Effects of Ketamine on Major Depressive Disorder in a Patient With Posttraumatic Stress Disorder

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Ketamine has been used in anesthesia for many years and in various environments with an acceptable safety margin. The side effects of hallucinations and paranoid thoughts need to be overcome for acceptance of ketamine infusion in mainstream psychiatry. In this case report, the anesthesia department was consulted because of familiarity with the medication and the ability to modulate unacceptable side effects with its use as is done in monitored anesthesia care. It is proposed that ketamine has potential for treatment of major depression associated with posttraumatic stress disorder (PTSD) in combat veterans. This patient, who had debilitating and treatment-resistant major depression and PTSD, was treated by intravenous infusion of ketamine and experienced substantial short-term resolution of symptoms.

Keywords: Combat veterans, depression, ketamine, *N*-methyl-D-aspartate, posttraumatic stress disorder (PTSD).

Ketamine is an anesthetic drug that has recently seen a resurgence of uses outside the operating suite. For years the medication has been used in burn care units and intensive care units for dressing changes and emergency departments for painful procedures. Ketamine was used to treat resistant depression in 2000 by Berman et al,[1] indicating a potential role for *N*-methyl-D-aspartate (NMDA) receptor–modulating drugs in the treatment of depression. Ketamine has been studied for rapid conversion of suicidal to nonsuicidal intentional thought processes in patients presenting to the emergency department[2,3] with success. Intravenously (IV) or intramuscularly administered ketamine has an acceptable window of dosage range and safety margin. Recent uses of ketamine in pain management for complex regional pain syndrome, formerly known as reflex sympathy dystrophy, have proved effective at low doses and without untoward side effects when administered daily over 10-day periods.[4]

In this case, discussion with the anesthesia department and psychiatry division was initiated by the patient's psychiatrist as to whether there are methods to abate or minimize the potential severe side effects of ketamine. In monitored anesthesia care situations, patients have received subtherapeutic doses of ketamine in propofol IV infusions ("drips"), and the effects were synergistic in providing anxiolysis and pain decrement without having the troubling side effects exhibited by adults when ketamine is given as a sole agent.[5] It was also hypothesized that by starting the patient with an injection of midazolam and sedation-level propofol, we could better control the setting, thereby intensifying relaxation and anxiolysis to further mitigate any emergence delirium.

A literature search found that several studies are being conducted to evaluate the effects of this medication in the depressed patient who is unresponsive to current oral medications.[1,3,6] To our knowledge, there are no published studies evaluating ketamine as a treatment for posttraumatic stress disorder (PTSD). Ketamine was used in this single event in a patient with a history of severe depression and combat-related PTSD that was unresponsive to an oral medication regimen. His psychiatric history for this event included combat-related PTSD with 2 sessions of admitting considering suicide, rarely maintaining sleep of greater than 2 hours, and loss of interest in family life. This was disheartening to his wife, who was pregnant at the time with their first child.

Case Summary

The patient was brought to the healthcare clinic in an outpatient status. The diagnoses were PTSD and chronic and major depressive disorder. Except for these diagnoses, the physical examination findings and health history from an anesthesia viewpoint were normal. The patient was a 26-year-old male combat veteran, 172.7 cm (5 ft, 8 in) tall, with a stated weight of 71.1 kg (158 lb, but 70 kg was used for simplicity). Preprocedural patient evaluation included an adequate airway, nothing to eat or drink for greater than 8 hours, no allergies to medications, denial of alcohol or tobacco use, a systems review negative for surgeries or medical treatments, and discontinuation of all medications to include antidepressants for more than 24 hours.

Baseline vital signs were obtained, which included heart rate, blood pressure, and pulse oximetry, and were recorded every 5 minutes. Oxygen by nasal cannula was

administered at a rate of 2 L/min. An IV line was started, and the patient received midazolam, 3 mg (0.04 mg/kg), IV as a preinduction medication. With an anxiolytic effect from the midazolam, evidenced by relaxed posturing and verbal admission of relaxation, the patient was administered propofol, 70 mg (1 mg/kg), combined with an IV bolus of 30 mg of lidocaine (arbitrary dose). When a hypnotic state was achieved, evidenced by loss of eyelid reflex, a 20-minute infusion by IV piggyback was administered of propofol, 30 mg (for an infusion rate of 20 μg/kg/min), and ketamine, 35 mg (0.5 mg/kg, according to the protocol for an ongoing study[7]). The patient maintained spontaneous respirations without need for oral or nasal adjuncts.

Fifteen minutes after the completion of the infusion, the patient was arousable and responding appropriately to verbal stimuli. Vital signs monitoring was continued every 15 minutes for 1 hour after he became responsive to verbal stimuli. At this time the patient was awake and conversant, although he stated that he was having trouble focusing his vision. The patient appeared to be improved in mental conditioning and was smiling and joking with the attendant staff. He was amorous with his wife and began touching his wife's pregnant abdomen. These behaviors represented improvement from the preinfusion state and were out of character for him from his recent mental standpoint.

At 1 hour after responsiveness, the IV line was removed and the patient was allowed to ambulate to the restroom. His gait was steady and he was able to void without difficulty. He returned to the stretcher where the infusion had taken place and continued to be conversant. After an additional 30 minutes of observation, the patient was discharged, with his spouse as an escort. He did complain of a slight headache at the completion of the infusion. No other untoward effects were noted by the patient; nor was there any increase in heart rate or lability of blood pressure.

The patient was followed up by his psychiatrist. The patient's initial self-reports were of complete resolution of anxiety and depression lasting from day 1 to day 14 after infusion. Of particular note was his experience of normalized and restorative sleep, as well as disappearance of all debilitating nightmare events. He participated in his wife's birthing class and so impressed the instructor that she invited him and his wife to assist in future classes. He experienced greater satisfaction and enjoyment in activities and uncharacteristic gregarious and social well-being not experienced previously with treatment. At 14 days after infusion he began to relapse into his preinfusion state of depression.

Discussion

Ketamine has a perhaps exaggerated negative perception among some clinical providers in its potential deleterious effects, including hallucinations, flashbacks, and fear of persecution or paranoia. These potential side effects were of concern to the treatment team, as any hallucinogenic experience could be harmful to a patient already living with PTSD. These possible side effects would have been unacceptable in this situation. The patient had conducted his own Internet searches on ketamine and was concerned about the unfavorable potential effects. Recent admissions of contemplating suicide and inability to stabilize after multiple attempted antidepressant medication trials made the need to minimize the side effects a priority.

Previous studies looking at ketamine in treatment-resistant depression used no other anxiolytics or anesthetics to avoid influencing the study. Minimal levels of ketamine are necessary for effective results, and furthermore ketamine is available as a pharmacy-compounded topical application medication (eg, used to treat postherpetic neuralgia). It is therefore hypothesized that for longer term positive effects a minimal number of IV infusions could be administered; then the patient could potentially switch to topical ketamine application while continuing psychiatric intervention. Results of the Ketamine as a Rapid Treatment for Post-Traumatic Stress Disorder trial[7] may add useful information.

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