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Hyponatraemia induced by low-dose intravenous pulse cyclophosphamide

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Abstract

Background. Cyclophosphamide is an alkylating agent and was traditionally known to potentiate the renal action of vasopressin. Although low-dose intravenous pulse cyclophosphamide therapy is being used extensively in the treatment of malignant and rheumatological diseases, there have been only a few case reports of cyclophosphamide-induced hyponatraemia.

Methods. Clinical data were retrospectively analysed from 84 patients (42 lupus nephritis; 42 non-Hodgkin's lymphoma; a total of 112 treatment episodes) admitted for intravenous pulse cyclophosphamide (500–750 mg/m^2) therapy. In all patients, half-isotonic saline was used for prophylactic hydration. Cyclophosphamide-induced hyponatraemia was defined as serum sodium concentration <135 mEq/L at 24 hours after the therapy in patients whose basal serum sodium concentrations were normal.

Results. After the low-dose intravenous pulse cyclophosphamide, serum sodium concentration significantly decreased from 139.9 ± 3.5 to 137.9 ± 5.1 mEq/L ($P < 0.001$). Cyclophosphamide-induced hyponatraemia occurred in 15 treatment episodes (13.4%) from 12 patients (14.3%). Patients with hyponatraemia were significantly older than those without hyponatraemia (57.3 ± 14.7 *vs.* 40.0 ± 17.0 years, $P < 0.01$). Hyponatraemia was associated with male sex on univariate analysis ($P < 0.05$), but not on multivariate analysis. No factors were found to independently predict the occurrence of cyclophosphamide-induced hyponatraemia when multivariate analysis was performed including parameters age, sex, underlying disease, presence or absence of comorbidities associated with hyponatraemia, presence or absence of concurrent medications associated with hyponatraemia and dose of cyclophosphamide.

Conclusions. Hyponatraemia occurring after low-dose intravenous pulse cyclophosphamide is not rare, especially when hypotonic solutions are adopted for hydration protocol. Thus, the use of hypotonic fluids should be avoided when using cyclophosphamide. Instead, isotonic solutions should be used if a forced diuresis is required.

Keywords: cyclophosphamide; hyponatraemia; lupus; lymphoma; risk

Introduction

Cyclophosphamide is an alkylating agent used extensively in the treatment of malignant and rheumatological diseases. Its side effects include bone marrow suppression, infection, alopecia, sterility, bladder malignancy and haemorrhagic cystitis [1]. However, it is less well known that intravenous cyclophosphamide reduces the ability of the kidney to excrete water. Since forced hydration is used routinely to prevent haemorrhagic cystitis, treated patients may retain water, and rapidly develop severe hyponatraemia [2].

Previously, when high doses (>50 mg/kg) of cyclophosphamide were used to induce immunosuppression before bone marrow transplantation and to treat neoplastic diseases, hyponatraemia might have been a major complication

[3–6]. These days, on the other hand, low-dose (<20 mg/kg) intravenous pulse cyclophosphamide therapy is being used with increasing frequency in the treatment of lymphoma and systemic lupus erythematosus, but there have been only a few case reports of cyclophosphamide-induced hyponatraemia [1,7,8]. This study was undertaken to examine how frequently hyponatraemia occurs after low-dose intravenous pulse cyclophosphamide therapy and to evaluate risk factors for cyclophosphamide-induced hyponatraemia.

Subjects and methods

We retrospectively analysed the data from our inpatients over the recent 3 years. Between March 2005 and February 2008, 84 patients (42, lupus nephritis; 42, non-Hodgkin's lymphoma) were admitted to Hanyang University Hospital in Seoul for intravenous pulse cyclophosphamide therapy. They had several admissions for each treatment of intravenous pulse cyclophosphamide: 216 treatment episodes in lupus patients and 194 treatment episodes in lymphoma patients. Among them, we evaluated 123 treatment episodes in which both basal and follow-up serum sodium data were available. Considering all reports of cyclophosphamide-induced water intoxication [1–3,6–8], cyclophosphamide-induced hyponatraemia was defined as serum sodium concentration <135 mEq/L at 24 hours after the therapy in patients whose basal serum sodium concentrations were normal. Thus, 112 treatment episodes from 84 patients were enrolled in this study after excluding 11 treatment episodes whose basal serum sodium concentration was abnormal.

The new-onset hyponatraemia was evaluated by comparing demographic parameters and laboratory data. We investigated whether the presence of pre-existing hyponatraemia-predisposing comorbidities affect occurrence of cyclophosphamide-induced hyponatraemia. Cases with hyponatraemia-predisposing comorbidites accompanied patients with nephrotic syndrome, congestive heart failure, chronic renal insufficiency, adrenal insufficiency and hypothyroidism. In addition, concurrent medications that can be associated with hyponatraemia were investigated.

Each patient with lupus received a single intravenous cyclophosphamide 500 mg/m^2 BSA, and each patient with lymphoma received a single intravenous cyclophosphamide 750 mg/m^2 along with single intravenous dose of doxorubicin (50 mg/m^2), a single intravenous vincristine (1.4 mg/m^2) and oral prednisone 100 mg/day for 5 days. To minimize the risk of haemorrhagic cystitis, intravenous hydration was carried out just before and after cyclophosphamide administration using 1 and 2 L of half-saline in patients with lupus and lymphoma, respectively. In patients with lymphoma, 40 mg of intravenous furosemide was given at the same time.

Continuous data were described as means ± standard deviation. Statistical comparisons between the groups were performed using Wilcoxon signed rank test for paired data or Mann–Whitney *U*-test for unpaired data. Correlations between variables of interest were analysed by linear regression. $P < 0.05$ was considered as statistically significant.

Categorical data were analysed using contingency tables and chi-square test. Logistic regression was used to model odds ratios and 95% confidence intervals as measures of the association between predictors and cyclophosphamide-induced hyponatraemia.

Results

In this retrospective analysis from 112 treatment episodes in 84 patients, cyclophosphamide-induced hyponatraemia occurred in 15 treatment episodes (13.4%) from 12 patients (14.3%). When all the treatment episodes were taken, the serum sodium concentration significantly decreased from 139.9 ± 3.5 to 137.9 ± 5.1 mEq/L after the cyclophosphamide therapy ($P < 0.001$, Figure 1). Table 1 shows findings from the 15 treatment episodes with cyclophosphamide-induced hyponatraemia. Follow-up serum Na^+ concentration taken 24 hours after the cyclophosphamide therapy was decreased to 130.3 ± 3.5 mEq/L from the basal 139.7 ± 2.8 mEq/L ($P < 0.001$). Although most of them (14 treatment episodes from 11 patients) had mild to moderate hyponatraemia (125 mEq/L or higher), the serum sodium concentration in one patient with lymphoma was 123 mEq/L. Three patients had symptoms of mild nausea. The degree of hyponatraemia appeared unrelated to symptomatology (Table 1). About half of the treatment episodes with cyclophosphamide-induced hyponatraemia resolved spontaneously. Isotonic saline was administered in five treatment episodes, and intravenous furosemide was given in two treatment episodes. The serum sodium concentration taken from the patients with cyclophosphamide-induced hyponatraemia 48 hours after the intravenous pulse cyclophosphamide was 134.6 ± 4.9 mEq/L, indicating that hyponatraemia was almost recovered.

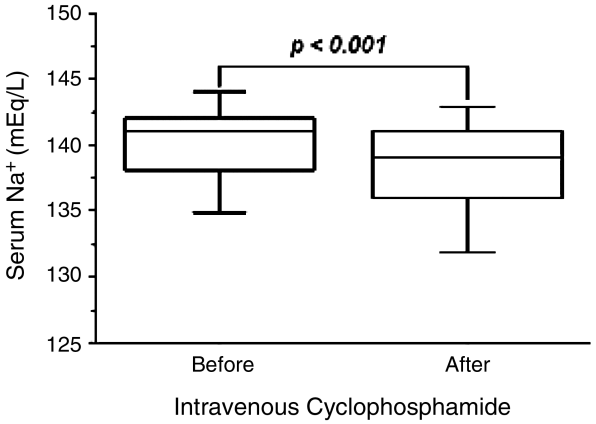

Fig. 1. Changes of serum sodium concentrations at 24 hours after low-dose intravenous pulse cyclophosphamide (box plots of serum Na^+ concentration are shown before and after cyclophosphamide administration).

To characterize cyclophosphamide-induced hyponatraemia, we obtained urinary data from eight treatment episodes when they were hyponatraemic. Urine osmolality was 327 ± 195 (range, 182 to 790) mOsm/kg H_2O, urine sodium 68 ± 47 (range, 31 to 176) mEq/L, urine potassium 35 ± 21 (range, 14 to 77) mEq/L and urine chloride 82 ± 87 (range, 23 to 293) mEq/L. Table 2 shows serum electrolytes taken 24 hours after the cyclophosphamide therapy from the treatment episodes with and without hyponatraemia. Those with hyponatraemia had significantly lower serum chloride and total CO_2 concentrations.

We compared demographic and basal laboratory characteristics between patients with and without cyclophosphamide-induced hyponatraemia. Patients with cyclophosphamide-induced hyponatraemia were significantly older than those without cyclophosphamide-induced hyponatraemia (57.3 ± 14.7 *vs.* 40.0 ± 17.0 years of age, $P < 0.01$). Male sex was more frequently associated with cyclophosphamide-induced hyponatraemia ($P < 0.05$ by chi-square test). However, body mass index and blood pressure were not significantly different between patients with and without cyclophosphamide-induced hyponatraemia (Table 3). Basal serum biochemical data including serum sodium, potassium, urea, creatinine, albumin and lactate dehydrogenase were not significantly different between patients with and without cyclophosphamide-induced hyponatraemia.

Some of our patients had hyponatraemia-predisposing comorbidities including nephrotic syndrome (15 treatment

Table 1. Findings from treatment episodes with cyclophosphamide-induced hyponatraemia

No.	Underlying disease	Comorbidities	Concurrent medications	Serum Na^+ (mEq/L)		Symptoms	Treatment
				Basal	Follow-up		
1	LN	0	+	143	133	0	None
2	NHL	0	0	143	123	0	Isotonic saline
3	NHL	+	0	138	133	+	Isotonic saline
4	NHL	0	0	137	127	+	Isotonic saline
5	NHL	0	0	138	134	0	None
6	NHL	0	0	142	134	0	None
7	NHL	0	0	141	134	0	None
8	NHL	0	0	142	131	0	i.v. furosemide
9	LN	+	0	142	126	0	i.v. furosemide
10	NHL	0	0	140	130	0	Isotonic saline
11	NHL	0	0	137	126	0	Isotonic saline
12	NHL	0	0	136	132	+	None
13	NHL	+	0	137	129	0	None
14	NHL	0	0	144	130	0	None
15	NHL	0	0	136	133	0	None

Comorbidities represent associated diseases including nephrotic syndrome, congestive heart failure, chronic renal insufficiency, adrenal insufficiency and hypothyroidism. Concurrent medications include drugs that can be associated with hyponatraemia such as thiazide diuretics, neuropsychiatric agents and nonsteroidal anti-inflammatory drugs. Follow-up serum Na^+ concentrations were taken 24 hours after the cyclophosphamide therapy. LN, lupus nephritis; NHL, non-Hodgkin's lymphoma; 0, absent; +, present.

episodes), congestive heart failure (three episodes), chronic renal insufficiency (two episodes), adrenal insufficiency (one episode) and hypothyroidism (one episode). No differences in serum sodium concentrations before and after the low-dose intravenous pulse cyclophosphamide therapy were found between patients with and without hyponatraemia-predisposing comorbidities.

During the study period, 13 treatment episodes were taking thiazide diuretics, 11 treatment episodes were using nonsteroidal anti-inflammatory drugs and 11 treatment episodes were receiving anticonvulsants. None of our patients were taking antidepressants, and the majority of the anticonvulsants was diazepam. We found no significant association between these medications and cyclophosphamide-induced hyponatraemia.

Finally, multivariate analysis was used to evaluate independent predictors of cyclophosphamide-induced hyponatraemia. The possible parameters tested were age (>40 years *vs*. ≤40 years), sex (female *vs.* male), underlying disease (lymphoma *vs.* lupus), presence or absence of comorbidities associated with hyponatraemia, presence or absence of concurrent medications associated with hyponatraemia and dose of cyclophosphamide (750 mg/m^2 or less *vs.* more). However, no significant factors were found to independently predict the occurrence of cyclophosphamide-induced hyponatraemia. Although the incidence of hyponatraemia increased with advancing age on univariate analysis (Figure 2), old age was not independently associated with cyclophosphamide-induced hyponatraemia.

Table 2. Comparison of serum electrolytes taken 24 hours after the cyclophosphamide therapy between treatment episodes with and without hyponatraemia

	No hyponatraemia (n = 97)	Hyponatraemia (n = 15)	P
Na^+ (mEq/L)	139.9 ± 5.9	130.3 ± 3.5	<0.0001
K^+ (mEq/L)	3.91 ± 0.58	3.95 ± 0.50	NS
Cl^- (mEq/L)	105.2 ± 3.4	96.9 ± 3.6	<0.0001
Total CO_2 (mEq/L)	23.5 ± 3.0	21.7 ± 2.3	<0.05

NS, not significant.

Discussion

It has been clearly demonstrated that cyclophosphamide impairs the kidney's ability to dilute urine when high doses (>50 mg/kg) are used [3]. In contrast to the past years, low-dose intravenous pulse cyclophosphamide therapy predominates these days. This low dosage may reduce the risk of water intoxication, but the risk of hyponatraemia induced by cyclophosphamide should be considered because the therapy is very frequently applied to many patients with lupus nephritis and lymphoma.

In this retrospective analysis, we concluded that hyponatraemia occurring after low-dose intravenous pulse cyclophosphamide was not rare especially when hypotonic solutions were adopted for hydration protocol. The overall incidence of cyclophosphamide-induced hyponatraemia was 13.4% (by treatment episode number) or 14.3% (by patient number) when patients were enrolled whose basal serum sodium concentrations were normal. Most of the

Table 3. Comparison of demographic characteristics between treatment episodes with and without hyponatraemia

	No hyponatraemia (n = 72)	Hyponatraemia (n = 12)	P
Age (years)	40.0 ± 17.0	57.3 ± 14.7	<0.01
Male (%)	28	58	<0.05
Height (m)	1.60 ± 0.1	1.61 ± 0.02	NS
Weight (kg)	58.6 ± 11.2	61.5 ± 13.5	NS
Body mass index (kg/m^2)	23.0 ± 3.7	22.9 ± 1.5	NS
Systolic BP (mmHg)	118.9 ± 15.6	120.0 ± 8.5	NS
Diastolic BP (mmHg)	75.4 ± 11.7	76.7 ± 4.9	NS

BP, blood pressure; NS, not significant.

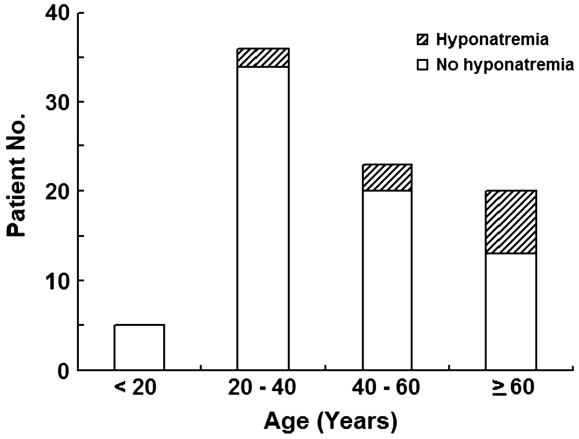

Fig. 2. Occurrence of cyclophosphamide-induced hyponatraemia by age.

patients had mild hyponatraemia, and all of them recovered without any sequelae. To the best of our knowledge, this study is the first one which reports how frequently hyponatraemia occurs after low-dose intravenous pulse cyclophosphamide therapy.

Cyclophosphamide diminishes the ability of the kidney to excrete water. Our findings of urine electrolytes and osmolality from the patients with cyclophosphamide-induced hyponatraemia are consistent with dilutional hyponatraemia. In particular, the available urine osmolalities ranging from 182 to 790 mOsm/kg H_2O showed inappropriate antidiuresis, suggesting a water-retaining state. Impaired water excretion occurred acutely and resolved after discontinuation of the high-dose cyclophosphamide, and a relationship was observed between the appearance in the urine of an active alkylating metabolite of cyclophosphamide and the rise in urine osmolarity [3]. Therefore, the antidiuretic effect seems to be related to the alkylating metabolites of cyclophosphamide, potentiating renal action of vasopressin.

The half-life of cyclophosphamide in blood has been variously measured at 6 to 7 hours, while the peak antidiuretic effect in adult patients has occurred at 10 to 14 hours [9,10]. This is consistent with the action of some metabolic products of the drug, either through a direct vasopressin-like effect on the kidney or indirectly by causing vasopressin release.

However, the water retention may involve a direct effect of cyclophosphamide on the collecting duct epithelium, as plasma vasopressin levels are not elevated in patient following the administration of intravenous cyclophosphamide [11,12]. In addition, antidiuresis was reported to occur in response to intravenous cyclophosphamide in an 8-year-old girl with central diabetes insipidus [13], excluding the possibility of a syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Vincristine, which was used in our lymphoma patients, can also induce hyponatraemia. However, we believe that hyponatraemia occurring within 24 hours was unrelated to vincristine because vincristine has different mechanism and onset of hyponatraemia from cyclophosphamide [14]. In patients with hyponatraemia induced by vincristine, plasma and urinary vasopressin levels are remarkably elevated [15,16], and it has been suggested that true SIADH may be induced by a direct neurotoxic effect of vincristine on the hypothalamus, the neurohypophyseal tract, or the posterior pituitary itself, involving sites of vasopressin synthesis and storage [17]. Consistent with this, symptomatic hyponatraemia was reported to occur in at least 4 days after vincristine administration [16]. In contrast, cyclophosphamide-induced hyponatraemia usually occurs 4–12 hours after the intravenous administration of the drug, although sometimes not until 48 hours afterwards, and returns to normal in around 24 hours [1–6]. These pharmacodynamics and aforementioned pharmacokinetics of cyclophosphamide led us to define cyclophosphamide-induced hyponatraemia in this study.

We adapted a hydration protocol using half-saline before and after cyclophosphamide administration to minimize the risk of haemorrhagic cystitis. Additionally, the patients might have been advised to drink water abundantly. Although urinary dilution normally occurs in response to a water load, hypotonic fluid intake, either oral or parenteral, would promote dilutional hyponatraemia. Thus, the use of half-isotonic saline in our hydration protocol may have increased the incidence of hyponatraemia, and hydration with normal saline would be preferable in usual patients.

Another factor that may contribute to hyponatraemia is emesis because nausea stimulates vasopressin release. In our patients, however, emesis does not seem to be contributory to the cyclophosphamide-induced hyponatraemia that occurred within 24 hours since only three patients were mildly nauseous. The fact that serum potassium was not decreased and total CO_2 was significantly reduced suggests that vomiting did not contribute to the observed electrolyte disturbances. Besides, we used an effective antiemetic agent as a prophylaxis, and cyclophosphamide typically causes delayed emesis [18].

The reason why total CO_2 concentration was decreased in treatment episodes with hyponatraemia is not clear. It may include any causes of metabolic acidosis and respiratory alkalosis, but exact acid–base diagnosis could not be made because blood gas analysis was not carried out in our patients. To the best of our knowledge, there have been no reports demonstrating association between acute metabolic acidosis and use of cyclophosphamide. In patients with hyponatraemia from adrenocorticotropic deficiency, however, hypobicarbonataemia was reported mostly due to a compensated respiratory alkalosis [19].

We investigated possible risk factors for cyclophosphamide-induced hyponatraemia. It is conceivable that patients who already have hyponatraemia-predisposing comorbidities such as nephrotic syndrome or concurrent medications that can be associated with hyponatraemia will be at risk of hyponatraemia when they are exposed to cyclophosphamide administration. In our study, however, occurrence of cyclophosphamide-induced hyponatraemia was not affected by either predisposing condition. This is probably because our patients were all in a compensated state as reflected by normal basal sodium concentrations. On the other hand, this negative result may suggest the causative role of cyclophosphamide in producing hyponatraemia.

In summary, low-dose intravenous pulse cyclophosphamide as well as high dose can induce hospital-acquired hyponatraemia especially when hypotonic solutions are used for prophylactic hydration. Thus, serum sodium concentra-

tion needs to be followed soon after the intravenous pulse cyclophosphamide therapy, and furosemide may be considered in high-risk patients [20]. Instead, isotonic solutions should be used if a forced diuresis is required. Although most of the cases with cyclophosphamide-induced hyponatraemia are mild or moderate, some of them may progress to severe hyponatraemia [1,7,8]. Prospective studies on a large scale are required to define more characteristics of cyclophosphamide-induced hyponatraemia.

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Conflict of interest statement. None declared.

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Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience

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Abstract

Background. Intravenous conivaptan is a novel therapeutic agent indicated for the treatment of euvolaemic and hypervolaemic hyponatraemia. However, there is paucity of reported clinical experience using conivaptan for the treatment of the syndrome of inappropriate secretion of anti-