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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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be separated into pure enantiomers, one of which is less potent on calcium channels and the cardiovascular system [3–5], a novel class of antitumour drugs might emerge.

The idea for this new approach originated in our finding that the calcium channel blocker niguldipine is also a potent calmodulin antagonist [6]. Moreover, niguldipine and its optical antipode B859–35 were equipotent in inhibiting the calmodulin-dependent enzymes phosphodiesterase (concentration producing 50% inhibition [IC_{50}] 0.5 μmol), calcium-transporting ATPase and myosin light-chain kinase (for methods see reference [7]). Studies of the fluorescent probes 9-anthroylcholine bromide and 2-*p*-toluidinylnaphthalene-6-sulphonic acid [8] revealed that binding of niguldipine and B859-35 to calmodulin occurred, which provides the molecular basis for inhibition of calmodulin-dependent cellular functions. Both B859-35 and niguldipine exhibited identical binding characteristics when interacting with calmodulin, which is consistent with the observed inhibition of calmodulin-dependent enzymes.

There has been much debate that treatment of tumours may be a therapeutical implication for calmodulin antagonists [9]. This hypothesis and the discovery of the calmodulin antagonistic properties of B859-35 initiated our research into the effects of B859-35 on proliferation of the following human cell lines: ZR-75-1 and MCF-7 (mammary tumours), A-549 (lung tumour), Molt-4 and HL-60 (leukaemia) and FL (amnion cell line derived from normal tissue). Growth of tumour cells measured after incubation for 6 days in Richter's IMEM-ZO and 2% fetal calf serum with the respective drug was determined by total DNA content [10]. Our experiments showed that B859-35, less potent on calcium-channels than its optical antipode, had the same potency of inhibition as niguldipine for a given tumour cell line. This finding is also valid for the enantiomers of isradipine. However, the anti-proliferative potency of B859-35 (IC_{50} 0.3 μmol) on the mammary tumour cell line ZR-75-1 is about 100 times greater than that of isradipine. In addition, B859-35 showed selectivity for the investigated cell line and the following order of decreasing potency was assessed: ZR-75-1 > MCF-7 > A-549 > FL. Significantly, no effect has been observed on Molt-4 and HL-60 in the concentration range 0.01–10 μmol. Neither isradipine (IC_{50} 25 μmol), diltiazem (IC_{50} 30 μmol) nor nitrendipine (IC_{50} 22 μmol) showed selectivity for any of the cell lines, as is also the case for the unspecific antineoplastic drug doxorubicin.

The high potency of B859-35 to suppress tumour cell growth in contrast to its low toxicity, due to low affinity for calcium channels, favours its potential use in the treatment of tumours. Calmodulin antagonism may be involved in inhibition of cell proliferation since both effects showed no stereospecificity for the optical antipodes B859-35 and niguldipine and occurred in the same concentration range (0.3–0.5 μmol). The results argue against the possibility that calcium channel blockade might be the rationale for arrest of tumour cell growth.

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Amonafide in Metastatic Colorectal Carcinoma

Werner Scheithauer, Gabriela Kornek, Karin Haider and Dieter Depisch

AMONAFIDE (nafidimide, NSC 308847) is a new imide derivative of naphthalic acid with DNA intercalative properties [1]. Preclinical data in murine leukaemia and solid tumour models suggested significant activity [2] that, with a reversible toxicity profile, encouraged evaluation of amonafide in clinical trials. Reasonable tolerance with myelosuppression as the dose-limiting toxicity was found in phase I/II trials [3–5]. Antitumour effects were observed in breast [4], non-small cell lung [3] and prostate cancer [3, 5]. We have investigated the antitumour activity of amonafide in patients with advanced metastatic colorectal cancer.

Patients with progressive, histologically confirmed metastatic colorectal cancer, with bidimensionally measurable disease and with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or under were eligible. Pretreatment laboratory values had to indicate adequate bone marrow (white cells 4000/μl or higher, platelets 100 000/μl or higher), renal (creatinine 1.5 mg/dl or less, or creatinine clearance 75 ml/min or less) and hepatic function (bilirubin 1.5 mg/dl or less, aspartate aminotransferase twice normal or less). All patients gave informed consent.

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