Computerized Evaluation of Psychic Effects of Ketamine

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In 1965, we reported the pharmacologic effects of ketamine hydrochloride in volunteer subjects from a prison population,[1] and subsequently we presented our initial clinical experience with this new "dissociative" anesthetic.[2] In both reports we called attention to the drug's psychotropic action and described the various psychic reactions that occurred in some of the volunteer subjects and in a few clinical patients during emergence from ketamine anesthesia. The typical psychic alterations included changes in mood and affect, some individuals becoming apprehensive and others expressing feelings of estrangement, isolation, negativism, hostility, apathy, drowsiness, or inebriation.

Although transient, such reactions had to be considered a potential threat to the overall usefulness of this highly promising new agent. Therefore, in further exploring ketamine with regard to its psychic effects in man, we conducted various laboratory studies which confirmed the unique ability of ketamine to simultaneously depress and stimulate certain parts of the central nervous system.[3] In addition, we documented, clinically, the highly selective action of ketamine on the frontal regions of the cortex,[4] presumably the association area, depriving the individual of the ability to properly interpret afferent impulses which seem to travel unimpaired from the periphery to the association region, where they are interrupted.

With regard to ketamine's psychotropic action, it is clear that the drug may induce emergence delirium reactions in certain individuals. It should be emphasized, however, that effective means are available to minimize the incidence and degree of such

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emergence reactions, including the use of morphine[5] and droperidol[6] as part of the preanesthetic medication and the avoidance of premature stimulation while the patient awakens from ketamine.[7]

The present study was undertaken to determine whether the drug could cause prolonged and even permanent psychic alterations in man.

PRELIMINARY STUDIES

Followup studies, including repeated interviews of patients who previously had received ketamine for general anesthesia, have suggested that ketamine does not cause long-lasting psychic effects.[8] However, clinical investigations of this type may be considered of limited value since they may lack objectivity, and bias in the interpretation of the patient's responses to questioning cannot be ruled out with certainty. Therefore, reliable, highly differentiated, and well-established methods were selected to study this problem objectively. The Minnesota Multiphasic Personality Inventory (MMPI) appeared particularly suitable for our investigation, since this test is the most widely used method for screening groups of subjects for signs of any psychiatric abnormality.[9-11] This method was viewed as preferable to the more informal technics, such as rating scales and Q-sorts, because of the extensive and widely accepted norms now available.

The MMPI test [10,12] consists of 550 questions which the individual answers as true or false as applied to himself. The questions cover a wide variety of topics related to psychiatric symptoms, physical health, general habits, and attitudes regarding sex, politics, and social problems.

The material is organized into groups based on the manner in which certain respondents answer the questions. The early scales were designed in relation to psychiatric diagnoses such as Pa (paranoid) or Sc (schizophrenic). Many additional groups have been added and today there are several hundred scales available to analyze the test.

Three scales of the MMPI, known collectively as the validity scales, help determine the attitude of the respondent at the time of testing. The L scale reveals an attempt to give answers that are "acceptable" rather than true; the F scale may reveal that the individual did not understand the questions; and the K scale reflects the tendency of the respondent to be defensive or to deny certain types of symptoms. Elevated scores on any of these three scales would tend to invalidate the test.

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The MMPI has been particularly valuable in screening groups of subjects for signs of psychiatric abnormalities, regardless of the type. Recently, the test has become even more useful, and its application significantly facilitated, with the development and availability of computer-based programs for proper interpretation.

Most suitable among the recently developed automated systems for personality interpretations has been a program developed by Fowler,[13] which produces a narrative report similar in style and content to that written by a clinical psychologist. The test utilizes the interrelationships and configurations of the scores as well as the level of the scores for accurate interpretation of the answers. This method has been adopted by the Roche Psychiatric Service Institute[13] and is now offered as a service for the scoring and interpretation of the MMPI for researchers and clinicians throughout the world.

METHOD

In our study, the MMPI was initially administered to 110 volunteers among the inmates of a correctional institution for youthful first offenders. The ages of the subjects ranged from 21 to 32 years. The material was then sent to the central computer service for analysis. From this preliminary screening, 30 subjects were chosen to participate in the experiment. Three criteria were observed to insure that only psychologically healthy and stable individuals were included in the study: first, exclusion of subjects whose validity scores left the interpretation open to question; second, exclusion of subjects whose computer analysis indicated any significant psychologic disorder; and finally, exclusion of subjects who had scale scores on the MMPI profile, other than 4 and 9, which were above T score of 70. Scale 4, indicating psychopathic tendencies, and scale 9, representing manic tendencies, were high in all these subjects.

The 30 subjects chosen on the basis of the above criteria were randomly divided into three groups of 10 each. Group I, the experimental group, received the experimental drug, ketamine hydrochloride; group II, the drug comparison group, received the intravenous barbiturate, thiopental, whose effects on the central nervous system are well known; and group III, the control group, received no treatment. This latter group was included because of the possibility that certain personality changes might be a result of incarceration.

The testing of the initial 110 subjects and the subsequent screening of the 30 subjects involved in this study required approximately 3 weeks. The 30 volunteers were then gathered in the prison dispensary, where 20 were given an intravenous injection of either ketamine (1 mg./lb. of body weight) or thiopental (2.5 mg./lb. of body weight). With the subject resting comfortably on the bed in supine position, the drugs were administered over a period of 30 seconds.

In all instances, unconsciousness ensued with either drug within 15 to 30 seconds after completion of the injection. The subjects were left undisturbed until they had fully recovered and were able to get up without help and participate in the various prison activities. In particular, no attempt was made to awaken them. The duration of recovery varied significantly in the 20 volunteers, ranging from 15 to 30 minutes.

One week later, the MMPI was again administered to the 20 volunteers who had received either ketamine or thiopental and to the 10 control volunteers. A final test was conducted 30 days after the administration of the agent.

After the completed test forms had been received from the computer service, each individual protocol was examined by one of us (P.R.), to identify any incidents in which the re-tests had scores which exceeded the original criteria. Then, the protocols, paired but not identified according to first or second administration, were presented to an experienced MMPI clinician* (who was also the developer of the computer interpretation system). Neither individual knew to which group any of the subjects belonged. The information gathered from the preinjection tests was used as a baseline and a decision was made in each case with regard to changes in the test profile, with particular attention to either increased or decreased pathologic reactions.

RESULTS

Of the 30 subjects involved, 4 subjects, including members of all 3 groups, demonstrated significant changes. One individual of group III, the control (no drug) group, showed a heightened score on scale 6 (paranoid) 1 week after the "treatment," indicating a trend toward increased irritability.

This trend showed a tendency of stabilization on the test given 3 weeks later. The changes manifested in this individual were not considered significant enough to warrant the diagnosis of psychosis. The rest of the subjects in this group showed no significant change in any of the other characteristics considered.

In group II, the drug control (thiopental) group, 8 of the subjects showed no change. One subject who showed an increase in scale 1 (hypochondria) at the test given 7 days later was reportedly ill at that time, which could well account for this increase in somatic concerns. On the subsequent test, his scores returned to the same level as the pretreatment test. Another individual in this group showed marked changes in personality. On the screening test his profile met all the criteria for acceptance, indicating a "normal" individual. On the test given after 7 days, a marked elevation in scales 8 (schizophrenic) and 6 (paranoid) was recorded, resulting in an interpretation of marked increase in pathologic reactivity. This seemed to suggest that the subject had gone through a minor psychotic episode. On the test given 3 weeks later, this diagnosis was confirmed, the test showing marked increase in scale 9 (manic) which along with the heightened scale 6 strongly suggested a major emotional disorder.

With regard to the post-treatment testing, only one person of the ketamine group (group I) indicated any detectable change. While this individual showed a slightly elevated scale 6 at the initial testing, which did not warrant his rejection, he showed a lowering of the scale on the test given 7 days later; 3 weeks later the score was back within the normal range.

Of the 10 subjects in group I (the ketamine group), only 2 showed any evidence of unusual behavior during recovery from the ketamine effect. One individual showed a mild form of delirium which seemed to contain a neutral affect, neither pleasant nor unpleasant. The other subject went through a period of delirium during which he showed a great deal of verbal aggression.

DISCUSSION

Behavior problems of two types might be associated with the administration of ketamine. First, in certain individuals, ketamine may induce transient bizarre behavior patterns, including psychotic-like reactions during emergence from the drug effect. Second, the drug might cause permanent psychic alteration. It was primarily the second question that these studies were designed to answer. To implement this, assurance was necessary that the subjects could be observed over long enough periods of time for the drug effect to manifest itself.

The psychologic test instrument we chose to explore the problem, the MMPI, is the most widely used objective measure of personality available at present and is particularly sensitive in detecting psychotic changes. To this point, we established a reliable baseline on each subject included in the study and tested each at 1 week after ketamine administration and again 1 month later.

Test results so far lend no support to the supposition that ketamine induces permanent psychologic changes. The subjects will be tested again after 6 months and finally after 12 months. Results will then be reported.

ADDENDUM

After a period of six months had elapsed from the time of the injections, a fourth testing of the subjects was conducted. The protocols were analyzed following the same procedures as outlined earlier. Due to the rapid turnover of the population of a correctional institution for youthful first offenders, only 18 of the original 30 were available for the 6 months test. Seven of these belonged to the ketamine group, six to the drug control (Thiopental) group while five were in the control (No drug) group. Out of these 18 subjects, seven showed significant deterioration of personality, evidenced by an increase of schizoid tendencies, a trend not entirely unexpected in view of the isolation of these men from their normal home and social environment. Only one of the seven was in the ketamine group while the other six were in the two control groups (2 in group II, 4 in group III).

These six months test results still lend no support to the supposition that ketamine may induce permanent psychic changes.

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Generic and Trade Names of Drugs
Ketamine—Ketalar, Ketaject
Sodium thiopental—Pentothal® Sodium
Droperidol—Innovar,® Inapsine

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Silence makes no mistakes.

—*French Proverb*

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Keep cool and you command everybody.

—*Louis Lé de Saint—Just*