Acta Derm Venereol (Stockh) 1990; 71: 214–218

Multihormonal Response to Dexamethasone

A Study in Atopic Dermatitis and Normal Controls

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Although minor disturbances of the circadian serum cortisol rhythm and diminished excretion of steroid metabolites have been reported in patients with atopic dermatitis, test assays regarding subtle neuroendocrine alterations have not been employed so far. We therefore studied the serum concentrations of cortisol, prolactin and adrenocorticotropin under baseline conditions, after 1 mg dexamethasone and after a defined methylprednisolone treatment in 15 patients with atopic dermatitis, in comparison with 10 healthy controls. The assessment of the hormones revealed no remarkable differences between either group at any of the blood sampling time points. However, in 3 patients and 2 control subjects, though exhibiting no concomitant disease, we could find no suppression of endogenous cortisol to below 5 µg/dl after oral intake of 1 mg dexamethasone. These cortisol non-suppressors showed lower dexamethasone serum concentrations in the morning after its administration, as compared with the suppressors. Acute (1 mg dexamethasone) or prolonged (40 mg methylprednisolone over 6 days) intake of glucocorticoids suppressed prolactin levels in both groups, demonstrating that the effect of glucocorticoids on the hormone system is not restricted to the hypothalamic-pituitary-adrenal axis. Our results indicate an intact feedback response of this hormonal axis to 1 mg dexamethasone and the ability of long-term as well as acute glucocorticoid administration to influence the prolactin secretion in patients with atopic dermatitis. ***Key words: Cortisol; Prolactin; ACTH; Feed-back regulation.***

(Accepted October 29, 1990.)

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Apart from various immunological and pharmacological disturbances hitherto described in atopic dermatitis (AD) (1–4) findings of blunted central thermoregulation to peripheral temperature stimuli (5) as well as neuroendocrinological studies revealing a minor disturbance of the circadian rhythm of cortisol and melatonin secretion point to an additional and probably subtle dysfunction of the hypothalamic system in AD (4,6), cortisol serum levels were found to be slightly lowered or normal under baseline conditions in AD (3,7,8). Abnormal skin reactions of patients with AD to both intracutaneous injection (histamine, acetylcholine) and epicutaneous application of vasodilating agents (nicotinic acid ester) supported the hypothesis of a disturbed β-receptor function in atopics (9), yet studies on β-receptor pharmacology yielded conflicting results (10,11). Dexamethasone has been shown to influence, apart from the hypothalamic-pituitary-adrenal (HPA) system, also serum levels of prolactin (12, 13, 14), thyroid hormones (12, 15, 16) and melatonin (17, 18).

A blunted suppression of prolactin by dexamethasone has been found in patients with endogenous depression (13, 14). As patients with AD are often prone to psychological imbalance (19) and as only a few studies have so far dealt with the neuroendocrine behaviour in AD, we studied the influence of 1 mg dexamethasone used as hormonal test assay on the plasma levels of adrenocorticotropin (ACTH), cortisol and prolactin in patients with AD and in healthy controls, in order to determine whether or not such an effect is different in either group.

MATERIAL AND METHODS

Subjects

Fifteen consecutive in-patients (3 men and 12 women), aged between 18 and 32 (mean ± SD: 23.8 ± 5.8) were studied after obtaining their informed consent. The diagnosis of AD was based on the criteria established by Hanifin & Rajka (20). Severity of cutaneous involvement, scored according to Costa et al. (21), revealed moderate to marked disease activity.

Additionally, 10 healthy volunteers (4 men and 6 women) between 19 and 28 years (mean ± SD: 29.3 ± 6.7) were examined as controls (with informed consent). All participants were withdrawn from any systemic therapy

Table I. *Cortisol mean ± SD values [μg/dl] in patients and controls.*

A = baseline levels, B = after oral administration of 1 mg dexamethasone, C = after oral methylprednisolone treatment (40 mg over 6 days)

	A		B		C
	7 a.m.	4 p.m.	7 a.m.	4 p.m.	4 p.m.
Patients	27.5±13.8	13.4±11.3	1.6±1.4	4.1±4.0	5.6±6.9
Controls	25.1± 8.6	14.6± 6.9	2.3±1.5	3.3±3.3	7.7±5.7

with corticoids or ACTH at least 2 months prior to the study. Medication, if any, with β-blocking and/or sleep-inducing drugs was stopped 3 or more days before entering the study. The only treatment of AD was with corticoid-free ointments at least one week before and during the study.

Dexamethasone suppression test

Venous blood samples were taken at 7 a.m. and 4 p.m. in EDTA-containing plastic tubes on day 1. At 11 p.m. of the same day 1 mg dexamethasone was given orally. Post-dexamethasone blood values were drawn on day 2 as described for day 1. After centrifugation the obtained plasma samples were immediately frozen at –80°C until measured. The criterion for cortisol non-suppression was defined as recommended in the psychiatric literature (22, 23) as failure to suppress post-dexamethasone cortisol levels to below 5 μg/dl. This procedure was followed by a consecutive oral methylprednisolone administration in both groups. Daily dosis at 7 a.m. from day 3 to day 6 was 8 mg methylprednisolone, and on days 7 and 8, 4 mg methylprednisolone. On day 8, blood was drawn at 4 p.m.

Cortisol assay

Cortisol was measured by an enzyme-linked immuno assay (Elias, Freiburg, FRG). The lower detection limit was 1 μg/dl, and the intra- and interassay coefficients of variation (CV) were 6%.

Prolactin assay

Prolactin was measured by an enzyme-linked immuno assay (Elias, Freiburg, FRG). The lower detection limit was 1 ng/ml, and the intra- and interassay CV were 5% and 9%, respectively.

ACTH assay

ACTH was measured by a newly developed IRMA supplied by the Nichols Institute (San Juan Capistrano, Calif.), which does not require extraction procedures (24). The lower detection limit was 7 pg/ml, and the intra- and interassay CV were 3% and 6.8%, respectively.

Dexamethasone assay

Dexamethasone was measured in unprocessed plasma using a direct RIA method with antibodies raised against the C-3-oxime of dexamethasone as described in detail elsewhere (25). The cross-reactivities of this antiserum against cortisol and corticosterone are 0.1% and 0.2%, respectively. The lower detection limit was 20 ng/dl. The intra- and interassay CV were 6.7% and 14.7%, respectively.

Statistical analysis

Data were analysed using the *t*-test for paired or group samples. All significance levels are two-tailed.

RESULTS

Mean cortisol levels did not differ between patients and controls at any of the four blood sampling time points (Table I). Dexamethasone administration resulted in both groups in a significant reduction of the post-dexamethasone cortisol levels ($p < 0.02$). However, 3 patients and 2 control subjects fulfilled the criterion for cortisol non-suppression. The post-dexamethasone cortisol values of these patients at 7 a.m. were 2.2, 5.3, 1 μg/dl and at 4 p.m. 12.0, 29.9, 7.2 μg/dl, and of these controls at 7 a.m. 2.2, 1.7 μg/dl and at 4 p.m. 11.7, 5.2 μg/dl. These non-suppressors had significantly lower dexamethasone plasma concentrations than suppressors in the morning after dexamethasone intake (mean 242.6 ± 54 vs. 414.3 ± 176 ng/dl, $p < 0.002$). On the other hand, none of the non-suppressors reached dexamethasone plasma levels less than 200 ng/dl at 7 a.m. after dexamethasone. The mean plasma concentrations of dexamethasone did not differ between the whole patient population (7 a.m.: 373.1 ± 204; 4 p.m.: 152.9 ± 54) and controls (7 a.m.: 386.2 ± 127; 4 p.m.: 142.8 ± 40.8) after dexamethasone. Methylprednisolone administration was followed by a significant fall of cortisol levels in both groups ($p < 0.04$) as compared with baseline values but showed no further decrease when compared with the 4 p.m. post-dexamethasone cortisol levels. Baseline and post-dexamethasone ACTH levels, as well as ACTH levels after methylprednisolone therapy, did not differ significantly between patients and controls (Table II).

Table II. *ACTH mean ± SD values [pg/ml] in patients and controls.*

A = baseline levels, B = after oral administration of 1 mg dexamethasone, C = after oral methylprednisolone treatment (40 mg over 6 days)

	A		B		C
	7 a.m.	4 p.m.	7 a.m.	4 p.m.	4 p.m.
Patients	59.0±27.8	15.8± 7.9	8.7±5.5	11.7±8.3	7.8±1.7
Controls	62.4±32.2	24.0±14.9	8.0±2.2	11.9±5.9	10.6±6.8

ACTH levels at 7 a.m. were significantly suppressed by dexamethasone in both groups ($p < 0.001$), whereas the comparison of the afternoon baseline and post-dexamethasone ACTH levels revealed a significant reduction in the control group only ($p < 0.05$). After methylprednisolone treatment a significant reduction in the ACTH values compared with the corresponding baseline levels was found in both groups ($p < 0.02$). However, in relation to the 4 p.m. post-dexamethasone levels, no further suppression of ACTH was observed.

Prolactin (PRL) levels exhibited no significant differences between patients and controls under the conditions studied (Table III). Dexamethasone administration resulted in the controls in a significant reduction of the afternoon post-dexamethasone PRL level when compared with the morning baseline values ($p < 0.05$). In patients there was also a significant reduction in both the morning and afternoon PRL levels vis-à-vis their baseline values ($p < 0.01$). Methylprednisolone administration resulted in both patients and controls in a significant decrease in the PRL levels when compared with the 4 p.m. baseline values ($p < 0.04$) and was able to further depress PRL levels in either group when compared with the afternoon post-dexamethasone levels ($p < 0.01$).

DISCUSSION

The normal cortisol levels in our patients with atopic dermatitis (AD) are consistent with a previous report (7) and earlier findings in our laboratory (8) but at variance with others (3). The low rate of cortisol non-suppressors in both patients and healthy controls may represent an unspecific finding as far as cortisol non-suppression has been observed, not only in endogenous depression but also, to a minor extent, in various diseases and even in healthy controls due to numerous interfering factors (26, 27). According to Berger & Klein (28) only dexamethasone concentrations above 200 ng/dl, which were reached in this study by all of the non-suppressors, can exclude low dexamethasone concentrations, e.g., due to an inhibited resorption simulating an abnormal cortisol suppression. Thus, an enhanced elimination rate of dexamethasone may entail insufficient cortisol suppression.

The suppressive effect of dexamethasone on plasma PRL levels is consistent with previous findings in healthy controls (13, 14). The decrease in PRL values following 1 mg dexamethasone and after methylprednisolone treatment indicates that both short-term and prolonged glucocorticoid administration not only affect the HPA system but also PRL secretion. Interestingly, application of 40 mg methylprednisolone over 6 days influenced the PRL

Table III. *Prolactin mean ± SD values [ng/ml] in patients and controls.*

A = baseline levels, B = after oral administration of 1 mg dexamethasone, C = after oral methylprednisolone treatment (40 mg over 6 days)

	A		B		C
	7 a.m.	4 p.m.	7 a.m.	4 p.m.	4 p.m.
Patients	10.5±4.9	7.0±4.5	6.0±3.0	6.7±3.3	4.9±1.9
Controls	9.9±4.6	5.6±2.0	7.4±3.3	7.0±3.2	4.4±1.8

secretion to a greater extent than a single dose of 1 mg dexamethasone, in contrast to the levels of cortisol and ACTH.

In conclusion, this study revealed normal baseline levels of cortisol, prolactin and ACTH and an adequate feed-back regulation of the HPA system to single or oral administration of glucocorticoids over 6 days in AD. However, our results do not exclude the possibility of minor disturbances of the circadian endogenous cortisol rhythm in AD, as indicated by earlier investigations (4). The test times chosen in the present study, however, were appropriate to answer a question of clinical importance, since glucocorticoids are still the mainstay of successful treatment of severe or recalcitrant AD.

ACKNOWLEDGEMENTS

We thank Miss Nistelweck and Mrs Schedo for their excellent technical assistance. The Johannes and Frieda Marohn Stiftung, University of Erlangen-Nürnberg, provided financial support for this study.

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