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ORIGINAL ARTICLE

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Adrenocorticotropic hormone response to hypoglycemic stress was preserved by a single bedtime 3-mg dose of prednisolone in patients with rheumatoid arthritis

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Abstract We have studied the effect of low-dose prednisolone administered before sleep on the hypothalamic–pituitary–adrenal axis and the symptoms of patients with rheumatoid arthritis (RA). Plasma adrenocorticotropic hormone (ACTH) and serum cortisol levels were measured in the basal state and after hypoglycemic stress induced by the insulin tolerance test in 21 patients receiving prednisolone at 3–5 mg daily. The patient's global assessment of their disease activity scores on a 100-mm visual analogue scale (VAS) and self-reporting of their functional status using the health assessment questionnaire (HAQ) were evaluated. While both the cortisol and the ACTH responses were impaired dose-dependently in patients treated with prednisolone, the ACTH response was maintained in patients treated with a single daily 3-mg dose of prednisolone before sleep. There was an inverse correlation between the extent of the ACTH response and disease activity as revealed by the VAS ($r = 0.521$, $P < 0.05$). There was also a weak correlation between VAS and the self-rating depression scale (SDS) ($r = 0.443$), especially when only patients with an HAQ score > 10 were included in order to exclude any possible contribution of the limitations in the activities of daily living to the SDS score ($r = 0.859$, $P < 0.05$). These results suggest that a single daily low dose (3 mg) of prednisolone administered before sleep maintains the ACTH response in RA patients, and patients with a good ACTH response appear to be less depressed and have milder symptoms.

Key words Adrenocorticotropic hormone (ACTH) response · Depression · Hypothalamic–pituitary–adrenal (HPA) axis · Low-dose prednisolone · Rheumatoid arthritis (RA)

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Introduction

There has been considerable conjecture about the contribution of psychosocial stress to the flare-up and disease progression of rheumatoid arthritis (RA).[1–3] Previous studies have shown that there is a significant correlation between depression and chronic pain in patients with RA, although the causal direction remains unclear.[4–7] It has also been shown that under depressed or stressful conditions, corticotropin-releasing hormone (CRH) was oversecreted from the hypothalamus, thus enhancing the hypothalamic–pituitary–adrenal (HPA) response.[8–10] The inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-1, and IL-6, the secretion of which is increased in RA, also stimulate CRH release.[11] CRH activates the HPA axis and ignites behavioral adaptation responses against environmental stressors, thus maintaining the basal and stress-related homeostasis of the host. It is therefore likely that a mutual interaction between the immune system and the central nervous system significantly modulates both the arthritis and the emotional abnormalities in RA.[11,12] Previous studies indicated that the HPA axis was impaired in RA,[13,14] thus significantly inhibiting the secretion of adrenocorticotropic hormone (ACTH) and cortisol in response to inflammatory stimuli.[15]

While chronic painful stress and arthritis, as well as prednisolone, significantly affect the HPA axis of patients,[16] we previously reported that low-dose prednisolone administered before sleep significantly suppressed the daybreak IL-6 production and relieved the morning stiffness of patients with RA.[17] We have extended that previous study to exam-

Table 1. Study design and patient profile

	Single bedtime dose			Divided dose
	3 mg/day	4 mg/day	5 mg/day	4 or 5 mg/day
No. of patients	5	4	6	6
CRP (mg/dl)	1.12 ± 1.74	2.08 ± 1.62	2.78 ± 2.22	1.20 ± 0.67
ESR (mm/h)	36.2 ± 27.5	63.3 ± 22.4	49.5 ± 26.1	57.5 ± 26.1
VAS (mm)	34.2 ± 39.6	33.8 ± 14.5	53.8 ± 25.4	48.0 ± 22.3
HAQ score	6.4 ± 7.8	13.8 ± 5.68	15.2 ± 6.97	13.4 ± 7.37

Values are expressed as mean ± SD
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; HAQ, health assessment questionnaire

ine the contribution of a bedtime dose of prednisolone to the HPA axis in patients with RA. The response of plasma ACTH and serum cortisol to hypoglycemic stress induced by the insulin tolerance test (ITT) was evaluated in patients receiving low-dose prednisolone. The results showed that a single daily dose of 3 mg prednisolone administered before sleep significantly improved the ACTH response of patients, and that patients with a good ACTH response appeared to be less depressed and more comfortable.

Patients and methods

Patients

Twenty-one outpatients with RA (18 women and 3 men; mean age 60 years (range 43–80 years) who fulfilled the diagnostic criteria of the American College of Rheumatology[18] were included in this study (Table 1). All 21 patients were treated with 3–5 mg prednisolone daily, and were divided into four groups: 5 patients received 3 mg prednisolone as a single dose at bedtime, 4 received 4 mg prednisolone at bedtime, and 6 received 5 mg prednisolone at bedtime. The other 6 patients received 2 or 2.5 mg prednisolone both in the morning and at bedtime (divided dose group). The mean duration of the prednisolone treatment was 13.8 ± 15 months for the 3-mg group, 20.8 ± 22.7 months for the 4-mg group, 29.7 ± 16.5 months for the 5-mg group, and 42.2 ± 18.1 months for the divided 5-mg group. The patients were also treated with disease-modifying antirheumatic drugs, including methotrexate ($n = 6$), bucillamine ($n = 12$), salazosulfapyridine ($n = 3$) and 4-acetylaminophenylacetic acid (actarit) ($n = 3$). The inflammatory activity in each patient was estimated by measuring their erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. The patients' global assessment of their disease activity scores on a 100-mm visual analogue scale (VAS)[19] and their self-reporting of their functional status using the health assessment questionnaire (HAQ)[20] were evaluated. There were no significant differences in the parameters of the patients' profiles between groups (Table 1). All the 21 outpatients included in this study at Kanebo Memorial Hospital gave informed written consent for participation, and the study protocol was approved by the Institutional Review Board of the hospital.

Insulin tolerance test

The ITT was performed at 13:00 h before lunch by injecting a regular insulin bolus of 0.1 u/kg i.v. Blood samples were collected to determine the cortisol, ACTH, and glucose levels before and 30, 60, and 120 min after the injection. Cortisol was measured using competitive radioimmunoassay and ACTH by noncompetitive sandwich immunoradiometric assay.

Assessment of the depressive state of patients

The self-rating depression scale (SDS) was used to assess the depressive state of the 21 patients with RA. The SDS is a self-administered written questionnaire designed to assess the depressive state of patients, and contains 20 items that evaluate their emotional, physiological, and psychiatric symptoms.[21] The patients are instructed to answer all 20 items on the scale with a response of "seldom," "sometimes," "often," or "always," and the total score ranges between 20 and 80 points. A higher score means a greater tendency toward depression. The score ranges between 23 and 47 (average 35) in healthy controls, between 39 and 59 (average 49) in patients with neurosis, and between 53 and 67 (average 60) in patients with depression.[22]

Statistical analysis

The unpaired Student's *t*-test was used to compare differences between groups. The basal levels were the average of values obtained at 0 min, and the peak levels were the highest values achieved during the test period. The delta-ACTH and cortisol levels were expressed as the levels calculated by the peak value minus the basal value. In the patients treated with a single dose of prednisolone ($n = 15$), the correlation between delta-ACTH and clinical presentation was assessed using Pearson's correlation coefficient test. Values were expressed as mean ± SD, and P values < 0.05 were considered to be significant.

Results

Basal levels of ACTH and cortisol

The basal cortisol levels in patients with RA treated with a divided dose (4 or 5 mg daily) of prednisolone were significantly lower than those of patients receiving a single bedtime dose (3 mg): 3.0 ± 1.1 μg/dl vs. 5.6 ± 1.2 μg/dl ($P < 0.01$) (Table 2). While the basal ACTH levels decreased insignificantly in patients treated with a divided dose of prednisolone, the ACTH/cortisol ratio decreased significantly in those patients compared with the ratio in those treated with a single bedtime dose of 5 mg prednisolone: 2.0 ± 0.4 vs. 4.1 ± 1.5 ($P < 0.05$), suggesting that basal ACTH release was significantly suppressed by treatment with the divided dose of prednisolone.

Table 2. Response to the insulin tolerance test

	3 mg/day	4 mg/day	5 mg/day	4 or 5 mg/day
ACTH (pg/ml)				
Basal	34.6 ± 29.7	12.0 ± 7.26	11.8 ± 6.10	6.4 ± 2.9
Peak	309.2 ± 239.9	109.8 ± 90.28	96.3 ± 80.2	30.0 ± 15.6
Delta	274.6 ± 210.3*	96.8 ± 83.0	84.5 ± 83.0	23.5 ± 13.3*
Cortisol (μg/dl)				
Basal	5.6 ± 1.2**	4.2 ± 1.0	3.3 ± 2.1	3.0 ± 1.1**
Peak	14.7 ± 2.07	10.2 ± 3.07	7.8 ± 3.1	6.8 ± 3.8
Delta	9.1 ± 2.2***	6.0 ± 2.8	4.5 ± 2.3***	3.9 ± 2.7***
ACTH/Cortisol				
Basal	5.6 ± 3.8	3.0 ± 2.0	4.1 ± 1.5*	2.0 ± 0.4*
Peak	21.4 ± 18.0	12.7 ± 14.4	13.3 ± 8.61	4.4 ± 1.3
Delta	34.8 ± 36.1	23.0 ± 30.0	18.0 ± 11.2	7.8 ± 3.0

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.01$

Response to insulin tolerance test

The cortisol response to the ITT was inhibited in patients treated with prednisolone in a dose-dependent manner (Fig. 1). However, the serum cortisol level increased from 5.6 ± 1.2 μg/dl to 14.7 ± 2.1 μg/dl in patients who received a single 3-mg bedtime dose of prednisolone. The delta-cortisol value decreased significantly in patients treated with a single 5-mg bedtime dose or a divided dose of prednisolone as compared with those treated with a single 3-mg bedtime dose: 4.5 ± 2.3 μg/dl, 3.9 ± 2.7 μg/dl vs. 9.1 ± 2.2 μg/dl ($P < 0.01$) (Table 2). Furthermore, the ACTH response against ITT was more pronounced in patients treated with a single 3-mg bedtime dose as compared with those treated with a single 4-mg or 5-mg bedtime dose of prednisolone (Fig. 1). Instead, the ACTH response was markedly inhibited in patients treated with a divided dose of prednisolone as compared with those treated with a single bedtime dose of 3 mg prednisolone: 23.5 ± 13.3 pg/ml vs. 274.6 ± 210.3 pg/ml ($P < 0.05$) (Table 2).

Relationship between ACTH response and clinical presentation

There was an inverse correlation between the ACTH response and VAS ($r = 0.521$, $P < 0.05$), although the correlation between the ACTH response and CRP ($r = 0.296$) or HAQ ($r = 0.420$) scores was not significant (Fig. 2a–c). The VAS score showed a positive correlation with the HAQ score ($r = 0.578$, $P < 0.05$) (Fig. 2d). The VAS also showed a very weak correlation with the SDS score ($r = 0.443$) (Fig. 2e). However, when patients with a HAQ score < 10 were excluded to eliminate the possible contribution of the limitation in the activities of daily living to the SDS, the VAS score showed a significant positive correlation with the SDS ($r = 0.859$, $P < 0.05$) (Fig. 2f). The delta-ACTH value also showed a weak inverse correlation with SDS ($r = 0.554$) (data not shown).

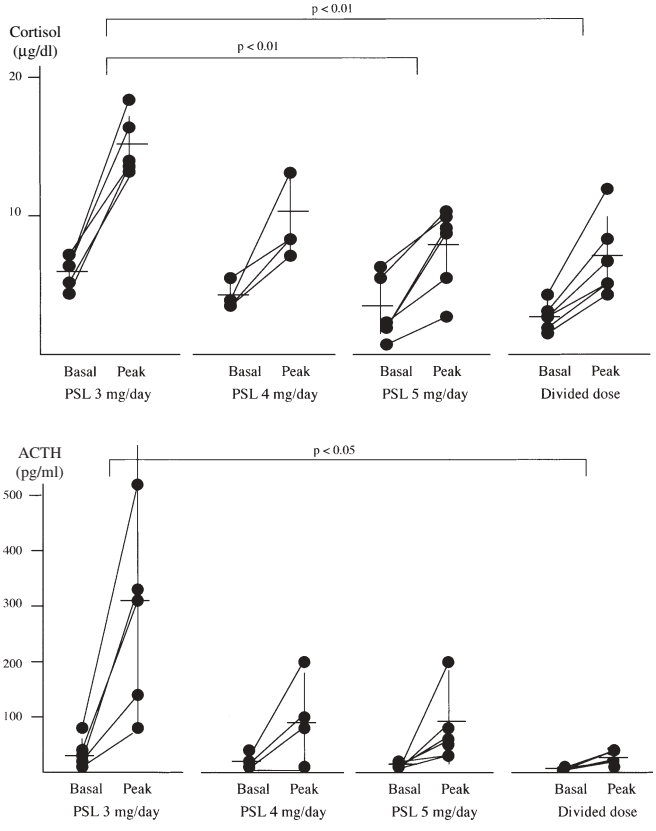

Fig. 1. Cortisol and adrenocorticotropic hormone (*ACTH*) response to the insulin tolerance test. Each *point* represents different individuals. *Basal*, the basal levels were the average of values obtained at 0 min. *Peak*, the peak levels were the highest values achieved during the test period. *PSL*, prednisolone. The mean ± SD is indicated. Delta values were compared between groups, and statistical analyses were performed using the unpaired Student's *t*-test

Discussion

While previous studies indicated that the ACTH response against ITT is impaired in 85% of rheumatoid patients who do not receive corticosteroids,[23] patients who did not receive prednisolone were not included in this study. We

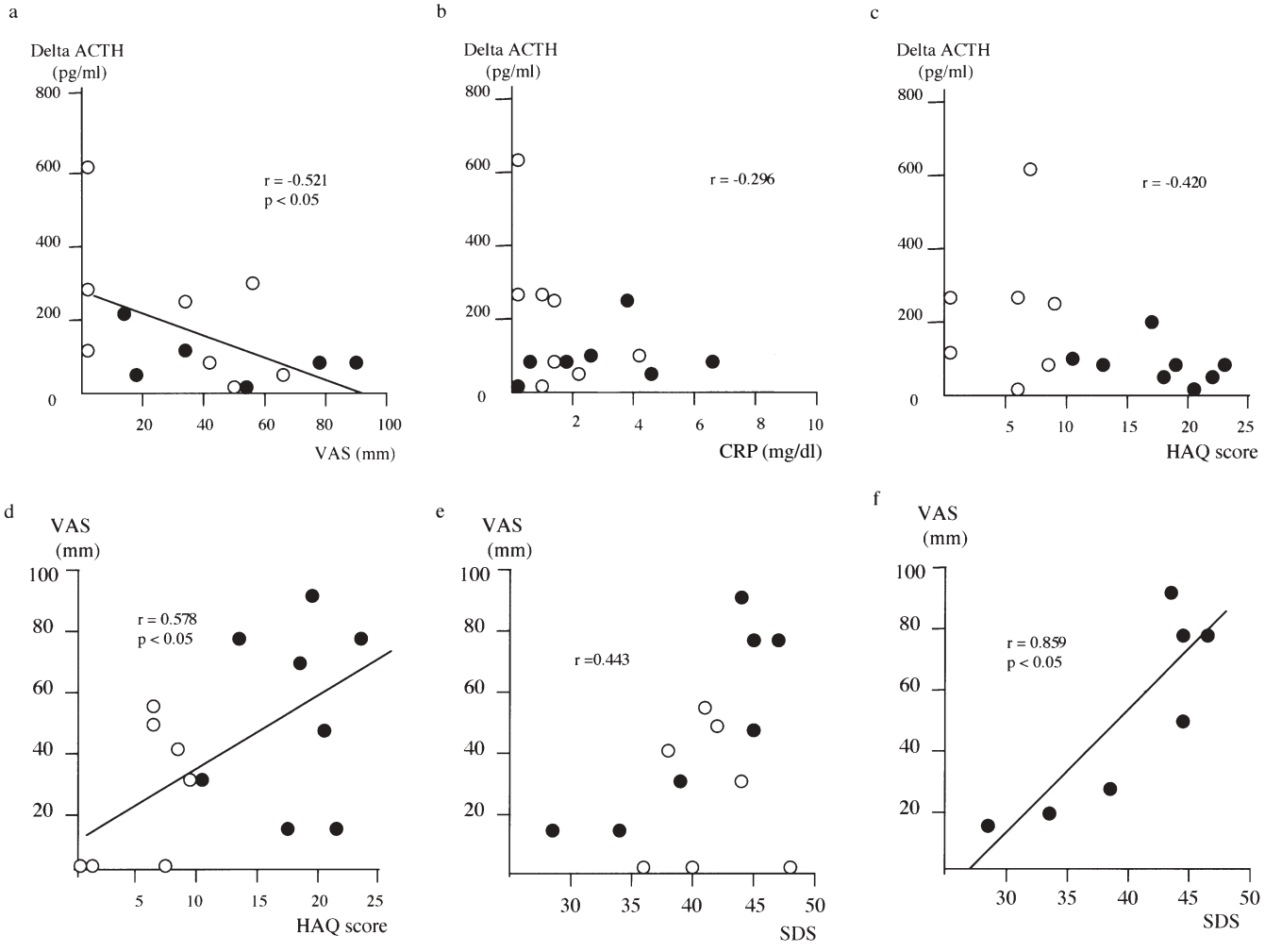

Fig. 2. Relation between ACTH response and VAS, CRP, HAQ, and SDS. *VAS*, visual analogue scale; *CRP*, C-reactive protein; *HAQ*, health assessment questionnaire; *SDS*, self-rating depression scale. Delta ACTH shows the difference between peak ACTH and basal ACTH. Each point represents a different individual. *Open circles*, patients with HAQ scores < 10; *closed circles*, patients with HAQ scores > 10. Statistical analysis was performed using the unpaired Student's *t*-test

therefore cannot assess whether the ACTH response of patients treated with 3 mg prednisolone daily before sleep was overstimulated or not. However, we may conclude that a single bedtime dose of 3 mg prednisolone significantly improved the patients' ACTH response against hypoglycemic stress. A good ACTH response appeared to be inversely correlated with the patients' VAS scores, and the VAS score was positively correlated with the SDS of patients with high HAQ scores. Since the VAS faithfully reflects the patient's global disease activity and is sensitive to changes in the disease outcome, it is likely that the augmented ACTH response may improve the patients' adaptation responses against stressors and make their symptoms feel less troublesome. As to the reason why patients with an augmented ACTH response had lower VAS scores, we simply speculate that the β-endorphin released simultaneously with ACTH, and which is an important molecule that exerts an adaptation response against stressors by increasing the appetite and the pain threshold,[24] might have relieved the patients' emotional stress. ACTH is derived from proopiomelanocortin, a common precursor of β-endorphin and other related peptides, and thus ACTH and β-endorphin are released simultaneously from the pituitary gland upon CRH stimulation.[25]

There have been several reports on the effectiveness of low-dose prednisolone in RA. However, most previous studies used daily doses of 5–10 mg.[26,27] Although one previous study showed that ACTH-stimulated cortisol secretion was unimpaired in patients treated with 10 mg prednisolone daily,[28] we found that ITT-induced cortisol secretion was significantly suppressed in our patients treated with 5 mg prednisolone daily. It thus appears that prednisolone at doses higher than 5 mg inhibit the responses of the HPA axis against stressors, especially when given in a divided dose. While increased cortisol does suppress the HPA axis, endogenous corticosteroids also regulate the basal HPA activity, including the ACTH response.[29–31] A homeostatic circadian rhythm also exists. Since the diurnal rhythm of serum cortisol levels is markedly disturbed and reduced in patients with RA,[32] it is likely that a single dose of

3 mg prednisolone affected the fine tuning of endogenous corticoisteroid regulation.

Taking these findings together, while we need further studies to evaluate the long-term effects and any unexpected adverse effects of prednisolone, including osteoporosis, we speculate that 3 mg prednisolone daily, taken before sleep, could be beneficial to patients with RA not only in terms of clinical well-being, but also for adaptation against stressors.

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