the incidence of CIN and variation of SCr and CrCl

Figure 1a, b show Δ SCr (maximum SCr minus baseline SCr) in the first cycle and in all subsequent cycles, respectively. Changes in SCr were significantly smaller in the magnesium group compared to the control group during the first cycle and

in all subsequent cycles. In the control group, CIN occurred in five patients (17.2 %) in the first cycle and in six patients (20.7 %) in all cycles. There was no incidence of grade 2 SCr elevation in the magnesium group throughout the DCF treatment. Additionally, magnesium premedication also significantly prevented the degradation of CrCl during the first cycle and in all subsequent cycles, respectively (Fig. 1c, d).

Variation of serum magnesium level

Comparison of the variation in serum magnesium level in all cycles between the two groups is shown in Fig. 2. There was no difference regarding the degree of Δ serum magnesium level (lowest serum magnesium level minus baseline serum magnesium level) in all cycles between the two groups.

Adverse effects caused by DCF regimen

Adverse effects that occurred in the DCF treatment are shown in Table 2. There were no significant differences between the two groups in the incidence of hematological or non-hematological adverse effects other than CIN (data not shown). With regard to the degrees of severity of these symptoms, severities of neutropenia and nephrotoxicity were significantly less in the

Table 1 Patient characteristics

	Control group	Magnesium group	<i>P</i> value
No. of patients	29	29	
Gender: male/female	26/3	26/3	1.00
Median age (range)	58 (46–69)	63 (37–69)	0.22
Performance status (ECOG)			
0	4	6	
1	24	23	
2	1	0	0.35
Body surface area (m ²)			
Median (range)	1.72 (1.37–2.12)	1.63 (1.23–1.95)	0.08
Alb (g/dL)			
Median (range)	4.2 (2.8–4.5)	4.0 (3.1–4.7)	0.65
Hb (g/dL)			
Median (range)	14.2 (9.8–16.2)	13.5 (10.6–17.6)	0.33
Serum magnesium (mg/dL)			
Median (range)	2.1 (1.6–2.4)	2.2 (1.8–2.6)	0.30
Serum creatinine (mg/dL)			
Median (range)	0.70 (0.39–1.02)	0.72 (0.46–0.95)	0.63
Hypertension	6	9	0.55
Diabetes mellitus	4	2	0.67
Co-administration of NSAIDs	6	1	0.10

Fig. 1 Comparison of Δ Scr and Δ CrCl, and the incidence of CIN between the control group and magnesium group in the first cycle and in all subsequent cycles. **a** Variation of serum creatinine level in the first

cycle. **b** Variation of serum creatinine level in all subsequent cycles. **c** Variation of creatinine clearance in the first cycle. **d** Variation of creatinine clearance in all subsequent cycles

magnesium group than in the control group. No patients in the control group received prophylactic granulocyte colony-

stimulating factor (G-CSF) while 24 of 29 patients in the magnesium group received prophylactic G-CSF.

Fig. 2 Comparison of Δ serum magnesium level between the control group and magnesium group in all subsequent cycles

Rate of response to DCF

Rates of response to the DCF regimen were 89.7 % in the control group and 96.6 % in the magnesium group (data not shown). DCF efficacy was similar in the two groups ($P=0.30$).

Risk or preventive factors for CIN

Univariate analysis was performed to identify risk or preventive factors for CIN during all DCF cycles (Table 3). It was found that the significant independent risk factor for CIN was co-administration of NSAIDs and that intravenous magnesium premedication is a preventive factor.

Table 2 Severity of adverse effects

	Grading of adverse effects according to CTCAE (n, %)								<i>P</i> value
	1		2		3		4		
	C	M	C	M	C	M	C	M	
Leukopenia	1 (3.4)	2 (6.9)	1 (3.4)	5 (17.2)	17 (58.6)	14 (48.3)	10 (34.5)	7 (24.1)	0.10
Neutropenia	1 (3.4)	0 (0)	1 (3.4)	1 (3.4)	2 (6.9)	10 (34.5)	25 (86.2)	17 (58.6)	0.03*
Febrile neutropenia	–	–	–	–	17 (58.6)	11 (37.9)	1 (3.4)	1 (3.4)	0.13
Anemia	14 (48.3)	17 (58.6)	12 (41.4)	12 (41.4)	2 (6.9)	0 (0)	0 (0)	0 (0)	0.57
Thrombopenia	12 (41.4)	7 (24.1)	1 (3.4)	3 (10.3)	3 (10.3)	0 (0)	0 (0)	0 (0)	0.13
Nausea	16 (55.2)	15 (51.7)	5 (17.2)	6 (20.7)	3 (10.3)	0 (0)	0 (0)	0 (0)	0.28
Anorexia	7 (24.1)	16 (55.2)	9 (31.0)	7 (24.1)	10 (34.5)	5 (17.2)	0 (0)	0 (0)	0.13
Diarrhea	5 (17.2)	10 (34.5)	7 (24.1)	3 (10.3)	3 (10.3)	4 (13.8)	2 (6.9)	0 (0)	0.51
Constipation	7 (24.1)	14 (48.3)	2 (6.9)	0 (0)	0 (0)	0 (0)	1 (3.4)	0 (0)	0.51
Stomatitis	8 (27.6)	10 (34.5)	5 (17.2)	5 (17.2)	2 (6.9)	0 (0)	0 (0)	0 (0)	0.73
Fatigue	9 (31.0)	15 (51.7)	11 (37.9)	11 (37.9)	0 (0)	0 (0)	0 (0)	0 (0)	0.37
Nephrotoxicity	21 (72.4)	20 (69.0)	5 (17.2)	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)	<0.01**

C control group; M magnesium group

* $P < 0.05$, ** $P < 0.01$

Discussion

For safer and more effective administration of cisplatin-combination chemotherapy regimens, it is necessary to manage cisplatin-induced nephrotoxicity. This study is the first study in which the nephroprotective effect of intravenous magnesium premedication alone on CIN and the relationship between its nephroprotective effect and serum magnesium level in a single regimen were evaluated. In this study, we evaluated the nephroprotective effect of intravenous magnesium administration prior to a cisplatin-containing DCF regimen. It was revealed that 20 mEq magnesium sulfate effectively prevents CIN caused by DCF, and our results are compatible with the results of those previous studies [3, 16, 17, 19].

Our study also indicated that co-administration of NSAIDs is an independent risk factor for CIN. This finding is also consistent with the results of previous studies [3, 19] and suggesting that NSAIDs should not be administered concurrently with chemotherapy regimens containing cisplatin. However, NSAIDs are critical in managing mild to moderate pain in oncology patients and the avoidance of these valuable analgesics could be detrimental to their care. Alternative medications such as acetaminophen, tramadol, or oxycodone could be utilized and would require further patient and provider education.

It was also suggested that the severity of neutropenia was significantly reduced and the incidence of febrile neutropenia was less among the magnesium group. Because the DCF regimen is used in induction chemotherapy for head and neck cancer, it is important to maintain a high-dose intensity of

chemotherapy. We propose that these results were caused by an increase in use of prophylactic G-CSF administration for the prevention of febrile neutropenia in the magnesium group.

It has been reported that cisplatin organ toxicity is kidney-specific, and renal transporters that transport cisplatin from blood to the proximal tubule (organic cation transporter 2, OCT2) and from the proximal tubule to urine (multidrug and toxin extrusion protein 1, MATE1) have important roles in cisplatin renal accumulation and toxicity [20–22]. It is known that OCT2 has single-nucleotide polymorphisms (SNPs) [23, 24], and it has also been reported that the 808G>T SNP in *OCT2* ameliorates CIN without alteration of disposition [25]. As previously mentioned, magnesium works as a cofactor of cellular enzymes, and it is therefore possible that magnesium premedication affects the expression and/or function of these transporters. Since Yokoo et al. reported that rats with magnesium depletion show the increment of OCT2 expression in the kidney [26], magnesium premedication might have evoked downregulation of the renal expression of OCT2, resulting in the prevention of CIN.

Aside from the possibility of transporter-mediated drug interaction, it has also been reported that magnesium itself possesses antioxidant properties, scavenging oxygen radicals possibly by affecting the rate of spontaneous dismutation of the superoxide ion [27]. It is known that oxidative stress is a contributory factor for the development of CIN, and there is the possibility that the antioxidative effect of magnesium premedication might be involved in the alleviation of CIN. Solanki et al. reported that mice fed a magnesium-deficient diet developed renal oxidative stress and that the oxidative stress was enhanced by cisplatin administration but was

Table 3 Univariate analysis of risk factors for CIN during all subsequent cycles

	Cisplatin-induced nephrotoxicity		<i>P</i> value
	Yes (<i>n</i> = 6)	No (<i>n</i> = 52)	
Gender			
Male	6	46	1.00
Female	0	6	
Age (years)			
≥60	4	27	0.68
<60	2	25	
Performance status			
0	6	42	0.58
1 or 2	0	10	
BSA (m ²)			
≥1.5	5	47	0.50
<1.5	1	5	
Alb (g/dL)			
≥3.5	4	47	0.15
<3.5	2	5	
Hb (g/dL)			
≥11.0	5	50	0.28
<11.0	1	2	
Hypertension			
Yes	2	13	0.64
No	4	39	
Diabetes mellitus			
Yes	1	5	0.50
No	5	47	
Co-administration of NSAIDs			
Yes	3	4	0.02*
No	3	48	
Magnesium premedication			
Yes	0	29	0.02*
No	6	23	

**P* < 0.05

completely inhibited by magnesium supplementation [28]. Even though the dose of cisplatin in their study was much higher than the clinical dosage, these results support to explain the mechanism of CIN.

However, there was no difference between the two groups with regard to Δ serum magnesium level in all cycles in this study, indicating that 20 mEq (2.46 g) intravenous magnesium premedication was not able to prevent serum magnesium depletion during cisplatin-containing chemotherapy. It has been reported that the serum magnesium store is only 0.3 % of total magnesium in the entire body [8], and it is therefore unknown

whether serum magnesium level alone is able to explain the systemic magnesium store including that in the kidney. In this study, a renal protective effect was seen from the first course of chemotherapy and the degree of serum magnesium depletion was not different, suggesting that it is difficult to establish the hypothesis that the mechanism of the magnesium renoprotective effect against CIN is prevention of serum magnesium depletion. Further studies are needed to reveal the renal protective mechanism(s) of magnesium premedication against CIN with the clinical dose of cisplatin in fundamental experiments.

It has been shown that 8 [3], 20 [19], and 40 mEq [17] of intravenous magnesium premedication have preventive effects against CIN in controlled prospective or retrospective studies. In addition to the nephroprotective mechanism of magnesium premedication, it is also unclear what the most appropriate dose of magnesium is for ameliorating CIN. In Japan, magnesium sulfate products are packed by 20 mEq, and we therefore used 20 mEq of magnesium sulfate injection in terms of the risk management against preparation mistake. In this study, it was found that 20 mEq of magnesium premedication effectively prevented the incidence of CIN and degradation of SCr and CrCl and also had no influence on other adverse effects or anti-tumor effects. Consequently, it is possible to conclude that 20 mEq of intravenous magnesium premedication alone is useful in preventing CIN. A study to elucidate the most appropriate magnesium dose for prevention of CIN is also needed.

There are some limitations for evaluation of the protective effect of intravenous magnesium premedication against CIN in this study. First, this study was a retrospective study with a relatively small population of patients. Therefore, it is necessary to carry out a large-scale prospective study to confirm these results. Another limitation is gender bias since approximately 90 % of the patients enrolled in this study were males. There have been conflicting results regarding the risk factors of CIN in terms of gender difference in clinical trials [29–31]. It has also been reported that CIN occurred more frequently in male than female rats, being related to the fact that the expression level of OCT2 is higher in males than in females [32, 33]. Considering these results, a study that includes a population with equal gender enrollment should be conducted.

In conclusion, our study revealed that intravenous magnesium premedication alone has a protective effect against cisplatin-induced nephrotoxicity without an impact on other adverse effects or anti-tumor effect, and that the prevention of the serum magnesium depletion might not be involved in the nephroprotective effect of magnesium premedication. However, further studies are needed to validate these results and to

determine the possible mechanism of the nephroprotective effect of magnesium premedication.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of interest All authors declare that they have no conflict of interest.

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