

Antidepressant Treatment and Dehydroepiandrosterone Sulfate: Different Effects of Amitriptyline and Paroxetine

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Key Words

Depression · Dehydroepiandrosterone sulfate
Hypothalamus-pituitary-adrenal system · Tricyclic
antidepressant · Selective serotonin reuptake inhibitors

Abstract

Background: There is evidence for activation of the hypothalamus-pituitary-adrenal system in depressed patients to be associated with increased secretion of adrenal androgens. However, there is only limited information about the effect of different classes of antidepressants on the course of adrenal androgens. **Methods:** Dehydroepiandrosterone sulfate (DHEA-S) serum concentrations were measured in 80 patients being treated with amitriptyline (AMI) or paroxetine (PAROX) for a period of 35 days. **Results:** Using analysis of variance with repeated measures, we found a significant effect of treatment upon DHEA-S serum concentrations that declined more in AMI-treated (before vs. after: 1.89 ± 1.16 vs. 1.46 ± 0.96 mg/l), compared to PAROX-treated patients (1.56 ± 1.09 vs. 1.50 ± 1.04 mg/l). **Conclusions:** Our results show changes in DHEA-S serum concentrations during antidepressant treatment to depend on medication.

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Introduction

In addition to hypercortisolemia [1], there is evidence for a dysregulation of the hypothalamus-pituitary-adrenal (HPA) system at the level of adrenal androgens in affective disorders. Epidemiological studies found plasma concentrations of dehydroepiandrosterone (DHEA) and its sulfated form (DHEA-S) to be negatively associated with depressive symptoms [2]. In contrast, most – albeit not all [3, 4] – clinical studies have reported increased plasma and urine concentrations of DHEA and DHEA-S in depressed patients [5–8].

Treatment with the tricyclic antidepressant (TCA) clomipramine has been shown to decrease DHEA in 11 responders to treatment [7], but not in nonresponders to TCAs [8]. Similarly, Fabian et al. [9] found DHEA-S to decline during a 12-week period of treatment with nortriptyline or paroxetine (PAROX) in 44 responders, but not in 16 nonresponders to treatment. The finding of Romeo et al. [10] of unchanged DHEA in 8 patients being treated with fluoxetine indicates a possible different effect of TCAs and selective serotonin reuptake inhibitors (SSRIs) upon adrenal androgen concentrations. Different findings in these studies with regard to changes of DHEA-S in the course of treatment with SSRIs may be due to differences in study designs and small sample sizes.

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Table 1. Description of the study population

	Open treatment		Placebo-controlled double-blind treatment	
	PAROX	AMI	PAROX	AMI
Subjects, n	21	22	24	13
Gender, f/m	14/7	18/4	16/8	9/4
Age, years	56.7 ± 15.0	50.1 ± 15.8	58.3 ± 15.5	49.8 ± 18.2
HAMD day 1	23.5 ± 3.3	24.4 ± 5.3	23.4 ± 3.9	21.6 ± 3.3
Age, </≥ 60 years	13/8	18/4	15/9	8/5
HAMD day 35	10.4 ± 6.3	9.0 ± 5.1	11.8 ± 9.2	10.8 ± 6.3
Responders/nonresponders	13/8	18/4	15/9	8/5

Therefore, we expected to clarify these controversies by using a larger sample. Increased DHEA-S predicted non-response to electroconvulsive therapy [11] and sleep deprivation [12].

In accordance with another group, we have recently reported TCAs, but not SSRIs, to lead to declining saliva cortisol concentrations in responders to treatment [13, 14].

Since glucocorticoids and adrenal androgens may contribute to the pathophysiology of depression in different ways, the ratio of these steroids and the change of this ratio may be relevant during the course of antidepressant treatment.

In order to test the hypothesis that amitriptyline (AMI) and PAROX also exert differential effects with regard to adrenal androgens, we studied DHEA-S serum concentrations and the saliva cortisol/DHEA-S ratio in this group of depressed patients.

Subjects and Methods

Study Design

We studied patients with a major depressive episode according to DSM-IV during antidepressive treatment (35 days) with AMI (150 mg/day) or PAROX (40 mg/day).

Patient Population

Inclusion criteria were (1) nonpsychotic major depression according to DSM-IV, and (2) a minimal score of 18 on the 21-item Hamilton Depression Scale (HAMD). Exclusion criteria were (1) a history of substance dependency, bipolar I disorder or schizophrenia, and (2) neurological or relevant medical diseases.

The original sample consisted of 126 patients with a diagnosis of a major depressive episode. Excluding responders during washout (n = 18), drop-outs (n = 14) and patients with incomplete sampling of saliva (n = 4), we have recently reported on the effect of antidepressants upon cortisol in saliva in a matched subset of 80 patients (study completers: n = 90). In an overlapping group of 80 depressed inpa-

tients [age, 21–87 years (54.3 ± 16.1); gender, 57 females, 23 males; body mass index, 18.1–45.7 kg/m² (26.5 ± 5.4); HAMD, 18–36 (23.4 ± 4.1)], complete sets of samples allowed measurement of DHEA-S before and after treatment. The data of 1 patient were excluded due to extreme outlier of DHEA-S concentrations. Twenty-one patients had not been treated with antidepressants or antipsychotics within the last 2 months (8 AMI/13 PAROX). Most patients received pretreatment with TCAs (10/15), SSRIs (4/4), TCAs and SSRIs (5/1), monoamine oxidase inhibitors (MAO-Is 1/1), TCA and MAO-I (1 AMI), mirtazapine (2 PAROX), hypericum (2/1), antipsychotic medication (AP: 4/5), TCA and AP (1 PAROX) and lithium (3 PAROX). None of the patients had received fluoxetine within the last 2 months.

Ethical Consideration

This study was approved by the local ethics committee and all subjects had given informed written consent.

Treatment Schedule

Patients received a standardized treatment with a fixed dose of AMI 150 mg or PAROX 40 mg. Thirty-seven patients (24 PAROX/13 AMI) were treated under randomized double-blind conditions with placebo-controlled washout and 43 were treated under open conditions using the same medication regime (21 PAROX/22 AMI). The first part of the study was done under open conditions. The same treatment regime was used under double-blind randomized conditions during the second part of the study (table 1).

Lorazepam and zolpidem were allowed as comedication. Compared to PAROX-treated patients, AMI-treated patients needed less lorazepam (16.3 ± 21.7 vs. 26.3 ± 21.5 mg, p < 0.04) and zolpidem (12.5 ± 18.6 vs. 22.7 ± 21.2 tablets, p < 0.03).

After a period of at least 6 days without psychotropic medication (except: lorazepam, zolpidem), and after 35 days of treatment, blood was drawn for analysis of DHEA-S at 08.30 h. During the drug-free run-in period (week -1) as well as during the 5-week period of active treatment, saliva was sampled each day at 8.00, 16.00 and 22.00 h.

Laboratory Tests

Blood samples were immediately centrifuged and stored at -20°C for DHEA-S measurements using an immunoassay from Roche Diagnostics, Mannheim, Germany. Interassay variation was below 4%. Cortisol in saliva was measured as described earlier [13].

Table 2. Concentration of DHEA-S and saliva cortisol (8.00 h)/DHEA-S ratio before and after treatment in AMI- and PAROX-treated patients, divided according to responders and nonresponders

Medication	Response	DHEA-S pretreatment, mg/l	DHEA-S posttreatment, mg/l ²	Saliva cortisol (8.00 h)/DHEA-S ratio	
				pretreatment ($\times 1,000$)	posttreatment ($\times 1,000$) ³
AMI	response (n = 26)	1.83 \pm 1.19	1.42 \pm 0.96 ¹	9.6 \pm 8.4	7.1 \pm 4.9 ¹
AMI	nonresponse (n = 9)	2.05 \pm 1.11	1.57 \pm 1.03	8.0 \pm 8.1	11.7 \pm 11.3
PAROX	response (n = 28)	1.61 \pm 1.14	1.44 \pm 1.02 ¹	10.0 \pm 8.4	10.6 \pm 9.1
PAROX	nonresponse (n = 17)	1.56 \pm 1.02	1.60 \pm 1.10	8.9 \pm 6.7	9.0 \pm 8.5

¹ Paired t test: $p < 0.05$.

² Effect of repeated measures: $F_{1,76} = 20.7$, $p < 0.0001$; interaction effect: repeated measures \times medication: $F_{1,76} = 11.9$, $p < 0.001$.

³ Interaction effect: repeated measures \times response: $F_{1,76} = 3.2$, $p < 0.08$; interaction effect: repeated measures \times medication \times response: $F_{1,76} = 3.6$, $p < 0.07$.

Statistics

Response to treatment was defined as a reduction of HAMD scores by at least 50% on day 35.

We used log-transformed DHEA-S serum concentrations in order to achieve normally distributed values for parametric analyses. Only study completers with complete sets of data were used for analysis of variance with repeated measures (ANOVA-rm) using 'medication' (AMI vs. PAROX) and 'response' as independent variables and logDHEA-S serum concentrations before and after treatment as repeated measures. The independent variables 'gender', 'generation' (<60 years vs. ≥ 60 years) or 'study design' (blind-random vs. open) were additionally introduced in order to assess their additional effects. The mean concentrations of cortisol in saliva of weeks -1 to 5 were used to assess the effect of antidepressant treatment upon cortisol secretion. Also, we used the saliva cortisol (8.00 h)/DHEA-S ratio as a dependent variable. The relationship between the changes of saliva cortisol and DHEA-S was assessed by correlational analyses. Student's t tests were performed for univariate analyses.

Results

Both treatment groups did not differ with regard to severity of depression (AMI vs. PAROX: 23.4 ± 4.8 vs. 23.4 ± 3.6) or gender (27 female/8 male vs. 30 female/15 male), but AMI-treated patients were younger than PAROX-treated subjects (50.0 ± 16.4 vs. 57.6 ± 15.1 years, $p < 0.04$). Severity of depression after treatment (AMI vs. PAROX: 9.6 ± 6.7 vs. 11.1 ± 7.9) and the proportion of responders (74 vs. 62%) were similar.

Effect of Treatment and Medication on the Course of DHEA-S

ANOVA-rm revealed an effect of treatment upon logDHEA-S serum concentrations ($F_{1,78} = 29.3$, $p < 0.0001$). Additionally, we noted a 'medication' \times 're-

peated measures' interaction ($F_{1,78} = 10.7$, $p < 0.002$) with more pronounced declining logDHEA-S concentrations in AMI- compared to PAROX-treated patients. Most AMI- (33/35), but not PAROX-treated patients (25/45) showed declining DHEA-S concentrations (table 2).

Effect of Response on the Course of DHEA-S

Adding the factor 'response' to the model did not change the aforementioned results and there were no effects of 'response' or 'response' interaction upon logDHEA-S (F values < 1.4). In responders to AMI ($p < 0.0001$) and PAROX ($p < 0.02$), but not in nonresponders, paired Student t tests showed declining DHEA-S levels. The 24% decline of DHEA-S in the small group of AMI nonresponders failed to reach statistical significance. Adding the factor 'study design' to this model did not affect the aforementioned results and did not reveal any effect of 'study design' upon the course of DHEA-S (table 2).

Effect of Age and Gender on the Course of DHEA-S

DHEA-S serum concentrations were negatively associated with age ($r = -0.62$, $p < 0.0001$). Adding 'age' to the model revealed an effect on logDHEA-S concentrations (<60 years vs. ≥ 60 years: $F_{1,72} = 24.0$, $p < 0.0001$), but had no influence on the aforementioned effects. Treatment with AMI was found to reduce DHEA-S serum concentrations in young and elderly patients (table 2). Adding 'gender' to the model did not change the effect of treatment.

Effect of Treatment upon Saliva Cortisol Concentrations

These data have been presented earlier [13]. Shortly, ANOVA-rm revealed a significant effect of 'treatment' (8.00 h: $F_{1,76} = 6.3$; 16 h: $F_{1,76} = 13.3$; 22.00 h: $F_{1,76} = 4.2$; all $p < 0.05$) and 'treatment' \times 'medication' \times 'response' interaction (8.00 h: $F_{1,76} = 5.9$, $p < 0.02$). Saliva cortisol declined in responders to AMI [8.00 h: 27.5 ± 11.9 (week -1), 17.2 ± 7.5 (week 5); 16.00 h: 9.0 ± 3.5 (week -1), 6.2 ± 2.9 (week 5); 22.00 h: 5.3 ± 2.8 (week -1), 3.9 ± 2.4 (week 5)], but not so in responders to PAROX [8.00 h: 25.3 ± 9.6 (week -1), 25.1 ± 10.8 (week 5); 16.00 h: 8.9 ± 4.2 (week -1), 7.1 ± 3.6 (week 5); 22.00 h: 5.8 ± 3.2 (week -1), 4.3 ± 2.0 (week 5)].

Relation between Changes of Saliva Cortisol and DHEA-S

The relative changes of DHEA-S serum and cortisol saliva concentrations were not related in the total group ($r = 0.05$) or in subgroups [AMI responders: $r = 0.13$; AMI nonresponders: $r = -0.61$ ($n = 9$); PAROX responders: $r = -0.15$; PAROX nonresponders: $r = 0.00$; all $p > 0.08$].

Effect of Treatment on Saliva Cortisol/Serum DHEA-S Ratio

ANOVA-rm revealed 'repeated measures \times response' and 'repeated measures \times medication \times response' interaction effects of borderline significance ($F_{1,76} = 3.2$, $p < 0.08$; $F_{1,76} = 3.6$, $p < 0.07$) upon the saliva cortisol (8.00 h)/serum DHEA-S ratio. The cortisol/DHEA-S ratio declined in AMI responders, but not in SSRI-treated patients.

Discussion

Our data confirm previously reported evidence that antidepressant treatment lowers DHEA-S serum concentrations [7–9]. Additionally, our findings suggest a differential effect of AMI and PAROX upon the concentration of DHEA-S.

Although logDHEA-S declined in responders to AMI and PAROX, ANOVA-rm found this effect to be significantly stronger in the AMI compared to the PAROX subgroup. These findings may explain conflicting findings with regard to DHEA and DHEA-S concentrations in depressed patients, with some studies describing lowered [3] and others increased adrenal androgen concentrations [5–8]. The majority of patients in the aforementioned study were treated with TCAs or MAO-Is. In accordance

with our findings, this may explain a decline of DHEA-S or DHEA in these patients. In a study of 11 patients with 9 being treated with TCAs, Romeo et al. [10] did not find a decline in DHEA-S serum concentrations. This difference could be due to the shorter washout period, the inhomogeneity of TCAs with three different drugs being used or the different observation period of 55 days.

The pattern of a concurrent increase in DHEA-S and cortisol in depressed patients [6] and their common reduction in the course of AMI and, to some extent, PAROX treatment [13] suggests glucocorticoid and DHEA secretion to underlay a common regulatory pathway. Since adrenal androgens are regulated by ACTH [15], DHEA-S concentrations in depressed patients can be considered to also be, at least partially, dependent on ACTH. AMI (TCA [16]), PAROX (SSRI [17]) and other antidepressants like tianeptine [17] have been shown to reduce HPA system activity as measured by the DEX/CRH test. In contrast to the DEX/CRH test that is considered to be a test of glucocorticoid receptor function, the effect of antidepressants upon saliva cortisol (AMI > PAROX) is similar to the effect upon DHEA-S (AMI > PAROX).

Although more pronounced in AMI-treated responders, PAROX-treated responders showed declining DHEA-S concentrations. This result is in accordance with findings in elderly depressed patients reporting a decrease in DHEA-S serum concentrations in both responders to TCAs and SSRIs during a 12-week trial [9].

Lowering glucocorticoid concentrations [18] and enhancing the activity of adrenal androgens may contribute to improvement of depression [19, 20]. Although, saliva cortisol may be less adequate than serum cortisol to assess the glucocorticoid/adrenal androgen ratio, our findings indicate a difference between the AMI- and PAROX-treated groups. Therefore, the beneficial glucocorticoid-lowering effect of AMI on psychopathology goes hand in hand with the disadvantage of declining DHEA-S, so that the cortisol/DHEA ratio, considered to be of prognostic value [21], may not be improved. Hence, adjunctive DHEA treatment may be most appropriate in nonresponders to TCAs and SSRI-treated patients due to their lowered DHEA-S in the presence of unchanged cortisol levels.

There are some limitations of this study. Acute treatment with benzodiazepines may increase DHEA, although not DHEA-S concentrations [22]. Therefore, we cannot exclude that the different amount of benzodiazepines contributed to our findings. Since adding the factor study design to the ANOVA models did not change our

results, we can exclude that inclusion of nonrandomized patients explains our findings. However, the limited power of the analyses did not allow to fully control for a bias due to uneven distribution of age and gender. DHEA, but not DHEA-S, shows relevant fluctuations. Therefore, we measured morning DHEA-S in order to avoid variation due to circadian and ultracircadian variations of the serum level of adrenal androgens.

In summary, our results show DHEA-S serum concentrations to decline stronger in TCA-, compared to SSRI-treated depressed patients. Although, due to the restricted

power, subgroup analyses await replication, this major finding not only has implications for the regulation of the HPA system in depressed patients but may also be relevant for augmentation strategies.

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