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DEXAMETHASONE SUPPRESSION TEST AND SELECTION OF ANTIDEPRESSANT MEDICATIONS

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SUMMARY

Endogenous depressives with abnormal dexamethasone suppression tests (DSTs) respond better to somatic antidepressant treatments than those with normal DSTs. Whether the DST also aids in the selection of specific antidepressants has not been determined. A pilot report suggested that patients with abnormal DSTs might be noradrenaline-deficient and respond preferentially to imipramine or desipramine, whereas those with normal DSTs might be serotonin-deficient and respond best to amitriptyline or clomipramine. Attempting to replicate this observation, we studied 26 patients diagnosed with Research Diagnostic Criteria as major depressive disorder, endogenous subtype, and with DSM-III as having melancholia. All were drug-free during baseline evaluation. All had abnormal DST results, with post-dexamethasone plasma cortisol levels exceeding 5 μg/dl. We treated subjects with either imipramine or amitriptyline and compared clinical response with weekly Hamilton Depression Rating Scales, completed by raters blind to both DST results and the research question. Therapeutic plasma levels were documented. We found no significant differences in treatment response between the subgroups. Twenty of the 26 subjects did well. The imipramine-treated group failed to have either earlier response or better final outcome. These data fail to replicate suggestions that DST results assist in the selection of either imipramine or amitriptyline.

INTRODUCTION

The dexamethasone suppression test (DST) is a remarkably specific laboratory marker of endogenous depression (melancholia) (Brown et al. 1979;

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Schlesser et al. 1979; Carroll et al. 1981a). An abnormal DST occurs when patients have early escapes from suppression of plasma cortisol secretion following a midnight dose of 1 mg dexamethasone. These premature escapes are not due to changes in dexamethasone metabolism (Carroll et al. 1980). Instead, they presumably reflect disinhibition of the limbic-hypothalamic-pituitary-adrenal axis (Carroll et al. 1976). The DST has thus far been used mostly for nosological purposes in patients with major affective syndromes or related variants. Other clinical applications have been described, however. Greden et al. (1980a) reported that if abnormal DSTs fail to normalize with antidepressant treatment, early relapse is likely. Goldberg (1980) used a still-unproven modification of the DST (in which one plasma cortisol sample is drawn 34 h after administering dexamethasone), and suggested that antidepressant medications might be safely discontinued once the test had normalized. Gold et al. (1980) agreed with Greden et al. (1980a) that treatment should be continued if the DST failed to normalize, but felt that Goldberg's suggestion was still premature. Greden and Carroll (1979) and Carman et al. (1980) used the DST to assist with diagnosis and treatment of patients with catatonia, since non-suppression helped identify those with affective disorder rather than schizophrenia. The DST has similarly been used to help identify significant affective syndromes in borderline patients (Carroll et al. 1981b). Finally, several reports describe how periodic repetitions of the DST can be used to serially monitor clinical response to electroconvulsive treatments (ECT), and all agree that the test progressively normalized among responders (Dysken et al. 1979; Albala et al. 1980, 1981).

It is uncertain whether the DST predicts response to specific antidepressant medications. An early report (McLeod 1972) suggested that patients with abnormal DST results had poor responses to tricyclic antidepressants. Subsequent studies have consistently concluded that abnormal DST results predict better response to tricyclic antidepressants, at least among non-delusional depressives. Brown and colleagues (Brown et al. 1979; Brown and Shuey 1980a) found that 82% of endogenous depressives with abnormal DSTs had good clinical responses, compared to only 37% of those with a normal test. Greden et al. (1980b) found similar trends. Carman and associates (1980) concluded that the DST was better than clinicians' judgements in predicting the response of depressed catatonics to thymoleptic agents.

In an expansion of their initial findings, Brown et al. (1980b) later suggested that abnormal DSTs might assist in the precise selection of antidepressants. Specifically, they reported that patients who had abnormal non-suppressive DSTs responded well after 2 weeks to desipramine or imipramine treatments, but poorly to amitriptyline or clomipramine. They felt these findings conformed to the hypothesis that depressed patients who have abnormal DSTs might be noradrenaline-deficient and those with normal DSTs might be serotonin-deficient. Differential drug response would then occur because antidepressants presumably differ in their respective effects upon noradrenergic or serotonergic reuptake (Iverson and MacKay 1979).

If clinicians were able to use the DST to assist treatment selection, the practical value of the test would increase greatly. To study this issue, we attempted to replicate the portion of the observations by Brown et al. (1980b) that suggested that abnormal DST results predicted better response to imipramine than to amitriptyline. In contrast to their findings, we failed to identify any significant differences in treatment response.

METHODS

Twenty-six subject (Ss) were hospitalized on the Clinical Studies Unit (CSU), a 10-bed research unit specializing in affective disorders, located within the University of Michigan Department of Psychiatry. All Ss provided informed consent. Baseline evaluations occurred following a drug-free period of at least 10—14 days. The evaluation consisted of 2 independent, unstructured clinical interviews, a structured interview using the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott 1975), a family diagnostic interview, a review of previous medical records, and a thorough physical and laboratory screening. Each subject met DSM-III (1980) criteria for melancholia and Research Diagnostic Criteria (RDC) (Spitzer et al. 1977) for Major Depressive Disorder, primary and endogenous subtypes.

The dexamethasone suppression test, described in detail elesewhere (Carroll et al. 1981), was considered abnormal if any of 3 post-dexamethasone plasma cortisol concentrations (08.00, 16.00, 23.00 h) exceeded 5 μg/dl. Samples were analyzed using a modification of Murphy's (1967) competitive protein-binding technique. All investigators, clinicians and raters were blind to DST results until after patients were discharged. Because the research question was formulated retrospectively, they were also blind to the study question.

Treatments were selected solely on clinical grounds. Nineteen subjects received imipramine and 7 were treated with amitriptyline. The discrepancy in subgroup size is explained by the retrospective nature of the study. Therapeutic tricyclic plasma levels were documented for each subject. No other psychotropic medications were prescribed. The groups did not differ significantly on the basis of unipolar or bipolar history. Treatment progress was monitored with weekly 17-item Hamilton Depression Rating Scale (HDRS) scores (Hamilton 1960). We assessed response by calculating the percentage of reduction from baseline HDRS scores and comparing imipramine-treated patients with amitriptyline-treated patients at 2, 3, 4 weeks and at discharge. We operationally defined "good treatment response" as at least a 50% reduction from baseline HDRS, *and* a final HDRS score of 13 or less, and also compared subgroups using this criterion.

RESULTS

Comparisons between the two subgroups are displayed in Table 1. Antidepressant plasma levels and ratios between imipramine/desipramine and

TABLE 1

COMPARISON BETWEEN IMIPRAMINE (IMI) AND AMITRIPTYLINE (AMI) TREATMENTS IN ENDOGENOUS DEPRESSIVES WITH ABNORMAL DEXAMETHASONE SUPPRESSION TEST

Item	IMI-treated + abnormal DST (N = 19) (mean ± SD)	AMI-treated + abnormal DST (N = 7) (mean ± SD)	Significance (two-sample *t*-test)
Baseline Hamilton Depression Score	25.7 ± 4.9	29.3 ± 5.2	n.s.
Baseline post-dexamethasone plasma cortisol (μg/dl) [a]	13.1 ± 5.7	16.8 ± 9.4	n.s.
Length of hospital treatment (weeks)	4.7 ± 1.4	4.3 ± 0.8	n.s.
Final Hamilton Depression Score	9.6 ± 7.7	10.0 ± 9.4	n.s.
Percentage reduction in Hamilton Depression Score			
2 weeks	38.9 ± 26.9	39.0 ± 36.5	n.s.
3 weeks	45.9 ± 19.8	36.8 ± 30.8	n.s.
4 weeks	58.6 ± 30.3	61.7 ± 34.7	n.s.
discharge	62.5 ± 29.7	69.3 ± 32.0	n.s.

[a] The highest plasma cortisol concentration from each test was used. Logarithmic transformations of these concentrations were used for statistical analysis, but actual values are presented in this table.

amitriptyline/nortriptyline, respectively, are shown in Table 2. As illustrated in Table 1, the imipramine-treated subjects did not differ significantly from the amitriptyline-treated subjects on the basis of severity (baseline HDRS scores), baseline post-dexamethasone plasma cortisol values, or length of treatment prior to discharge. When treatment responses between the two groups were compared at weekly intervals and at final evaluation, there were also no significant differences. Indeed, at the completion of this hospital course of treatment, the patients with abnormal DSTs who received amitriptyline had a 69% reduction, thus showing slightly more improvement than the imipramine-treated group with a 62% reduction. Furthermore, 20 of the 26 total subjects (77%) had "good clinical response" as operationally-defined (14 of 19 in the imipramine-treated group and 6 of 7 in the amitriptyline-treated group). Thus, most Ss did well regardless of selected treatment, and there were again no significant differences between the imipramine- and amitriptyline-treated subgroups (chi-squared = 0.38, df = 1). These data do not support the claim that abnormal DSTs predict a better response to imipramine than to amitriptyline.

TABLE 2

TRICYCLIC ANTIDEPRESSANT PLASMA LEVELS (ng/ml) FOR IMIPRAMINE-TREATED AND AMITRIPTYLINE-TREATED SUBGROUPS [a]

Subgroup plasma concentrations and ratios	Stage of treatment			
	2 weeks	3 weeks	4 weeks	Final
Imipramine-treated				
IMI				
Mean ± SD	134.00 ± 139.5	118.21 ± 96.58	127.71 ± 144.88	140.16 ± 57.8
(N)	(10)	(14)	(14)	(6)
Range of levels	56—520	35—410	40—590	88—235
DMI				
Mean ± SD	104.80 ± 76.3	105.79 ± 68.97	129.71 ± 76	143.00 ± 91.29
(N)	(10)	(14)	(14)	(6)
Range of levels	24—230	33—210	40—330	48—310
Mean of ratios				
(IMI/DMI)	1.57 ± 0.85	1.26 ± 0.62	1.08 ± 0.65	1.36 ± 0.96
(N)	(10)	(14)	(14)	(6)
Amitriptyline-treated				
AMI				
Mean ± SD	104.00 ± 56.10	205.40 ± 54.48	225.20 ± 164.00	121.67 ± 12.28
(N)	(3)	(5)	(5)	(3)
Range of levels	50—162	112—245	116—290	112—135
NT				
Mean ± SD	106.33 ± 48.40	124.60 ± 54.15	163.40 ± 53.66	171.00 ± 53.69
(N)	(3)	(5)	(5)	(3)
Range of levels	66—160	52—190	125—246	125—230
Mean of ratios				
(AMI/NT)	0.94 ± 0.17	2.04 ± 1.38	1.34 ± 0.74	0.74 ± 0.15
(N)	(3)	(5)	(5)	(3)

[a] Assays conducted by radioimmunoassay (Carroll et al. 1981c).

DISCUSSION

Had we confirmed that DST results helped select the most effective antidepressant medication, the implications would have been exciting. Our failure to replicate the report of Brown et al. (1980b) is thus disappointing. What accounts for this discrepant result? One obvious consideration is that baseline DST abnormalities do not predict better *final* response to imipramine, but might predict *earlier* improvement with eventual "washout" of differences. This possibility had credence because Brown et al. (1980b) conducted a single evaluation after only 2 weeks of treatment. We found no differences even at 2 weeks, however. At 3 weeks, the imipramine-treated group did have slightly greater improvement than the amitriptyline-treated subjects, but the inverse actually occurred at 4 weeks and at discharge. In conclusion, the evidence for DST results predicting either earlier response or better ultimate response to imipramine is weak or non-existent.

The proposed hypothesis that 2 relatively-distinct biochemical subtypes of endogenous depression are being treated — noradrenaline (NA)-deficient and serotonin (5-HT)-deficient — might also be flawed and meaningless. Stewart et al. (1980), e.g., designed a study to test this hypothesis by comparing initial responses to desipramine (DMI) with later responses to clomipramine if Ss failed to respond to DMI. They found that DMI, a drug which presumably blocks primarily neuronal adrenergic reuptake, produced improvement in almost all Ss. They therefore had to cancel the clomipramine portion of the study. Still another perspective of this same issue is that the serotonin vs. noradrenaline hypothesis might have validity, but cannot be tested in drug trials because of serious flaws in claims that various antidepressants predominantly effect one or the other of the two systems. Iverson and Mackay (1979) emphasized that most of the current popular tricyclic antidepressants — including those used by Brown et al. (1980b) in their study and by us in this study — act with almost equal potency on both NA and 5-HT mechanisms, despite prevailing beliefs to the contrary. Although effects on NA uptake occur at drug concentrations lower than those affecting 5-HT uptake, the spectrum of activity clearly covers both. Even clomipramine, which Brown et al. (1980b) utilized as a more perfect "serotonergic blocker", has some blocade of NA reuptake. Imipramine and amitriptyline are also both demethylated to the active compounds desmethylimipramine and nortriptyline, respectively. Changes in the ratios between parent compounds and these secondary amine metabolites further alter the spectrum of reuptake blockade. New antidepressants, such as maprotiline and fluoxetine, are significantly "cleaner" than traditional ones in their relative blockade potencies. Perhaps the same study strategy can be repeated in the future with these agents. Even then, investigators need to recognize that the mechanism of action of antidepressants is still unknown. A growing body of evidence suggests, for example, that the major effects of antidepressants might be due to downregulation of alpha-2-adrenergic presynaptic receptors, or decreased

sensitivity of postsynaptic beta-noradrenergic receptors and have little to do with blockade of reuptake (Crews and Smith 1978; Sulser et al. 1978; Maas and Huang 1980).

Endogeneous depressives with abnormal DSTs, when compared with those with normal DSTs, seem to have a better response to somatic antidepressants in general. This finding is clinically meaningful. Patients with abnormal DSTs should receive an established somatic antidepressant treatment. Conclusions about *which* specific treatment, however, cannot yet be gleaned from the DST.

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