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PHARMACOLOGIC ADVANCES IN
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NEW DRUGS OF ABUSE

Kimberlie A. Graeme, MD

Emergency physicians frequently are called on to evaluate and manage acute intoxications and overdoses. A new group of drugs of abuse includes 3,4-methylenedioxymethamphetamine (MDMA, or *ecstasy*), gamma-hydroxybutyrate (GHB), GHB prodrugs, and ketamine. These agents are promoted on the internet and at dances known as *raves*. Their use has become increasingly popular, and emergency physicians should be prepared to recognize and manage their effects.

3,4-METHYLENEDIOXYMETHAMPHETAMINE

History

MDMA was first synthesized in Germany and patented as an appetite suppressant in 1914; however, it was never produced commercially.[11, 38, 40, 43, 45] MDMA gained popularity as an adjunct to psychotherapy and as a drug of abuse in the 1970s.[5, 11, 34, 40, 43] By the 1980s, MDMA had become a popular street drug.[5, 26] On the streets, MDMA became known as *ecstasy, XTC, Adam, E, hug drug,* and *M&M*.[5, 26] In 1985, the US Drug Enforcement Administration (DEA) declared MDMA a Schedule I controlled substance on an emergent basis, resulting in a transient decline in usage.[5, 40]

Through the 1990s, MDMA abuse escalated.[11, 16, 34, 45] MDMA became widely used in British raves, and this trend has spread to the United States.[11, 26, 43] Raves are all-night events, held at clandestine locations, where hundreds to thousands of young people dance vigorously to synthesized rock music, known as *techno* or *house music,* accompanied by laser light displays.[18, 34, 43, 45] There is objective evidence that MDMA abuse is increasing exponentially; by June 1999, US Customs officials had seized more than 950,000 MDMA tablets. This was more than

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twice the previous annual record of 381,000 tablets in 1997.[16] Recent national and state surveys reveal significant increases in MDMA use.[43] MDMA use was reported by 24% of undergraduates surveyed at Tulane University in 1990; this exceeded cocaine usage.[43] Several studies performed in the late 1990s indicate that 5% to 9% of high school senior students have used MDMA.[43]

Source

MDMA synthesis is relatively simple, and local synthesis provides a continuous source of drug. How-to books on the synthesis of methamphetamines are readily available by mail order on the Internet. On the streets, purity of MDMA varies. MDMA may be mixed or cut with other substances, such as lysergic acid diethylamide (LSD), amphetamine, ephedrine, or ketamine.[18, 43]

MDMA tablets generally contain 50 mg to 150 mg of drug and cost approximately $20 at raves; however, the price can be as high as $45 per pill.[10, 16, 43] Users can "stack" (take several tablets at one time) MDMA and then partake in marathon dancing, in a hot environment, contributing to dehydration and hyperthermia.[34, 43] Some raves provide "smart drinks" or "power drinks," which contain vitamins and powdered amino acids, as a means of hydration.[43, 45] "Chill out" rooms also are present at some raves.[18]

Pharmacokinetics

MDMA is metabolized by N-demethylation to 3,4-methylenedioxyamphetamine (MDA), an active metabolite.[18, 43] In fact, MDA, commonly known as *love drug*, also is used illicitly as a drug of abuse.[26, 38] Humans metabolize MDMA by side-chain deamination.[42] MDMA has a short duration of action. Users experience a high that lasts approximately 5 hours.[38, 40] Approximately 65% of MDMA is excreted in the urine.[43]

Mechanisms of Action

MDMA increases the release of serotonin, dopamine, and norepinephrine from presynaptic neurons. MDMA also inhibits the reuptake of these neurotransmitters into presynaptic neurons and prevents the destruction of these neurotransmitters by inhibiting monoamine oxidase.[3, 38, 49] Further, MDMA can increase dopamine synthesis.[49] This results in excessive amounts of serotonin, dopamine, and norepinephrine being available at synapses in various areas of the brain and accounts for the clinical presentation. MDMA possesses some properties of amphetamines, acting as a central stimulant by increasing catecholamines that act at α- and β-adrenergic receptors and also possesses some psychedelic properties that are likely mediated by dopamine and serotonin.[5, 40]

Hallucinogenic amphetamines are thought to induce hallucinations by activation of serotonergic receptors. Although MDMA has very little hallucinogenic activity, some of MDMA's effects, such as hyperthermia and locomotor hyperactivity, are probably mediated by serotonin.[18, 38, 43, 45, 49] Studies with mice reveal that the behavioral and toxic effects of amphetamines are markedly increased when mice are grouped or aggregated rather than being housed alone.[18] This aggregation phenomenon could contribute to the hyperthermia of MDMA seen in users at raves; however, hyperthermia has been reported without crowding.[8]

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Clinical Presentation

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MDMA is addictive, it appears to increase the amount of extracellular dopamine in the nucleus accumbens, which is thought to be important for the reward properties of drugs of abuse.[49] This increased extracellular dopamine is associated with elevated serotonin levels as well.[49]

Recent concern has arisen from the possible long-term neurotoxicity of MDMA. Long-term neurotoxicity has been demonstrated in nonhuman primates, but the effects in humans remain to be elucidated. The administration of large doses of MDMA given to monkeys results in long-term damage to both serotonin and dopamine neurons in the brain.[18, 42, 44] Recent positron emission tomography studies indicate that human MDMA users suffer long-term serotonin neural injury, just as nonhuman primates do.[35] Some authorities believe that delayed panic attacks, anxiety, depression, flashbacks, psychosis, cognitive dysfunction, memory disturbances, and other neuropsychiatric disorders could be related to long-term changes in neurotransmission.[35, 49]

Clinical Presentation

Initial effects generally begin at 30 to 60 minutes, with peak effects at 90 minutes and persistent effects for 8 hours or longer.[43] Desired effects comprise enhanced empathy and insight, feelings of closeness to others, mood alteration with sensual and emotional overtones, euphoria, increased energy, increased self-esteem, and altered visual perceptions.[5, 43, 45] Generally, MDMA users present to the ED only if they experience adverse effects. Adverse effects encompass neurologic, respiratory, cardiovascular, and muscular effects, as well as end-organ damage from hyperthermia.[18] In severe poisonings, death ensues.[10, 12, 19, 43]

Sympathetic nervous system stimulation can cause diaphoresis, mydriasis, tachycardia, hypertension, and increased psychomotor drive. Serotonergic stimulation can cause psychedelic effects, including sensory enhancement, distortion, illusions, and hallucinations (visual and tactile). Mild neurologic effects include dysphoria, confusion, altered time perception, delirium, paranoia, obsessive behavior, panic attacks, fatigue, difficulty concentrating and retaining information, headaches, hyperreflexia, ataxia, dizziness, blurred vision, nystagmus, anorexia, depression, insomnia, restlessness, irritability, and lethargy.[5, 18, 43, 45] More serious neurologic effects also can be seen, including frank psychosis, coma, seizures and status epilepticus, intracranial hemorrhage, and cerebral infarction. Respiratory failure can occur as a secondary complication of these neurologic effects.[5] Chronic abuse can result in a paranoid psychosis clinically indistinguishable from schizophrenia.[5]

Cardiovascular complications, such as hypertension, tachycardia, arrhythmias, palpitations, atrioventricular block, cardiogenic shock with hypotension and pulmonary edema, and asystole can occur. Some deaths could be due to exacerbations of underlying dysrhythmias.[18, 45] Of added concern, patients could have underlying cardiac disease from chronic illicit drug abuse.[5, 18] Diffuse vascular spasm could cause mesenteric ischemia or necrosis.[5]

Muscular effects include muscle tension or spasms, rigidity, trismus, bruxism, muscle aches, motor tics, and rhabdomyolysis, which could precipitate renal failure.[5, 12, 45] Hyperthermia can also produce or contribute to end-organ damage, including acute hepatic and renal failure, disseminated intravascular coagulation (DIC) complicated by bleeding, and adult respiratory distress syndrome (ARDS).[4, 5]

Metabolic effects, such as metabolic acidosis, hyperkalemia, and hypona-

tremia have been noted. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur rarely following MDMA ingestion.[21]

Diagnostic Studies

Frequent blood pressure and continuous cardiac monitoring are recommended for moderately to severely toxic patients and for patients known to have recently ingested large quantities of methamphetamines. Core temperatures should be assessed, with thermometers capable of measuring severe hyperthermia (>108°F). Chemistry panels, assessing electrolytes to check for dehydration and acidosis are helpful. Elevated creatine phosphokinase (CPK) levels can suggest rhabdomyolysis. Liquid chromatographic methods can be used to detect MDMA.[36] Computed tomography (CT) of the brain and lumbar puncture could be necessary to exclude intracranial hemorrhage and other causes of hypertension, hyperthermia, and altered mental status.

Treatment

Airway, breathing, and circulation should be assessed and maintained. Often, tachycardia and hypertension subside with benzodiazepine sedation. If hypertension is severe and does not resolve with sedation, it should not be treated with pure β-adrenergic blocking agents, which can cause unopposed α-stimulation.[5] Instead, easily titratable α-adrenergic blocking agents (e.g., phentolamine), mixed agents or vasodilators (e.g., nitroprusside) should be used.[5]

Core temperatures should be measured promptly to assess for hyperthermia. Rapid cooling, rehydration, and monitoring of electrolytes and end-organ function are paramount if hyperthermia is noted.[10, 18, 43] Rapid cooling generally involves sedation with benzodiazepines and occasionally administration of paralytic agents to prevent further heat generation.[5, 8] Cooling generally can be accomplished by wetting bare skin with a tepid-water mist and employing large fans to promote evaporative cooling. Shivering should be prevented, with pharmacologic paralysis if needed.[8] The core temperature should be monitored continuously. Once core body temperature has been reduced to approximately 38°C or 39°C, cooling measures should be withdrawn to prevent introgenic hypothermia.[8]

Patients can present with syndromes that appear consistent with serotonin syndrome or even neuroleptic malignant syndrome (NMS)[11]; usually, however, treatment for agitation, hyperthermia, and muscle rigidity (e.g., as benzodiazepines, cooling measures, and pharmacologic paralysis) are adequate. Specific treatment for serotonin syndrome or NMS (e.g., cyproheptadine and dantrolene) are not generally indicated for the MDMA-poisoned patient.

These patients are often dehydrated and can demonstrate hypernatremia, requiring intravenous fluids.[18] Hyponatremia has also been seen on presentation, however, and can be associated with seizures and cerebral edema.[21] Convulsions should be controlled with benzodiazepines; status epilepticus can require phenobarbital for adequate control. Alkalinization of the urine with bicarbonate drip solutions (1 liter D5W with 2 ampules of sodium bicarbonate and supplemental potassium), providing adequate urine formation (1–2 mL/min), and occasionally mannitol are recommended for the patient at high risk for rhabdomyolysis.[26]

Prognosis

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History

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and "date rape" drug, GHB beca
streets variously as *Grievous Bodily
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and *Organic Qualude.*[17, 23] In 1990,
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Sources

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Prognosis

Patients with serious poisoning sometimes do not survive despite appropriate, aggressive medical treatment. Most MDMA-associated deaths occur early and are secondary to arrhythmias, hyperthermia, seizures, or intracerebral hemorrhage.[5, 34] Fatal complications also can include DIC and bleeding, as well as multiple organ system failure.[34] These fatal complications are sometimes secondary to drug-induced hyperthermia.[8] Outcome in the hyperthermic patient is closely related to how rapidly and effectively the patient is cooled.

GAMMA-HYDROXYBUTYRATE, GAMMA-BUTYROLACTONE AND 1,4-BUTANEDIOL

History

Gamma hydroxybutyrate (GHB) was synthesized and introduced into clinical medicine by Laborit in 1960.[14, 28, 32] Used initially as an anesthetic agent in the 1960s, GHB's poor analgesic effect and seizure-like EEG patterns produced in experimental animals diminished its popularity as an anesthetic.[47] Years after its introduction, GHB was found to be endogenous in mammalian brains.[14] By 1995, central GHB receptors were detected, helping to establish GHB as a possible endogenous neurotransmitter.[6, 14]

Although GHB is used to treat opiate and alcohol addiction in some countries, its use legally is limited to narcolepsy treatment trials (Orphan Med) in the United States.[1, 14, 28] In the 1980s, GHB became popular with bodybuilders and was advertised as an agent that would increase muscle development, burn fat, produce euphoria, and improve sleep.[17, 28, 47] Purported to be an aphrodisiac and "date rape" drug, GHB became popular at raves, and was known on the streets variously as *Grievous Bodily Harm, Georgia Home Boy, Liquid Ecstasy, Liquid X, Liquid E, Soap, Easy Lay, Scoop, Salty Water, G-riffick, Cherry Meth, Somatomax,* and *Organic Qualude.*[17, 23] In 1990, 57 cases of toxicity were reported by the CDC, resulting in the FDA prohibiting the sale of GHB.[7] GHB is a schedule I drug in some states.[23, 28] This has led to the production and sale of GHB *prodrugs,* such as gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), which have been marketed to induce sleep, release growth hormone, burn fat, enhance sexual activity and athletic performance, and relieve depression. On January 21, 1999, the FDA asked manufacturers to recall GBL-containing products and warned consumers of the dangers of GBL through press releases. This fueled internet chat rooms among GBL users, and advertisements for sale of hoarded GBL products became prominent on the internet.

Sources

Prodrugs of GHB have entered health food store and internet markets, filling the gap left by restrictions on GHB sales. GHB-synthesizing kits are advertised on the internet and include sodium hydroxide, GBL, and pH paper. Sodium hydroxide is used to convert GBL to GHB. GBL is also converted to GHB in vivo; therefore, kits that convert GHL from GBH are unnecessary, as was soon discovered by the lay public.[7] GBL is rapidly converted by a blood-borne gamma-lactonase to form GHB.[6, 31] GBL products are now advertised as sole agents rather than as prodrugs. Products containing GBL have been sold under

brand names including Revivarant, RenewTrient, Firewater, and Blue Nitro Vitality.[30] Accidental exposures have occurred with GBL products sold as industrial and household solvents of acrylate polymers.[7] More recently, 1,4-BD abuse has been reported. 1,4-BD is converted in vivo, by alcohol dehydrogenase and then by aldehyde dehydrogenase, to GHB.[9, 31] 1,4-BD is sold under the names *Pine Needle Oil, Serenity, Revitalize Plus, Enliven, GHRE, SomatoPro, NRGE, Thunder Nector, Weight Belt Cleaner, Cherry fx Bombs, Lemon fx Drops,* and *Orange fx Rush.* It is readily available through chemical supply catalogues and in some local stores.[9, 13]

Pharmacokinetics

GHB is water soluble and rapidly absorbed from the gastrointestinal tract.[2, 28] GBL is better absorbed than GHB and has a greater bioavailability.[9] Both GBL and 1,4-butanediol are converted to GHB in vivo.[32] GHB readily crosses both blood–brain and placental barriers.[28] GHB is metabolized to succinic semialdehyde and gamma-aminobutyric acid (GABA).[28] The elimination half-life of GHB is 27 minutes.[28] GHB usually is excreted within the first few hours after ingestion.[23]

Mechanisms of Action

GHB is found endogenously in the central nervous system (CNS), with its highest concentrations in the substantia nigra, hypothalamus, and thalamus.[46] GHB is thought to mediate sleep cycles, temperature regulation, cerebral glucose metabolism and blood flow, memory and emotional control; it also could have neuroprotective effects.[28, 32] Clinical and experimental work indicate that GHB can protect both central and peripheral tissues from the damaging effects of hypoxia and excessive metabolic demands.[28, 32] Despite marked degrees of metabolic depression induced by GHB, full tissue recovery generally occurs.[32]

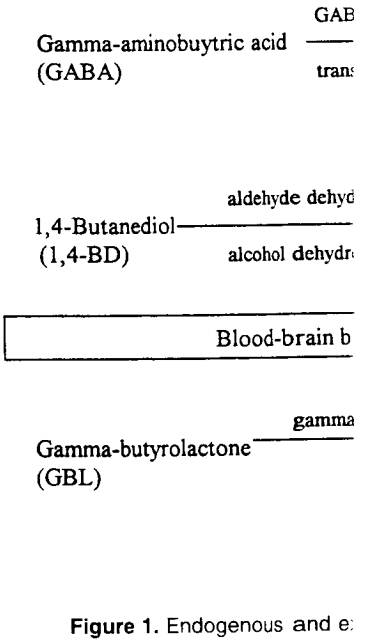
Endogenous GHB is generated, in part, from gamma-aminobutyric (GABA); however, this is probably a minor pathway.[14] Endogenous GHB be formed from endogenous succinic semialdehyde and 1,4-butanediol within the brain as well (Fig. 1).[14, 31]

Although the exact mechanism of action is not well established, GHB appears to influence dopaminergic activity, probably through GHB receptors.[14, 46, 47] In fact, most actions of GHB probably are mediated through specific brain receptors for GHB. At higher concentrations, GHB can mediate some effects by interacting with $GABA_B$ receptors. Interaction with $GABA_B$ receptors can be direct, with GHB binding at the $GABA_B$ receptor, or indirect, with GHB being converted to GABA prior to interacting with the $GABA_B$ receptor or with GHB binding to a site that shares the same intermediary, such as a G-protein, as the $GABA_B$ receptor.[17, 28, 47] GHB has a much higher affinity for its own receptor than for $GABA_B$ receptors.[47] GBL appears to be more GABAnergic than GHB.[14]

GHB is probably addictive. Tolerance, and a withdrawal syndrome clinically similar to ethanol withdrawal have been reported.[1]

Clinical Presentation

Case reports of clinical presentation after GHB, GBL, and 1,4-BD exposure are essentially indistinguishable and of similar duration; therefore, these are considered together.[7, 13]



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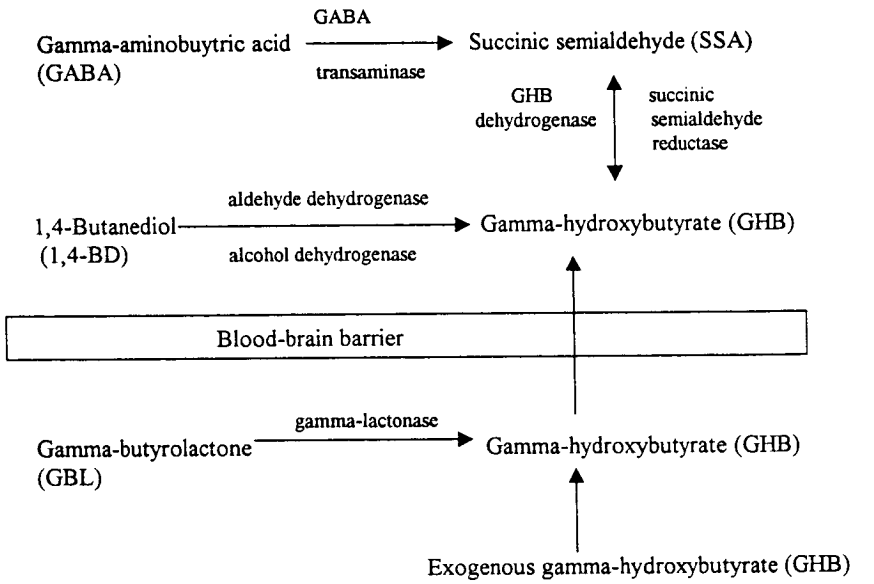

Figure 1. Endogenous and exogenous sources of gamma-hydroxybutyrate.

Users of GHB and similar products tend to be adolescents or young adults. In one report of patients ingesting GBL-containing products in New Mexico and Texas, ages ranged from 11 to 41 years; most subjects were male.[7] Many had ingested other drugs, including ethanol, and 44% ingested another substance of abuse.[7] GHB appears to have a synergistic effect with ethanol, producing CNS and respiratory depression; however, significant impairment in operating motor vehicles has been noted, even when GHB is taken as the sole agent.[7, 30] GHB demonstrates a dose-dependent response. An oral dose of 10 mg/kg induces sleep; a dose of 30 mg/kg induces memory loss; and a dose of 50 mg/kg or more can result in general anesthesia.[17]

Neurologic toxicity includes nervous system depression, aggressive behavior, drowsiness, confusion, alternating agitation and coma, amnesia, syncope, hypotonia, incontinence, ataxia, nystagmus, tunnel vision, twitching and tremors, random clonic movements of face and extremities, and possibly seizures.[7, 17, 28] Although seizure activity has been noted in experimental animals, it is debated whether GHB causes true seizure activity in humans. Human experiments with "therapeutic" doses of GHB have not found EEG changes consistent with seizure activity.[28, 47] GHB is frequently associated with random clonic movements of the face and extremities without epileptiform EEG changes.[28] Others have reported "generalized seizures" in patients presenting after GHB abuse and overdose.[47] Interestingly, patients with a rare inborn error of metabolism, which disrupts the normal metabolism of GABA that causes GHB to accumulate, reportedly experience seizures.[17]

Cardiovascular toxicity includes bradycardia that can be followed by tachycardia as the patient recovers.[7] Pulmonary toxicity can involve respiratory depression and apnea.[7, 28] Patients are at risk for aspiration pneumonia.[28] Gastrointestinal toxicity includes nausea and vomiting.[7] Patients also sometimes

demonstrate hypothermia, flushing, and diaphoresis. All symptoms of intoxication generally resolve within 2 to 7 hours; however, some require mechanical ventilation and occasionally admission to intensive care units.

With chronic abuse, withdrawal syndromes may be seen.[47] A case of GHB-induced Wernicke-Korsakoff syndrome has also been reported.[17, 47]

Diagnostic Studies

GHB and GHB prodrugs are missed by conventional first-line urine drug screens.[2] Badcock and Zotti describe a rapid and sensitive qualitative spot test that could be implemented as a screening test in most hospital laboratories.[2] GHB and GBL can be differentiated in urine by using gas chromatography and flame ionization.[30]

Treatment

Supportive care is paramount. Some have suggested that patients with very low Glasgow Coma Scale scores and intermittent apnea might not require intubation; however, in light of the hypersalivation and vomiting that can occur with GHB intoxication, this approach seems risky. The airway should be protected, as with other causes of CNS depression, until the toxicity resolves. Rapid sequence intubation is recommended.[28] If symptomatic or prolonged bradycardia ensues, atropine can be administered.[28]

Prognosis

Patients generally do well, recovering rapidly. Most can be discharged from the ED after 6 hours of observation.[28] Other sedating agents have an additive effect and can prolong the CNS depression.[28] Deaths after GHB and GHB prodrugs have occurred but are rare events.[7, 20, 23, 28]

KETAMINE

History

Ketamine, a phencyclidine hydrochloride (PCP) derivative, was introduced into clinical practice in the 1960s as a dissociative anesthetic, and is known to disrupt the flow of information from consciousness to unconsciousness.[25, 37] Abuse began on the West Coast in the early 1970s.[15] By the 1980s, ketamine use was popular among New Age spiritualists.[22] Ketamine use at raves could have been introduced initially as an adulterant in MDMA tablets but is currently used as a sole agent.[22, 24, 37, 50] Its use appears to be increasing.[50] Ketamine is a controlled substance in Arizona, California, New Mexico, Oklahoma, and Connecticut.[22]

Sources

On the streets and the Internet, ketamine is referred to as *Special K, vitamin K, K, Super K, Ketaset, Jet, Super Acid, Green, Purple, Mauve,* and *Special LA Coke.*[15]

A vial of liquid ketamine (Ketas
sells for about 10 times that
$80/g.[22] Ketamine can be adm
more commonly it is taken in
snorted. The powdered form is
into Pyrex baking dishes so tha
also can be smoked.[48]

Pharmacokinetics

Ketamine is highly bioav
administration; oral doses are
metabolism.[41] Ketamine is met
P450 isoenzymes.[25] The prima
potent than ketamine.[25, 41] Nork
tion.[41] Norketamine is hydroxyl
that are excreted in the urine.
hours.[25, 41]

Mechanisms of Action

Ketamine is chemically rel
acts with N-methyl-D-aspartate
nicotinic and muscarinic cholin
receptors, opioid receptors, an
binds primarily to the PCP rece
glutamate activation of the cl
stimulates NO synthesis and
dopamine, and serotonin.[25, 41]

Clinical Presentation

In social situations, the
effects come on abruptly and
minutes.[22, 24]

Signs and symptoms of n
agitation, slurred speech, deliri
ety, vivid dreams, hallucinatio
ments, such as bizarre facial
movements, dystonic reactions
shouting.[15, 24, 33] Rhabdomyolys

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ences.[24, 25, 37] Users state that
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A vial of liquid ketamine (Ketaset), which would cost a veterinarian about $6, d sells for about 10 times that on the street. Street cost is approximately $80/g.[22] Ketamine can be administered intravenously or intramuscularly, but more commonly it is taken in a powdered form, either mixed into a drink or snorted. The powdered form is prepared by pouring vials of liquid ketamine into Pyrex baking dishes so that it can be boiled down into crystal.[22] Ketamine also can be smoked.[48]

Pharmacokinetics

Ketamine is highly bioavailable following intravenous or intramuscular administration; oral doses are not as well absorbed and undergo first-pass metabolism.[41] Ketamine is metabolized extensively by the hepatic cytochrome P450 isoenzymes.[25] The primary metabolite, norketamine, is active but less potent than ketamine.[25, 41] Norketamine levels are higher after oral administration.[41] Norketamine is hydroxylated and conjugated to water-soluble compounds that are excreted in the urine.[25, 41] The elimination half-life is approximately 2 hours.[25, 41]

Mechanisms of Action

Ketamine is chemically related to PCP and cyclohexamine.[41] Ketamine interacts with N-methyl-D-aspartate (NMDA) and non-NMDA-glutamate receptors, nicotinic and muscarinic cholinergic receptors, sigma receptors, monoaminergic receptors, opioid receptors, and calcium and sodium channels.[25, 27, 41] Ketamine binds primarily to the PCP receptor within the NMDA channel, where it inhibits glutamate activation of the channel noncompetitively.[25, 27, 39, 41] Ketamine also stimulates NO synthesis and inhibits the neuronal uptake of norepinephrine, dopamine, and serotonin.[25, 41]

Clinical Presentation

In social situations, the drug is often taken intranasally or orally.[24] The effects come on abruptly and are generally brief, lasting approximately 30 to 45 minutes.[22, 24]

Signs and symptoms of neurologic toxicity include nystagmus, mydriasis, agitation, slurred speech, delirium, floating sensations, hypertonus, rigidity, anxiety, vivid dreams, hallucinations, and seizures.[15, 41, 48] There are effects on movements, such as bizarre facial expressions, loss of coordination, bizarre limb movements, dystonic reactions, persistent repetition of acts or words, and, rarely, shouting.[15, 24, 33] Rhabdomyolysis can ensue.[48]

Studies with healthy volunteers reveal that ketamine produces positive and negative symptoms of schizophrenia, alterations in perception, impaired performance on tests of vigilance and verbal fluency, and disrupted word recall. These behaviors and cognitive deficits resemble endogenous psychoses, particularly schizophrenia and dissociative states.[27] Patients can have psychological dissociation, resulting in hallucinations, vivid dreams and illusions, and subjective experiences of being out of the body, or states similar to near-death experiences.[24, 25, 37] Users state that ketamine takes the mind to "K-land" or into "K-holes," producing dissociative or out-of-body experiences with floating

sensation.[22, 37] The dissociation can be so profound that the user experiences a separate reality and difficulty with movement.[24] Emotional withdrawal and psychomotor retardation are sometimes noted.[27] Subjects report that initiating or sustaining interpersonal interactions demands increased effort.[27] Flashbacks have been reported as long as months after receiving ketamine.[50] Long-term use of high doses can interfere with memory and learning.[24]

Cardiovascular toxicity reflects central sympathetic stimulation of the cardiovascular system, and includes palpitations, tachycardia, elevated blood pressure, elevated systemic vascular resistance, and increased cardiac output.[25, 37, 41, 48] Signs of respiratory toxicity include respiratory depression and apnea.[25, 41] Increased circulating catecholamines cause bronchodilation.[41] Patients are at risk for aspiration pneumonia and anoxia.[41] Massive pulmonary edema has been noted on autopsy after ketamine overdose and death.[29, 37]

Diagnostic studies

Levels of ketamine, and its metabolite, norketamine, can be obtained but generally are not readily available nor helpful to the emergency physician.[50] Immunoassays for PCP might not cross react with ketamine.[48] If rhabdomyolysis is of concern, one should measure CPK levels. If aspiration pneumonitis or pneumonia is of concern, obtain a chest radiograph.

Treatment

Patients can require sedation with benzodiazepines and treatment for rhabdomyolysis.[48] Midazolam is preferable over diazepam for sedation.[41]

Prognosis

Patients generally do well with supportive care. Most can be discharged from the ED, but some may require hospital admission.[48] Death is rare.

SUMMARY

Newer drugs of abuse, such as MDMA, GHB, GBL, 1,4-BD and ketamine, are frequently used in the settings of raves and are often promoted on the internet. The popularity of these agents is increasing; therefore, emergency physicians should become familiar with the clinical presentations and management of the toxicity induced by these agents.

References

1. Addolarato G, Caputo F, Capristo E, et al: A case of gamma-hydroxybutyric acid withdrawal syndrome during alcohol addiction treatment: utility of diazepam administration. Clin Neuropharmacol 22:60–62, 1999
2. Badcock NR, Zotti R: Rapid screening test for gamma-hydroxybutyric acid (GHB, fantasy) in urine [letter]. Ther Drug Monit 21:376, 1999
3. Battaglia G, DeSouza EB: Pharmacologic profile of amphetamine derivatives at various brain recognition sites: Selective 94:240–258, 1989
4. Brauer RB, Heidecke CD, Nathr fulminant hepatic failure induce 1997
5. Buchanan JF, Brown CR: Designe Adverse Drug Exp 3:1–17, 1988
6. Cash CD: Gammahydroxybutyr neurotransmitter and/or a usefi 304, 1994
7. CDC: Adverse events associated New Mexico, and Texas, 1998–1
8. Chan TC, Evans SD, Clark RF: 808, 1997
9. Chin RL, Dyer JE, Sporer KA: [letter]. Ann Emerg Med 33(4):4
10. Dar KJ, McBrien: MDMA-induc current therapy. Intensive Care
11. Demirkiran M, Jankovic J, Dean syndrome and neuroleptic ma 1996
12. Downing J: The psychological teers. J Psychoactive Drugs 18:3
13. Dyer JE, Galbo MJ, Andrews K toxic profile of GHB [abstract].
14. Feigenbaum JJ, Howard SG: G Neurobiol 50:1–7, 1996
15. Felser JM, Orban DJ: Dystonic 675, 1982
16. Fields G: Ecstasy drug seizures
17. Gibson KM, Hoffmann GF, Ho phenotype of succinic semialc GABA metabolism. Neuropedi
18. Green AR, Cross AJ, Goodwin cology of 3,4-methylenedioxyn macology 119:247–260, 1995
19. Greer G, Tolbert P: Subjective Psychoactive Drugs 18:319–327
20. Hendrix A: 'Blue nitro' under
21. Holmes SB, Banerjee AD, Ale use. Postgrad Med J 57:32–46,
22. Holthouse D: Ket nip. New Yo
23. Iven VG: Recreational drugs.
24. Jansen KLR: Nonmedical use
25. Kohrs R, Durieux ME: Ketam 87:1186–1193, 1998
26. Kolecki P, Thomas R: Designe 1997
27. Krystal JH, Karper LP, Seibyl NMDA antagonist, ketamine, neuroendocrine responses. Ar
28. Li J, Arnaud-Stokes S, Woeck effects of gamma-hydroxybut Emerg Med 31:729–736, 1998
29. Licata M, Pierini G, Popoli 1320, 1994
30. LoVecchio F, Curry SC, Bagn

brain recognition sites: Selective effects on serotonergic systems. NIDA Res Monogr 94:240–258, 1989
4. Brauer RB, Heidecke CD, Nathrath, et al: Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy. Transpl Int 10:229–233, 1997
5. Buchanan JF, Brown CR: Designer drugs: A problem in clinical toxicology. Med Toxicol Adverse Drug Exp 3:1–17, 1988
6. Cash CD: Gammahydroxybutyrate: An overview of the pros and cons for it being a neurotransmitter and/or a useful therapeutic agent. Neurosci Biobehav Rev 18:291–304, 1994
7. CDC: Adverse events associated with ingestion of gamma-butyrolactone—Minnesota, New Mexico, and Texas, 1998–1999. MMWR 48:137–140, 1999
8. Chan TC, Evans SD, Clark RF: Drug-induced hyperthermia. Clin Crit Care 13:785–808, 1997
9. Chin RL, Dyer JE, Sporer KA: gamma-Hydroxybutyrate intoxication and overdose [letter]. Ann Emerg Med 33(4):475–476, 1998
10. Dar KJ, McBrien: MDMA-induced hyperthermia: Report of a fatality and review of current therapy. Intensive Care Med 22:995–996, 1996
11. Demirkiran M, Jankovic J, Dean JM: Ecstasy intoxication: An overlap between serotonin syndrome and neuroleptic malignant syndrome. Clin Neuropharmacol 19:157–164, 1996
12. Downing J: The psychological and physiological effects of MDMA on normal volunteers. J Psychoactive Drugs 18:335–340, 1986
13. Dyer JE, Galbo MJ, Andrews KM: 1,4-Butanediol, "pine needle oil": Overdose mimics toxic profile of GHB [abstract]. J Toxicol Clin Toxicol 35:554, 1997
14. Feigenbaum JJ, Howard SG: Gamma-hydroxybutyrate is not a GABA agonist. Prog Neurobiol 50:1–7, 1996
15. Felser JM, Orban DJ: Dystonic reaction after ketamine abuse. Ann Emerg Med 11:673–675, 1982
16. Fields G: Ecstasy drug seizures multiplying. USA Today, June 7, 1999, p IA
17. Gibson KM, Hoffmann GF, Hodson AK, et al: 4-Hydroxybutyric acid and the clinical phenotype of succinic semialdehyde dehydrogenase deficiency, an inborn error of GABA metabolism. Neuropediatrics 29:14–22, 1998
18. Green AR, Cross AJ, Goodwin GM: Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"). Psychopharmacology 119:247–260, 1995
19. Greer G, Tolbert P: Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 18:319–327, 1986
20. Hendrix A: 'Blue nitro' under fire. Arizona Republic, Jan 15, 1999, p A6
21. Holmes SB, Banerjee AD, Alexander WD: Hyponatremia and seizures after ecstasy use. Postgrad Med J 57:32–46, 1999
22. Holthouse D: Ket nip. New York Times, July 3–9, 1997
23. Iven VG: Recreational drugs. Clin Sports Med 17:245–259, 1998
24. Jansen KLR: Nonmedical use of ketamine. Br Med J 306:601–602, 1993
25. Kohrs R, Durieux ME: Ketamine: Teaching an old drug new tricks. Anesth Analg 87:1186–1193, 1998
26. Kolecki P, Thomas R: Designer drugs and hallucinogens. Top Emerg Med 19:53–63, 1997
27. Krystal JH, Karper LP, Seibyl JP, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214, 1994
28. Li J, Arnaud-Stokes S, Woeckener A: A tale of novel intoxication: A review of the effects of gamma-hydroxybutyric acid with recommendations for management. Ann Emerg Med 31:729–736, 1998
29. Licata M, Pierini G, Popoli G: A fatal ketamine poisoning. J Forensic Sci 39:1314–1320, 1994
30. LoVecchio F, Curry SC, Bagnasco T: Butyrolactone-induced central nervous system

depression after ingestion of RenewTrient, a "dietary supplement" [letter]. N Engl J Med 339:847–848, 1998
31. Maitre M: The gamma-hydroxybutyrate signaling system in brain: Organization and functional implications. Prog Neurobiol 51:337–361, 1997
32. Mamelak M: Gammahydroxybutyrate: An endogenous regulator of energy metabolism. Neurosci Biobehav Rev 13:187–198, 1989
33. Marai W: Exaggerated psychomotor response to intravenous bolus dose administration of ketamine. Ethiop Med J 32:131–133, 1994
34. McCann UD, Slate SO, Ricaurte GA: Adverse reactions with 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy"). Drug Saf 15:107–115, 1996
35. McCann UD, Szabo Z, Scheffel U, et al: Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. Lancet 352:1433–1437, 1998
36. Moeller MR, Steinmeyer S, Kraemer T: Determination of drugs of abuse in blood. J Chromatogr 713:91–109, 1998
37. Moore KA, Kilbane EM, Jones R, et al: Tissue distribution of ketamine in a mixed drug fatality. J Forensic Sci 2:1183–1185, 1997
38. Nichols DE, Oberlender R: Structure-activity relationships of MDMA-like substances. NIDA Res Monogr 94:1–29, 1989
39. Oye I: Ketamine analgesia, NMDA receptors and the gates of perception. Acta Anaesthesiol Scand 42:747–749, 1998
40. Rattray M: Ecstasy: Towards an understanding of the biochemical basis of the actions of MDMA. Essays Biochem 26:77–87, 1991
41. Reich DL, Silvay G:-Ketamine: An update on the first twenty-five years of clinical experience. Can J Anaesth 36:186–197, 1989
42. Ricaurte GA, McCann UD: Neurotoxic amphetamine analogues: effects in monkeys and implications for humans. Ann N Y Acad Sci 648:371–382, 1992
43. Schwartz RH, Miller NS: MDMA (ecstasy) and the rave: A review. Pediatrics 100:705–708, 1997
44. Seiden LS, Sabol KE: Methamphetamine and methylenedioxymethamphetamine neurotoxicity: Possible mechanisms of cell destruction. NIDA Res Monogr 163:251–276, 1996
45. Steele TD, McCann UD, Ricaurte GA: 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy"): Pharmacology and toxicology in animals and humans. Addiction 89:539–551, 1994
46. Tunnicliff G: Significance of gamma-hydroxybutyric acid in the brain. Gen Pharmacol 23:1027–1034, 1992
47. Tunnicliff G: Sites of action of gamma-hydroxybutyrate (GHB)—a neuroactive drug with abuse potential. J Toxicol Clin Toxicol 35:581–590, 1997
48. Vieira L, Weiner A: Ketamine abusers presenting to the emergency department: A case series. J Tox Clin Tox 36:505, 1998
49. White SR, Obradovic T, Imel KM, et al: The effects of methylenedioxymethamphetamine (MDMA, ecstasy) on monoaminergic neurotransmission in the central nervous system. Prog Neurobiol 49:455–479, 1996
50. Zacny JP, Galinkin JL: Psychotropic drugs used in anesthesia practice abuse liability and epidemiology of abuse. Anesthesiology 90:269–288, 1999

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A Review

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ANTIDEPRESSANTS

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