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A Comparison of 2,3-Dihydro-Lysergic Acid Diethylamide with LSD-25

By

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With 1 Figure in the Text

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Introduction

The diethylamide of lysergic acid (LSD-25) induces increased sympathetic tonus by central actions (ROTHLIN *et al.* 1956; CERLETTI *et al.* 1963). Since these enhanced sympathetic responses seem to be closely correlated with the mental effects of LSD-25 and similar drugs, they have been used in screening new compounds for LSD-like activity. The simplest procedure showing a good correlation with psychotomimetic action in man has been the determination of pyretogenic activity in rabbits (CERLETTI 1963). Recently, it has been shown that 2,3-dihydrolysergic acid diethylamide (2,3-DH-LSD) was only $^1/_{25}$ as potent as LSD-25 in inducing fever in rabbits but was equally toxic for mice[1]. Accordingly, it seemed of interest to determine whether the low pyretogenic activity of 2,3-DH-LSD in rabbits would be associated with low (as compared with LSD-25) psychotomimetic, pyretogenic and sympathomimetic activity in man.

Methods

Six physically healthy former morphine addict males volunteered for these experiments. Their ages varied between 23 and 33. They were housed in a special ward devoted to clinical investigation and observed by specially trained aides with long experience in detecting drug-induced behavioral changes.

Experimental observations. The following observations were made according to methods previously described (ISBELL *et al.* 1961) after the patients had rested quietly in bed for 10 min: rectal temperature, respiratory and pulse rates, systolic blood pressure, threshold for the

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kneejerk (in terms of degrees of arc through which a hinged hammer had to fall to elicit a barely perceptible response), and pupillary area (determined photographically under conditions of constant light and accommodation). These observations were made at the following times: one hour before administration of the drugs, just before the administration of the drugs, and 1, 2, 3, 4, 5, 6, 7, 9 and 11 hours after the drugs were given.

A special 54-item questionnaire (ISBELL *et al.* 1961) was administered by an aide $^1/_2$ hour before the drug and $^1/_2$, $1^1/_2$, $2^1/_2$, $3^1/_2$, $4^1/_2$, $5^1/_2$, $6^1/_2$, $7^1/_2$, $9^1/_2$ and $11^1/_2$ hours after the drug. A "clinical grade" (0—4) was assigned by a physician on the basis of a short mental status examination at the height of the reaction using the criteria of ISBELL *et al.* (1956). In this rating system 0 represents no change after the drug while 4 indicates the occurrence of hallucinations without insight.

Drugs. All drugs were administered intramuscularly at 8 a.m. LSD-25 was given as the tartrate, 2,3-DH-LSD as the maleate. Doses were calculated in terms of the bases rather than the salts. The six patients received in randomized order at weekly intervals 0.5 and 1.0 mcg/kg of LSD-25, 1.5 and 3.0 mcg/kg of 2,3-DH-LSD and a placebo (saline). As the experiment proceeded it became apparent that a larger dose of 2,3-DH-LSD was needed, so the patients were given an unrandomized dose of 4.5 mcg/kg of 2,3-DH-LSD at the end of the experiment. The patients did not know what drugs they were receiving ("single-blind" procedure).

Analysis of data. The various observations were tabulated and averaged for each observation time and each dose of both drugs, and the times of maximal (peak) action identified. Each set of peak data on each parameter for all doses of both drugs were then compared statistically with the appropriate sets of placebo data at corresponding times. The "*t*" test for paired observations (EDWARDS 1946) was used to evaluate the significance of differences between means. Since the time-action curves of 2,3-DH-LSD differed markedly from those of LSD-25 (Fig. 1), only peak values are reported. Relative potencies of LSD-25 and 2,3-DH-LSD were calculated according to the method of GADDUM (1953).

Results

The results are summarized in the Table. The mean peak effects of both doses of LSD-25 were significantly different ($p<0.05$ by the paired "t" tests) from the effects of placebo on every parameter except respiratory rate. The mental effects of LSD-25 included nervousness, change in mood, perceptual distortion (chiefly visual), and with the 1.0 mcg/kg dose, hallucinations in most patients.

Table. *Peak effects of placebo, LSD and 2,3-DH-LSD in 6 subjects*

Measure	Placebo	LSD-25, mcg/kg	
		0.5	1.0
Rectal temperature[1]	37.1 ±0,1 (4)	37.4* ±0,1 (4)	37.6* ± 0.06 (5)
Pulse rate[1]	74 ±4.2 (4)	82.3* ±6.5 (4)	89.7* ±11.2 (1)
Respiratory rate[1]	19.7 ±1.6 (4)	21.3 ±1.9 (4)	21.7 ± 1.7 (1)
Systolic blood pressure[1]	129 ±3 (11)	144* ±5.4 (2)	146* ± 9.1 (1)
Threshold for kneejerk[2]	36 ±6.5 (7)	22.5* ±5.0 (2)	20* ± 4 (2)
Area of pupils[3]	12.4 ±2.5 (7)	21.2* ±1.98 (3)	24.8* ± 3.5 (2)
Questions[4]	1.0 ±0.5 ($1/2$)	12.0* ±4.2 ($2\,1/2$)	30.0* ± 5.6 ($2\,1/2$)
Clinical grade[5]	0.08 ±0.08	1.67* ±0.3 ($2\,1/2$)	2.83* ± 0.17 ($2\,1/2$)

Measure	2,3-DH-LSD, mcg/kg		
	1.5	3.0	4.5
Rectal temperature[1]	37.5* ±0.08 (11)	37.5* ±0.07 (10)	37.6* ±0.06 (11)
Pulse rate[1]	75.6 ±3.2 (7)	76.7 ±5.7 (4)	79.3* ±5.9 (4)
Respiratory rate[1]	21.2 ±2.6 (6)	22.3 ±8.7 (3)	20.3 ±1.7 (3)
Systolic blood pressure[1]	139 ±7.7 (11)	135* ±4.4 (6)	140* ±6.7 (4)
Threshold for kneejerk[2]	31 ±5.9 (3)	29 ±5.3 (6)	25* ±2.7 (3)
Area of pupils[3]	18.2* ±3.4 (5)	22.1* ±3.0 (6)	23.2* ±5.5 (5)
Questions[4]	8.0* ±4.1 ($4\,1/2$)	10.7* ±5 ($3\,1/2$)	11.3* ±2.4 ($3\,1/2$)
Clinical grade[5]	0.8* ±0.48 ($4\,1/2$)	1.16* ±0.4 ($3\,1/2$)	1.8* ±0.17 ($3\,1/2$)

All figures not in parentheses represent means ± standard errors. Figures in parentheses show the number of hours after ingestion of the drug at which the greatest (peak) effect occurred.

[1] Expressed in conventional units: degrees Centigrade (temperature), beats per minute (pulse rate), etc.

[2] Expressed in degrees of arc through which a hinged hammer had to fall to elicit a barely perceptible kneejerk.

[3] Expressed in square millimeters.

[4] Shows number of responses on questionnaire not scored positively before drugs were given.

[5] Expressed in terms of a rating scale from 0 (no effects) to 4 (hallucinations with loss of insight).

* Significantly different from placebo ($p < 0.05$) by paired "t" test.

The effects of 2,3-DH-LSD were similar to those of LSD and included autonomic changes (fever, tachycardia, increase in blood pressure, and

mydriasis), decrease in the threshold for the kneejerk and LSD-like mental changes (changes in mood with all doses, perceptual distortion with the 3.0 and 4.5 mcg/kg doses, and occasional hallucinations with the 4.5 mcg/kg dose).

The time-action courses of the two drugs differed markedly (Fig. 1). Both the autonomic and mental effects of 2,3-DH-LSD appeared more slowly and reached maximal intensity later than those of LSD-25.

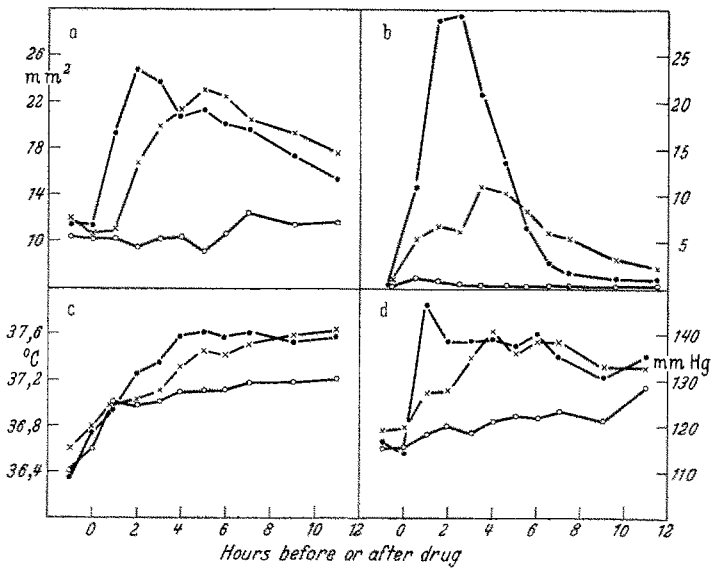

Fig. 1a—d. Time course of responses to placebo (o—o), LSD-25 (●—●) (1.5 mcg/kg) and 2,3-DH-LSD (△—△) (4.5 mcg/kg). a Pupillary diameter expressed in mm²; b number of positive responses to the questionnaire; c rectal temperature in °C; d systolic blood pressure

A valid relative potency calculation meeting requirements for significance of slope, parallelism, and equivalence of dosage was obtained only on the peak data for pupillary dilatation. This calculation showed that 1 mcg of LSD was equivalent to 5.92 mcg of 2,3-DH-LSD in dilating pupils (95% confidence limits of 5.65—7.15 mcg). The assay on the data for clinical grade met requirements for slope and parallelism but did not meet the requirements for equivalence of dosage. According to this calculation 1 mcg of LSD was equivalent to 8.0 mcg of 2,3-DH-LSD in inducing mental change (95% confidence limits of 4.0—17.45 mcg).

Discussion

2,3-DH-LSD induced both autonomic (including fever) and mental effects similar to those of LSD-25, but was less potent. Thus, the low pyretogenic potency of 2,3-DH-LSD in the rabbit was correlated with

a relatively low potency in inducing autonomic and psychotomimetic effects in man. The difference was, however, not as great as might have been predicted from the animal screening tests, since the data in this paper suggest that 2,3-DH-LSD is approximately $^1/_6$—$^1/_8$ as potent as LSD in man.

In addition, it is also apparent that hydrogenation of LSD-25 at positions 2 and 3 had effects other than simply reducing potency. The relatively slow appearance of autonomic and psychotomimetic changes after 2,3-DH-LSD must mean that some factor, or factors such as slower absorption, slower penetration of the blood brain barrier, or slower metabolic change to a more active substance, may also be contributing to the difference between 2,3-DH-LSD and LSD-25.

Summary

1. The 2,3-dihydro-diethylamide of lysergic acid induces LSD-like autonomic and mental changes in man but is less potent than LSD.

2. The effects of 2,3-DH-LSD appear more slowly than those of LSD-25.

3. The low potency (relative to LSD-25) of 2,3-DH-LSD in inducing fever in rabbits correlates with a relatively low potency in inducing autonomic and psychotomimetic effects in man.

References

CERLETTI, A.: Personal communication 1963.

—, E. SCHLAGER, F. SPITZER, and M. TAESCHLER: Psychopharmaka. 4. Mitt. Psychodysleptica. Schweiz. Apoth.-Ztg **101**, 210—240 (1963).

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

GADDUM, J. H.: Bioassays and mathematics. Pharmacol. Rev. **5**, 87—134 (1953).

ISBELL, H., R. E. BELLEVILLE, H. F. FRASER, A. WIKLER, and C. R. LOGAN: Studies on lysergic acid diethylamide (LSD-25). I. Effects in former morphine addicts and development of tolerance during chronic intoxication. Arch. Neurol. Psychiat. (Chic.) **76**, 468—478 (1956).

—, A. B. WOLBACH, A. WIKLER, and E. J. MINER: Cross tolerance between LSD and psilocybin. Psychopharmacologia (Berl.) **2**, 147—159 (1961).

ROTHLIN, E., A. CERLETTI, H. KONZETT, W. R. SCHALCH u. M. TAESCHLER: Zentrale vegetative LSD-Effekte. Experientia (Basel) **12**, 154 (1956).

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