

A Comparison of LSD-25 with (—)- Δ^9 -Trans-Tetrahydrocannabinol (THC) and Attempted Cross Tolerance between LSD and THC

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Received July 24, 1968

Final Version: October 22, 1968

Summary. 1. The objective and subjective effects of 0.5 and 1.5 mcg/kg of LSD intramuscularly were compared with those of 75 and 225 mcg/kg of (—)- Δ^9 -trans-tetrahydrocannabinol by smoking in the same eight subjects.

2. The objective effects of LSD and THC differed markedly. LSD increased body temperature, systolic and diastolic blood pressure, lowered the threshold for the knee-jerk, and dilated the pupils. THC had none of these effects but caused more marked tachycardia than did LSD.

3. The subjective effects of the two drugs could not be readily distinguished by the methods used. Both LSD and THC are psychotomimetic drugs.

4. Patients tolerant to LSD were not cross-tolerant to THC, indicating that the mental effects of the two drugs are probably mediated by different mechanisms.

Key-Words: Cannabis — Marihuana — (—)- Δ^9 -Tetrahydrocannabinol — Lysergie Acid Diethylamide — LSD Tolerance — LSD and THC Cross-Tolerance.

The psychotomimetic effects of *Cannabis sativa* (marihuana, hashish) have been known for thousands of years and described in many ancient writings (LEWIN, 1961; CHOPRA, 1939). These descriptions have mentioned subjective phenomena resembling those seen after administration of lysergie acid diethylamide (LSD). Research on *Cannabis* has been hampered by the very difficult chemistry of the resin of that plant, which meant that pharmacological investigations were performed with crude and impure mixtures or with synthetic materials that were not known to correspond exactly in chemical structure to those isolated from the plant. Recently it has been shown (ISBELL *et al.*, 1967) that

(-)- Δ^9 -*trans*-tetrahydrocannabinol¹ (hereafter referred to as THC) causes the same kind of mental effects as those described after administration of crude *Cannabis* preparations. Furthermore the psychotomimetic effects of THC were shown to be dependent on dose. Because of the resemblance of the subjective mental effects caused by THC to those caused by LSD, a direct comparison of the effects of the two drugs in the same subjects was thought of interest in order to delineate further any resemblances and differences between the syndromes produced by the two drugs. In addition, an attempt to determine whether patients tolerant to LSD would be cross-tolerant to THC might give some indication as to whether the two drugs caused their effects by similar mechanisms.

Methods

Experiments

Two experiments were performed—the *comparison study* and the *cross-tolerance study*. In the *comparison study* the same patients received at weekly intervals in randomized order a placebo, 0.5 mg/kg and 1.5 mg/kg of LSD intramuscularly, and 75 mg/kg and 225 mg/kg of THC by smoking. In the *cross-tolerance study* ten patients received in randomized order at weekly intervals placebo, 1.5 mg/kg of LSD I.M., and 225 mg/kg of THC by smoking (control doses). The subjects were made tolerant to LSD by daily injection of 0.5 mg/kg of LSD increasing to 1.5 mg/kg over a period of 10 days. They were challenged with 1.5 mg/kg LSD I.M. (test of direct tolerance) on the eleventh day, and then on the following day with 225 mg/kg of THC by smoking (test of cross-tolerance).

Subjects. Former opiate addicts serving sentences for violation of the United States narcotic laws volunteered for the experiments. Their ages ranged from 22 to 53 years. All were physically healthy and presented no evidence of serious mental disturbances. All had been abstinent from opiates for six months or more before beginning the experiments. All had used marihuana at one time or another prior to being arrested. All smoked tobacco cigarettes habitually. Originally, 10 subjects began the comparison study. Two of these dropped out after experiencing psychotic reactions following THC, so that only 8 subjects completed

¹ Supplied by courtesy of Prof. F. KORTE and associates, Organisch-chemisches Institut der Universität Bonn. The material was isolated from hashish by extraction with organic solvents and purified by countercurrent distribution. The name (-)- Δ^9 -*trans*-tetrahydrocannabinol uses the official numbering system of the American Chemical Society to designate the location of the double bond. The compound has also been designated (-)- Δ^1 -tetrahydrocannabinol by other chemists using a different numbering system.

that experiment. Ten subjects began the cross-tolerance study and all completed it. Five of the same subjects who served in the comparison study also served in the *cross-tolerance* study.

General Conditions. All experiments were conducted in a special ward devoted to clinical investigation. In the comparison study, the subjects entered the ward the night before drugs were given and remained through the night following completion of the observations. In the cross-tolerance study, the subjects were housed in the experimental ward for the duration of the experiment.

Observations. In the comparison study the following observations were made at 7:00 AM, 8:00 AM, 9:00 AM, 10:00 AM, 11:00 AM, 1:00 PM, and 3:00 PM by specially trained attendants after the subjects had rested quietly in bed for ten minutes: rectal temperature, pulse rate, systolic and diastolic blood pressure, threshold for the knee-jerk (the number of degrees of arc through which a hinged reflex hammer had to fall to elicit the patellar reflex), and pupillary diameter by photographing the pupils under conditions of constant light and accommodation. These measures were termed "objective" parameters.

At 7:30 AM, 8:30 AM, 9:30 AM, 10:30 AM, 11:30 AM, 1:30 PM and 3:30 PM the patients completed, with the help of an aide, a special questionnaire containing 63 items². Ten of these questions were taken from the general drug scale of the Addiction Research Center Inventory (HAERTZEN, 1966), ten from the LSD scale, and 10 from the marihuana (Ma) scale of the same instrument, which was developed using DMHP [1-hydroxy-3-(1',2'-dimethyl heptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydrocannabinol], a potent congener of THC. The items constituting the LSD and marihuana scales have been shown empirically (HAERTZEN, 1966) to give high scores after LSD and DMHP compound (ADAMS *et al.*, 1948), a synthetic drug with marihuana-like effects, and the items constituting the general drug scale give high scores with nearly all types of drugs with central nervous system effects. The remaining 33 questions were taken from the questionnaire previously used in studies of LSD and similar agents (ABRAMSON *et al.*, 1955) and consisted of items dealing with alterations in mood, distortion of sensory perception, alterations in body image, illusions, delusions, and hallucinations. These 33 questions were termed the "psychotomimetic scale". The questions making up the various scales were placed in random order throughout the questionnaire.

In the cross-tolerance study the same observations were made and the same questionnaire was administered at the same times on control and test days, except that the observations at 3:00 PM and the questionnaire at 3:30 PM were not obtained.

² Copies of the various scales will be made available on request.

Drugs

Lysergic acid diethylamide monotartrate was dissolved in distilled water in a concentration of 100 mcg/ml and sterilized by autoclaving. The solution also contained 1 mg/ml of ascorbic acid as an anti-oxidant and was stored in a refrigerator and protected from light. (—)- Δ^9 -*trans*-tetrahydrocannabinol was dissolved in 95% ethanol in a concentration of 10 mg/ml, refrigerated and protected from light. The LSD placebo was sterile isotonic saline solution. The calculated dose of tetrahydrocannabinol was injected with a syringe and needle into the second and third fifths of an ordinary tobacco cigarette on the night before an experiment and the cigarette dried without heating. The THC placebo consisted of an ordinary tobacco cigarette into which 95% ethanol had been injected and dried. Cigarettes were smoked in 5 min or less. In the comparison study each patient received an intramuscular injection and smoked a cigarette on each test day. At weekly intervals and in randomized order each patient received the following five combinations: LSD placebo plus THC placebo; 0.5 mcg/kg of LSD plus THC placebo; 1.5 mcg/kg of LSD plus THC placebo; 75 mcg/kg of THC plus LSD placebo; and 225 mcg/kg of THC plus LSD placebo. Neither patients nor observers knew what drugs were being given on any particular day ("doubleblind" technique).

In the cross-tolerance study, the patients received at weekly intervals in random order the following drugs prior to chronic administration of LSD: THC placebo plus LSD placebo; THC 250 mcg/kg plus LSD placebo; and THC placebo plus 1.5 mcg/kg of LSD. These experiments constituted the controls. The patients then received at 8:00 AM each morning an intramuscular injection of LSD. The initial dose on the first day was 0.5 mcg/kg and was increased by 0.25 mcg/kg daily until the patients were receiving 1.5 mcg/kg by the 5th day. This dose was then maintained through the 10th day. On the eleventh day the patients received LSD, 1.5 mcg/kg, and smoked a placebo cigarette—test of direct tolerance to LSD. On the next day they received a placebo injection and smoked a cigarette containing 250 mcg/kg of THC—test of cross-tolerance to THC. On both days the observations described under "Methods" were made. Sufficient THC was not available for a study of possible development of direct tolerance to THC and cross-tolerance to LSD.

Statistical Analysis

In the comparison study the data for each objective parameter for each dose of each drug were tabulated for each patient each observation time and means calculated so as to obtain time action curves for each

measurement. In addition, the total number of correct responses (for some items in the LSD, marihuana, and general drug scales the correct response that counted in the scoring was a negative one) at each time was tabulated for each patient and each dose of each drug. The areas under the time action curves for each objective parameter for each dose of each drug and each patient were calculated by the method of WINTER and FLATAKER (1950). The total number of correct responses on the questionnaire was obtained by summing the totals at each observation time for each patient. Means and standard errors of means were calculated by standard statistical methods. The significance of differences between means was evaluated by the "*t*" test for correlated data (EDWARDS, 1946).

In order to calculate relative potencies in the comparison study, the scores on each scale (psychotomimetic, general drug effect, marihuana and LSD scales) were tabulated and summed for each subject and for each dose of each drug, using the data for the 8:30 AM and 9:30 AM observations only. The times were chosen because of differences in the time action curves of LSD and THC. They represent "peak" rather than total time action effects. The relative potencies of LSD and THC were then calculated, where possible, for each of the scales using the method described by FINNEY (1964).

In the cross-tolerance study the areas under the time action curves were approximated by summing each response for the most significant objective parameters (pupillary size for LSD and pulse rate for THC). The total number of correct responses on the questionnaire was counted for all drugs. The confidence limits of the response to the placebo were calculated by the standard method (EDWARDS, 1946). The significance of differences between the control and test doses of LSD were evaluated by the "*t*" test for correlated data (EDWARDS, 1946).

Results

Comparison Study. The effects of LSD and THC over the total observation period are summarized in Table 1. LSD caused the expected effects of increasing body temperature, pulse rate, systolic and diastolic blood pressure, lowering the threshold for the knee-jerk and increasing pupillary size. In contrast, THC had no significant effects on temperature, systolic blood pressure, threshold for the knee-jerk and pupillary diameter. No ataxia could be detected by clinical observation. The outstanding effect of THC was induction of marked tachycardia. Similar comparisons utilizing the data at time of peak effect (2 hours for the objective parameters and $1\frac{1}{2}$ hours for subjective effects) gave results similar to those for the total effects and are accordingly not reported.

Table 1. Comparison of objective and subjective effects of (—)- Δ^9 -trans-tetrahydrocannabinol (THC) and LSD. Areas and responses on questionnaire

Measure	Drug and Dose				
	Placebo	LSD 0.5 mcg/kg	LSD 1.5 mcg/kg	THC 75 mcg/kg	THC 225 mcg/kg
Temperature	+ 2.8 $\pm$ 0.32	+ 4.1 $\pm$ 0.26	+ 3.2 $\pm$ 0.6	+ 2.85 $\pm$ 0.7	+ 2.5 $\pm$ 0.8
Respiratory rate	— 0.75 $\pm$ 6.5	+ 11.2 $\pm$ 7.5	+ 8.9 $\pm$ 6.3	+ 6.5 $\pm$ 13.7	+ 18.8 $\pm$ 4.0
Pulse rate	+ 39.5 $\pm$ 14.8	+ 62 $\pm$ 15.4	+ 67.8 $\pm$ 8.2	+ 79.5 $\pm$ 20.4	+ 94.25 $\pm$ 21.1
Systolic blood pressure	+ 40.8 $\pm$ 6.7	+ 64.5 $\pm$ 14.0	+ 67.8 $\pm$ 11.7	+ 38.5 $\pm$ 14.4	+ 26.3 $\pm$ 16.6
Diastolic blood pressure	+ 3.1 $\pm$ 13.2	+ 16.0 $\pm$ 11.7	+ 27.2 $\pm$ 14.5	— 14.75 $\pm$ 13.8	— 22.5 $\pm$ 12.2
Pupillary size	— 0.19 $\pm$ 0.5	+ 4.66 $\pm$ 0.66	+ 6.5 $\pm$ 0.95	+ 0.31 $\pm$ 0.22	+ 0.7 $\pm$ 0.8
Threshold for knee-jerk	+ 4.4 $\pm$ 13.0	— 36.6 $\pm$ 7.0	— 45.9 $\pm$ 10.1	— 10.0 $\pm$ 14.6	— 14.1 $\pm$ 14.6
Total questions	8.6 $\pm$ 7.2	45.6 $\pm$ 9.7	101 $\pm$ 18.4	29.8 $\pm$ 12.8	69.9 $\pm$ 22.1

Figures represent means ($N = 8$) of areas (see text) under time action curves $\pm$ one standard error except for questions where figures are means of total positive responses on questionnaires $\pm$ one standard error. Figures are in terms of "degree-hours" (temperature), "breath-hours" (respiration), "beat-hours" (pulse), "mm/hours" (blood pressure), "mm/hours" (pupil), and "degree-hours" (knee-jerk). A positive sign indicates an increase over the average of the two pre-drug observations, a negative sign indicates a decrease.

Table 2. Tolerance to LSD and test of cross-tolerance to (—)- Δ^9 -trans-tetrahydrocannabinol

Parameter	Placebo ^a	LSD ^b			THC ^b		
		Control	Test	" <i>t</i> "	Control	Test	" <i>t</i> "
Pupillary change	— .3 (—1.1 to .5)	+ 4.3	+ 1.4	4.01 ^c	+ .1	+ 0.6	0.84
Pulse change	+ 22 (10 to 33)	+ 51	+ 26	2.28 ^d	+ 69	+ 77	1.11
Positive questionnaire responses	6 (—3 to 15)	81	5.7	4.67 ^c	51	40	1.70

^a The figures for placebo represent the mean of the areas under the time action curves with the 95% confidence limits in parenthesis.

^b The figures are the means of the areas under the time-action curves ($N = 10$) done before (control) and after (test) daily administration of LSD. Note that the responses to the test dose of LSD are markedly attenuated as compared with control, indicating direct tolerance, whereas those after the test dose of THC are not, indicating no cross-tolerance.

^c For this value of "*t*", $p < 0.05$. ^d For these values of "*t*", $p < 0.01$.

Both drugs caused the expected subjective effects, including distortions, alterations in mood and, with the higher doses, hallucinations. As mentioned above, two patients withdrew after experiencing psychotic reactions following THC.

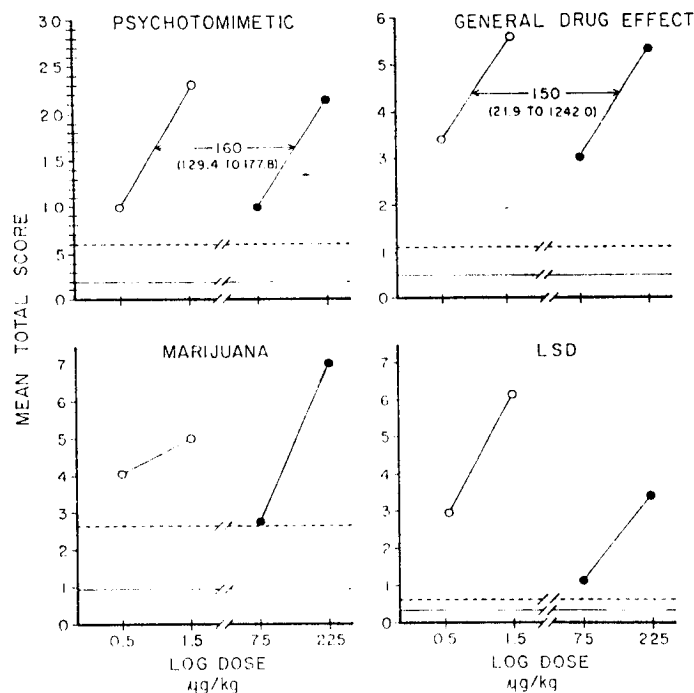


Fig. 1. Responses on the four scales of subjective effects. Open circles represent the mean number of responses to LSD at the doses indicated. Solid circles represent the mean number of responses to THC. The figures in the arrows on the psychotomimetic and general drug scales represent the relative potency of LSD as compared with THC, with the confidence limits being shown in parentheses underneath

The comparisons on the four scales are shown in Fig. 1. Valid assays meeting the statistical requirements for slope, parallelism, and equivalence of response were obtained with the psychotomimetic and general drug effect scales. LSD was 160 times as potent as THC (95% confidence limits 129.4–177.8) on the psychotomimetic scale and 150 times as potent as THC on the general drug scale (95% confidence limits 21.9 to 1242.0). Valid assays were not obtained with the marihuana and LSD scales. LSD did not produce a significant dose-related response on the

marihuana items and THC was less effective in producing a response on the LSD scale than it was on the psychotomimetic and general drug scales.

Cross-Tolerance Study. The results of the cross-tolerance study are summarized in Table 2 and Fig. 2. All responses to the test dose of LSD after chronic administration were significantly reduced when compared with the control dose, indicating that a high degree of direct tolerance had developed. The responses to the test dose of THC were, however, not significantly reduced, indicating that no cross-tolerance to THC was present in patients tolerant to LSD.

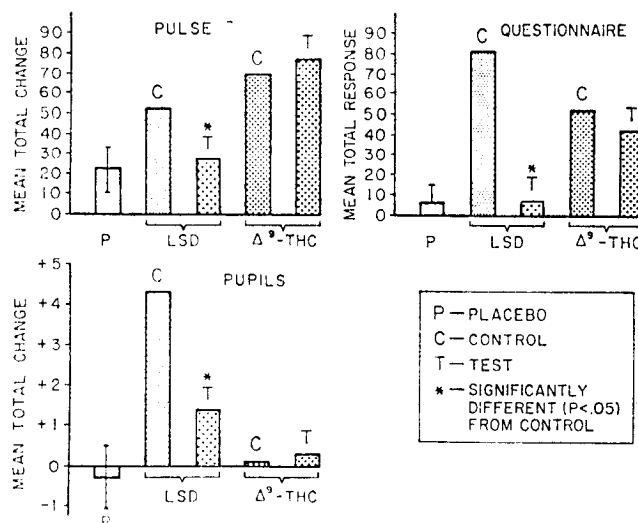


Fig. 2. Attempted cross-tolerance between LSD and THC. Note the significant reductions in the responses to the test dose of LSD as compared with control, indicative of tolerance to LSD. In contrast there were no significant responses to the test dose of THC as compared with control, indicating no cross-tolerance

Discussion

The patterns of the objective effects of LSD and THC can easily be distinguished. THC does not cause the temperature and blood pressure increases, pupillary dilatation and hyperreflexia so characteristic of LSD. The lack of effect of THC on pupillary size is particularly noteworthy, since mydriasis (as judged clinically) is frequently mentioned as a sign of marihuana intoxication. On the other hand, THC causes a much greater increase in pulse rate at the time of peak effect than does LSD. In addition, THC causes injection of the conjunctivae and pseudoptosis, effects not characteristic of LSD.

The subjective effects caused by the two drugs could not be distinguished as expected by the general drug scales, but in addition could not be differentiated by the psychotomimetic scale, even when the responses on that scale were broken down into classes of items dealing with alterations in mood, sensory distortion, hallucinations, etc. On the other hand, the subjective states produced by THIC and LSD can be distinguished by the mean group responses on the marihuana and LSD scales. The number of items in the LSD and marihuana scales and the number of subjects were too few to allow meaningful pattern analyses. For this reason, specific differences in the subjective states produced by the two drugs cannot be determined at this time.

The results of the cross-tolerance study were unequivocal—patients tolerant to LSD were not cross-tolerant to THC. Because of this fact, and because of the distinct differences in objective effects, it seems certain that the mental effects of THIC are due to mechanisms within the central nervous system which differ from the mechanisms underlying the effects of LSD.

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