Dose-Related Ethanol-like Effects of the NMDA Antagonist, Ketamine, in Recently Detoxified Alcoholics

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Background: This study evaluated the dose-related ethanol-like subjective effects of the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine hydrochloride in recently detoxified alcoholics.

Methods: Twenty male inpatients meeting DSM-III-R criteria for alcohol dependence and who had not consumed alcohol for 10 to 27 days prior to the study completed 3 test days that involved the intravenous infusion of ketamine hydrochloride (0.1 mg/kg or 0.5 mg/kg) or saline solution under randomized double-blind conditions. Ethanol-like subjective effects were assessed using the Sensation Scale; the Biphasic Alcohol Effects Scale; visual analog scales to measure “high” and degree of similarity to ethanol, cocaine, and marijuana; a scale assessing the number of standard alcohol drinks producing similar subjective effects; and visual analog scales measuring ethanol craving.

Results: Ketamine produced dose-related ethanol-like effects on each scale measuring its similarity to ethanol. Its effects were more similar to the sedative or descending limb effects of ethanol than to the stimulant or ascending limb effects. Ketamine effects also were more like ethanol than marijuana or cocaine. Ethanol-like effects were more prominent at the higher ketamine dose, a dose rated as similar to greater levels of ethanol intoxication. However, ketamine did not increase craving for ethanol.

Conclusion: The production of ethanol-like subjective effects by ketamine supports the potential clinical importance of NMDA receptor antagonism among the mechanisms underlying the subjective effects of ethanol in humans.

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A GROWING body of research indicates that the capacity of ethanol to block glutamate effects at the N-methyl-D-aspartate (NMDA) receptor contributes to its acute behavioral effects and to the natural history and neuropathology of alcoholism.1 Ethanol reduces NMDA-stimulated ion currents in a non-competitive and concentration-dependent fashion across the range of ethanol concentrations (5-100 mmol/L) associated with human ethanol intoxication.2-7 Long-term ethanol administration increases the levels of NMDA receptor subunits, up-regulates NMDA receptor-related binding, and produces cross-tolerance with other noncompetitive NMDA antagonists.8-12 Increased NMDA receptor function produced by long-term ethanol administration contributes to withdrawal-related seizures13 and neurotoxic effects.14

The NMDA antagonists ketamine hydrochloride, phencyclidine (PCP), and dizocilpine maleate (MK-801) substitute for ethanol in preclinical drug discrimination paradigms.14-17 In these studies, the capacity of NMDA antagonists to substitute for ethanol was greater with increasing reference doses of ethanol. This finding suggested that NMDA receptor blockade contributed more prominently to the subjective effects of higher ethanol doses.15

Our study evaluated whether ketamine produced ethanol-like subjective effects in recently detoxified alcoholic patients. To our knowledge, there are no previous clinical studies evaluating the contributions of NMDA receptors to the behavioral effects of ethanol in humans.

RESULTS

EVIDENCE OF ETHANOL-LIKE EFFECTS

Sensation Scale

Ketamine produced significant dose-related ethanol-like effects as assessed by the Sensation Scale (Figure 1; RMANOVA, dose × time interaction: F_{12,228}=12.1;
PATIENTS AND METHODS

PATIENTS

Twenty male inpatients (mean±SD age, 44.0±10.5 years; weight, 74.7±9.0 kg) who met criteria for alcohol dependence4 as determined by the Structured Clinical Interview for DSM-III-R10 participated in testing. Patients began drinking at a mean±SD of 15.3±2.9 years of age, began regular drinking at 17.8±5.5 years of age, and began regular drinking to intoxication at 21.1±7.1 years of age, and their heaviest level of drinking was at 32.7±13.8 years of age. Patients had a 23.0±10.1-year history of alcoholism. They had undergone a mean±SD of 5.8±9.7 inpatient alcohol detoxifications (range, 0-40). Their mean daily consumption of alcohol was equivalent to 391.5±170 mL of absolute alcohol per day. The mean±SD Michigan Alcoholism Screening Test score19 was 38.7±6.5. Sixteen (80%) of the 20 patients in this study met the von Knorring et al11 criteria for type 2 alcoholism, defined as age of onset before 23 years of age and 2 or more social consequences of alcoholism. Twelve (60%) of the 20 patients had a first-degree relative with a history of alcoholism. Patients were medically stable at study entry based on medical history, physical examination, and routine laboratory testing.

Patients were excluded if they met the criteria for another substance use disorder other than nicotine dependence in the year prior to testing. Fifteen patients (75%) reported lifetime marijuana use, but no use occurred in the year prior to testing. Ten patients (50%) had lifetime cocaine use. Of these patients, 1 used cocaine 6 months prior to testing at a subabuse level and the remainder had not used cocaine for at least 1 year prior to testing. The absence of other current substance abuse support was by negative results of urine toxicological screens prior to testing. Subjects were also excluded if they had another DSM-III-R Axis I diagnosis during a period that was free of alcohol consumption.

Subjects were inpatients at the Substance Abuse Treatment Research Unit of the Veterans Affairs Connecticut Healthcare System, West Haven. They participated in testing for a mean±SD of 17.6±4.2 days (range, 10-27 days) after consuming their last alcoholic beverage. Fourteen patients completed detoxification with pharmacologic supports prior to study entry (benzodiazepines, n=10; nimodipine, n=4). The mean±SD period between the administration of the last benzodiazepine dose and the first pharmacologic test day was 15.7±5.9 days (range, 7-26 days). On their first test day, patients received placebo (n=5), 0.1 mg/kg ketamine hydrochloride (n=9), or 0.5 mg/kg ketamine hydrochloride (n=6).

TESTING PROCEDURE

This research protocol was approved by the Human Subjects Subcommittee of the Veterans Affairs Connecticut Healthcare System and the Human Investigations Committee of the Yale University School of Medicine, New Haven, Conn. After giving informed consent for human investigation, each patient completed 3 test days separated by 48 to 96 hours in a randomized order under double-blind conditions. The information presented to patients while obtaining consent included that the effects of ketamine might resemble alcohol intoxication and might stimulate craving for alcohol. On each test day, patients received a 40-minute intravenous infusion containing either saline solution, 0.1 mg/kg ketamine hydrochloride, or 0.5 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis, Kalamazoo, Mich). This method of administration was similar to that reported previously in healthy subjects.21 For each test session, participants fasted overnight and remained in a fasting state during the test session. They presented for testing at approximately 8:30 AM and an intravenous line was placed at that time. Blood was drawn to determine ketamine levels at 10 and 80 minutes after the initiation of ketamine infusion.

P<.001). Post hoc RMANOVAs revealed that 0.5 mg/kg ketamine hydrochloride produced greater Sensation Score increases than both 0.1 mg/kg ketamine hydrochloride (dose × time interaction: F6,114=13.1; P<.001) and saline solution (dose × time interaction: F6,114=12.4; P<.001). However, 0.1 mg/kg ketamine hydrochloride effects were not significantly different from saline solution.

Self-reported High

As depicted in Figure 1, ketamine increased self-rated high in a dose-related manner (RMANOVA, dose × time interaction: F12,228=8.6; P< .001). Post hoc RMANOVAs revealed that 0.5 mg/kg ketamine hydrochloride produced greater euphoria than both 0.1 mg/kg ketamine hydrochloride (dose × time interaction: F6,114=7.3; P<.001) and saline solution (dose × time interaction: F6,114=15.3; P<.001). Effects of 0.1 mg/kg ketamine hydrochloride were not significantly different from saline solution.

Number of Drinks Scale

Ketamine produced a dose-dependent increase in the perceived number of standard ethanol drinks administered

Continued on next page

ARCH GEN PSYCHIATRY/VOL 55, APR 1998

335

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Ratings were performed to characterize subjective responses to ketamine that mirrored a previous psychopharmacologic study. Patients completed visual analog scales of anger, anxiety, high, nervousness, and sadness. Anxiety was defined as "a mental awareness of worry." Nervousness was defined as a "physical feeling of jitteriness, tension, heart throbbing, breathlessness, or other similar symptoms." These scales consisted of 100-mm lines (0=none; 100=maximum possible) marked proportionately to the perceived intensity of the experience.

Patients completed measures of ethanol-like subjective effects: the Sensation Scale self-rated visual analog scales measuring similarity to acute behavioral effects of alcohol, cocaine, and marijuana (0=not at all similar; 100=identical); a scale measuring the number of standard drinks of ethanol comparable to their drug responses; and the Biphasic Alcohol Effects Scale. The Biphasic Alcohol Effects Scale measures stimulant effects associated with the ascending limb of ethanol intoxication and sedative effects associated with the descending limb of ethanol intoxication. Items associated with the ascending limb of ethanol intoxication include energized, excited, stimulated, talkative, "up," and vigorous. Items associated with the descending limb include difficulty concentrating, "down," heavy head, inactive, sedated, slow thoughts, and sluggish. Inspection of the data on the visual analog scales measuring similarity to ethanol, cocaine, and marijuana revealed no clear discriminative effects of ketamine beyond 80 minutes after the initiation of drug infusion. To simplify the analysis and reduce lack of sparsity, time points up to 80 minutes after the initiation of drug infusions were analyzed. For comparison purposes, standard drinks were defined as equivalents of 15 mL of absolute ethanol, approximately comparable to 12 oz of beer, 4 oz of wine, 1.25 oz of 80-proof alcohol, or 1 oz of 100-proof alcohol. Ethanol craving was assessed using a self-rated visual analog scale evaluating "desire to drink alcohol" used in a previous study. Assessments of ethanol-like effects, mood states, and craving were completed at 60 and 15 minutes prior to ketamine infusion and 10, 40, 80, 110, 170, and 230 minutes after the initiation of ketamine infusion.

KETAMINE LEVELS

Plasma ketamine levels were determined by gas chromatography–mass spectrometry by 1 of the authors (P.S.) according to methods reported previously. Triplicate quality control samples were assayed on each of 3 consecutive days. The calibration curve was calculated for ketamine concentrations ranging between 20 ng/mL and 500 ng/mL. The concentration means for seeded control samples containing 50 ng/mL and 200 ng/mL were found to be within 1.3% and 3.1% of the theoretical values. The assay was found to have coefficients of variation ranging between 3.7% and 4.9%.

DATA ANALYSIS

Data were evaluated initially using repeated-measures analysis of variance (RMANOVA) with within-subjects factors of drug (placebo, 0.1 mg/kg ketamine hydrochloride, or 0.5 mg/kg ketamine hydrochloride) and time. These RMANOVAs were tested for lack of sphericity and Huynh-Feldt adjustments were made to the degrees of freedom to reduce type I error. Significant RMANOVAs were followed with post hoc RMANOVAs comparing the responses following the low and high doses of ketamine to placebo. Significant main effects were also followed with post hoc within-subjects contrasts with significance adjusted for multiple comparisons using Bonferroni corrections. The means of the baseline values were compared between test days using paired t tests with Bonferroni correction made to decrease the effect of multiple comparisons. No significant baseline differences emerged in these analyses.

As depicted in Figure 3, ketamine increased scores on the sedative or descending limb items on the Biphasic Alcohol Effects Scale, but not the stimulant or ascending limb items. The overall RMANOVA performed on subjects completing the Biphasic Alcohol Effects Scale (n=18) revealed significant effects of dose × time interaction: F12,204=6.2; P<.001; limb × dose × time interaction: F12,204=4.1; P=.001. There were no significant main effects or interactions in the RMANOVA performed on ascending limb data. However, the RMANOVA conducted on descending limb data revealed highly significant ketamine effects (dose × time interaction: F12,204=8.4; P<.001). Post hoc contrasts revealed that the 0.5 mg/kg ketamine hydrochloride dose effect was greater than both 0.1 mg/kg and placebo effects (F1=7.9; P=.009) and the 0.1 mg/kg ketamine hydrochloride dose effect was greater than the placebo effect (F1=4.6; P=.04).

Differential Similarity to Ethanol, Cocaine, and Marijuana

Ketamine effects were rated as more similar to those of ethanol than to marijuana or cocaine (Figure 4, visual analog scale). In the initial analysis, the 10 patients who had previous experience with the effects of ethanol, marijuana, and cocaine compared the similarity of ketamine effects with each of these drugs of abuse. The RMANOVA performed on these data revealed significant effects of the reference drug of abuse (ethanol, marijuana, or cocaine; F6,114=3.8; P=.04), ketamine dose (F1,18=7.3; P=.01), and the ketamine dose × time interaction (F6,54=6.0; P=.002). There was a nonsignificant trend toward significance for the drug × ketamine dose × time interaction (F12,108=1.9; P=.1). A post hoc within-subjects contrast revealed that ketamine effects were significantly more similar to ethanol than to both marijuana and cocaine (F1=6.7; P=.02).

Ethanol

Ketamine effects showed a dose-related similarity to ethanol effects (RMANOVA, dose × time interaction: F6,114=12.1; P<.001). Post hoc RMANOVAs revealed that 0.5 mg/kg ketamine hydrochloride was more similar to ethanol than both 0.1 mg/kg ketamine hydrochloride (dose × time interaction: F6,114=12.9; P<.001) and saline solution (dose × time interaction: F6,114=16.6; P<.001). However, 0.1 mg/kg ketamine hydrochloride effects were not significantly different from saline solution.
Marijuana

In patients reporting a history of marijuana use, ketamine had dose-related marijuana-like effects. The RMANOVA performed on data from the visual analog scale assessing similarity to marijuana revealed a significant ketamine dose $\times$ time interaction ($F_{6,84}=4.6; P=.02$).

Cocaine

In patients reporting a history of cocaine use, there was a trend for ketamine to produce cocaine-like effects. The RMANOVA performed on data from the visual analog scale measuring similarity to cocaine revealed a nonsignificant ketamine dose $\times$ time interaction ($F_{6,54}=3.1; P=.09$).

SELF-RATED VISUAL ANALOG SCALES OF CRAVING AND MOOD STATES

There was no significant increase in self-rated desire to drink alcohol following high doses of ketamine (baseline craving [mean±SD], 19.5±7.0 mm; 10 minutes after initiating the infusion, 25.8±7.8 mm) or low doses of ketamine (baseline, 18.2±6.8 mm; 10 minutes after initiating the infusion, 23.2±7.1 mm) relative to placebo (baseline, 15.0±4.7 mm; 10 minutes after initiating the infusion, 18.9±5.6 mm). The RMANOVA performed on these data found a significant time effect ($F_{6,114}=3.9; P=.03$), but no other main effects or interactions. No significant ketamine effects were found on the visual analog scales for anger, anxiety, drowsiness, nervousness, or sadness.

PLASMA KETAMINE LEVELS

Ketamine blood levels increased in a dose-dependent fashion (Figure 5). RMANOVA, dose $\times$ time interaction: $F_{4,64}=30.7; P<.001$).

COMMENT

The principal finding of this study was that ketamine produced dose-related ethanol-like subjective effects in recently detoxified type 2 alcoholics across several response measures. Ketamine effects were rated more similar to items associated with the sedative or descending limb than the stimulant or ascending limb of the Biphasic Alcohol Effects Scale. These data suggested a possible differential contribution of NMDA receptors to the stimulant and sedative effects of ethanol. Ketamine hydrochloride produced effects similar to 1.5±2.5 standard alcohol drinks at the 0.1 mg/kg dose and 8.7±8.1 standard alcohol drinks at the 0.5 mg/kg dose. As predicted by the preclinical literature,15 ketamine doses associated with greater similarity to ethanol produced effects that were attributed to higher levels of ethanol consumption.

Ketamine effects were rated more similar to ethanol than to either marijuana or cocaine. Thus, NMDA receptor antagonism may figure more prominently in the behavioral effects of ethanol than marijuana or cocaine. In contrast, patients found mCPP effects comparably similar to ethanol, marijuana, and cocaine.13 Although more modest than its ethanol-like effects, ketamine effects did show some similarity to the effects of marijuana and cocaine in our study. The NMDA antagonists also showed cocaine-like effects in patients reporting a history of cocaine use, but the effects were not statistically significant.
However, the current study design may have biased the results in favor of finding ethanol-like effects. For example, this study evaluated a patient group who identified ethanol as their primary substance of abuse. Also, the comparisons of ketamine with cocaine were limited to a smaller subsample of alcoholics with cocaine use histories, reducing the statistical power of this analysis. In addition, the slow intravenous ketamine infusion used in the current study may have minimized the stimulant effects and enhanced the sedative or descending limb effects of ketamine. Stimulant effects in this study may have been more prominent had ketamine been administered as a rapid intravenous bolus.

Ketamine did not stimulate craving relative to placebo in our study. However, both ketamine and placebo infusion briefly increased craving, suggesting that test day instructions may have created an expectancy that craving would develop. The current findings contrasted with previous studies of mCPP, in which the production of ethanol-like subjective effects was accompanied by craving. The failure to produce craving was not likely caused by the absence of rewarding effects of ketamine. In animals, NMDA antagonists produce conditioned place preference, enhance brain stimulation reward, and are usually self-administered. Further, ketamine and PCP abuse has been a significant clinical problem. However, ketamine may have failed to produce dysphoric emotional states that have been linked to the elicitation of craving in other studies. In addition, the lower ketamine dose may not have been sufficiently similar to ethanol to facilitate the induction of craving. In contrast, the higher ketamine dose may have sated the desire for further consumption of an NMDA antagonist–like compound. It is possible that an intermediate ketamine dose might have been more effective in stimulating ethanol craving.

The inability of ketamine to prime craving in the patient group may also have been related to the similarity of its effects to the sedative effects of ethanol that emerge as blood alcohol levels plateau or decline. Stimulant effects associated with the ascending limb of ethanol intoxication are more closely tied to the development of craving than are the sedative or descending limb effects. Currently, there is no clear evidence implicating NMDA antagonism in the stimulant effects of ethanol. Instead, clinical studies have implicated both catecholamine and opiate systems in these effects.

The neuropharmacology of the ethanol-like effects of ketamine remains to be clarified. The generalization between ethanol and the other NMDA antagonists is not symmetri-
and serotonin receptors. Thus, it is possible that an asymmetry in animals than the selective noncompetitive NMDA receptors to the ethanol-like effects of ketamine.43,56 Thus, future studies will be needed to more fully assess the contributions of µ-antagonists to the discriminative properties of ethanol.14,23,44,45 Animals trained to discriminate ketamine recognize dizocilpine do not recognize ketamine as a similar drug.15,46 Consistent with this view, ethanol also shows asymmetrical generalization with selective agents acting at other sites of ethanol action, such as γ-aminobutyric acid and serotonin receptors.53,57 Thus, it is possible that an appropriate combination of drugs acting at NMDA, serotonin, γ-aminobutyric acid, and other receptors might produce symmetrical generalization with ethanol.

Ketamine also appears to be a more complex stimulus in animals than the selective noncompetitive NMDA antagonist dizocilpine (MK-801), as suggested by the asymmetrical generalization between these drugs. Animals trained to discriminate ketamine recognize dizocilpine as ketamine-like,31 while animals trained to identify dizocilpine do not recognize ketamine as a similar agent.49 The complexity of the ketamine stimulus may arise from its differential relative affinity for NMDA receptor subunits,56 its agonism of the µ-opiate receptor,51,52 and its blockade of dopamine transporters.53 The µ-agonist actions of ketamine may be of limited importance to its ethanol-like effects. The discriminative properties of NMDA antagonists, particularly their ethanol-like effects, are not dependent on their affinity for µ-receptors.15,54 Similarly, µ–receptor agonism does not appear to contribute to the discriminative properties of ethanol in animals.53 However, µ-antagonists reduce aspects of human ethanol intoxication.53,56 Thus, future studies will be needed to more fully assess the contributions of µ-receptors to the ethanol-like effects of ketamine.

Modulation of dopamine systems also may have contributed to the current findings. Ketamine has direct dopaminergic effects via its low affinity for dopamine reuptake sites as well as its NMDA receptor–mediated modulation of dopaminergic neuronal activity.57,58 However, ketamine effects on dopamine neurons do not correlate well with its NMDA antagonist-like discriminative properties.59 Also, the euphoric effects of ketamine in humans seem to be insensitive to haloperidol pretreatment.60

Our data support the hypothesis that the capacity of ethanol to block NMDA receptors contributes significantly to its subjective effects in humans. Future studies should explore a wider range of ketamine doses and rates of administration. Further, the similarity of ketamine to drugs of abuse should be evaluated in populations primarily dependent on cocaine or marijuana. These studies should also consider employing training doses of ethanol, cocaine, and marijuana to facilitate the accuracy of interpreting the similarity between ketamine effects and those of these other drugs. Comparisons of ketamine and sedative-hypnotic agents would also provide insights into the specificity of the similarity between ketamine effects and the sedative effects of ethanol. In addition, the dependence on subjective report is a potential limitation of our study. Physiologic measures might aid the evaluation of neurobiological contributions to the acute behavioral effects of ethanol.

The NMDA antagonist properties of ethanol may have therapeutic implications in humans. For example, acamprosate reduced ethanol consumption in clinical trials.61,62 This drug has both NMDA agonist and antagonist-like effects, making it difficult to extrapolate a therapeutic mechanism at this time.63 One potential strategy would be to explore agents that reduce ethanol effects at the NMDA receptor. One class of candidate agents to serve this function would be agonists of the strychnine-insensitive glycine modulatory site of the NMDA receptor complex. These drugs reduce ethanol effects in some preclinical studies.64,65 Preliminary human data also suggest that the strychnine-insensitive glycine partial agonist, D-cycloserine, exacerbates ethanol intoxication at doses associated with NMDA antagonistslike amnestic and euphoric effects.62 Thus, NMDA receptors may become an important focus for future drug development in the alcoholism field.

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