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Alcohol Triggers Re-emergence of Ketamine-Like Experience in A Ketamine Ex-user

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Ketamine, a derivative of phencyclidine (PCP), was first introduced as an anesthetic and later shown to have dissociative and psychedelic properties and abuse liability.¹ At low dose, ketamine induces distortion of time and space and mild dissociative effects. However, at plasma levels of 150 ng/ml or greater,² ketamine induces more severe dissociative symptoms, termed as the “K-hole” by recreational ketamine users,¹ commonly including a sensation of floating or hovering in a weightless condition, melting into the surroundings, body or sensory distortions, and out-of-body experiences. Pharmacologically, ketamine is an uncompetitive antagonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor. Likewise, ethanol also acts as an NMDA receptor (NMDAR) antagonist. Previous study showed that ketamine produces ethanol-like effects.^{3, 4} In alcohol-dependent patients² and healthy individuals with a family history of alcohol dependence,⁵ their response to ketamine is altered, such that dysphoric effects are blunted while euphoric effects are preserved, presumably increasing the abuse liability ketamine and, by inference, the NMDAR antagonist component of ethanol.² Here, we present a patient with a history of alcohol and ketamine dependence experienced ketamine-like dissociative symptoms after alcohol consumption in the context of ketamine abstinence.

CASE REPORT

Mr. C, a 35-year-old man, worked as a tool-and-die maker for 20 years. He started drinking alcohol regularly at the age of 15 and developed alcohol dependence at the age of 22. At the age of 32, after the break-up with his girlfriend, Mr. C suffered from depressed mood, loss of interests, poor appetite, insomnia, and suicidal ideation. At that point, he began to use ketamine intranasally to replace alcohol drinking for a rapid relief from depressive mood. The dose of ketamine use had increased up to 3 grams per day in 6 months, during which time he soon developed ketamine dependence with a use frequency of 5-6 times per day for almost one year while in the meantime alcohol consumption was remarkably reduced to less than 1 drink per day. He reported that he had had “K-hole experiences” ever since the first

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few doses of ketamine without a concomitant alcohol consumption. The experiences, including floating sensations, being “at one with the universe” (“oceanic boundlessness”), grotesque perceptual distortions related to the shape or size of subjects, melting together with people or things in the environment (“ego dissolution”), and loss of the sense of time, typically appeared within 10 minutes after each time of ketamine use and lasted for 20-40 minutes. Mr. C did not seek medical treatment at that time.

At the age of 34, Mr. C quit ketamine after developing ketamine-related cystitis and maintained abstinent of ketamine use. During this period, he resumed alcohol drinking with an amount increasing up to 15-20 drinks per day. When intoxicated at this level, he reported the re-emergence of “K-hole experiences”, but the symptoms diminished when he drank less. At the age 35, Mr. C decided to admit for the treatment of alcohol dependence. The last drink of alcohol was about 8-9 hours before admission. Physical and neurological examination and laboratory data revealed no remarkable findings except Hb (12.9 g/dL) and MCV (63.8 fL). Urine drug screening did not find evidence of the use of ketamine, ecstasy, morphine, amphetamine or marihuana. We prescribed benzodiazepines and multi-vitamins to treat the alcohol withdrawal symptoms. The withdrawal severity peaked at the third day and ameliorated after one week. We did not observe any signs of disorientation or occurrences of psychosis, seizures or delirium. Mr. C reported he still experienced intermittent episodes of “K-hole” symptoms after admission. But the symptoms declined with time, with no relation with alcohol withdrawal severity, and gradually subsided after two weeks.

DISCUSSION

This case illustrates that high dose alcohol may directly produce “K-hole experiences” or perhaps trigger conditioned ketamine-like experiences in a patient who had been abstinent from ketamine for at least one year and was admitted for alcohol withdrawal treatment. In either case, this case illustrates the potential clinical importance of common discriminative stimulus effects of ketamine and ethanol, both of which share the common property of NMDAR antagonism.

The blockade of NMDAR is among the most potent actions of ethanol in the brain and the effects are dose-related.⁶ Previous evidence showed a ketamine dose that was sufficient to produce dissociative symptoms in alcohol dependent patients was deemed similar to the subjective effects produced by 8 or more standard alcohol drinks.² Thus, the level of alcohol consumed by this patient (15-20 drinks) may have been sufficient to produce prominent dissociation via blockade of NMDAR function in a patient who was otherwise quite tolerant to the effects of ethanol. Chronic administration of both NMDAR antagonists and ethanol leads to an upregulation of NMDAR.² The NMDAR alterations have been associated with not only development of tolerance or sensitization to both substances but also drug-cue association and relapse.⁷ It is possible that by substituting as a ketamine-like cue, high dose ethanol might have evoked other ketamine-like symptoms as a conditioned response.⁸ This might explain the paradox that this patient seemed to have heightened dissociative symptoms in response to ethanol even though his tolerance to other effects of ethanol had reached the

point where he routinely tolerated the behavioral and physiologic effects of 15-20 drinks per day, a large amount of alcohol by any standard.

However, it is difficult to predict the combined impact of ketamine and alcohol intoxication on the patient's response to alcohol. In addition to NMDAR alterations, many neurobiological changes could also lead to unpredictable alterations in ketamine or alcohol response, such as synaptic loss⁹ or reductions in white matter integrity.¹⁰ Thus, it is possible that in our patient these neurobiological changes might paradoxically increase the sensitivity to the dissociative effects of ethanol that may be mediated by NMDAR antagonism or other ethanol actions in the brain.⁸

In summary, we have described the case of a patient that illustrates a distinctive clinical feature of the comorbidity of alcohol and ketamine dependences, the emergence of ketamine-like behavioral effects during alcohol intoxication. We hypothesize that this surprising clinical observation emerges from the common discriminative stimulus effects of these two substances, which appear to be mediated by their common inhibitory effects on NMDA glutamate receptors.

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