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Inappropriate Antidiuretic Hormone Secretion Induced by Ifosfamide

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THE SYNDROME of inappropriate antidiuretic hormone secretion (SIADH) has been described as a paraneoplastic entity or an anticancer drug-related side-effect [1]. Vincristine, cyclophosphamide [1] and in one case vinblastine [2] and cisplatin [3] have been incriminated. We report a case of SIADH induced by ifosfamide in a patient with a prostatic cancer and bone metastases.

A histologically proven metastatic well-differentiated adenocarcinoma of the prostate was diagnosed in January 1986 in a 77-year-old man. The primary treatment was bilateral orchiectomy which yielded an objective stabilization according to NPCP criteria for 9 months. In October 1986 the disease progressed and the patient received successively cyproterone acetate, aminoglutethimide and flutamide. He was referred to us in August 1988. The disease was confined to the bone, without major biological disturbances. He was receiving flutamide 150 mg per day, as well as nifedipine 30 mg and metoprolol 200 mg daily for coronary insufficiency. He did not receive corticosteroids or diuretics. The patient was included in a phase II trial of chemotherapy with ifosfamide 2 g/m^2 and mesna 2.4 g/m^2 per day for 2 days in a continuous infusion every 3 weeks.

Before the second cycle, clinical examination and biological values were normal. 12 h after the completion of the first infusion, the patient developed drowsiness and muscle twitching with no evidence of localized neurological abnormalities, hypovolaemia or heart failure. Blood pressure was normal. Serum electrolytes (mmol/l) were: sodium 113, potassium 3.4, bicarbonate 24.5. Proteinaemia 12.4 mmol/l, glycaemia 12.2 mmol/l and blood urea nitrogen 6.0 mmol/l caused serum osmolality of 250 mmol/l. Renal function was normal with serum creatinine 73 μmol/l and creatinine clearance 52 ml/min. Diuresis was 1700 ml/24 h without loss of water and electrolytes by other means than renal excretion. The 24 h inputs were 4000 ml of dextrose 5% with 16 g NaCl and 6 g KCl during the 2 day treatment. Urinalysis showed (mmol/24 h): sodium 143, potassium 95, urea 326, and glucose 83. Urinary osmolality was 510 mmol/l.

Cerebral computerised tomography was normal and an electro-encephalogram showed diffuse slow waves without evidence of any specific pattern of encephalopathy. Plasma cortisol and thyroid-stimulating hormone were, respectively, 0.41 nmol/l (normal 0.3–0.7 nmol/l) and 0.12 ml U/l (normal 0.05–0.2 ml U/l). After treatment by sodium and water restriction the patient recovered in 1 day. Plasma sodium was 140 mmol/l on the second day of this regimen.

The clinical and biological features of this episode are consistent with a SIADH [4]. No other drug-related aetiology could be found. SIADH has been reported in prostatic cancer [5], but at no time during his disease did our patient present hyponatraemia. SIADH has not been associated with ifosfamide/mesna therapy, although this side-effect is well known after cyclophosphamide administration [6], and oxazaphosphorins alkylating metabolites seem to be involved in the mechanism of SIADH [7]. The fact that common metabolites can be found in the urine of patients treated with these two drugs [8] might explain the occurrence of SIADH after ifosfamide administration. It is significant that administration of mesna did not seem to interfere with the toxic effect of these metabolites.

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Inhibition of Tumour Cell Growth by a Novel Dihydropyridine Derivative

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BLOCKERS OF the slow calcium channel exhibit a low potency of inhibition of tumour cells *in vitro* [1]. Our present study confirms this view for several calcium-channel blockers. However, we discovered that a novel dihydropyridine (DHP) derivative can suppress cell proliferation more potently than available calcium-channel blockers. Because of the profound effects of DHP derivatives in the submicromolar concentration range on calcium channels and hence on the cardiovascular system [2], effects which occur at much lower concentrations than those required for anti-proliferative action, their use in antitumour therapy is prohibited. However, because racemic DHP compounds may

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