Hypopituitaric patients with corticotropin insufficiency show marked impairment of the cortisol response to ACTH (1-24) independently of the duration of the disease


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ABSTRACT. It is widely accepted that the classical dose of 250.0 μg ACTH (1-24) (tetracosactin) is clearly supra-maximal while 1.0 and 0.03 μg have been shown as the maximal and the lowest stimulatory ACTH doses for cortisol (F) secretion in normal young subjects. Testing with low ACTH dose would better evaluate adrenal sensitivity to corticotropin. The aims of the present study were: a) to clarify the adrenal sensitivity to ACTH in patients with different duration of corticotroph insufficiency by testing with low and very low tetracosactin doses; and b) to evaluate diagnostic implication regarding the ability of ACTH tests to distinguish patients with corticotroph insufficiency from normal subjects. In 24 hypopituitaric patients (HYPOPIT, 15 male and 9 female, age 22-50 yr, BMI: 22-26 kg/m²) with corticotroph deficiency we studied the F, DHEA and aldosterone (A) responses to challenges with low ACTH doses (0.06 or 0.5 μg iv at 0 min) followed by 250 μg iv (at +60 min). The results in HYPOPIT were compared with those recorded in 12 normal controls (NS, 6 male and 6 female, age 22-34 yr, BMI: 20-25 kg/m²). Basal F and DHEA levels in HYPOPIT were lower than in NS, while A levels were similar in both groups. The F responses to ACTH in HYPOPIT were dose-independent and markedly lower (p<0.0001) than in NS. After the 0.06 and 0.5 μg ACTH dose, 16% of HYPOPIT patients showed ΔF peak within the range of normal response. No HYPOPIT showed ΔF peak within the normal range after 250 μg ACTH. The DHEA responses to ACTH in HYPOPIT were dose-independent and markedly lower than in NS (p<0.0001). Overlap between individual DHEA responses in HYPOPIT and NS was present after 0.06 μg and 0.5 μg but not after 250 μg tetracosactin. The A responses in HYPOPIT were dose-dependent and overlapped with those in NS. The adrenal responses to ACTH in HYPOPIT were not associated with the duration of the disease. In conclusion, the present study shows that the mean F and DHEA but not the A responses to ACTH (1-24) are markedly impaired in hypopituitaric patients with corticotroph insufficiency independently of the duration of the disease. The impaired F and DHEA response to ACTH is also independent of the dose, suggesting the existence of relatively enhanced sensitivity of the fasciculata and reticularis adrenal zone to ACTH but meantime remarkable impairment of the adrenal function due to corticotroph deficiency. In the present study, testing with submaximal ACTH doses did not distinguish patients with secondary adrenal insufficiency from normal subjects.


INTRODUCTION

The short ACTH test is widely used for the diagnosis of secondary adrenal insufficiency (1-4) but the optimal ACTH dose, which is to be administered, is still a matter for debate. It has been clearly shown that 250.0 μg ACTH (1-24) (tetracosactin) is a very supra-maximal dose (1-5). Recently, the maximal ACTH dose stimulating cortisol (F) secretion in normal subjects has been reported to be 1.0 μg by
some Authors (6-12) and 0.5 μg by others (6, 13, 14). Testing with 1.0 μg ACTH dose has been proposed to verify the function of the hypothalamo-pituitary-adrenal axis in patients with suspected secondary adrenal insufficiency, though controversial results have been obtained (1-5, 14, 17-19).

The 250.0 μg ACTH dose is very supramaximal also for the stimulation of aldosterone (A) and dehydroepiandrosterone (DHEA) (14-16). Interestingly, it had been reported that the sensitivity of A to ACTH is even greater than that of F, which, in turn, seemed similar to that of DHEA (14).

In a recent dose-range study, we showed that the maximal and the lowest stimulatory ACTH (1-24) doses of F secretion in normal subjects are 1.0 and 0.03 μg, respectively (12); in term of absolute F levels, however, an ACTH dose of 0.06 μg was needed to induce significant hormonal increase in all normal subjects (12). We also demonstrated that 1.0 μg is maximal dose for DHEA but not for A release and that DHEA seems even more sensitive than F to very low ACTH doses (12).

Independently of the diagnostic value, it is clear that testing with low ACTH dose could better evaluate adrenal sensitivity to corticotrophin (1-5); theoretically, patients with secondary adrenal insufficiency could be hypersensitive to ACTH in order to maintain some adrenal function as long as possible. It is also still unclear whether the impaired adrenal responsiveness to ACTH in the presence of corticotrophin insufficiency is dependent on the duration of the disease, i.e. if the impaired adrenal response to ACTH occurs early or after prolonged corticotrophin insufficiency.

Based on the foregoing, the aims of the present study were: a) to clarify the adrenal sensitivity to ACTH in patients with longstanding or new onset corticotrophin insufficiency by testing with low and very low tetracosactin doses; and b) to evaluate diagnostic implication regarding the ability of ACTH tests to distinguish patients with corticotrophin insufficiency from normal subjects. Therefore, in the present study we analyzed the F, A and DHEA responses to low (0.5 μg) and very low (0.06 μg) tetracosactin doses, followed by the classical supramaximal dose of 250 μg in hypopituitary patients with secondary adrenal insufficiency; the results were compared with those in a group of normal subjects.

SUBJECTS AND METHODS

Drugs

Vials containing 250.0 μg of ACTH (ACTH (1-24), tetracosactin, Synacthen) were purchased from Norvartis-Pharma (Huningue, France).

Study design

Twenty-four pan-hypopituitary patients (HYPOPIT, 15 male and 9 female, age 22-50 yr, BMI 22-26 kg/ m²) in optimal hormonal replacement therapy (thyroid, gonadal hormone and IGF-I levels in the median levels of the normal age-related ranges) and 12 healthy young volunteers (NS, 6 male and 6 female, age 22-34 yr, BMI: 20-25 kg/ m²) were studied.

In the patients a clear reduction in 24 h UFC levels (<30 μg/24 h, the cut-off of normal response for our lab) was assumed as definitive evidence of corticotrophin insufficiency and was always associated to low serum F levels in the morning; in these patients (no.=17) testing with ITT or metyrapone was contraindicated. On the other hand, ITT or metyrapone test was performed in hypopituitary patients with low-normal 24 h UFC (no.=7). Corticotrophin insufficiency was shown by F peak <180 μg/l after ITT or by 11-deoxycortisol peak <70 μg/l and ACTH peak <150 μg/ml after metyrapone (1).

Taking into account the duration of the disease, it was estimated lasting from less than 12 months in 3, 13-24 months in 4, 3-5 yr in 11 and more than 5 yr in 6 patients.

All subjects gave their informed consent to participate in the study, which had been approved by an independent Local Ethical Committee of the University of Turin.

All subjects underwent the following two testing sessions: a) ACTH 0.5 μg (at 0 min) +ACTH 250.0 μg (at 60 min); b) ACTH 0.06 μg (at 0 min) +ACTH 250.0 μg (at 60 min). ACTH dose preparations were performed as follows:

the standard ACTH dose was prepared by adding 250 μg to 250 ml of 0.9% NaCl, 0.5 μg ACTH dose was prepared by taking 0.5 ml (in a insulin syringe) and by adding 0.5 ml of saline, to obtain 1 ml to be injected. For 0.06 μg ACTH dose we added 9 ml of saline to 1 ml saline containing 1 μg ACTH; then, we took 0.6 volume of this mixture, and we added saline to obtain 1 ml of volume.

The resulting solutions were used immediately after preparation.

The tests were performed in the morning starting at 08:30 h - 09:00 h, after an overnight fasting. Tests were done in random order and at least 3 days apart. None of the subjects were on sodium restriction or potassium loading and received the same meal the night before testing. None had been taking any medication other than appropriate hormonal replacement including glucocorticoid replacement; the last administration of glucocorticoid replacement was in the day before the morning testing session.