CASE REPORT
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Maintenance Ketamine Treatment Produces Long-term Recovery from Depression

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ABSTRACT

Patients not responding to conventional treatment for depression are classified as having treatment-resistant depression (TRD). Electroconvulsive therapy is effective in ~50% of the patients diagnosed with TRD. Recent reports of rapid antidepressant effect with a single dose of ketamine suggest a potential benefit for TRD patients. However, there are no studies characterizing optimal dosing parameters (eg, frequency and inter-dose interval). The following case describes the effects of two ketamine administration regimens in a patient with a 15-year history of depression.

FOCUS POINTS

- Treatment-resistant depression affects up to 15% of patients with major depressive disorder, and there are few options after electroconvulsive therapy failure.
- Ketamine can be administered in an outpatient setting with nurse monitoring during the infusion.
- Adverse events associated with ketamine infusions are rare and can be avoided by using ideal body weight for dosing.
- Multiple infusions may increase the length of remission. However, optimal dose, frequency, and inter-dose interval for ketamine administration require further study.

INTRODUCTION

Despite substantial advances in the therapeutic options for managing patients with major depressive disorder (MDD), treatment-resistant depression (TRD) continues to be a serious public health problem. It is estimated that up to 15% of patients diagnosed with MDD do not respond to conventional treatments and can be classified as treatment resistant.[1] Attempting successive pharmacologic trials in the quest for an effective agent increases risk for the patient and can produce significant health, social, and economic burdens.[2]

A growing body of evidence indicates that *N*-methyl-D-aspartate (NMDA) receptor antagonists significantly and rapidly improve depressive symptoms in MDD patients. Two randomized controlled trials, one including TRD patients, reported a rapid antidepressant response from a single infusion of ketamine in patients with MDD.[3,4] However, there are no available data or general guidelines on optimal dose, frequency, or inter-dose interval for ketamine administration to sustain remission. This case delineates a dosing regimen and may provide guidance to achieving sustained remission in TRD patients.

CASE REPORT

In January 2008, a 46-year old female with MDD was hospitalized for a course of electroconvulsive therapy (ECT). Successive interventions over 15 years had included trials of 24 psychotropic medications and 273 ECT treatments, 251 of which were bilateral. No intervention had produced remission but only a short-lived response to treatment. She had no history of an Axis II diagnosis, chemical dependency or other major medical illnesses.

ECT during this admission was administered with ketamine as the anesthetic at 2 mg/kg given over 60 seconds. Surgical anesthesia occurred ~30 seconds after the end of intravenous injection and lasted ~10 minutes. There was no significant change in depression symptoms with the ketamine used as an

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anesthetic during the ECT treatment. Alternative treatments were reviewed for potential use. In addition to no significant recovery from her depression, the long-term use of ECT caused problems with memory loss and focused attention. She was unable to remember much of her history over the previous 15 years. Re-learning the information became futile since each course of ECT would eliminate what had been gained.

Based on recent reports of rapid antidepressant effect of single dose ketamine in MDD patients,[3,4] the authors of this case report reviewed the information available with the patient and obtained her consent. They discussed potential side effects known to be associated with the anesthetic dose of ketamine, such as psychosis during or after the treatment, elevations in liver enzymes, hypertension, a harlequin-like skin change, and malignant hyperthermia. At lower doses used for antidepressant treatment[4] reported in the literature, side effects included perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, and increased libido, as well as gastrointestinal distress, increased thirst, headache, metallic taste, and constipation. These side effects appeared to abate within 80 minutes after the infusion. Ketamine was administered at 0.5 mg/kg of ideal body weight (IBW) over 40 minutes on February 28, 2008.

The first ketamine treatment led to a dramatic remission of depressive symptoms: the Beck Depression Inventory (BDI) score decreased from 22 to 6 (Figure). Three additional infusions administered every other day over 5 days produced remission lasting 17 days after the last infusion in this series. Three series of six ketamine infusions given every other day except weekends were repeated over the next 16 weeks (Figure). Each infusion sequence produced remission lasting 16, 28, and 16 days, respectively, followed by a relapse. After three remission/relapse cycles and before relapse could occur after the fourth infusion series, a maintenance ketamine regimen was established on August 27, 2008 using 0.5 mg/kg IBW at a 3-week inter-dose interval. The authors' estimation for the maintenance dosing interval was based on the time frame between remission and relapse for this patient. Relapse to depression was prevented by treating prior to the onset of a relapse.

As shown in the Figure, with maintenance infusions the patient has been in remission for >15 months. No concurrent pharmacotherapeutic agents have been administered or required during this time period, no adverse events have emerged, and there has been no cognitive impairment as is typical with ECT, polypharmacy, or from MDD itself.

Generally, weight-based dosing (eg, mg/kg) is a sound pharmacologic strategy. However, data and experience with weight-based dosing in a previous patient who was substantially overweight[5] resulted in perceptual distortion, though antidepressant benefit was evident. In consultation with the authors' Anesthesia department, they selected IBW to establish the dosing regimen. The Metropolitan Life Insurance weight tables[6] can be used to determine IBW based on sex, age, height, and body frame.

For this case, ketamine infusions were administered with nursing supervision as a day patient procedure and treatment was well tolerated. Vital signs were monitored during the infusion. No psychotic or dissociative symptoms were noted during or after the ketamine infusions and no other adverse events occurred. Ketamine was safe in an outpatient setting without cognitive or physical impairment once ketamine was metabolized (usually within 2 hours post infusion). Repeated administration did not produced tachyphylaxis or tolerance.

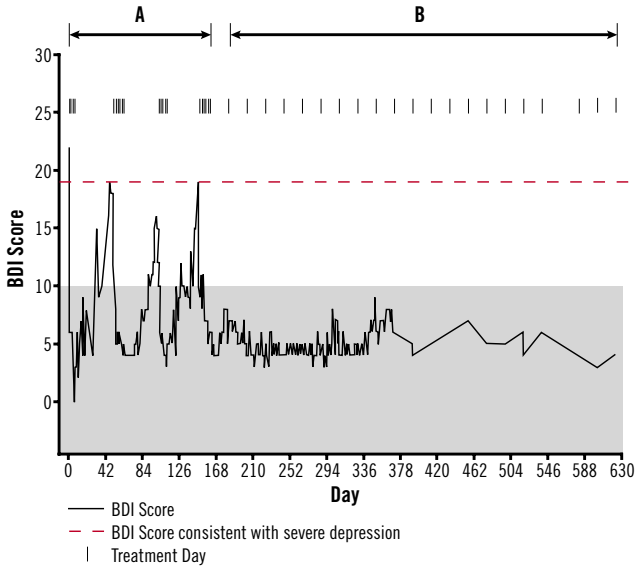
Maintenance ketamine treatments described here continue to sustain this patient's recovery from depression. Moreover, in this patient, maintenance treatments were more effective than the recurrent series of infusions for maintaining recovery.

CONCLUSION

While there is no consensus regarding the definition of TRD,[2,7] it is generally regarded as a resistance to treatment when the patient has not experienced a 50% reduction in depressive symptoms after ≥2 courses of appropriate antidepressant, given in an adequate dose and duration.

FIGURE

LONGITUDINAL OBSERVATION OF DEPRESSION SYMPTOMS (BDI) IN RESPONSE TO KETAMINE TREATMENT (2/28/08–11/11/09) IN ONE PATIENT WITH TREATMENT-RESISTANT DEPRESSION



Shaded area represents BDI score range consistent with non-depressed state. Horizontal dashed line represents BDI score consistent with severe depression. Vertical marks indicate infusion days. Period A: series of six ketamine infusions followed by remission and relapse. Period B: maintenance ketamine treatment with continuous remission.

BDI=Beck Depression Inventory.

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As indicated by the designation TRD, there are no consistently effective interventions. Options include medications from various classes of antidepressants either alone or in combination with other psychotropics, or ECT alone or in combination with a range of medications. ECT is given in a series of treatments and with TRD may also be given as a maintenance treatment. Most current treatments for TRD take several weeks to achieve full clinical effect. In comparison, ketamine in this case had a rapid onset of action.

The cost implications of ECT must also be taken into consideration when this becomes the primary antidepressant intervention. Ketamine treatments require infusion capability and ongoing nursing observation. The cost and personnel needed for a ketamine treatment are far less than that of ECT since no charges associated with anesthesia or operating room use are needed. The data from our institution suggest that the charges associated with one ketamine treatment are ~33% of the charges for one ECT.

The combination of ketamine and ECT has received very little attention in the literature. Although others have noted a potential benefit from using ketamine during ECT either as induction treatment[8] or an anesthetic,[9] the authors did not see any changes in mood symptoms in this patient when ketamine was used as an anesthetic to ECT. This lack of response could be attributed to the patient's significant exposure to ECT. Alternatively, antidepressant benefit may be attenuated by the amnestic effect of ECT or anesthetic doses, with the latter suggesting a "state-dependent" effect.

A growing body of evidence suggests that the glutamatergic system, known to play a role in neuronal plasticity and cellular resilience, is also involved in the pathophysiology and treatment of MDD.[10-12] Ketamine, an NMDA receptor antagonist with rapid antidepressant effect, emerged as a potential agent for treatment of mood disorders,[3,4] specifically TRD. Zarate and colleagues[12] have described the putative mechanism of action of NMDA receptor antagonists. It is postulated that the NMDA-glutamate receptor complex signals morphologic changes that produce cell loss or atrophy. Ketamine, a high-affinity NMDA-receptor antagonist, causes the release of brain-derived neurotrophic factor (BDNF). The presence of BDNF increases the size of cells and increases arborization of dendrites which is reduced under circumstances of stress in animal models that are analogous to depression. The function of BDNF is considered to be a part of the antidepressant effect of electroconvulsive treatments, antidepressants, and ketamine.

Optimal ketamine regimens to sustain remission have not been defined. Previously, the authors successfully treated two patients with TRD using a series of ketamine infusions[5] over a 12-day period. The patient who received two ketamine treatments separated by 6 days was symptom-free for 18 days and the patient who received six ketamine treatments (every other day over 12-day period) was symptom-free for 29 days.[5] As reported by others, remission was followed by relapse.

In the case described here, a maintenance ketamine treatment was more successful in preventing relapse of depression than repeated series of infusions. It may also have some economic and quality of life advantages compared to ECT. As NMDA receptor antagonist action on TRD is explored, a maintenance treatment protocol requires further investigation as a means to sustain recovery from depression. ***PP***

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