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Recreational ketamine use and its impact on health

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Abstract

Ketamine, also known as 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, is a dissociative anesthetic that has gained popularity as a recreational substance among young people, especially in nightclubs and at parties. It acts as a noncompetitive NMDA receptor antagonist, inducing a dissociative state that manifests as catalepsy, unconsciousness and amnesia. Recreational use of ketamine and the number of illicit seizures of ketamine have increased in recent years, prompting a review of current evidence on its toxicity. Recreational ketamine use is associated with a number of toxic effects, both acute and chronic. Predominant among the acute effects are psychotic symptoms, hallucinations and aggression, which can lead to serious injuries. Chronic ketamine use leads to intractable urological problems and neuropsychiatric problems, Long-term effects also include gastrointestinal problems such as abdominal pain and liver function abnormalities. This review summarizes current evidences on the acute and chronic ketamine toxicity associated with its recreational use.

Keywords: ketamine; recreational drugs; acute toxicity; chronic toxicity; drug abuse;

Introduction

Ketamine or 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (colloquially called ‘K’, ‘Special K’, ‘Kit-Kat’ and ‘Cat Valium’) is a dissociative anesthetic which was first synthesized in the United States in 1962 by professor Calvin L. Stevens at Parke Davis as an analog and alternative to the hallucinogenic agent phencyclidine [1,9]. The World Health Organisation placed ketamine as an essential medicine [2] therefore it is commonly used as a general anesthetic drug, both in veterinary and medicine. Ketamine acts as an N-methyl-D-aspartic acid (NMDA) receptor uncompetitive antagonist causing dissociative anesthesia by generating an electrophysiological dissociation between the limbic and thalamoneocortical systems [3] what causes cataleptic-like state, unconsciousness, amnesia and analgesia whithout substantial respiratory depression [4] the result of which is recreational, non-medical use among young people, especially in nightclubs, bars and on parties where it is usually ingested intranasally [5]. Studies show that in recent years recreational use of ketamine and illicit ketamine seizures have increased in many countries and appears to be continuing its upward trajectory. [6,7,8].

Pharmacology

Ketamine causes electrophysiological dissociation between the thalamoneocortical and limbic

systems, what results in a trance-like cataleptic state (described by users as a ‘k hole’) exhibiting unconsciousness, amnesia, deep analgesia with intact ocular, laryngeal and pharyngeal reflexes [9]. Ketamine interacts with many receptors. Primarily, it is an antagonist of the glutaminergic N-methyl-Daspartate receptor (NMDA-R), both centrally and in the spinal cord where it binds non-competitively to the NMDA receptor and prevents neuronal Ca2+ influx what disrupts cortical-cortical and cortical-subcortical signalling [22,23]. It has been also reported that ketamine binds with opioid, cholinergic, dopaminergic, serotonergic and adrenergic receptors [4,14,24]. Dissociative anesthesia occurs at ketamine doses 1-2 mg/kg for intravenous injection (bolus) or 4–11 mg/kg administered intramuscular [19]. Ketamine is a chiral molecule with two stereoisomers, where the S-isomer (esketamine) is approximately twice as potent as racemic mixture and three times as R-ketamine [11,20]. It dissolves both in water and in lipids what allows many routes of administration (intravenous, intramuscular, subcutaneous, oral, intranasal, and rectal) [4,12]. After administration ketamine is rapidly distributed cousing anesthesia within 1–2 minutes [21]. Main metabolic path is by N-demethylation by CYP3A4 and CYP2B6 isoenzymes into active metabolite norketamine (about 3 times less potent as ketamine) [13,15] which later is converted by CYP2A6 and CYP2B6 into hydroxynorketamine and dehydronorketamine [14]. Ketamine and its metabolites are all excreted in urine; 2% is excreted in unchanged form, 2% as norketamine, 16% as dehydronorketamine and 80% as conjugates of ketamine metabolites with glucuronic acid [16,17]. Ketamine and its metabolites can be detected in urine for many days after administration (up to 10 days for dehydronorketamine) [18].

Epidemiology

Ketamine non-medical use started in 70s. primarily among those with access to them (veterinarians, anaesthetists etc.) [25]. Shortly after it spread to community-at-large and became mainstream ‘club drug’ at ‘post-rave’ clubbing and youth dance culture [3]. Effects reported by recreational users are: altered senses, auditory and visual hallucinations, enhanced colour vision, out of body experiences, euphoria, escaping reality, enhancing the effect of other drugs, energy, creativity and stress release. According to the Global Drug Survey, the mean global value-formoney rating for ketamine in 2019 was 7.2 (where 1 = poor, 10 = excellent) [27]. The precise prevalence of recreational ketamine use is unknown but studies suggest that main groups of users are those frequenting the night-time economy (dance music scene, ‘gay’ club/party scene), injecting heroin users but also self-exploratory people [26,36]. Ketamine is popular among people preffering electronic music genres (trance, funky house, drum and bass). It is often mixed with another drugs and alcohol, which can lead to serious adverse

pharmacological and toxicological interactions [27,29,30,32]. The most common method of ketamine non-medical administration is by nasal insuffulation [32]. The onset of effects following IV injection is practically instantaneous and for nasal administration 5–10min [4]. A typical intranasal recreational dose of ketamine reported by users was 125mg. Snorted low dose of 10–75 mg may lead to mild euphoria what makes ketamine an alternative to the Ecstasy. People who took medium dose of 60–125mg reported problems with coordination and feeling everything in slow motion. A larger dose of 100–250 mg leads to feeling light, losing track of time, body dysmorphia, being at one with the universe and so colled 'K-hole', in which user undergoes out-of-body experiences [33,34,35].

Ketamine-related acute toxicity

The main acute toxicity associated with recreational use of ketamine is related to its psychedelic and hallucinogenic properties. Administration of ketamine can lead to 'schizophrenialike or psychotomimetic symptoms with large effect sizes' [37]. The content of hallucinations may be unwanted and in some cases is described as very unpleasant [38]. Ketamine-induced aggression can increase the risk of physical harm. By reducing awareness of the immediate environment, reducing perception of pain and in higher doses causing loss of consciousness, ketamine users put themselves at risk of significant injury (jumping from heights, road traffic accidents), drowning and hypothermia [12]. Recreational ketamine users may experience numbness of the limbs, panic attacks, analgesia, pyrexia, nausea and vomiting which can cause asphyxiation. Due to sympathomimetic activity, ketamine causes mild stimulation of the cardiovascular system. However, high doses can cause tachycardia, hypertension and respiratory depression. The most often seen cardiovascular effect is a sinus tachycardia, which resolves of its own but palpitations and chest pains are being also reported [26,39,40,41]. The management of acute ketamine toxicity is largely supportive and involves removing the individual from excessive auditory and visual stimulation until symptoms resolve. In cases of severe symptoms, particularly agitation/aggression, the use of benzodiazepines may be required [40]. There were also a number of suicides where ketamine was the only drug implicated [31].

Urological toxicity

The potential long-term consequences of recreational, non-medical ketamine use have recently been the subject of increased scrutiny. Dysuria, increased frequency of small volume micturition, suprapubic pain and painful haematuria have been reported amongst long-term

ketamine users [42,43]. In an animal study conducted subsequent to the emergence of human pathology, mice that received intraperitoneal ketamine for up to six months exhibited pathological alterations, with mononuclear infiltration occurring throughout the urinary tract in the glomeruli, ureters, and bladders [44]. To date, three retrospective case series have been published, encompassing 93 patients who have experienced chronic urological effects as a result of long-term recreational ketamine use. In all of these cases, patients have reported using ketamine for a period exceeding three months, with ketamine use preceding the onset of lower urinary tract symptoms [42,45,46]. Patients who underwent cystoscopy exhibited cystitis, with abnormal histology being documented in biopsy samples. The histological analysis of bladder biopsies from patients with ketamine-associated cystitis reveals a uniform pattern of urothelial ulceration, characterised by the presence of eosinophilic infiltration within the lamina propria and reactive urothelial atypia in the surrounding tissue. The appearance is comparable to that of carcinoma in situ, with nuclear enlargement, disorganisation, high p53 immunoreactivity and moderate-to-high Ki67 immunoreactivity [47,48]. It is believed that the urinary tract pathology observed among recreational users is directly related to ketamine and/or its metabolites. The bladder is exposed to ketamine and its active metabolites for over a week following a single dose of ketamine which suggests that frequent ketamine users would have a prolonged exposure. The evidence for a dose-dependent relationship is reinforced by evidence from a case report of a palliative care patient whose urinary symptoms paralleled the use, discontinuation, reintroduction, and repeat discontinuation of analgesic ketamine [17,18,49]. There is no evidence to suggest that either the symptoms or the underlying pathology will spontaneously resolve in individuals who have been using ketamine on a persistent basis. In those who resume ketamine use, both the recurrence of symptoms and an exacerbation of the underlying pathology have been documented [49,50].

Neuropsychological effects and neurotoxicity

The use of ketamine has been linked to the emergence of both neuropsychiatric symptoms and direct neurotoxic effects. As previously outlined, the administration of ketamine can result in the onset of a range of acute neuropsychiatric manifestations. Chronic ketamine abuse has been linked to long-term cognitive impairment, mood disorders, psychotic and dissociative symptoms. In a case-control study, frequent ketamine users (defined as those who used the drug

at least four times per week) were compared with infrequent users, abstinent users, poly-drug users, and non-drug users. The results indicated that frequent ketamine use was associated with impairment of working memory, episodic memory, executive function, and psychological well-being. The same studies demonstrated a positive correlation between the frequency of ketamine use and the occurrence of delusional thinking, which persisted even after abstinence [10]. Furthermore, frequent ketamine use is characterised by the emergence of dissociative and depressive symptoms, as well as a subtle visual anomaly. The precise mechanism through which ketamine exerts these effects remains unclear. However, research suggests that antagonism of the NMDA-R and dopaminergic depletion in the prefrontal cortex may play a pivotal role [57,58]. Additionally, ketamine has been demonstrated to possess direct neurotoxic properties. Experimental evidence from animal studies indicates that the induction of apoptotic neurodegeneration in the developing rodent brain can be attributed to the action of NMDA-R antagonists, a category of which ketamine is a member. In monkeys, neuronal death was observed following the administration of ketamine anaesthesia for a duration of nine hours or more. However, no neuronal death was observed following the administration of anaesthesia for a duration of three hours [60]. Recently, evidence for harm in humans following frequent ketamine use has been presented. This evidence includes the observation of bilateral frontal and left temporoparietal white matter degeneration on brain magnetic resonance imaging. This degeneration is positively correlated with self-reported ketamine dosages [61]. There is evidence that ketamine causes a psychological dependency rather than a physical one. The World Health Organisation's International Classification of Diseases (ICD-10) substance dependence definition [62] holds true for frequent, long-term ketamine use. It should be noted that the use of ketamine can be uncontrolled, overprioritised and linked with tolerance. However, it does not cause a physical withdrawal state. It is widely acknowledged that tolerance is a significant contributing factor to the development of dependency, particularly in the context of frequent ketamine use. It is probable that tolerance is the result of ketamine auto-induction of metabolism. The administration of ketamine prior to treatment has been shown to double the hepatic microsomal metabolism in rats. Furthermore, repeated daily administration of ketamine has been demonstrated to enhance both the catalytic activity and protein expression of the rat microsomal cytochrome P-450 system [63,64]. As might be expected, those who regularly use ketamine tend to increase their dosage in order to achieve the same effect. During the initial stages of chronic use, for example, a sixfold increase in dosage has been reported, with frequent users typically taking twice the dose of those who use the drug less frequently [57,65].

Gastrointestinal toxicity

It has been established that regular ketamine use is associated with the occurrence of vague abdominal pains of unknown aetiology. These are colloquially termed 'K Cramps' [12]. In addition, many forums on the internet describe and verify abdominal pain as a common for ketamine non-medical use describing the pain as a sensation intense pressure on the organs, radiating from the upper abdomen and extending to the chest. The pain is often described as a sharp, stabbing [55]. The occurrence of choledochal cysts, benign cystic dilatations of the common bile duct, in conjunction with anomalous liver function tests, has been documented in individuals who have used ketamine in the United Kingdom and Hong Kong [50-52]. Abnormal liver function tests have been linked to the use of ketamine, although the underlying mechanism remains unclear [53,54].

Conlusion and further directions

The recreational, non-medical use of ketamine represents a significant public health concern, with mounting evidence indicating its increased prevalence among specific demographic groups, notably among youth engaged in clubbing activities. In the acute setting, the neuro-behavioural and neuropsychiatric effects of ketamine increase the risk of injury and harm to the individual. Long-term use of ketamine has been linked to psychological dependency and a range of adverse neuropsychiatric and urological effects. These include the potential for the development of schizophrenia-like symptoms, poor psychological well-being, memory difficulties and an increased risk of haemorrhagic cystitis with its associated lower urinary tract symptoms. Further research is required to gain a deeper understanding of the epidemiology of ketamine use and the underlying pathophysiological mechanisms of the chronic neuropsychiatric and urological harms associated with its use.

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