

Therapeutics & Toxins News

Newsletter for the TDM and Toxicology Division of AACC

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Ketamine, a drug with ever broadening clinical uses and abuses

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Ketamine (C₁₃H₁₆ClNO, 2-(ortho-chlorophenyl)-2-methylaminocyclohexanone) is a drug commonly used in medicine that is structurally and pharmacologically similar to phencyclidine (PCP). Over forty years of extensive use in emergency and operating rooms has established that it provides effective short term surgical anesthesia and sedation. However, due to its psychoactive dissociative side effects ketamine is also a popular recreational drug abused by teens and young adults. Easy access to ketamine has led to illicit use reaching peak levels and there is great concern about its use to facilitate sexual assaults. Ketamine has also recently become a popular research drug for off-label mental illness treatment targeting depression and post-traumatic stress disorder (PTSD).

History: In the 1950s, Parke Davis Laboratories made a concerted effort to identify an intravenously administered anesthetic that had a rapid onset of action with limited cardiovascular and respiratory depression effects. In the early 1960s, they marketed PCP under the trade name Sernyl because of the apparent serenity it gave to non-human primates. However, they quickly found that a substantial minority of human patients receiving PCP developed postoperative psychosis and so the drug was soon discontinued. In their attempt to discover an analog to PCP with significantly less deleterious side effects, ketamine was synthesized in 1962 by Calvin Stevens. In 1963, ketamine was patented in Belgium as a veterinary anesthetic, and after several years of testing on humans it was shown to have a shorter duration of action and produced less hallucinatory effects than PCP. In fact, ketamine is estimated to have 10% of the potency of PCP; the chemical structures of both drugs is shown in Figure 1. Ketamine was approved for public use in 1970 by the Food and Drug Administration (FDA). Soon thereafter the U.S. military began utilizing it for surgical anesthesia on soldiers wounded in the Vietnam War.

In 1971, the first observed recreational abuse was noted on the American West Coast. A decade later drug abusers began heavily experimenting with ketamine diverted from legitimate medical, dental and veterinary sources. The same properties that led to ketamine replacing PCP in the medical field led to its nonmedical popularity with youth at nightclubs and all-night "rave parties". Based upon its clear abuse potential, the Drug Enforcement Agency (DEA) listed ketamine as a Schedule III controlled

substance in 1995. At present, illicit ketamine largely originates from Mexico as well as sources in India and China. While ketamine abuse started in the U.S., it is now observed across the world.

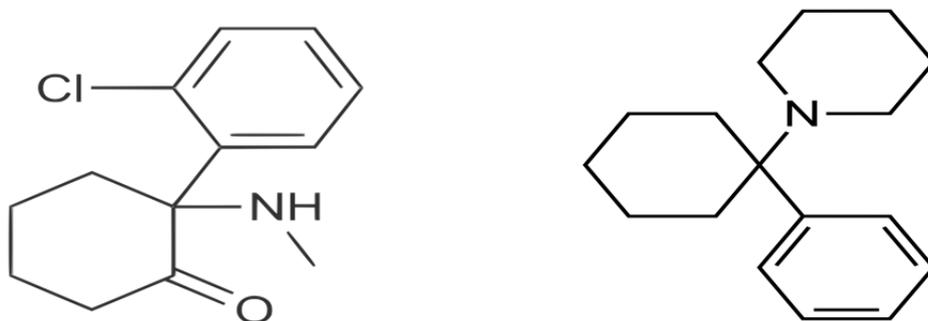


Figure 1. Chemical structures of Ketamine (left) and PCP (right).

General Properties, Administration and Dosage: Ketamine is water soluble with a high lipid solubility that allows it to rapidly enter the central nervous systems (CNS). It has a pKa of 7.5, an apparent volume of distribution of 3 -5 L/kg and is ~30% protein bound (1, 2). It exerts its effects on the NMDA (N-methyl-D-aspartate) receptor where it acts as a noncompetitive antagonist though the mechanism of action is currently not well understood. Ketamine contains a chiral center and is commercially sold as a racemic mixture often as a generic drug.

Globally, ketamine has been widely used as an inexpensive anesthetic agent that is administered in liquid form. It is commercially sold as a hydrochloride salt in a 10-100 mg/mL solution for intravenous injection at doses of 1-4.5 mg/kg or intramuscular injection at doses of 6.5-13 mg/kg doses (1). Common trade names include Ketalar, Ketaject and for veterinary use, Ketavet. Due to it commonly causing emergence delirium in patients (i.e. hallucinations and an altered sensory state), it is now primarily used as a secondary anesthetic. However, it is the preferred surgical anesthetic when ventilators are unavailable, and it is necessary to preserve pharyngeal reflexes and respiratory function. Unlike other anesthetics, ketamine typically stimulates rather than depresses the circulatory system.

Ketamine has often been recreationally abused since the 1980s and it is currently one of the most popular drugs consumed by youth at clubs. According to the 2012 Monitoring the Future study, ~1.5% of high school seniors had used ketamine in the prior year. A recent analysis of U.S. poison center reports from 2000-2015 indicated that ketamine incidents peaked around 2001, decreased until 2008 and then escalated to peak levels in 2015 (3).

Illicit ketamine can be snorted, injected, taken orally, or smoked. Most abusers prefer nasal insufflation or oral ingestion; it is seldom injected. Illicit ketamine is usually sold as a white powder, tablets or capsules that is typically produced by evaporating the aqueous form of the drug. Common street names include special K, vitamin K, cat valium or just "K". It is often adulterated with 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy), heroin, caffeine, and ephedrine. According to the DEA, the average insufflation dose is ~100 mg and up to 300 mg orally. The onset of hallucinogenic effects usually occurs within a few min post-consumption and lasts from 30-60 min. Higher doses can lead to significant CNS toxicity.

Off-label medical uses: It is highly unusual that a drug with such a long clinical history has so many current off-label uses. Many clinical studies have been conducted to test ketamine's effectiveness in treating mental illnesses; specifically, treatment-resistant depression in bipolar and major depressive disorders as well as PTSD. A study published in 2000 concluded that small doses of ketamine could dramatically reverse symptoms of treatment-resistant depression by up to 75% (4). The first U.S. ketamine clinic opened in 2011 and this business has rapidly expanded. At present, there are over 1,000 clinics where ketamine infusions are administered under the supervision of professional clinicians, typically psychiatrists or anesthesiologists. The doses administered are less than that used illicitly, commonly a single 0.5 mg/kg infusion. This often causes a rapid but transient antidepressant response and can be repeated up to 3 times per week for a total of 6 infusions. The mechanism of action remains unclear but is likely in part related to increased dopamine activity with ketamine usage (5). Two meta-analyses have shown strong evidence of the treatments efficacy but there is a lack of consensus on optimal dosing. The pharmaceutical industry may be close to introducing this as a prescribed treatment to the American public; an intranasal formulation is currently in a phase 3 clinical trial. Ketamine infusions are not without controversy as frequent use results in the need to increase the dose to retain similar effects. Beyond tolerance, many clinicians also fear potential cognitive deficits and psychiatric complications. It is worth noting that ketamine is also used in an off-label therapeutic capacity to treat chronic pain and acute asthma.

Pharmacology: The serum half-life of ketamine is estimated to be from 3-4 hr (1). The drug is extensively metabolized in the liver by the cytochrome (CYP) P450 isozyme CYP2B6 and to a lesser extent by CYP3A4 and CYP2C9 (5). Its biotransformation is complex with numerous metabolites; the major pathway involves N-demethylation to norketamine, an active metabolite. This and other metabolites are usually hydroxylated and glucuronidated with most ketamine products being excreted in urine within 24 hr (5).

In small doses ketamine can produce euphoric feelings and numbness that often resembles alcohol intoxication. Common effects include slurred speech, blurred vision, motor discoordination, tachycardia, diaphoresis, hypertension, nystagmus, and hallucinations. These effects are dose dependent and high doses may result in seizures, comas, and very rarely death from respiratory failure. As a dissociative anesthetic ketamine produces effects that have led to its use in drug-facilitated sexual assaults. Unknowing victims have had a ketamine tablet or liquid slipped into their drink at a bar or party which has led to marked CNS depression and confusion as well as anterograde amnesia. In 2000, a fake online biotech company was forced closed by New York City police for selling ketamine and other date rape drugs.

Human Toxicity: Ketamine has a wide therapeutic index, very rarely have overdoses resulted in death. However, it can cause severe adverse events as illustrated in the following three case studies. An 11-month-old developed prolonged apnea after receiving intramuscular ketamine as a surgical anesthetic (6). The infant was intubated, put on positive pressure ventilation and fully recovered after 90 min. In another case, a healthy 8-year-old girl treated intramuscularly with 125 mg ketamine for a first-degree burn soon developed labored breathing, cyanosis, bilateral crepitations and a low PaO₂ (7). She was diagnosed with pulmonary edema and promptly received ventilation treatment that led to her quick recovery. Last, a study of nine daily ketamine users showed that all exhibited severe dysuria and gross hematuria (8). Lab tests and bladder biopsies revealed that each had thickened bladder walls, perivascular stranding, and extreme ulcerative cystitis. It was concluded that the chronic use caused this toxicity to the urinary system as abstinence from ketamine usually reduced the adverse effects.

Blood concentrations of ketamine have been shown to poorly correlate with clinical findings though overdoses generally involve levels above 3 mg/L. There is no specific antidote for a ketamine overdose. In most cases, the patient is managed with supportive care. If possible, patients should be isolated in a quiet dark room with minimal stimuli until they recover. If the patient is aggressive, diazepam or an alternative benzodiazepine may be administered. Patients with significant respiratory depression should receive ventilatory support. Ketamine may exhibit post-mortem redistribution (1).

Laboratory Testing: Few labs currently have the capability to test for the presence of ketamine in biological fluids. The drug and its metabolites can be detected in urine from 1-2 days following use with gas or liquid chromatography coupled with a mass spectrometer. Many large reference labs have this capability such as NMS, Quest, LabCorp, and Mayo with limits of quantitation in the low ng/mL level. Ketamine can also be detected via thin layer chromatography in the Toxi-Lab system with a limit of detection at 1 mcg/mL. At present, there is no FDA-approved commercial high throughput immunoassay to screen samples for its presence. It is worth noting that commercially available PCP immunoassays do not cross-react with ketamine despite the similarity in their structures (2).

Conclusion: Ketamine is a widely used, inexpensive surgical anesthetic that has been globally used for over 40 years. Its clinical utility has prompted it to be on the World Health Organization's List of Essential Medicines. It is also a very popular club drug with young adults due to its short-term hallucinogenic properties and relative safety. In the U.S., ketamine has recently reached peak abuse levels. Recent clinical research has led to ketamine infusions being widely used off-label to treat depression and this may approach may be soon approved by the FDA. More research is warranted on this potentially promising treatment to determine if there are any long-term adverse effects.

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Editor's Corner:

Communication from Dr. Ronald N. Kostoff, member of our Division:

A monograph examining the differences (for randomly selected toxic substances) between

- the Federal legally enforceable occupational Permissible Exposure Limits (PELs) set by OSHA and
- low-level exposures reported in the biomedical literature associated with serious adverse effects

has been published recently [1]. In these selected cases, the PELs are orders of magnitude higher than what the premier biomedical literature would suggest is protective. The monograph also shows these large gaps are not restricted to OSHA PELs.

The monograph is Open Access, and is available at the following link [2]. The findings may be of interest to toxicology researchers and practitioners; health policy professionals and decision-makers; and, anyone interested in reducing their exposure to hazardous substances.

References

[1] Kostoff RN. OSHA Permissible Exposure Limits (PELs) are too Permissive. Georgia Institute of Technology. 2018. PDF. <http://hdl.handle.net/1853/60067>

[2] <http://hdl.handle.net/1853/60067>

Pradip Datta, Editor.

AACC TDM TOX Web Resources:

<https://www.aacc.org/community/divisions/tdm-and-toxicology/>

Upcoming Conferences/Courses

8th Annual Mass Spectrometry and Separation Sciences for Lab Medicine Conference

Oct 4-5, 2018: Philadelphia, PA

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