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Delayed Thyroid-Stimulating Hormone Suppression by L-Thyroxine in the Management of Differentiated Thyroid Carcinoma

Carlo L. Maini, Rosa Sciuto and Anna Tofani

THYROID STIMULATING hormone (TSH) SUPPRESSION BY L-thyroxine (THY) is a cornerstone in the management of patients with differentiated thyroid carcinoma (DTC) after thyroidectomy, as is radioiodine ablation to avoid any TSH stimulation of tumour growth [1–3]. Induction of hypothyroidism by the withdrawal of THY once or twice a year is necessary to perform diagnostic ^{131}I total body scanning (TBS) or radioiodine treatment. After the TBS and treatment, shortening of the exposure period to inappropriate elevated TSH serum levels is advisable. Prolonged exposure to TSH stimulation can greatly increase the chance of further mutation and allow tumour progression by clonal selection [4]. Accordingly, THY therapy is restarted 24 h after radioiodine administration and continued thereafter with the highest tolerated dosage. Mean recommended THY suppressive doses range from 150 to 300 μg/day [5–8]. Unfortunately, these dosages may be dangerous if administered from the beginning in highly hypothyroid patients because of cardiovascular side-effects. Administration of a low THY dose is often mandatory in elderly subjects or those with cardiac disease to avoid tachyarrhythmias or angina. This is a limiting factor in the approach to TSH suppressive treatment in patients with DTC. Most studies report on the adequacy of TSH suppression by THY therapy in terms of final TSH serum concentrations but provide limited information on the time-course necessary to obtain such results [9,10].

We have evaluated short-term TSH suppression in 30 patients with DTC after TBS and THY. Patients were divided into three groups in relation to THY dosage; they were selected according to age, body weight and clinical condition. 10 patients received 100 μg/day (group 1), 10 patients received 150 μg/day (group 2) and 10 received 200 μg/day (group 3). Serum TSH, T_3 and T_4 were measured on the day of TBS (day 0) and after 7, 14, 21, 30, 45, 60 and 90 days. Serum levels of T_3 and T_4 were assayed by specific radioimmunoassays (RIA) (Radim) and TSH by an ultrasensitive immunoradiometric assay (Byk-Mallinckrodt). A TSH level below 0.5 mU/l was taken as evidence of complete suppression. The results are reported as mean concentration values and S.E.M. in Fig. 1. Mean basal TSH serum levels do not differ significantly among the three groups, ranging from 117 to 100.3 mU/l. The pattern of TSH inhibition was, however, different. Complete TSH suppression was achieved after 3 months in group 1, between 45 and 60 days in group 2 and between 30 and 45 days in group 3. Serum T_4 and T_3 increased

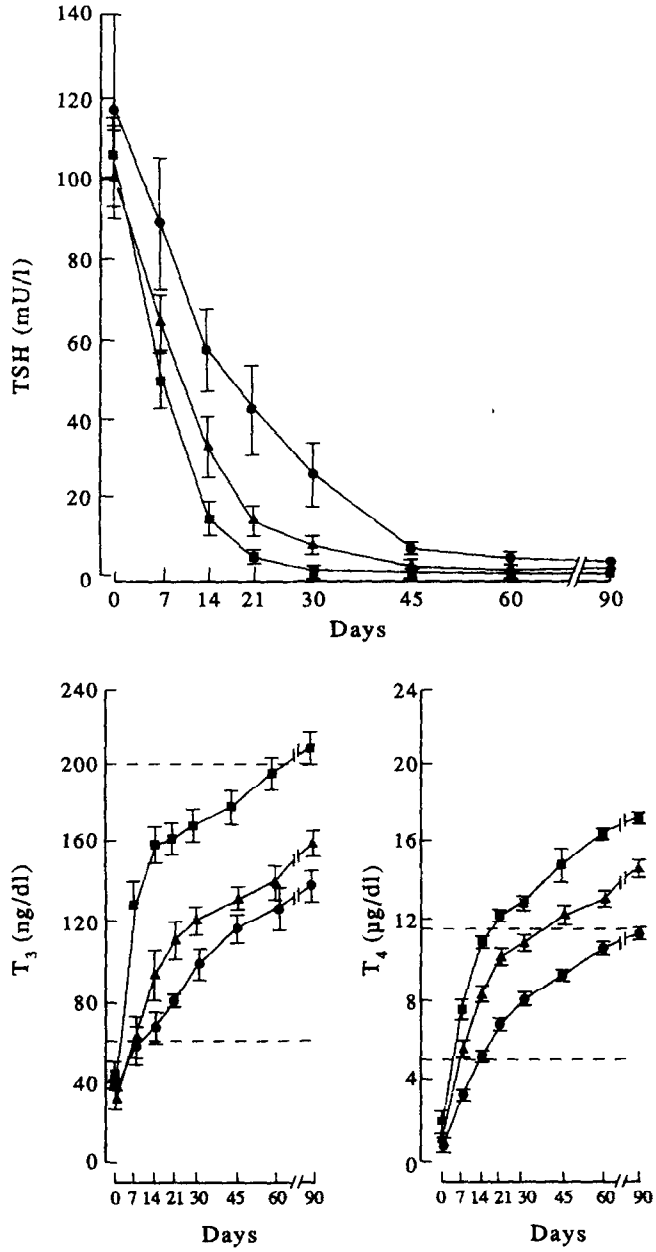

Fig. 1. Mean serum TSH (top panel) and T_3 and T_4 (bottom panel) levels and S.E.M. in three groups of patients with differentiated thyroid carcinoma after restarting of different doses of L-THY. Group 1 : 100 μg of L-THY (circles); group 2 : 150 μg of L-THY (triangles); group 3 : 200 μg of L-THY (squares). Normal range for T_3 and T_4 is shown by broken lines.

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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.

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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.

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