KETAMINE DEPENDENCE: CASE REPORT AND REVIEW

Avinash De Sousa, Archana Prabhu, Yusuf Macheswalla

ABSTRACT

Ketamine has been in medical circles since the past three deacdes but has recently emerged as a party drug and drug of abuse. The literature regarding ketamine abuse and dependence is presented and the relevant neurobiology and mechanism of addictive action is discussed. We also present a case of ketamine dependence that was admitted to our centre.

Key words: Ketamine Dependence

INTRODUCTION

Ketamine is a commonly used, safe, effective and well-known anesthetic agent that has been available as a schedule III agent for close to 4 decades[1]. It has been known as a drug of abuse since its discovery and introduction as a medicine and has most recently become associated as a "club drug" used primarily by adolescents, young adults, and gay men at "raves" and circuit parties[2]. It is primarily thought of as a drug of abuse; however, it has also been used to treat addictive disorders by taking advantage of its ability to be used as an adjunct to psychotherapy, where its ability to produce psychedelic and spiritual states of consciousness has been successfully applied to induce sobriety in addicted individuals, mostly in Russia[3]. Recent studies also report the use of ketamine as an adjunct to psychotherapy in the management of major depression[4].

Ketamine was synthesized by the American chemist Calvin Stevens in 1962 at the University of Michigan for use as a novel anesthetic agent after phencyclidine (PCP) was discovered to be too psychotigenic when used as an anesthetic[5]. In 1965, Domino coined the term "dissociative anesthetic"[6] to describe its properties of disconnecting mind from body unlike conventional anesthetics that completely suppressed consciousness. It was patented in 1966 by Parke-Davis and in 1970 the Food and Drug Administration approved its use for anesthesia in children, adults, and the elderly.

Avinash De Sousa, Consultant Psychiatrist, Carmel, 18, St. Francis Avenue, Off SV Road, Santacruz (West), Mumbai – State – Maharashtra, India
E-mail: avinashdes999@yahoo.co.uk

Archana Prabhu, Resident, Department of Psychiatry, Masina Hospital – Mumbai

Yusuf Macheswalla, Senior Consultant Psychiatrist, Prof and Head, Department of Psychiatry, Masina Hospital – Mumbai.

Correspondence:

Dr. Avinash De Sousa

Neurobiology and mechanism of action

It has a well-established biologic safety profile based on more than 7,000 published reports. There is some evidence it may prevent neurotoxicity from strokes, head trauma, and seizures, likely a result of its antagonist properties at the N-methyl-D-aspartate (NMDA) receptor. In addition, there is no evidence of long-term neurotoxicity or prolonged adverse psychological effects when used in controlled environments[7-8].

Illicit use and abuse of ketamine started soon after its introduction in 1970. Soldiers returning from Vietnam who received ketamine as an anesthetic reported vivid hallucinogenic experiences. It became linked with "intellectual hedonism" in the 1970s and 1980s, particularly in the United States, and the first reports of abuse by healthcare workers began to appear[9]. Today, there are two main groups of users, namely those who use in a solitary fashion seeking transcendental, psychedelic experiences and seeking spiritual growth, and those who use ketamine as a '"club drug" as part of the rave and circuit party scene. It is difficult to establish the true prevalence of ketamine use disorders as the users remain a mostly hidden group[10]. These include positron emission tomography studies demonstrating that ketamine leads to increases in dopamine in the ventral tegmental area (VTA) in humans cor-relating with elevated mood[11]; ketamine induces increases in dopamine in the nucleus accumbens in humans[12]; ketamine induces self-administration in animal models[13]; repeated ketamine administration causes behavioral tolerance in animals[14] and humans[15]; and heavy, habitual use of ketamine has been described in humans, including in anesthesiologists[16].

Ketamine mainly acts at the pre-frontal cortex (PFC) and limbic system, with the highest density of NMDA receptors being in the PFC and hippocampus[17]. Alcohol, as one of its several mechanisms of action, also antagonizes the NMDA receptor, and ketamine produces alcohol-like subjec-tive effects in humans[18]. In addition, ketamine has opioidergic effects (mu and sigma opiate agonism)[19] contributing to its analgesic properties and stimulant-like properties by enhanc-ing monoaminergic transmission (dopamine, norepinephrine, serotonin) through inhibition of re-uptake pumps[20]. The above effects have led some to describe ketamine's subjective state as "alcohol-like intoxication, cocaine-like stimulation, opiate-like calming, and cannabis-like imagery[21].

Two effects that likely contribute significantly to the addicted state are changes in midbrain dopamine as well as PFC dopamine and glutamate function. Damage to the dopamine system leads to decreased dopamine receptor density and release in the nucleus accumbens and PFC, diminishing the ability of dopamine to signal novel salient events, leading to under-excitability to biologically relevant stimuli[22]. As addiction progresses, the neurocircuitry of the reward pathway becomes corrupted, re-organized, and dysregulated whereby the behavioral system changes from a dopamine-oriented one in the nucleus accumbens (involved in the acute high and the initiation of learning and conditioned responses) to a glutamate-based system in the PFC (especially the anterior cingulate and orbitofrontal cortex) marked by altered glutamatergic transmission in projections from the PFC to the nucleus accumbens[23]. Specifically, the system becomes hyperexcitable to drug-conditioned cues and under-excitable to biologically oriented ones. As part of these dopaminergic and glutamatergic changes, pharmacotherapy development of anti-addictive agents is currently focusing on agents that can strengthen the saliency of natural reinforcers, such as enhancing dopamine function, and agents that can alter the dysfunctional response to conditioned cues (either drug related or biologically relevant) by altering glutamatergic transmission[24].

Along the lines of hyper-glutamatergic states being associated with addiction, it is key to consider that subanesthetic doses of NMDA antagonists (ie, ketamine) may actually enhance glutamatergic transmission by disinhibiting glutamate release, shunting glutamate to the other glutamatergic receptors other than NMDA (α-amino-3-hydroxy-5-methyl-4-isoxazole pro-pionic acid [AMPA], kainite, and the metabotropic G protein coupled glutamate receptor) and causing a hyperglutamatergic state[25]. There is some evidence to suggest that NMDA receptor blockers may antagonize Y-aminobutyric acid (GABA) neurons with a greater potency than their inhibition at the NMDA receptor. The NMDA antagonism may therefore diminish activation of GABA inhibitory neurons, with a diminution of cortical extracellular GABA levels, which in turn would decrease GABA's normal inhibition of glutamate neurons, causing a net disinhibition of glutamate neurons and an increase in glutamatergic transmission in non-NMDA glutamate receptors[25]. As part of this, extracellular dopamine levels are increased in reward-related areas (i.e. VTA and nucleus accumbens) thereby likely explaining ketamine's addictive liability[26].

Ketamine has also been used widely in chronic pain disorder, complex regional pain syndromes and for cancer related pain[27] in addition to its anaesthetic uses. Not much is known about ketamine withdrawal and its management. Studies have suggested that routine detoxification procedures along with atypical or typical antipsychotics may be used to counter withdrawal symptoms. Haloperidol has been used in certain case reports along with Clonazepam[28].

We present herewith a case of pure ketamine dependence which was admitted to our centre.

CASE HISTORY

A 35 year old married female patient who was a graduate and was working as a president of an NGO was brought by her with husband complaints of sadness of mood and reduced social interaction with others since 4 years. She also showed withdrawn aloof behavior with death wishes which had increased since the past 2 years. She had been using injectable ketamine since the past 2 years.

The patient was alright 4 years back, then after knowing about her husband's extramarital relationship with his colleague, she began experiencing low mood, most of the day. She experienced irritability on minimal provocation with disinterest in enjoyable activities and easy fatigability with tiredness. The sadness and irritability gradually increased, and she had frequent fights with her husband on different issues. She started complaining of low self esteem, excessive worry with rumination of negative thoughts leading to a feeling of being hopeless and helpless. This resulted in crying spells and inability to concentrate in work. She had consulted a psychiatrist and was started on medicines with which she perceived 50% improvement. Details of the medication were not available. She discontinued medicines after 3 months as she felt better. She worsened since the past 3 years and attempted suicide 2 years ago by consuming 50 Clonazepam tablets after a fight with her husband. She was rushed to a hospital and managed in the intensive care where she recovered.

2 years ago she started working in an NGO that used to sterilize stray dogs. The anesthetist working there introduced her to ketamine in view of her sad mood and suggested that she take an injection (2ml) of ketamine daily. She started with 2 to 3 ml of pure form of injectable ketamine which she used to self administer intramuscular in the thigh initially once and she gradually increased the quantity to about 10–20 ml/ day.

The patient denied any suspiciousness, psychotic symptoms or symptoms suggestive of bipolar disorder. Through clinical interview all other psychiatric disorders were ruled out. The patient was an adopted child of her parents hence birth details were not available. She was an average student at school. She has a son who is currently 10 years old. Her premorbid personality was normal. Mental status examination on admission revealed no major abnormality with a grade 3 insight. A diagnosis of Ketamine Dependence and Major Depressive Disorder was made.

The patient was admitted to the female psychiatric ward and was detoxified of ketamine using intravenous fluids, multivitamins and a course of antibiotics. The patient experienced visual hallucinations in the form of moving objects and certain illusions on day 3 and 4 of admission. To counter the same, she was given Risperidone 2mg per day in divided doses. She was started on Sertraline 100mg in divided doses in view of her depression and was also given regular individual cognitive behavior therapy sessions to treat both her major depression and ketamine dependence. Her husband was called in for counseling sessions individually and as a couple to help improve their interpersonal problems. The husband was educated about depression as well as ketamine dependence. She was discharged after a period of 5 weeks and was lost to follow up.

DISCUSSION

To the best of our knowledge there are no reports of ketamine dependence or abuse from India while many reports exists worldwide. Among the signs and symptoms of ketamine dependence, ketamine is known to cause dissociation, a disconnection between the sensory system and the limbic/cortical system, resulting in lack of awareness of pain sensations. Patients describe fantastic dreams while under ketamine's influence. Some report flashback phenomena for several days after surgery. Others experience agitation requiring sedation with benzodiazapines to prevent accidental self-harm. In reality ketamine was not very different from PCP except that it had a much shorter half-life, and therefore the "emergence phenomena" were easily controlled and short lived. In addition tolerance develops quickly to the drug[29-30].

Almost immediately, ketamine has become a popular street drug. Recreational users value it for dreamlike hallucinations, floating sensations, perceptions of increased efficiency and creativity, feelings of arousal and euphoria, and mystical experiences of self-transcendence. Unlike hallucinogen induced hallucinations, these sensations are usually peaceful. Users under ketamine's influence are generally not aggressive. Immediate noxious effects included ataxia, slurred speech, blurred vision, dizziness, confusion, cognitive impairment, hyperexcitability, unpleasant imagery, decreased sociability, anxiety, nausea, and insomnia[31-32]. Long-term adverse effects include flashbacks, attentional dysfunction, memory impairment, tolerance, and high dependency potential[33].

There are not many reports or controlled studies available regarding the treatment of ketamine dependence. Treatment of ketamine-induced toxic effects or overdose includes supportive care and, in instances of severe agitation or anxiety, one or several doses of a benzodiazepine or a high-potency antipsychotic drug[34,35]. Great caution should be used if an antipsychotic substance with high potency is used, because such treatment can lower seizure threshold, aggravate dystonia, precipitate hypotension, and cause neuroleptic malignant syndrome and myoglobinuria. Since high ketamine doses can induce vomiting, aspiration precautions should be taken in stuporous patients. If rhabdomyolysis takes place, it should be treated with liberal hydration; physicians should be aware that polydrug use is common and that concomitant complications due to other drugs are possible (eg, MDMA-induced hyponatraemia). As with MDMA, fluid and electrolyte management in ketamine-induced concomitant rhabdomyolysis and hyponatraemia should proceed after the patient's volume status is determined and the severity of metabolic derangement is considered. Since the duration of ketamine pharmacological effects is less than 1 h, alternative diagnoses should be sought if symptoms of agitation or psychosis (or both) persist for extended periods. A persistent psychosis, perhaps related to the cortical neurotoxic effects described earlier, has been noted by some investigators in some individuals with a history of phencyclidine abuse[36].

FUTURE RECOMMENDATIONS

It is essential that we ask about ketamine dependence in all patients of polysubstance abuse that present to our clinics. In an era of designer drugs, it is prudent that we are aware about drugs like ketamine, their effects and mechanism of action to facilitate better treatment of our patients.

REFERENCES

1. Hirota K, Lambert DG. Ketamine – its mechanism of action and unusual clinical uses. Br J Anaesth 1996;77:441-3.
2. Freese TE, Miotto K, Reback CJ. The effects and consequences of selected club drugs. J Subs Abuse Treatment 2002;23:151-6.
3. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. J Psychoactive Drugs 1997;29:165-83.
4. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351-4.
5. White PF, Way WL, Trevor AJ. Ketamine – its pharmacology and therapeutic uses. Anesthesiology 1982;56: 119-36.

6. Domino EF, Chodoff P, Corrsen G. Pharmacological effects of a new dissociative anesthetic in man. Clin Pharmacol Ther 1965;6:279-91.

7. Perry EB, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, et al. Yale Ketamine Study Group. Psychiatric safety of ketamine in psychopharmacology research. Psychopharmacology 2007;192:253-60.

8. Morgan CJA, Riccelli M, Maitland CH, Curran HV. Long term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug Alcohol Dependence 2004;75:301-8.

9. Jansen KL. A review of the non medical uses of ketamine : use, users and consequences. J Psychoactive Drugs 1993;32:419-33.

10. Lee SJ, Galanter M, Dermatis H, McDowell D. Circuit parties and patterns of drug use in a subset of gay addicts. J Addict Dis 2003;22:47-60.

11. Vollenweider FX, Vontobel P, Oye I, Hell D, Leenders KL. Effects of ketamine on striatal dopamine: a PET study of a model of psychosis in humans. J Psychiatr Res 2000;34:35-43.

12. Hunt MJ, Kessal K, Garcia R. Ketamine induces doapmine dependent depression of evoked hippocampal activity in the nucleus accumbens in freely moving rats. J Neuroscience 2005;25:524-31.

13. Klein M, Calderon S, Hayes B. Abuse liability assessment of neuro-protectants. Ann NY Acad Sci 1999;890:515-25.

14. Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther 1987;242:203-12.

15. Trujillo KA. Are NMDA receptors involved in opiate induced neural and behavioral plasticity. Psychopharmacology 2000;151:121-41.

16. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. Psychosomatics 1999;40:356-9.

17. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005;162:1403-13.

18. Krystal JH, Petrakis IL, Krupitsky EM, Schutz C, Trevisan L, D'souza DC. NMDA receptor antagonism and the ethanol intoxication signal: from alcoholism risk to pharmacotherapy. Ann NY Acad Sci 2003;1003:176-84.

19. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG. Sterioselective interaction of ketamine with recombinant mu, kappa and delta opioid receptors expressed in Chinese hamster ovary cells. Anesthesiology 1999;90:174-82.

20. Abraham HD, Aldridge AM, Gogia P. The psychopharmacology of hallucinogens. Neuropsychopharmacology 1996;14:285-98.

21. Ross S. Ketamine and addiction. Prim Psychiatry 2008;15:61-9.

22. Carpenter WT. The ketamine schizophrenia challenge study debate. Biol Psychiatry 1999;46:1081-91.

23. Reich DL, Silvay G. Ketamine: an update on the first twenty five years of clinical experience. Can J Anaesth 1989;36:186-97.

24. Krupitsky EM, Burakow AM, Romanova TN. Attenuation of ketamine effects by nimodipine in recently detoxified ethanol dependent men: psychopharmacological implications of the interaction of NMDA and L-type calcium channel anatagonists. Neurpsychopharmacology 2001;25:936-47.

25. Krystal JH, Petrakis IL, W ebb E. Dose related ethanol like effects of NMDA anatagonist ketamine in recently detoxified alcoholic men. Arch Gen Psychiatry 1998;55:354-60.

26. Tso MM, Blatchford KL, Callado LF, McLaughlin DP, Stamford JA. Stereoselective effects of ketamine on dopamine, serotonin and noradrenaline release and uptake in rat brain slices. Neurochem Int 2004;44:1-7.

27. Blonk MI, Koder BG, Van dem Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. Eur J Pain 2009;14:466-72.

28. Doston JW, Ackerman DL, West LJ. Ketamine abuse. J Drug Issues 1995;25:751-7.

29. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence of the role of NMDA receptors. J Pharmacol Exp Ther 1992;260:1209-13.

30. Kamaya H, Krishna PR. Ketamine addiction. Anesthesiology 1987;67:861-2.

31. Hurt P, Ritchie EC. A case of ketamine dependence (letter). Am J Psychiatry 1994;151:779.

32. Dalgarno P, Shewan D. Illicit use of ketamine in Scotland. J Psychoactive Drugs 1996;28:191-9.

33. Jansen KR. Ketamine: can chronic use impair memory. Int J Addict 1990;25:133-9.

34. Graeme KA. New drugs of abuse. Emerg Med Clin North Am 2000;18:625-36.

35. Pal HR, Berry N, Kumar R. Ketamine dependence. Anaesth Intensive Care 2002;30:282-4.

36. Curran HV, Morgan C. Cognitive, dissociative and psychotogenic effects of ketamine in recreational drug users on the night of drug use and 3 days later. Addiction 2000;95:575-90.