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Steroids and Moods: Correlations in Schizophrenics and Subjects Treated With Lysergic Acid Diethylamide (LSD), Mescaline, Tetrahydrocannabinol, and Synhexyl

LEO E. HOLLISTER, M.D. Palo Alto, Calif.

For the last 15 years, a great many attempts have been made to relate various types of emotional stress with rates of urinary excretion of various corticosteroids or plasma levels of 17-hydroxycorticosteroids (17-OHCS). The conflicting results of such reports have been reviewed recently.[1] The consensus has been that acute states of anxiety may be related to increased levels of 17-OHCS in plasma and increased excretion in urine; depressive states have been related to high levels of steroid excretion as well.[2-6]

Although both cross-sectional and longitudinal studies of steroid excretion have been reported, the latter have been generally preferred. One reason for their preference is that they have been associated with considerably more significant correlations between steroids and mood; another, that they take into account individual variability over time; and finally, they compare the patient with himself rather than with some comparison group. However, it is possible to compare patients with themselves using a cross-sectional technique, both over short and long periods of time. Accordingly, the cross-sectional technique was employed in a series of experiments using newly admitted schizophrenic patients and normal volunteers treated with psychotomimetic drugs.

Material and Methods

Experiment 1. In this experiment, 22 newly admitted schizophrenics were observed over a six-week period, at the beginning and end of which they were rated by a mental status examination coded on the Brief Psychiatric Rating Scale (BPRS). This scale contains 18 symptoms and signs of psychopathology which can be quantitatively rated so that the severity of each is apparent; the 18 items can be summed to provide a total pathology score indicative of the severity of the disturbance. On the day the interview ratings were made, a 24-hour collection of urine was taken for determination of total con-

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tent of 17-OHCS, 17-ketogenic steroids (17-KGS), and 17-ketosteroids (17-KS). The main interest was in detecting any relationship of steroid excretion to specific symptoms and to total degree of disturbance at any specific time. The treatment used in these patients was an experimental one, metronidazole, but the main interest was relating symptoms to steroid excretion, regardless of the type of treatment offered.

Experiment 2. Fourteen volunteer subjects, all men, were observed on two consecutive days. On the first day, the experimental protocol was followed from 7 A.M. to 5 P.M., with no active treatment being given. On the second day, the same procedure was followed, but at 9 A.M. a dose of the psychotomimetic drug, lysergic acid diethylamide (LSD), was administered in doses of either 1.5 or 2 micrograms/kg. Urine samples were taken for the period of 9 A.M. to 5 P.M. and from 5 P.M. to 7 A.M. the next morning. Each specimen was used separately for measuring 17-OHCS, 17-KGS, and 17-KS.

Experiment 3. The same procedure was performed as in the second experiment above except that ten volunteer men were given doses of 5 to 6 mg/kg of mescaline on the second day. It was expected that the doses of LSD and mescaline used in experiments 2 and 3 would produce substantial emotional reactions in the subjects treated and that these might be expected to be reflected in the rates of steroid excretion.

Experiment 4. Nine male volunteers were treated with doses of tetrahydrocannabinol (THC) ranging from 30 to 50 mg, and ten were treated with doses of a synthetic tetrahydrocannabinol-like material, synhexyl, in doses of 75 to 200 mg. Just prior to treatment, blood was drawn for determination of plasma 17-OHCS; 3 hours later, another specimen was taken for the same purpose. As in the case of LSD and mescaline, acute drug administration was expected to rapidly and profoundly affect the mood of the subjects.

Results

Experiment 1. Steroid excretion in schizophrenics was usually within the laboratory limits of normal, and when deviations were present they were only slightly abnormal. Only 14 of 132 values were outside the range of normal, occurring in seven of the 22 patients. The mean, standard deviation, and range of values observed for the steroid measurements, both before and after treatment, are shown in the top half of Table I.

It was of some interest to determine the degree to which individual measurements of steroid excretion correlated on repeated measurements at a six-week interval, as well as how the three measurements correlated with each other when done at the same time. These results are summarized in the lower half of Table I. As is evident, the separate measurements correlated more with each other when done at the same time than the same measurement correlated with itself over a period of time. As might have been expected, 17-OHCS and 17-KGS had the highest intercorrelations.

Another question of interest was the correlation between the excretion of individual steroid fractions and the total degree of schizophrenic illness as measured by the BPRS total pathology score. These data are summarized in Table II. Neither before treatment nor after was steroid excretion correlated highly with the total pathology score of the BPRS.

A somewhat similar question was whether or not changes in urinary excretion of steroids were correlated with the degree of change in clinical symptoms. These relationships are also shown in Table II. It would appear that change in steroid excretion was significantly correlated with change in severity of illness, an increased steroid excretion being as-

TABLE I

Steroid Excretion in 22 Schizophrenic Patients Before and After Metronidazole Treatment

	Normal Range	Before	After
17-OHCS	3–10	5.8 ± 2.6 (2.3–15.0)	5.5 ± 2.7 (2.1–13.0)
17-KGS	5–23	11.6 ± 4.7 (6.3–25.0)	12.9 ± 4.8 (5.6–27.0)
17-KS	9–22	14.7 ± 4.2 (6.8–26.0)	14.2 ± 5.8 (8.1–29.0)

Values in mg/24 hours: means ± SD (range).

Correlations Among Measurements

Same measurement, same patient, 6-week interval

17-OHCS	.54
17-KGS	.52
17-KS	.45

Between measurements, same patient, before treatment

17-OHCS–17-KS	.59
17-OHCS–17-KGS	.89
17-KGS–17-KS	.60

Between measurements, same patient, after treatment

17-OHCS–17-KS	.56
17-OHCS–17-KGS	.71
17-KGS–17-KS	.65

sociated with greater degrees of improvement. The regression lines for these correlation coefficients are quite steep, with the majority of patients showing changes in steroid excretion of only small degrees. Thus, the correlations, while relatively high, still do not have much clinical meaning.

Finally, was the excretion rate of steroids prior to treatment any predictor of the degree of clinical change which might be anticipated? As indicated on the bottom of Table II, the correlation pattern for all three steroid fractions tended to be negative, suggesting that high initial rates of steroid excretion were associated with small clinical changes, and vice versa.

An additional question concerned the relationship between the excretion of steroid fractions and the level of specific symptoms. In this regard it must be emphasized that these were schizophrenic patients. Despite the fact that symptoms such as anxiety and depression are measured by the BPRS, the relationships uncovered in these analyses only apply to such symptoms as they occur in schizophrenics. These relationships, both before and after treatment, are shown in Table III, only those correlations of possible significance being noted. In general, symptoms of psychosis, such as grandiosity, hostility, uncooperativeness, disorientation, excitement, conceptual disorganization, and unusual thought content, correlated positively with the rate of steroid excretion, while the primary symptom of depression, depressive mood, showed a rather consistent negative correlation. The latter finding is somewhat different from that previously observed in nonpsychotic depressed patients.[1,4]

Experiments 2 and 3. As these two experiments were entirely comparable, they are summarized together in Table IV. Despite the fact that every subject receiving LSD or mescaline experienced to varying degrees the complete clinical syndromes to be expected, including some

TABLE II

Correlation Between Steroid Excretion and Schizophrenic Pathology (BPRS Total Pathology Score) Before and After Metranidazole Treatment in 22 Patients

Excretion of steroids and severity of illness	
Before treatment	
17-OHCS-BPRS	.02
17-KGS-BPRS	.10
17-KS-BPRS	—.04
After treatment	
17-OHCS-BPRS	.25
17-KGS-BPRS	.18
17-KS-BPRS	.05
Change in excretion of steroids and change in illness	
17-OHCS ch-BPRS ch	.49*
17-KGS ch-BPRS ch	.47*
17-KS ch-BPRS ch	.55**
Initial steroid excretion and ultimate change in illness	
17-OHCS pre-BPRS ch	—.22
17-KGS pre-BPRS ch	—.27
17-KS pre-BPRS ch	—.42

* P=.05 or less.
** P=.01 or less.

degree of stimulation and euphoria, changes in steroid excretion were rather small. The only significant increase in excretion during the span of action of the drugs was a significant increase in 17-KGS following LSD. Attempts were made to relate individual steroid levels to "stress scores" derived from clinical observations, mood scale scores, and questionnaire data, as well as to other physiological measures such as increase in plasma free fatty acid levels and evidence of antidiuresis. The only significant rank-order correlation was one of −.50 for 17-KS excretion and antidiuretic effect from mescaline.

Experiment 4. Mean plasma cortisol level prior to treatment of nine subjects with varying doses of THC was 18.2 micrograms/100 ml. After treatment, the mean value had risen to 21.8 micrograms/100 ml. Before and after synhexyl, values were 17.6 and 21.2 micrograms/100 ml, respectively. Although these mean levels would suggest that a slight increase occurred with each drug, much of it could be attributed to a single subject in each group who experienced an abnormally great increase. If these two subjects are excluded, the mean plasma cortisol value before and after THC became 17.0 and 15.8 micrograms/100 ml, respectively; before and after synhexyl, 17.4 and 19.0 micrograms/100 ml, respectively. Thus, it appears that the predominant clinical effects of these drugs, which include euphoria, sedation, and some psychotomimetic experiences, were not as-

TABLE III

Correlation Between Steroid Excretion and Level of Specific Psychiatric Symptom Before and After Metronidazole Treatment in 22 Patients

	Before	After
17-KS with		
somatic concern	—.39	
anxiety	.32	
guilt	.47	none
hallucinatory behav.	—.37	
17-OHCS with		
depressive mood	—.54	—.36
motor retardation	.36	—.38
grandiosity	—	.37
hostility	—	.50
uncooperativeness	—	.31
disorientation	—	.41
17-KGS with		
somatic concern	—.38	—.39
conceptual disorganization	.30	.45
depressive mood	—.38	—.37
excitement	.42	.56
anxiety	—	—.34
withdrawal	—	.34
grandiosity	—	.44
unusual thoughts	—	.33

Only correlations of possible significance are noted.

TABLE IV

Mean Levels of Steroid Excretion Before and After LSD and Mescaline in Normal Volunteers

Time	17-OHCS		17-KS		17-KGS	
	Before	After	Before	After	Before	After
LSD (N=14)						
9 AM–5 PM	5.0	5.9	7.5	7.4	8.8	12.1*
5 PM–7 AM	4.6	4.8	6.1	5.1	10.7	11.1
9 AM–7 AM	9.5	10.7	13.6	12.5	19.5	23.2*
Mescaline (N=10)						
9 AM–5 PM	2.3	3.0	6.6	6.9	4.5	5.1
5 PM–7 AM	2.0	2.8	8.7	10.3	6.2	8.0*
9 AM–7 AM	4.4	5.7	15.1	17.3	10.6	13.1

All values in mg.
* $P<.05$ or less, t-test of correlated means.

sociated with any meaningful rise in plasma cortisol levels. It is of some interest that both subjects with aberrant elevations after treatment had clearly apparent causes. One experienced a faint and thought he had undergone a heart attack, becoming most anxious; on a prior trial with synhexyl, he had shown only minor changes in steroid levels. The other, during his first trial with synhexyl, became quite frightened; he did not report back for a second trial with THC. Thus, while acute fear and anxiety may cause striking elevations in plasma cortisol levels, the usual mood changes from marihuana-like drugs were not associated with changes of significant degree.

Attempts were made to correlate cortisol levels and changes in cortisol levels with levels of plasma free fatty acids (FFA), circulating eosinophils, and total leukocyte counts. Cortisol levels were not correlated with FFA levels (.06), were weakly correlated negatively with eosinophil counts (−.15), but were significantly correlated with total leukocyte counts (.38). Changes in plasma cortisol levels correlated slightly better, but still not significantly, with changes in FFA (.18) or eosinophil counts (−.37); once again, total leukocyte counts were correlated significantly (.48).

Discussion

Our difficulties in the present study of relating the severity of schizophrenic illness to any measure of steroid excretion are similar to the experiences of others.[1] Neither before nor after treatment was there any clear relationship between the excretion of steroids and the severity of illness. Because the actual shifts in steroid excretion fell mostly within narrow ranges, one could not use the positive relationship between increase in steroid excretion and clinical improvement as a clinical laboratory indicator. A high initial level of steroid excretion, even though not necessarily related to an increased severity of illness, tended to mitigate against great clinical improvement. A number of psychotic symptoms seemed to be correlated positively with levels of steroid excretion. In general, schizophrenic patients had relatively normal steroid excretion values; the variance in them did not seem to be especially large, and it was considerably smaller than that reported in a previous series of chronic schizophrenics.[7]

Conclusions about the relationship of steroid excretion to the symptom of depression are limited by the fact that depression in schizophrenics could conceivably be different from that in patients with primary depressive illnesses. Still, these results showed a consistent negative correlation between this symptom and 17-OHCS or 17-KGS excretion. These findings are different from the usual positive correlations reported repeatedly in depressive patients.[2,4,5]

The psychotomimetic drugs LSD and mescaline, despite producing marked changes in the mood of patients, produced relatively few changes in steroid excretion. Most fractions tended to increase, but only 17-KGS did so to a significant degree. One would ordinarily describe this change as a nonspecific indicator of "stress," yet correlations with clinical or physiologic indicators of stress were poor.

Plasma levels of cortisol were little influenced by tetrahydrocannabinol (THC) or synhexyl despite the numerous effects of these drugs on mood. Only in two subjects, who showed acute fear or anxiety, were the levels sharply raised. Plasma cortisol levels or changes in such levels were not well correlated with plasma free fatty acid levels, were weakly correlated negatively with circulating eosinophils, but were consistently correlated positively with total leukocytes.

Summary

Urinary excretion of steroids or plasma steroid levels were measured in situations in which psychic change was expected. In 22 newly admitted schizophrenics observed over a six-week period, excretion of steroids was generally normal and showed little relationship to the severity of illness. Increases in steroid excretion were correlated with improvement, but not to any clinically useful degree. Some psychotic symptoms were correlated positively with increased steroid excretion. The symptom of depression in schizophrenics, unlike that in depressed patients, was negatively correlated with steroid excretion. The psychotomimetic drugs LSD and mescaline produced slight increases in 17-ketogenic steroids (17-KGS), but this sign of possible "stress" was poorly correlated with other clinical or physiologic signs of stress. Tetrahydrocannabinol and synhexyl, two marihuana-like compounds, had no appreciable effect on plasma cortisol levels in the absence of secondary fear or anxiety. This lack of change might be consistent with the generally sedative and euphoriant effects of these drugs.

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