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Preliminary communication

A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression

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ABSTRACT

Background: Acute administration of subanesthestic doses of intravenous ketamine have been shown to elicit a rapid antidepressant response in patients with treatment-resistant depression. However, it remains to be seen if repeated doses over a longer period of time will have the same effects. Here, we assess the long-term efficacy of repeated intravenous ketamine infusions in three patients with high treatment-resistant depression via a naturalistic observation study.

Method: Three patients consented to intravenous ketamine infusions as a therapy for their treatment-resistant depression. Patients were administered ketamine at 0.5 mg/kg of ideal body weight over 40 min followed by a saline flush until discharge. Severity of depressive symptoms was rated with the Montgomery-Asberg Depression Rating Scale.

Results: All three patients responded to the ketamine infusions, but each went through an individualized course of treatment based on their own response.

Limitations: This was an open-label naturalistic observation without blinding, randomization, or a placebo control.

Conclusions: These cases add to the literature supporting the therapeutic effect of low-dose repeated intravenous ketamine for patients with treatment-resistant depression. Further study is needed to define the risks, benefits, indications, and contraindications of this potential treatment.

1. Introduction

Serious depressive states, whether unipolar or bipolar, have a lifetime prevalence of 15–20%, and are projected to become the second leading cause of disability by 2020 (Murray and Lopez, 1996). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study found that less than one-third of patients achieved full remission after four months of traditional antidepressant treatment (Thase et al., 2005). Although definitions of "Treatment-Resistant Depression" (TRD) vary (Berlim and Turecki, 2007), clinicians agree that a significant proportion of patients are antidepressant refractory despite adequate dosage, duration, and compliance. A subgroup of these patients is refractory to multiple monotherapy medications, combination and augmentation strategies, and the use of mood stabilizers. Many of these patients receive ElectroConvulsive Therapy (ECT) but some of these patients even become refractory to ECT. These patients may be referred for treatment using Deep Brain Stimulation (DBS). A new, effective, and less intrusive treatment (than ECT or DBS) for TRD patients would be a significant advance in alleviating suffering and disability for these patients and their families.

Recent research has focused on the involvement of the glutamatergic system in mood disorders. Altered glutamate levels and glutamate receptors have been reported in a variety of human studies of depression (Krystal et al., 2002; Zarate et al., 2002; Scarr et al., 2003; Sanacora et al., 2004; Yildiz-Yesiloglu and Ankerst, 2006; Hashimoto et al., 2007; Hasler et al., 2007), with one study even relating "treatment resistance" to abnormal glutamate/glutamine/gamma-amino butyric acid cycling (Price et al., 2009). Drugs that target this system, specifically ketamine, have been shown to have a rapid onset of antidepressant effects. Although its exact mechanism of action remains unclear, it is postulated that by blocking the N-methyl-D-aspartate (NMDA) receptors, ketamine simultaneously activates and potentiates alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) throughput (Maeng and Zarate, 2007; Maeng et al., 2008; Li et al., 2010; Zarate et al., 2010; Koike et al., 2011). In addition, ketamine

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increases the release of Brain-Derived Neurotrophic Factor (BDNF; Garcia et al., 2008) and stimulates the mammalian Target of Rapamycin (mTOR; Li et al., 2010), both of which may play a part in its antidepressant effects.

Subanesthetic doses of ketamine have produced rapid antidepressant effects in animal models of depression (Maeng et al., 2008; Yilmaz et al., 2002; Hashimoto, 2009), as well as in patients who have a treatment-resistant form of depression (Berman et al., 2000; Diazgranados et al., 2010; Messer and Haller, 2010). Antidepressant effects have been reported within hours of the infusion with a sustained benefit lasting days (Messer and Haller, 2010; aan het Rot et al., 2008; Messer et al., 2010). These rapid and sustained antidepressant effects have been demonstrated in patients with TRD (Berman et al., 2000; Zarate et al., 2006; Phelps et al., 2009) and treatment-resistant bipolar depression (Diazgranados et al., 2010), as well as in patients with TRD and comorbid alcohol dependency, pain syndrome, and advanced cancer (Kudoh et al., 2002; Liebrenz et al., 2007; 2009; Stefanczyk-Sapieha et al., 2008; Irwin and Iglewicz, 2010). In addition, a single dose of ketamine has been shown to reduce suicidal ideation within 24 h (Price et al., 2009) and repeated doses of ketamine (every other day for two weeks) have shown prolonged benefit, lasting up to three weeks (Messer et al., 2010; Messer and Haller, 2010; aan het Rot et al., 2010).

Although the research supports an acute effect by ketamine, it remains to be seen if repeated doses over a longer period of time will have the same effects. In this report, we present three case reports of repeated intravenous ketamine infusions in TRD patients over a 12-month period.

2. Methods

Three adult patients with a Major Depressive Episode, current, without psychotic features, as determined by a psychiatric clinical interview and confirmed by the Mini Neuropsychiatric International Interview (MINI; Sheehan et al., 1998), were admitted to the inpatient psychiatric unit and offered the option of another course of ECT or intravenous (IV) ketamine infusions. Patients understood that this was not a Food and Drug Administration-approved use of ketamine. Patients consented to IV ketamine infusions after a full description of a procedure approved by Lutheran Hospital's Departments of Anesthesia, Medicine, Nursing, Pharmacy, Psychiatry and Medical Executive Committee. Institutional Review Board approval was not required for this naturalistic observation study, but it approved the consent form. Per standard of care, a toxicology screen and medical clearance was obtained prior to the first infusion.

In line with previous research (Berman et al., 2000; Zarate et al., 2006; aan het Rot et al., 2008; Diazgranados et al., 2010; Messer and Haller, 2010; Messer et al., 2010), ketamine was administered at 0.5 mg/kg of ideal body weight over 40 min. Vital signs were monitored throughout each infusion, as well as any side effects of the treatment. No medication changes or washouts occurred prior to the initiation of the treatment. Severity of depressive symptoms was measured by the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). During the acute phase, outcome measures were completed prior to the infusion, 4-h post-infusion, and 24-h post infusion. Infusions were performed every other day, for up to six infusions. Once the patient reported a reduction in depressive symptoms, they were discharged and given infusions on an outpatient basis. The outpatient infusion schedule was individualized as described below. Outcome measures were completed prior to each infusion and 24-h post-infusion via a telephone conversation. Remission of the depressive symptoms was defined as a MADRS score of ≤ 8 (Hawley et al., 2002).

3. Results

3.1. Patient 1

This patient was hospitalized after a suicide attempt by hanging. Patient was diagnosed with Major Depressive Disorder (MDD) at the age of 17, with co-morbid Panic Disorder without Agoraphobia, and had a history of multiple suicide attempts with over 20 hospitalizations. The patient had no history of an Axis II disorder, chemical dependency, or major medical illness. The family history was significant for mood disorders. Patient 1 had failed greater than 20 antidepressants, mood stabilizers, and augmentation treatments, and had received 35 ECT treatments in three separate acute trials with good benefit. However, significant cognitive symptoms developed after each trial, severe enough to cause job loss with the last two trials.

At the time of the ketamine trial, the patient was taking fluoxetine 80 mg, quetiapine 200 mg, lamotrigine 50 mg, and lorazepam 0.5 mg. The patient received 27 mg of ketamine throughout the 12-month course of treatment. Pre-treatment MADRS scores were severe. Four hours post-infusion 1, the MADRS score dropped to zero. The patient remained stable, was given the second infusion 4 days later, and discharged. The third infusion took place 8 days after the second. Patient 1 reported mild depressive symptoms prior to the infusion, which resolved post-infusion. A week was added to each subsequent infusion until ketamine was being infused approximately every 6–7 weeks. The patient experienced a moderate relapse in month 8, precipitated by anxiety related to school, work, and a failed relationship. However, they responded to an acute series of three ketamine treatments. The patient reported no cognitive issues and had become more functional in all facets of life. At the 12-month point, the medication regime included fluoxetine 60 mg, quetiapine 50 mg, and lorazepam as needed. The number of treatments totaled 16 (see Fig. 1).

3.2. Patient 2

This patient was hospitalized after reporting suicidal ideation to their outpatient psychiatrist. The patient's depression began in 2008 after surgical complications which led to a cascade of losses including job, car, and home. Patient 2 had failed 20 antidepressants, mood stabilizers, and augmentation treatments and had 15 ECTs with little improvement, resulting in 7 hospitalizations and

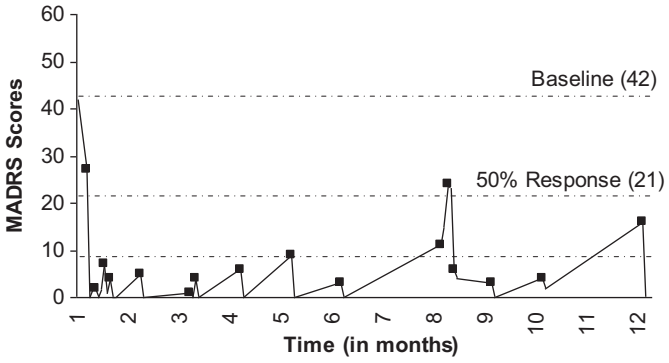

Fig. 1. Patient 1's response to ketamine infusions; each marker indicates an infusion (pre-treatment score) and the lowest line indicates remission (MADRS ≤ 8).