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Two Case Reports of Severe Hyponatremia following Cyclophosphamide Infusion in Breast Cancer Patients

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Abstract

Cyclophosphamide is an important component of breast cancer therapy. A less common side effect of cyclophosphamide is hyponatremia. This paper describes two cases of severe hyponatremia with neurologic side effects in breast cancer patients undergoing neoadjuvant chemotherapy with cyclophosphamide. Although rare, it is important for physicians to be aware of this side effect and treat accordingly.

Introduction

Cyclophosphamide has become a cornerstone of breast cancer therapy in the neoadjuvant, adjuvant, and metastatic setting. Common side effects of cyclophosphamide include myelosuppression, nausea, emesis, diarrhea and alopecia. A less common side effect of cyclophosphamide is hyponatremia. Hyponatremia is more commonly associated with high dose cyclophosphamide. This paper describes two cases of severe hyponatremia after low dose cyclophosphamide infusion in breast cancer patients.

Case One

The first case involved a 56 year-old female receiving neoadjuvant chemotherapy with Doxorubicin 60 mg/m² and Cyclophosphamide 600 mg/m² for early stage breast cancer. Medications were notable for clonazepam, ondansetron, prochlorperazine, tramadol and zolpidem.

The day following her second cycle of chemotherapy, the patient was found to have a witnessed seizure. Labs revealed a serum sodium of 116 mmol/L, serum osmolality 253 mOsm/L, urine osmolality 273 mOsm/kg, and urine sodium 49 mmol/L. While in the Emergency Center, the patient was noted to have a seizure and was intubated. Hypertonic saline was initiated. EEG was notable for generalized slowing, and MRI brain showed no evidence of metastatic disease or ischemia. Over three days, the patient's sodium improved and she was extubated. The patient's sodium remained within normal limits and she had no further seizures.

Case Two

The second case involved a 70 year-old female with early stage breast cancer who was initiated on neoadjuvant Doxorubicin 60 mg/m² and Cyclophosphamide 600 mg/m².

Medications included ondansetron, temazepam, and prochlorperazine. The patient had recently been prescribed venlafaxine, which she had taken in the past for anxiety without significant side effects. The patient presented to the Emergency Center after receiving her first cycle of chemotherapy with lethargy and confusion. The patient also reported drinking large quantities of water in order to prevent dehydration. Labs were notable for a serum sodium of 109 mmol/l, serum osmolality 221 mOsm/l, urine osmolality 327 mOsm/kg, and urine sodium 13 mmol/l. CT head showed no acute intracranial events. The patient was started on hypertonic saline. The patient's home venlafaxine was held given concern it may have contributed to her hyponatremia. The patient's sodium was trended and improved to 135 mmol/l on discharge. Her mental status had also returned to baseline.

Discussion

This paper describes two cases of breast cancer patients experiencing severe hyponatremia after receiving cyclophosphamide. The first patient experienced severe hyponatremia with seizures. Notably none of the premedications were associated with hyponatremia. The patient's serum osmolality was consistent with hypotonic hyponatremia. The patient's high urine osmolality and urine sodium were more consistent with SIADH. Other causes of SIADH, including CNS disturbances and pulmonary disease, were ruled out. Malignancy resulting in SIADH is less likely as her sodium normalized and remained within normal limits. Therefore it reasonable to conclude her hyponatremia was secondary to cyclophosphamide.

The second case involved a patient with confusion and lethargy in the setting of severe hyponatremia. Notably this patient was on venlafaxine prior to presentation. This may have contributed although large studies have only shown an incidence of hyponatremia between 0.08% to 4% in patients taking venlafaxine (1). Furthermore, she had taken venlafaxine in the past without significant side effects. Although the patient drank large quantities of water prior to presentation, the patient's high urine osmolality makes psychogenic polydipsia unlikely. The patient's serum osmolality was consistent with hypotonic hyponatremia. Therefore it reasonable to conclude cyclophosphamide largely contributed to the patient's severe hyponatremia.

There are a small number of case reports of patients who developed severe hyponatremia after receiving low dose cyclophosphamide for breast cancer (2–6, Table 1). The exact mechanism by which cyclophosphamide results in hyponatremia is unclear. An early study showed high dose cyclophosphamide impaired water secretion by the kidney and led to a decrease in serum osmolality and increase in urine osmolality with resulting decrease in serum sodium (7). An early case report proposed SIADH as the mechanism for hyponatremia in a pediatric patient receiving cyclophosphamide (8). Later, it was proposed that cyclophosphamide resulted in a direct toxic effect on the renal tubules or that the alkylating metabolites of cyclophosphamide caused anti-diuretic hormone like activity (9).

Although rare, cyclophosphamide infusion can result in severe hyponatremia with serious neurologic toxicities and may be life threatening. It is important for physicians to be aware of this side effect and treat accordingly.

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Table 1.

Published reports of hyponatremia in breast cancer patients receiving cyclophosphamide.

Indication	Age	Serum Sodium on presentation (mmol/l)	Symptoms	Other possible contributing factors	Reference
Adjuvant	64	107	seizure	Citalopram	2
Adjuvant	56	116	seizure	Enalapril, prior cerebral hemorrhage	3
Adjuvant	54	120	Hand twitching	None	4
Adjuvant	58	124	Lower extremity edema	None	4
Metastatic disease	58	117	Generalized weakness, confusion, headaches	None	5
Metastatic disease	56	113	seizure	None	5
Adjuvant	43	112	seizure	Chlorthalidone	6