A.M.A.Arch.gen.Psychiat. 2, 89-93 (1960).

Lysergic Acid Diethylamide (LSD-25) Antagonists

III. Modification of Syndrome by Prior Administration of Prednisone

HAROLD A. ABRAMSON, M.D., Cold Spring Harbor, N.Y., and BERNARD SKLAROFSKY, A.B., Glen Cove, N.Y.

The influence of therapeutic doses of the corticosteroids on the mood is well known. More frequently a euphoric rather than a depressed state is encountered. The psychic effect of drugs like cortisone and prednisone has not systematically been investigated in terms of their role in the therapy of illness in general, or in mental illness itself, although some important data are available.[1-3]

This report deals with the result of 49 experiments designed to test the effect of prednisone on the model psychosis produced by lysergic acid diethylamide (LSD-25) in man. It has been found that prednisone administered for three to seven days proir to the patient's taking LSD either reduced or eliminated anxiety due to the drug, without diminishing other symptoms usually induced by LSD, as measured by a questionnaire previously used in this series of experiments.

Method

The doses of both prednisone and LSD-25 were not known to the subjects. Controls with placebo capsules indistinguishable from the capsules containing the prednisone were employed. Both placebo and prednisone capsules were taken at home by the subjects for from three to seven days, during which time the subjects continued with their daily tasks. Experiments were conducted in a social setting during the evening from about 7 p.m. to 1 a.m., as reported previously.[4] Five subjects familiar with the LSD experience (two years of prior experiments) were employed. These subjects could, in general, detect 25μg. of LSD-25. The three male and two female subjects were paid $20 per experimental session. The subjects filled out their own questionnaire to evaluate the effects.

Results

The Table itemizes the effects of the prior administration of prednisone on the LSD reaction in five nonpsychotic subjects. As indicated in the Table, prednisone was administered from three to seven days when the dose of LSD was 25μg. or more. In nine experiments in which placebo capsules were administered for several days preceding LSD, anxiety occurred in seven out of nine experiments following LSD. When LSD-25 itself was administered without prior administration of either a placebo or prednisone, the usual LSD responses, including anxiety peculiar to each particular subject, occurred in all cases (10 out of 10 times). When prednisone was administered in 30 experiments, anxiety was either eliminated or markedly decreased in 23 instances.

Analysis of the number of responses to the questionnaire shows that the minimum number of responses to LSD-25 following prior administration of prednisone was roughly equal to the number of responses obtained when the placebo was administered or when nothing at all was administered. The mean number of responses to the questionnaire averaged for all five subjects is 17.6 for the placebo, 18.9 when nothing was administered, and 18.9 for prednisone administration.

Subject A showed anxiety about as often with prednisone as without predni-

Submitted for publication June 9, 1959.

From the Biological Laboratory, Cold Spring Harbor, Long Island, and the Community Hospital at Glen Cove.

This research has been supported by grants from the Josiah Macy, Jr. Foundation, New York, and the Foundation for Research in Pulmonary Disease, New York.

Effects of Prior Administration of Prednisone on LSD Reaction

Subject	Date	Prednisone, Mg.	No. Days Administered	LSD	Total Questionnaire Responses Pt. I	Pt. II	Comments
A	11/18/55	40	2	15	22	0	Strong phys. reaction; no anxiety
	1/27/56	Placebo	3	25	18	0	Subdued 25μg. phys. reaction; no anxiety
	2/10/56	50	4	25	20	0	Strong phys. & psych. reaction
	12/ 2/55	70	3	25	14	1	Mild phys. reaction; no anxiety
	2/24/56	120	4	25	22	0	Strong phys. reaction; no anxiety
	3/ 9/56	Placebo	4	25	14	0	Normal 25μg. reaction
	12/16/55	165	5	25	22	1	External stress situation intensified phys. reaction
	3/30/56	110	7	25	26	0	Strong phys. reaction; ambivalent mental attitude
	3/16/56	0		50	21	0	Normal 50μg. reaction
	3/23/56	160	6	50	26	4	Slightly heightened phys. reaction; no anxiety
	5/25/56	0		35	24	0	Normal 35μg. reaction; anxiety
B	11/18/55	70	3	15	16	0	Strong phys. reaction; no anxiety
	1/27/56	Placebo	4	25	22	15	Strong phys. reaction; anxiety
	2/10/56	50	4	25	19	18	Strong phys. reaction; no anxiety
	12/ 2/55	90	3	25	10	6	Mild phys. reaction; no anxiety
	2/24/56	120	4	25	20	18	Strong phys. reaction; no anxiety
	3/ 9/56	Placebo	4	25	20	4	Mild phys. reaction; no anxiety
	12/16/55	165	5	25	15	3	Severe phys. reaction; no anxiety
	3/16/56	0		50	34	8	Strong phys. & psych. reaction
	3/23/56	160	6	50	28	10	Strong phys. reaction; no anxiety
	5/25/56	0		35	20	2	Normal 35μg. reaction
C	11/18/55	85	3	15	6	1	Normal 15μg. reaction; anxiety
	1/27/56	Placebo	4	25	16	0	Strong phys. reaction; anxiety
	2/10/56	50	4	25	17	1	Strong phys. reaction; anxiety
	12/ 2/55	70	3	25	12	2	Mild phys. reaction; less anxiety
	2/24/56	120	4	25	22	3	Strong phys. reaction; no anxiety
	3/ 9/56	Placebo	4	25	11	0	Mild phys. reaction; some anxiety
	12/16/55	165	5	25	10	1	Normal 25μg. phys. reaction; some anxiety
	3/30/56	110	7	25	7	0	Mild phys. reaction; no anxiety
	3/16/56	0		50	12	1	Mild 50μg. phys. & psychol. reaction
	3/23/56	160	6	50	12	1	Mild phys. reaction; no anxiety
D	11/18/55	70	3	15	3	0	Normal 15μg. reaction
	2/10/56	50	4	35	2	0	Very mild reaction
	12/ 2/55	85	3	25	11	0	Strong phys. reaction; no anxiety
	2/24/56	120	4	35	13	0	Strong phys. reaction; no anxiety
	3/ 9/56	Placebo	4	35	12	1	Strong phys. & psych. reaction
	3/30/56	110	7	35	13	0	Strong phys. reaction; some anxiety
	3/16/56	0		50	14	0	Strong phys. reaction
	3/23/56	150	6	50	14	0	Strong phys. reaction; no anxiety
	5/25/56	0		35	15	0	Normal 35μg. reaction
E	1/27/56	Placebo	4	35	19	0	Normal 35μg. reaction
	2/10/56	50	4	35	15	0	Normal 35μg. reaction
	12/ 2/55	0		25	11	3	Normal 25μg. reaction
	2/24/56	120	4	35	22	0	Strong phys. reaction; no anxiety
	3/ 9/56	Placebo	4	35	11	0	Mild reaction
	12/16/55	165	5	35	24	2	Severe phys. but mild psych. reaction
	3/30/56	110	7	35	12	0	Mild reaction
	3/16/56	0		50	17	1	Normal 50μg. reaction
	3/23/56	160	6	50	15	4	Strong phys. reaction; no anxiety
	5/25/56	0		35	5	0	Normal 35μg. reaction

sone. Subject B never had anxiety when prednisone was administered. Subjects C, D, and E showed anxiety in the presence of prednisone between 20% and 40% of the time, as compared with 100% of the time when a placebo or nothing was administered. Since the production of anxiety is a complicated process, it appears that under our experimental conditions there is a smaller proportion of anxiety when prednisone is given prior to LSD administration.

In spite of the large number of experiments presented, there are serious limita-

tions attached to the data of this type, and it would be desirable to redesign the experimental method so that more statistically significant data might be obtainable. Qualitatively, however, there is no doubt that in these experiments the prior administration of prednisone reduces anxiety, as compared with the placebo administration or with no prior medication.

Comment

The casualness of the group toward their LSD symptoms when they were treated with prednisone was most remarkable. It differs markedly from the effects of oral chlorpromazine in the LSD reaction, in which the number of symptoms may be the same or increased, with often, however, an increased anxiety state developing.[5]

The primary effect of the prednisone may be restated as follows: The subjects became comparatively euphoric with respect to the autonomic storm produced by LSD. This euphoriant effect of prednisone is, of course, well known. Rather surprising, however, is the fact that prednisone acted specifically on the mood, and not on any other phase of the LSD response, as measured by the questionnaire. This specificity of action by prednisone may lead to speculation on the mechanism by which LSD might act. For example, does LSD affect an enzyme system which leads to mobilization of potassium in those parts of the brain producing anxiety as part of the LSD reaction? And does prednisone block this reaction? In general, prednisone, in the doses used, may decrease intracellular potassium and increase water and salt (NaCl) retention. Let us discuss this aspect of the reaction briefly.[6]

1. In what way is a disturbance of electrolyte equilibrium of this type connected with the activity of the nervous system?

2. How may this electrolyte disturbance be influenced by corticosteroids?

A. Corticosteroid increase leads to increase of extracellular fluids and sodium, depletion of intracellular potassium and phosphate, hypokalemia, and, occasionally, extracellular alkalosis.

B. Corticosteroid decrease, if severe, leads to extracellular dehydration, acidosis, hyperkalemia, hyperphosphatemia, and hyponatremia.

An interesting review by Quarton, Clark, Cobb, and Bauer[7] covers the complicated mechanisms proposed for the action of corticosteroids in mental processes. Hoefer and Glaser[8] report significant changes in the electroencephalogram in patients given corticotropin. The electroencephalographic changes usually appeared three to five days after treatment started and consisted in reduction of amplitude, regularity, and continuity of the basic alpha activity and the appearance of large amounts of slow activity (3 to 7 cps), occurring at random or in bursts, and often increased in incidence and amplitude by hyperventilation. Although other workers have failed to confirm this high incidence of abnormality developing on corticotropin, changes in the electroencephalogram were also reported by Pine, Engel, and Schwartz.[9] Nekhorocheff[10] attributes abnormality in the electroencephalogram in children to hormone therapy with steroids. It is well known that the electroencephalogram of animals and children becomes abnormal with adrenalectomy and in Addison's disease.

In Addison's disease, administration of corticosteroids leads to electroencephalographic changes (alpha-rhythm slowing and beta-wave decrease), as well as electrocardiographic changes.[11] Improvement in the electroencephalogram may be observed within a few days after the administration of 50 to 100 mg. of cortisone daily. Similarly, the electrical activity of the conduction system of the heart in Addison's disease is modified by cortisone. This was evidenced by restoration of the vertical position of the T wave and decrease in the P-R interval, as well as shortening of a prolonged Q-T interval. Normal subjects on large doses of cortisone may have

electrocardiographic changes unless supplementary potassium is administered.[12]

As mentioned, the electrolyte equilibrium is changed by corticosteroids. There is no doubt that the intracellular structure modifies the electrical activity of the brain. Clinical reports indicate that potassium deficiency may be of importance in the occurrence of mental disturbances from corticosteroids and that the administration of potassium may correct this disturbance.[13]

The fluctuations in our data, especially in regard to Subject A, who did not consistently show a decrease in anxiety, fit in with the action of prednisone observed clinically. Unpleasant moods, irritability, and depression may also be produced by prednisone. It is possible, therefore, that our observations that the LSD reaction was severe would fit in with the depressant effect of prednisone working simultaneously with its euphoriant effect. Directly related to these experiments of prednisone on the LSD reaction are those of Mirsky.[14] Mirsky has studied the effects of corticotropin upon conditioned behavior in monkeys. Animals treated with corticotropin, in contrast to the controls, were more aggressive and adventurous in their behavior, and were able to overcome effects determined by previous conditioning to fear. Extinction of an avoidance reaction worked more rapidly in another group treated with corticotropin. The emotional meaning of unpleasant experiences was modified by treatment, in that the experience became less anxiety-producing. In our subjects, prednisone led to the same type of denial of fear in spite of the presence of a severe LSD response.

It appears to be desirable, on the basis of these data, to reinvestigate the role of electrolyte equilibrium in the production of and in the treatment of the psychoses, as well as of the neuroses, where anxiety prevents psychotherapy. Since there is such a diversity of symptomatology, the control of anxiety might well be achieved through closer control of electrolyte balance. The new types of corticosteroids available broaden this field of investigation considerably.

Summary

Prednisone was administered to five nonpsychotic adults for three to seven days before a lysergic acid diethylamide (LSD-25) psychosis was induced.

The dose of LSD was 25μg. to 50μg.

In this dose range prednisone either reduced or eliminated anxiety in four of the subjects without changing the usual LSD symptomatology, as measured by a standardized questionnaire.

Since prednisone diminishes experimental anxiety produced by LSD, it appears desirable that the effect of LSD on clinically occurring anxiety, especially in the psychotic states, be reinvestigated systematically.

Biological Laboratory, Long Island Biological Association.

REFERENCES

1. Hardwick, S. W.; Pearse, J. J., and Petrow, V.: 6β-Hydroxy-3:5-Cyclopregnan-20-one in Mental States, J. Ment. Sc. 103:835, 1957.
2. Clark, L. D., and Clark, L. S.: Effects of Cortisone on LSD-25 Intoxication in Schizophrenic Patients, J. Nerv. & Ment. Dis. 123:561, 1956.
3. Bellak, L., and Benedict, P. K., Editors: Schizophrenia: A Review of the Syndrome, New York, Logos Press, Inc., 1958, pp. 206-207.
4. Abramson, H. A.; Jarvik, M. E.; Kaufman, M. R.; Kornetsky, C.; Levine, A., and Wagner, M.: Lysergic Acid Diethylamide (LSD-25): I. Physiological and Perceptual Responses, J. Psychol. 39:3, 1955.
5. Abramson, H. A.: Neuropharmacology, Transactions of the First Conference, The Josiah Macy, Jr. Foundation, New York, 1955, pp. 33-35.
6. Roberts, K. E., and Randall, H. T.: The Effect of Adrenal Steroids on Renal Mechanisms of Electrolyte Excretion, Ann. New York Acad. Sc. 61:306, 1955.
7. Quarton, G. C.; Clark, L. D.; Cobb, S., and Bauer, W.: Mental Disturbances Associated with ACTH and Cortisone: A Review of Explanatory Hypotheses, Medicine 34:13, 1955.
8. Hoefer, P. F. A., and Glaser, G. H.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J.A.M.A. 143:620, 1950.

9. Pine, I.; Engel, F. L., and Schwartz, T. B.: The Electroencephalogram in ACTH and Cortisone Treated Patients, Electroencephalog. & Clin. Neurophysiol. 3:301, 1951.

10. Nekhorocheff, I.: L'EEG des enfants traités par l'ACTH ou la cortisone, Electroencephalog. & Clin. Neurophysiol. 4:248, 1952.

11. Thorn, G. W.; Sheppard, R. H.; Morse, W. I.; Reddy, W. J.; Beigelman, P. M., and Renold, A. E.: Comparative Action of Aldosterone and 9-Alpha-Fluorohydrocortisone in Man, Ann. New York, Acad. Sc. 61:609, 1955; in Transactions of Second Conference on Adrenal Cortex, edited by E. P. Ralli, New York, Josiah Macy, Jr. Foundation, 1951, pp. 164-1740.

12. Lepeschkin, E., and Surawicz, B.: Electrocardiographic Aspects of Hypopotassemia, Heart Bull. 7:114, 1958.

13. Ransohoff, W.; Brust, A. A.; Reiser, M. F.; Mirsky, I. A., and Ferris, E. B.: Effect of Sodium and Potassium on the Metabolic and Physiologic Responses to ACTH, Proc. Cen. Soc. Clin. Res. 2386, 1950; J. Lab. & Clin. Med. 36:978, 1950.

14. Mirsky, A.: The Significance of Psychotic Responses to ACTH Therapy as Revealed by Studies in Monkeys, Proceedings Third ACTH Conference, edited by John R. Mote, The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 1954.