Case report

Long acting somatostatin treatment of paraneoplastic Cushing's syndrome in a case of Zollinger-Ellison syndrome

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SUMMARY Cushing's syndrome, caused by ectopic ACTH production during Zollinger-Ellison syndrome, raises difficult therapeutic problems. We report a case of clinical and biological efficacy of long acting somatostatin (SMS) in this condition. In a short term study with 200 µg SMS bid, symptoms of hypercorticism disappeared while cortisol and ACTH serum concentrations fell below the normal values. Longterm treatment was instituted with 50 µg SMS bid. Excellent clinical efficacy as well as normal cortisol and ACTH serum concentrations were maintained during the nine month follow up. Lipotropic hormone (LPH) serum concentration remained raised. No decrease in size of hepatic metastases was observed. Long acting somatostatin analogues may be useful in endocrine paraneoplastic syndromes.

Cushing's syndrome is not an exceptional feature in the course of Zollinger-Ellison syndrome (ZES).¹⁻³ Nevertheless, it raises difficult therapeutic problems, especially in sporadic gastrinomas, where it is associated with widespread metastatic diffusion and very poor prognosis.³

Long acting somatostatin analogue SMS 201-995 (mentioned as SMS in the text) has recently been used in various endocrine neoplasia, to control related hormonal hypersecretion(s) and its (their) clinical consequences.⁴⁻⁷ In the case of ZES, longterm treatment with SMS acts both on the target organ – that is, inhibits gastric acid overproduction – and on gastrin tumoral secretion.^{8,9}

We report here the longterm beneficial effects of this substance in the management of Cushing's syndrome occurring in the course of ZES.

Case report

In 1979, a 49 year old woman presented with relapsing peptic ulcer and diarrhoea. Zollinger-Ellison syndrome was diagnosed according to the usual criteria: basal acid output 57.6 mmol/h, basal serum gastrin concentration 1167 pg/ml (normal <100) increasing to 1700 pg/ml during the secretin infusion test.¹⁰ Plasma calcium level was 2.20 mmol/l, with normal urinary cyclic AMP excretion (0.59 µmol/mmol of creatinine, normal <0.60) and normal plasma parathormone level (64 pg/ml, normal <76). Plasma prolactin concentration (227 mU/l, 130 <normal<450) and computed tomography (CT) scan of pituitary fossa were normal. Thus, multiple endocrine neoplasia type I (MEN I) was excluded. Clinical and biological parameters of pituitary-adrenal axis function – that is, plasma cortisol and ACTH concentrations, urinary excretion of 17 hydroxy and ketosteroids, urinary free cortisol – were normal. The primary tumour was located by CT scan in the pancreatic corpus tail junction. Distal

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Table Pretreatment investigation of the pituitary-adrenal axis (normal values in brackets)

	Basal values	DXM 2 mg/day×2	DXM 8 mg/day×2
Plasma hormones (8 am values)			
Cortisol (ng/ml)	165 (60–120)	185 (<10)	125 (<10)
ACTH (pg/ml)	138 (<10–80)	142 (<10)	114 (<10)
LPH (pg/ml)	2650 (<20–200)	2210 (<20)	1750 (<20)
Urinary steroid excretion			
17-hydroxysteroids (mg/day)	13 (3.1–6.2)		
17-ketosteroids (mg/day)	15 (6–6.2)		
Free cortisol (pg/day)	836 (30–100)		

splenopancreatectomy and total gastrectomy were carried out. Four small hepatic metastases were also removed. Serum gastrin concentration decreased to 136 pg/ml in July 1980.

In August 1984, serum glucose concentrations rose to 10.0 mmol/l in the fasting state and to 18.0 mmol/l one hour after the meal. Serum glucagon concentrations were normal. This diabetes mellitus was attributed to pancreatic excision and treated with 32 units of insulin per day.

From February 1983 to February 1985, serum gastrin concentration rose from 1000 pg/ml to 5600 pg/ml. The patient did well during this period,

however, and ultrasonography did not show any abnormality. The patient was then referred to our care. Computed tomography scan disclosed two hepatic metastases of 40 mm in diameter each. Four courses of chemotherapy with Streptozotocin and 5 Fluorouracil were administered, according to Moertel's regimen,¹¹ without objective response.

In September 1985, weight gain, lassitude, facial fullness, and mild hypertension (170/100 mmHg) were found. There was no abnormal pigmentation. Diabetes mellitus worsened and hypokalaemic alkalosis was noted (serum potassium and bicarbonate concentrations were 2.7 and 32 mmol/l, respectively). Cushing's syndrome was diagnosed on the basis of raised plasma cortisol, ACTH and lipotropic hormone (LPH) concentrations (Table). Cortisol concentrations failed to decrease after a dexamethasone suppression test (2 mg/day for 48 hours, increasing to 8 mg/day for 48 hours) (Table). X-ray and CT scan of pituitary fossa were normal, as well as adrenal CT scan scintigraphy with iodomethyl-cholesterol.

In respect to the above considerations, SMS treatment was started.

Methods

The patient was studied at Hôpital Bichat (Paris) before treatment and at 1, 6, 10, 15, 22, 37 weeks after the beginning of the treatment. Clinical examination, abdominal ultrasonography and CT scan were performed. Plasma cortisol¹² and urinary free cortisol concentrations were determined by radio-

Fig. 1 Effect of a single injection of SMS (200 µg sc) on plasma cortisol (●—●) ACTH (◇—◇) and LPH (□—□) concentrations. Upper limit normal values are represented in dotted lines (cortisol ●—●, ACTH ◇—◇, LPH □—□).

Fig. 2 Long term effect of SMS (50 µg sc bid) on plasma cortisol (▨), ACTH (■) and LPH (□) concentrations. Upper limit normal values are represented in dotted lines (cortisol ●—●, ACTH ◇—◇, LPH □—□).

competition. Adrenocorticotrophic hormone and LPH concentrations were determined by specific radioimmunoassay.^{13,14} Serum gastrin concentrations were measured by radioimmunoassay using rabbit antigastrin antibody (G17) (CA-101, Clinical Assays).

Results

ACUTE RESULTS AND CHOICE OF DOSAGE FOR LONGTERM TREATMENT

Somatostatin was initially administered at 200 µg bid as previously used in ZES to control acid hypersecretion.¹⁵ In a pilot study, a single injection of SMS caused cortisol and ACTH serum concentrations to fall dramatically; they remained low 36 hours later (Fig. 1).

A three day treatment at the same dosage resulted in an evident clinical improvement with respect to the lassitude and facial fullness; blood pressure was 120/80 mmHg, without postural hypotension. Serum 8 am cortisol concentration dropped to 30 ng/ml —

that is, below the normal value (60–120 ng/ml). Serum ACTH and LPH decreased respectively to 37 pg/ml and 350 pg/ml. Return of the three hormone concentrations to their pretreatment values was observed 10 days after treatment was discontinued. These results were reproduced during a second test under the same conditions. Thus, on January 1986, longterm SMS treatment was started. A dosage of 50 µg sc was chosen, lower than usually prescribed, in order to avoid cortisol and ACTH values falling far below the normal ranges.

LONGTERM THERAPEUTIC RESULTS

The patient rapidly felt better and recovered normal activity. Facial fullness and erythema disappeared, blood pressure (130/80 mmHg) and plasma potassium (3.5 mmol/l) remained normal during the nine-month treatment. Plasma cortisol, ACTH and LPH concentrations iteratively determined by radioimmunoassay promptly decreased (Fig. 2) as did urinary free cortisol, from 2200 µg to less than 20 µg/24 hours. Simultaneously, serum gastrin concentrations fell

from 10850 to 309 pg/ml. Size and number of liver metastases estimated by ultrasonography and CT scan at one and three months remained stable, but slightly increased at nine months.

SIDE EFFECTS

Tolerance of SMS 201-995 was excellent. No local complications at the sites of injection were observed.

Diabetes mellitus improved with a fall of insulin requirement from 32 to 16 UI per day. Faecal fat excretion slightly increased from 7.8 to 15 g/day.

Other clinical parameters and routine chemical tests were normal.

Discussion

This case fits within the framework of an ectopic source of ACTH with hypercortisolism not suppressed by high doses of dexamethasone and high circulating levels of ACTH. The simultaneous measurement of lipotropic hormones (beta and gamma LPH) shows a proportionally higher circulating level than might be expected, given ACTH levels. This discrepancy, although not diagnostic, is often noticed in ectopic Cushing's syndrome.¹⁶

The dramatic decrease of plasma cortisol and ACTH induced by SMS on three different occasions allows us to rule out the hypothesis of spontaneous fluctuation of the tumoral secretion. The efficacy of SMS in this case is fully documented: the clinical symptoms of Cushing's syndrome disappeared a few days after onset of treatment; plasma cortisol and ACTH returned to strictly normal concentrations in less than four hours; a nine month treatment was able to maintain plasma ACTH and cortisol within the low normal range. During the same time, LPH plasma concentration remained abnormally high.

The effectiveness of short acting somatostatin on ACTH secretion has been shown in man in the cases of pituitary hypersecretion, either in pituitary tumours of Nelson's syndrome¹⁷ and Cushing's disease¹⁸ or in Addison's disease.¹⁹ *In vitro*, ACTH secretion is reduced by pharmacological doses of somatostatin added to the medium.²⁰ The use of the continuous line of mouse pituitary tumour cells (AtT20/D16) confirms this result.^{21,22}

An increase in number and size of hepatic metastases was noticed at nine months. Indeed, CT scan disclosed four lesions of 60, 40, 10, and 10 mm in diameter respectively. This is at variance with previously published cases where a regression of tumoral volume under SMS was observed.^{7,23,24} This is not invariably the case, however.²⁶ Among the various biological signs, only the recent LPH increase may suggest that in the near future higher SMS dosage may be necessary.

In conclusion, SMS appeared in this case to be a valuable and well tolerated drug for the management of paraneoplastic ACTH and LPH over-production in gastrinoma. Discrepancy between dramatic regression of clinical and biological symptoms and lack of tumour regression, suggests that SMS acts mainly at hormone processing level.

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