Review

Ketamin Intoxication Review: Pathophysiology And Management

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Abstract

Background: The first reported non-medical use of ketamine appears to date from the 1960s. However, recreational use of this medication as a drug was not common until the 1990s; But in recent years, the recreational use of ketamine has increased in many parts of the world and has created many problems. Visual hallucinations, severe personality duality and the feeling of leaving the body following the use of ketamine are the most attractive aspects of drug abuse. Although many studies have been done on the mechanism and effects of ketamine anesthesia, research on the side effects of ketamine on the body is very limited and intoxication is less marked. Therefore, in the present study, we tried to review ketamine intoxication based on its pathophysiology and management methods. Based on our review, ketamine might be available in various routes of administration as well as intravenous, intramuscular, subcutaneous, sublingual, intranasal, and oral. Symptoms of hallucinations, nightmares, increased bronchial and salivary secretions, and palpitation may happen following the toxicity. Clinical signs of intoxication are increased blood pressure, CSF pressure, and IOP, altered level of consciousness and tachycardia. Treatment strategies mainly include application of benzodiazepines; while lacking clinical evidence in lethal doses.

Keywords: Ketamine, intoxication, Toxicity, recreational use, Drug abuse.
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Introduction

Ketamine is a phencyclidine derivative, a selective and non-competitive antagonist of the N-methyl d-aspartate receptor, which exerts its anesthetic effect by inhibiting the stimulatory neurotransmitter effect of glutamate on these receptors. In addition to N-methyl-di-aspartate receptors, ketamine interacts with other receptors such as opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive calcium channels. Also, ketamine is a cataleptic analgesic that theoretically blocks pain receptors in the spinal cord and causes analgesia without causing respiratory depression [1]. Low doses of ketamine administered before surgery relieve pain during and after surgery. In humans, low doses of ketamine can also be used as a local anesthetic [2]. Low-dose ketamine is also effective in treating Complex regional pain syndrome (CRPS) [2]. Ketamine is also used to relieve acute pain, manage intensive care in cases of long-term epilepsy and seizures [3]. This drug is effective in treating patients with depression and in some cases is even used instead of electroconvulsive therapy [4]. Ketamine is rapidly getting distributed to all tissues in the body, including the brain. Its metabolism is hepatic and its excretory half-life is 2-3 hours. Onset of action is 15-30 seconds after intravenous injection and 3-4 minutes after intramuscular injection. The duration of action of the drug after intravenous injection is about 5-10 minutes and after intramuscular injection is about 12-25 minutes. Recovery time from the drug is rapid, and drug excretion is mainly renal [5]. Ketamine in the presence of severe cardiovascular disease, severe hypertension, recent myocardial infarction, heart attack, concussion, bleeding, or mass inside the skull, or any condition that may lead to increased blood pressure, increased cerebrospinal fluid pressure, increased intraocular pressure, mental disorders such as schizophrenia or thyroiditis should be prescribed with extreme caution [6]. Hallucinations, dreams, increased saliva, increased blood pressure, tachycardia, tonic and clonic muscle movements, and tremors are common side effects of ketamine that may occur at high doses. To prevent these side effects, concomitant use of low doses of benzodiazepines such as diazepam and midazolam is used [7]. Ketamine is only available as Injection ampules, but in various studies, it has been injected intravenously, intramuscularly, subcutaneously, sublingually, intranasally and even in combination with oral fluids such as fruit juice and Alcohol has been used orally to relieve patients' pain [8].

What is Ketamine?

Ketamine is a dissociative anesthetic and recreational substance that is structurally similar to phencyclidine (PCP) [1-3]. Ketamine produces analgesia and forgetfulness in the same way as phencyclidine does, but without the circulatory and respiratory depression that conventional anesthetics do [1]. Ketamine, formerly known as CI-581, is one-tenth the potency of PCP and produces less severe dysphoria and hallucinations [1]. Ketamine was originally produced in 1965, and FDA approval came in 1970 [2-4]. The substance was first discovered to have anesthetic characteristics, similar to its close cousin, phencyclidine, and it was only later that its analgesic capabilities became sought for [3-5]. During the Vietnam War, ketamine was the most commonly utilized battlefield anesthetic (fact file on ketamine). Ketamine is routinely used to deliver pediatric anesthesia in both intramuscular and intravenous versions, especially for high-risk youngsters or patients in low-resource settings. [4] Ketamine is frequently coupled with benzodiazepines in surgical settings, which can help to decrease the negative psychological symptoms that might arise after emergence. [5] Subanesthetic ketamine dosages are widely used off-label for acute and chronic pain management, drowsiness, and the treatment of severe

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depression. [6] Its application for postoperative analgesia has been noted in multuple research throughout this study. Ketamine has also been used to treat depression [7], CRS [8], cancer pain [9], alcoholism [10], heroinism [11], asthma exacerbations [12], wheeze [13], and pain associated with propofol injection [14]. Irritability, nightmares, dissociation, headaches, decreased memory, transitory increases in blood pressure and heart rate, urinary tract symptoms, and hepatotoxicity are only some of the side effects [15].

Ketamin toxicity

Studies have shown that high doses of ketamine can be associated with some side effects such as hallucinations, nightmares, increased bronchial and salivary secretions, and increased intracranial or pulmonary pressure. There is. Following epidural administration, side effects such as blurred vision, increased heart rate, hypertension, and hallucinations have been reported, but there is still no consensus on neurotoxic damage [8-10]. Some of the properties of ketamine include catatonia, forgetfulness, analgesic effects, as well as the development of some psychological states such as lack of recognition of time and place, sensory and perceptual hallucinations, visual hallucinations and experience leaving the body due to abuse of this drug in recent years. The recreational use of ketamine has increased in many parts of the world and has created new problems [11, 12]. Although ketamine is not currently controlled by the International Anti-Narcotics Network in many countries and actual statistics on drug abuse are not available, according to the United Nations, the drug is used throughout East Asia, Australia, North America and Europe are expanding [12]. Although long-term use of ketamine as a recreational drug is increasing in human societies [13], most studies on ketamine have focused on its medicinal properties and effective doses in various cases, except for limited studies on the long-term effect of ketamine on the Urinary system [15-13],

Pathophysiology of Ketamine toxicity:

Ketamine is a structurally similar arylcycloalkylamine to phencyclidine (PCP). Ketamine is a hallucinogen and dissociative anesthetic. It predominantly inhibits the N-methyl-D-aspartate (NMDA) receptor, although it also has opioid receptor action and sympathomimetic characteristics. The latter leads to an increase in central and peripheral monoaminergic transmission and a decrease in central and peripheral cholinergic transmission [16]. The thalamocortical projection system appears to be the principal location of ketamine's central nervous system action, where it induces depression of some cortical and thalamic processes while stimulating sections of the limbic system [17]. Tachycardia and hypertension are typical side effects of ketamine usage because it activates the sympathetic nervous system, masking its direct cardiac depressant effects. Ketamine, on the other hand, can cause hypotension among patients in the critical care unit who are catecholamine-depleted. Naloxone does not prevent ketamine's analgesic effects, despite the fact that it binds to mu and other opioid receptors. [18]

Toxicokinetics:

There is still a lack of data on the toxicokinetics of ketamine in the human population. The safety ratio (defined as the percentage of a typical recreational dose to a fetal or deadly dose) has been used in animal experiments to assess the acute danger associated with ketamine. The lethal dosage (LD50) is defined as the quantity of substance that causes death in 50% of experimental animals examined. Gable et al. calculated the oral ketamine safety ratio for rats to be 25, and projected that the median fatal dosage for a 70 kg person would be 600 mg/kg, or 4.2 g. [19, 20]

Ketamine has been used to offer analgesia in patients with intractable chronic pain and even anesthesia for minor procedures. However, the safety evidence on its toxicity in animals when given neuraxially is conflicting, with some

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writers believing that the neurotoxicity is caused by preservatives. The administration of spinal ketamine was designated as a 6-line adjuvant used in conjunction with other neuraxial analgesics in individuals with refractory cancer or other terminal chronic pain conditions, according to the most recent Polyanalgesic Consensus Conference for intrathecal drug delivery. Several of the main pain and anesthesia journals have placed a prohibition on the publishing of studies with intrathecal analgesics that lack appropriate safety evidence. [21]

History and Physical:

The symptoms of a ketamine overdose are similar to those of a PCP overdose, although the effects of ketamine fade faster. Through the loss of consciousness, physical indications and symptoms are dose-dependent. Patients may be unable to offer a meaningful history, thus physicians should rely on witnesses to provide essential clinical information. Clinicians should also be conversant with ketamine's street names. During ketamine usage and intoxication, the following symptoms may occur:

- General appearance – sedation, impaired consciousness
- Head, Ear, Eyes, Nose, Throat – horizontal, vertical or rotary nystagmus, mydriasis, excessive salivation
- Cardiovascular – hypertension, tachycardia, palpitations, arrhythmias, chest pain
- Abdominal – abdominal pain, abdominal tenderness, nausea, vomiting
- Neurological – altered mental status (disorientation), paranoia, dysphoria, anxiety, confusion, slurred speech, dizziness, ataxia, dysarthria, trismus, muscular rigidity, psychomotor, psychomimetic, or acute dystonic reactions
- Genitourinary – lower urinary tract symptoms
- Trauma – a thorough examination for evidence of trauma is needed as injuries secondary to ketamine intoxication can occur due to the diminished perception of pain.

Symptoms mostly unique to overdose, overly rapid infusion, or combined with other drugs include:

Respiratory – respiratory depression, apnea (uncommon)

Cardiovascular – hypotension, bradycardia, myocardial infarction

Neurological – seizure, stupor, coma

Symptoms mostly unique to iatrogenic, intravenous delivery include:

Respiratory – respiratory depression, laryngospasm

Adverse Effects:

Ketamine is a medication that has been reported to be safe and well-tolerated [22, 23]. Despite the advantages and growing popularity of ketamine as an anesthetic and analgesic, there are some concerning side effects connected with its usage. These side effects are normally quite brief, but they can be extremely unpleasant for individuals. As a result, it is critical to examine these consequences. Long-term usage can cause sensations of inebriation, nausea, psychotomimetic effects, and headaches, which can lead to impairments in cognition, memory, and mood [24].

The most prominent concerns concerning ketamine's use as an analgesic are its mind-altering properties. Katalinic's team looked into these issues and found that the majority of studies involving subanesthetic ketamine dosages exhibited temporary elevations in the following mental symptoms: positive and negative symptoms of schizophrenia, dissociative symptoms, and manic symptoms. Fortunately, these effects emerge only at the moment of administration and normally go away within 60 minutes [25]. When ketamine is delivered alone, the prophylactic use of a sedative drug such as 3.75–7.5 mg oral midazolam has often minimized their occurrence and severity [26].

Feelings of drunkenness, increased confusion, diminished inhibition, and perceptual

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abnormalities are all psychotomimetic consequences of ketamine usage. Furthermore, studies demonstrate that persistent ketamine use can affect various memory processes, including episodic and working memory. These effects, however, have been limited to the duration of administration and are temporary. Furthermore, the consequences of these effects have not been observed to be dosage or route of administration dependent [25]. Low-dose ketamine has not been linked to any serious physical side effects, although studies have found that it can cause lightheadedness, headaches, nausea, diplopia, sleepiness, and dizziness. Unlike psychotomimetic effects, these effects are usually dose-dependent. They are also restricted to the moment of administration and a little period afterward [25].

Almost 200 instances of ketamine-induced uropathy have been documented in the literature, most of which occurred as a result of chronic misuse, but five of which occurred as a result of medical analgesic usage [25]. Case studies show a relationship between ketamine addiction and urological symptoms, urinary tract injury, and renal impairment, with some but not all symptoms recovering after stopping the drug. Symptoms of ketamine-induced cystitis included dysuria, urgency, frequency, incontinence, macroscopic hematuria, and suprapubic discomfort, according to Chu et al. In 97 percent of cases, urine cultures were negative, and cystoscopy revealed epithelial injury in 71 percent [27].

The use of ketamine has been linked to neuronal cell death in the literature. The direct inhibition of NMDA receptors causes this to happen. The effect was shown in rats after several doses of 20 mg/kg [28]. However, following a single bolus at this dosage, no impact was observed [29]. This is particularly problematic in the developing brain, where ketamine can disrupt neuronal proliferation and differentiation [30]. Ketamine has previously been shown to cause long-term cognitive impairments in a monkey model in recent investigations. Paule et al. investigated this impact in rhesus monkeys that were given enough ketamine during their first week of life to sustain anesthesia for a 24-hour procedure. Control monkeys began to outperform ketamine-dosed monkeys in a battery of tests at the age of ten months. The ketamine monkeys still outperformed the controls at three and a half years of age [31].

In a patient with traumatic brain injury, Chang et al. [32] observed a significant and abrupt rise in intracranial pressure (ICP) after ketamine induction. However, it should be emphasized that this patient's ICP was already fairly high before induction. When mechanical ventilation was started, the ICP dropped quickly. Higher opening pressures during lumbar puncture in children have been observed after sedation with ketamine, although this effect, like the psychotomimetic effects, can be mitigated with midazolam [33]. In research to assess the safety and efficacy of ketamine for the treatment of refractory status epilepticus, it was discovered that the medication produced probable adverse effects in 5 of the 60 trial participants. Severe acidosis, a state comparable to propofol-related infusion syndrome, supraventricular tachycardia, and atrial fibrillation were among the complications [34].

The risk of addiction from prolonged or repeated ketamine usage is alarming. Cravings for the drug, physiological tolerance, and probable withdrawal symptoms have all been reported in studies of recreational ketamine users. Physiological tolerance is important since it has been proposed that it is important for those who have had many operations needing ketamine anesthesia [25]. The development of tolerance to ketamine as an analgesic is less certain. Perry et al. [35] observed healthy volunteers for up to 6 months after they were administered subanesthetic ketamine dosages. Outside of the trial, there were no complaints of cravings or misuse,

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suggesting that ketamine in moderate doses is less likely to cause dependence.

Treatment / Management:

Patients with ketamine toxicity usually simply require supportive treatment. Intoxication with ketamine can last anywhere from 15 minutes to several hours, depending on the dose, method of administration (e.g., oral rather than intravenous), metabolic capacity, and innate susceptibility to the drug's effects, which is determined by heredity and numerous other variables. [36] Patients who are asymptomatic at the time of presentation but have recently used ketamine should be monitored for six hours. Patients who have symptom alleviation after intoxication should be monitored for 1 to 2 hours after the final symptom has gone away. Because ketamine can induce cardiac impairment, especially when combined with other medicines, it is important to keep track of the patient's airway, breathing, and circulation. To minimize airway compromise and aspiration, the patient should bend forward or lie on the left side with the head looking downward if he or she vomits. Although there have been cases of aspiration, ketamine has been proven to promote bronchodilation and preserve a protective airway better than other sedatives. [37] Intubation can offer breathing assistance if airway compromise develops. Other symptoms, including hyperthermia, should be watched together with the patient's vital signs, particularly temperature. If the patient develops serious symptoms or problems, he or she should be monitored and brought to the hospital for monitoring.

There are no drugs authorized by the US Food and Drug Administration to treat a ketamine overdose, according to the toxicology data network, however pharmaceuticals can help with agitation and psychosis. Agitation, psychomimetic effects, hypertension, hyperthermia, and seizures can all be treated with benzodiazepines like lorazepam and diazepam. Lorazepam is usually administered in doses of 2 to 4 mg intravenously or intramuscularly, whereas diazepam is usually given in doses of 5 to 10 mg IV. Haloperidol and other butyrophenones have been used to treat psychotic episodes and agitation. [38]

Other drugs can be used to treat different symptoms. Clonidine and other alpha-2 agonists can alleviate or avoid the psychomimetic side effects of ketamine, improve hemodynamic stability by lowering blood pressure, and produce synergism with ketamine's analgesic benefits. [39-41] Clonidine is usually administered in oral form of 2.5-5 mcg/kg, however, patches are an alternative for long-term inpatient infusions, and intravenous clonidine can be used to treat acute symptoms. Excess salivation caused by ketamine usage can be prevented and treated with atropine or glycopyrrolate, while nystagmus and impaired vision can be treated with physostigmine. Dehydration can be improved by hydrating using crystalloids.

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