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ORIGINAL ARTICLE

ACTH responses to somatostatin, valproic acid and dexamethasone in Nelson's syndrome

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Abstract

OBJECTIVE: Pituitary tumours occuring in patients bilaterally adrenalectomized because of Cushing's disease (Nelson's syndrome) are frequently invasive and a complete their resection is not possible in most of them. Administration of the drugs decreasing ACTH secretion could be helpful in such unresectable tumours. We tried to evaluate the influence of somatostatin and valproic acid, compared to dexamethasone, in short-term studies, on plasma ACTH levels in Nelson's syndrome (NS).

MATERIAL AND METHODS: Basal ACTH levels were determined within 18 h after last dose of hydrocortisone and next, 1 and 2 hours following oral administration of 20 mg of hydrocortisone. Somatostatin was injected sc. in two patients with NS while sodium valproate and dexamethasone were administered orally for three days in three patients with NS (two with an invasive pituitary tumour and one with a localized, intrasellar adenoma). The blood for ACTH and cortisol determination was drawn before the tests (two hours after 20 mg of hydrocortisone ingestion) as well as 1 and 2 hours following somatostatin injection and after 3 days of valproic acid or dexamethasone administration.

RESULTS: High plasma ACTH levels were found before the tests. Somatostatin lowered ACTH levels in both patients, more effectively in the patient with non-invasive pituitary adenoma. Valproic acid decreased moderately ACTH concentration in two patients, while following dexamethasone administration a fall in ACTH levels was observed in all three patients, the most evident in the patient with a non-invasive Nelson's adenoma.

CONCLUSION: Somatostatin seemed to be more effective in its inhibitory action on ACTH secretion than valproic acid, thus its administration in invasive cases of NS could be tried as a supplementary method to neurosurgery. The response to dexamethasone administration indicates that a feed-back regulation, although impaired, exists in these cases.

Abbreviations and Units

NS	Nelson's syndrome
ACTH	Adrenocorticotropin hormone
IRMA	radioimmunometric method
ILMA	chemiluminometric method
ng/l	nanogram per liter
µg/dl	microgram per deciliter

Introduction

Pituitary tumours appearing in a significant number of the patients treated by bilateral adrenalectomy for Cushing's disease (Nelson's syndrome) [19] are frequently invasive and a supplementary, efficient method of treatment apart of neurosurgery is needed. The frequency of Nelson' tumours in the medical literature varies between 8% [18] and 38% [1]. In our material the incidence of Nelson's syndrome (NS) ranged from 28% in 1983 [6] to 44% in 2003 [12]. Bilateral adrenalectomy was accepted as an efficient method of treatment of Cushing's disease in the sixties and seventies. Later it was performed rarely because it was replaced by transsphenoidal adenomectomy. However, in the last few years, laparoscopic adrenalectomy became rather frequent method of treatment of Cushing's disease and one may expect development of NS more frequently again.

Neurosurgery is a treatment of choice in NS however invasive tumours are rarely resectable [14]. Pharmacotherapy has been tried in NS, however such reports were not frequent. Cyproheptadine was successfully administered in some patients with NS [3,4,16] but in some cases no improvement was attained [4]. Sodium valproate appeared to reduce the hypersecretion of ACTH during a 5–32 weeks therapy with remained suppression for 3–5 weeks on discontinuing treatment [2]. Our own experience with sodium valproate in NS was also positive [7], similarly as with magnesium valproate [8]. The best result was achieved in a man with NS and visual field deficiencies, following three neurosurgical interventions, in whom a fall in ACTH concentrations from more than 4000 ng/l to 68 ng/l was observed during 15 years of administration of sodium valproate; visual abnormalities remissed, too. The efficacy of a somatostatin analogue was found in a small group of patients [17].

The aim

According to the above described experience we chose sodium valproate and a somatostatin analogue to observe their ability to reduce ACTH level, and we compared it with the effect of dexamethasone, in a short-term study, in patients with Nelson's syndrome.

Material and methods

Three female patients with NS were studied, two (No. 1 and 2) with an invasive pituitary tumour and one (No. 3) with an intrasellar tumour, aged 43, 48 and 55 years, respectively.

The blood for ACTH and cortisol examinations was drawn at 9.00 am:

1) before, one hour and two hours after oral administration of 20 mg of hydrocortisone,
2) before, one hour and two hours after subcutaneous administration of 100 mcg of an analogue of somatostatin, Sandostatin (Novartis), two hours after ingestion of 20 mg of hydrocortisone (in two patients)
3) before, one hour and two hours after 20 mg of hydrocortisone administration, following three days of sodium valproate therapy, 400 mg three times daily,
4) before, one hour and two hours after 20 mg of hydrocortisone ingestion, following three days of dexamethasone administration, 1 mg three times daily.

Plasma ACTH concentration was determined by IRMA [5] (normal, 20–60 ng/l), while cortisol levels by LIA (Immulite 2000 – DPC) (normal, 5–25 µg/dl).

Informed consent for the above mentioned methods of treatment was obtained from all the patients.

Results

The basal plasma ACTH levels, before the tests, after the overnight interval in replacement therapy, were significantly elevated, especially in the patients with an invasive pituitary tumour. A substitutive dose, 20 mg of hydrocortisone, lowered ACTH concentration, within two hours, by more than 50% of the control values (Table 1).

Subcutaneous injection of Sandostatin resulted in a fall in ACTH levels, more evident in the patient with an intrasellar adenoma (Table 2).

Following three days treatment with sodium valproate a decrease in plasma ACTH concentrations after hydrocortisone administration (Table 3) was greater in the cases No. 1 and 3, as compared to the control levels (Table 1).

Dexamethasone pretreatment caused a fall in plasma ACTH levels after hydrocortisone administration in all the cases, however it was more prominent in the cases No. 2 and 3 (Table 4).

The cortisol levels before hydrocortisone administration ranged from 1.0 to 1.5 µg/dl. One hour following hydrocortisone ingestion cortisol levels varied between 26.1 and 42.0 µg/dl while after two hours they varied between 22.3 and 34.8 µg/dl.

Discussion

Nelson's syndrome is a specific form of Addison's disease thus all the measurements after a night interval in replacement therapy demonstrate significantly elevated plasma ACTH levels [15]. In our department a standard method of taking blood for ACTH determinations in NS, two hours after 20 mg of hydrocortisone ingestion, is routinely used [11]. In the patients with invasive Nelson's tumours significantly increased plasma ACTH levels have been usually found (6,13,15). A moderate increase in plasma ACTH has been consid-

Table 1. Plasma ACTH levels (ng/l) before and after hydrocortisone administration in Nelson's syndrome.

Time	Patient 1	Patient 2	Patient 3
0 min	40 000	110 000	20 600
60 min	38 000	82 000	12 200
120 min	17 300	50 000	1 500

Table 2. Plasma ACTH levels (ng/l) before and after subcutaneous octreotide administration in Nelson's syndrome.

Time	Patient 2	Patient 3
0 min	67 500	22 600
60 min	35 300	2 340
120 min	44 600	1 640

Table 3. Plasma ACTH levels (ng/l) before and after hydrocortisone administration, following sodium valproate pretreatment, in Nelson's syndrome.

Time	Patient 1	Patient 2	Patient 3
0 min	14 300	150 000	24 200
60 min	7 450	100 000	6 500
120 min	3 500	50 000	1 610

Table 4. Plasma ACTH levels (ng/l) before and after hydrocortisone administration, following dexamethasone pretreatment, in Nelson's syndrome.

Time	Patient 1	Patient 2	Patient 3
0 min	43 000	100 000	13 440
60 min	59 600	46 000	9 260
120 min	17 900	13 800	800

ered as an early sign of NS [10]. In our experience, in a full-blown NS cortisol does not inhibit ACTH secretion sufficiently, however such inhibition is possible during remission [9].

The observations of Dornhorst et al. [2] indicated that treatment with sodium valproate resulted in lightening of skin pigmentation and in a reduction in size of a pituitary microadenoma in some patients with NS, simultaneously with a decrease of plasma ACTH concentrations. The clinical trials with possible ACTH inhibitors intend to achieve a remission in the patients with Nelson's syndrome, who were not completely treated by neurosurgery. The most hopeful in our experiments appeared to be octreotide administration, similarly as in invasive pituitary tumours in acromegaly [20]. A long-term treatment with this analogue of somatostatin would be necessary to evaluate its action in NS. The results of our study and those of other authors [2] indicate that sodium valproate could be useful in responders. It seems to be rather safe in a prolonged therapy, as in our patient treated with this drug for 15 years. Dexamethasone administration made the pituitary more sensible to the hydrocortisone inhibitory effects. The daily dose of dexamethasone administered in our study for three days is too high for a quotidian use, but in some patients with Nelson's syndrome we have added 0.25 mg to 0.5 mg of this drug in the evening to the replacement therapy, to suppress ACTH hypersecretion in the night.

Neurosurgery is still the best way of NS treatment [13], however some supplementary methods of treatment are needed in the patients with non-completely resectable pituitary tumours.

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