Clinical Syndromes and Biochemical Alterations Following Mescaline, Lysergic Acid Diethylamide, Psilocybin and a Combination of the Three Psychotomimetic Drugs

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AN EARLIER STUDY of mescaline, lysergic acid diethylamide (LSD-25) and psilocybin in the same subjects indicated a considerable similarity between the three drugs in their clinical syndromes, effects on color perception, and some selected biochemical measurements.[1] Two other studies have also compared the three drugs, showing substantially similar clinical syndromes.[2,3] The former study also emphasized the similar autonomic and neurologic effects of the drugs. All studies showed that psilocybin differed slightly from the others in having a briefer duration of action and in producing a slightly less intense clinical reaction. A further study demonstrating cross-tolerance between mescaline and LSD-25 reaffirmed the close relationship of their probable mechanisms of action.[4]

We were curious to see if combining these three similar drugs would alter their over-all clinical and biochemical effects, either by synergistic or antagonistic action. Furthermore, the present study provided an opportunity to replicate and expand our previous obseravtions of the clinical syndromes and biochemical effects of these three drugs.

Methods

Twenty-four volunteer subjects were treated with each of three psychotomimetic drugs, alone and in combination. As one subject did not complete all drug trials, an additional subject was re-assigned his sequence. The three drugs and doses were: lysergic acid diethylamide (LSD-25), 1.5 mcg./K; mescaline, 5 mg/K; psilocybin, 225 mcg/K. One-third the single dose of each drug was used in the combination, the combined fractional doses being administered simultaneosuly. Drugs were administered in white capsules without the subject or experimenter knowing which treatment was being given on any occasion. Assignment of treatments at weekly intervals followed a latin-square order.

Subjects were all men beween the ages of 21 and 40 years, in good general health. A previous history of emotional problems, psychotherapy or psychotomimetic drug experience was disqualifying. Prior to being accepted for the study, they were interviewed and given a series of psychologic tests, the hope being that this procedure would eliminate subjects with overt emotional disorders. With two or three exceptions, we feel this technique accomplished its purpose.

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Clinical Study

Three sources of data were used to assess clinical syndromes produced by the drugs, each based on patient reports. A 75-item questionnaire regarding the psychotomimetic drug experience was devised by expanding a previous 43-item questionnaire used in earlier studies.[1,5] Nineteen items were specifically concerned with somatic effects, 16 with perceptual and 40 with psychic effect: Answers ranged from "no" to "whole lot" on a four-point scale. The questionnaire was administered six and one-half hours after the drug had been given, being applicable to the entire trial.

The Clyde Mood Scale consists of 133 cards, each bearing an adjective describing a feeling or state of mind.[6] Six separate mood factors can be derived and scored: Friendly, energetic, clear-thinking, aggressive, jittery and depressed. Subjects sort the cards into four piles ranging from "not at all" to "extremely," depending on the applicability of the word to his feelings at the moment, the whole test taking only a few minutes for the subject to administer to himself. This test was performed at the very beginning of the test session and again near the end of the predrug data collection, usually a period of about one hour. It was then repeated at one, three and six hours after administration of the drug.

The Hoffer-Osmund Diagnostic (HOD) test has been proposed as a simple device for distinguishing patients suffering schizophrenic reactions and organic brain syndromes from each other and from normals.[7] It consists of statements on cards covering various areas of thinking, perception and somatic complaints. Patients are given a shuffled deck of cards and directed to sort them into two piles, "true" and false." Many of the statements are qualified by degree adjectives, such as "often," "frequently," "sometimes," "rarely," and the like. As the test was designed mainly for clinical diagnosis rather than for drug trials, some items were not appropriate and were deleted; others required slight modifications of wording. One-hundred-ten of these items were retained for the present study. The test was administered approximately seven hours after the drug was given, at a time when effects had almost completely subsided, but were still fresh in the subject's memory. He was instructed to sort the deck into appropriate piles depending upon whether the statement on the card described any experience during the entire immediately preceding drug trial.

Laboratory Study

Subjects were instructed to fast after the evening meal, except for water. Smoking was to be omitted the morning of the drug trial. At 7:00 A.M., the subjects were to empty their bladders, take 600 ml. of water and begin collection of a timed urine specimen. Additional water was given if urine flow did not soon begin. From 7:30 to 9:00 A.M., preliminary psychologic studies were done, blood was drawn for base-line laboratory determinations, and the first two-hour urine collection completed. Another 500 ml. of water was administerd at the same time as the drug. During the entire pre-treatment period,

subjects were reasonably inactive physically and emotional stress was reduced as much as circumstances permitted.

Additional blood specimens were drawn one-half, one, two, and four hours following drug. Base-line determination included plasma creatinine, glucose, and free fatty acids (FFA), serum calcium, phosphorus and triglycerides. Free fatty acids were done by a modified Dole technique.[8,9] Triglycerides followed the method of Van Handel and Zilversmit.[10] Determinations of plasma FFA and glucose were repeated at all subsequent time periods. Determinations of serum triglycerides were repeated at one, two and four hours after drug. Two hours after drug, the second timed specimen of urine was collected and concomitantly serum calcium and phosphorus were measured. Both timed urine specimens were used for determinations of total creatinine, phosphorus and calcium excretion for calculating clearances of each of these moieties. Urinary calcium was measured by a specifically developed technique.[11] Total circulating eosinophils were counted just prior to drug and two hours later.

Results

Clinical Study

In general, LSD produced somewhat more positive responses than other treatments, largely based on increased psychic and perceptual effects. Mescaline produced slightly increased positive answers on questions regarding somatic effects. Psilocybin and the combination had the least overall effects, being strikingly comparable. Analysis of variance indicated no significant differences between drugs in eliciting positive questionnaire responses. Sequence of administration had no effect on the number of positive responses.

Items in the questionnaire most often answered positively were concerned either with somatic effects (dizziness, weakness, drowsiness, shaking of hands, nausea) or with evidence of varying degrees of intellectual impairment (difficulty in attention or verbal expression, poor immediate memory). On the other hand, a surprising number of items of perceptual nature were answered negatively (synesthesia, disturbed depth perception, organized visual hallucination. The same was true of those psychic manifestations most psychotic in nature (auditory hallucinations, paranoid thoughts, depersonalization, distortion of body image). In either instance, differences between treatments were not great.

Data from the Clyde Mood Scale showed a rather striking similarity between mean scores on the two pre-test trials (table 1). Equally striking were the rather similar patterns of responses evoked by the various drugs. The first three factors (friendly, energetic, clear-thinking), which might be thought of as "favorable," were decreased by the drugs in the first two hours, the effects occasionally persisting to the fourth hour. Mescaline had the greatest tendency to do this; LSD and psilocybin less. The last three factors (aggressive, jittery, depressed), which might be thought of as "unfavorable," tended to be increased by the drugs, both early and late. While these results

Table 1.—*Mean Scores on Clyde Mood Scale Done by Subjects Twice Prior to Drug and One, Three and Six Hours After*

		Pre-Drug		Post-Drug		
		1st	2nd	1st	2nd	3rd
Mescaline N = 24	Friendly	47.6	47.1	40.1*	45.3	48.0
	Energetic	49.7	48.7	41.1*	45.5	45.2
	Clear-thinking	53.2	52.9	43.4*	43.7*	48.8
	Aggressive	45.1	45.0	46.8	50.2*	47.9
	Jittery	44.9	45.2	54.0*	52.2*	49.4*
	Depressed	44.3	43.6	49.2*	48.4*	46.5
LSD-25 N = 24	Friendly	46.6	45.8	43.9	45.6	47.1
	Energetic	48.8	46.8	47.1	46.0	46.7
	Clear-thinking	51.8	49.2	47.4	42.8*	50.0
	Aggressive	44.7	44.0	44.5	50.0*	48.0
	Jittery	44.5	45.1	49.0*	53.8*	48.8*
	Depressed	42.1	41.7	44.0	48.2*	46.4*
Psilocybin N = 24	Friendly	46.9	46.7	44.6	44.7	46.5
	Energetic	48.3	48.2	44.4	44.7	46.0
	Clear-thinking	53.9	52.1	44.8*	47.0*	50.1
	Aggressive	43.7	43.6	48.4*	49.8*	45.1
	Jittery	45.9	45.0	51.3*	47.7	44.1
	Depressed	42.8	42.7	46.7*	47.7*	43.3
Combination N = 24	Friendly	45.9	45.2	41.9	47.0	47.2
	Energetic	48.1	48.0	44.0	46.4	46.2
	Clear-thinking	52.4	51.7	45.3*	43.8*	51.5
	Aggressive	44.5	44.2	48.6*	52.4*	46.5
	Jittery	45.2	45.2	50.8*	49.1	46.0
	Depressed	42.9	42.7	46.9*	47.5*	44.8

*$p < .05$ or less, analysis of variance.

are not too surprising, they are at variance with many other accounts of the effects of psychotomimetic drugs.

The HOD test was administered after 87 drug trials. Responses which were most often positive consisted predominately of perceptual alterations involving fluctuating time sense, increased auditory and tactile acuity, and visual effects including organized hallucinations. Somatic effects were primarily those of anxiety and fatigue. The predominant psychic effect was one of unreality and difficulty in maintaining attention. Those statements least often answered positively included most relating to frank psychotic symptoms such as mis-perceptions, auditory hallucinations, somatic delusions, depersonalization, paranoid delusions, and changes in affect.

Results from the HOD tests obtained from our 22 subjects who received LSD were compared with 17 of Hoffer's.[3] Our subjects reported significantly less positive answers on 21 cards, mainly those in the perceptual area but including some indicating impairment of intellect ("mind goes blank," "mind races"), depersonalization ("feel I have left my body") or paranoid thoughts ("people watch me more," "people's eyes are frightening"). Our subjects reported more visions of people with the eyes closed. These differ-

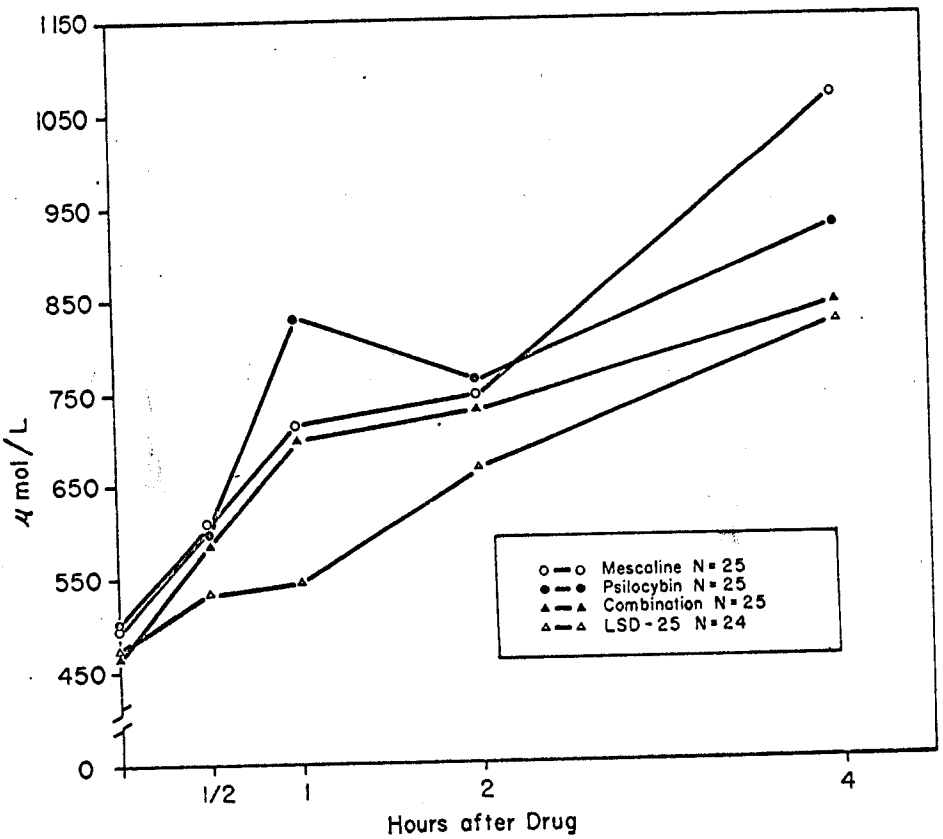

Fig. 1.—Mean rise in plasma free fatty acids following psychotomimetic drugs.

ences, which indicate increased positive responses in the Hoffer group as compared with ours, could be due to different selection of subjects, different experimental settings or different expectations regarding the experiment; doses of drug were comparable.

Laboratory Study

Free fatty acids rose consistently following each drug treatment. The types of mean responses were roughly similar between the four treatments given (fig. 1). Somewhat surprisingly, LSD-25 produced the least rise throughout while psilocybin produced a more substantial rise; these findings were somewhat opposite the rank of the drugs in producing clinical effects. Mescaline produced the greatest elevations, usually late, consistent with its somewhat longer duration of clinical effect. All increases in FFA levels were statistically significant as compared to base-line levels.

As an FFA elevation following drugs might be considered a physiological indicator of stress, we were curious to see if it correlated with data from the clinical questionnaire. The average of two- and four-hour levels of FFA was used to calculate the per cent change from the base-line and patients were rank-ordered according to this degree of change. A similar ranking was based

on total scores on the questionnaire, as well as scores on the psychic symptoms portion. Non-parametric analysis of these rankings revealed no apparent correlation of FFA increase with the amount of positive answers to the entire questionnaire or the psychic symptoms portion.

All treatments depressed creatinine clearance to a slight but significant degree (see table 2). Clearance of phosphorus and calcium were assessed by means of their ratio to creatinine clearance, to compensate for the slightly decreased glomerular filtration rate. Correcting for this, clearance of phosphorus was still significantly decreased by each drug treatment. A parallel rise in serum phosphorus levels indicated an actual retention of inorganic phosphorus. No evidence of a reciprocal relationship between phosphorus and calcium clearance could be demonstrated, ruling out a parathormone-inhibiting effect. Actually, calcium clearance also tended to be depressed, though only significantly in the case of the drug combination. Little apparent change was found in serum levels of calcium as the actual amounts of calcium excreted were quite small.

The effects of these four drug treatments on plasma glucose and serum triglycerides were negligible. Levels of circulating eosinophils showed a constant tendency to decline over the first two hours of treatment, though not to a significant degree from any single treatment.

Discussion

Once again, LSD-25, mescaline and psilocybin produced similar clinical syndromes when each was given to the same subjects under similar conditions. Doses of LSD-25 and psilocybin were slightly higher than in a previous study (1.5 mcg/K and 225 mcg/K as compared with 1.0 and 150 respectively) and probably more equivalent to the dose of mescaline (5 mg/K) used in both. Combining fractional doses of the three drugs appeared to produce an additive effect, the intensity and quality of the clinical syndrome being comparable to full doses of either drug alone; no evidence was found either for potentiation or antagonism.

Release of free fatty acids following oral administration of these drugs has again been demonstrated. After a twelve-hour fast, FFA levels rise only slowly during a subsequent four-hour period, usually not more than 25 per cent above base-line values. Therefore, the increase in the present study attributable to the drugs is believed to be quite real. Further substantiation for this belief has been afforded by a subsequent experiment in which the FFA elevation four hours after LSD-25 was comparable to that of epinephrine after 30 minutes, the only difference being that effect produced by LSD-25 was slower but more sustained. Unfortunately, FFA as a measure of emotional stress did not correlate with the severity of the clinical syndrome as measured by subjective reports. This disparity could merely be a reflection of the importance of the psychologic "set" of the subject over the physiologic response in determining what is reported. On the other hand, the mechanism of FFA release might be mediated by catecholamine release or neurogenic stimulation which is independent of emotional stress.

Table 2.—*Phosphorus and Calcium Clearances and Serum Levels Before and Following Treatment with Three Psychotomimetic Drugs, Alone and Combined, Two-Hour Measurements*

	LSD-25		Mescaline		Psilocybin		Combination	
	0-Hours	2-Hours	0-Hours	2-Hours	0-Hours	2-Hours	0-Hours	2-Hours
Creatinine Cl ml./min. N = 24	138	120†	139	125†	147	124†	135	123*
P Cl/CrCl x 100 N = 24	14.8 (5.7)	10.4 (5.0)‡	12.1 (4.2)	7.6 (3.5)‡	12.9 (4.0)	9.3 (3.7)‡	12.5 (4.2)	8.7 (5.1)†
Serum P (mg. %) N = 24	3.39 (.48)	3.55 (.52)*	3.39 (.39)	3.45 (.45)	3.21 (.39)	3.52 (.39)‡	3.42 (.44)	3.60 (.45)†
CaCl/CrCl x 100 N = 10	.77 (.43)	.80 (.70)	1.03 (.82)	.80 (.52)	1.09 (.78)	.94 (.73)	1.02 (.59)	.69 (.42)
Serum Ca (mg. %) N = 10	9.32 (.65)	9.24 (.59)	8.92 (.48)	9.10 (.72)	9.27 (.77)	9.25 (.51)	9.18 (.82)	9.21 (.79)

*$p < .05$.
†$p < .01$.
‡$p < .001$, t-test of correlated means (2-tail).

In the earlier study, we thought that the decrease in urinary excretion of inorganic phosphorus which followed these drugs could be accounted for by decreased glomerular infiltration rate. While the present study indicates that the latter does occur, it also indicates that excretion of inorganic P is diminished still further than can be accounted for by decreased creatinine clearance. Were this difference accounted for by inhibition of parathyroid hormone, one might have expected to see an inverse relationship with calcium excretion, but such was not the case. One can also postulate an inhibiting effect on adrenocortical hormones or an increased cellular retention of phosphate, though increased serum levels do not support the latter idea.

We could not confirm our previous finding of a decrease in circulating eosinophils following these drugs, though the tendency was in this direction. The conflicting reports in the literature about the effect of these drugs on eosinophils doubtless reflects an inconstancy of this effect.

Summary

Twenty-four volunteer subjects were treated with mescaline (5 mg./K), LSD-25 (1.5 mcg./K), psilocybin (225 mcg./K) or a combination of all three drugs using one-third doses of each. The four treatments were given orally in a latin-square order.

Clinical effects as assessed by a 75-item questionnaire, the Clyde Mood Scale and the Hoffer-Osmund Diagnostic (HOD) test were remarkably alike for all 4 treatments. Somatic effects or varying degrees of intellectual impairment were most apparent on the questionnaire; many perceptual and psychic symptoms were denied. Of the six factors on the Clyde Mood Scale, three (friendly, energetic and clear-thinking) were uniformly decreased by the drugs in the first two to four hours; three other factors (aggressive, jittery and depressed) tended to be increased by the drugs, both early and late. Questions most often answered positively on the HOD test were concerned with somatic effects or perceptual alterations (fluctuating time sense, increased auditory and tactile acuity, and visual effects); once again, frankly psychotic symptoms were seldom reported.

All treatments increased plasma free fatty acids, but the degree of mobilization of FFA was not related to the severity of the clinical reaction. All treatments decreased urinary creatinine clearance slightly; clearance of inorganic phosphorus was more substantially reduced, along with increased serum phosphorus. Little effect was noted on urinary calcium excretion, serum calcium, plasma glucose, or serum triglycerides. Levels of circulating eosinophils declined, but not to a significant degree. The biochemical alterations probably represent nonspecific reactions to stress.

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