Journal of Affective Disorders, 7 (1984) 265–272
Elsevier

JAD 00237

The Metyrapone Test in Affective Disorders and Schizophrenia II

Changes upon Treatment

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(Received 14 September, 1983)
(Revised, received 15 March, 1984)
(Accepted 19 March, 1984)

Summary

The metyrapone test was applied to groups of patients suffering from major depressive illness with melancholia, mania or schizophrenia, before and after treatment. There were interesting individual correlations between post-metyrapone cortexolone values, cortexolone/cortisol ratios and clinical improvement in depressives. Two patients who had exhibited abnormal metyrapone responses displayed a normalization of post-metyrapone cortexolone values upon clinical improvement, whereas the opposite trend was observed in a patient who did not improve and in another who became manic. These preliminary results may indicate that abnormal metyrapone responses in depression are state dependent.

Key words: *Metyrapone – Depression – Mania – Schizophrenia – Psychotropic drugs*

Introduction

The neuroendocrine strategy in clinical psychiatric research has been used increasingly to monitor treatment progress. In particular, changes in responses to the

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Supported in part by grants No. 24211 from the National Institutes of General Medical Sciences, N.I.H. and No. 2507RR0540021 from the Division of Research Resources, N.I.H., to the School of Medicine, State University of New York at Buffalo.

dexamethasone suppression test (DST) in melancholic patients have attracted attention. Most DST non-suppressors show progressive normalization of DST responses in conjunction with clinical improvement and upon pharmacological treatment (Holsboer et al. 1982; Greden et al. 1983; Holsboer et al. 1983a).

In a previous report (Fava et al. 1984), the metyrapone test was applied to patients suffering from major depressive illness with melancholia, from mania and from schizophrenia. The metyrapone test (MT), in its single-dose version (Spiger et al. 1975), is a useful and reliable procedure for assessing the integrity of the hypothalamic–pituitary–adrenocortical (HPA) axis. Metyrapone inhibits 11-beta-hydroxylase, the enzyme which converts cortexolone (11-deoxycortisol or compound S) to cortisol in the adrenal cortex. Following a single dose of metyrapone at night, plasma cortexolone concentrations in normal subjects increase from less than 1 μg/dl to 7–22 μg/dl at 0800 h the following day (Spiger et al. 1975). Patients with adrenal insufficiency have subnormal cortexolone responses to metyrapone, whereas a high normal or exaggerated response is observed in patients with pituitary Cushing's syndrome (Spiger et al. 1975). Hypoactivity of the HPA axis as assessed by the test appeared to be present in affective disorders and schizophrenia although it occurred infrequently. A few patients (most of whom were melancholic DST non-suppressors) displayed high normal or exaggerated responses upon metyrapone challenge (Fava et al. 1984). Whether these abnormal responses to metyrapone in melancholia can be used as state-related laboratory tests, is a question of considerable interest. The aim of this report was to provide such information, examining possible changes in response to metyrapone following pharmacological treatment and/or recovery from depression. If the relationship of DST and MT to clinical progress were similar, one would expect a normalization of abnormal metyrapone responses in conjunction with good clinical response and failure to normalize when the clinical outcome is poor.

Little is known about the effects of drug treatment and/or recovery upon metyrapone responses in psychiatric disorders. Endo et al. (1974) administered 1 g of metyrapone at midnight to 7 depressive subjects and assessed plasma ACTH levels at 0800 h the following day, before and after treatment. ACTH levels after metyrapone were almost identical during depression and after recovery. However, their metyrapone dosage was low and not adjusted to body weight (Spiger et al. 1975), and post-metyrapone cortexolone and cortisol levels were not assayed or reported, so that it is not possible to ascertain whether adequate suppression of 11-beta-hydroxylase had been achieved in their sample. Brambilla et al. (1975) evaluated the neuroendocrine effects of haloperidol therapy in 62 male schizophrenics. ACTH secretion after metyrapone was reduced or absent in most of the patients before the beginning of the therapy; haloperidol induced an improved response to metyrapone. Unfortunately there were insufficient details about their methods and values, so that their observations do not go beyond an anecdotal stage. Recently, Holsboer et al. (1983b) evaluated plasma ACTH levels after oral ingestion of 2 g of metyrapone in 6 healthy subjects before and after administration of zimelidine, a relatively selective serotonin re-uptake inhibitor antidepressant, and placebo. Changes in plasma ACTH levels were reported. The cortisol/cortexolone

ratios were taken as measures of 11-beta-hydroxylase activity depending upon ACTH secretion (Ganguly et al. 1977; Kramer et al. 1983), and were found increased after zimelidine treatment when compared to placebo (Holsboer et al. 1983b).

Methods

The subjects were 10 consecutive depressed, 7 schizophrenic and 3 manic patients admitted to the Erie County Medical Center and the Veterans Administration Medical Center, Buffalo, New York. All subjects voluntarily provided informed consent. Diagnoses were established by the consensus of 2 psychiatrists using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978). Depressed patients had to meet both DSM-III criteria for major depressive disorder with melancholia (American Psychiatric Association 1980) and RDC criteria for primary endogenous major depressive disorder (Spitzer et al. 1981). Five schizophrenic patients met both DSM-III criteria and RDC criteria for schizophrenia; 2 patients were classified as suffering from schizoaffective disorder, manic type, according to RDC criteria.

Demographic and diagnostic characteristics of patients are summarized in Tables 1 and 2. Part of the results concerning the first metyrapone test were reported in the previous paper (Fava et al. 1984). On the first day of their hospital-stay patients underwent extensive psychometric evaluation, including the SADS (Endicott and Spitzer 1978). Prior to discharge (in conjunction with the second metyrapone test), patients were tested again with the SADS-Change Version (SADS-C), and were rated on a 9 point bipolar relative global rating scale with cues from 'A lot better' through 'no change' to 'a lot worse' (Kellner 1972). In depressives, Hamilton Depression Rating Scale scores (Hamilton 1960) were extracted from the SADS and SADS-C scores, according to the method developed by Endicott et al. (1981). A satisfactory clinical response to treatment was considered to be a rating of 'better' or 'a lot better' on the global scale (Kellner 1972) and a decrease of at least 50% in the total score of the Hamilton Depression Rating Scale (Hamilton 1960). In patients suffering from mania or schizophrenia, a satisfactory response involved a rating of 'better' or 'a lot better' on the global scale and a decrease of at least 50% in the total score of the SADS (Endicott and Spitzer 1978).

Most depressed patients reported being drug-free for at least 1 week prior to hospitalization and after admission received no medication until the first metyrapone test was completed. Manic and schizophrenic patients were receiving psychotropic drug treatment; drugs are listed in Table 2. No patients had medical illnesses or fulfilled any of the medical or drug exclusion criteria outlined by Cohen (1977). After completion of the first metyrapone test, depressed patients were started on antidepressant medication, generally imipramine (see Table 1). Two to three weeks after treatment, generally prior to discharge, the metyrapone test was repeated in all patients. Each patient received the same dose of metyrapone for each of the 2 tests. Results on the dexamethasone suppression test (Carroll et al. 1981) were available in

TABLE 1

METYRAPONE TEST RESULTS BEFORE AND AFTER TREATMENT IN DEPRESSED PATIENTS WITH MELANCHOLIA

Patient	Age (yr)	Sex	1st test		Drug	2nd test		Treatment response
			Cortexolone (μg/dl)	Cortisol (μg/dl)		Cortexolone (μg/dl)	Cortisol (μg/dl)	
1	44	F	9.6	2.0	Imipramine	10.1	1.8	Improved
2	41	F	10.2	5.9	Imipramine	9.6	5.0	Improved
3	65	F	11.9	7.3	Imipramine	13.7	3.8	Improved
4	36	M	20.6	5.4	Imipramine	13.7	9.4	Improved
5	35	M	11.1	6.0	Amitriptyline	14.4	7.2	Same
6	61	M	20.4	1.5	Doxepin	13.2	5.9	Improved
7	56	M	13.2	7.8	Chlorpromazine	21.3	6.1	Worse
8	40	M	8.8	1.9	Amoxapine	9.9	<1	Improved
9	60	F	12.6	1.0	Imipramine	20.0	1.9	Manic switch
10	52	F	1.9	1.7	Imipramine	3.3	6.2	Same

TABLE 2

METYRAPONE TEST RESULTS BEFORE AND AFTER TREATMENT IN MANIC AND SCHIZOPHRENIC PATIENTS

Patient	Age (yr)	Sex	Drug	Diagnosis	1st test		2nd test		Treatment response
					Cortexolone (μg/dl)	Cortisol (μg/dl)	Cortexolone (μg/dl)	Cortisol (μg/dl)	
1	22	F	Lithium	Mania	6.5	2.1	8.4	3.8	Improved
2	37	M	Lithium	Mania	8.0	4.5	6.4	4.0	Improved
3	44	M	Lithium, chlorpromazine	Mania	9.2	2.1	23.2	4.5	Improved
4	47	F	Chlorpromazine, haloperidol	Schizoaffective, manic	17.4	8.1	18.9	5.4	Same
5	30	M	Chlorpromazine	Paranoid schizophrenia	5.9	<1	13.5	3.7	Improved
6	55	M	Fluphenazine	Residual schizophrenia	20.9	9.0	9.0	13.5	Improved
7	37	M	Chlorpromazine	Undifferentiated schizophrenia	6.4	8.3	5.6	6.2	Improved
8	30	M	Haloperidol	Paranoid schizophrenia	11.0	6.3	6.0	3.8	Improved
9	25	M	Thiothixene, lithium	Undifferentiated schizophrenia	10.1	2.7	16.2	3.4	Same
10	55	M	Chlorpromazine, diazepam	Schizoaffective, manic	9.9	1.3	9.9	<1	Improved

conjunction with the first metyrapone test only and were reported in the previous work (Fava et al. 1984).

The metyrapone test was performed according to its standardized single-dose version (Spiger et al. 1975). Metyrapone, 2–3 g, was administered orally at midnight with a glass of milk and a snack; doses were adjusted according to body weight (Spiger et al. 1975). Blood for plasma cortexolone determination was drawn at 08.00 h the following morning. All the subjects were awakened at least 1 h before the morning blood samples were obtained.

Post-metyrapone cortexolone and cortisol concentrations were determined by normal phase high pressure liquid chromatography (HPLC) with ultraviolet detection (Carson and Jusko 1984). Interassay and intraassay coefficients of variation for the HPLC techniques ranged from 2 to 16% at low and high concentrations. The assay detection limit was 0.5 μg/dl.

The two-tailed paired Student's *t*-test was employed to test the significance of findings.

Results

The results of the MT are set out in Tables 1 and 2. In depressed patients, there were no significant changes in post metyrapone cortexolone values before (12.0 ± 5.5 μg/dl) and after (12.9 ± 5.2 μg/dl) treatment. Also when the cortexolone/cortisol ratio, a reliable indicator of ACTH secretion (Ganguly et al. 1977), was considered, differences were not significant (the ratio decreased from 4.75 to 4.13). Similar results were obtained in the non-depressed patients: cortexolone increased from 10.5 (± 4.9) μg/dl to 11.7 (± 6.0) μg/dl and the cortexolone/cortisol ratio decreased from 3.35 to 3.20, neither change being significant. These results were not surprising, since most of the patients had exhibited normal metyrapone responses on the first test and also the DST has no apparent value as a serial marker in patients with normal DST findings (Greden et al. 1983). More interesting findings were obtained when individual changes in relation to clinical state were examined. In some depressed patients, cortexolone values tended to remain unchanged; these patients had exhibited a normal range of metyrapone responses prior to treatment (patients 1, 2, 3, 5, 8). All of them but one displayed a satisfactory clinical response. Patients 4 and 6, who had a high normal response to metyrapone prior to treatment, displayed much lower cortexolone levels afterwards and their cortexolone/cortisol ratios showed dramatic decreases (from 3.81 to 1.46 and from 13.60 to 2.24, respectively). Both were clinically improved after treatment. Patients 7 and 10 did not report a satisfactory improvement. Patient 7 had an exaggerated response to metyrapone after treatment and his cortexolone/cortisol ratios increased from 1.69 to 3.49; patient 10 had abnormally low cortexolone values in both instances. Patient 9 was extremely interesting. This 60-year-old melancholic woman, with a long-standing history of recurrent depression and no previous bipolar history, was for the first time treated with an antidepressant and exhibited a manic switch after 2 weeks of treatment. This patient was re-tested 1 week after imipramine had been discontinued

when she was still in a manic state and drug-free. Her cortexolone level rose from 12.6 to 20.0 μg/dl, but her cortexolone/cortisol ratio decreased from 12.6 to 10.53.

In manic and schizophrenic patients (Table 2), individual results and clinical states were difficult to correlate.

Three patients (1, 5 and 7) had subnormal metyrapone responses on the first test and they all improved after treatment with lithium and chlorpromazine. In 2 patients, however, cortexolone values returned to normal range (patients 1 and 5) whereas in the other (patient 7) they did not. Patient 8 was rated as clinically improved after treatment with haloperidol, yet he exhibited a subnormal response to metyrapone on re-test. Opposing trends also took place with high normal responses (see patients 3 and 6), regardless of clinical improvement. In summary, in manic and schizophrenic patients, metyrapone responses after treatment went in all possible directions. A confounding variable in this sample was the fact the patients were not drug-free on their first MT and chlorpromazine, as well as probably other neuroleptics, may contaminate MT results (Metcalf and Beaven 1968).

Discussion

These preliminary results suggest that, in depressives, metyrapone responses may correlate with clinical response to treatment. Two patients who had exhibited hyperfunction of the HPA axis as assessed by the MT had their cortexolone values revert to a normal range upon clinical improvement, whereas the opposite trend was observed in a patient who did not recover and in another who became manic. Another patient who displayed HPA axis hypofunction on both tests responded poorly to treatment. This may indicate that the aberrant responses to MT in depression are state dependent. In those patients, the cortexolone/cortisol ratios changed considerably as well, confirming the suggestion by Holsboer et al. (1983b) about their potential clinical usefulness. Holsboer et al. (1983c) observed that the sensitivity of the DST is remarkably increased when based on a cortisol/cortexolone ratio instead of plasma cortisol concentrations alone. Some preliminary findings from our laboratory would confirm the sensitivity of this ratio when the DST is performed before and after treatment with amitriptyline (Carson et al. unpublished data).

Obviously, the implications of the findings of this study are still tentative and await proper replication and confirmation in larger samples of depressed patients and unmedicated schizophrenic and manic patients.

Acknowledgements

The authors are indebted to Drs. Ismaele Mastrogiacomo and Nicoletta Sonino for their helpful comments and Ms. Luisella Pezzoli for valuable secretarial assistance.

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