X, Liquid E, and Special K - The Abuse of Drugs at Clubs and Raves

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PROLOGUE
Clinical toxicology is a topic instructed at some level in most colleges of pharmacy. Traditionally, instruction involves an array of commonly encountered toxic ingestions that might include: acetaminophen, tricyclic antidepressants, and benzodiazepines. Recently, an emerging group of chemicals known as “club drugs” have become increasingly popular substances of abuse. Commonly cited in the lay press, club drugs have become especially popular across college campuses in the United States(1).

Methylenedioxymethamphetamine (e.g., MDMA, ecstasy) has been reported to be the fastest growing abused drug in the US(1). In 2000, 1.3 million high school seniors consumed MDMA, while approximately 450,000 admitted to being current users(2). The Community Epidemiology Working Group (CEWG) reported the spread of MDMA use to 17 of 21 metropolitan areas assessed, with use expanding to a variety of settings including house parties(3). Of patients aged 14 to 24 enrolled in a recovery program in Seattle, 44 percent had used ecstasy, while 43 percent of those older than 25 years had also done so. Based on trends identified by CEWG, the National Institute on Drug Abuse (NIDA) launched a multimedia campaign to address emerging club drug use trends in 2000.

To assess club drug knowledge, we conducted a survey of baseline club drug knowledge amongst third year professional students at the University of Kentucky College of Pharmacy(1). Seventy-two of seventy-eight students completed the survey for a response rate of 92 percent. When asked to describe a club drug, only six percent of students were able to correctly identify these substances as agents used to enhance social interactions and reduce inhibitions within party and club settings. Only 50 percent of respondents could correctly identify the most common age group and socioeconomic status of club drug users. When questioned specifically about individual agents, 53 percent of respondents correctly identified MDMA, 57 percent of respondents correctly identified two clinical effects of MDMA, 57 percent of respondents correctly identified two clinical effects of gamma hydroxybutyrate (GHB), and 14 percent of respondents correctly identified two clinical effects of ketamine. In general even fewer students could accurately describe management strategies for club drug ingestions. Six percent of students could correctly identify one management strategy for MDMA ingestion, 68 percent for GHB ingestion, and 10 percent for ketamine.

In response to statistics reflecting the increasing abuse of club drugs and considering the low level of knowledge amongst both pharmacy students and pharmacists regarding the clinical effects and management strategies for club drug ingestions, a “Club Drug Module” was designed for instruction to third year professional students. Information provided to students included drug sources, clinical presentation, pharmacology, and therapeutic management strategies. The module also incorporates a presentation regarding preventative efforts provided by a state law enforcement official.

METHYLENEDIOXYMETHAMPHETAMINE (MDMA)
MDMA was initially developed in 1914 as an appetite suppressant(4). The drug product was never marketed but did demonstrate some efficacy in the 1970s as a means to enhance communication in behavioral therapy sessions(5). In the 1980s, MDMA became popular among young adults attending raves and all nightclubs. More commonly known as X or ecstasy, MDMA is classified as a schedule I controlled substance(6). In 2001, the FDA approved a clinical trial examining MDMA’s effects on post-traumatic stress disorder. This will be the first FDA approved clinical trial involving MDMA since the drug was made illegal(7).

MDMA is commonly manufactured in clandestine laboratories throughout Europe and the U.S. A great deal of the product is imported from Amsterdam, which is considered by many to be the “Ecstasy Capital of the World.” Beyond ecstasy, various street names for MDMA exist including: X, ADAM, XTC, and Hug drug(6). Tablets, which typically contain from 50-150 mg. of active drug, are usually imprinted with a popular icon such as the Nike® swoosh or Motorola® symbol. Users sometime refer to MDMA by these imprints (e.g., “a smurf pill”). MDMA is typically purchased in the setting where it will be abused, most commonly raves. Raves are party venues characterized by the presence of loud music, marathon dancing, and laser light shows. Raves are often held in abandoned ware houses or factory buildings. Prices of MDMA range from $20-40 per tablet and it is not uncommon for tablets to be adulterated with other chemicals, including aspirin, dextromethorphan, pseudoephedrine, and other drugs of abuse such as lysergic acid, heroin, and phencyclidine(8).

MDMA is structurally similar to the stimulant methamphetamine and to the hallucinogen mescaline, lending to its effects as both a stimulant and hallucinogen(8). MDMA will affect neurotransmitters, including serotonin, dopamine, and norepinephrine(9). Release of these neurotransmitters by

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presynaptic neurons is often increased and their metabolism by monoamine oxidases inhibited, resulting in excessive synaptic concentrations(9).

The clinical effects of MDMA typically begin within 30 to 60 minutes of ingestion, with a duration of action lasting approximately six to eight hours(10). The term “ecstasy” comes from many of the desired effects produced by the drug, which include euphoria, feelings of closeness, altered visual and sensory perception, increased libido, and increased energy(11). Diminished hunger and thirst are also common effects. MDMA abuse is usually accompanied by characteristic paraphernalia, including pacifiers or candy suckers, which are used to avoid bruxism, a common finding associated with the drug. Glowsticks and brightly colored necklaces and bracelets may be displayed to heighten visual hallucinations. Vicks® Vaporub is also commonly used to enhance the effects of MDMA(A12). Vicks® may be directly inhaled, rubbed above the upper lip, or applied to the inside of a surgical or painter’s mask. The distinctive odor and sensations produced by the Vicks® product are often amplified and exaggerated by MDMA abuse. Because MDMA alone or in combination with physical activity can quickly result in elevated body temperature, consumption of large quantities of water or other fluids is a common practice among abusers. Abusers must be cautious as excessive consumption of water may result in hyponatremia. MDMA may also promote excessive dancing among abusers, a phenomenon commonly known as marathon dancing. Marathon dancing may contribute to dehydration and hyperthermia(13). In an effort to combat dehydration, many raves supply beverages which are known as “power drinks” or “smart drinks” that are fortified with amino acids and vitamins. Serious adverse effects have been reported following the ingestion of as little as one MDMA tablet(14). Tachycardia and hypertension are the result of sympathomimetic stimulation and the psychedelic effects of the drug result from serotoninergic stimulation(15). More severe complications of ingestion including seizures, cerebral edema, and serotonin syndrome have been reported(16). Confusion, depression, insomnia, anxiety, and paranoia have been reported to occur up to weeks following ingestion. Chronic abuse of MDMA has been correlated with cognitive impairment in both humans and animals. Cognitive impairment is believed to be related to changes in the structural components of serotoninergic neurons(17). Positron emission tomography (PET) brain scans of MDMA users have revealed significant reductions in the number of serotonin transporters, of which magnitude of loss was associated with greater use of MDMA(A17).

Diagnosis is primarily based upon history and presentation. The most common findings on presentation include: agitation, anxiety, tachycardia, and hypertension(15). Clinicians should be particularly suspect of patients presenting with MDMA-associated paraphernalia (e.g., brightly colored bracelets/jewelry, pacifiers, bottled water) as discussed previously.

While no antidote exists for MDMA ingestion, management involves monitoring for serious adverse effects including arrhythmias, hyperthermia, and rhabdomyolysis. Gastric decontamination with activated charcoal may be helpful within 60 minutes of ingestion; unfortunately few patients will present within this time frame. Supportive care should be provided. Agitation and anxiety can be controlled with benzodiazepines, and hypertension with labetalol, phentolamine, or nitroprusside. Pure beta-adrenergic blocking agents may worsen hypertension by causing unopposed alpha-stimulation and should be avoided(8). Hyperthermia can be managed with rapid external cooling using tepid water. Neuromuscular blockade to induce paralysis is the most effective method for core body temperature reduction, but requires intubation. Treatment of serotonin syndrome with dantrolene and/or cyproheptadine may be effective, but aggressive supportive care with rapid cooling remains the mainstay of therapy(16). Rhabdomyolysis is managed by alkalinizing the urine with the administration of intravenous sodium bicarbonate. In severe cases of renal failure, hemodialysis may be required.

Detection of MDMA remains a conundrum for clinicians. MDMA may be detected in samples by immunologic assay for related chemicals such as amphetamine and methamphetamine(18). In order to detect the presence of MDMA alone, larger concentrations of the drug must be present in the serum and testing procedures for MDMA alone are only 50 percent as sensitive as those for amphetamine/methamphetamine(10). Traditional toxicology screens that employ thin-layer chromatography can detect MDMA metabolites in the urine. Gas chromatography/mass spectrometry may be used to confirm positive immunoassay tests.

GAMMA-HYDROXYBUTYRATE (GHB)

GHB is a naturally occurring fatty acid derivative of the central nervous system (CNS) neurotransmitter gamma-aminobutyric acid (GABA)(20). In the U.S., GHB was originally introduced as an anesthetic agent, but a lack of analgesic effects coupled with reports of seizure-like activity destined the drug for failure(20). Since that time, placebo-controlled trials have examined the role of the GHB analogue oxybate sodium (Xyrem®) for the management of narcolepsy-associated cataplexy(21). The drug remains an investigational product but does appear to have a promising role in this arena. Street and slang names for GHB include: Liquid Ecstasy, “G,” Georgia Home Boy, Gib, Liquid X, salty water, and soap(22).

Originally introduced as a dietary supplement in 1990, GHB was touted by many trainers and bodybuilders as a means to increase muscle mass, metabolize fat, and stimulate libido(23). As the agent’s popularity increased, users became familiar with its ability to produce a euphoric state. In late 1990, the FDA banned all over-the-counter sales of GHB(24). Unfortunately, by this time GHB had already entered the “club drug” scene and many had become aware of its potential use as a “date rape drug.” In early 2000, GHB was designated a schedule II substance in the U.S. Despite stringent controls in the U.S., GHB is often imported from European sources or manufactured in clandestine laboratories. Many internet sites advertise “recipes” for the home production of GHB and GHB manufacturing kits. GHB is most commonly available as an oral solution (i.e., “Liquid X,” “Liquid E”). In settings of abuse, the chemical is commonly available in small vials or mixed with bottled water. A common dose of GHB is one capful of the liquid, which typically sells for S5-10.

Since the re-classification of GHB to schedule I, chemical precursors of GHB have become popular sources of the drug. Gamma-butyro lactone (GBL) and 1,4-butanediol (1,4-BD) are both chemical precursors of GHB that produce similar effects. GBL is widely used in the chemical industry and is available from many chemical supply companies as well as health stores(25). Following ingestion, GBL is rapidly converted to GHB by endogenous lactonase enzymes(8). When compared to GHB, GBL is more rapidly absorbed and produces a longer
duration of action(26). In 1999, the FDA issued a warning alerting the public of the dangers of GBL and asked manufacturers for a voluntary recall of the product. 1,4-BD is also available in health stores and the FDA has warned of its abuse potential. Following ingestion, 3,4-BD is metabolized by alcohol dehydrogenase to gamma-hydroxybutyraldehyde, which is in turn metabolized to GHB by aldehyde dehydrogenase(8). Because ethanol preferentially binds alcohol dehydrogenase, prolonged toxicity may occur when 1,4-BD is ingested concurrently with ethanol.

GHB is thought to mediate various processes including sleep cycles, temperature, cerebral glucose metabolism, and memory(27). GHB, a metabolite of GABA, is normally found within the CNS in concentrations that are 1/1000th that of GABA(28). GHB is also believed to influence endogenous dopamine levels, possibly increasing concentrations through interactions with GABA receptors(29). GHB is commonly abused by bodybuilders who believe in the agent’s purported ability to increase muscle mass. The agent is thought to prolong slow wave sleep, which is the period when the greatest concentration of growth hormone is released(30). While GHB has been associated with some short-term increases in growth hormone, these findings have never been demonstrated in large, well-controlled clinical trials. GHB’s lipophilic properties lend to its ability to rapidly cross the blood brain barrier(31). The drug is primarily metabolized by the lungs and expired as carbon dioxide(32). Additionally 2-5 percent of the drug is eliminated renally. Peak plasma concentrations occur within 20 to 60 minutes of ingestion, and the half-life of the agent is 20 minutes.

Clinical effects following GHB ingestion usually develop within 15-30 minutes(22). These effects are amplified with coingestions of alcohol or other CNS depressants(8). Dose-related CNS depression is the most common manifestation of ingestion(28,31). With increasing doses, CNS depression progresses from amnesia and hypotonia to drowsiness, dizziness, and euphoria. GHB is often ingested to counter-act the stimulant properties associated with other “club drugs” such as MDMA. Tonic-clonic seizures have been reported in a number of cases and EEG changes have been seen in animal models. Garrison et al. reported a case series of 78 patients who had ingested GHB, nine percent of whom developed some form of seizure-like activity(33). However, in another case series involving 88 patients with GHB ingestion, Chin et al. found no of seizure-like activity(33). However, in another case series involving 88 patients with GHB ingestion, Chin et al. found no patients had reported any seizure activity(34). These reports are difficult to interpret because random muscular contractions caused by GHB are often misinterpreted as seizures.

Respiratory depression is also a common manifestation of GHB ingestion. Most patients will maintain airway patency although some may require intubation with mechanical ventilation(34). Cardiovascular effects include bradycardia and hypotension. Bradycardia has been reported in as many as 36 percent of users and is correlated with level of consciousness. Gastrointestinal effects include vomiting and hypersalivation(35). Vomiting is more common when GHB is co-ingested with ethanol. Hypothermia (e.g., a core body temperature of less than 35.0°C) has been reported commonly in as many as 31 percent of patients (34).

GHB has been associated with cases of facilitated sexual assault(22). The drug is easily administered because of its liquid dosage form. GHB’s powerful intoxicating properties will cause victims to lose consciousness as well as the ability to resist or recall a sexual assault(36). These effects make assault cases involving GHB difficult to prosecute as attackers may claim that the incident was consensual.

No antidote exists for GHB ingestion(36). Generally, most ingestions are self-limiting and managed with supportive care. Most patients recover within seven hours of ingestion without the need for intubation(34,36). Certain patients with severe ingestions will require intubation. Since GHB is a sedative amnestic, rapid sequence intubation may be accomplished with paralytics alone(28). Aggressive suction will be needed as patients may be hypersecretive. While most cases of GHB ingestion may be self-limiting, clinicians should be cognizant of cases involving 1,4-BD and ethanol co-ingestion, as these patients may be present with prolonged or recalcitrant toxicity requiring more conservative management.

GHB is not detected by routine urine or serum toxicology screening(37). Diagnosis is most often made based upon history and presentation(22,28). Gas chromatography/mass spectroscopy are the most precise methods for the detection of GHB; however, it should be noted that these testing methods will not differentiate GHB from its precursors, GBL and 1,4-BD. Serum levels greater than 50 mg/ml are associated with a loss of consciousness, and levels greater than 260 mg/ml with unresponsive coma(38). Clinicians should be aware that GHB is rapidly metabolized and therefore any delay in testing will lower the likelihood of detection. Generally, delays beyond 12 hours post-ingestion will lead to undetectable results(22).

KETAMINE

Ketamine, a derivative of phencyclidine hydrochloride (PCP), was introduced in the 1960s as a dissociative anesthetic(39). The advent of safer, more effective anesthetic products has greatly diminished the clinical use of ketamine. Ketamine may still be used in some pediatric critical care settings and is commonly used by veterinarians for animal sedation. Street and slang names for ketamine include: Special K, “K”, Kit-Kat, Super Acid, Super K, and Jet(40).

Prescription ketamine is available as an injection formulation (Ketalar®) and is classified as a controlled substance in most states. Federally, the substance is classified as a schedule III drug product. Ketamine is difficult to manufacture and therefore the most common mode of acquisition is through diversion of the prescription product. Theft of ketamine from veterinary clinics and animal hospitals is very common. Ketamine is believed to have entered the club drug scene in the 1980s. Originally, the drug is thought to have been a common adulterant in ecstasy tablets(41). As abusers became familiar with ketamine’s effects, its use as a sole agent emerged.

Street cost of ketamine is estimated to be approximately $80.00/gram. Abusers may inject, ingest, or snort the product. However, ingestion is a less common form of abuse since the product undergoes extensive first pass metabolism(40). Because the drug may be easily administered to unsuspecting victims, increasing numbers of facilitated sexual assault cases involving ketamine have been reported(42).

Ketamine’s structural resemblance to PCP lends to its ability to interact with the N-methyl-D-aspartate (NMDA) channel, inhibiting it noncompetitively and also preventing...


4Food and Drug Administration, FDA warns about products containing gamma butyrolactone or GBL and asks companies to issue recall (January 21, 1999).
glutamate activation(43). Ketamine also indirectly interacts with a number of cellular receptors including the muscarinic, nicotinic, cholinergic, and opioid receptors. Inhibition of neuronal re-uptake of norepinephrine, dopamine, and serotonin has also been demonstrated(39).

In social settings, ketamine is most commonly snorted and its effects are abrupt in onset, while lasting only 30-45 minutes(41). Lower doses of the drug result in analgesic effects, while increasing doses will produce amnestic effects(22). Patients often describe a dissociative feeling of “floating over one’s body”(44). These out-of-body experiences are often referred to by abusers as “trips to K-land or K-holes”(44). Visual hallucinations and a lack of coordination are also common and not surprising given the drug’s similarities to PCP(22,44). Cardiovascular toxicity has been reported in the form of reflex sympathetic activation, hypertension, tachycardia, and arrhythmias(39). Because ketamine is an amnestic agent, respiratory depression and apnea are also commonly encountered manifestations of ingestion. Interestingly, many abusers of ketamine report that the drug’s effects are dependent upon the setting within which it is abused. Noisy or rowdy settings may be correlated with negative effects and therefore certain abusers prefer not to use the drug in rave or club settings(45).

The tasteless, odorless, and colorless characteristics of ketamine have made it an increasingly common “date rape” drug(22). The chemical can be easily and surreptitiously added to most beverages. Loss of consciousness accompanied by anterograde amnesia and vivid hallucinations are common. Thus the victim is rendered uncombative and potentially unreliable as a witness.

Similarly to PCP ingestion, supportive care remains the cornerstone of management for ketamine ingestion(22). Attention should be paid to respiratory and cardiac function. The vivid hallucinations associated with ketamine may be minimized by placing the patient in a tranquil environment void of external stimuli. Clinicians should be aware that co-ingestion of ethanol or other club drugs will only compound toxic effects. Death from ketamine ingestion is rare(46). Serum levels of both ketamine and its active metabolite norketamine can be obtained but are generally not available to most clinicians(47). Of note, many PCP immunoassays will cross react with ketamine(48).

CONCLUSION

The abuse of drug and prescription products is an evolving area. Preferred agents of abuse differ from region to region and time period to time period. Recently, club drugs have emerged as popular agents of abuse particularly amongst young, middle to upper-class, Caucasian-Americans. Many pharmacy school curricula provide little to no instruction in this area and graduates may be ill-prepared to provide consultation and information to other healthcare providers and patients. Concentrated efforts must be made to include these topics within professional curricula. In order to reach practicing clinicians, continuing education modules and seminars on this topic should be made available.

References

(42) Fox, M., “Date rape drugs widely abused; Congress told [news wire release]. Reuters: March 11, 1999.