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

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.\textsuperscript{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\textsuperscript{2}, epirubicin 100 mg/m\textsuperscript{2} and cyclophosphamide 500 mg/m\textsuperscript{2} (FEC) with a three-week time interval. Her medical history included depression and anxiety disorder for which she was treated with fluoxetine 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 euvoletic 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 asymptatically 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). There are a small number of cases of severe hyponatraemia after administration of low-dose cyclophosphamide therapy (<15 mg/kg). 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. Post-mortem examination revealed

<table>
<thead>
<tr>
<th>Table 1. Serum electrolytes, clinical chemistry values and neurological state pre and post chemotherapy</th>
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<tr>
<td><strong>Normal range</strong></td>
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<td>Haemoglobin</td>
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<td>TSH</td>
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**ND** = not determined, **TSH** = thyroid-stimulating hormone.
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 cannot 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.

REFERENCES


ANSWER TO PHOTO QUIZ (PAGE 184)

A POSTOPERATIVE PUZZLE

DIAGNOSIS

An aberrant location of a central venous catheter is observed in approximately 5 to 10% of all procedures. The majority of malpositions concern the descending aorta, a persistent left superior vena cava or one of the local smaller veins (e.g., the left internal thoracic vein, the cardiophrenic vein or the left superior intercostal vein). Among the more serious complications of malpositioning are hydromediastinum after perforation of a small vein and pericardial tamponade due to a lesion of the pericardiophrenic vein. Extravascular (e.g., mediastinal, pericardial or pleural) positioning of the venous catheter has also been described. Extravascular malpositions are excluded in the presence of smooth aspiration of blood through all lumina. Additionally, diagnostic procedures such as a chest radiography, administration of intravenous contrast, blood gas analysis, and assessment of the venous pressure, can clarify the situation. In the present case the malposition, in a superior intercostal vein (figure 2), did not have consequences.

ACKNOWLEDGEMENT

A. Sikkenk, radiologist, evaluated the chest radiograph.

REFERENCES