Long-Term Outcome of Patients Who Receive Ketamine during Research

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Background: *To comprehend the pathophysiology of schizophrenia and to facilitate drug discovery, animal and human models of schizophrenia are necessary. Ketamine, a noncompetitive* N-*methyl-*D*-aspartate antagonist, has been used to probe glutamatergic function in normal and schizophrenic volunteers. These studies and others have provided data consistent with a putative involvement of a glutamatergic dysfunction in the pathophysiology of schizophrenia; however, these studies have also raised concerns about the distress inflicted on patients, the potential for adverse events, and the serious long-term effects that could possibly be induced by symptom-simulating action.*

Methods: *For all patient volunteers (n = 30) who participated in these studies, we reviewed the acute safety during and in the immediate postketamine administration. Patients available for long-term follow-up (n = 25) were matched to a group of patients (n = 25) who participated in research but did not receive ketamine. We compared their long-term outcome in terms of psychopathology, the need for psychiatric care, and the amount of antipsychotic medication required for optimal therapeutic response.*

Results: *There were no serious adverse events in more than 90 ketamine interviews. Distress to patients was minimal, which is shown by the lack of anxiety ratings. Over a mean follow-up period of 8 months, we found no differences between patients who did and did not receive ketamine on any measures of psychopathology, psychiatric care, or the amount of antipsychotic medication.*

Conclusions: *In a controlled environment and paying close attention to subject safety features, administering subanesthetic doses of ketamine causes no adverse events and little distress to schizophrenic volunteers. This study strongly indicates that administering ketamine does not change any aspect of the course of schizophrenic illness.*
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Introduction

Schizophrenia is a devastating illness that is incompletely understood. Current treatment is hampered by poor response of primary negative symptoms and cognitive deficits to antipsychotics, as well as patients with treatment resistant positive symptoms. These limits of treatment can be approached using models of psychosis to facilitate drug discovery and further clarify the pathophysiology of schizophrenia.

The interest in glutamate as a potentially important neurotransmitter system in schizophrenia was suggested by the observation that phencyclidine (PCP) could exacerbate symptoms in schizophrenia (Luby et al 1959). Phencyclidine, an antagonist at the *N*-methyl-D-aspartate (NMDA)–sensitive glutamate receptor (Anis et al 1983), could mimic the signs and symptoms of schizophrenia in normal persons more closely than other psychotomimetic drugs (Javitt and Zukin 1991; Pearlson 1981).

Ketamine, a structural congener of PCP and agonist at the PCP site of the NMDA receptor complex, has been used to probe glutamatergic function in normal and schizophrenic volunteers. It induces schizophrenic-like psychotomimetic symptoms in normal volunteers and a short-lived reactivation of psychotic symptoms in schizophrenic volunteers. The ketamine model has been proposed to study the pathophysiology of psychosis and as a screen to evaluate new drug action (Javitt and Zukin 1991; Krystal et al 1994; Lahti 1995b, 1999; Malhotra et al 1996).

Ketamine is an approved anesthetic agent used for diagnostic and surgical procedures in adults, obstetrical patients, and children. Its use has been associated with reports of vivid dreams and dissociative reactions on emerging from anesthesia; however, it has remained a desirable anesthetic because of its short half-life and the lack of respiratory depression associated with its use. Over the past 25 years, ketamine has been administered as an

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anesthetic to several million people and has a good safety profile (Corrsen et al 1988; Reich and Silvay 1989; White et al 1982).

However, its use as a research tool has raised concerns about distress inflicted on patients, its potential for adverse events, and the serious long-term effects that could be induced by symptom-stimulating action. Several review papers have addressed the question of prolonged psychological effects in the general population secondary to its anesthetic use and concluded that ketamine does not place recipients at a greater risk than other anesthetics (Hersack 1994; Reich and Silvay 1989; Schorn and Whitwam 1980; White et al 1982). Isihara followed a group of schizophrenic subjects ($n = 14$) after ketamine anesthesia at doses more than 10 times higher than used in challenge studies. They reported no evidence for long-lasting adverse psychological events in the one-month follow-up period (Ishihara et al 1997).

Carpenter (1999) has systematically collected short-term outcome and potential patient distress data during ketamine challenge interviews from three North American institutions that conduct these studies. These studies suggest that ketamine administration has short-lasting effects on symptoms, usually less than 60 min and never longer than 2 hours. The increase in psychosis is also generally not distressing to volunteers.

The aim of this study was twofold: (1) to review the safety of ketamine during challenge and the immediate postadministration period in a group of schizophrenic patients who receive ketamine at the Maryland Psychiatric Research Center (MPRC) and (2) to compare their long-term outcome with a group of patient volunteers who did not receive ketamine, but participated in other research projects.

Methods and Materials

Research Setting

All patients who volunteered for these research studies were hospitalized on the Residential Research Unit of the MPRC, University of Maryland School of Medicine. People with schizophrenia are actively recruited from Maryland to participate in ongoing research protocols. Before hospitalization, candidates, and their families are informed about the research nature of the program and are encouraged to visit and evaluate the facilities whenever possible. Generally, patient volunteers are not admitted during an early stage of their illness, but rather when they have active but stable symptoms and/or have experienced several exacerbations of the illness and still require hospitalization.

To be selected to participate, patients must be competent and clinically judged to be capable of understanding and appreciating the risks involved in these studies. This selection is made by an independent, designated State of Maryland Mental Health Administration (MHA) representative and clinician. A lengthy process is followed to obtain consent with schizophrenic volunteers. The protocol is presented on several occasions by different people, including the protocol principal investigator. Family members are involved whenever available. Patients are given detailed verbal descriptions of the procedures and risks described in the protocol by the physician, the social worker, and the nurse.

After being informed, patient volunteers' knowledge is assessed. They are required to list the key features and risks of the protocol to show their understanding. A designated ombudsman monitors the quality of the consent procedures and works closely with patients throughout the research project, maintaining awareness of their knowledge of the requirements and risks of the protocol. The roles of the independent MHA representative and the MPRC ombudsman were instituted in 1998.

All research protocols had been approved by the University of Maryland Institutional Review Board (IRB).

Baseline Admission Psychiatric Workup

Once admitted, each patient volunteer receives an initial psychiatric and medical workup. For all research volunteers, two experienced clinicians make a diagnosis of schizophrenia, using DSMIV criteria based on all historic and direct assessment information available.

The following assessments are obtained in a systematic fashion for all patients who are admitted to the Residential Research Unit (RRU) at the MPRC. SCID interview and for the mental status evaluation, we use the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), and the Schedule for the Assessment of Negative Symptoms (SANS) (Andreasen 1984). We obtain the BPRS and the SANS throughout the patient's hospitalization. To maintain adequate reliability, raters are trained and re-trained periodically. The representative intraclass correlation coefficient for the BPRS total score is 0.86.

Hospital Course

Once admitted, patients are informed and educated about the nature of research in general and the specific project for which they have volunteered. These volunteers often chose to participate in projects related to mechanistic questions in the illness, as well as therapeutics research. Research protocols include new medication trials, imaging studies, and challenge interviews. Characteristically, some studies include medication withdrawal as part of their design. Throughout their hospitalization, patients participate in a psychosocial rehabilitation program that includes psychosocial skill training, classes, and other activities. When the research program is completed, patients generally transition to outpatient supervised programs, at higher psychosocial levels than at admission. Because of lengthy waiting lists for access to these facilities, prolonged periods sometime elapse between completion of research and discharge. This waiting period allows time for close clinical observation and optimizing the medication regimen. A final predischarge BPRS is usually obtained.

Ketamine and Control Research Subjects

Subjects in the ketamine group received up to four subanesthetic doses of ketamine (range: 0.1–0.5 mg/kg), usually over 2 weeks.

Table 1. Demographics

	Age	Gender	Race	Length of illness (years)	Diagnosis	Deficit symptoms	Index BPRS total score	Index BPRS psychosis score[a]	PAS[b]	PRO[c]
Ketamine (+) volunteers (n = 25)	33.6 ± 8.8	19 M 6 F	14 W 7AA 4A	14.0 ± 7.8	11 undifferentiated 8 paranoid 3 disorganized 3 schizoaffective	21 ND 4 D	36.9 (± 8.4)	9.1 (± 3.4)	2.6 (± 1.1)	12.6 (± 5.9)
Control volunteers (n = 25)	36.8 ± 9.7	20 M 5 F	18W 3AA 4A	13.8 ± 7.9	10 undifferentiated 9 paranoid 6 disorganized	19 ND 6 D	38.3 (± 10.2)	8.2 (± 3.6)	2.2 (± 1.0)	15.1 (± 7.6)

W, white; AA, African American; A, Asian; ND, nondeficit symptoms; D, deficit (primary negative) symptoms.
[a]Brief Psychiatric Rating Scale (BPRS) Psychosis score, items 12, 15, and 4.
[b]Premorbid Adjustment Scale, General Items total score (lower score is better).
[c]Prognostic Scale, total General Items score (higher score is better).

Each dose was administered as a bolus over 60 sec in a double-blind fashion. We used the BPRS to rate symptoms at baseline and 20, 90, and 180 min following drug administration. All patients were tested while receiving concurrent antipsychotic medication; six were retested with ketamine while withdrawn from their medication.

We matched a control patient group to the ketamine group available for follow-up using the following criteria: starting from the time of the first ketamine challenge (fall 1992), we selected consecutively admitted patients if they actively participated in a research protocol involving a drug-free period but did not receive any ketamine protocols. Because most of the patients who received ketamine had participated in protocols involving medication withdrawal, this selection criteria (drug-free period) allowed to control for any possible effect of drug withdrawal on outcome.

Outcome Measures

For index BPRS, we selected the BPRS obtained as part of the baseline admission psychiatric workup. For follow-up BPRS, we selected the last BPRS obtained on research patients following completion of research, before discharge. Follow-up days are the number of days elapsed between the start of the research study (either ketamine or withdrawal) and the follow-up BPRS.

For all patients, we tabulated the number of adverse clinical events noted by any staff member in the clinical chart and the number of PRN medications by retrospective chart review. Adverse clinical events could include a significant change in clinical symptoms (such as in paranoid or other psychotic symptoms) or in behavior (such as destruction of property or fighting with peers). Adverse events (AE) were thus spontaneously occurring and reflected in clinical observation and intervention. Supplementary (PRN) medications given on a PRN basis included psychotropic medications, such as antipsychotic and anxiolytic medications or sleep inducers. Both the adverse events and PRN medications reflect the patients clinical status and overall stability over the rating period, generally extending over several months. For each patient, AE and PRN rates were calculated using the following equation: number of AEs and PRN × 100 divided by number of follow-up days. We calculated discharge antipsychotic medication in haloperidol equivalents.

Statistics

To test the effect of 0.3 mg/kg of ketamine on behavioral symptoms, we analyzed BPRS total and subscale scores. We performed a univariate repeated measures analysis of variance to test for a main effect of dose (0.3 mg/kg, placebo) and one repeated measure: time (baseline, 20, 90, 180). We used a Greenhouse-Geiser correction following significant dose-by-time interactions, and post hoc contrasts to contrast each time point to baseline. This effect of 0.1 mg and 0.5 mg/kg has been reported elsewhere (Lahti et al 1995b).

Clinical outcome for the comparison groups (ketamine/nonketamine) was evaluated on the (1) BPRS total score both before and after the identified research; (2) on a measure of psychiatric care, such as adverse events recorded in the chart and the number of PRN medication; and (3) on the final dose of antipsychotic medication.

To test for differences between the medication groups, a t test was performed for all measures except for AE and PRN mean rates where a Wilcoxon test was performed because the data were not normally distributed.

Results

Thirty patient volunteers on the RRU participated in a ketamine interview. Ketamine interviews comprised either a dose range (0.1, 0.3, 0.5 mg/kg), study (n = 9), or single doses of 0.3 mg/kg (n = 21). Twenty-five of these patients had been discharged from the RRU and were available for follow-up. Five patients were still inpatients on the RRU and actively participating in other research projects. Twenty-five control patients forming a comparison group were matched to the ketamine group according to our operational criteria. The ketamine and nonketamine group were similar on demographic descriptors, such as age, gender

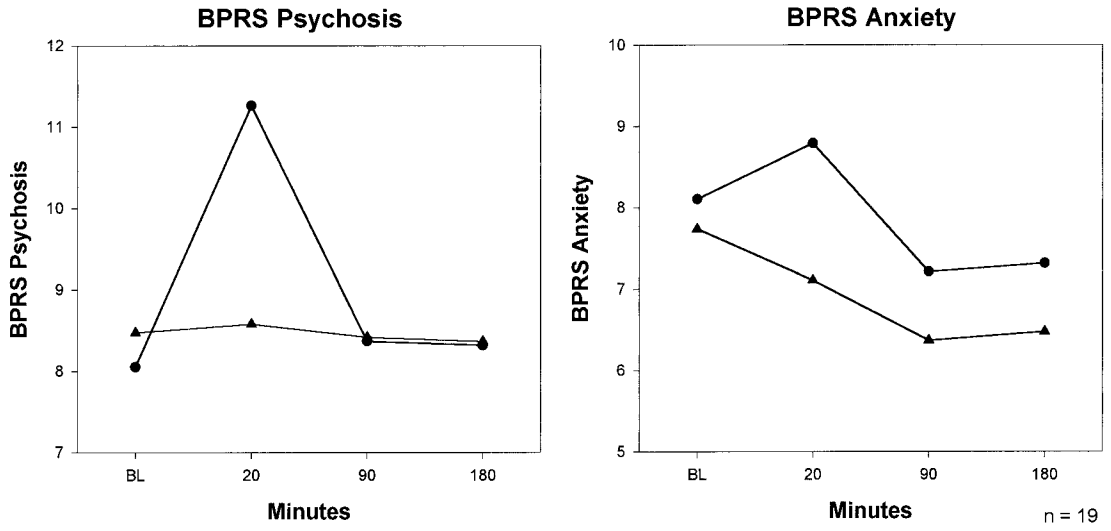

Figure 1. Time course of mental status changes after acute injection of ketamine 0.3 mg/kg (●) and a placebo (▲) in schizophrenic volunteers. The Brief Psychiatric Rating Scale (BPRS) Thought subscale was significantly increased at 20 min after ketamine. There were no statistically significant increases in the BPRS Anxiety score at any time point after ketamine.

ratio, race distribution, length of illness, general psychopathology measures, measures of premorbid symptoms, and prognosis (Table 1).

All patients in the control group and 22 of the 25 patients who receive ketamine participated in medication withdrawal while hospitalized on the RRU. The groups showed no significant difference in the number of days of withdrawal (ketamine group $n = 28.1 \pm 14.5$ days; control group $n = 36.2 \pm 21.0$ days).

There was a difference, however, in the number of research studies in which subjects agreed to participate. Patients who participated in the ketamine interviews participated in a mean of 4.4 (± 2.3) studies, whereas the other group participated in a mean of 2.8 (± 1.1) studies.

Acute Safety

The 30 patients in the ketamine group participated in 90 ketamine and 36 placebo infusions. No serious adverse events occurred during any ketamine administration. One placebo infusion was aborted in the ketamine group because a volunteer was restricted from using the bathroom and became anxious. Two other patients had an unpleasant first experience with ketamine and declined to participate in further ketamine interviews. One experienced a 10-min increase in paranoid ideation that resolved quickly without need for any medication; the other became anxious secondary to light-headedness and numbness, but returned to her usual mental status without need for PRN medication. Three patients declined further testing after completing at least one dose of ketamine. Two of them disliked the experience, and the third changed his mind for reasons that were unclear but apparently not related to a bad experience.

In the 24-hour follow-up interviews, one patient reported increased dreaming; one, increased visual hallucinations; and two, increased delusions between 60 min and 24 hours postinfusion. None of these events required treatment or lasted beyond 48 hours, and ketamine could not be established as the cause.

Acute Response

We evaluated the acute response to ketamine by comparing the 0.3 mg/kg dose to placebo. Nineteen patients were included in this analysis. We did not include four patients who did not have a placebo challenge and seven who were still in a blinded study.

With ketamine, the BPRS total and Psychosis subscale scores were significantly increased at 20 min following challenge—a 30% increase in positive symptoms compared with placebo. Both scores were returned to baseline value at 90 and 180 min postchallenge.

This pattern was not seen with placebo. Neither the BPRS withdrawal nor the anxiety scores were significantly increased at 20, 90, or 180 min with ketamine or placebo (Figure 1).

Long-Term Outcome

Table 2 reports the baseline symptomatology, the number of follow-up days, the measures of clinical outcome, and discharge medication expressed in haloperidol equivalent for the ketamine and nonketamine groups. Both groups

Table 2. Comparison Between Groups at Follow-Up

	"Index" BPRS total score	"Follow-up" BPRS total score	No. of follow-up days	AE rate[a]	PRN rate[a]	Discharge medications[b]
Ketamine (+) volunteers (n = 25)	36.9 ± 8.4	33.9 ± 8.6	285.9 ± 212.6	0.3 ± 0.6	0.9 ± 2.4	17.4 ± 8.6
Control volunteers (n = 25)	38.3 ± 10.2	38.5 ± 11.0	246.0 ± 200.2	1.0 ± 2.0	2.8 ± 5.7	14.0 ± 6.8

There were no differences between the groups in terms of Index Brief Psychiatric Rating Scale (BPRS) [$t(48) = -0.5$, $p = .6$]; follow-up BPRS [$t(48) = -1.6$, $p = .1$]; number of follow-up days [$t(48) = 0.7$, $p = .5$]; rate of adverse events (AEs) [$\chi^2(1) = 2.2$, $p = .14$]; rate of medication given as supplementary (PRN) [$\chi^2(1) = 2.9$, $p = .09$]; and discharge medications at follow-up

[a]AE (PRN) rate = no. of AEs (PRN) × 100/no. of follow-up days.

[b]Expressed in haloperidol equivalent (mg).

were similar in terms of baseline symptomatology (index BPRS, mean difference = 1.4, 95% CI [−4.0 to 6.7]) and the number of follow-up days (mean difference = 39.9, 95% CI [−77.5 to 157.4]). There was no difference between the groups in the psychopathology rating obtained at follow-up [follow-up BPRS, mean difference = 4.6, 95% CI [−1.1 to 10.2]).

While hospitalized, both patient groups recorded a similar number of incidents, such as an increase in suspicious behavior or fighting with peers (AE rate, mean difference = 0.6, 95% CI [−0.2 to 1.5]). They received a similar number of PRN medications (PRN rate, mean difference = 1.9, 95% CI [−0.6 to 4.4]). There was no difference in discharge medication, as expressed in mg haloperidol equivalent.

Because all 25 control volunteers and only 22 of 25 in the ketamine group had a withdrawal period, we repeated this follow-up analysis to include only those ketamine patients who had undergone medication withdrawal. We found no differences between the two groups, all with drug-free intervals, on any of the follow-up characteristics.

Discussion

This study addressed the safety of ketamine during and in the immediate postadministration period. It also compared the outcomes of schizophrenic inpatient volunteers who received ketamine as part of a research study with inpatients who did not but participated in other research projects—over a mean follow-up period of 8 months.

No serious adverse events were associated with the more than 90 ketamine interviews. The increase in psychosis was short-lasting and mild. Distress to patients was minimal, which is shown by the lack of increase in anxiety ratings during the interview. Few volunteers chose to terminate the experiment and were balanced between placebo and ketamine. We found no long-term outcome differences between the groups on any measures of psychopathology, on any measure of psychiatric care, or on the amount of antipsychotic medication needed for optimal response.

These data strongly indicate that ketamine administered on several different occasions at subanesthetic doses in schizophrenic volunteers does not induce adverse events, cause serious distress, or change the course of their schizophrenic illness over an 8-month follow-up period.

This is a retrospective study, and follow-up measures were obtained unblinded to the patient's research status; however, several important methodologic considerations mitigate this point. We identified the research control group using operational criteria (consecutively admitted, participated in research). The selection criteria for control subjects also included a period of medication withdrawal, which allowed us to select groups that were equivalent in participation in research protocols with more than minimal research risks. Also, we derived baseline assessments from a standardized baseline set obtained before research during a time of symptom stabilization. Predischarge ratings were routine and collected without knowledge that this comparison would be done. Moreover, the two patient groups were similar in terms of demographic characteristics and baseline symptomatology.

The two patient groups had a similar level of psychopathology. They were both treated on the same clinical unit and therefore received comparable care. Both groups received a similar amount of medication at outcome. All control subjects had undergone some days of medication withdrawal during research. We had matched our control group based on participation in a drug-free period because most of the patients who received ketamine participated in drug-free protocols; however, no change in psychopathology was seen or expected as part of this intervention. At least two studies have demonstrated that short medication withdrawals during research protocols do not affect a patient's long-term outcome (Carpenter et al 1997; Craig et al 2000; Johnstone et al 1999; Wyatt 1997).

This study is not of the magnitude to rule out negative effects and our findings can only be applied to control settings under optimized conditions; however, in 30 years of clinical experience with ketamine, there are only a few reports of prolonged psychological changes, none clearly attributable to ketamine (Hersack 1994).

Challenge or symptoms provocation studies are held to higher requirements than other studies. These requirements usually include strong theoretical basis, pursuit of the ill population only if healthy volunteers cannot be

used, and careful risk benefit assessment. The theoretical basis of those studies is the psychotomimetic profile of PCP in humans and postmortem studies documenting glutamatergic dysfunction in schizophrenia. The need to assess the similarities and differences between ketamine-induced behavioral changes and schizophrenic symptoms was the impetus to pursue this research in patients. The increase in symptoms was expected to be short-lived (i.e., minutes); the procedure was carried out in a well-controlled environment with an easy follow-up because of the inpatient setting of the research ward. The potential benefit was the possible opening of new leads into the pathophysiology of schizophrenia that would suggest new treatment strategies.

Ketamine at subanesthetic doses is an effective and selective human probe of glutamatergic function in schizophrenia (Lahti et al 1995b). Research on glutamatergic function has extended into several additional aspects of schizophrenia research. Various laboratories have reported physiologic abnormalities produced in healthy volunteers by ketamine that mimic changes found in schizophrenia, such as changes in cognition (Harborne et al 1996; Krystal et al 1994; LaPorte et al 1996; Newcomer et al 1999a), eye tracking (Radant et al 1998; Weiler et al 2000), and event-related brain potentials (ERP) (Oranje et al 2000; van Berckel et al 1998). These studies may provide a way to identify glutamatergic abnormalities associated with the signs and symptoms of schizophrenia.

Imaging studies have already identified brain regions whose activity is altered by ketamine (Breier et al 1997; Lahti et al 1995a; Vollenweider et al 1997) and have probed possible interaction between glutamate and neurotransmitters, such as dopamine (Breier et al 1998). These studies provide information for new sites to target for drug development and to guide postmortem work.

In schizophrenic patients, ketamine-induced psychosis is not reversed by traditional antipsychotics such as haloperidol (Lahti et al 1995b) but is reported to be blunted by clozapine (Malhotra et al 1997). Thus, it is possible that ketamine identifies a mechanism accounting in part for the superior antipsychotic actions of clozapine. Beyond this, this model may provide a technique to test new drugs for an entirely new spectrum of antipsychotic drug action. Various drugs have already been tested for unique actions in psychosis using this model (Anand et al 2000; Krystal et al 1998; Lahti et al 1999; Newcomer et al 1999b).

In summary, administering subanesthetic doses of ketamine in a controlled environment is a safe procedure that causes little distress to schizophrenic volunteers. This study—which compared the outcomes of schizophrenic inpatient volunteers who received ketamine with inpatients who did not over a period of several months—strongly indicate that ketamine does not change the course of schizophrenic illness.

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