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Effects in man of single and combined oral doses of reserpine, iproniazid, and D-lysergic acid diethylamide

The use of d-lysergic acid diethylamide, LSD, as a reference standard for the evaluation of psychopathologic symptoms was tested. A group of healthy male volunteers took weekly doses of LSD in order to become familiar with the temporary mental changes induced by the drug.

The subjects were able to identify three dose levels of LSD and to differentiate LSD from placebo and other drugs. A standard curve of the responses to LSD could be constructed for these subjects.

A combination of reserpine plus iproniazid was found not to produce LSD-like psychopathologic symptoms. The addition of reserpine and iproniazid to LSD did not change the degree or intensity of LSD-induced psychopathologic symptoms in man.

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The psychic effects of *d*-lysergic acid diethylamide (LSD) mimic certain psychopathologic symptoms which are observed in psychiatric conditions such as schizophrenia. Reserpine treatment diminishes the psychotic symptoms of some schizophrenic individuals, but, when administered orally, does not antagonize the mental effects of LSD in normal man.[7] A possible difference may thus exist in the action of reserpine on these two types of psychopathologic reactions.

Reserpine decreases the content of norepinephrine and 5-hydroxytryptamine (5-HT) in the rabbit brain.[2,6] The normal destruction of 5-HT is inhibited by the monoamine oxidase inhibitor iproniazid.[10] The combined administration of reserpine and iproniazid has been reported to produce LSD-like symptoms in the rabbit.[9] These symptoms have been attributed to an increase in the free 5-HT in the brain, resulting from its release by reserpine and the subsequent prevention of its destruction by iproniazid. For these reasons, it has been suggested that free 5-HT may be

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involved in the development of psychopathologic symptoms in man. The combined administration of 11-desmethoxyreserpine and iproniazid, however, decreases the severity of the psychopathologic symptoms of schizophrenic patients.[4] The effects of the drug combination, reserpine plus iproniazid, on normal man have not been reported.

We have compared, in normal man, the mental and physical effects of the drug combination, reserpine plus iproniazid, with those of LSD. To study the possibility of a decrease or an increase of the LSD-effect by reserpine plus iproniazid, the combination of all three drugs also has been employed. The use of LSD as an investigative tool in psychopharmacology requires a method of mathematical measurement of the mental response. The effect of LSD is experienced by a human subject in various ways. Subjects report changes in mood, either in the direction of euphoria or depression, anxiety and nervousness in the form of muscular stiffness and "inner tremors," difficulties in concentration and in orientation in time, feelings of strangeness and dreamlike states. Other changes are alterations in sensory modalities, distortions of the body image, changes in the appreciation of taste, smell, and sound, and a number of visual phenomena which include blurring of vision, perceptual changes in distance, size, shape, and color, and the appearance of kaleidoscopic patterns.

Conventional psychometric tests do not measure these alterations in status and performance of the mind. Questionnaires can be used on untrained subjects to distinguish between LSD and placebo,[1] but cannot be used to distinguish significantly between dose levels of LSD with 25 μg intervals. When a subject has received LSD several times, apparently he then becomes able to identify the drug and to quantify the dose given with a high degree of precision.[3,8] In this study we have relied on these subjective reports by trained subjects. The experimental design employed rigidly controlled and standardized conditions to make this subjective evaluation as uniform as possible.

Methods

Selection of subjects. The experimental subjects were a group of 16 volunteers, all inmates of the U.S. Federal Penitentiary in Atlanta, Georgia. They were in good physical health, their mean age was 34 years, and their mean weight was 160 pounds. A Rorschach test was performed on them to detect subjects with latent psychotic tendencies. The latter as well as emotionally unstable individuals were excluded from the study. Of the subjects chosen, the I.Q. ranged from 90 to 123, and the "psychopathic deviant" scores of the Minnesota Multiphasic Personality Inventory had a mean of 68.1, with a range from 50 to 90. Except for character disorders, no psychiatric abnormalities were present in these subjects.

Administration of drugs. Treatments were administered orally, 2 hours after a light breakfast, once a week. A double-blind control was used. Each time 50 ml. quinine-flavored liquid and four tablets were given. The treatments tested were: 2 mg. reserpine with 100 mg. iproniazid; LSD in doses of 25, 50, and 100 μg; LSD in doses of 25 or 50 μg with 2 mg. reserpine and 100 mg. iproniazid; 2 mg. reserpine; 100 mg. iproniazid; and LSD in doses of 25 or 50 μg in combination with either 2 mg. reserpine or 100 mg. iproniazid.

Procedures. The subjects were divided into 8 groups of 2 each. All groups were tested in a hospital room with 4 groups of subjects present each time. The subjects were encouraged to stay in bed during the trials. The objective signs of drug effect were measured and recorded by one of the physicians participating in the project. These included hourly measurements of blood pressure, pulse rate, pupil diameter, oral temperature, and hand steadiness. The latter was measured with a technique which required the subject to introduce a round metal stylus into a hole with a di-

ameter of 2, 3, or 4 mm. The subject was instructed to hold the stylus in the hole for a period of 30 seconds and to avoid contact with the edges. The number of contacts for each hole was expressed in counts (errors) per 30 seconds. An increase in the number of counts indicated a decrease in hand steadiness. The scores provided only a rough estimate of the steadiness.

The subjective mental effects were assayed on the basis of an interview with the subjects on their experiences 3 hours after medication. Each subject had experienced during his training the effects of single doses of 25, 50 (either one of them twice), and 100 μg LSD, at least 4 times. He was able to identify typical symptoms of the LSD effect and had learned to associate the number and the intensity of symptoms with particular doses of LSD. During the interview the subject was asked to identify his symptoms with the help of a series of questions.[1] The questions were arranged in an order of decreasing effects with those at the highest dose level appearing at the top and those with placebo at the bottom. Questioning was started alternately at the top or at the bottom of the list. The list follows:

1. Are things moving around you?
2. Do you have "funny" feelings on your skin?
3. Do you feel unsteady?
4. Do you feel as if in a dream?
5. Do you tremble inside?
6. Is there pressure in your ears?
7. Do you have difficulty in focusing vision?
8. Do you feel weak?
9. Do your hands and feet feel light or peculiar?
10. Is your skin sensitive?
11. Is salivation increased?
12. Is your appetite increased?
13. Do you feel ill in any way?
14. Do your hands and feet feel heavy?
15. Are you nauseated?
16. Do you have a "funny" taste in your mouth?
17. Do things seem too far away?
18. Is your hearing more acute than usual?
19. Do things seem too close?
20. Are your palms dry or cold?
21. Do you see double?
22. Does light bother you?
23. Are you cold?
24. Do you feel fatigued?
25. Is your appetite decreased?
26. Are you anxious?
27. Does your head ache?
28. Do you feel drowsy?

Finally the subject was asked whether he thought he had received LSD, and if so, what dose. The subject had a choice of six dose levels: 0, 25, 50, 75, 100, and over 100 μg. The dose level stated was recorded and used in the assays as the quantitative value of the drug response to LSD.

Twenty-four hours after the administration of the drugs, the subjects prepared a written statement in which they compared the duration of the mental effects of this drug with the effect of the drug given the previous week and indicated whether there were any prolonged effects beyond 3 hours after medication. After they had prepared their written statement, the subjects were told the drug and the dose administered. This learning process increases their sophistication for discerning the mental effects of the drug.

Design. The main data in these experiments were collected from 2 blocks of treatments. They were designed with 4 objectives in mind:

1. Do the subjects discriminate between LSD and other drugs?
2. Do the subjects discriminate between doses of LSD?
3. Does the combination of iproniazid plus reserpine induce LSD-like effects?
4. Does the addition of reserpine and iproniazid to LSD alter the number and the intensity of the psychopathologic symptoms?

Before the first block of treatments was started, the subjects were acquainted with the mental and physical effects of a 100 mg. dose of iproniazid and 2 and 4 mg.

Table I. *Subjects' groups*

Trial	*1 and 5*	*2 and 6*	*3 and 7*	*4 and 8*
1	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 50 μg + Iproniazid 100 mg.
2	LSD 50 μg	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 50 μg + Iproniazid 100 mg.	Reserpine 2 mg. + Iproniazid 100 mg.
3	LSD 25 μg + Iproniazid 100 mg	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg	LSD 50 μg
4	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg + Iproniazid 100 mg.	Reserpine 2 mg. + Iproniazid 100 mg.	Reserpine 2 mg. + Iproniazid 100 mg.

Table II. *Subjective identification of LSD*

Medication received	*Reported as*	
	LSD	*No LSD*
LSD	15	0
Reserpine + iproniazid	3	24
LSD + iproniazid	14	3
Iproniazid	1	8

doses of reserpine. Following iproniazid alone, 4 subjects reported no effects at all, and 5 reported flush and warmth associated with a feeling of well-being or relaxation. One subject identified iproniazid once as a dose of 50 μg LSD. The reported side effects of reserpine were diffuse headache, nasal stuffiness, and facial flush. Doses of 25, 50, and 100 μg LSD were included in the treatments to maintain the sophistication of the subjects for the effects of LSD.

Results

In the first block of 4 treatments (Table I), the combination reserpine-plus-iproniazid was matched with LSD in doses of 25 or 50 μg, and similar doses of LSD-plus-iproniazid. The objective was to test whether the combination of iproniazid-plus-reserpine induced an LSD-like effect.

The combination of 2 mg. reserpine-plus-100 mg. iproniazid was given 27 times. The LSD-like effect was reported only 3 times. All subjects indicated feelings of warmth, showed facial flushing and conjunctival injection. Later they reported congestion of the nasal mucosa. Feelings of drowsiness or relaxation were reported 5 times. Five trials were missed.

Inspection of the scores made for identification of LSD and the scores made for the combination of reserpine and iproniazid shows that the subjects are able to discriminate between LSD and other drugs and, therefore, that there is no reason to assume that an LSD-like effect is induced by the reserpine-iproniazid combination in these subjects (Table II).

The physical findings do not reveal any similarities in man between LSD and this

combination in the doses and route used. The combination does not induce the most constant LSD effect, dilatation of the pupil. There is a lowering of systolic and diastolic blood pressure, while LSD induces a rise in systolic blood pressure.

This first testing procedure gave information about the absence or presence of an LSD effect in the range from zero to a 25 or 50 μg dose. A smaller LSD-like effect may be detectable by testing for an additive, potentiating, or antidotal effect of reserpine and iproniazid on the LSD responses. This method may be more sensitive. A second block of treatments was set up with these objectives in mind (Table III).

The objectives 2 and 4 were now considered. Do the subjects discriminate between doses of LSD? Furthermore, does the addition of reserpine and iproniazid to LSD change the number and the intensity of the psychopathologic symptoms? For the evaluation of the presumed change a standard dose response curve of the group, acting as a whole, for the mental effects of LSD had to be determined.

In a quantitative method of evaluation

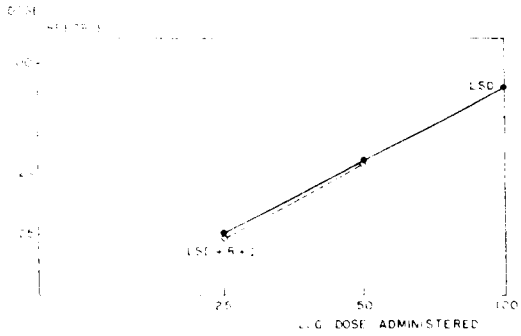

Fig. 1. Response curves of the quantitative estimation are plotted for *d*-lysergic acid diethylamide alone and in combination with reserpine, 2 mg., plus iproniazid, 100 mg., on a semilogarithmic scale. The ordinate is the dose of LSD recorded. The abscissa is the actual dose administered plotted on a logarithmic scale.

the estimated doses for LSD alone at the three dose levels have been pooled and their means plotted against the log of the administered doses. These 3 points can be joined by a straight line (Fig. 1). Table IV gives the means of the values obtained. Table V gives the results of the analysis of variance on the data, including the controls, obtained from the administration of LSD alone. The log-dose response rela-

Table III. *Subjects' groups*

Trial	*1 and 3*	*2 and 4*	*5 and 8*	*6 and 7*
1	LSD 25 μg	LSD 50 μg	LSD 100 μg	Reserpine 2 mg. + Iproniazid 100 mg.
2	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg + Reserpine 2 mg. + Iproniazid 100 mg.	LSD 50 μg + Reserpine 2 mg. + Iproniazid 100 mg.	LSD 50 μg
3	LSD 25 μg + Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg	LSD 50 μg	LSD 50 μg + Reserpine 2 mg. + Iproniazid 100 mg.
4	LSD 50 μg	Reserpine 2 mg. + Iproniazid 100 mg.	LSD 25 μg + Reserpine 2 mg. + Iproniazid 100 mg.	LSD 100 μg

Table IV. *Quantitative evaluation of LSD*

Medication received	*Mean of doses reported and standard error of the mean*
LSD 25 μg	26.3 ± 3.8
LSD 50 μg	57.9 ± 3.9
LSD 100 μg	91.1 ± 8.5
LSD 25 μg + Reserpine 2 mg. + Iproniazid 100 mg.	24.3 ± 6.3
LSD 50 μg + Reserpine 2 mg. + Iproniazid 100 mg.	57.3 ± 3.2

Table V. *Analysis of variance of the results of experiments to show the ability of the group to identify doses of d-lysergic acid diethylamide*

Source of variation	*SS*	*df*	*MS*	*F*	*P*
Curvature	46445.20	2	23222.60	55.2	0.05
Linear regression	71427.80	1	71427.80	169.5	0.0
Doses	117873.00	3	39291.00	93.3	-
Error	50944.46	121	421.03	—	—
Total	168817.46	124	—	—	—

tionship is significantly linear, $P>0.01$ and <0.05. The curve is straight from 25 to 100 μg. There is a curvature from zero to 25 μg. All three errors were pooled because the variations due to subjects and the variations due to the interaction between doses and subjects were not larger than the variation between replicate tests using the same dose on the same subject.

A relationship does exist between the doses administered and the doses reported for the group acting as a whole. Therefore, the standard curve in Fig. 1 can be used as a measure of the psychic effects of LSD in graded doses. It shows that this group of subjects is able to identify the intensity of psychopathologic symptoms and to correlate these symptoms with a certain dose of LSD.

The number and the intensity of the psychopathologic symptoms induced by 25 and 50 μg of LSD as shown in this assay and those induced by the combination of LSD plus reserpine and iproniazid were compared. There was no significant difference between these two curves and hence between these two treatments (Fig. 1). No difference in duration of the effects was revealed by the written statement.

The effects of LSD either in combination with reserpine only or with iproniazid only also were tested in 10 and 17 trials, respectively, to exclude the possibility that the resultant LSD-combination curve was the algebraic sum of two gross opposite effects. The mean reported doses of these two treatments did not differ from the LSD-standard values.

In a final evaluation of the results of all trials the objective was to determine whether subjects can discriminate between LSD and other drugs. The results of 172 trials were available for analysis. Of this total, 122 were administrations of LSD, either alone in doses of 25, 50, or 100 μg or in combination with other drugs. The remaining 50 were administrations of other drugs alone. In 122 administrations of LSD, the subjects reported an LSD-like effect 113 times. "No LSD" was reported 49 times. Analysis by chi-square test of the scores gave a value of 116.8, $P<0.001$. Thus, it was established that the ability of the subjects to discriminate between the treatments was highly significant.

Discussion

The use of *d*-lysergic acid diethylamide as a reference standard for the evaluation of psychopathologic symptoms was examined. Within the range of dose levels of 0, 25, 50, and 100 μg, a group of subjects was able to establish a relationship between the doses administered and the doses of LSD reported. The measurement of such a highly individual response as the amount and degree of intensity of psychopathologic symptoms based on the estimation of the dose administered has the advantage of being simple and rapid. The highly significant value for the difference obtained in identification scores between LSD and other drugs indicates usefulness of LSD in an assay of this type of psychic activity.

An estimate of how many of these responses in general are required for a reliable assay, however, cannot be given for these data. In this study the error of the assay has been small, partly because of the inclusion of a large number of zero responses on zero dose. The number of responses required will of course depend on such variables as the background and training of the subjects. The maintenance of a constant group of well-trained subjects makes this technique difficult, unless special experimental conditions such as a closed ward or penitentiary are available. Even in spite of the rigidly controlled experimental conditions some subjects were absent at one or two trials and two had to be replaced during the course of these experiments. These exclusions disrupted the Latin square design of the experiment and therefore no information on possible changes in drug or subject responses with time was obtained.

In previous studies atropine, niacin, and 2-brom-*d*-lysergic acid diethylamide were shown to be ineffective as modifiers of the LSD response in man.[8] Chlorpromazine[7] and amobarbital were reported to diminish the response.[5] In this study the combination of reserpine and iproniazid did not alter the development of LSD-like psychopathologic symptoms.

In the quantitative assay of this study identical curves were obtained for LSD alone and in combination with doses of reserpine and iproniazid. Therefore, these treatments were similar in their psychic effects. The conclusion may be drawn that there was no extensive change by the action of reserpine plus iproniazid on LSD-induced psychopathologic symptoms, which would be expected if free 5-HT were related to or interfered with the development of LSD psychopathologic symptoms. The results of the present study fail to support this concept.

Conclusions

1. The subjective and physical effects of the drug combination reserpine plus iproniazid have been compared with the effects of *d*-lysergic acid diethylamide on trained healthy male volunteers.

2. Evaluation of psychic effects has been based on interviews 3 hours after drug administration and on written statements prepared 24 hours later.

3. Subjects can discriminate between the mental effects of LSD and those of the drug combination and are able to estimate the three dose levels of LSD administered.

4. The scores for qualitative identification of LSD and the combination of reserpine plus iproniazid indicate that the psy-

chic and physical effects of these two treatments are dissimilar. Therefore, the effects of the combined administration of reserpine plus iproniazid do not mimic those of LSD.

5. The log-dose response curves for the dose identification of the two dose levels of LSD and the two dose levels of LSD plus reserpine and iproniazid show that these treatments do not differ in their psychic effects. The combination of reserpine plus iproniazid neither increases nor decreases the degree and intensity of LSD-induced psychopathologic symptoms in man.

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