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PRELIMINARY STUDY OF A NEW ANTI-DEPRESSANT DRUG

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Recently, with the reintroduction of iproniazid as a "psychic energizer," a great deal of interest has been stimulated in the chemical treatment of seriously depressed patients. The search for effective agents for the treatment of depression has been encouraged by the failure of tranquilizers to provide relief in most severe depressions. Preliminary studies with 2-amino-1-(3,4-methylene-dioxyphenyl)-propane hydrochloride (SKF #5) (see Figure 1) led us to feel that it might be a useful drug in this area.

SKF #5 is an analog of the well known central nervous system stimulant and anorexigenic agent, dextro-amphetamine sulfate. Like the amphetamines, it has the property of increasing motor and mental activity. Unlike amphetamine, however, SKF #5 has a very considerable activity in blocking the response to a conditioned escape stimulus. This animal test appears to be one means of identifying compounds which have a potential utility in the management of behavioral changes in the mentally disturbed human. To date, this property has been associated only with agents which have some central depressant activity as well. However, the data on SKF #5 suggests that its effect on a conditioned response is not directly related to generalized depression or stimulation of the central nervous system.

Previous studies in animals (3) and in human subjects (1, 2) indicated that this drug did not produce serious toxic or side effects. The LD_{50} in rabbits was found to be 20 mg./kg. intraperitoneally, and by oral administration in rats was 50 mg.–350 mg./kg. This represents about one-half the toxicity of dextro-amphetamine sulfate.

On the basis of these activities in animals and in a small group of humans, it was felt that SKF #5 merited further trial in a group of schizophrenic patients to determine its tranquilizing properties, and in a group of seriously depressed patients to determine its effectiveness in altering mood.

OBJECTIVES

In a preliminary investigation of this nature, in which expectations of drug efficacy are largely unknown, it was felt that thorough study of smaller groups of patients by as objective an approach as possible was preferable to a large double-blind study. Our intentions were to obtain evidence of efficacy, if any, to derive information on dose range and optimal dose, and to elicit all possible side effects developing during a one-to-four week period of drug usage.

METHOD

All new admissions, in whom the appropriate diagnosis was concluded by two psychiatrists to be unequivocal, were included in the study if they met the following criteria:

1. Their age was between 14 and 65.
2. They had no observable serious physical abnormalities after a physical and laboratory examination.

The patients who were selected were placed on placebo for from three to seven days to offset the effects of prior drugs, to eliminate patients who recover quickly and spontaneously, and to establish a baseline of vital signs and somatic complaints.

In order to objectify as must as possible clinical impressions of patients, an evaluation scheme was established which permitted

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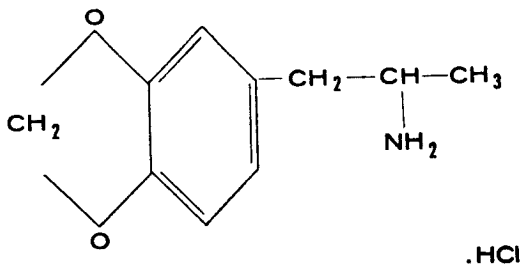

FIG. 1. Structural formula of SKF #5

estimation of the patients' progress from a number of different viewpoints.

1. The patients were evaluated daily by a psychiatrist who made a record of improvement relative to the patient's condition on admission. His function was also to evaluate the patient's physical status and any side effects elicited by him or reported by the nurse assigned to the project.

2. A weekly evaluation was made by means of a 38-item rating scale devised for this study and based on the mental status examination. This was scored by a second psychiatrist, independently of the first psychiatrist's clinical impression, and also without reference to ratings in prior weeks.

3. The hygiene, appearance, relationships, and participation of the patient were rated daily by a psychiatric nurse, whose sole function was to observe the patient and to dispense medication.

4. Psychological tests were obtained on a limited number of patients.

5. Laboratory studies were run once a week, with the first tests done before initiation of drug treatment. The routine tests run in this study consisted of:

Complete blood count
Urinalysis, including determination of bile and urobilinogen
Cephalin flocculation
Alkaline phosphatase
Serum bilirubin

TABLE 1

Results of Treatment of Schizophrenic Patients

Total No. Of Patients	Mean Maximum Dose	Mean Days On Drug	Results		Per cent Improved
			Improved	Unimproved	
32	88 mg.	23	2	30	6

DEFINITION OF TERMS

I. *Diagnosis*

A. Category

Diagnoses follow the official classification of the American Psychiatric Association.

B. Chronicity

1. *Chronic:* This refers to patients who have a history of their present illness for periods exceeding six months prior to admission.
2. *Acute:* This refers to patients in whom there was no history of present illness prior to six months ago.

II. *Clinical Results (Mental Status)*

Severe:[2] Seriously disturbed, withdrawn, or depressed; may be incapacitated by delusions or thinking difficulties. Virtually completely dominated by illness.

SCHIZOPHRENIC STUDY

A total of 32 schizophrenic patients were treated for from six to fifty-four days, with doses ranging from 15 to 225 mg. Only two of these patients evidenced significant clinical improvement. No significant change in either mental status or ward behavior was noted in the other 30 patients. Most of the patients appeared to be somewhat more alert and energetic. However, this effect was insufficient to be reflected in their ratings. The data on these schizophrenics was not subjected to statistical analysis because of the obvious ineffectiveness of the drug on inspection of the results. These results are summarized in Table 1.

[2] All patients in this study were considered to be severely ill.

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DEPRESSION STUDY

A total of 25 seriously depressed patients were placed on SKF ※5 for periods varying between ten and forty-two days, with doses ranging from 30 to 300 mg. At the same time, another group of patients were placed on placebo. Two patients were assigned to the drug group for each patient assigned to the placebo group, resulting in a final group of 25 patients on active drug and 12 on placebo. Both drug and placebo groups were treated for an average of two weeks, with a range of from ten days to six weeks. A description of the patients is summarized in Table 2.

RESULTS

An analysis of changes in the rating scale scores demonstrated a significant drop in the scores of patients on the drug—from 13.1 initially, to 8.7 after treatment. On this scale a lower score indicates improvement. The mean score of the patients on placebo was unchanged (see Table 3). A comparison of the initial scores indicates that there was no significant difference in the severity of illness between the drug and the placebo groups before treatment. The large change in the score of the drug group after treatment is statistically significant (t test: $P < .01$). Analysis of the differences in each group with regard to diagnosis, chronicity, severity, age, or sex indicates that these differences do not significantly influence the results. This statistical data is in accord with a clinical impression of improvement in 76 per cent of the drug group, as compared with 24 per cent of the placebo group.

In addition, seven patients were rotated from drug to placebo and back to drug. Of this group, five patients improved during drug administration and then relapsed in three to five days on placebo. Subsequent readministration of drug resulted in improvement of all five patients. The other two patients improved on drug, but did not relapse after two weeks on placebo.

Four of the depressed patients in the study subsequently had electric shock treatment, either after withdrawal of the drug and relapse, or because of failure to improve on the drug. One of the four improved on the drug and, also, later improved on EST. Three of the patients treated were unimproved on the drug and only one of these subsequently improved on shock treatment.

Inasmuch as it was not possible at the time of the study to maintain patients on

TABLE 2

Classification of Depressed Patients

	Number of Patients			
	Drug Group		Placebo Group	
	No.	%	No.	%
Diagnosis				
Schizophrenic Reaction, Schizoaffective Type	4	16	2	17
Involutional Psychotic Reaction	12	48	4	33
Psychotic Depressive Reaction	3	12	3	25
Manic Depressive Reaction	1	4	0	0
Neurotic Depressive Reaction, Severe	5	20	3	25
Chronicity				
Acute	12	48	7	58
Chronic	13	52	5	42
Sex				
Male	6	24	2	17
Female	19	76	10	83
Mean Age	47		49	
Total Number of Patients	25		12	

TABLE 3

Results of Treatment of Depressed Patients

Group	No. of Patients	Number Improved	Mean Rating Scale Scores	
			Pre-Treatment	Post-Treatment
Drug	25	19 (76%)	13.1	8.7
Placebo	12	3 (24%)	14.4	14.4

this medication at home, it was necessary to discontinue treatment on all patients. Most patients tended to relapse after discontinuation of the drug and, therefore, required further hospitalization. As a result, a comparison of the final disposition of patients in the drug group and in the placebo group is not meaningful.

The three following case histories will illustrate the clinical findings, and course, in two patients who improved as a result of treatment with SKF ⅍5 and one patient who did not improve.

Case 1. A 57 year old, unmarried woman was brought to the hospital at the suggestion of her physician. In the past few months she had complained of increasingly severe "burning" in the stomach and "whirling in the head." She had been unable to sleep and her appetite was poor. Prior to the onset of these symptoms she had been working and had had no history of previous episodes.

In the hospital she was depressed and agitated, and complained that she had not moved her bowels for two weeks and that her stomach burned. She stated repeatedly that she had "not done enough" to help her ill sister. Physical examination was noncontributory.

A diagnosis of involutional psychotic reaction was made and treatment was begun with SKF ⅍5, 50 mg., t.i.d. In two days the patient admitted to bowel movements, and her agitation was lessened. Therapy was continued for 19 days, with a maximum dose of 75 mg., t.i.d. At the end of that time depression was not evident, and she was eating and sleeping well. Relapse did not occur on withdrawal of drug, and the patient was discharged.

The Rating Scale changed from an initial value of 11 to a low of 1 at termination of treatment. No side effects other than dilated pupils were noted.

Case 2. The patient, a 38 year old married woman, was admitted to the hospital after her husband noted that she had been depressed and tearful for one month. The first episode of depression had occurred 15 years ago and cleared after three month's hospitalization without specific treatment. Since that time she had had periodic mild depressions, but was first hospitalized two months prior to her present admission. At that time she had received eight electric shock treatments and was discharged much improved. After several weeks, however, she again became depressed. She has never had manic episodes.

On examination the patient appeared depressed, tearful and retarded. She was preoccupied with ideas of suicide. She stated that she could not sleep or eat. No delusions or hallucinations were evident, and the patient's sensorium was clear.

A diagnosis of manic depressive reaction, depressed type, was made and treatment was begun with 25 mg. of SKF ⅍5, t.i.d. After several days the dose was increased to 50 mg., t.i.d. With this increase the patient appeared less tense and more relaxed, but remained depressed. A further increase in dose to 75 mg., t.i.d., resulted in clearing of symptoms. The patient reported that she felt well and that her appetite and sleep were restored to normal.

Medication was discontinued on the 12th day of treatment. After two days the patient's original symptoms returned. Medication was reinstituted, and in one week she again improved. When medication was again discontinued, the patient again relapsed. Since it was not possible to continue her on this treatment outside the hospital, she was referred for EST. After 14 treatments she was much improved and was discharged.

The Rating Scale changed from a high of 13 to zero at the peak of improvement. The only side effect noted was mild drowsiness.

Case 3. A 56 year old unmarried woman was admitted to the hospital in a state of agitation and depression. She had been hospital-

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ized four years ago with an episode of depression, but was discharged after several weeks without specific treatment.

The present episode started two months prior to her present admission, at which time she began to lose her appetite and was unable to sleep. Before the onset of these symptoms, she had been working full time as a seamstress. Gradually, she had begun to feel depressed and became tearful and agitated. At the time of admission she paced the floor and appeared depressed, tearful and apprehensive. She stated repeatedly, "I'm dying from an incurable illness . . . and my mouth feels like smoke is coming from it." The patient had many other somatic complaints. Her sensorium was clear.

A diagnosis of involutional psychotic reaction was made and treatment was begun with 15 mg. of SKF ※5, t.i.d. Dosage was increased to 50 mg. over a period of eight days, with no apparent improvement in status. No side effects other than dry mouth and dilated pupils were noted. However, because of the patient's intense agitation, it was decided to discontinue drug treatment and institute electric shock treatment. She had six treatments over the course of two weeks, without any improvement. During the shock therapy she developed memory impairment and other organic signs. Treatment was discontinued and the patient was ultimately transferred to a state hospital.

Rating Scale scores changed from an initial value of 16 to a post-treatment value of 18.

TOXICOLOGICAL EFFECTS AND LABORATORY STUDIES

Alkaline phosphatase was noted to rise during the drug treatment in twelve patients. In one patient the alkaline phosphatase decreased during the drug trial. Five of the twelve patients who developed elevated alkaline phosphatase were followed further, and in three of these patients the levels returned to normal in from one to three weeks.

No other evidence of liver involvement was noted in these patients.

The most persistent side effects were dilated pupils and dry mouth on higher doses. Other side effects felt to be related to the drug were mild tremors, drowsiness usually during the first few days of treatment, and transient anorexia and insomnia. One patient developed an itching erythematous dermatitis, which disappeared when the drug was withdrawn. This was felt to be an allergic drug reaction. One patient developed marked flushing and sweating when the dose was raised to 300 mg. On subsequent lower doses this did not appear. Another patient had a grand mal seizure after one dose of 30 mg. No history of previous seizures was elicitable. After a second dose on a subsequent day, however, no seizure occurred. The relationship of this seizure to drug ingestion is indefinite. EEG studies of the patient were negative.

Repeated weight determinations were made on 24 patients receiving the drug. Twelve patients lost from one to 8½ pounds, for a mean loss of four pounds over a mean time of 18 days. Eight patients gained from 2½ to 9 pounds, for a mean gain of five pounds over a mean time of 20 days. Four patients maintained a constant weight. No correlation existed between weight change and improvement.

In general, blood pressures tended to drop slightly for the first few days on the drug, but then returned to their base line levels which were maintained throughout the balance of the study.

PSYCHOLOGICAL TESTS

Improved performance on the Wechsler-Bellevue Intelligence Scale, Form I, was noted in some patients receiving the drug. In general, correlation with clinical results was low. Many problems exist in the use of psychological tests for evaluating improvement with drugs, however, and a discussion of these problems is not within the purview of this paper.

DISCUSSION

This drug appears to be of little value in the treatment or tranquilization of schizophrenics. Even in the higher dosage ranges results were few, while the number of side effects increased. The six per cent of the schizophrenics who improved during the study is consistent with what would be expected from hospitalization alone.

The 76 per cent of the depressed patients who improved on the drug constitute a significant number over that of the 24 per cent who improved on placebo. Inasmuch as this improvement was determined by three independent approaches, and as improvement was also noted in the patients' ward behavior, it is felt that this drug is effective in the treatment of some seriously depressed patients.

Further evidence of the efficacy of SKF ℵ5 is seen in the results of the rotation studies. The close correlation between remission and drug administration, and relapse and placebo administration, confirms the effectiveness of the drug. Furthermore, without reference to rating scales, 76 per cent improvement in the drug group of seriously depressed patients is far in excess of what would be expected from spontaneous remission, hospitalization, or other extraneous factors, in a short period of time.

The quality of response, however, is also important. In general, patients' sleep and appetite improved, and apprehension diminished. This occurred despite the close relationship of this drug to the anorexigenic and sleep-inhibiting amphetamines. Nonetheless, the patients who recovered could not be considered cured in the sense that symptoms had entirely cleared. While the subjective feeling of depression and restlessness or retardation disappeared, most of the improved patients appeared tense. Furthermore, withdrawal of the drug usually led to relapse in from three to five days. Whether this tense appearance was due to the drug, or was a residuum of the patient's illness, was difficult to establish. The dilated pupils usually accompanying the use of the drug lent further to this appearance of tension.

The effective dose range appears to be from 60 to 300 mg. per day in divided doses. Initial doses as low as 25 to 30 mg. per day should be given, as initiation of treatment with high doses frequently produced marked tension and apprehension.

The increased alkaline phosphatase and cephalin flocculation in several patients should be further evaluated in longer-range studies.

None of the side effects were of such nature as to interfere with the use of SKF ℵ5 with either in-patients or out-patients.

SUMMARY

1. In this controlled study thirty-two schizophrenic patients were given various doses of SKF ℵ5 without significant improvement.

2. Twenty-five seriously depressed patients were treated with this drug and improvement was noted in 76% of the group.

3. The development of high levels of alkaline phosphatase in twelve patients suggests that further appraisal of these findings should be done in a longer range study.

4. The observable side effects were not of a serious nature.

5. The effective dose appears to be between 60 and 300 mg. per day. Initial doses should be as low as 25 to 30 mg. per day.

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