progressively after the beginning of THY reaching normal values in 14–20 days (groups 1 and 2) or by 7 days (group 3). In group 3 patients, mean serum T_3 and T_4 rose to the upper limits of the normal range after 60 and 14 days, respectively.

Three clinically relevant issues stem from these results. Firstly, the time course necessary to obtain inhibited TSH serum levels in patients with DTC, treated with conservative doses of THY, is clearly inappropriate ranging from 30 to 90 days. Secondly, achievement of clinical and biochemical euthyroidism is not associated with adequate TSH suppression. Thirdly, alternative and/or additional pharmacological approaches should be tried since THY alone cannot be used in fully suppressive dosages in many patients.

1. Clark OH. TSH suppression in the management of thyroid nodules and thyroid cancer. *World J Surg* 1981, 5, 39–47.
2. Staunton MD, Greenings WP. Treatment of thyroid cancer in 293 patients. *Br J Surg* 1976, **63**, 253–258.
3. Mazzaferri EL, Young RL, Oertel JE, Kammerer WT, Page CP. Papillary thyroid carcinoma: the impact of therapy in 576 patients. *Medicine* 1977, **56**, 171–196.
4. Williams DW, Wynford-Thomas D, Williams ED. Control of human thyroid follicular cell proliferation in suspension and monolayer culture. *Mol Cell Endocrinol* 1987, **51**, 33–40.
5. Hoffman DP, Surks MI, Oppenheimer JH, Weitzman ED. Response to thyrotropin releasing hormone: an objective criterion for the adequacy of thyrotropin suppression therapy. *J Clin Endocrinol Metab* 1977, **44**, 892–901.
6. Lamberg BA, Rantanen M, Saarinen P, Liewendal K, Sivula A. Suppression of TSH response by THYR therapy in differentiated carcinoma patients. *Acta Endocrinol* 1979, **91**, 248–256.
7. Hufner M, Munzinger H, Papke H *et al.* Prinzipien der hormonsubstitution bei thyrektomierten shilddrusenkarzinom-patienten. *Radiologe* 1975, **15**, 245–250.
8. Bartalena L, Martino E, Pacchiarotti A, *et al.* Factors affecting suppression of endogenous thyrotropin secretion by THYR treatment: retrospective analysis in athyreotic and goitrous patients. *J Clin Endocrinol Metab* 1987, **64**, 849–855.
9. Edmonds CJ, Hayes S, Kermode JC, Thompson BD. Measurements of serum TSH and thyroid hormones in the management of treatment of thyroid carcinoma with radioiodine. *Br J Radiol* 1977, **50**, 799–807.
10. Busnardo B, Bui F, Girelli ME. Different rates of thyrotropin suppression after total-body scan in patients with thyroid cancer: effect of regular doses of THYR and triiodothyronine. *J Endocrinol Invest* 1983, **6**, 35–40.

Eur J Cancer, Vol. 29A, No. 14, pp. 2072–2073, 1993.
Printed in Great Britain
0959-8049/93 $6.00 + 0.00

Hyponatraemia Secondary to Administration of Ifosfamide

R. Izquierdo and M. Leinung

IFOSFAMIDE (IF) is a chemotherapeutic agent that is frequently used, in combination with the uro-protective agent mesna, to treat various malignancies. There have only been two previously reported cases of ifosamide-induced hyponatraemia [1, 2], and in the present report we describe another case, and report studies which suggest that the hyponatraemia was secondary to inappropriate antidiuretic hormone (ADH) secretion.

The patient was female, 69 years of age, with recurrent liposarcoma of the right neck. Admission medications are listed in Table 1. An infusion of 1.5 g of IF and 560 mg of mesna was administered in 1 l of 5% dextrose in water, daily for 5 days. On the first day, 50 mg of VP-16 was also administered.

On day 5 of the infusion, the patient was found to be confused and somnolent. The serum sodium level was reduced from 137 to 108 mmol/l, while urine osmolality was inappropriately high (Table 1). Other standard serum parameters were also measured but were unremarkable (data not shown). Following cessation of the infusion and subsequent administration of 3% sodium chloride, serum sodium normalised and the patient became fully alert during the next 2 days. Serum cortisol at 8 a.m. was 704 pmol/l (normal range 138–690), indicating that adrenal insufficiency was not the cause of the hyponatraemia. The patient was found to be hypothyroid, with a thyroid stimulating hormone (TSH) level of 29.1 mU/l (normal range 0.6–4.8) and a free T_4 of 5.14 pmol/l (normal range 9–25). Levothyroxine was

Table 1. Medications and serum and urine changes following IF infusion

	First admission		Second admission	
	Before IF	After IF	Before IF	After IF
Admission medications	CTZ 2 × 250 mg/day SLD 150 mg/day AAP 325 mg/OXD 5 mg every 6 h as needed	3% NaCl 65 ml/h LVT 75 mcg/day	HCT 25 mg/day SLD 2×150 mg/day AAP 325 mg/OXD 5 mg every 6 h as needed TAT 50 mg/day LVT 75 mcg/day	HCT 25 mg/day TAT 50 mg/day
Serum sodium (mmol/l; NR 135-145)	137	108	137	124
Serum osmolality (mmol/kg; NR 281-297)	NM	220	277	267
Urine osmolality (mmol/kg; NR 50-1200)	NM	222	419	409
ADH levels (ng/l; NR 1-13)	NM	NM	2.7	1.7

CTZ = chlorothiazide; SLD = sulindac; AAP = acetaminophen; OXD = oxycodone; NaCl = sodium chloride; LVT = levothyroxine; HCT = hydrochlorothiazide; TAT = triamterene; NM = not measured; NR = normal range.

Correspondence to M. Leinung.
The authors are at the Department of Medicine, Division of Endocrinology and Metabolism, Albany Medical College (A-44), 47 New Scotland Avenue, Albany, New York 12208, U.S.A.
Revised and accepted 5 July 1993.

administered at 75 mcg/day, which restored the level of free T_4. It is unlikely that the hypothyroidism caused the hyponatraemia, for although hypothyroidism impairs free water excretion, severe hyponatraemia is very infrequent even in patients who are severely hypothyroid [3].

A month later the patient received a second infusion of IF, and was monitored carefully for hyponatraemia. Prior to therapy, the patient appeared euvolemic on examination, blood pressure and heart rate were normal. Admission medications are listed in Table 1. An infusion of 2.7 g IF and 540 mg of mesna in 1 l of 5% dextrose in normal saline was administered, this time over 24 h. In addition, 50 mg of VP-16 intravenously (i.v.) over 1 h, three doses of 11 mg of ondansetron, and one i.v. dose of 20 mg of dexamethasone over 15 min were given to prevent nausea and vomiting.

The patient tolerated the chemotherapy well without nausea or vomiting. However, her serum sodium level decreased from 137 to 124 mmol/l, and concurrently the urine osmolality was inappropriately concentrated at 409 mmol/kg (Table 1). Similarly, the plasma ADH (measured in Nichols Institute Reference Laboratory, San Juan Capistrano, California) was inappropriately high at 1.7 ng/l, normal levels are less than 1.0 ng/l when the serum osmolality is lowered [4]. This suggests that the hyponatraemia was due, at least in part, to IF-stimulated ADH release.

Hypovolemic hyponatraemia secondary to the patient's diuretic use is unlikely as the patient had normal blood pressure, pulse and creatinine. In addition, the uric acid and blood urea nitrogen (BUN), which are usually elevated in hypovolemia were normal.

IF was given along with mesna and VP-16 on both occasions, so it is conceivable that either of these agents, rather than IF, induced the hyponatraemia. However, there has been no report of hyponatraemia developing following administration of mesna or VP-16 without IF. Further, cyclophosphamide which has a chemical structure almost identical to IF has been shown to cause hyponatraemia [5]. Therefore, we propose that it is highly likely that IF rather than mesna or VP-16 caused hyponatraemia in this patient.

It is important to realise that IF can cause severe hyponatremia in as little as 24 h. Patients treated with this agent should have their serum electrolytes monitored in order to prevent a catastrophic event.

1. Cantwell BMJ, Idle M, Millward MJ, Hall G, Lind MJ. Encephalopathy with hyponatraemia and inappropriate arginine vasopressin secretion following an intravenous ifosfamide infusion (letter). *Ann Oncol* 1990, **1**, 1232.
2. Culine S, Ghosn N, Droz J-P. Inappropriate antidiuretic hormone secretion induced by ifosfamide (letter). *Eur J Cancer* 1990, **26**, 922.
3. Skowsky WR, Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. *Am J Med* 1978, **64**, 613–621.
4. Personal Communications, Nichols Institute Reference Laboratory 1993.
5. DeFronzo RA, Braine H, Colvin OM, Davis PJ. Water intoxication in man after cyclophosphamide therapy. *Ann Intern Med* 1973, **78**, 861–869.

Acknowledgements—We acknowledge the assistance and the contribution of A. David Goodman and Reinhardt von Roemeling.