Dexamethasone suppression test in first-episode schizophrenia

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Abstract

OBJECTIVES: Higher rates of dexamethasone test (DST) nonsuppression in schizophrenia have been attributed to depressive symptoms, suicidality and negative symptoms. No study concerning first-episode schizophrenia has yet been published.

DESIGN: In patients hospitalised for the first time with first-episode schizophrenia the DST has been performed before, at the end of the acute treatment and after one year. At the same time the clinical evaluation with PANSS was performed. A cortisol value >5 microgram/dl in either of the postdexamethasone samples indicated nonsuppression of cortisol.

RESULTS: A total of 56 males were included. 18% of pts were DST nonsuppressors at medication-free baseline, 5% and 16% after acute treatment and after one year respectively. After 1 year 42/56 of patients fulfilled the criteria of remission. The rate of nonsupression was 21.4%, 5% and 16.4% in remitters and 7%, 7% and 14.3% in nonremitters. Significant differences in the whole group were found between postdexamethasone cortisolemia at discharge on the one hand and on admission and at the one-year follow-up on the other. Significant correlations were observed between postdexamethasone cortisolemia and negative symptoms at the end of acute treatment.

MAIN FINDINGS: In first-episode schizophrenia the short-term treatment led to a decrease in cortisolemia and rates of nonsupression and an increase at a one-year follow-up.

CONCLUSIONS: Rates of DST nonsuppression in schizophrenia including first-episode schizophrenia are influenced by the stage of illness and medication status. The impairment of feedback regulation of cortisol secretion may be related to different biopathogenetic mechanisms depending on the phase of the illness.

ORIGINAL ARTICLE

INTRODUCTION

There has been evidence that, as far as mood disorders are concerned, schizophrenic disorders appear to be present as a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Dexamethasone test (DST) non-suppression, due to the lack of glucocorticoid secretion feedback mechanisms, occurs frequently also in schizophrenia, with percentages varying between 11 and 55% [4]. A higher rate of DST nonsuppression has been associated with depressive symptoms [18, 9], suicidality [15] and negative symptoms of schizophrenia [22, 23, 9]. It has also been suggested that DST nonsuppression in schizophrenia may prognosticate a better outcome [8]. Available data suggest that phase of illness and medication status influence rates of DST nonsuppression [24] and may partially account for some discrepant findings in the literature. No study of first-episode schizophrenia has yet been published. The aim of this study was to assess cortisolemia and DST in first-episode schizophrenia and identify their clinical correlates.

MATERIAL AND METHODS

Subjects

Males, consecutively hospitalised for the first time with first-episode schizophrenia at the Department of Psychiatry in Brno, who underwent DST on admission (before treatment), at discharge and after one year and who provided written informed consent, were included. ICD-10 diagnoses were made on the basis of a comprehensive assessment of symptoms and history, and all other available patient information. The diagnosis was confirmed by consensus of two psychiatrists in two separate interviews.

Clinical assessment

The psychic state of the patients was evaluated using the Positive and Negative Syndrome Scale (PANSS) [16], at the same time points (baseline – on admission; end of the acute treatment – at discharge; at follow-up after one year). The patients were divided into remitters and nonremitters when they were reassessed after one year. A score of 3 (mild) or less was required on all eight of the following PANSS items: P1 delusions, P2 conceptual disorganisation, P3 hallucinatory behaviour, G5 mannerisms and posturing, G9 unusual thought content, N1 blunted affect, N4 passive/apathetic social withdrawal, N6 lack of spontaneity and flow of conversation for a minimum of 6 months [5]. Individual items concerning depression (G2 anxiety, G4 tension, G6 depression) from a general subscale of PANSS and negative and positive subscales were chosen as potential clinical correlates of postdexamethasone cortisol levels.

During the index hospitalization all patients were treated openly by monotherapy with an antipsychotic chosen by the patient's clinician and individually dosed. Most patients were drug-naive.

DST

A 1-mg DST [6] was performed on admission, at discharge from the index hospitalization and after one year. The patients took 1 mg of dexamethasone orally at 11.00 p.m. and provided blood samples at 4.00 p.m. the same day and at 4.00 p.m. the next day. Cortisol levels (S-cortisol) were determined by chemiluminiscent immunoanalysis (Bayer, Centaur). A cortisol value greater then 5 microgram/dl in either of the postdexamethasone samples indicated nonsuppression of cortisol. Plasma dexamethasone levels were not measured in this study.

Table 1: Mean values of psychopathology

	G2 anxiety	G4 tension	G6 depression	G2+G4+G6	Positive PANSS	Negative PANSS	General PANSS	Total PANSS
Baseline:	2.9 (1.5)	2.5 (1.5)	2.5 (1.4)	7.9 (3.5)	22.9 (6.1)	27.0 (9.7)	47.6 (12.9)	97.5 (25.0)
End:	1.4 (0.7)*	1.6 (0.8)*	1.6 (1.0)*	4.6 (1.9)*	10.2 (3.4)*	17.4 (6.0)*	29.5 (7.4)*	57.2 (15.0)*
Follow-up	1.3 (0.7)*	1.5 (0.8)*	1.6 (1.0)*	4.5 (2.1)*	9.8 (5.0)*	15.5 (7.9)*	27.0(11.0)*	52.3 (22.4)*

* significant difference compared with baseline values ($p<0.01$)

Table 2: DST in first-episode schizophrenia

		Total sample (n=56)		Remitters (n=42)		Nonremitters (n=14)	
Baseline:	suppression	46	82.1%	33	78.6%	13	93%
	Nonsuppression	10	17.9%	9	21.4%	1	7%
End:	suppression	53	94.7%	40	95%	13	93%
	Nonsuppression	3	5.3%	2	5%	1	7%
Follow-up:	suppression	47	84%	35	83.3%	12	85.7%
	Nonsuppression	9	16%	7	16.7%	2	14.3%

Table 3: Pre- and postdexamethasone cortisolemia in patients with first-episode schizophrenia (median, minimum-maximum)

Cortisolemia		Total sample (n=56)		Remitters (n=42)		Nonremitters (n=14)	
Baseline:	cort. 1	9.74	(0.36–24.76)	8.07	(0.36–24.76)	11.06	(5.80–17.87)
	cort. 2	2.91	(0.26–16.68)	1.63	(0.26–16.68)	1.63	(0.36–8.87)
End:	cort. 1	7.19	(1.81–19.21)	5.84	(1.81–19.21)	7.23	(3.66–17.12)
	cort. 2	1.05	(0.04–9.71)	0.40	(0.04–6.56)	0.64	(0.24–9.70)
Follow-up:	cort. 1	11.47	(2.29–24.29)	10.63	(2.96–23.09)	10.70	(2.29–24.29)
	cort. 2	2.54	(0.00–21.74)	0.70	(0.00–21.74)	0.74	(0.20–13.18)

Cort. 1 …predexamethasone cortisolemia (4 p.m.)
Cort.2 … postdexamethasone cortisolemia (4 p.m.)

Table 4: Correlation between cortisolemia (microgram/dl) and PANSS (Spearman's correlations)

Cortisolemia		G2 anxiety	G4 tension	G6 depression	G2+G4+G6	Positive PANSS	Negative PANSS	General PANSS	Total PANSS
Baseline:	cort. 1	0.267*	0.234	0.059	0.217	0.062	0.010	0.087	0.071
	cort. 2	0.036	–0.028	0.200	0.061	–0.015	0.031	0.149	0.100
End:	cort.1	0.063	0.023	–0.110	0.025	0.142	0.140	0.089	0.154
	cort.1	0.150	–0.002	–0.091	0.019	0.175	0.265*	0.151	0.201
Follow-up:	cort.1	–0.167	–0.183	0.064	–0.122	0.033	0.140	0.092	0.089
	cort.2	0.010	–0.043	0.035	0.011	–0.002	0.125	0.084	0.079

* significant correlation ($p<0.05$)

RESULTS

Study sample

A DST was performed on 56 patients at all three time points. The average age was 23 (SD 5.7) years. The mean duration of the hospitalisation, which was based on the clinician's judgement about the severity of the symptoms, was 44.5 (15.3) days. The average duration of the illness was 0.77 years (SD=1.04). The patients were treated mostly with second generation antipsychotics, risperidone being the drug of first choice. Scores for the total PANSS and all PANSS subscales decreased significantly at discharge across the whole patient group (see Table 1). There was no additional significant reduction of psychopathology after one year. After one year 75% (42/56) of the patients fulfilled the remission criteria.

DST

1. DST nonsuppression

17.9% (10/ 56) of the patients were DST nonsuppressors at medication-free baseline. After acute treatment 5.3% (3/56) of these patients remained DST nonsuppressors and 16% (9/56) after one year.

In the 42 remitters the rate of nonsuppression was 21.4% (9/42), 5% (2/42) and 16.7% (7/42) before and at the end of acute treatment and after one year respectively; the same values were 7.1% (1/14), 7.1% (1/14) and 14.3% (2/14) in the 14 nonremitters (see Table 2).

It was not possible to calculate the differences between remitters and nonremitters in DST nonsuppression due to the small number of patients. We could only observe a trend towards a higher baseline rate in nonsuppression remitters. Only one patient remained a nonsuppressor from the baseline through discharge until the reassessment after 1 year, but he was a remitter.

2. Cortisolemia

Significant differences in the whole group were found between mean postdexamethasone cortisolemia at discharge on the one hand and on admission and at the one-year follow-up on the other (see Figure 1).

There was no significant difference between remitters and nonremitters in pre- and postdexamethasone cortisolemia at any time point (see Table 3).

3. Correlations

Significant correlations were found between cortisolemia and anxiety at the beginning of the acute treatment and between postdexamethasone cortisolemia and negative symptoms at discharge (at the end of acute treatment) – see Table 4.

DISCUSSION

DST non-suppression, due to the lack of glucocorticoid secretion feedback mechanisms, occurs frequently also in schizophrenia, with percentages varying between 11 and 55%, according to the review by Altamura [4]. The most recent publication [10] reported an even higher variability in the rate of DST non-suppression in schizophrenia from 0% to 70%, with a mean rate of approximately 20%. The range appears to reflect the type of patients, the presence of symptoms and the stage of illness.

To our knowledge this study is the first to focus on hypothalamic-pituitary-adrenal (HPA) axis abnormalities in first-episode schizophrenia. In our patients experiencing their first hospitalization for first-episode schizophrenia the DST nonsuppression rate was 17.9% before treatment, 5.3% at the end of acute treatment

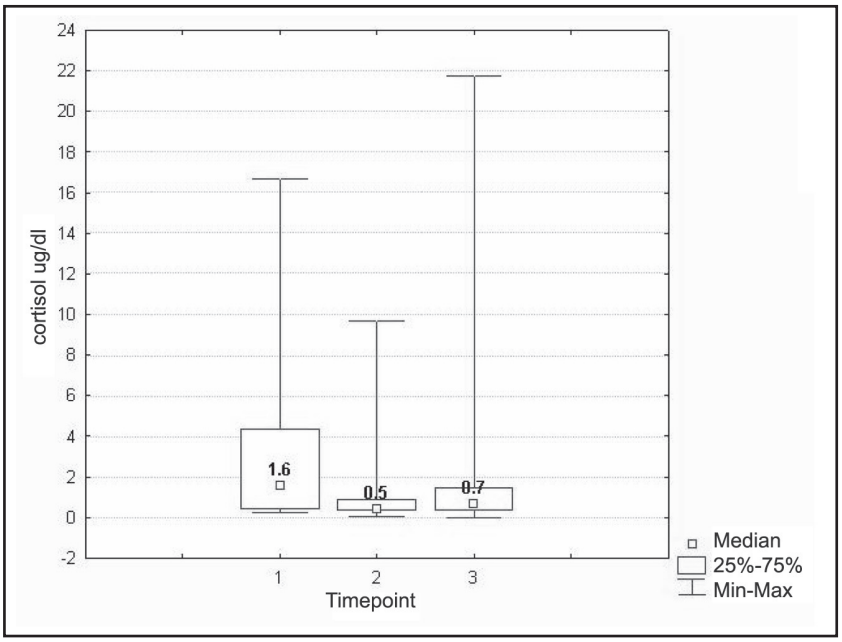

Fig. 1: Change of postdexamethasone cortisolemia over time (Friedman ANOVA)

and 16% at one-year follow-up. These data are in agreement with literature. Rates of DST nonsuppression are higher in drug-free schizophrenic patients in the acute phase of the illness. A meta-analysis of studies concerning DST in schizophrenia reported a DST nonsuppression rate of 36% in the drug-free state and 20% in the medicated state [24]. The reduction in rates of DST nonsuppression that we observed after 6 weeks of antipsychotic treatment is also consistent with the findings of other studies in which the DST was performed before and after neuroleptic treatment [17]. The increase in the rate of DST nonsuppression and postdexamethasone cortisolemia at 1-year follow-up can partially be explained by the clinical deterioration of some patients and non-compliance. There are usually subjects who go off medication at some point and resume it following other interventions or the return of symptoms. This limits our ability to detect the effect of medication on the outcome of treatment accurately.

All these data suggest that phase of illness and medication status influence rates of DST nonsuppression in schizophrenia including patients with first-episode schizophrenia. Our data add to the evidence that patients who are drug-free or in the acute phase of the illness have a desinhibited HPA axis, but patients who are clinically stable and receiving treatment tend to have a normal HPA axis [13, 24, 14].

Persistent nonsuppression was associated with poor outcome [3, 19]. In our sample only one patient was a nonsuppressor at all three points and was classified as a remitter after one year. Baseline postdexamethasone cortisol levels did not correlate with the outcome at 4 weeks and 1 year [24]. But we have to take into consideration that our sample included only young men in the early phase of the illness, in which case the further development may vary to a great extent.

Some researchers believed concurrent depression in schizophrenia to be the major determinant of DST non-suppression in schizophrenia[1]. Other authors pointed out that there is an association of DST non-suppression with negative symptoms in schizophrenia [9, 2]. Several authors investigated the association between cortisolemia and psychopathology [11, 19, 24]. We found a significant correlation between anxiety and predexamethasone cortisolemia before the beginning of the treatment, which may be a reflection of stress associated with experiencing psychotic symptoms for the first time. The acute phase of the schizophrenic illness is the period most likely to be associated with a stress-related elevation of glucocorticoids [10, 12]. Apart from that, a significant correlation between negative symptoms (negative PANSS subscale score) and postdexamethasone cortisolemia was observed after 6 weeks of antipsychotic treatment. A significant correlation between negative symptoms and post-DST cortisol levels was reported by Newcomer et al. [19], too. Moreover, the same study found that cognitive impairment on several measures was also correlated with post-DST cortisol concentration. Tandon et al. [24] reported that in 58 schizophrenics tested at drug-free baseline, postdexamethasone plasma cortisol levels were significantly correlated with negative symptoms but they found no correlation after 4 weeks of neuroleptic treatment; postdexamethasone plasma cortisol was not related to global severity, positive, or depressive symptoms at either time point or to VBR [24]. Faustman [11] found that negative and positive symptoms significantly correlated with post-dexamethasone cortisol in unmedicated schizophrenics.

The partially discrepant findings may be due to the early phase of the disease and the generally good acute treatment responsivity in patients suffering from first-episode schizophrenia [7, 21]. Resistance to treatment,

regional functional and structural change in the brain (hippocampus) and more pronounced impairment of feedback regulation of cortisol secretion leading to hypercortisolism may develop after the first manifestation of psychotic symptoms in some patients. Targeting these latter processes may open new therapeutic opportunities [20].

Short-term treatment of first-episode schizophrenia led to a decrease in cortisolemia and rates of nonsuppression and an increase at a one-year follow-up. Post-dexamethasone cortisolemia correlated significantly only with negative symptoms at the end of acute treatment. Rates of DST nonsuppression in schizophrenia including patients with first-episode schizophrenia are influenced by stage of illness, type of patient and medication status. The impairment of feedback regulation of cortisol secretion may be related to different biopathogenetic mechanisms depending on the phase of the illness.

Statistics

The statistical analysis was based on descriptive statistics and nonparametric methods (the Mann-Whitney U test and Friedman ANOVA, Spearman's correlation). The statistical analysis was performed using STATISTICA software, version 6 (StatSoft, Inc. 2001).

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