Psychopharmacologia (Berl.) 8, 331-339 (1966).

From the Department of Medicine, Section on Clinical Pharmacology, University of Kentucky Medical Center, and the National Institute on Mental Health, Addiction Research Center, Lexington, Kentucky, U.S. Department of Health, Education and Welfare, Public Health Service/U.S.A.

Effect of Alkaloids of Ololiuqui in Man

By
HARRIS ISBELL and C. W. GORODETZKY

(Received June 11, 1965)

In 1941 SCHULTES reported that Indians in Mexico ingested the seeds of a wild morning glory, called ololiuqui, either in religious rituals or in the therapy of disease. The plant was identified as *Rivea Corymbosa* (SCHULTES 1941). MACDOUGALL (1960) reported that another variety of morning glory (*Ipomea violacea*, also known as *Ipomea tricolor*) was used in a similar fashion. According to WASSON (1963), the seeds of *Ipomea violacea* are more potent than those of *Rivea Corymbosa*. Because of SCHULTES' report, OSMOND (1955) ingested 14 to 100 seeds (chewed or ground to a powder) in a number of self experiments. He developed apathy, irritability, lack of energy and hypnagogic phenomena that disappeared after several hours. KINROSS-WRIGHT (1959) fed up to 125 seeds to 8 human volunteers without obtaining any subjective effects. ISBELL gave former addicts finely ground seeds of *Rivea Corymbosa* in doses ranging up to 6 g (approximately 300 seeds) and observed only slight sedation and nausea.

In 1960 HOFMANN and TSCHERTER (1960) reported the isolation of *d*-lysergic acid amide, *d*-iso-lysergic acid amide, and chanoclavine from seeds of *Rivea Corymbosa*. These authors took 2 mg of the crude extract of ololiuqui alkaloids and developed dreamy states, with alterations in the perception of colors and objects. HOFMANN (1963) further reported that the seeds of *Rivea Corymbosa* contained 0.012 percent of indole alkaloids, whereas seeds of *Ipomea violacea* contained 0.06 percent. He also found that in addition to *d*-lysergic acid amide, *d*-iso-lysergic acid amide, and chanoclavine, the seeds of both plants contained elymoclavine. Lysergol was found in *Rivea Corymbosa* and ergometrine in *Ipomea violacea*.

Some information is available concerning the subjective effects of *d*-lysergic acid amide. HOFMANN (1963) took 0.5 mg of this drug hypodermically and reported fatigue, sedation, and sleep. SOLMS (1956a, b) likewise found that *d*-lysergic acid amide caused decreased psychomotor activity, sedation, and sleep. ISBELL obtained similar results with

d-lysergic acid amide in former morphine addicts. HOFMANN (1963) experienced tiredness, apathy, and "mental emptiness" after 2.0 mg of *d*-isolysergic acid amide. Elymoclavine elicits excitation and central stimulation in animals (YUI 1958), but ISBELL found that elymoclavine caused chiefly sedative effects in former addicts.

Law enforcement officers and garden seed companies in the United States have recently become concerned because of reports in the lay press that students, psychologists and maladapted persons of Bohemian habits ("beatniks") were ingesting seeds of cultivated morning glories sold in garden supply shops. Some of the persons who report they have used the seeds state they have also taken LSD-25, mescaline, psilocybin, or peyote. COHEN (1964) has reported one case of suicide following ingestion of morning glory seeds, and INGRAM (1964) has recently described a psychic reaction after eating 250 seeds that was sufficiently severe to require hospitalization. Thus fears have arisen that a new type of potentially dangerous psychoactive drug abuse might be arising in the United States.

Because of the varying reports concerning the efficacy of the whole seeds of ololiuqui in inducing subjective effects, it seemed of interest to study the effects of the crude extract of alkaloids of ololiuqui prepared by HOFMANN and coworkers, since use of the extracts would avoid differences in absorption and potency of different lots of the seeds. Such a study would also be valuable in assessing possible behavioral pathology arising from ololiuqui abuse. A comparison of the effects of the crude extract of ololiuqui seeds with those of a mixture of synthetic alkaloids compounded in the same proportions might also shed light on the question as to whether the alkaloids identified in ololiuqui account for all the effects of the seeds. The purpose of this paper is to describe the autonomic and subjective effects of a crude extract[1] of the alkaloids of ololiuqui in man, and to compare the effects of the crude extract with those of a mixture of synthetic alkaloids[2] containing the drugs in the same percentages as

[1] We ware indebted to Dr. A. HOFMANN and coworkers of Basel, Switzerland, and to Dr. R. BIRCHER, Sandoz, Hanover, New Jersey, for this material, which was an extract of the alkaloids of *Ipomea violacea*. The material contained (in terms of the percentage present in fresh seeds): *d*-lysergic acid amide, 0.035 percent; *d*-isolysergic acid amide, 0.005 percent; chanoclavine, 0.005 percent; elymoclavine, 0.005 percent; and ergometrine, 0.005 percent. Total alkaloids amounted to 0.06 percent. For details on the method of extraction and analysis, see the paper of HOFMANN (1963).

[2] This mixture was supplied through the kindness of Dr. R. BIRCHER, Sandoz, Hanover, N. J. It consisted of 45 percent *d*-lysergic acid amide, 25 percent *d*-isolysergic acid, 10 percent ergonovine, 10 percent chanoclavine, 5 percent elymoclavine, and 5 percent lysergol. These percentages were calculated in terms of the bases and not the salts.

in the crude extract. In addition, the effects of both the crude and synthetic mixtures of ololiuqui alkaloids were compared with those of LSD-25 and placebo.

Methods

Subjects. Former opiate addicts who were serving sentences at the PHS Hospital in Lexington, Kentucky, for violations of the United States narcotic laws volunteered for the experiments. All were physically healthy males between 21 and 40 years of age, none of the patients presented any evidence of the major psychoses on psychiatric examination, all were familiar with the subjective effects of several kinds of psychoactive drugs, and all had been abstine frontm opiates for at least several months before the experiments were begun.

General Conditions. The experiments were carried out in the closed wards of the Addiction Research Center devoted to clinical research. The patients entered this ward the night before experiments were conducted and remained until the morning after experiments were completed. Observations were made by specially trained aides with long experience in observing the effects of psychoactive drugs.

Drug and Doses. Appropriate stock solutions of the crude alkaloidal extract (hereafter designated V-E-5), the synthetic mixture[1] (V-E-6) and LSD-25 were prepared in one percent tartaric acid solution and refrigerated in brown bottles. Doses were measured into medicine glasses with pipettes and diluted with 15ml of cherry syrup. The patients drank the mixture, rinsed the glass twice with water, and drank the rinsings. The cherry syrup served as the placebo. Drugs were always given at 8 a. m., with the patients fasting.

Observations. One hour before and 1, 2, 3, 4, 6 and 8 hours after the drugs were given, rectal temperatures, pulse rate, systolic and diastolic blood pressures and pupillary size were determined. Pupillary diameter was measured by comparing the size of the pupil with those of circles of known diameter, under conditions of constant light and accommodation. Measurements were made after patients had rested quietly in bed for 10 min.

In addition a questionnaire (Table 1) of 31 items was administered one-half hour before, and at $1^1/_2$, $2^1/_2$, $3^1/_2$, $5^1/_2$ and $7^1/_2$ hours after the drug was given. The questions were selected from a questionnaire that has been used extensively in evaluating responses to LSD-25 and other psychotomimetic drugs (ABRAMSON et al., 1955). Short mental status examinations were made two to three hours after the drug.

Statistical Analyses. The results for all subjects were tabulated and averaged for each measurement at each observation time. These tabulations permitted identification of the time of maximal (peak) effect. The

[1] See footnote [2], p. 332.

areas under the time-action curves for each measurement on each drug were calculated according to the method of WINTER and FLATAKER (1950) and means and standard errors calculated for the areas on each measurement for each drug. The significance of the differences between means was evaluated by the *t*-test for paired observations (EDWARDS 1964). The number of responses on the questionnaires were counted for each hour, for the entire time course, and for each individual question. Questions 3 through 31 were then ranked for each drug according to the relative magnitude of the total responses to each question, as shown in Table 1. Spearman rank order correlation coefficients were then calculated in order to compare the pattern of subjective effects (as measured by the questionnaire) of different pairs of drugs.

Experiments

Preliminary. Before definitive comparisons could be made, it was necessary to determine the effective dose range of both the extract and the synthetic mixture. Two patients were tested at a time. The first pair of men received 0.5 mg (total dose) of either V-E-5 or V-E-6. The second pair of men received 1.0 mg. The doses were gradually increased in this step-wise fashion until 5 mg of both V-E-5 and V-E-6 were given. Temperature, pulse rate, respiratory rates and subjective effects, as measured by the questionnaire, were monitored in these experiments. Urine analyses, tests of liver function, and blood counts were unaltered in these preliminary experiments. Subjective effects began to be reported with doses of 2 to 3 mg, but were not intense even with the 5 mg dose. No serious untoward effects were observed with any dose. Doses larger than 5 mg could not be studied because of limited supplies of both mixtures. The data obtained in these dose-ranging trials are not presented in this paper.

Definitive Experiments. Six patients received at weekly intervals in random, order 5.0 mg of the crude extract (V-E-5), 5.0 mg of the synthetic extract (V-E-6), 1.5 mcg/kg of LSD-25 (as tartrate), and placebo. The data obtained on these 6 patients are presented below.

Results

The results are summarized in Tables 1, 2 and 3. The autonomic effects of the two mixtures were quantitatively small. As compared with placebo (Tables 2 and 3), neither V-E-5 nor V-E-6 caused any statistically significant ($P < 0.05$) elevation in temperature, pulse rate, or systolic blood pressure. V-E-5 did not create any significant mydriasis, but did block the diurnal miosis seen after placebo. V-E-6 caused a slight mydriasis. In contrast, LSD-25 was followed by marked increases in temperature, systolic blood pressure, and pupillary size. The synthetic

Table 1. *Number of responses by question*

Question		Drug and Dose					
		LSD 1.5 mcg/kg		V-E-5 5.0 mg		V-E-6 5.0 mg	
		total	rank	total	rank	total	rank
1.	I feel the medicine	34		28		33	
2.	It is like a blank	0		0		0	
3.	It is like a golfball	0	27.5	4	8	4	10
4.	It is like coke	9	18	0	22.5	0	21.5
5.	It is like a reefer	12	16.5	1	14.5	0	21.5
6.	It is like LSD	12	16.5	0	22.5	0	21.5
7.	It is like dope	0	27.5	0	22.5	0	21.5
8.	I am nervous	23	5	0	22.5	8	7.5
9.	I am hungry	4	22.5	5	6.5	8	7.5
10.	I am afraid	7	19.5	0	22.5	0	21.5
11.	The walls are moving	16	13	0	22.5	0	21.5
12.	I am very sleepy	1	25	22	2	28	1
13.	Distances are changing	15	14	0	22.5	0	21.5
14.	I feel very gay	26	3	0	22.5	0	21.5
15.	My mouth is dry	13	15	10	5	15	5
16.	I am relaxed	23	5	27	1	19	2
17.	I feel silly	20	10	0	22.5	0	21.5
18.	Time passes slowly	4	22.5	2	12.5	1	13
19.	Colors are changing	20	10	3	10	2	11.5
20.	I am sad	0	27.5	3	10	17	4
21.	I am high	27	1.5	13	3	18	3
22.	Time goes fast	6	21	0	22.5	0	21.5
23.	My body feels light	20	10	1	14.5	0	21.5
24.	I can think clearly	0	27.5	0	22.5	0	21.5
25.	I like the feeling	22	7	11	4	0	21.5
26.	People look funny	17	12	0	22.5	0	21.5
27.	I have no appetite	3	24	0	22.5	0	21.5
28.	I laugh easily	27	1.5	0	22.5	0	21.5
29.	My hearing is keen	21	8	3	10	6	9
30.	My mouth is numb	7	19.5	5	6.5	2	11.5
31.	I feel confused	23	5	2	12.5	12	6

Spearman Rank Order Correlation Coefficients: 1. LSD vs V-E-5 $r_s = +0.106$; 2. LSD vs V-E-6 $r_s = +0.134$; 3. V-E-5 vs V-E-6 $r_s = +0.814$[1].

[1] Significant correlation at $P < 0.05$.

The figures under "total" represent the total number of positive responses to each question. The maximum possible number (6 subjects times 6 observations) of positive response is 36.

The figures under "rank" represent the rank of each question according to the relative number of total positive responses (i.e., rank 1 equals question with greatest number of total positive responses, etc.).

The number of responses to placebo were so small that data on placebo have been omitted.

Table 2. *Results of comparisons of V-E-5, V-E-6, placebo and LSD-25 using the paired T-test*

Measure	Placebo vs			V-E-5 vs		V-E-6 vs
	V-E-5	V-E-6	LSD	V-E-6	LSD	LSD
Temperature	0.89	0.67	3.3[1]	0.54	3.22[1]	5.27[1]
Pulse rate	1.64	1.31	3.77[1]	0.51	0.6	1.4
Systolic blood pressure	0.85	2.14	4.17[1]	2.65[1]	4.1[1]	3.1[1]
Diastolic blood pressure	2.17	2.7[1]	2.36	2.95[1]	1.99	0.93
Respiratory rate	1.39	0.58	0.5	0.44	1.37	1.05
Pupillary size	1.03	4.61[1]	7.73[1]	2.96[1]	6.3[1]	6.19[1]
Total positive answers	7.17[1]	9.58[1]	13.91[1]	2.46	12.2[1]	9.2[1]

[1] Statistically significant values ($P < 0.05$).

The figures in the table are the "t" values calculated from data on the same 6 subjects who received all drugs.

Table 3. *The effects of the natural alkaloids (V-E-5) of ololiuqui, a synthetic mixture of alkaloids simulating those of ololiuqui (V-E-6), LSD-25 and placebo*

Measurement	Drug and dose			
	Placebo	V-E-5, 5 mg	V-E-6, 5 mg	LSD-25 1.5 mcg/kg
Temperature[1]	+ 3.06 ± 0.6	+ 2.22 ± 0.74	+ 1.66 ± 0.5	+ 5.54 + 0.5
Pulse rate[1]	+ 39.3 ± 17.3	+ 68.2 ± 20.0	+ 38.8 ± 18.0	+ 79.0 ± 10.8
Systolic blood pressure[1]	+ 37.8 ± 13.2	+ 51.3 ± 13.7	+ 92.0 ± 15.0	+ 136.5 ± 15.9
Diastolic blood pressure[1]	− 7.2 ± 13.6	+ 20.7 ± 13.65	+ 43.3 ± 16.7	+ 60.5 ± 20.5
Respiratory rate[1]	+ 16.5 ± 5.0	+ 9.5 ± 2.4	+ 11.9 ± 3.6	+ 22.5 ± 8.7
Pupillary size[1]	− 2.88 ± 0.41	− 0.3 ± 2.3	+ 4.92 ± 0.5	+ 12.8 ± 1.8
Total positive answers[2]	5.8 ± 2.0	24.2 ± 3.3	30.0 ± 3.1	68.3 ± 5.8

[1] Figures represent means ± standard errors of areas under time-action curves "degree hours" (temperature); mm hours (blood pressure); etc. A positive sign indicates an increase over predrug measurements; a negative, a desrease.

[2] Figures represent total number of questions scored positively on the questionnaire that were not scored positively before the drug was given.

mixture (V-E-6) caused significantly greater changes in systolic and diastolic blood pressures and pupillary size than did the natural mixture (V-E-5). LSD-25 created greater increases in temperature, systolic blood pressure, and pupillary size than did either mixture.

Compared to placebo, both the crude extract and the synthetic mixture caused significant subjective effects which differed qualitatively and

quantitatively from those of LSD-25. These appeared $1^1/_2$ hours after the drugs were taken, were maximal at $2^1/_2$ hours, and had largely subsided in $7^1/_2$ hours. The subjective effect most consistently reported was sleepiness (question 12, Table 1), plus the questions (1 and 21) dealing with general nonspecific drug effects. Neither V-E-5 nor V-E-6 were identified as being like LSD (question 6), marihuana (question 5), or cocaine (question 4). There were very few reports of distortion in sensory perception (question 11, 13, 19, 26 and 29). Hallucinations did not occur. Though not included in the questionnaire, nausea and headache were spontaneously reported by most patients. In contrast, LSD caused nervousness (question 8) rather than sleepiness, marked perceptual distortion (questions 11, 12, 19, 26 and 29), and "euphoria" (questions 14, 21, 25 and 28). LSD was frequensly identified as being like LSD (question 6), marihuana (question 5), and cocaine (question 4). Though not covered in the questionnaire, all patients receiving LSD had simple optical hallucinations (light, colors, patterns), and some subjects reported "true" hallucinations. Correlation coefficients indicate a significant positive correlation (i.e., a significant similarity) between the pattern of subjective effects of V-E-5 and V-E-6. However, neither V-E-5 nor V-E-6 had a significantly similar pattern of subjective effects to LSD.

Discussion

Though both V-E-5 and V-E-6 caused definite subjective effects, the pattern of symptoms of the mixtures of ololiuqui alkaloids was distinctly different from that caused by LSD. These mixtures had predominantly sedative properties and, in the doses used, were not "hallucinogenic". Our results are probably very similar to those of HOFMANN and CERLETTI (1961) since these authors experienced — like our patients — fatigue, sedation, and sleep. Similarly OSMOND (1955) reported apathy rather than hallucinations. Therefore it seems more appropriate to speak of ololiuqui and its alkaloids as "sedatives" rather than "psychotomimetics" The results also agree with the sedative effects reported after *d*-lysergic acide amide (HOFMANN 1963; ISBELL; SOLMS 1956), *d*-iso-lysergic acid amide (HOFMANN 1963), and elymoclavine (ISBELL). The slight autonomic changes that followed V-E-5 and V-E-6 also contrast sharply with the spectacular autonomic changes seen after LSD.

There was no indication in these experiments that the crude extract of ololiuqui (V-E-5) contained significant amounts of active substances not found in the synthetic mixture (V-E-6). In fact, V-E-6 caused significantly greater effects on pupillary size and blood pressure than did V-E-5.

Because the effects of these mixtures of alkaloids were relatively mild and were dysphoric rather than euphoric, the chances of abuse of morn-

ing glory seeds becoming widespread do not seem great. This view is reinforced by the paucity of effects observed in another group of addicts who ingested 6 g of ground ololiuqui (*Ipomea violacea*) seeds (ISBELL). The number of seeds that would have to be taken to obtain the amounts of alkaloids equal to those used in these experiments is very great. The highest reported content of alkaloids in morning glories are 0.06 percent in *Ipomea violacea* (HOFMANN 1963) and 0.057 in the Pearly Gates variety (TABER et al. 1963). Using either of these figures one can calculate that a minimum of 400 morning glory seeds (8.7 g) would have to be ingested to furnish 5 mg of alkaloids. Since extraction of the alkaloids from the seeds would not be complete, even larger doses would probably be required. It is quite possible that the effects reported after ingestion of the seeds by maladjusted persons are due as much to suggestion from the social situation in which the seeds are used to the pharmacological effects of the alkaloids contained in the seeds. In addition, other drugs (alcohol, marihuana, etc.) that are frequently taken with the seeds may contribute to the marked mental effects that have been reported.

Summary

Five mg of either a crude extract of seeds of ololiuqui or a mixture of synthetic alkaloids caused drowsiness in former morphine addicts but few other subjective effects. Perceptual distortion was reported only rerely, and hallucinations did not occur. In contrast, LSD-25 caused nervousness, perceptual distortion, euphoria and hallucinations. The alkaloids of ololiuqui did not cause fever or marked mydriasis. Ololiuqui and the alkaloids of ololiuqui should be regarded principally as sedatives rather than as psychotomimetics.

References

ABRAMSON, H. A., M. E. JARVIK, M. R. KAUFMAN, C. KORNETSKY, A. LEVINE, and M. WAGNER: Lysergic acid diethylamide (LSD-25); I. Physiological and perceptual responses. J. Psychol. **39**, 3–60 (1955).

COHEN, S.: Suicide following morning glory seed ingestion. Amer. J. Psychiat. **120**, 1024–1025 (1964).

EDWARDS, A. L.: Statistical analysis for students in psychology and education. New York: Rhinehart and Co. 1946.

HOFMANN, A.: The active principles of the seeds of *Rivea Corymbosa* and *Ipomea Violacea*. Botanical Museum Leaflets, Harvard University **20**, 194–212 (1963).

—, u. A. CERLETTI: Die Wirkstoffe der dritten aztekischen Zauberdroge oder die Lösung des „Ololiuqui-Rätsels". Dtsch. med. Wschr. **86**, 885–888 (1961).

—, and H. TSCHERTER: Isolierung von Lysergsäure-alkaloiden aus der Mexikanischen Zauberdroge Ololiuqui (Rivea Corymbosa [L.] Hall. f.). Experientia (Basel) **16**, 414 (1960).

INGRAM, A. L.: Morning glory seed reaction. J. Amer. med. Ass. **190**, 1133–1134 (1964).

ISBELL, H.: Unpublished observations.

Kinloss-Wright, V. J.: Research on ololiuqui: the Aztec drug. Proc. First Internat. Congr. Neuropsychopharm. 1958. In Bradley, P. B., P. Deniker, and C. Raudoco-Thomas (Eds.): *Neuropsychopharmacology*, p. 453. Amsterdam, London, New York: Elsevier Publishing Co. 1959.

MacDougall, T.: *Ipomea Tricolor*. A hallucinogenic plant of the Zapotecs. Bol. Cent. Invest. Antropolog. Mex. **6**, Mar. 1 (1960).

Osmond, H.: Ololiuqui. The ancient Aztec narcotic. J. ment. Sci. **101**, 526—537 (1955).

Schultes, R.: A contribution to our knowledge of *Rivea Corymbosa*, the narcotic ololiuqui of the Aztecs. Cambridge, Mass. Botanical Museum, Harvard University 1941.

Sours, H.: Chemische Struktur und Psychose bei Lysergsäurederivaten. Praxis **45**, 746—749 (1956).

— Relationships between chemical structure and psychoses with the use of psychotoxic substances. J. clin. exp. Psychopath. **17**, 429—430 (1956).

Taber, W. A., L. C. Vining, and R. A. Heacock: Clavine and lysergic acid alkaloids in varieties of morning glory. Phytochem. **2**, 65—70 (1963).

Wasson, R. G.: Notes on the present status of olioliuqui and other hallucinogens of Mexico. Cambridge, Mass.: Botanical Museum Leaflets, Harvard University **20**, 161—193 (1963).

Winter, C. F., and L. Flataker: Studies on heptazone (6-morpholino-4-4-diphenyl-3-heptanone hydrochloride) in comparison with other analgesic agents. J. Pharmacol. exp. Ther. **98**, 305—317 (1950).

Yui, R., and Y. Takeo: Neuropharmacological studies on a new series of ergot alkaloids. Jap. J. Pharmacol. **7**, 157—161 (1958).

Dr. Harris Isbell,
National Institute of Mental Health, Addiction Research Center, P.O. Box 2000, Lexington, Kentucky 40501, U.S.A.