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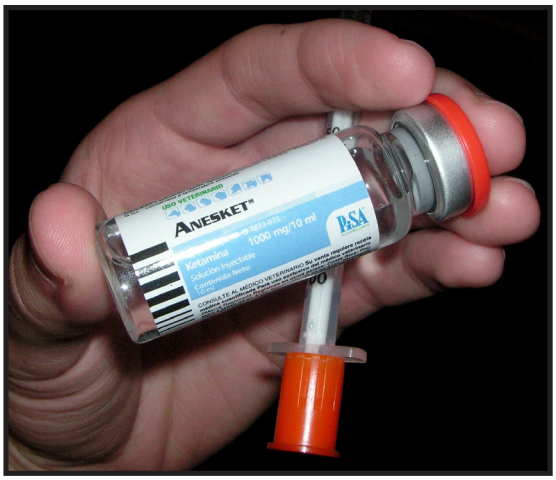
KETAMINE

By Nena Bowman, PharmD, Clinical Toxicology Fellow

INTRODUCTION

Ketamine was first synthesized in 1964 and was used primarily as anesthesia for surgery during the Vietnam War.[1,2] In 1970, ketamine became available for medical civilian use, but it soon was recognized as a drug of abuse.[1] Today, ketamine has Food and Drug Association (FDA) labeled indications for general anesthesia and procedural sedation and is categorized as a Schedule III controlled substance in the United States. Off-label use has been described for agitated delirium, depression, addiction treatment, and chronic pain. This article will briefly describe the mechanism of action, pharmacokinetics, clinical effects, FDA-approved clinical use, off-label clinical use, and abuse and overdose of ketamine.



Vial of Ketamine © User:Psychonaught/ Wikimedia Commons / CC0 1.0

Ketamine is primarily administered intravenously (IV), but is occasionally administered intramuscularly (IM) or intranasally (IN). It is available as a sterile solution for injection in concentrations of 10 mg, 50 mg, and 100 mg per 1 mL.

MECHANISM OF ACTION

Although ketamine's molecular mechanisms are not completely understood, it acts within the central nervous system with anesthetic and analgesic properties. Ketamine directly antagonizes N-methyl-D-aspartate (NMDA) receptors. It also binds to reuptake complexes and inhibits the reuptake of catecholamines, including norepinephrine, epinephrine, and dopamine, leading to sympathomimetic and psychomotor effects.[3] In overdose, ketamine stimulates Sigma receptors, and at high concentrations inhibits both cholinergic receptors (nicotinic and muscarinic) and opioid receptors.[3]

PHARMACOKINETICS

Ketamine has a high lipid solubility, allowing it to easily cross the blood-brain barrier. It is quickly distributed, with peak concentrations occurring within 1 minute when administered IV and 5 minutes when administered IM. It is not well absorbed by the oral or rectal routes.[3] It is primarily metabolized in the liver by CYP2B6, with minor metabolism through CYP3A4 and CYP2C19. Ketamine is metabolized to norketamine, an active metabolite with 33% of ketamine's anesthetic potential.1 The duration of action of ketamine varies by route of administration and averages 15 minutes when administered IV, 40 to 90 minutes when administered IN, and 30 to120 minutes when administered IM.[3]

CLINICAL EFFECTS

At therapeutic doses, ketamine causes an increase in blood pressure, heart rate, and cardiac output. It has no effect on temperature.[1] *(cont. on pg. 2)*

Weight-Loss Supplements

By Sherrie Pace, MS, MCHES

Losing weight safely and effectively involves eating healthy food, reducing calories, and being physically active. But because changing one's lifestyle is not easy, many people often look for a quick fix. Consumers do not have to look far to find "magic diet pill" supplements that claim they can melt away fat without diet or exercise. Research has found little evidence to support these claims since the supplements have not been adequately studied in humans. Although there may be anecdotal stories of successful weight loss, some dieting supplements actually have the potential to cause serious harm. Adding to the confusion are weight-loss products touting labels such as "all natural" or "herbal" which contain ingredients that may interact with medications or are dangerous for at-risk groups such as the very young, the very old, or those with certain medical conditions.

Weight-loss supplements can be sold without Federal Drug Administration (FDA) approval, and manufacturers do not have to prove the supplement is effective to sell the product. The FDA can take action and recall the supplement when a product is suspected to cause harm. Most supplements that are recalled contain hidden ingredients found in prescription drugs or other potentially harmful substances. For example, the FDA recently found weight-loss products that contained the prescription drug ingredient sibutramine. This ingredient was in the prescription drug Meridia that was approved by the FDA in 1997 but removed from the market in 2010 because of links to heart problems and stroke. The FDA has tested suspect supplements and found active ingredients contained in seizure medications, blood pressure drugs, and antidepressants. Some of the side effects reported to the FDA from weight-loss products include heart palpitations, increased blood pressure, tachycardia, stroke, seizure, and in the worst cases, even death.

Unfortunately, there are many tainted products not on the recall list that are sold online and in stores and are readily available to consumers. For a current list of recalled supplements, visit www.fda.gov and search "Tainted Weight Loss Products." The FDA cautions consumers to speak with their health care professionals before using any dietary supplement.

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3. Beware of products promising miracle weight loss. U.S. Food and Drug Administration Web site. http://www.fda.gov/forconsumers/consumerupdates/ucm246742.htm. Last updated February 11, 2015 Accessed July 17, 2015

(cont. from pg. 1)

Ketamine

Analgesia and sedation are the most desired clinical effects for ketamine use. Ketamine is known for its unique dissociative properties. Dissociation is described as an out-of-body experience. Dissociative drugs keep the limbic system from communicating with other parts of the brain.[1] The limbic system is also referred to as the emotional brain; it is responsible for several fundamental functions including autonomic response, behavior, memory, and emotions such as fear.[4] This separation of brain pathways puts patients in a cataleptic state making them less responsive to fear, anxiety, and pain.[1] Ketamine's dissociative properties allow it to be effectively used for conscious sedation in the healthcare setting without the need for concomitant use of opiates or local anesthetic injections for wound repair.[1]

ADVERSE EFFECTS

Adverse effects associated with ketamine include increases in salivary secretions, hypertension, tachycardia, emergence reactions, psychosis, cardiac dysrhythmias, laryngeal spasms, increased intraocular pressure, cognitive impairment with the development of aphasia, diplopia, nystagmus, dizziness, delirium, hallucinations, and respiratory depression.[1,5] Ketamine is associated with emergence reactions that are acute psychotic reactions characterized by violent hallucinations, delirium, and agitation that occur as the drug is wearing off.[3,6]

The most common adverse effects in children during recovery are emesis (8.4%), agitation (6.3%), and respiratory depression (0.8%).[7] Children are less likely to experience emergence reactions than adults. Risk factors for emergence reactions include rapid IV administration, a psychiatric history, patients 10 years and older, patients who have a history of vivid dreams, and women.[3] Children mistakenly given 5, 10, or 100 times the intended dose of ketamine in one case series experienced prolonged sedation, while brief respiratory depression was noted in four of the nine children.[8]

Ketamine is absolutely contraindicated in patients less than 3 months old and in patients with schizophrenia.[7] Relative contraindications for the use of ketamine include major procedures that stimulate the pharynx and increase the risk of laryngospasm including tracheal surgery, stenosis or airway instability, cardiovascular disease including angina or hypertension, CNS abnormalities or hydrocephalus, glaucoma, porphyria, and thyroid disorder.[7]

CLINICAL USE

Ketamine has been used since the 1970s for procedural sedation and anesthesia. The American College of Emergency Physicians published a statement in 2014 supporting the use of and showing strong evidence for ketamine in pediatric patients for procedural sedation.[9] Also noted in this statement is the potential for ketamine use to be acceptable in adults for procedural sedation, though weaker evidence is described.[9] Ketamine has also been used for several off-label indications, including chronic pain, depression, opioid or cocaine addiction, and agitated delirium. Evidence and literature are still lacking for the majority of these off-label indications. The two off-label indications are agitated delirium and depression.

Agitated delirium is an excitatory state with altered mental status and extreme sympathetic response with complications that include agitation, confusion, hyperthermia, rhabdomyolysis, and in severe cases, death from cardiac arrest. There are many causes of agitated delirium, but drug ingestion, *(cont. on pg. 3)*

Healthcare Professionals tell us what you think about the UPCC
Survey Link

(cont. from pg. 2)

Ketamine

substance abuse, and mental illness are the most common causes.[10] These patients require sedative treatment in the prehospital setting. Two cases reported in 2013 describe the successful treatment of agitated delirium in the prehospital setting.[11] One of the patients experienced agitated delirium associated with schizophrenia; the second patient experienced agitated delirium associated with psychiatric and polysubstance abuse problems.[11] Both patients were treated early, and both patients were discharged after treatment without severe complications or long-term effects often associated with agitated delirium.[11]

A recent Minnesota prehospital trial of IM ketamine for agitated delirium has shown that as many as 50% of patients presenting with agitated delirium require emergency endotracheal intubation on arrival in the emergency department.[12] Since the prehospital providers in that EMS agency did not have the ability to do drug-facilitated intubation with a paralytic agent, this practice remains risky and needs greater study before any conclusion can be drawn on where it fits in prehospital use from the preliminary trail.

Ketamine has also demonstrated potential as a fast-acting treatment for difficult-to-treat cases of depression. A randomized, controlled trial conducted in New York randomly assigned 73 patients with treatment-resistant major depression who were experiencing a major depressive episode to receive either a single 40-minute IV infusion of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg).[13] Compared to 28% who received midazolam, approximately 64% of patients who received ketamine had a positive change in depression severity 24 hours after drug administration, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).[13] Ketamine's antidepressant effect persisted over time, as demonstrated by minimal changes in the 7-day post-treatment depression scores of the ketamine-treated patients.[13] The most common adverse events reported in the ketamine group were dizziness, headache, dry mouth, blurred vision, restlessness, nausea or vomiting, and poor coordination and concentration.[13] Dissociative symptoms were reported in 17% of the patients receiving ketamine but had improved by 2 hours post-infusion with no severe psychotic symptoms observed.[13] However, even with low doses, dissociative effects still occur. Risk versus benefit needs to be closely evaluated before patients receive ketamine as an off-label treatment for depression.

KETAMINE ABUSE AND OVERDOSE

In illicit use, ketamine goes by several names including K, special K, super K, super acid, cat valium, and even vitamin K.[3,14] Ketamine is difficult to synthesize due to the requirement of several reagents, so the majority of ketamine abused is diverted from healthcare facilities and veterinary hospitals. The parenteral liquid is dried into powder and then snorted.[3,15] Ketamine bought off the street may be adulterated with heroin, MDMA, or cocaine.[3] Ketamine induces a state of sedation (feeling calm and relaxed), mild hallucinations, distortion or loss of sensory perception, euphoria, and increased energy.[3] Other effects following abuse and misuse of ketamine include immobility, loss of motor coordination, significant changes in time perception, amnesia, and disorientation. Chronic abuse of ketamine can lead to ulcerative cystitis as well as chronic abdominal pain associated with abnormal liver function that resolves when ketamine use is discontinued.

Acute overdose typically is an extension of the side effect profile and includes rhabdomyolysis, hyperthermia, and in large overdose, CNS depression and coma.[3] Chronic abuse has different implications regarding toxicity: fatalities have been reported.[16,17] The National Poison Data System, which collects poison data from all the poison centers in the United States, reported 327 exposures to ketamine and its analogs in 2014, with one case resulting in death (0.3%).[18]

OVERDOSE TREATMENT

There is no antidote for ketamine. Patients are managed through supportive care alone, focusing on acute symptoms.[3] Severe cases of ketamine overdose may require assisted ventilation or supplemental oxygen. Electrocardiogram (ECG), blood pressure, and respiratory function should be closely monitored in an ICU setting. Benzodiazepines may be used to treat agitation, and glycopyrrolate may be useful if excessive salivary secretions occur.[3]

SUMMARY

Ketamine acts within the central nervous system and generates a unique combination of anesthetic, analgesic, and cardiovascular effects. It is used and is FDA-approved for procedural sedation and general anesthesia, with off-label use in agitated delirium, depression, cocaine and opioid addiction, and pain. It has several adverse effects that are not common with use, which can result in dangerous and difficult management situations for health care providers. Overdose can be a dangerous and life-threatening event for a patient. Supportive and symptomatic care is not only the gold standard of care but must be done well to optimally care for these patients. The Utah Poison Control Center welcomes the opportunity to consult on any patient experiencing adverse effects from ketamine use.

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No Sugar, Just Spice: It's Still Not Very Nice

By Nena Bowman, PharmD, Clinical Toxicology Fellow

Spice / Photo Credit : DEA

Causing everything from kidney injury to seizures, synthetic cannabinoids, otherwise known as "Spice," are far from nice. Synthetic cannabinoids are often misunderstood by users to be a legal form of marijuana. While the user may expect an experience comparable to a marijuana high without the risk of legal prosecution, the effects of synthetic cannabinoids are not at all similar to marijuana and have a much higher risk of toxicity. Emergency departments and emergency medical services are now seeing and treating more patients with synthetic cannabinoid toxicity.[1] In one city, 20% of all EMS calls last summer were due to abuse of these synthetic cannabinoids. In a review published by the American Journal of the Medical Sciences, one in nine 12th-grade students reported having used or abused Spice in 2011.[2] According to Winstock and associates in a study published this year, only 0.2% of cannabis users sought emergency medical treatment for adverse effects, while 1% of synthetic cannabinoid users sought emergency medical treatment.[1] The relative risk of needing emergency medical treatment after using synthetic cannabinoids was reported to be 30 times the risk of cannabis users.[1] The active compounds in these synthetic cannabinoid products are continually evolving. They are commonly dissolved in acetone or ethanol and applied by spraying these chemicals onto a plant source.[2] Due to the lack of regulations, as well as the illicit nature of these substances, products do not consistently contain the ingredients advertised. A few of the formulations are described below.

XLR-11 (Black Dragon, Blueberry Spice, Clown Royal, Mr. Happy)[3]

This synthetic cannabinoid derivative acts as a full agonist at the CB^2 receptor with less potent activity at CB^1. There are several case reports where intoxication with this specific synthetic cannabinoid has been identified in blood samples postmortem and has been named as cause of death.[3] A relatively large outbreak of acute kidney injury associated with this synthetic cannabinoid use was reported in 16 patients from 6 different states in 2012.[4] All 16 patients were hospitalized for the treatment of kidney injury, with none of the patients having a past medical history significant for kidney disease.[4] Five of the 16 patients needed hemodialysis, but none of the 16 patients died.[4]

AKB-48 and 5f-PB-22 (Psyclone)[5]

An analysis of Psyclone revealed that it is actually two similarly named synthetic products with very different contents. The first formulation (AKB-48) had two synthetic cannabinoids identified that are applied to herbal matter for smoking. With this product, patients have reported stomach cramps, excessive sedation, paranoia, hypersalivation, chest pain, and seizures.[5] The other product (5f-PB-22) had 20% lidocaine, 50% ethylphenidate, and 30% caffeine, with no identification of any synthetic cannabinoid.[5] Effects from this product include tachycardia, stroke, arrhythmias, numbness, anxiety, and cardiac arrest.[5]

Summary

Synthetic cannabinoids can cause a variety of significant and potentially life -threatening effects. There is no standard formulation for Spice. Because of the increase in use and public misunderstanding, emergency departments and poison centers continue to see an increase in patient exposure to these chemicals. With new synthetic cannabinoids being produced, it is not possible to predict contents of the product or potential effects. Healthcare providers should arm themselves with this knowledge and be aware of the possibility of exposure as well as the need for a thorough patient history. Call the poison center (800-222-1222) for advice whenever a patient's symptoms seem out of proportion to typical marijuana use.

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The Silent Killer

Carbon monoxide (CO) is often referred to as the silent killer. According to the CDC, deaths from unintentional CO poisoning average over 400 per year (MMWR 1-14/63(03);65). CO is an odorless, tasteless, invisible gas. The source of CO is incomplete burning of any flame-fueled, non-electric, device. Examples of these fuels include; natural gas, wood, kerosene, gasoline, propane, charcoal, and oil.

Initial symptoms of CO exposure are much like the flu, although without the fever: headache, fatigue, shortness of breath, nausea, and dizziness. Exposure to higher levels of CO include: mental confusion, vomiting, loss of muscular coordination, loss of consciousness, and potentially death.

The only safe way to know if carbon monoxide is present is to install CO detectors on every level of the home and in sleeping areas. Check CO detectors regularly to be sure they are functioning correctly. One way to remember to check your CO detectors and fire alarms yearly is to inspect them when you reset your clocks for Daylight Savings. Other prevention tips:

- Have heating system inspected and serviced annually
- Operate portable generators and gasoline-powered tools at least 20 feet from the home, doors, and windows
- Install CO detectors in recreational vehicles
- For boating safety, swim and play away from areas where engines vent exhaust
- Never use gas appliances to heat the home
- Never leave a car running in the garage, even if the garage door is open

For additional information on CO poisoning facts and surveillance, visit this website: http://www.cdc.gov/co

TOXINS IN THE NEWS

Flakka: Next-Generation "Molly"

The drug Flakka has made news in Florida and Ohio, where deaths from its use have been reported. Chemically, this substance has been identified as alpha-pyrrolidinopentiophenone (alpha-PVP), one of many novel stimulants synthesized since bath salts became a drug of abuse three years ago. Often referred to as "Molly," these synthetic stimulants come from many chemical classes but share similar pharmacologic properties. All stimulants, including Flakka, increase heart and blood pressure and put users at risk for cardiac arrhythmias and seizures. Flakka can induce acute severe psychosis or excited delirium, making the user behave unpredictably and prone to becoming violent when confronted by police or EMS. Unlike other synthetics, Flakka has gained popularity due to its low price of about $5 a dose. Becasue of its cost as well as its delirium-causing properties, Flakka has been nicknamed "five dollar insanity" on the street. It comes as a granular white powder that is also called "Gravel" due to its appearance. It is often used inside an e-cigarette cartridge to be smoked, or "vaped." Its effects can last up to 4 hours, and associated medical problems, such as severe hyperthermia with body temperatures above 109 degrees, rhabdomyolysis, and acute kidney injury have all been reported. Aggressive intravenous benzodiazepines, rapid cooling, and volume resuscitation are key to treating these medical effects.

MEET THE UPCC STAFF

Brianna Cajacob, BA joined the UPCC staff as a Poison Information Provider in May of 2014. Brianna graduated from the University of San Diego with a Bachelor of Arts degree in environmental studies. She was then commissioned in the US Navy and worked as a Surface Warfare Officer. After several years, she decided to pursue a career in health care and went back to school to earn a PharmD. She is now a third-year graduate student in the University of Utah's College of Pharmacy. In her free time, Brianna enjoys camping, fishing, and trail running with her husband. She also regularly fosters dogs to help the Humane Society. Brianna loves calls that enable her to learn something new.

Nena Bowman, PharmD joined the UPCC staff as a fellow-in-training in July of 2014. Nena graduated from Middle Tennessee State University with her bachelor's degree in biochemistry in 2010 and Lipscomb University College of Pharmacy with a doctorate in pharmacy in 2014. Nena was born in Iowa City, Iowa, but grew up in Lewisburg, Tennessee. The oldest of three, Nena grew up playing soccer with her family, cooking Peruvian food, and singing in the concert choir at her school. Nena lives with Will, her husband of 7 years, in Sandy with their baby, an eight-year-old black lab named Midnight Mischief, or "Little Miss" for short. She enjoys spending time reading, hiking all of the amazing trails Utah has to offer, and baking Southern pies to bring a little bit of the South to the great west. Her clinical interests include naloxone distribution, opioid death prevention, and public education.

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Thank You

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials, and toxicology colleagues that work together to treat and prevent poisonings.

POISON Help
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