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Short communication

Continuation phase intravenous ketamine in adults with treatment-resistant depression

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ABSTRACT

Background: Little is known about the antidepressive effects of repeated intravenous ketamine infusions beyond the acute phase of treatment in patients with refractory depression.
Methods: Twelve subjects with treatment-resistant non-psychotic unipolar or bipolar major depression and suicidal ideation were given repeated (up to 6) thrice-weekly acute-phase intravenous infusions of ketamine (0.5 mg/kg, administered over 100 min). Those who remitted during acute-phase treatment received continuation-phase treatment that consisted of 4 weekly ketamine infusions, followed by 4 weeks of post-continuation phase follow-up (during which no further ketamine infusions were administered). Clinical measures were assessed at baseline, at 24 h following each infusion, at the last acute-phase observation, and during continuation and post-continuation follow-up (acute phase remitters only).
Results: Of the 12 enrollees, 5 (41.7%) remitted and 7 (58.3%) responded to ketamine treatment during the acute-phase. All five subjects who remitted during the acute-phase experienced further depressive symptom improvement during continuation-phase treatment. Four subjects lost remission status during the post-continuation phase, but all were still classified as positive treatment responders at the end of the post-continuation phase. Adverse effects were generally mild and transient during acute- and continuation-phase treatment; however, one subject developed behavioral outbursts and suicide threats during follow-up while hospitalized, and one subject died by suicide several weeks after the end of follow-up.
Limitations: This was an uncontrolled feasibility study with a small sample size.
Conclusions: The continuation-phase administration of ketamine at weekly intervals to patients with treatment-resistant depression who remitted during acute-phase ketamine treatment can extend the duration of depressive symptom remission. The antidepressive effect of ketamine persisted for several weeks after the end of continuation-phase treatment. Our results highlight the need for close monitoring of subjects who are at high baseline risk for suicide but do not respond clinically to ketamine.
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1. Introduction

Multiple controlled trials have demonstrated the short-term effectiveness of both single and repeated administration of sub-anesthetic doses of intravenous (i.v.) and intranasal ketamine, a potent non-competitive glutamatergic N-methyl-D-aspartate (NMDA) antagonist, for treating the symptoms of non-psychotic treatment-resistant unipolar and bipolar major depression (McGirr et al., 2015; Newport et al., 2015). In these trials, subjects who benefitted from ketamine experienced rapid (within hours) onset of clinical antidepressive response lasting 3–14 days on average, with generally benign and transient adverse effects.

The field has now focused its attention on translating ketamine clinical trial protocols to routine practice, with a focus on repeated administrations of ketamine to sustain initial therapeutic benefit over longer-term treatment (Bobo et al., 2016). Repeated acute-phase infusions of ketamine provided over 12–14 days have been associated with larger reductions in depressive symptoms than single infusions for up to 14 days (Coyle and Laws, 2015). However, relapse rates in these studies were high—generally occurring within 18–19 days (aan het Rot et al., 2010; Murrough et al., 2012). There is a paucity of studies of the antidepressive effects and safety of repeated i.v. ketamine infusions beyond the acute-phase of treatment.

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We thus conducted an open label trial of i.v. ketamine in 12 adults with treatment-resistant unipolar or bipolar major depression, followed by 4 weeks of continuation i.v. ketamine treatment for subjects who achieved depressive symptom remission during the acute-phase.

2. Methods

2.1. Participants

The study protocol was approved by the Mayo Clinic Institutional Review Board. Adults (aged 18–64 years) meeting DSM-IV-TR criteria for non-psychotic, treatment-resistant major depressive disorder (MDD) or bipolar I or II disorder (BP) who were psychiatrically hospitalized for acute suicidal ideation were enrolled between December 30, 2014 and May 18, 2016. The subjects in this study are unique from those of a previously published report by our group (Rasmussen et al., 2013). MDD or BP diagnoses were established by clinical interview and confirmed using the Structured Clinical Interview for DSM-IV (SCID). Treatment resistance was defined as failure to respond to at least two therapeutic trials of antidepressants or mood stabilizers (for patients with bipolar disorders) that were of adequate duration and dose, or electroconvulsive therapy during the current depressive episode. The number and adequacy of previous therapeutic trials was systematically assessed at the time of study enrollment using the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Eligible subjects had a 9-item Patient Health Questionnaire (PHQ-9) suicide item (item 9) score of ≥ 1 at the screening visit. Exclusionary criteria included psychotic symptoms, duration of the current depressive episode > 2 years, current alcohol or non-nicotine substance use disorder (unless in remission for ≥ 12 months), history of developmental delay or intellectual disorder, pregnancy, unstable medical condition, and involuntary psychiatric hospitalization. The determination of current disqualifying substance use disorders was made on the basis of clinical assessment, supplemented by a negative urine drug screen. All participants provided written informed consent.

2.2. Study design

This was a single-arm, open-label trial conducted in two phases. During the acute-phase, i.v. ketamine was administered thrice-weekly for up to 2 weeks. Those who achieved depressive symptom remission (Montgomery Åsberg Depression Rating Scale (MÅDRS) (Montgomery and Åsberg, 1979) total score ≤ 9 measured 24 h after any acute-phase infusion) received continuation-phase treatment that consisted of once-weekly i.v. ketamine infusions for 4 additional weeks (Hawley et al., 2002). Remission could occur after any of the 6 acute-phase infusions, at which point the next infusion was the first (of four) continuation-phase infusions. Individuals who remitted during acute-phase and completed continuation-phase treatment had 4 additional weekly post-continuation follow-up visits. Those who responded to i.v. ketamine ($\geq 50\%$ reduction from baseline in MÅDRS total score) but did not remit during acute-phase were not eligible for continuation-phase treatment. Suicidal ideation was assessed clinically throughout the trial, supplemented by scores on the MÅDRS suicide item (item 10). The PHQ-9 was used as an assessment instrument at the screening visit only.

2.3. Ketamine administration

Ketamine (0.5 mg/kg) was administered i.v. over 100 min for all acute- and continuation-phase infusions. During the infusions, heart rate, ECG, and pulse oximetry were continuously monitored. Blood pressure was measured at 15 min intervals. Monitoring of vital signs continued in this manner until 60 min after the end of infusion. Initial acute ketamine infusions were provided in the hospital, and continuation-phase infusions were generally provided as outpatients in a dedicated Clinical Research Unit.

2.4. Outcome measures

Depressive symptoms were measured using the MÅDRS prior to each infusion, at the end of each infusion (100 min), at 24 h post-infusion, and at all 4 post-continuation phase follow-up visits. Additional effectiveness measures were assessed at the same time points and included the Clinical Global Impression severity (CGI-S) and change (CGI-C) subscales (Guy, 1976) and MÅDRS factor scores (sadness [Factor 1], negative thoughts [Factor 2], detachment [Factor 3], and neurovegetative symptoms [Factor 4]) (Williamson et al., 2006). Withdrawal from the study was based on worsening depressive symptoms (CGI-S rating of much or very much worse, or at the discretion of the clinical investigator).

Treatment-emergent manic symptoms were assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978). Adverse effects were also assessed in 15 min intervals by direct questioning during all infusions and for up to 60 min post-infusion. Dissociative and psychotic (hallucinatory) effects were assessed clinically by spontaneous report and direct questioning. For example, spontaneous reports of feeling as though one were floating, disconnected, or "spacey" (but not lightheaded) were classified as representing dissociation. Subjects were also asked directly whether they experienced any of these sensations. CGI-S ratings were completed by study clinicians. All other clinical ratings were completed by trained research staff. Baseline scores for all measures were taken before the first acute-phase infusion.

2.5. Concomitant treatments

All subjects continued to receive hospital or outpatient care as usual during their participation in this study, including changes to pharmacotherapy when necessary and psychosocial interventions. Based on preliminary data suggesting benzodiazepine use may attenuate ketamine response, administration of benzodiazepines at ≥ 4 mg/day lorazepam equivalents was not allowed (Frye et al., 2015). No benzodiazepine doses were given on the morning of ketamine administration. Treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation, or deep brain stimulation was not allowed.

2.6. Statistical procedures

Statistical analyses included all subjects who received at least one acute-phase ketamine infusion. Change in baseline to endpoint values (24 h after the last infusion received during acute-phase treatment) for continuous efficacy measures were assessed using paired *t*-tests at a 2-tailed α level of 0.05. *T*-tests were used to compare mean baseline and mean percent change (baseline to last observed value during acute-phase) in efficacy measures between groups defined by remission status (remitters vs. non-remitters). Descriptive statistics were used to summarize demographic and other discrete variables, including rates of response and remission. All analyses were performed using STATA Version 14 statistical software (STATA Corp., College Station, TX, USA).

3. Results

3.1. Subject demographic and clinical characteristics

All 12 enrolled subjects received at least one acute-phase ketamine infusion. Subjects were predominantly middle-aged (mean