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Recurrent Ifosfamide-induced Hyponatraemia

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HYPONATRAEMIA, RELATED to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), has been associated with various antineoplastic agents, including vincristine and cyclophosphamide [1]. Recently, three well-documented cases of SIADH have been reported with ifosfamide, an isomeric analogue of cyclophosphamide [2–4]. Oncologists should be particularly aware of this life-threatening complication, since its clinical features may be mistaken for the more frequent direct neurotoxicity [5]. We report a case with severe, symptomatic hyponatraemia which recurred during the second chemotherapy cycle.

The patient was an 18-year-old female in whom a grade II olfactory neuroblastoma was diagnosed. First-line chemotherapy, including dacarbazine, cyclophosphamide, vincristine, epidoxorubicin and cisplatin, elicited no response. Another chemotherapy regimen containing carboplatin, etoposide and ifosfamide was proposed. On day 1, before initiation of chemotherapy, serum sodium was 140 mmol/l and renal function was normal. Thyroid function test results were unremarkable. The patient received 2400 mg of ifosfamide and mesna, followed 5 h later by cisplatin. Concomitant hydration (within 24 h) included 6.75 l of water and 27.5 g sodium chloride. On day 2, the patient again received 2400 mg of ifosfamide and mesna in 1 l of 5% dextrose over 3 h. On day 3, she gradually developed impairment of consciousness and was admitted to the intensive care unit (ICU). At admission, she was comatose with a Glasgow score of 8 and generalised hypotony. Laboratory studies showed the following: serum sodium 114 mmol/l, serum uric acid 147 μmol/l, plasma osmolality 230 mOsm/kg, urinary sodium 131 mmol/l, urinary osmolality 504 mOsm/kg. A computer tomography (CT) scan disclosed diffuse cerebral oedema with collapsed ventricles. Electroencephalogram showed status epilepticus. Furosemide, hypertonic saline and intravenous phenobarbital were administered. Serum sodium gradually rose to 122 mmol/l after 24 h and 131 mmol/l after 48 h of aggressive management. By this time, clinical examination and electroencephalogram had normalised. When determined, plasma vasopressin was 3.7 pmol/l both at admission and after correction of hyponatraemia. Serum sodium remained normal during initial follow-up. One month later, a second chemotherapy course was initiated in the ICU setting. Baseline serum sodium was 140 mmol/l. On day 3, after two doses of 2400 mg of ifosfamide, serum sodium decreased to 128 mmol/l and remained stable around 123 mmol/l during the following days, despite substantial water restriction associated with increased sodium intake. The patient remained alert but complained of headaches. Plasma vasopressin was 13.1 pmol/l. Serum sodium gradually returned to baseline during follow-up.

In this case, elevated plasma vasopressin despite dramatically low plasma osmolality confirmed that hyponatraemia was related to SIADH. Although SIADH has been associated with olfactory neuroblastoma [6], hyponatraemia in our patient appeared to be clearly drug-related since it occurred twice following chemotherapy, with normal water metabolism before and after administration of anticancer agents. Among the drugs employed, only ifosfamide has been associated with hyponatraemia and SIADH [1–4]. Interestingly, despite a close structural analogy between ifosfamide and cyclophosphamide, previous chemotherapy with this latter compound in our patient has not been complicated by hyponatraemia.

As in the case described by Izquierdo and Leinung [4], hyponatraemia in our case recurred during the second chemotherapy cycle despite careful metabolic monitoring. Guidelines for subsequent management of patients who develop SIADH following cyclophosphamide or ifosfamide are lacking in the literature [1–4]. These patients have to be vigorously hydrated to avert urological complications, and dramatic water restriction cannot be systematically recommended. Demeclocycline has been used, since it induces nephrogenic diabetes insipidus [1]. However, the prolonged administration of this agent is not desirable in patients who often receive multiple nephrotoxic drugs. The systematic use of isotonic hydration fluids has been proposed [7], but may not be sufficient in patients with severe antidiuresis.

On the basis of these data, we think that careful metabolic monitoring is warranted in patients receiving ifosfamide for the first time. The occurrence of hyponatraemia during the first chemotherapy cycle should prompt dramatic changes in the hydration procedure with global liquid restriction and at least isotonic fluids. Worsening of hyponatraemia and/or neurological deterioration should dictate the patient's admission to the ICU, where hypertonic saline and diuretics together with symptomatic treatment can be given. If justified, subsequent chemotherapy courses using ifosfamide should be performed under strict monitoring, ideally in the ICU setting.

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