Ketamine Associated Psychedelic Effects and Dependence

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ABSTRACT
Ketamine, a dissociative anaesthetic in use since 1970, produces prominent psychoactive effects in humans. Its non-medical use has raised concerns in many countries, including Singapore. This paper narrates the psychedelic and psychotic effects of ketamine in two ketamine dependent patients who have presented to the psychiatric service. These effects were dose-related and comprised multimodal hallucinatory experiences, a sense of slowing, paranoid ideation and enhancement of sexual, musical and sensory enjoyment. In both ketamine users the psychotic symptoms resolved quickly with symptom-targeted treatment. However, breaking the ongoing addiction cycle seemed more difficult. The neuro-pharmacological mechanisms of these phenomena are largely due to its complex multi-receptors actions, notably through the excitatory amino acids through mainly the N-methyl-D-aspartate (NMDA) receptors. The detection of ketamine abuse requires a high index of suspicion and needs to be considered when there is an acute presentation with multimodal hallucinations and psychosis.

Keywords: Ketamine, psychedelic effects, psychosis, dependence, management

INTRODUCTION
Ketamine is a dissociative anaesthetic used primarily for veterinary purposes. It is commonly known as “K”, “Vitamin K”, or “Super K” and its use is identified with psyche exploration due to its potent psychedelic or “mind-revealing” effect(1). These effects include dissociation, multi-modal hallucinatory experience, altered sensory perception, out of body experiences and more frighteningly, near-death experiences(2,3). In addition, ketamine is capable of producing a wide-ranging physiological, neuro-endocrine(4), toxic and psychotic effects(5,6); along with cognitive fragmentation(3,7), memory(9) and behavioural disturbances in humans. It is commonly injected intravenously or intramuscularly but can also be taken orally or snorted(10).

Chemically, ketamine is an ary-cyclohexamine compound, a close relative of the more dangerous street drug phencyclidine (PCP)(10,11). They both act principally on the ion channel associated with the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Compared to PCP, which has been reported to produce violent, erratic behaviour, pain tolerance and ataxic symptoms, ketamine has always been regarded somewhat more favourably by users due to the fact that it is a manufactured drug(12). Furthermore, ketamine is of lower potency(13) and shorter half life(14), with relatively milder and safer effects(15). Its acute effects usually last 15 to 20 minutes, although some people experience weakness or tiredness lasting up to a few hours. It produces tolerance quickly but the tolerance dissipates with discontinuation of drug use. It is generally not reported to cause physical withdrawal symptoms(16).

Synthesised in 1962 in Michigan and first approved for human use in 1970, ketamine became a popular battlefield anaesthetic(2). Since then, the non-medical use of ketamine had begun to be described in the developed countries, initially within selected communities (e.g. Veterinary) for recreation and for self-medication for depression or anxiety(15-17); by “mind explorers” and those seeking alternative spirituality; and gradually becoming popularised in the street drug scene(18). Even though dependence on ketamine was sporadically described much later(19) it was suspected to be not uncommon. In Singapore, ketamine has been available from the underground market and has been a feature on the local drug scene for quite a few years. It is usually used in combination with other street drugs, especially in the “dance culture” of techno-pop and parties. As a drug of dependence with potential for widespread misuse, significant concerns were raised...
by the authorities to control its use, possession and trafficking, such that ketamine became a controlled “Class B” drug under the Misuse of Drugs Act on 9 September 1999. The trafficking of ketamine carries a maximum penalty of twenty years’ imprisonment and ten strokes of the cane(19).

KETAMINE USER 1

Alan Sum (not his real name), a Chinese man in his mid-thirties, ran his own successful business and was referred by his general practitioner for assessment and assistance to rid his problematic ketamine use. At the time of presentation, Alan described being “hooked desperately” onto ketamine for five months, which he had first come to know accidentally from the disco pubs. Within weeks he began snorting up to 4 grams of ketamine per day, sometimes as often as hourly. As a result of constant snorting he developed frequent epistaxis. He was unable to reduce or stop its repeated use despite the fact that he was spending up to 4,000 dollars per month on the drug and having to work even harder to keep his business going. Initially alcohol, benzodiazepines and marijuana were concomitantly used but soon ketamine became his sole preoccupation for at least two months until his presentation.

Alan recounted a background history of multi-substance abuse, including “Ecstasy”, inhalants, benzodiazepines, marijuana, heroin and alcohol. He also reported compulsive sexual activities and used ketamine to enhance his sexual experiences. He was not known to have any other psychiatric or medical illnesses. Similarly there was a family history of multi-substance abuse but not that of any mental illness. He described his use of the drugs as a means to fill the void in his life produced by an absent father figure and a deprived childhood with constant financial constraints. The task of running a chain of business ventures left him stressed. Although driven and industrious, his self-esteem was, nevertheless, low.

The varied psychedelic effects of ketamine he experienced included an immediate slowing effect followed by a sense of happiness, confidence and relaxation. The newly-found clarity of thought allowed him to plan his business expansion. This euphoric effect lasted about half an hour but soon waned with escalating use of ketamine and the placid effect progressively shortened. Auditory hallucinations – of a hostile god condemning him to hell and making other unpleasant commentaries – soon emerged, along with paranoid ideation, usually in relation to intoxication, and lasting sometimes for days. He experienced withdrawal symptoms of chills, autonomic arousal, lacrimation, restlessness, nightmares and psychological cravings whenever he attempted to stop ketamine. These symptoms drove him to seek further drug sources, and sent him desperately around different doctors looking for a cure. He was given Fluoxetine, Naltrexone, Chlorpromazine, and benzodiazepines by various doctors for temporary relief of these symptoms. Unable to stop its use, he came intermittently for follow-up when the psychotic symptoms became intolerable or when he feared getting into trouble with the law. Eventually he elected for an inpatient withdrawal of ketamine. During the brief stay of two days, his psychotic symptoms resolved quickly with Lorazepam 3 mg/day, Propranolol 40 mg/day, Diazepam 10 mg nocte and Naltrexone 50 mg/day. He defaulted follow-up thereafter.

KETAMINE USER 2

Benny Chai (not his real name), a Chinese man in his early thirties and self-employed, presented with a four-month history of a rapidly escalating use of ketamine, coupled with multiple unsuccessful attempts to quit. He was arrested by the police for exhibiting abnormal talk and behaviour in public. Prior to the arrest he had gone to seek voluntary detoxification for ketamine from a general hospital.

Benny shared that he had used ketamine to cope with multiple intercurrent psychosocial stressors which included a long-standing conflict with his family, low self-esteem and unresolved grief over his multiple childhood losses. He had initially used ketamine to enhance his enjoyment of techno-pop music and the taste of food but quickly developed tolerance with an escalating consumption up to 4 grams per day with peer encouragement, and an expenditure up to 3,000 dollars a month on the drug. He also gave a background history of benzodiazepines, codeine-based cough mixture, “Ecstasy”, alcohol, marijuana abuse and problem gambling. He had no history of any past psychiatric illness and no known family history of psychiatric or substance use disorders.

Soon, Benny began to lose his sense of smell due to constant snorting of the drug. Olfactory and auditory hallucinations poorly defined initially but becoming clearer with progressive abuse, began to emerge. The latter took the form of a demon’s voice communicating with him, commanding and controlling him by “making his ear move”. During intoxication, he felt invincible and would experience his soul leaving the body, although sometimes unable to re-enter it. He described feeling himself becoming a cartoon character, “walking like a crab”.
The aftermath of the intoxication was occasionally amnesic, often accompanied by dysphoria and a deep sense of guilt and frustration. Visual, olfactory and tactile hallucinations would appear one or two days following abstinence, and were promptly relieved by ketamine. In between doses, he resorted to alcohol and benzodiazepines to calm himself. After his arrest and while admitted to the hospital, he became increasingly restless and paranoid. He soon absconded from the ward because of a delusional perception that his mother had conspired with the hospital staff to harm him. He then proceeded to a fast food outlet and caused a disturbance there. On re-admission he was incoherent and behaviourally grossly disturbed, such that physical restraint was required due to the safety risk he posed. He insisted that people were trying to catch his soul and experienced intermittent visual and auditory hallucinations which seemingly “lasted for months”. The acute psychotic episode actually lasted six days and resolved with a short course of haloperidol up to 4.5 mg/day. Subsequently, he underwent a residential drug rehabilitation programme but, despite a promising start, defaulted after three months.

DISCUSSION

Both ketamine dependent patients shared similar demographic and background characteristics: a history of multi-substance misuse, the presence of other behavioural addictions, relatively high income to support ongoing drug habits, a permissive subculture of drug use, and a dysfunctional childhood and family background. In this context a strict drug enforcement regulation might have contributed to the delay and reluctance. They both satisfied the DSM-IV dependence criteria for a substance use disorder and presented with a range of psychiatric symptoms typical of an average ketamine user

A rapid development of tolerance suggests that ketamine is of a high addictive potential. Its short half-life of 17 minutes and a fast clearance from the urine within two hours make its detection a near impossibility in the clinical setting if a history of its use is not forthcoming. Correspondingly the psychedelic effects experienced are generally short-lived. Therefore, a high index of suspicion with corroborative history will improve the detection rate during the initial assessment. As physical dependence had not usually been described, it was unusual that Alan experienced withdrawal symptoms. The toxicology of a sample of drug he consumed indeed confirmed only the presence of ketamine, whereas in Benny’s case, the adulterated toxicology sample might have confounded his clinical presentation. Some of the apparent withdrawal symptoms might have been due to the lingering effect of nor-ketamine, a metabolite of ketamine, which could produce mood, attentional and hypervigilance symptoms.

Rob Poole (1996) outlined seven categories of drug-related psychoses and recognised true drug induced psychosis as rare. In the latter case, it might either be an idiosyncratic or a dose-dependent syndrome. The psychotic symptoms experienced by both persons appeared to be related to intoxication, and possibly withdrawal of the drug and dose related.

The psychotomimetic effects of ketamine include dose-dependent exacerbation of both positive and negative schizophrenic symptoms which tend to occur in association with dissociative, cognitive, anaesthetic and other psychedelic effects. The negative symptoms are qualitatively different from those found in schizophrenic illness and less delineated. The neuro-biological mechanisms underlying these psychotic and psychedelic manifestations appear to be complex and needing further elucidation. A possible pathophysiology is the disruption of the association functions and dopaminergic neuro-transmission of the prefrontal cortex, which is a possible site of NMDA-associated psychosis; mediated through a number of excitatory amino acids (EAA) via different receptors. Apart from the principal action through the NMDA receptors in the cortical and hippocampus cortices, ketamine also reduces the mean opening time or the frequency of opening of the voltage-dependent calcium channels with secondary inhibitory effects on the NMDA receptors.

There is as yet no satisfactory pharmacological management of the intoxication and withdrawal effects of ketamine. Although a number of medications were trialled in Alan’s case by different doctors, they were based on weak neuro-pharmacological bases. The action of ketamine on the opiate and serotonergic systems remains inadequately understood. Similarly for Benny, although he settled with haloperidol, the exact mechanisms of action of haloperidol remained unclear. Although haloperidol might offer partial protection for the neurons from NMDA antagonist toxicity and reduce impairments in executive cognitive functions produced by ketamine, it might still fail to block the capacity of ketamine to produce psychosis, due to a functionally delineated modulation of ketamine effects by dopamine-2-receptors at sites outside those of haloperidol action.
CONCLUSION

Ketamine, an emerging drug of abuse, produces wide-ranging psychedelic and psychotic symptoms. These symptoms appear to be mediated through complex neuro-physio-chemical mechanisms of ketamine and its multiple receptor actions. Clinically, given a history of a multi-substance abuse with an acute presentation of multi-modal hallucinations and psychotic experiences, ketamine should be considered a possible cause.

REFERENCES