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CASE REPORT

Cyclophosphamide-induced symptomatic hyponatraemia

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ABSTRACT

Cyclophosphamide is an alkylating agent used in antineoplastic and immunosuppressive therapies. Symptomatic hyponatraemia is a rare but life-threatening complication in patients treated with cyclophosphamide. We report the case of a 64-year-old woman with breast cancer who developed severe symptomatic hyponatraemia with a generalised seizure and convulsions after a second cycle of adjuvant chemotherapy with 5-fluouracil, epirubicin and cyclophosphamide. She completely recovered after correction of the serum sodium concentration without neurological deficits. Physicians prescribing cyclophosphamide, irrespective of the treatment indication and dosage, should be aware of this potentially life-threatening complication.

KEYWORDS

Cyclophosphamide, adverse effects, hyponatraemia

What was known on this topic?
Severe hyponatraemia after administration of low-dose cyclophosphamide therapy (<15 mg/kg) is extremely rare. The exact mechanism of action is unclear. A direct toxic effect of cyclophosphamide or its metabolites on renal collecting tubules or an antidiuretic hormone-like activity of cyclophosphamide metabolites has been suggested.

What does this case add?
In this case, severe hyponatraemia with neurological symptoms occurred shortly after administration of low-dose cyclophosphamide. No definite mechanism of action could be elucidated. A potential role for citalopram as a contributing causal factor can not be excluded. Physicians should be aware of contributing factors, such as renal failure, drug interactions and extreme water intake.

INTRODUCTION

Severe hyponatraemia (serum sodium <120 mmol/l) is a serious electrolyte disorder with potential life-threatening neurological complications. It has been reported in association with a variety of anticancer drug regimens including cytotoxic agents as vinca alkaloids, platinum compounds and alkylating agents.[1]
Cyclophosphamide, an alkylating agent, is widely used to treat malignant neoplasms and can be effective in the treatment of several rheumatic diseases. We report a patient with severe, symptomatic hyponatraemia which occurred during the second chemotherapy cycle containing cyclophosphamide.

CASE REPORT

A 64-year-old woman, suffering from a pT1cN1aG1M0 carcinoma of the left breast, was planned to receive three cycles of adjuvant chemotherapy containing 5-fluouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 (FEC) with a three-week time interval. Her medical history included depression and anxiety disorder for which she was treated with flurazepam and alprazolam. Three months before chemotherapy, citalopram was prescribed with a stepwise increase in dosage. Seven years before she also had been treated with citalopram in a dose of 40 mg for her depression, without any side effects.

The first cycle of chemotherapy was uneventful. Ten days before the second cycle the dosage of citalopram was increased from 30 mg to 40 mg daily. On day 1 of the second cycle, normal renal function and serum potassium were observed. The serum sodium concentration was 134 mmol/l (normal 135 to 145 mmol/l). Concomitant with chemotherapy, the patient was hydrated with 0.5 litre of isotonic saline. Antiemetic therapy consisted of dexamethasone and ondansetron. Furthermore, the patient ingested approximately 1.5 to 2 litre of tea and water after administration of chemotherapy. She reported dizziness in the evening of day 1 and was advised to take extra dexamethasone. On the second day, 28 hours after chemotherapy, she developed a generalised seizure with convulsions, after a period of impaired consciousness and incoherent speech. At the emergency ward a Glasgow Coma Score of 3 was observed. Her blood pressure was 128/54 mmHg with a pulse of 68 beats/min. She was euvolaemic and had an urine output of 80 ml in the first hour after admission. Laboratory tests showed a serum sodium of 107 mmol/l, urinary sodium of 29 mmol/l and serum potassium at 4.6 mmol/l (normal 3.5 to 5.0 mmol/l). The CT scan of the brain revealed no abnormalities.
Her sodium deficit was calculated at 480 mmol, with a desired serum sodium of at least 120 mmol/l. Because of the severity of the symptoms, urgent intervention with hypertonic saline infusion (800 ml NaCl 3% at 100 ml/h) was initiated on the intensive care unit and the citalopram was discontinued. Within 12 hours, the serum sodium concentration rose gradually from 104 mmol/l to 120 mmol/l and the patient slowly recovered from her neurological symptoms. During the next five days, the serum sodium concentration was slowly corrected up to 135 mmol/l by infusion of isotonic saline (*table 1*). The patient was discharged asymptomatically after seven days.
Reintroduction of citalopram in a dose of 20 mg did not induce a fall of the serum sodium concentration.
On day 22 the patient received the third chemotherapy cycle without administration of cyclophosphamide. This cycle was well tolerated without neurological symptoms or electrolyte imbalances.

DISCUSSION AND REVIEW OF THE LITERATURE

A deep hyponatraemia with severe neurological symptoms was observed in our patient within 28 hours after administration of the second cycle of FEC chemotherapy. In the absence of structural brain lesions, no evidence for renal, heart or liver failure, no hypothyroidism, and adrenal insufficiency highly improbable with dexamethasone gifts before and after chemotherapy, the hyponatraemia is considered to be chemotherapy related and very likely cyclophosphamide related.

Cyclophosphamide can induce severe hyponatraemia. This life-threatening side effect was first described in patients treated with high-dose i.v. cyclophosphamide (30 to 40 mg/kg), and later in patients treated with moderate doses (20 to 30 mg/kg).[2,3] There are a small number of cases of severe hyponatraemia after administration of low-dose cyclophosphamide therapy (<15 mg/kg).[4-11] These data are summarised in *table 2*.

The exact mechanism of action is unclear. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been proposed in a fatal case of severe hyponatraemia in a patient who had received high-dose i.v. cyclophosphamide.[3] Post-mortem examination revealed

Table 1. *Serum electrolytes, clinical chemistry values and neurological state pre and post chemotherapy*

	Normal range	1 hour before chemotherapy	28 hours post chemotherapy	42 hours post chemotherapy	5 days post chemotherapy
Haemoglobin	7.2-9.8 mmol/l	7.4	6.7	ND	ND
Haematocrit	0.35-0.47 l/l	0.34	0.29	0.30	ND
Glucose	3.5-7.8 mmol/l	8.0	7.5	6.3	ND
Sodium	135-145 mmol/l	134	107	120	135
Potassium	3.5-5.0 mmol/	4.8	4.6	4.3	ND
Creatinine	50-90 µmol/l	60	54	ND	ND
Urea	2.0-4.0 mmol/	ND	3.8	ND	ND
Urinary sodium	(variable) mmol/	ND	29	ND	ND
TSH	mU/	ND	ND	2.6	ND
Neurological symptoms		Generalised seizure and convulsions	Sedated and intubated	Sedated and intubated	No neurological deficits

ND = not determined, TSH = thyroid-stimulating hormone.

Table 2. *Published reports of hyponatraemia after low-dose i.v. cyclophosphamide*

Indication of treatment	Age (years) and sex	Cyclophosphamide dosage	Serum sodium (mmol/l)	Possible influencing factors	(Estimated) fluid intake (l/h)	References
Multiple myeloma	68, male	500 mg, iv	108	Concomitant use of indomethacin	3l/24h	4
SLE	59, female	10 mg/kg, iv	116	-	2.4l/24h	5
Sjögren's disease	57, female	780 mg, iv	117	-	>0.95l/6h	6
SLE	48, female	750 mg, iv	119	-	3l/24h	7
SLE	53, female	500 mg, iv	119	-	3l/2h	7
ANCA-related glomerulonephritis	70, female	50 mg, iv	108	Renal failure and hypoalbuminaemia	>2l/12h	8
Neuro-Behcet	43, male	15 mg/kg	107	High fluid intake	6l/6h	9
Polyarteritis nodosa	46, female	15 mg/kg	112	High fluid intake	10l/12h	9
SLE	30, female	15 mg/kg	106	Renal involvement in SLE, high fluid intake	5l/8h	9
Diffuse cutaneous systemic sclerosis	49, female	500 mg	106	-	Unknown	10
Metastatic adenocarcinoma of the small salivary glands	69, female	500 mg/m^2	116	Concomittant administration of cisplatin	Unknown	11
Breast cancer	64, female	500 mg/m^2	107	-	2l/24h	This case

ANCA = antineutrophil cytoplasmic autoantibodies, iv = intravenous, SLE = systemic lupus erythematosus.

loss of Herring's bodies and degranulation of various hypothalamic neurosecretory organelles, which supported this hypothesis. In other cases, no rise of antidiuretic hormone (ADH) concentrations could be demonstrated.[2,8] Interesting is the case of a girl with established diabetes insipidus who developed hyponatraemia after cyclophosphamide infusion despite an inability to secrete ADH.[12] A direct toxic effect of cyclophosphamide or its metabolites on renal collecting tubules or an antidiuretic hormone-like activity of cyclophosphamide metabolites, has been suggested.[4] Solely based on the euvolaemic state of our patient and the urinary sodium of >20 mmol/l neither mechanism can be confirmed or ruled out in this case.

Patients in a recent series of three cases of severe hyponatraemia were reported to have ingested extreme amounts of fluids in a short time after cyclophosphamide infusion (*table 2*). Since our patient drank only two litres of fluids after the cyclophosphamide, this is insufficient to explain her deep hyponatraemia. In general, physicians should be aware of extreme water intake in patients treated with cyclophosphamide. Not seldom patients are advised to drink substantial amounts of water to reduce the risk of the side effect of haemorrhagic cystitis.

Other factors that may contribute to the severity of the hyponatraemia as described in previous cases are the presence of renal failure and hypoalbuminaemia and drug interactions with non-steroidal anti-inflammatory drugs or concomitant administration of platinum compounds, such as cisplatin (*table 2*). In our case, a potential role for citalopram in the induction of the severe hyponatraemia can not be excluded, although treatment with citalopram in the past was uneventful and rechallenge with citalopram did not induce a rebound hyponatraemia. Based on the Naranjo causality scale, a ten-question-based method for estimating the causality of adverse reactions and drug use, the causal relationship between cyclophosphamide and citalopram and the hyponatraemia is estimated as probable and possible, respectively.[13] Causality of an interaction phenomenon between cyclophosphamide and citalopram using the drug interaction probability scale of Horn *et al.* was estimated as doubtful.[14]

In conclusion, physicians prescribing cyclophosphamide, irrespective of the treatment indication and dosage, should be aware of the acute, potentially life-threatening complication of severe hyponatraemia.

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