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Does parenteral magnesium sulfate have an antiemetic effect during chemotherapy with *cis*-platinum?

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Summary. Cisplatin is a chemotherapeutic agent with a high emetic potential; it can lead to hypomagnesemia, which is caused by a renal wasting. Because of beneficial effects of magnesium in the therapy of motor disorders of the upper gastrointestinal tract and its sedative, anticonvulsive effect in eclampsia, we tested parenteral magnesium sulfate as a potential antiemetic in patients receiving cisplatin. A prosepctive, randomized, double-blind, crossover study was carried out in 20 patients receiving $\geqslant 60$ mg/m^2 cisplatin. A standard antiemetic regimen consisting of a single dose of 10 mg diazepam and five times 0.5 mg/kg metoclopramide (every 2 h) was used. Simultaneously, 8 g magnesium sulfate or isotonic sodium chloride was infused over 4.5 h. The efficacy of magnesium was analyzed with an emetic score system; no difference was found between magnesium sulfate and sodium chloride. Only two patients were hypomagnesemic, and they had a better emetic score with the magnesium infusion. We conclude that the i.v. administration of magnesium during cisplatin therapy has no antiemetic effect, at least in normomagnesemic patients.

Introduction

cis-Diamminedichloroplatinum(II) (DDP) is a chemotherapeutic agent that has been in clinical use since 1972 [20]. It is well known for its potent antitumor activity as well as its severe side effects [3, 12, 13, 20]. DDP is the anticancer drug with the highest emetic potential, leading to vomiting in up to 90% of patients. Current antiemetic therapy includes benzodiazepines [19], corticosteroids [1, 5, 24, 26], and, particularly, dopamine antagonists [5, 9, 12, 17, 18, 24, 26]. However, these drugs do not sufficiently control vomiting [31]. Hypomagnesemia [6, 7, 14, 29] is often encountered after the administration of DDP and is thought to be a consequence of acute tubular damage [2, 7, 23, 24, 29].

Hypomagnesemia can cause central nervous and neuromuscular symptoms such as convulsions, tremor, and myoclonic seizures, which may be cured by the administration of magnesium [7, 11, 15]. Therefore, the use of magnesium is well established in the treatment of convulsions in toxemias of pregnancy [16, 30]. The magnesium-mediated central suppression might also be efficient in blocking chemosensory input to the emetic center [3]. On the other hand, magnesium seems to act directly on striated and smooth muscles, leading to relaxation [7]. Hypomagnesemia causes dysphagia and esophageal spasms [10, 21], which are successfully treated by the administration of magnesium [27]. We therefore hypothesized that magnesium could have a positive effect on the peripheral organs involved in vomiting, i.e., the esophagus and stomach [25]. This hypothesis might be further supported by the peripheral antiemetic effect of domperidone, which blocks dopamine receptors in the lower esophagus and stomach [26].

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Patients and methods

A total of 20 patients (10 men and 10 women) receiving $\geqslant 60$ mg/m^2 cisplatin as chemotherapy were studied; their median age was 44.9 years (range, 18–65 years). Exclusion criteria were: serum creatinine levels $\geqslant 130$ mmol/l or creatinine clearance of $\leqslant 60$ ml/min, congestive heart failure, respiratory insufficiency, and the regular intake of psychotropic drugs. Chemotherapeutic agents given simultaneously included mitomycin C, vindesine, methotrexate, bleomycin, hydroxyurea, vincristine, melphalan, and etoposide (VP-16). Details of the chemotherapy and the types of tumors are shown in Table 1.

Each patient received a basic antiemetic treatment with 10 mg i.v. diazepam (Valium) (7.5 mg when the body weight was 50 kg) 30 min before cisplatin infusion and 0.5 mg/kg i.v. metoclopramide (Primpéran) 30 min before cisplatin, the latter being repeated (four times) every 2 h (total dose, 2.5 mg/kg). In a double-blind fashion, either 2 g magnesium sulfate (1 g = 8.1 mval $MgSO_4 \times 7\ H_2O$) in 500 ml 0.45% sodium chloride or 500 ml 0.54% sodium chloride (isomolar to the magnesium infusion) were infused for 30 min prior to the administration of cisplatin, followed by either 6 g magnesium sulfate (in 500 ml 0.45% NaCl) or 500 ml 0.73% sodium chloride (isomolar) given over 4.5 h.

The blood pressure and pulse rate were monitored by a nurse every 30 min for the first 3 h, and every 2 h thereafter. The efficacy of the antiemetic treatment was quantified with the help of a scoring system described by Joss et al. [12]:

Table 1. Patients' data, including emetic scores with and without magnesium sulfate

Tumor type	Number of patients	Age (years)	DDP[1] dose during		Other agents[2]	Emetic scores	
			Mg	NaCl		Mg	NaCl
Ovarian cancer	8	63	120	120	L-PAM	22[7]	12
		54	100	150	L-PAM	11[7]	32
		18	130	120	L-PAM	23	25[7]
		50	120	–	L-PAM	22[7]	–[3]
		50	130	130	L-PAM	24	11[7]
		53	140	140	L-PAM	17	6[7]
		37	120	120	L-PAM	30	28[7]
		65	130	–	L-PAM	25[7]	–[4]
Lung cancer	5	59	110	110	VDS/MMC	10[7]	14
		46	110	110	VDS/MMC	15	14[7]
		43	100	–	VDS/MMC	0[7]	–[4]
		63	100	–	VDS/MMC	0[7]	–[5]
		42	90	90	VDS/MMC	10	10[7]
Testicular cancer	3	23	100	100	VCR/BLM	27[7]	25
		27	100	100	(VDS) BLM	5[7]	16
		25	100	100	VP-16/BLM	6	11[7]
Other cancer	4	39	100	120	–	5	2[7]
		37	100	90	MTX/BLM/HU	0	0[7]
		62	110	–	MTX/BLM/HU	2[7]	–[6]
		42	100	100	MTX(BLM)	0	0[7]

[1] DDP, *cis*-diamminedichloroplatinum in mg absolute
[2] MMC, mitomycin C; VDS, vindesine; BLM, bleomycin; L-PAM, melphalan; MTX, methotrexate; HU, hydroxyurea; VCR, vincristine; VP-16, etoposide; in parentheses if agent not given the same day as cisplatin
[3] Dropout due to severe vomiting
[4] dropout due to reduced cisplatin dose
[5] dropout due to dyspnea
[6] dropout due to tumor progression
[7] First course of treatment

Symptoms during the previous hour:	Score:
No nausea, retching, or vomiting	0
Nausea	1
Retching	2
Vomiting (single episode)	3
Vomiting (multiple episodes)	4

Patients were scored every hour, and the scores were cumulated over an 18-h period. The antiemetic efficacy was defined as follows:

Cumulative score (18 h):	Response:
0	Complete response
1– 6	Major partial response
7–12	Minor partial response
>12	Failure

Serum magnesium concentrations were measured before therapy and 12 h after the end of the magnesium infusion (calorimetrically with "calmagite" and EGTA) [8]. Potassium, sodium, chloride, phosphate, calcium (calorimetrically with *o*-cresolphtalein Komplexon), serum albumin, and serum creatinine (Jaffé reaction) levels were measured at the same time. For statistical analysis, Student's *t*-test for paired data was used. Informed consent was obtained from the patient before starting the therapy, and the study protocol was approved by the local ethics committee.

Results

Of the 20 patients admitted to the study, 5 did not receive the cross-over Mg or NaCl infusion during the following chemotherapy for various reasons given in Table 1. These five patients did not differ in any respect (emetic score, laboratory tests) from the group that completed the study. The remaining 15 patients were evaluated for the antiemetic effect of magnesium sulfate. Table 1 shows that the emetic scores of six patients (first, second, fifth, sixth, fifteenth and sixteenth) displayed a large difference between magnesium and placebo. Three patients had a low score with magnesium sulfate, three with sodium chloride; four patients had a low score during the first course of chemotherapy, two during the second course. Of the remaining nine patients with similar emetic scores, seven started with sodium chloride on the first course.

The response distribution for the two treatments is shown in Table 2. Note that the rate of failure was about 50% for both treatments. The mean emetic score was 13.7 ± 9.8 (SD) and 13.7 ± 10.0 for the Mg- and NaCl-treated patients, respectively. The maximum score for 18 h would be 72. Serum sodium, potassium, chloride, phosphate, calcium, and creatinine levels were similar in all pa-

Table 2. Distribution of the emetic responses in 15 patients receiving either magnesium sulfate or sodium chloride

Cumulative score (18 h)	Mg	NaCl
0	2 (patients)	2
1– 6	3	2
7–12	3	4
>12	7	7

Table 3. Serum magnesium concentrations (normal range, 0.70–0.95 mmol/l) before and after treatment with magnesium sulfate or sodium chloride (mean ± SD; $n = 15$)

	during Mg	during NaCl
Serum Mg before (mmol/l)	0.86 ± 0.20	0.80 ± 0.08
Serum Mg after (mmol/l)	1.06 ± 0.16*	0.79 ± 0.10

* $P < 0.01$ (Student's paired t-test) compared with serum Mg before

tients before and after treatment and were within the normal range. The serum albumin concentration decreased slightly after the treatment due to hemodilution by hydration (not shown).

Serum magnesium concentrations are shown in Table 3. Whereas the mean serum magnesium was unchanged after NaCl infusion, 12 h after the end of the magnesium infusion it increased by 23% and was above the normal range of 0.70–0.95 mmol/l. The maximal value was 1.36 mmol/l. The serum magnesium level measured in one patient immediately after the 30-min infusion of 2 g $MgSO_4$ was 0.98 mmol/l.

Only two patients had hypomagnesemia (0.69 and 0.65 mmol/l) at the beginning of the infusion. It is noteworthy that these very patients had better scores of 10 and 6, respectively, under magnesium infusion than those of 14 and 11 under NaCl infusion. A third patient with a good score of 5 under magnesium infusion (compared with 16 under NaCl infusion) showed a remarkable serum magnesium increase from 0.88 to 1.14 mmol/l. No side effects attributable to the magnesium infusion were noted, except possibly in one patient with lung cancer who complained about aggravated dyspnea.

Discussion

In this double-blind, cross-over trial we tested the antiemetic efficacy of i.v. magnesium sulfate vs isotonic sodium chloride, both of which were given together with a standard antiemetic regimen consisting of low-dose metoclopramide [5, 9, 12, 28] and diazepam [19]. According to our antiemetic response-evaluation system [12], the treatment of 7 of the 15 patients was classified as a failure during the infusion of magnesium sulfate, and 7 failures were recorded for sodium chloride infusion. The cumulative emetic scores of the two groups were similar. We also analyzed the data with respect to the occurrence of nausea without vomiting, which has a low score value (score 1) but can be very troublesome for the patient; no difference was found between magnesium and sodium chloride. The five patients who had to be excluded started with magnesium sulfate. Thus, the final evaluation was in a slight disequilibrium, with ten patients beginning with magnesium sulfate and only five beginning with sodium chloride.

It is important to realize that only 2 patients were hypomagnesemic before the infusion of DDP; this small number is explained by the fact that only 12 patients had previously undergone chemotherapy with DDP, which is known to induce hypomagnesemia [2, 22, 23]. Oral magnesium substitution does not seem to have a beneficial effect on hypomagnesemia after DDP chemotherapy [23], but the prophylactic i.v. administration of 3 g $MgSO_4$ has been proposed for DDP-induced hypomagnesemia [14]. Because hypomagnesemia can be responsible for several neuromuscular, myocardial, gastrointestinal, and psychiatric disorders, including depression [7, 15, 28], it should be particularly important to be prevented in these severely ill patients.

The serum magnesium levels recorded 12 h after the end of the magnesium infusion were above the normal range (Table 3) but not in the toxic range. The first sign of magnesium toxicity is usually the disappearance of the tendon reflexes [4]. Cardiac conduction abnormalities seem to occur at magnesium concentrations of > 2.5 mmol/l, and respiratory depression appears at magnesium levels of > 5 mmol/l [30]. Only one patient suffering from bronchial carcinoma showed signs possibly attributable to high serum magnesium levels, in the form of increased dyspnea; he had a magnesium concentration of 1.15 mmol/l, which is below the toxic range [30].

In conclusion, magnesium sulfate given as a continuous infusion together with low-dose metoclopramide and a single dose of diazepam could not alleviate nausea and vomiting in normomagnesemic patients under DDP chemotherapy as compared with a control. Particularly considering the five individuals who did not terminate the study, the small number of patients is not sufficient to rule out an antiemetic effect of magnesium. However, at the dose given, a therapeutically useful effect was lacking, although two hypomagnesemic patients with better emetic scores under magnesium sulfate infusion might support the proposal that magnesium could be an antiemetic substance in DDP chemotherapy. An additional study should be carried out in a larger group of hypomagnesemic patients to test this hypothesis.

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