Rapid Antidepressant Action of Ketamine in Psychiatric Patients with Suicidality - a Case Series

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Received March 27, 2014; Revised April 17, 2014; Accepted April 21, 2014

Abstract Ketamine, a non-competitive NMDA receptor antagonist with rapid antidepressant action, is a novel approach in modulating glutamate receptors for management of treatment-resistant major depressive disorder. It clinically engenders meaningful advances in depression therapeutics. This case series highlights the role of low dose intravenous ketamine infusion i.e., 0.5 mg/kg dissolved in 100 ml normal saline and given over a period of 40 minutes in patients of depression who were contemplating suicide.

Keywords: Ketamine, N-methyl D-Aspartate antagonist (NMDA), major depressive disorder (MDD), mammalian target of rapamycin (mTOR), brain derived neurotrophic factor (BDNF), Eukaryotic Elongation Factor 2 (eEF 2) kinase


1. Introduction

Major depressive disorder (MDD) is going to be the second most leading cause of years lived in disability by the year 2020 as per the World Health Organization (WHO) Health survey report [1]. A range of antidepressant agents are available, but 30% to 40% of patients do not respond to initial treatment and non response rate is even higher in depressed patients in bipolar disorder. In patients, who experience symptomatic relief after conventional antidepressant drug treatment, these improvements are generally not evident for 3 to 4 weeks. A monoamine neurotransmitter system (e.g. nor-epinephrine, dopamine, or serotonin) is the pharmacological mechanism underlying almost all current antidepressant agents. Indeed, the lag period in onset of action for several weeks is a major limitation which results in considerable morbidity and higher risk for suicidal behaviour [2]. Converging evidence from in vivo brain imaging studies, postmortem investigations and gene expression studies implicates abnormalities in glutamatergic signaling in the pathophysiology of depressive disorders [3,4].

Ketamine, a non-competitive NMDA receptor antagonist has a rapid antidepressant action within hours of a single sub-anaesthetic intravenous infusion [5,6] and decreases suicidality [7,8]; efficacious and safe [9,10,11] as reported in several small studies and case reports, thus representing a paradigm shift in therapeutic approaches for treatment-resistant major depressive disorder [12,14]; treatment-resistant bipolar depression [15] and obsessive compulsive disorder [8].

The spontaneous neurotransmission “at rest” causes robust trafficking of Vps 10 p-tail-interactor-1a (vti1a) synaptic vesicle to fuse with the presynaptic membrane as compared to more abundant vesicular SNARE synaptobrevin 2 (also called VAMP 2) and modulates action potential firing in neurons. Non-competitive NMDA receptor antagonist (ketamine) “at rest” deactivates eukaryotic elongation factor 2 (eEF 2) kinase, resulting in reduced phosphorylation and desuppression of rapid dendritic protein translation, including brain-derived neurotrophic factors (BDNF), which contribute to synaptic plasticity that mediates long term effects of the drug [17,18,19]. Synaptogenesis in response to mammalian target of rapamycin (mTOR) activation could be hypothesized to contribute ketamine's acute and sustained effects in depressed patients for 7 days to 2 weeks by increasing (mTOR) expression [20].

The repeated long administration of ketamine may have neurotoxic effects when the dose exceeds the therapeutic relevant range, causing reversible vacuolation in the posterior cingulated and retrosplenial cortex of rats [21]. This is not the universal phenomenon as other more selective NMDA antagonists e.g., eliprodil and Ro 63-1908 which are nicotinic receptor (NR2B) subunit antagonists have not reported vacuolation in rats [22]. NR2B antagonist Ro 25-6981 has antidepressant like activity and traxoprodil, an NR2B antagonist, has demonstrated expression of brain-derived neurotrophic factor (BDNF) which triggers the neuroplastic changes...
that hypothetically represent the final common pathway of antidepressant action [23].

A case series of psychiatric patients who had depression and suicidal tendency is reported. They were prescribed ketamine 0.5 mg/kg infusion (dissolved in 100 ml of normal saline) over a period of 40 minutes as per the procedure documented earlier in the literature for difficult to treat or treatment-resistant patients [5,6,7,10,11,12,13,14]. Various scales were administered e.g., psychopathology was assessed on brief psychiatric rating scale (BPRS)[26]; depression on Montgomery Asberg Depressive Rating Scale (MADRS) [27]; obsessive compulsive disorder on Yale-Brown Obsessive and Compulsive Scale (YBOCS) [28]; perceptual and dissociative changes on Clinician- Administered Dissociative States Scale (CADSS) [29]; and clinical outcome on Clinical Global Impression- Severity (CGI-S) and Clinical Global Impression- Improvement (CGI-I) Scale.

2. The Cases

2.1. Case 1

A 33 year old male, married graduate reported in the outdoor patient department unit of Psychiatry, Government Medical College, Rajindra Hospital, Patiala with symptoms of sadness of mood, describing his world as pale, stale and gloomy, with decreased appetite and sleep. He was having hopelessness, worthlessness and suicidal ideation, and a death wish of jumping in front of the train; but not completing the act. These symptoms were gradual in onset and worsened with time, during the last six months. He denied hearing any voices or self referential gestures, delusion of sin, guilt, poverty and nihilism. There was no past psychiatric, medical illness, substance abuse and family history of any psychiatric illness. Mental status examination showed depressed mood, appropriate affect, and low volume speech, slow in rate and rhythm, coherent and comprehensibility with no echolalia. Patient’s thoughts were slow in progression and goal directed, there was no loosening of association, thought insertion, broadcasting, withdrawal or blocking. His higher mental functions were normal; attention was aroused, but showed difficulty in concentration, memory and calculation with delayed responses. Judgement, insight to illness and contact with reality was intact. He was diagnosed on ICD-10 Classification of Mental and Behavioural Disorders, as F 32.2 Severe depressive episode without psychotic symptoms. His score on MADRS at the baseline was 35 and CGI –S score was 6. The sub-anaesthetic dose of ketamine i.e., 0.5 mg/kg dissolved in 100 ml of normal saline was given intravenously over a period of 40 minutes. During infusion, the most common side effects observed were dizziness, blurred vision, nausea, poor coordination, poor concentration, restlessness, and dissociative symptoms (i.e., feeling outside one’s body or perceiving that time is moving more slowly) and transient raise of blood pressure. The psychopathology of the symptoms was assessed on BPRS and severity on CGI-S with score of 47 and 4 respectively, indicating moderate illness. After two hours of infusion, he was reassessed on YBOCS, MADRS, BPRS, and CGI-I scales scoring 28, 11, 23 and 2 respectively, indicating much improvement.

2.2. Case 2

A 33 year old bachelor reported with symptoms of OCD (F 42.2) of over 10 years duration with comorbid bipolar affective disorder, current episode of moderate depression (F 31.3) for the last 3 months, characterized predominantly by obscene thoughts leading to guilt feelings and consequent depression. His depression became intense over the last few months along with suicidal thoughts. In the past, he had history of psychiatric illness with two episodes of mania and one episode of depression that remitted with medications. There was no history of any substance abuse or medical illness and family history of psychiatric disorder. He was, therefore, titrated on fluoxetine 40 mg/day, clomipramine SR 150 mg/day and divalproex sodium 1500 mg/day during the past one month. The unbearable guilt feelings caused by his obsessive blasphemous thoughts of spitting on photos of deities and sexual thoughts about them, forced him to attempt suicide, by slashing his wrist with a knife. He was rushed to the emergency department and timely surgical intervention got him saved. He was still harbouring suicidal thoughts, YBOCS score was 36; MADRS was rated at 21 and CGI – S score for illness was 6. ECT was considered but he refused to give consent. He was counselled for rapid antidepressant action of sub-anaesthetic dose of ketamine i.e., 0.5 mg/kg dissolved in 100 ml of normal saline and given over a period of 40 minutes which he readily consented. During infusion, the most common side effects were nausea, blurring of vision, dizziness, perspiration, ringing in ears, poor coordination, poor concentration, restlessness, and dissociative symptoms (i.e., feeling disconnected from the body, outside one’s body or perceiving that time is moving more slowly, things seems unreal, seeing things as if in tunnel, losing track of what is going on) and transient raise of blood pressure. The psychopathology of the symptoms was assessed on BPRS and severity on CGI-S with score of 47 and 4 respectively, indicating moderate illness. After two hours of infusion, he was reassessed on YBOCS, MADRS, BPRS, and CGI-I scales scoring 28, 11, 23 and 2 respectively, indicating much improvement.

2.3. Case 3

A 35 year old, self employed bachelor farmer, suffering from treatment-resistant depression for the last 7 years, had reported with a recent worsening of his symptoms due to death of his mother with guilt feeling that he could not take care of her ailing mother at the terminal end of her life. He had death wish that life was not worth living and planned to end his life by consuming poison. He described his mood as sad with feeling of despondency, lassitude, hopelessness, worthlessness and suicidal ideas. He was diagnosed on ICD-10 as F 33.2 recurrent depressive disorder, current episode severe depression without psychotic symptoms. He was prescribed drugs which were gradually titrated to maximum therapeutic levels i.e., dosulepin 450 mg /day, pramipexole 1.5 mg/day, modafinil 200 mg/day, clonazepam 1.5 mg/day. His MADRS score was 34 with a high score on the suicidality and CGI- severity score of 5. As he did not like to inform
his family about death wish and not willing for ECT, he was taken up for sub-anaesthetic ketamine infusion i.e., 0.5 mg/kg dissolved in 100 ml of normal saline and given over a period of 40 minutes to induce a quick relief from depression. He reported nausea, dizziness, salivations, perceptual changes and on CADSS items his scores were 3, 4 respectively, indicating effects to be considerable and extreme in the following areas, ‘as if looking at the things from outside body; feels separated from what is happening; as if spectator or observer; feels disconnected from the body; body change, seeing things as if tunnel/wide angle lens; things happening quickly; as if looking through fog; sound changed in intensity and special sense of clarity. He reported raised blood pressure which subsided gradually.

In Case 3, treatment-resistant depression with suicidality showed sudden decrease in depression as assessed on MADRS, CGI-S scores from 34, 7 to 14 and CGI-I score of 2, indicating marked therapeutic effects and side effects do not require any intervention; they were mild and remitted within about 2 hours. Aan het Rot et al., [10] administered a single ketamine (0.5 mg/kg) infusion to 10 patients with treatment-refractory depression; a day later, MADRS scores in nine patients showed >50% attenuation. These nine patients received five more ketamine infusions across the next 10 days. At the end of the ketamine course, there was 85% attenuation in MADRS ratings in the sample.

However, during infusion of ketamine in Case 3, patient manifested symptoms of perceptual changes, dissociative symptoms of depersonalization and derealization, which were due to pharmacodynamic nature of ketamine and resolved spontaneously. There are possibilities of neurotoxic effects, except in high doses causing reversible vacuolation which is not uncommon in animal studies but extrapolation on humans needs sufficient rigorous clinical trials [22,23].

4. Conclusion

Ketamine infusion (0.5 mg/kg) is associated with antidepressant and antisuicidal effects. It has a wide margin of safety. The benefits develop within 1-2 hours of the infusion. Adverse effects are confusion, dizziness, perceptual disturbances which usually last for not more than 2 hours. Infusion of ketamine in sub-anaesthetic doses may, therefore, be a useful antidepressant measure in patients with suicidality.

5. Limitation of Study

Although the above treatment reduces depression and suicidality for patients in extreme need yet, rigorous double blind randomized control trials are needed to generalize these findings.

6. Implication/Salient Features of this Study

This study gives an alternative approach to ECT for immediate intervention of depression with suicidality by subanaesthetic low dose ketamine infusion which is safe and efficacious.
7. Source of Support
Nil.

8. Conflict of Interest
None declared.

References


