COMPARISON OF THREE PSYCHOTROPIC DRUGS (PSILOCYBIN, JB-329, AND IT-290) IN VOLUNTEER SUBJECTS

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Clinical success with tranquilizers has rekindled interest in psychotomimetic drugs both as research tools and therapeutic agents. Recently, psilocybin and JB-329 ('Ditran') have been added to the list of psychotomimetic agents, though differing in chemical structure and origin. Psilocybin occurs naturally as an active principal of the hallucinogenic mushroom, *Psilocybe mexicana Heim*, while JB-329 is synthetic. Psilocybin has an indolic structure with a phosphoric acid grouping at the 4-position, making it unique among naturally-occurring indoles thus far known. Chemically, it resembles another psychotomimetic, bufotenin, as well as the possible neurohormone, 5-hydroxytryptamine (serotonin). JB-329 consists of two isomers: N-ethyl-2-pyrrolidylmethyl-phenylcyclopentyl glycolate hydrochloride and N-ethyl-3-piperidyl-phenylcyclopentyl glycolate hydrochloride. These compounds have strong central and peripheral anticholinergic effects comparable to atropine. However, the central effects of JB-329 do not appear to be related to cholinergic blockade as administration of anticholinesterase drugs reverses only the peripheral effects. Earlier studies of psilocybin and JB-329 indicated that in humans profound mental effects could be elicited (3, 6, 7, 10).

Having decided to study these two compounds concurrently, we further decided to introduce a comparison drug. For this purpose, we chose IT-290 (dl-alpha-methyltryptamine), the indole analog of amphetamine. Animal pharmacologic studies indicated some amphetamine-like properties, though IT-290 was less toxic and excitant. IT-290 seemed appropriate as a comparison agent because of its chemical relationship to psilocybin and pharmacologic effects mimicking in part those of psychotomimetic agents.

METHOD OF STUDY

Psilocybin was used in 27 trials in 16 subjects. Oral doses ranging from 60 to 209 mcg/K were taken in 18 trials, parenteral doses ranging from 37 to 203 mcg/K were taken in 9 trials. JB-329 was administered in 11 trials in as many subjects. All doses were oral, varying from 40 to 339 mcg/K. IT-290 was administered in eight trials in as many subjects. All doses were oral, ranging from 384 to 810 mcg/K. Seven subjects received one trial of each of the three drugs administered orally in a varying sequence using blind controls. This procedure was done in a special attempt to compare the three agents in the same subjects. These volunteer subjects were mostly graduate students who had been trained to make objective observations and possessed descriptive ability. Their age varied between 22 and 44 years (median 26 years). All were in good general health and had been screened to rule out overt psychiatric disorders. Drugs were administered early in the morning with the subjects fasting.

Trials were conducted on a medical ward of a psychiatric hospital. Subjects were placed in a private room, small and austerely furnished. To minimize the effects of external

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influence, subjects were visited by hospital personnel only for obtaining clinical or laboratory data. For the first 90 minutes of each trial, these interruptions were minimal.

Three parameters were studied, as follows.

Clinical Measures. Each subject was provided with a tape recorder for verbal recording of subjective experiences. Time cues were provided so that the onset and duration of each reported symptom could be recorded. Each tape was carefully reviewed to transcribe a chronologic log. Following the trial, each subject completed a questionnaire of 43 questions. Twenty-five of these were questions most frequently answered positively in a questionnaire previously used in studies of psychotomimetic drugs; 18 questions regarding specific symptoms of psychopathology were derived from another similar questionnaire (1, 8). These two sources of data were combined to establish the full clinical syndrome experienced. Prior to each trial, measures were taken of blood pressure, pulse rate, pupillary size, deep tendon reflexes, and simple coordination tests (finger-nose, heel-knee, Romberg test). These tests were repeated approximately two hours after taking psilocybin and IT-290 and approximately four hours after taking JB-329.

Biochemical Measures. Prior to administering each drug, blood was drawn for determination of fasting total eosinophil count, serum cholesterol, alkaline phosphatase and cholinesterase activity and serum glutamic oxalacetic transaminase (SGO-T) titer. These measures were repeated two hours later in the case of psilocybin and IT-290 and four hours later in the case of JB-329. A baseline electroencephalogram was also obtained, being repeated one and one-half to two hours after psilocybin and IT-290 and three and one-half to four hours after JB-329. A control urine sample was collected for determinations of total inorganic phosphorus and creatinine excretion. All urine voided during the first two hours of the trials with psilocybin and IT-290 and during the first four hours with JB-329 was collected for the same determinations.

Psychometric Tests. Two measures of mental function were used. One consisted of a series of simple arithmetic problems (Number Facility Test). The other consisted of linear drawings, each comprising four lines which had to be copied from a completed drawing (Flexibility of Closure) (9). Subjects were also tested for ability to estimate varying periods of time (5, 15, 30, and 60 seconds). Each of these tests were administered prior to each drug trial and hourly for four hours after drug administration.

RESULTS OF STUDY

Clinical Syndrome

The clinical syndromes from each of the three drugs are shown in Table 1. Despite the fact that these agents produced many symptoms and signs in common, the total clinical syndrome from each drug was distinctly different. The onset of action of psilocybin was fairly prompt, usually within 30 minutes, and the total duration of action was comparatively brief, usually having subsided after four hours. The predominant mental symptoms of the drug were an initial feeling of anxiety and tension, later succeeded by euphoria and a dreamy, introspective state with only slight loss of mental functions and ability to communicate. Visual effects were also predominant, beginning with blurring and increased definition of objects, proceeding to the illusion of apparent motion of objects or surfaces, and culminating in visions of a variety of colored patterns and shapes, generally pleasing, sometimes frightening, most often seen with the eyes closed but occasionally superimposed upon objects in the field of vision. The psilocybin experience was generally described as pleasant and conductive to insights, although the latter were particularly difficult to describe or document.

With IT-290, onset was slower than with

TABLE 1

Comparison of Clinical Syndromes From Psilocybin, IT-290 and JB-329

Psilocybin	IT-290	JB-329
0–30 Minutes	*0–30 Minutes*	*0–30 Minutes*
Dizzy, giddy	Euphoria	Dizzy, poor coordination
Nausea, abdominal discomfort	Nausea, heartburn	Nausea, dry throat, heartburn
Weakness, muscle aches and twitches, shivering	Yawning, drowsiness	Loss concentration, poor memory
Anxiety, restlessness		Blurred vision, decreased distance perception
Numbness of lips		Difficulty breathing
30–60 Minutes	*30–120 Minutes*	*30–120 Minutes*
Visual effects (blurring, brighter colors, sharper outlines, longer after-images, visual patterns with eyes closed)	Nausea, retching	Brighter colors, sharper outlines
Increased hearing	Dizzy, unsteady	Slurred, blocked, incoherent speech
Yawning, tearing, sweating, facial flushing	Euphoria, restlessness, jittery	Time sense distorted
Decreased concentration and attention, slow thinking, feelings of unreality, depersonalization, dreamy state	Yawning, lethargy	Body-image distorted
Incoordination, tremulous speech	Decreased concentration, silly, inappropriate smiling	Disorientation, confusion, memory loss
		Muscle spasms
60–120 Minutes	*120–240 Minutes*	*120–240 Minutes*
Increased visual effects (colored patterns and shapes, mostly with eyes closed)	Visual effects (blurring, apparent movement of objects, sharper outlines, brighter colors, longer after-images, decreased depth perception)	Confusion, speech disorders continue
Wave-motion of viewed surfaces	"Drunk", euphoria, poor coordination	Apparent motion of objects, wave-like motion of surfaces
Impaired distance perception	Tremors, numbness of extremities	Decreased appetite
Euphoria, ruminative state, increased perception	*4–12 Hours*	Tension, tremors, anxiety
Slowed passage of time	Visual effects (patterns, eyes closed)	Weakness, lethargy, dreamy state
120–240 Minutes	Muscle aching, shivering	Coughing
Waning and nearly complete resolution of above effects	Decreased appetite	Mood change (usually depression)
	Weakness, lethargy	*4–12 Hours*
4–12 Hours	*Later Effects*	Some waning of above effects, if dose small; otherwise may persist
Usually normal	Continued stimulation, insomnia, fatigue, muscle aching, headache, heartburn, "hangover"	*Later Effects*
Later Effects	*Less Common Effects*	Fatigue, lethargy, mental depression, poor coordination, dizziness, poor appetite, tremors
Headache, fatigue, contemplative state	General malaise, salivation increased, paresthesia, dreamy state, mild depersonalization	*Less Common Effects*
Less Common Effects		Depersonalization, visual or auditory hallucinations
Uncontrollable laughter, paresthesia and synesthesia, difficulty in breathing, decreased appetite, transient sexual feelings		

psilocybin and effects were longer, sometimes lasting over a 16 to 18-hour period. Direct stimulation was greater than with psilocybin, early symptoms of jitteriness, restlessness, and anxiety being more pronounced. The visual effects, not often present, were slight. Mental function was little impaired. Somatic symptoms were greater in number and

TABLE 2

Clinical and Biochemical Measures During Trials With Psilocybin, IT-290 and JB-329

Measure	Psilocybin 27 trials	IT-290 8 trials	JB-329 11 trials
Blood pressure	3 elevated	1 elevated	1 elevated
Pulse rate	No change	1 elevated	1 elevated
Pupils	Dilated 24, ave. 3 mm.	Dilated 8, ave. 3 mm.	Dilated 11, ave. 3 mm.
Reflexes	Increased in 19	Increased in 7	Increased in 9
Coordination tests	? pos. Romberg 13	? pos. Romberg 2	? pos. Romberg 5
Urine mgP/mg creatinine	Decreased ($p < 0.05$)	n.s.d.*	n.s.d.
Total eosinophil count	Decreased ($p < 0.05$)	n.s.d.	Decreased ($p < 0.05$)
Serum glutamic oxalacetic transaminase	n.s.d.	n.s.d.	n.s.d.
Serum pseudocholinesterase	n.s.d.	n.s.d.	n.s.d.
Serum alkaline phosphatase	n.s.d.	n.s.d.	n.s.d.
Serum cholesterol	n.s.d.	n.s.d.	n.s.d.
Electroencephalogram	No change	No change	No change

* n.s.d.: no significant difference ($p > 0.05$)

degree than with psilocybin, many subjects complaining of feeling ill for various reasons. With lower doses, these effects could be moderated without changing the general effect of the drug on mood. Except for the somatic effects, the drug experience was considered to be pleasant, though not as meaningful as with psilocybin.

The syndrome produced by JB-329 was considerably different from either other drug. Onset of action of this drug was rapid and effects prolonged. With any sizeable doses of the drug, subjects were generally so incapacitated as to require staying in the hospital overnight, much mental confusion persisting through these hours. The clinical syndrome more clearly resembled a toxic delirium, especially similar to that produced in the past by scopolamine (4). Mental confusion, disorientation, memory loss and marked impairment of speech were predominant features. A characteristic speech pattern was one in which at mid-sentence, a new and irrelevant subject would be introduced into the conversation. From one moment to the next, subjects had difficulty in remembering what they were talking about or what they had just said. Unlike the other two drugs, subjects were somewhat withdrawn, tending not to speak unless spoken to, maintaining a rather perplexed expression. Ideational apraxia was particularly frequent, several subjects attempting to drink from a urinal for collecting urine specimens and one attempting to wash his hands in a toilet bowl. Marked anxiety was also felt, though seldom mentioned until retrospectively. Mood tended to be depressed though less common or severe than the anxiety-provoking effects. On the whole, subjects found JB-329 extremely unpleasant, few considering additional trials of the drug at all. Most had only fragmentary memory for the experience, none describing any positive effects from it.

Clinical and Biochemical Measures

Results of clinical and biochemical measures during the drug trials are summarized in Table 2. Psilocybin significantly elevated blood pressure in three subjects, two having unusually low control blood pressures, and one being a borderline hypertensive. Pulse rate was not changed appreciably in either direction. Dilatation of pupils was almost constantly encountered, averaging 3 mm. over a 2-hour period. Deep tendon reflexes were increased during 19 trials, often becoming clonic in character. Incoordination was more subjective than objective, though sloppiness in coordination tests or swaying on the Romberg test could be detected.

Urinary excretion of inorganic phosphorus and total circulating eosinophils were both significantly reduced. No remarkable changes were noted in the SGO-T titer, serum cholesterol, serum cholinesterase, serum alkaline phosphatase, or electroencephalogram.

IT-290 increased blood pressure and pulse rate beyond physiologic limits in one subject who received the largest dose of the drug and was the oldest subject in the series. Dilatation of the pupils was constant, averaging 3 mm. over a 2-hour period. Deep tendon reflexes were increased in seven trials. Impairment of coordination tests was noted in two subjects. No changes were noted in the remaining biochemical tests nor on the electroencephalograms, though a decrease in total circulating eosinophils just missed statistical significance.

JB-329 increased blood pressure and pulse rate in one subject who had received a large dose. Another subject had an elevated pulse rate. Dilatation of the pupils was constant, averaging 3 mm. over a 4-hour period. Visual blurring was more frequent and severe with JB-329 than with the others despite similar degrees of pupillary dilatation. Deep tendon reflexes were increased in nine subjects. Coordination tests were impaired in five. The only physiologic measure significantly decreased by JB-329 was the total circulating eosinophil count. The remaining biochemical tests and electroencephalograms were not significantly changed from control values.

Psychometric Tests

Psilocybin administered orally decreased significantly the number of problems completed on the Number Facility test during the first hour, but following this, there were no significant differences. Parenteral psilocybin decreased significantly both the number of lines attempted during the first two hours (on the Flexibility of Closure test) and those correctly drawn during the first hour. The number of problems completed on the Number Facility test was significantly decreased during the first hour after the drug. Time estimates of 5, 15, 30, and 60 seconds were not significantly altered by the drug.

IT-290 produced no significant changes on the Number Facility test, Flexibility of Closure test, or time estimates during the first 4-hour period of drug administration as compared with the control measures. On the Flexibility of Closure tests, both the number of lines attempted and completed correctly showed a progressive increase during the first four hours, but failed to reach significance.

JB-329 impaired both psychometric tests. The number of problems correctly completed on the Number Facility test was significantly decreased at the third and fourth hours following drug administration. Two of the subjects were unable to complete any correct problems once the drug had been administered. Both the number of lines attempted and correctly completed were decreased on the Flexibility of Closure test but failed to reach significance during each of the four hours. Once again, two subjects were unable to attempt the test at all once the drug took effect. At four hours, the time estimate for 60 seconds was significantly shortened.

Chronic Administration of JB-329

In a previous report, tolerance to psilocybin was produced by chronic administration in one subject (5). By progressive increase in divided daily doses over a 21-day period, a subject took a large acute dose of the drug (203 mcg/K) with minimal effects. Subsequently, the same dose administered acutely without prior chronic dosage produced a characteristic clinical syndrome.

Another subject agreed to take JB-329 chronically while observed in the hospital. This subject had previously received a 20 mg. dose of the drug (339 mcg/K) which produced a profound clinical syndrome lasting for 24 hours. During the course of chronic administration, he received three divided doses of the drug for 21 days, beginning with a total daily dose of 0.3 mg.

on day 1, increasing to 3 mg. by day 5, 9 mg. by day 9, 18 mg. by day 15, and 27 mg. by day 21. On the 22nd day, he received a single acute dose of 20 mg. as he had received earlier. During the period of chronic administration, he complained within a few days of diminished taste sensation, mild visual blurring, and a slight increase in jitteriness. These complaints did not increase, being constant during the chronic trial. Otherwise, he was able to function normally with mental, speech, and motor functions unimpaired. Following the acute dose of 20 mg. on the 22nd day, he experienced no additional symptoms from what he had previously reported. In fact, he said that on this particular day he had less symptoms than for several days preceding, the latter being days when his total dose exceeded that of the single acute dose. Chronic administration of JB-329, as with psilocybin, apparently leads to tolerance for many of somatic and mental effects of this agent.

DISCUSSION

The two drugs resembling each other most were those chemically similar. Even so, distinct differences were noted between psilocybin and IT-290. Psilocybin resembled LSD-25 and can be properly classified as a psychotometic agent. The clinical syndrome from psilocybin could also have been produced by LSD-25 with a few differences. Psilocybin evoked a dreamy, introspective state at dose levels which did not produce predominant somatic effects nor marked impairment of mental functions. The total span of action was also briefer than with LSD-25 and the whole effect was more agreeable.

IT-290 had a mood-elevating effect similar to but stronger than dextroamphetamine. A peculiar mixture of other effects was also noted. Most patients complained of yawning, dreaminess, and lethargy, despite the fact that mental functions were not impaired. This aspect of the drug, as well as some of its somatic effects, was reminiscent of reserpine. Some of the visual effects resembled those from LSD-25 though less frequent and much milder. The long duration of action of IT-290 as compared with psilocybin may be due in part to the larger dose used.

JB-329 differed substantially from other psychotomimetic agents such as psilocybin, LSD-25, and mescaline. It produces a toxic delirium analogous to that from scopolamine or other belladonna alkaloids. The mental confusion, disorientation, memory loss, and fluctuating level of awareness represent an organic picture differing considerably from usual clinical manifestation of schizophrenic reactions. The long duration and marked impairment makes it imperative that JB-329 be used only in hospitalized patients.

Few biochemical abnormalities were noted from the drugs. Reduction in total circulating eosinophils from psilocybin and JB-329 might be nonspecific as other pharmacologic actions of these two agents are quite different. Effects on electroencephalograms were negligible, at least as observed by usual clinical interpretative techniques. The effects of these drugs on mental functions as measured by the psychometric tests showed clear differences. Psilocybin impaired motivation more than performance as the ratio of correct responses to line drawings attempted remained constant even though the number attempted was reduced. On the other hand, JB-329 decreased not only the attempts but the ratio of correct responses, suggesting impaired performance. With IT-290, confidence was increased with more drawings being attempted, although the ratio done correctly remained constant.

Each of these three drugs may prove to have therapeutic usefulness. Psilocybin has already been used for facilitating psychotherapy (2). IT-290 may be useful in similar fashion as well as an antidepressant. JB-329 has been recommended as an antidepressant. This drug might also be a useful agent for the experimental determination of delirium thresholds.

SUMMARY

Three new psychotropic drugs, psilocybin, IT-290 (dl-alpha-methyltryptamine) and JB-329 ('Ditran') were compared in volunteer subjects.

Psilocybin resembled lysergic acid diethylamide (LSD-25), producing a clinical syndrome of anxiety, euphoria, introspection and visual effects lasting about four hours. IT-290 more closely resembled amphetamine in producing mood elevation and reserpine in producing somatic effects. Effects of large acute doses persisted for 12 or more hours. JB-329 resembled scopolamine, producing a toxic delirium lasting 12 to 24 hours.

Total circulating eosinophils were significantly reduced by both psilocybin and JB-329. Psilocybin also reduced urinary excretion of inorganic phosphorus. IT-290 had no effect on either of these biochemical tests. None of the other tests measured (serum alkaline phosphatase, serum pseudocholinesterase and serum glutamic oxalacetic transaminase activity, or serum cholesterol) were altered by either drug. Electroencephalographic tracings showed no clinically detectable changes.

Psychometric tests revealed a decrement from psilocybin suggesting decreased motivation. A larger impairment from JB-329 was attributed to dereased performance. IT-290 did not change the tests significantly, though tending to increase both motivation and performance.

Chronic administration of JB-329 leads to tolerance.

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