

Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

Background: A growing body of preclinical research suggests that brain glutamate systems may be involved in the pathophysiology of major depression and the mechanism of action of antidepressants. This is the first placebo-controlled, double-blinded trial to assess the treatment effects of a single dose of an N-methyl-D-aspartate (NMDA) receptor antagonist in patients with depression.

Methods: Seven subjects with major depression completed 2 test days that involved intravenous treatment with ketamine hydrochloride (.5 mg/kg) or saline solutions under randomized, double-blind conditions.

Results: Subjects with depression evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion (i.e., mean 25-item Hamilton Depression Rating Scale scores decreased by $14 \pm SD 10$ points vs. 0 ± 12 points, respectively during active and sham treatment).

Conclusions: These results suggest a potential role for NMDA receptor-modulating drugs in the treatment of depression. *Biol Psychiatry* 2000;47:351–354 © 2000 Society of Biological Psychiatry

Key Words: Major depression, N-methyl-D-aspartate antagonist, excitatory amino acids, randomized clinical trial

Introduction

A growing body of preclinical research implicates the N-methyl-D-aspartate (NMDA) class of glutamate receptors in the pathophysiology of major depression and the mechanism of action of antidepressant treatments (Skolnick et al 1996). NMDA receptor antagonists have been shown to be effective in animal models of depression and models that predict antidepressant activity in many (Layer et al 1995; Meloni et al 1993; Moryl et al 1993;

Papp and Moryl 1994, 1996; Przegalinski et al 1997; Trullas and Skolnick 1990) but not all (Panconi et al 1993) studies. Conversely, antidepressant administration has been shown to affect NMDA receptor function (Mjellem et al 1993) and receptor binding profiles (Paul et al 1994). Chronic, but not acute, administration of antidepressant medications consistently decreases the potency of glycine to inhibit [3H]-5,7-dichlorokynurenic acid binding to the strychnine-insensitive glycine sites. These adaptations were found in 16 of 17 tested antidepressant treatments (Paul et al 1994), thereby making this a more sensitive predictor of antidepressant activity than the forced swim test or downregulation of beta-adrenergic receptors. A transcriptional mechanism for this phenomenon is suggested by recent evidence showing that repeated antidepressant administration regionally alters expression of mRNA that encodes multiple NMDA receptor subunits (Boyer et al 1998).

Although these compelling findings suggest that NMDA receptor antagonists have antidepressant activity, this hypothesis has received relatively little clinical evaluation. Preliminary studies with amantadine (Vale et al 1971), a weak NMDA antagonist, and the strychnine-insensitive glycine site partial agonist D-cycloserine (Crane 1959, 1961) have provided support for this hypothesis. Nevertheless, design issues and other limitations of these agents complicate the interpretation of these early investigations. Clinical investigation of NMDA receptor function in depression is currently limited by availability of selective compounds. Ketamine hydrochloride is a potent NMDA antagonist. The purpose of this study was to determine whether ketamine had antidepressant effects in patients with depression.

Methods and Materials

Nine patients (4 men, 5 women; age 37 ± 10 years, ranging 23 to 56 years; 2 Hispanic and 7 Caucasian) participated in the study, with two participants terminating prior to the last treatment condition (one each prior to placebo and ketamine treatment conditions). All participants fulfilled DSM-IV criteria for major depressive episodes ($n = 8$, recurrent unipolar major depression; $n = 1$, bipolar disorder, depressed), had no recent

From the Abraham Ribicoff Center Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven (RMB, GRH, DSC, JHK); the Affective Disorders Program of the Department of Psychiatry, West Haven Veteran Affairs Medical Center, West Haven (RMB, AA, DAO, DSC, JHK); and the Department of Psychiatry, Yale University School of Medicine, New Haven (RMB, AC, AA, DAO, GRH, DSC, JHK), Connecticut.

Address reprint requests to Robert M. Berman, M.D., Clinical Neuroscience Unit (Rm 360), Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519.

Received April 1, 1999; revised August 4, 1999; accepted August 12, 1999.

diagnosis of alcohol or substance abuse (two subjects had a history of alcohol abuse, in remission greater than 8 years), and had no lifetime diagnosis of any other Axis I disorder (except one patient with a comorbid diagnosis of panic disorder) as determined by the Structured Clinical Interview for Diagnosis, DSM-IV (First et al 1997). All patients were drug-free, in good health, and unmedicated for at least 2 weeks prior to the first treatment condition, as determined by medical history, physical exam, routine blood labs, electrocardiogram, urinalysis, and urine toxicology. After receiving a complete description of the study (AC, RMB), written informed consent was obtained. The participants were informed that the study challenge might lead to significant mood changes, possibly causing a worsening of their depressive symptoms and potentially distressing cognitive disturbances. The study was approved by the IRB of the Veterans Administration Connecticut Healthcare Services, West Haven Campus.

Patients underwent two treatment days separated by at least 1 week in a randomized, double-blinded manner, as described previously (Krystal et al 1994). A saline solution alone or containing ketamine hydrochloride (total dose of .5 mg/kg) was infused over 40 min. Ratings included the Hamilton Depression Rating Scale (HDRS; baseline as well as 80 min, 230 min, 24 hours, 48 hours, and 72 hours after starting infusion), Beck Depression Inventory (BDI; same time points plus 10, 40, and 110 min after infusion), Visual Analog Scales score for intoxication "high" (VAS-high; baseline as well as 10, 40, 80, and 110 min after infusion), and the Brief Psychiatric Rating Scale (BPRS; at baseline as well as 10, 40, 80, 110, and 230 minutes after infusion). Four participants were randomly assigned to receive ketamine (.5 mg/kg) prior to placebo infusion. Time points were chosen based on previous experience from our group (Krystal et al 1994).

Data were evaluated with repeated measures analyses of variance with Huyn-Feldt correction, examining condition (saline vs. ketamine), time, and time-by-condition effects on dependent variables (HDRS, BDI, BPRS, and VAS).

Results

Intravenous ketamine treatment produced significantly greater reductions on HDRS scores than saline treatment. Analyses included the seven participants who completed both active and sham treatment, with two patients electing to terminate the study (one each after active and sham infusions) for purposes of instituting antidepressant treatment. Analyses revealed significant condition-by-time ($F = 3.97$, $df 5,30$, $p = .02$) but not time ($F = 2.62$, $df 5,30$, $p = .09$) and condition ($F = 0.157$, $df 1,30$, $p = .71$) effects. Figure 1 depicts change in HDRS scores from baseline timepoint. Another patient, who was excluded from analyses because of completing only active treatment, experienced marked improvement in depressive symptoms (baseline HDRS 33, final HDRS 16). Mean baseline HDRS scores for ketamine (33.0 ± 6.7) and placebo (26.9 ± 5.8) infusions were not statistically

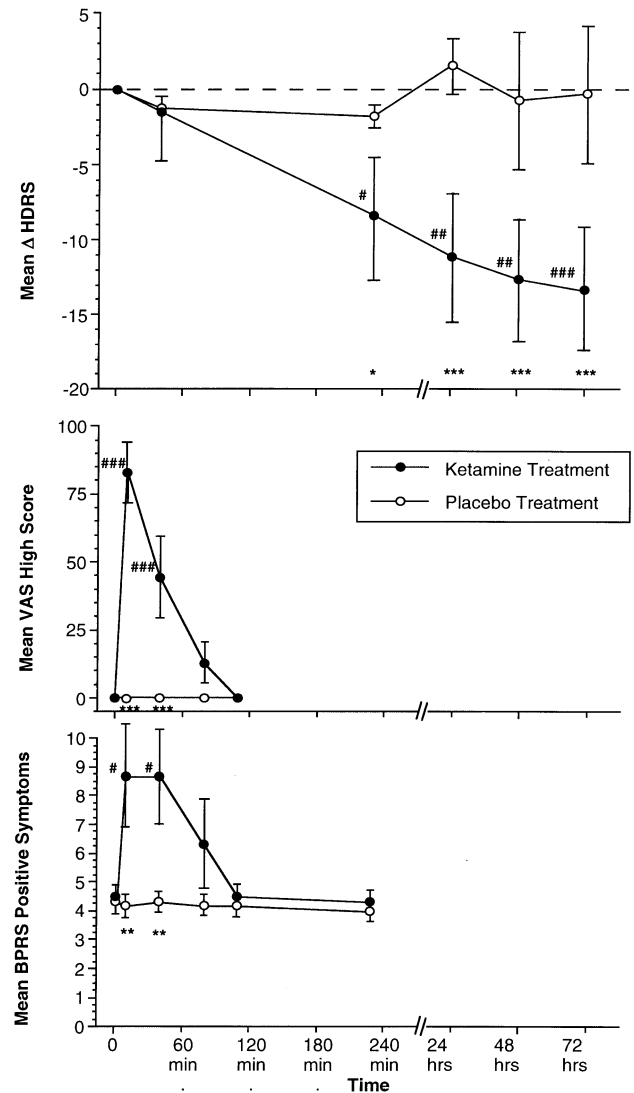


Figure 1. Mean changes (\pm SEM) from baseline in the 25-item Hamilton Depression Rating Scale scores (Δ HDRS), the mean Visual Analog Scale "high" scores (VAS-high), and mean positive symptom scores of the Brief Psychiatric Rating Scale (BPRS-positive) after ketamine (.5 mg/kg over 40 min) and saline infusions in seven subjects completing both treatment conditions. Omission of error bars signifies lack of variance. Post hoc contrasts represent comparison to baseline (# signifies $p < .05$; ##, $p \leq .01$; ###, $p \leq .001$) or between groups (*, $p < .05$; **, $p \leq .01$; ***, $p \leq .001$). The former statistic utilized absolute HDRS scores for the top panel. These contrasts were performed with Huyn-Feldt adjustments for lack of sphericity. Treatment-by-time effects on the repeated measures analysis of variance were significant for HDRS ($p = .02$) and VAS scores ($p < .001$), but not for BPRS-positive symptoms scores ($p = .07$).

different (paired t test, $p = 0.10$). Among patients receiving active ketamine versus saline testing first, baseline scores were respectively $10.3 (\pm 9.0$ SD) versus $3.0 (\pm 7.5)$ points lower for the second condition ($p = .29$).

Robust decreases in the BDI were observed during active (mean baseline score, 29.5 ± 8.2 ; final score, 16.8 ± 10.5) but not control (base, 23.0 ± 8.2 ; final, 25.2 ± 6.0) treatment. Drug-by-time ($F = 5.7$, df 8,48, $p = .0001$) but not drug ($F = .007$, df 1,48, $p = .94$) or time ($F = 1.63$, df 8,48, $p = .21$) effects were significant. Examined post hoc, order effects were not significant for HDRS and BDI measures ($p > .3$).

Four of eight patients demonstrated 50% or greater decreases in HDRS scores during the 3-day follow-up period (i.e., 7, 30, 45, 47, 52, 52, 63, and 83% decreases), whereas only one of eight subjects undergoing sham infusion demonstrated a similar response (i.e., 3, 6, 7, 8, and 74% decreases and three subjects remained 4, 22, and 33% above baseline during the follow-up period; Fisher Exact, $p > .05$). Ketamine-induced mood improvement returned to baseline levels (i.e., clinical impression and HDRS within 5 points of baseline) 1 to 2 weeks after infusion. An exception, one subject demonstrating marked mood improvement (i.e., baseline HDRS of 41 points; Day 3 HDRS of 7 points), was started on antidepressant medication without having returned to his baseline level of depression two weeks after the ketamine infusion (HDRS, 15 points).

Ketamine infusion produced markedly greater scores on the VAS-high item, with significant condition-by-time ($F = 16.9$, df 4,24, $p = .0001$), time ($F = 16.9$, df 4,24, $p = .0001$), and condition ($F = 26.3$, df 1,24, $p = .002$) effects. VAS-high scores returned to baseline by 110 min after infusion. All patients demonstrated a maximum VAS-high score ≥ 50 mm during ketamine testing, whereas no patients demonstrated any increases during sham testing.

Ketamine infusion produced significantly greater scores on the BPRS, especially the positive symptoms. Condition-by-time ($F = 4.14$, df 5,30, $p = .068$), time ($F = 3.97$, df 5,30, $p = .06$), and condition ($F = 3.71$, df 1,30, $p = .10$) effects were not statistically significant for BPRS-positive scores. Changes in BPRS or VAS-high scores did not correlate with percent decreases observed in HDRS scores ($R^2 < .05$, $p > .65$).

To determine how ketamine infusion affected specific symptoms of depression, baseline and final scores on individual HDRS items were compared. While undergoing active treatment, significant decreases were observed for items of depressed mood (paired t test, $p = .0025$), suicidality ($p = .02$), helplessness ($p = .008$), and worthlessness ($p = .015$), uncorrected for multiple comparisons. Control treatment was not associated with significant improvement in any of the HDRS items.

Discussion

Results of this study suggest that low-dose ketamine infusion, as compared to placebo, is associated with robust

decreases in depressive symptoms, emerging progressively within 3 days. Although ketamine is a high-affinity NMDA receptor antagonist, it has less, but potentially relevant, affinity for the μ opiate receptors and weak antagonist activity for the dopamine transporter (Eide et al 1997). Additionally, NMDA receptor agents may potentially affect mood via known secondary effects on monoamine (Lindfors et al 1997) and opiate (Elliot et al 1995; Wong et al 1996) systems. Profound and transient cognitive deficits and euphoria, as evidenced by increases in BPRS scores, were also induced by ketamine infusion, as also observed in other subject populations (Domino et al 1965; Krystal et al 1994).

The improvement associated with ketamine infusion reflects a lessening of core symptoms of depression and seems temporally disconnected from ketamine-induced euphoria or "high." In support, patients reported a diminution of depressive symptoms 3 days after infusion, whereas, feelings of "high" returned to baseline after hours. Nevertheless, patients were readily able to discern the active from placebo treatment based on ketamine's induced perceptual disturbances and "high." Hence, limitations in preserving study blind may have biased patient reporting by diminishing placebo effects, thereby potentially confounding results.

These results are consistent with limited reports on the use of NMDA receptor antagonists in animal models of depression. Rapid response, however, may potentially reflect route of drug administration, as some (Malhotra and Santosh 1996; Sallee et al 1997) but not all (Pollock et al 1989) studies demonstrate rapid antidepressant response to intravenous administration of tricyclic antidepressants. Overall, the results of this study are consonant with hypotheses of NMDA receptor dysfunction in depression. Although our findings suggest the potential benefit of further exploration of NMDA antagonists as potential antidepressant agents, clinical applicability of this strategy may be limited by the psychotomimetic effects and the potential for abuse of many of these agents. Conversely, NMDA receptor antagonists without psychotomimetic properties in humans (e.g., memantine, eliprodil, and 1-aminocyclopropanecarboxylic acid) merit testing for antidepressant activity.

This work was supported in part by a Donaghue Foundation (RMB), a Merit Review Grant from the Department of Veterans Affairs (DSC, JHK), and a VA-Yale Alcoholism Research Center. Research supported by a VA Merit Award (NNB), NIMH Program Grant, and the State of Connecticut. The authors thank Kathy Lynch-Colonese, Lisa Roach, and Jacques Reid for their excellent assistance.

References

- Boyer PA, Skolnick P, Fossom LH (1998): Chronic administration of imipramine and citalopram alters the expression of NMDA receptor subunit mRNAs in mouse brain. A quantitative in situ hybridization study. *J Mol Neurosci* 10:219-33.
- Crane GE (1959): Cycloserine as an antidepressant agent. *Am J Psychiatry* 115:1025-1026.
- Crane GE (1961): The psychotropic effects of Cycloserine: A new use for an antibiotic. *Compr Psychiatry* 2:51-59.
- Domino EF, Chodoff P, Corssen G (1965): Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther* 6:279-291.
- Eide P, Stubhaug A, Breivik H, Oye I (1997): Ketamine: Relief from chronic pain through actions at the NMDA receptor (letter; comment). *Pain* 72:289-91.
- Elliot K, Kest B, Man A, Kao B, Inturrisi CE (1995): N-Methyl-D-Aspartate (NMDA) receptors, μ and κ opioid tolerance, and perspective on new analgesic drug development. *Neuro-psychopharmacology* 13:347-356.
- First M, Spitzer RL, Gibbon M (1997): *Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition*. New York: New York State Psychiatric Institute, Biometrics Research Department.
- Krystal JH, Karper LP, Seibyl JP, et al (1994): Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 51:199-214.
- Layer RT, Popik P, Olds T, Skolnick P (1995): Antidepressant-like actions of the polyamine site NMDA antagonist, eliprodil (SL-82.0715). *Pharmacol Biochem Behav* 52:621-7.
- Lindfors N, Barati S, O'Connor WTO (1997): Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. *Brain Res* 759:205-212.
- Malhotra S, Santosh PJ (1996): Loading dose imipramine—new approach to pharmacotherapy of melancholic depression. *J Psychiatric Res* 30:51-8.
- Meloni D, Gambaro C, Graziella de Montis M, Pra P, Taddei I, Tagliamonte A (1993): Dizocilpine antagonizes the effect of chronic imipramine on learned helplessness in rats. *Pharmacol Biochem Behav* 46:423-426.
- Mjellem N, Lund A, Hole K (1993): Reduction of NMDA-induced behavior after acute and chronic administration of desipramine in mice. *Neuropharmacology* 32:591-595.
- Moryl E, Danysz W, Quack G (1993): Potential antidepressive properties of amantadine, memantine and bifemelane. *Pharmacol Toxicol* 72:394-7.
- Panconi E, Roux J, Altenbaumer M, Hampe S, Porsolt RD (1993): MK-801 and enantiomers: Potential antidepressants or false positives in classical screening models. *Pharmacol, Biochem Behav* 46:15-20.
- Papp M, Moryl E (1994): Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. *Eur J Pharmacol* 263:1-7.
- Papp M, Moryl E (1996): Antidepressant-like effects of 1-aminocyclopropanecarboxylic acid and D-cycloserine in an animal model of depression. *Eur J Pharmacol* 316:145-51.
- Paul IA, Nowak G, Layer RT, Popik P, Skolnick P (1994): Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. *J Pharmacol Exp Ther* 269:95-102.
- Pollock BG, Perel JM, Nathan RS, Kupfer DJ (1989): Acute antidepressant effect following pulse loading with intravenous and oral clomipramine. *Arch Gen Psychiatry* 46:29-35.
- Przegalinski E, Tatarczynska E, Deren-Wesolek A, Chojnacka-Wojcik E (1997): Antidepressant-like effects of a partial agonist at strychnine-insensitive glycine receptors and a competitive NMDA receptor antagonist. *Neuropharmacology* 36:31-37.
- Sallee FR, Vrindavanam NS, Deas-Nesmith D, Carson SW, Sethuraman G (1997): Pulse intravenous clomipramine for depressed adolescents: Double-blind, controlled trial. *Am J Psychiatry* 154:668-673.
- Skolnick P, Layer RT, Popik P, Nowak G, Paul IA, Trullas R (1996): Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: Implications for the pharmacotherapy of depression. *Pharmacopsychiatry* 29:23-6.
- Trullas R, Skolnick P (1990): Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J Pharmacol* 185:1-10.
- Vale S, Espejel MA, Dominguez JC (1971): Amantadine in depression. *Lancet* 2:437.
- Wong C-S, Cherng C-H, Luk H-N, Ho S-T, Tung C-S (1996): Effects of NMDA receptor antagonists on inhibition of morphine tolerance in rats: Binding at μ -opioid receptors. *Eur J Pharmacol* 297:27-33.