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The Dexamethasone Suppression Test and Thyroid Stimulating Hormone Response to TRH in RDC Schizoaffective Patients

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Summary. The dexamethasone suppression test (DST) brought to light significantly more non-suppression of cortisol secretion in RDC schizoaffectives of the depressed (89%) and of the manic type (67%) than in RDC schizophrenia (25%). However, only in the RDC endogenous depressives, whose pathological DST rate was 57%, was the thyroid stimulating hormone (TSH) response to thyrotrophin releasing hormone (TRH) found to be significantly "blunted". It is suggested that the DST results can be interpreted as partially validating DSM-III's wide major affective disorder since this concept also encompasses all cases with mood-incongruent psychotic features. Furthermore, it is hypothesized that the coupling of DST non-suppression and TSH "blunting" may be important for defining a valid depressive subgroup within these extended clinical boundaries for affective illness.

Key words: RDC schizoaffective disorder – Dexamethasone suppression test – Thyrotrophin releasing hormone test – DSM-III

Introduction

It would appear that the dexamethasone suppression test (DST) is not as specific for endogenous depression as originally claimed [3], since pathological results have also been demonstrated in various other forms of psychiatric illness. To cite just a few of several recent reports, non-suppression has been found in 45% of ICD manics [6], in 20% of ICD schizophrenics and even in a considerable number of patients with neurotic states, senile dementia and alcoholism [4]. However, as Coppen et al. [4] have recorded the greatest proportion of non-suppression in high-score Newcastle probands (85%), it is suggested that despite the lack of specificity the DST remains a powerful investigatory test.

Therefore, it is noteworthy that so little attention has been focused on the DST with respect to investigating the validity of the schizoaffective diagnostic grouping. The only major study, apparently, was carried out by Greden et al. [7]. They found DST non-suppression in only 24% of their 25 RDC depressed schizoaffective probands, a percentage much lower than the 67% reported for their large sample of patients with melancholia [3].

In the present study somewhat narrower RDC criteria for schizoaffective disorder were drawn upon to determine if depressed schizoaffective probands thus defined would demonstrate a higher DST non-suppression rate than the 24% found by Greden and co-workers, and to clarify the relationships of DST findings in schizoaffective illness, manic type. A second major aim was to investigate whether a "blunted" thyroid stimulating hormone (TSH) response to thyrotrophin releasing hormone (TRH), as previously described in depressive states [10], might also occur in RDC schizoaffective probands.

Method

Patients were selected on the basis of the Research Diagnostic Criteria (RDC) for schizoaffective disorder, acute type [16]. The criteria, however, were made more stringent by demanding that all the required affective and schizophrenic symptoms be actually present at the time of the initial mental state examination on index admission. Using this procedure 30 RDC schizoaffective patients—18 of the depressive, 12 of the manic type—were found within the course of 2 years. Furthermore, 30 patients with RDC major depressive disorder, endogenous subtype, and 20 RDC schizophrenics admitted during the same time period served as comparison groups.

All patients received complete medical and neurological work-ups and no serious somatic illness could be detected; in particular, no clinical evidence existed indicating any kind of endocrine disease. After informed consent had been obtained endocrinological investigations were started within 2 to 5 days of admission. On the first day, a blood sample for determining basal cortisol and TSH levels was taken at 9 a.m. Thereupon, 200 μg of TRH were injected IV and blood samples taken after 30 and 60 min to estimate TSH response values. At 11 p.m. patients were given 1 mg of dexamethasone orally; the next day, blood was taken at 9 a.m., 4 p.m. and at 11 p.m. in order to determine the corresponding cortisol levels. All samples were centrifuged for 10 min at 3000 rpm, the serum then separated and stored at −20° C. Commercially available radioimmunoassay kits were used for all estimations (cortisol: Travenol, USA; TSH: Becton and Dickinson, Belgium).

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Post-dexamethasone cortisol values were interpreted according to a rule formulated by Carroll et al. [3]. This stipulates that the DST can be considered pathological (that is, the patient is a non-suppressor), when any of the three values, recorded at 9 a.m., 4 p.m. or 11 p.m., exceeds 50 ng/ml.

As for the TSH response to TRH, this was calculated by subtracting the baseline value from the higher of the 2 TSH levels after TRH injection; each such difference formed the so-called Δ max TSH for every patient. Mean baseline values and mean Δ max TSH were compared between diagnostic categories. Comparing group means in this manner appears to be an efficient method of establishing if an abnormality exists [10].

Furthermore, we also set up a working definition of a "blunted" TSH response. Unfortunately, however, we lacked a group with a normal TSH response to TRH, which would have allowed the non-pathological cut-off point of this response to be determined. Therefore, we compromised by using the Δ max TSH mean of our schizophrenic group as the criterion of "non-blunting", since Kirkegaard et al. [9] and Prange et al. [13] had found that their schizophrenics responded normally to TRH. Thus, "blunting" was assumed to be present in any of our remaining diagnostic categories with a TSH response value below the criterion mean.

Since all patients were severely agitated on admission, it was not feasible to keep them completely drug-free during the period of endocrinological assessment. However, as little neuroleptic medication (prothipendyl or promethazine) as possible was used; chloral hydrate or triazolam were given as necessary for night time sedation. Moreover, no patient was under lithium therapy and no female patient was taking oral contraceptives.

All depressive and schizoaffective probands were rated for initial severitiy of illness at some time during the endocrinological study. The Hamilton Depression Scale [8] was used to evaluate the endogenously depressed and the schizoaffective, depressed type, probands, the Brief Psychiatric Rating Scale (BPRS) [12] patients with both types of schizoaffective disorder, and a manic rating scale [17] focused an the manic schizoaffectives.

Statistical calculations were carried out using χ^2-testing for frequency data, whereas quantitative differences were subjected to a one-way analysis of variance (ANOVA) with a follow-up Scheffé test where appropiate. Correlations between hormone values and rating scores were determined by means of Pearsons's product moment and then submitted to t-testing. The level of significance chosen was $P < 0.05$.

Results

The mean age for the RDC endogenously depressed patients was 50.7 ± 8.8 years, 36.5 ± 15.9 years for the schizophrenics, 42.3 ± 15.9 and 29.9 ± 10.8 years for the schizoaffectives, depressed and manic type respectively. Only the mean age difference between RDC depressives and RDC manic schizoaffectives was significant (one-way ANOVA: $F(3,76) = 7.09$, $P < 0.05$). Moreover no sex and no mean rating score differences between diagnostic groups was evident.

Baseline cortisol levels between clinical categories were not significantly different from one another (Table 1). According to the post-dexamethasone cortisol values non-suppression reached its highest sensitivity (89%) in the sample of 18 RDC depressed schizoaffectives, a rate significantly different from the 57% found in the endogenously depressed RDC category (Table 1). Interestingly, non-suppression was also quite prominent in the group of RDC manic schizoaffectives, the rate being higher (67%), but not significantly so, than the one found in endogenous depression. Moreover, the DST findings allowed for a separation of these three groups—all presenting with full affective syndromes—from the category of RDC schizophrenia. Furthermore, no significant correlations between individual cortisol levels and the rating results could be found, with only one exception: in the schizoaffective group, manic type, a negative correlation occurred between cortisol values and BPRS scores ($r = -0.64$, $P < 0.05$).

Probands in the RDC endogenous depressive group presenting with pathological DST non-suppression had lost significantly less weight up to the time of hospital admission than depressive patients with a normal DST (2.2 ± 3.3 kg and 9.0 ± 10.6 kg respectively. $F(1,28) = 5.2$, $P < 0.05$). Unfortunately, comparable weight change findings were not available for the remaining diagnostic categories examined; the same was also true with respect to information on weight status during the first week of hospitalisation. Thus, weight loss cannot with certainty be excluded as a possible source confounding our DST results.

In our study, whether or not a patient had suicidal tendencies had no effect on the DST non-suppression rate. Thus, the average score for the item Nr. 3 (suicide) on the Hamilton scale was not significantly different between non-suppressors and suppressors within the RDC endogenous depression and depressive schizoaffective groupings. Furthermore, the clinical data for the two remaining diagnostic categories showed that only 2 manic schizoaffectives were suicidal (one a suppressor, the other a non-suppressor), whereas among the schizophrenics 2 and 7 of those with suicidal tendencies had pathological and normal DST findings respectively.

As is also evident from Table 1, RDC depressives of the endogenous type had significantly lower TSH baseline values than did RDC manic schizoaffectives. Moreover, the RDC endogenous depressive group had the lowest Δ max TSH mean, one significantly different from that found in RDC schizoaffective disorder, manic type, and from RDC schizophrenia, on the one hand, but not from that found in the group of the RDC depressed schizoaffectives, on the other. In addition, this latter form of schizoaffective disorder could clearly be distinguished from RDC schizoaffective probands, manic type, on the basis of the Δ max TSH mean, but not from the other two groups. Within the endogenously depressed group, demonstrating a significantly "blunted" TSH response, no correlation was found between the Hamilton scores and the Δ max TSH, nor did the Δ max TSH correlate with baseline cortisol levels.

Discussion

The present data show that patients with RDC acute schizoaffective disorder, depressed type, have a significantly higher rate of DST non-suppression (89%) than patients with RDC major depressive disorder, endogenous subtype (57%). Furthermore, the DST findings allow for a clear separation of these depressed schizoaffectives from RDC schizophrenia (25%). When compared with the rather low 24% reported by Greden et al. [7] for their depressed schizoaffectives, the high non-suppression rate in our schizoaffective probands of depressed type may partially be the result of the stricter ver-

Table 1. Clinical ratings, DST and TSH response to TRH in various forms of RDC-orientated psychiatric disorders

	RDC major depressive disorder, endogenous subtype (D) $n = 30$	RDC acute schizoaffective disorder		RDC schizophrenia (S) $n = 20$	Statistical evaluation
		depressed type (SA-D) $n = 18$	manic type (SA-M) $n = 12$		
Clinical data					
Hamilton scores	28.3 ± 6.4	31.1 ± 8.3			
BPRS scores		47.2 ± 14.5	38.0 ± 12.5		
Mania scores			31.8 ± 6.7		
DST (1 mg)					
Baseline cortisol (ng/ml)	151.4 ± 47.5	202.3 ± 80.3	150.3 ± 94.2	171.1 ± 75.9	One-way ANOVA: $F(3,76) = 2.22$, NS
Post-dexamethasone cortisol (ng/ml):					
9 a.m.	54.7 ± 56.1	115.9 ± 82.8	53.7 ± 61.5	33.8 ± 38.2	Evaluation of the post-dexamethasone cortisol levels according to Carroll et al. [3]. The following differences were significant:
4 p.m.	65.2 ± 61.5	102.8 ± 57.4	71.3 ± 54.5	35.9 ± 47.8	
11 p.m.	43.0 ± 50.4	78.1 ± 65.4	22.2 ± 8.5	26.6 ± 30.3	
DST non-suppressors	17	16	8	5	D vs SA-D: $\chi^2 = 5.44$, $P < 0.025$
DST suppressors	13	2	4	15	D vs S: $\chi^2 = 4.88$, $P < 0.05$
Percentage non-suppression (%)	56.7	88.9	66.7	25	SA-D vs S: $\chi^2 = 15.6$, $P < 0.001$ SA-M vs S: $\chi^2 = 5.40$, $P < 0.025$
TRH-test (200 µg)					
Baseline TSH (µU/ml)	0.57 ± 0.18	0.74 ± 0.57	1.20 ± 0.20	0.89 ± 0.71	One-way ANOVA: $F(3,76) = 2.92$, $P < 0.05$. Scheffé Test: D vs SA-M: $P < 0.05$
Δ max TSH (µU/ml)	1.79 ± 2.19	2.50 ± 2.14	6.75 ± 7.42	4.85 ± 2.72	One-way ANOVA: $F(3,76) = 7.09$, $P < 0.001$. Scheffé Test: D vs SA-M: $P < 0.001$, D vs S: $P < 0.05$, SA-D vs SA-M: $P < 0.05$

sion of the RDC schizoaffective criteria we used. That is, only probands fulfilling schizoaffective criteria for the acute subgroup on index admission, on the one hand, and also actually satisfying all affective and schizophrenic symptom requirements cross-sectionally at initial mental state examination, on the other, were considered acceptable for the study. Another reason for the higher degree of non-suppression seen in our sample might have been due to the greater severity of illness found; whereas the Greden group's Hamilton mean score was 21, our own was 31.3.

Several authors [2, 11, 14, 15] have reported higher DST non-suppression in patients with "psychotic" depressions than in probands lacking such features. Unfortunately, they failed to specify whether the psychotic features involved were mood-congruent or not. This also applies to the recent publication by Evans et al. [5]. According to their data, 10 patients with DSM-III major depressive episode, psychotic type, had a significantly higher post-dexamethasone non-suppression rate (100%) than did either 9 patients diagnosed as DSM-III non-psychotic major depression with melancholia (66.7%) or 11 presenting with DSM-III non-melancholic major depression without psychotic symptoms (63.6%). In this connection it should be remembered that DSM-III major affective disorder, psychotic category, encompasses both mood-congruent and mood-incongruent psychopathology [1], whereas RDC schizoaffective disorder is primarily defined in terms of mood-incongruent psychotic symptoms; in fact, all our RDC schizoaffective probands were also positive for DSM-III major affective disorder. Indeed, the more the depressed probands of Evans and co-workers might have been psychotically mood-incongruent, the more their sample would tend to be clinically similar to our group of RDC schizoaffectives, depressed type. At any rate, their results, taken in conjunction with our own, suggest that the question of mood-congruency may be unimportant with respect to predicting a pathological DST. In other words, psychotic features per se in the presence of a full RDC or DSM-III depressive syndrome seem to be closely associated with a very high DST non-suppression rate.

In keeping with the trend reported in numerous studies [10] that TSH response to TRH is "blunted" in depressive states, our 30 RDC endogenously depressed patients also showed a significant abnormality of this kind (Table 1). Moreover, our RDC manic schizoaffectives failed to demonstrate "blunting", this in contrast to the finding of the abnormality in a manic sample examined by Kirkegaard's group [9]. As for our RDC depressed schizoaffectives, their TSH response occupied a position between the "blunted" RDC endogenous depressives and the "non-blunted" RDC schizophrenics; indeed, their TSH response was not significantly different from those of the latter two diagnostic categories.

Summing up, dexamethasone non-suppression was present to a marked degree in our cases of RDC schizoaffective disorder of both depressive and manic type, the rates being higher than that found in RDC endogenous depression. This again only highlights the relative lack of specificity that can be attached to the DST, a test once considered specific for endogenous depression. Yet, the high sensitivity (i.e. percentage of probands with non-suppression within one group) found in both our RDC schizoaffective samples suggests that RDC schizoaffective illness can be clearly separated biologically from RDC schizophrenia. The DST, therefore, may still prove a powerful laboratory method for identifying most instances of affective disorder, when broadly defined, in particular when mood-incongruent psychotic cases are also included. Thus, our DST results partially validate the wide concept of DSM-III's major affective disorder since it is one encompassing affective illness with psychotic mood-congruent and incongruent features.

In contrast to the DST data, our TSH response findings demonstrated different tendencies. Whereas the DST was clearly pathological in RDC endogenous depression and even more so in both RCD depressed and manic schizoaffective groups, a "blunted" TSH response was primarily restricted to the endogenously depressed probands. This might suggest that the coupling of DST non-suppression and TSH "blunting" may serve to identify a valid, more ideally typical depressive subgroup lacking mood-incongruent psychotic features within DSM-III major affective disorder.

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