REVIEWS OF THERAPEUTICS

A Comprehensive Review of MDMA and GHB: Two Common Club Drugs

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"Club drugs" have become alarmingly popular. The use of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and γ-hydroxybutyrate (GHB), in particular, has increased dramatically from 1997–1999. The pharmacokinetics of MDMA and GHB appear to be nonlinear, making it difficult to estimate a dose-response relationship. The drug MDMA is an amphetamine analog with sympathomimetic properties, whereas GHB is a γ-aminobutyric acid analog with sedative properties. Symptoms of an MDMA toxic reaction include tachycardia, sweating, and hyperthermia. Occasional severe sequelae include disseminated intravascular coagulation, rhabdomyolysis, and acute renal failure. Treatment includes lowering the body temperature and maintaining adequate hydration. Symptoms of GHB intoxication include coma, respiratory depression, unusual movements, confusion, amnesia, and vomiting. Treatment includes cardiac and respiratory support. Because of the popularity of these agents and their potentially dangerous effects, health care professionals must be familiar with these substances and the treatment options for patients who present with symptoms of a toxic reaction.
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The increase in the popularity of a socially designated class of drugs known as "club drugs" has been alarming. These drugs acquired this label because they are used most often at all-night dance parties known as "raves" or in dance clubs and bars. Drugs commonly included in this group are 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), γ-hydroxybutyrate (GHB), flunitrazepam ("Roofies"), ketamine, methamphetamine, and lysergic acid diethylamide (LSD). Many of these drugs are colorless,

tasteless, and odorless and can be placed covertly into beverages. Therefore, some of these drugs, in particular GHB and flunitrazepam, have been used to intoxicate or sedate unsuspecting individuals to facilitate sexual assault and have been given the name "date rape" drugs.[1]

Epidemiologic studies have shown that use of club drugs is on the rise.[2, 3] According to the Monitoring the Future Study,[2] the use of MDMA has risen sharply over the last couple of years. In 2000, 8.2% of 12th graders reported taking MDMA in the prior 12 months, an increase from 5.6% in 1999. Use also increased markedly among American college students, from 0.5% in 1994 to 5.5% in 1999. According to the principal investigator for the Monitoring the Future Study, two reasons explain why MDMA use may still be on the rise despite a great deal of attention in the media. First, young people may not yet see MDMA as a dangerous drug. Second, the perceived availability of MDMA has increased dramatically. By 2000, 51% of 12th graders stated that they could buy MDMA fairly or very easily. The same study reported that the prevalence rates of GHB and ketamine use are 1–2.5% in grades 8, 10, and 12. Ketamine and GHB were added to the ongoing Monitoring the Future Study in 2000, so it is not possible to obtain usage trends for these drugs. The use of flunitrazepam, crystal methamphetamine, and LSD has actually declined from peak levels in the mid-1990s through 2000.

The increase in the use of club drugs has been observed by medical care providers. According to the Drug Abuse Warning Network (DAWN) report,[3] emergency department episodes significantly increased for MDMA (p<0.01), GHB (p<0.01), and ketamine (p<0.05) from 1994–1999. These increases were especially dramatic from 1997–1999 for MDMA and GHB (Figures 1 and 2). Apparent increases in the use of flunitrazepam over the same time period were not statistically significant. Methamphetamine and LSD account for the largest number of emergency department "mentions" in this report overall; however, mentions of methamphetamine dropped significantly from 1994–1999, whereas mentions of LSD remained stable over these 6 years. (A mention refers to a specific substance that was mentioned in a drug abuse episode.)

The use of these drugs poses a serious public health problem, and health care professionals need to be familiar with these substances.

MDMA

History

The drug MDMA (Ecstasy, "E") is a ring-substituted amphetamine analog commonly taken as a recreational drug of abuse. It was synthesized in 1912 by Merck Pharmaceuticals and patented in 1914.[4] However, MDMA did not become popular until the 1970s when it was promoted as a useful adjunct to psychotherapy. It allegedly improved self-esteem and enhanced communication within significant emotional relationships.[5] Therapeutic applications for
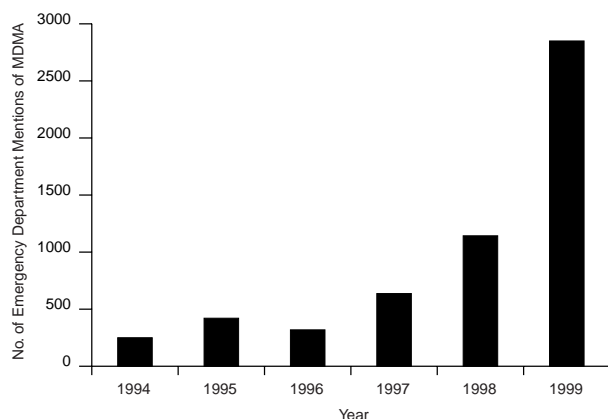

Figure 1. Drug Abuse Warning Network (DAWN) statistics of the number of emergency department mentions of 3,4-methylenedioxymethamphetamine (MDMA) from 1994–1999. (From reference 3.)
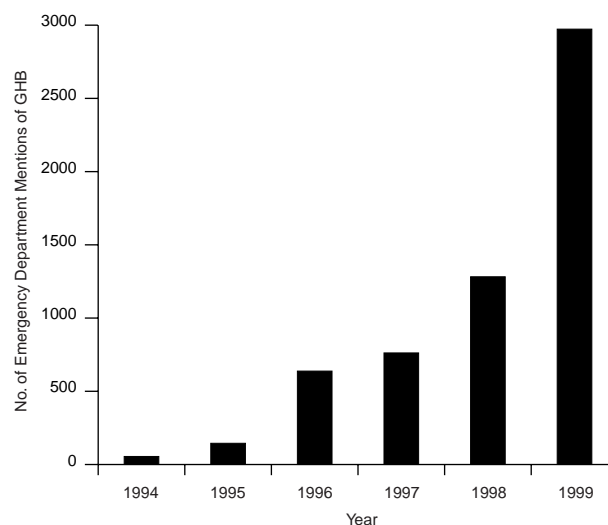

Figure 2. Drug Abuse Warning Network (DAWN) statistics of the number of emergency department mentions of γ-hydroxybutyrate (GHB) from 1994–1999. (From reference 3.)

MDMA were not well established, however, and the Drug Enforcement Administration (DEA) classified MDMA as a schedule I drug in 1985 after its recreational use became more widespread and publicized.[6] It also was shown that 3,4-methylenedioxyamphetamine (MDA), an analog and metabolite of MDMA, had a neurotoxic effect in animals.[7]

Availability

The drug MDMA is commonly distributed as small tablets, capsules, or white powder. Ecstasy tablets may contain various chemicals other than pure MDMA, including MDA, 3,4-methylene-dioxyethylamphetamine (MDEA), caffeine, dextromethorphan, ephedrine, phenyl-propanolamine, methamphetamine, amphetamine, diphenhydramine, ketamine, cocaine, and diazepam. Some have contained no active drugs at all.[8] Results of analyses of tablets from all over the United Kingdom, given to the Leeds Addiction Unit, confirm that there are many ingredients in Ecstasy tablets other than MDMA.[9] In another report, MDMA concentrations in 25 tablets varied 70-fold, and 9 of the tablets did not contain either MDMA or any related MDMA analog.[10] Furthermore, MDMA tablets collected by the Haight Ashbury Free Medical Clinic contained from 16–150 mg of MDMA/tablet. Owing to the great variability in the dose of MDMA in any given tablet, it is very difficult for users of MDMA to control their dose. Larger-than-expected doses of MDMA may be taken accidentally, leading to adverse effects.[11] Furthermore, because of the variety of substances that may be found in any given MDMA tablet, the clinical presentation of acute intoxication may vary significantly.

Chemistry

The chemical designation of MDMA is N-methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (Figure 3). Structurally it resembles both the stimulant amphetamine and the hallucinogen mescaline.[12] The drug MDMA is optically active, with the dextrorotatory isomer (S+) having higher central activity than the levorotatory isomer.[4, 13]

Pharmacokinetics

Pharmacokinetic Parameters

The pharmacokinetics of MDMA after oral ingestion have been studied by various researchers.[14–17] The time to maximum concentration (T_{max}) is 2 hours after oral ingestion of MDMA 50, 75, or 125 mg.[14–17] The half-life shows little variation after a wide range of doses. After a 50-, 75-, or 125-mg dose, the half-life is 8 hours.[16, 17] Other studies found the half-life to be 9.53 hours after a 75-mg dose and 9.12 hours after a 125-mg dose.[14] The maximum
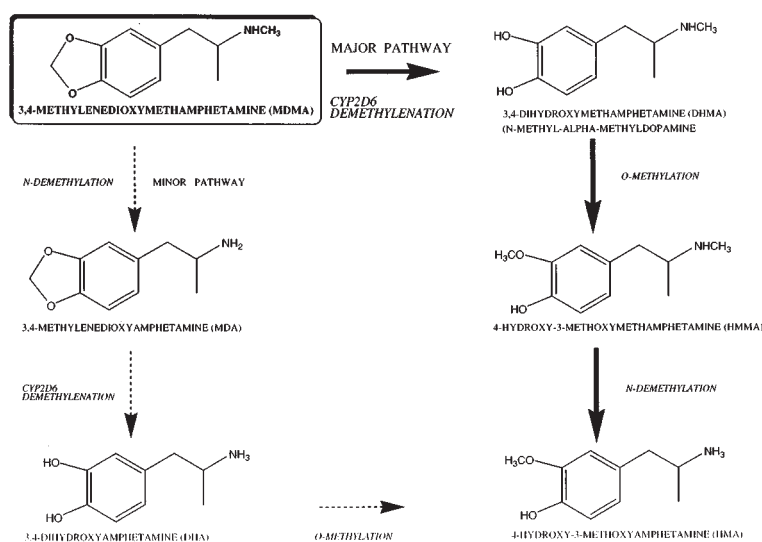

Figure 3. Mechanism of MDMA elimination. The parent compound MDMA and its metabolites are excreted in the urine to varying degrees (see text). Also, MDMA may be metabolized by ring hydroxylation and demethylenation to potential serotonergic neurotoxins.

concentration (C_{max}) after oral ingestion appears to be dose dependent. A C_{max} of 105.6 ng/ml was reported in a single subject who took a 50-mg dose,[16] whereas a C_{max} of 330 ng/ml was found in another subject who took MDMA 135 mg.[18] In a group of eight subjects, the C_{max} values after ingestion of MDMA 75 mg and 125 mg were 126.5 and 226.3 ng/ml, respectively,[14] whereas in another group of eight subjects, C_{max} values of 130.9 ng/ml and 236.4 ng/ml were obtained after ingestion of MDMA 75 mg and 125 mg, respectively.[17] In these studies, the C_{max} exhibits a slightly greater-than-expected increase compared with the increase in dose. According to these observations, after the usual recreational dose of 100–150 mg, the C_{max} should be 200–300 ng/ml. The area under the concentration-time curve (AUC) data from these studies also suggest nonlinearity. The AUC measured over 24 hours after ingestion of a 125-mg dose (2235.9 µg/L•hr) is more than twice the AUC after ingestion of a 75-mg dose (995.4 µg/L•hr).[14] Nonlinearity is further supported by other evidence, in which the dose ratio of MDMA was 1:3 (50 mg and 150 mg), whereas the AUC ratio over 24 hours after ingestion was greater than 1:10. The authors suggested that the nonrenal clearance of MDMA is dose dependent (i.e., HMMA, one of the many metabolites of MDMA metabolism [Figure 3], was the major product in plasma at lower doses, whereas MDMA was the predominant product at higher doses). This resulted in a disproportionate increase in plasma AUC and an increase in the proportion of MDMA excreted in the urine as the dose increased. It is possible that demethylenation may be inhibited as MDMA accumulates or one of the MDMA metabolites may inhibit cytochrome P450 (CYP) 2D6, which is responsible for a substantial proportion of MDMA nonrenal clearance. Alternatively, there might be an increase in the fraction of drug bioavailable as the dose increases.[15] Unfortunately, to our knowledge, the oral bioavailability of MDMA has not been determined in humans.

Primary Metabolism

The primary metabolic pathways for MDMA have been elucidated, with a number of metabolites having been identified in both animals and humans (Figure 3). The main metabolic pathway appears to be demethylenation to the catechol metabolite 3,4-dihydroxymethamphetamine (DHMA; also called *N*-methyl-α-methyldopamine).[19] The metabolite DHMA is the major metabolite of MDMA in rat liver[19, 20] and in rat brain microsomes.[21] Microsomes from yeast expressing human CYP2D6 demethylenate MDMA to the metabolite DHMA.[22, 23]

Furthermore, using human liver microsomes, CYP2D6 is the primary isoenzyme responsible for the demethylenation of MDMA.[24] If CYP2D6 is the isoenzyme responsible for the majority of MDMA metabolism in humans, then poor metabolizers could be sensitive to the acute physiologic effects of MDMA, but less prone to any long-term toxic effects of MDMA arising from metabolites. However, case reports have indicated that fatal MDMA intoxications have occurred in patients who were shown to be CYP2D6 extensive metabolizers,[25] and it also has been shown in vivo that in the absence of functional CYP2D6 a considerable amount of metabolism of MDMA analogs occurs by demethylenation.[24] It may be that more than one metabolic pathway can lead to an MDMA-induced toxic reaction.

Secondary Metabolism

A second pathway of MDMA metabolism is *N*-demethylation to MDA, which appears to be a minor metabolite of MDMA[14] and is an abused drug in its own right. Concentrations of MDA in plasma range from 3–5% of those corresponding to MDMA.[14] When formed from MDMA, the MDA formation rate constant is approximately 0.75/hour and the half-life is 16–28 hours, depending on the dose of MDMA given. The C_{max} for MDA occurs at 5–7 hours, and, on the basis of plasma AUC comparisons of MDMA and MDA, 8–9% of MDMA is converted to MDA, which may be further metabolized before elimination. The urinary recovery of unchanged MDA accounts for approximately 1% of the dose of MDMA.[17] It is unlikely that significant accumulation of MDA would occur after a single dose of MDMA. Given the prolonged half-life of MDA, however, it could accumulate in an individual taking MDMA 3 or more times/week.

Toxic Metabolites

It has been hypothesized that some of the neurotoxic actions of MDMA may result from quinones formed from the metabolism of DHMA, which can combine with glutathione and other thiol compounds.[19, 22] A 6-hydroxy-dopamine analog is formed by the aromatic hydroxylation

and demethylenation of MDMA that also could be neurotoxic.[22, 26] Catecholamines formed from MDMA, such as DHMA, are highly polar compounds that cannot cross the blood-brain barrier. However, these highly polar compounds have been detected in the brain after peripheral administration of MDMA,[27] indicating that some MDMA metabolism may occur in the brain.

Drug Interactions

There is a single report, to our knowledge, of a possible drug interaction involving MDMA and ritonavir.[28] A patient receiving ritonavir for the treatment of human immunodeficiency virus ingested MDMA in an estimated dose of 180 mg. The resultant blood MDMA level was 4.56 µg/ml, which is much higher than would be expected from this dose of MDMA. The authors suggest that the coadministration of MDMA and ritonavir (an inhibitor of CYP2D6) is the explanation for the unusually high levels of MDMA after a commonly used recreational dose.[28] Preincubation of MDMA with human liver microsomes and nicotinamide adenine dinucleotide phosphate (NADPH) resulted in significant inhibition of CYP2D6 activity. Therefore, MDMA may be a potent inhibitor of CYP2D6 in vivo, and the interaction of MDMA with this metabolic pathway may cause long-lasting drug interactions with other CYP2D6 substrates.[29] No clinical data are available in support of this theory.

Elimination

In humans, approximately 50–70%[15, 16] of the total MDMA dose is recovered in the urine as MDMA and other metabolites. Although MDMA is metabolized in the body, a large proportion is excreted unchanged in the urine. A report based on one patient indicated that after a single oral ingestion of MDMA 50 mg, 32.52 mg (65%) of unchanged drug was excreted in the urine over 72 hours.[16] In another study,[15] urine collection showed an increase in the amount of unchanged MDMA excreted by a factor of 20, from the 50-mg to the 150-mg dose, whereas the urinary recovery of 4-hydroxy-3-methoxymethamphetamine (HMMA), a metabolite of MDMA metabolism, remained unchanged. No significant changes in the urinary pH or creatinine clearance occurred during this study. Although the renal clearance remained fairly constant, the nonrenal clearance appeared to be dose dependent.[15]

Pharmacology

Receptor Biochemistry

The drug MDMA is a potent indirect monoaminergic agonist, which is thought to act by both increasing the release and inhibiting the reuptake of serotonin and, to a lesser extent, dopamine.[30] Serotonin is involved in the regulation of a variety of behavioral functions, including mood, anxiety, aggression, appetite, and sleep. Dopamine is the primary neurotransmitter of the "reward pathway" and is involved in motivational processes such as reward and reinforcement. Norepinephrine has important roles in the processes of attention and arousal. In vitro, MDMA causes release of serotonin, dopamine, and norepinephrine from synaptosomes[31, 32] and rat brain slices.[33, 34] In vivo, in freely moving rats, MDMA increases both serotonin and dopamine release in the caudate.[35] In a similar study, MDMA increased dopamine release in vivo in awake rats, resulting in region-, time-, and dose-dependent behavior.[36] In rat brain synaptosomes, MDMA inhibited the uptake of serotonin and norepinephrine and, to a lesser extent, dopamine.[37] The local administration of MDMA to the rat nucleus accumbens resulted in increases in the extracellular levels of both serotonin and dopamine in this region,[38] which is part of the reward pathway activated by other abused substances such as amphetamine and cocaine. These actions in the nucleus accumbens may account for the euphoric effects produced by MDMA.

In addition to causing the release of serotonin and inhibiting its reuptake, MDMA may have direct agonist effects on serotonin and dopamine receptors.[39] It has affinities for a broad range of neurotransmitter recognition sites[39, 40] and may act at both serotonin receptors, $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$.[41] Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and citalopram block the release of serotonin induced by MDMA, both in vitro[42, 43] and in vivo.[44, 45] They also reportedly block the subjective effects produced by MDMA in humans.[46] Consequently, the release of serotonin by MDMA may be dependent on the serotonin transporter. Different potencies for the neurotransmitter systems are shown by MDMA than by either amphetamines or the hallucinogens. Owing to its individual biochemical profile and the subjective effects it produces in humans, MDMA has been called an entactogen, which means, "producing a touching within."[13]

Abuse Liability and Psychomotor Performance

In controlled studies, MDMA produced marked feelings of euphoria and well-being[47, 48] and possessed amphetamine-like properties.[47] Indexes of positive psychologic states have been shown to increase with increasing MDMA dosage.[49] Subjective effects peak between 90 minutes and 2 hours after ingestion of MDMA and return to baseline approximately 4 hours after ingestion.[47] The drug MDMA produces mild changes in perceptions but does not commonly cause hallucinations or psychotic episodes.[47] It also produces moderate derealization and depersonalization, as well as anxiety without marked increases in psychomotor drive.[48]

Cardiovascular Effects

Ingestion of MDMA 75 and 125 mg causes an increase in blood pressure and heart rate, which occurs maximally at 90 minutes and 60 minutes, respectively.[17] Marked increases in blood pressure and heart rate have been seen after doses of MDMA 0.25–1.0 mg/kg[49] and 1.7 mg/kg, respectively.[48] In the latter investigation, peak increases in blood pressure occurred 2 hours after drug administration, and 12 of the 13 subjects had a peak blood pressure of 160/100 mm Hg, whereas blood pressure in the last patient peaked at 240/145 mm Hg.[48]

Neuroendocrine Effects

Plasma cortisol levels are significantly increased after ingesting MDMA at both 75 and 125 mg, and the 125-mg dose causes significant elevations in prolactin levels as well. The increases in cortisol and prolactin levels reach a peak at 2 hours after MDMA administration.[17] Other findings state that adrenocorticotropic hormone (ACTH) and prolactin concentrations are increased after the oral administration of MDMA 0.75–1.0 mg/kg[49] and that increases in serotonergic function increase both cortisol and prolactin levels. For example, fenfluramine, a drug that causes serotonin release, produces dose-related increases in the concentrations of both cortisol and prolactin.[50] In addition to cortisol and prolactin, plasma vasopressin (arginine vasopressin [AVP]) is significantly elevated 1–2 hours after MDMA administration, which may be accompanied by a small decrease in serum sodium levels and unchanged cortisol levels. Therefore, the slight hyponatremic effect could be related to the ability of MDMA to release AVP rather than a stress response, as elevated AVP levels may be accompanied by unchanged cortisol levels.[51] However, similar doses caused significant elevations in ACTH in a study by a different group of researchers.[49]

Ocular Effects

Ingestion of MDMA 75 and 125 mg produces significant mydriasis, with a maximal change in pupillary diameter occurring 1–2 hours after drug administration. Furthermore, MDMA 125 mg produces significant esophoria (tendency for the eyes to turn inward).[47]

Compound Lethality

The lethality of a compound (LD_{50}) is the dose of a drug that will kill 50% of the animals receiving that dose. Work done by the U.S. Army in 1953–1954 compared the 24-hour LD_{50} among five different animals (mice, rats, guinea pigs, dogs, and monkeys). Of the five known human hallucinogens that were tested, MDMA was the second most toxic agent.[52] The LD_{50} was 49 mg/kg in rats, 14 mg/kg in dogs, and 22 mg/kg in rhesus monkeys. It is difficult to extrapolate these data to humans because the animal data were obtained after intravenous or intraperitoneal administration, and MDMA is taken orally (its oral bioavailability in humans is unknown). However, these findings indicate that MDMA causes a significant dose-dependent toxic reaction and death in many animals.

Preclinical Neurotoxic Reactions

In animals, extensive data describe MDMA-induced neurotoxic effects to the serotonergic system.[53] Dose-related reductions in brain levels of both serotonin and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are caused by MDMA in the rat,[54–56] guinea pig,[56] and monkey.[57–59] The activity of tryptophan hydroxylase, which is the rate-limiting enzyme in the synthesis of serotonin, is decreased after MDMA administration.[55, 60, 61] Reductions in the density of serotonin uptake sites have been noted.[56, 62, 63]

Furthermore, immunocytochemical studies, which provide visualization of the serotonergic axons, have shown neurodegenerative changes including swollen, fragmented serotonin axons, with the fine serotonin axon terminals being especially vulnerable to the toxic effects of MDMA.[64–66] One study found a marked reduction in the number and density of serotonin-

immunoreactive axons throughout the cerebral cortex in monkeys who also displayed reductions in brain concentrations of serotonin and 5-HIAA. This is important as it provides some evidence that reductions in serotonin and 5-HIAA may be directly associated with morphologic findings of damage to serotonergic axons.[59]

In one study that used positron emission tomography (PET) in the nonhuman primate,[67] a substantial loss of serotonin transporters was found in the central nervous system (CNS) after MDMA treatment. Reasonably good agreement was noted between the PET data and reductions in serotonin, 5-HIAA, and serotonin transporter density, measured neurochemically in postmortem brain tissue 3 weeks after the last PET study was performed.[67] The neurotoxic effects of MDMA on the serotonergic system of the monkey may be long-lasting and still evident from 18 months[68] to 7 years[69] after the administration of MDMA. There is evidence of some regrowth of the axons, but it may be abnormal and incomplete,[69] with some reorganization of ascending serotonergic projections.[70]

Clinical Neurotoxic Reactions

In addition to the extensive animal data providing evidence for serotonergic neurotoxic effects, there is evidence of possible neurotoxic reactions in human users of MDMA. The serotonergic neurotoxic evidence can be classified into three domains: neurobiologic (i.e., neuroendocrine and brain imaging), psychologic and somatic, and psychiatric.

Neurobiologic Domain

Studies have shown dose-dependent decreases in the concentrations of the serotonin metabolite 5-HIAA in the cerebrospinal fluid of individuals taking MDMA.[71, 72] Another technique to assess serotonergic damage in humans is to administer serotonergic agonists and examine neuro-endocrine responses. Various serotonergic agonists such as L-tryptophan, *m*-chlorophenyl-piperazine (*m*-CPP), and D-fenfluramine (D-fen) have been used to assess the prolactin response.[71, 73–75] Two studies evaluated the prolactin response after the administration of L-tryptophan, a serotonin precursor known to increase serum prolactin concentration. One investigation found a nonsignificant trend toward a blunted prolactin response in those who took MDMA, as compared with control subjects,[74] whereas the other study did not find significant differences in the prolactin response to L-tryptophan in those who last took MDMA 18 weeks–2 years before the beginning of the study, in comparison with the control group.[71] With use of *m*-CPP, 25 individuals who took MDMA were less sensitive to the anxiogenic effects of *m*-CPP compared with 25 controls, and the men who took MDMA had a diminished prolactin and cortisol response to *m*-CPP.[73] A blunted neuroendocrine response also was found with the serotonin releaser, D-fen, in 15 individuals abstaining from taking MDMA in comparison with control subjects. Prolactin response to D-fen was significantly reduced in individuals taking MDMA at both 3 weeks and 12 months after last MDMA use. In contrast, cortisol response to D-fen was reduced at 3 weeks but had recovered by 12 months in those taking MDMA. The authors suggest that the cortisol response at 12 months may indicate either partial recovery to the neurotoxic actions of MDMA or selective neurotoxic actions of MDMA on different serotonin receptors and pathways.[75]

A study using PET with [^{11}C] McN5652 (a radioligand selective for the 5-HT transporter) found that individuals who abstained from taking MDMA (at least 3 weeks since last use) showed significant reductions in 5-HT transporter binding compared with that of control subjects who had never taken MDMA. This was attributed to a reduced density of serotonin uptake sites. Furthermore, reduced binding was positively correlated with the amount of previous MDMA use.[76] Another study using PET imaging found a reduction in the brain glucose metabolism in individuals taking MDMA. The PET scans were obtained in seven individuals who had taken MDMA from 1–39 months and seven age-matched control subjects with no history of illicit drug use. Glucose uptake was lowered in the hippocampus, amygdala, and cingulate bilaterally in the MDMA group.[77] A decrease in the density of serotonin uptake sites has been found with use of other brain imaging techniques as well. Ten men who had taken MDMA long term were compared with 10 individuals who had not taken MDMA, matched for the consumption of other drugs. Each subject was examined with single photon emission computed tomography (SPECT) with a 5-HT transporter ligand. The MDMA group showed a reduction in cortical serotonin transporter binding.[78] In another SPECT study,[79] cortical 5-HT$_{2A}$ receptor densities in the occipital cortex were increased in five individuals who abstained from taking MDMA (at least 2 months

since last use) compared with nine healthy control subjects. The authors suggested an upregulation of postsynaptic 5-HT$_{2A}$ receptors due to serotonin depletion.[80] Only the subjects with apparent high densities of postsynaptic 5-HT$_2$ receptors in the occipital area showed detectable decreases in memory function.

Psychologic and Somatic Domain

Memory decrements are more pronounced in those taking MDMA regularly (10 or more occasions) than in those just beginning (9 or fewer occasions).[81] In addition, both those just beginning to take MDMA and those regularly taking MDMA exhibit significantly lower immediate word recall and delayed word recall compared with control subjects.[81] Significant memory impairment has been reported in those who take only MDMA compared with those who take many drugs but who had never taken MDMA, suggesting that the memory impairments are caused primarily by the MDMA rather than the various other drugs consumed by these individuals.[82]

Psychiatric Domain

Two studies suggest a depression of mood in the days after taking MDMA.[83, 84] In one study, those who took MDMA scored in the mild-to-moderate clinical range for depression on the Beck Depression Inventory.[83] In the other study, visual analog mood scales were used to assess 16 mood states. Those taking MDMA reported feeling significantly more depressed, abnormal, unsociable, unpleasant, and less good tempered 2 days after the ingestion of MDMA than did the control subjects.[84]

Subjective Effects

There are very few controlled studies evaluating MDMA in humans, mostly because MDMA is a schedule I drug in the U.S. and therefore is difficult to obtain for study purposes. Also, the safety of human research subjects who take MDMA cannot be guaranteed. The information that is available, with the exception of a few small controlled trials, comes from information collected retrospectively from people who have taken MDMA outside of a controlled research environment. The high rate of concurrent multisubstance abuse, the uncontrolled content of active MDMA in any given pill, as well as the historical accuracy of information reported by the person who takes recreational drugs lend some uncertainty to the conclusions drawn from these reports. According to these reports, MDMA is ingested orally in a dose of approximately 100–150 mg, with an onset of effects usually around 30 minutes, which is described as an amphetamine-like rush.

The earliest reports of MDMA effects were primarily anecdotal. Although users stressed the positive feelings associated with MDMA, negative effects were also reported. Some of the positive effects include a sense of "closeness" toward others, heightened alertness, increased ability to interact with others, decreased defensiveness, decreased fear, decreased sense of alienation from others, increased awareness of emotions, decreased aggression, euphoria, increased energy, and sexual arousal.[85–87] The negative effects include tachycardia, trismus (jaw clenching), bruxism (teeth grinding), decreased appetite, lower back pain, and decreased desire to perform mental or physical activities.[85–87] Aftereffects ("hangover") most often described by those who have taken MDMA include lethargy, anorexia, decreased motivation, sleepiness, depressed mood, and fatigue.[85, 86] Of interest, many of the subjects reported that with regular MDMA usage ($\geq$ six separate doses), the positive effects lessened while the negative effects increased.[85] Consequently, many individuals space their usage.[5]

Two early reports on the effects of MDMA were prospective studies, involving 50 patients, that were completed before the government restriction of MDMA to schedule 1.[5, 88] In both studies, patients provided positive and negative descriptions of the experience. The positive experiences included a perception of enhanced communication, increased feelings of intimacy, cognitive enhancement, euphoria, increased self-confidence, a heightened sense of sensual awareness (with some subjects reporting increased sexual arousal and an increase in physical and emotional energy). Adverse effects that were described by all of the subjects include those similar to amphetamines such as tachycardia, dry mouth, palpitations, bruxism, trismus, nausea, anorexia, headaches, eyelid twitches, and insomnia. Unlike with amphetamines, there appeared to be no "crash" or depression up to 24 hours after ingestion.[5, 88]

Pharmacologic Pretreatment

Three studies have investigated the feasibility

of giving pharmacologic agents to block or attenuate MDMA effects. Citalopram is a serotonin reuptake inhibitor that should block the uptake of MDMA into the neuronal terminal. Pretreatment with intravenous administration of citalopram 40 mg attenuated the acute psychologic effects of MDMA 1.5 mg/kg in healthy volunteers. Some of the effects attenuated by citalopram included MDMA-induced increases in positive mood, derealization and depersonalization phenomena, and the loss of thought and body control. The attenuation of the psychologic effects induced by MDMA as a result of citalopram pretreatment suggests that MDMA actions are at least partly dependent on a carrier-mediated release of serotonin.[46] The same investigators performed another study designed to test the effect of haloperidol 1.4 mg intravenously (dopamine D_2 antagonist) on the psychologic and physiologic responses to MDMA. Haloperidol treatment before MDMA administration reduced the positive mood and euphoria induced by MDMA, but not the cardiovascular effects. The authors suggested that there may be a role for dopamine in the euphoria-producing effects of MDMA and that serotonin or norepinephrine may mediate the physiologic effects.[89] The final study, also by this group, used ketanserin (5-HT_2 antagonist) to examine the role of 5-HT_2 receptors on MDMA's actions. Ketanserin 50 mg was given orally to healthy volunteers before the oral administration of MDMA 1.5 mg/kg. Ketanserin attenuated perceptual changes and emotional excitation induced by MDMA but had little effect on MDMA-induced positive mood, well-being, and extroversion. Furthermore, body temperature was lower after the MDMA-ketanserin combination than with MDMA alone.[90]

Adverse Effects and Acute Toxic Reactions

Acute Syndrome

One of the dangers of MDMA is the apparent lack of relationship between alleged dose and severity of acute toxic reaction.[91, 92] Although one person attempted suicide after reportedly taking 42 pills of Ecstasy with a resultant plasma MDMA level of 7.72 µg/ml and displayed only hypertension and tachycardia,[93] others have died with much lower plasma MDMA levels ranging from 0.05–1.26 µg/ml.[91] Furthermore, serum MDMA levels do not correlate well with clinical symptoms.[94] Acute toxic reactions usually develop within 15 minutes–6 hours after the ingestion of MDMA.[91] Symptoms of an acute MDMA toxic reaction include agitation, tachycardia, hypertension, dilated pupils, trismus, and sweating, whereas the more severe cases may be characterized by hyperthermia, disseminated intravascular coagulation (DIC), rhabdomyolysis, and acute renal failure.[93] In more severe cases, elevated creatine kinase levels are often present,[95–98] with levels as high as 122,341–555,000 IU/L being reported.[97, 98] Other frequently reported acute adverse effects occurring after the ingestion of MDMA include lack of appetite, difficulty concentrating, impaired balance, and restless legs.[48]

The toxic effects of MDMA were divided into three categories in one investigation to help distinguish acute toxic reactions from long-term residual effects. These categories were acute reactions at therapeutic doses, overdose reactions, and residual effects.[11] At moderate doses (85–100 mg), acute effects included transient nausea occurring about 30 minutes after ingestion and lasting about 30 minutes, increases in both blood pressure and heart rate, and symptoms related to increased muscle tonicity, such as jaw clenching and teeth grinding. In those subjects who were particularly sensitive to MDMA, higher doses ($\geq$ 100 mg) caused numbness and tingling in the extremities, luminescence of objects, increased sensitivity to cold, increased color acuity, and vomiting. Residual effects occurring from 2 hours–2 weeks after ingestion included exhaustion, fatigue, and nausea. Doses higher than 200 mg result in a classic toxic psychosis with symptoms of paranoia and auditory and visual hallucinations.

Hyperthermia

Hyperthermia (temperature > 40°C) is the most common adverse effect associated with a severe acute toxic reaction to MDMA. The increase in body temperature is probably due to serotonergic actions of MDMA in the thermoregulatory center in the hypothalamus[99] because animal studies have shown that the hyperthermia caused by compounds such as MDMA is mediated by actions at serotonin receptors in the CNS.[100] Hyperthermia also may be caused by excessive heat production due to sustained muscle hyperactivity, increased metabolic rate, rigidity, and seizures.[101] Hyperthermia is believed to be the beginning of the cascade leading to DIC, rhabdomyolysis, myoglobinuria, and acute renal failure. However, the exact pathophysiology

of this cascade after MDMA intoxication has not been fully elucidated.

Cardiovascular Effects

Similar to cocaine and amphetamine, MDMA may cause sympathetic stimulation and increase myocardial oxygen demand, leading to varying degrees of tachycardia, vasoconstriction, changes in blood pressure, and arrhythmias. In severe cases, vasospasm leading to acute myocardial infarction and irreversible dilated cardiomyopathy may occur.[102] Abnormal electrocardiographic changes that show widespread ST segment elevation indicating acute myocardial infarction have been seen with laboratory evidence in the urine of MDMA users.[103] During postmortem evaluations, necrosis of the heart (contraction band necrosis or widespread foci of necrosis) has been seen[104] and may be due to excessive catecholamines.[102] These findings do not necessarily establish a cause and effect relationship, since other substances or circumstances may have contributed.

Cerebrovascular Effects

"Designer drugs" such as MDMA are associated with intracerebral hemorrhage, often in conjunction with an underlying vascular malformation.[105] Other investigators have postulated that those who take MDMA are at an increased risk for cerebrovascular accidents due to the altered 5-HT system because postsynaptic 5-HT receptors are involved in the regulation of the brain microvasculature.[106] Other cerebrovascular adverse effects that have been associated with MDMA include subarachnoid hemorrhage, cerebral infarction, and cerebral venous sinus thrombosis.[107] Magnetic resonance imaging revealed a left basal ganglia hematoma after the ingestion of MDMA in a patient with no apparent cardiovascular risk factors.[108]

Neuroendocrine Effects

Numerous cases of hyponatremia have been associated with MDMA use, often in combination with seizures, catatonic stupor, and incontinence of urine.[109-114] It is possible that hyponatremia is a direct result of MDMA neuroendocrine effects or from massive water intake leading to dilutional hyponatremia. Since many users take MDMA during all-night dancing parties, large amounts of fluid are ingested, both as a natural consequence of physical activity and because of MDMA-induced hyperthermia. Hyponatremia

may be due to the syndrome of inappropriate antidiuretic hormone,[111, 112] because MDMA causes the release of AVP.[51] In addition, the extreme dehydration caused by sweating and/or vomiting associated with MDMA use combined with massive water intake could lead to hyponatremia.[115] In one report of a fatality due to MDMA, hyponatremia leading to cerebral edema appeared to be the main cause of death.[116] Contamination of the MDMA tablets with other substances has been postulated as the cause of hyponatremia associated with MDMA use.[110] Postcards have been distributed in some clubs and bars advising patrons who take MDMA that they should drink about a pint of water an hour and eat or drink something salty, such as a sports drink, to replace lost sodium.[117]

Hepatotoxicity

Hepatotoxic effects have been associated with MDMA.[91, 93, 104, 118, 119] In one case series of seven fatalities associated with the use of ring-substituted amphetamines, including MDMA, necrosis of the liver was seen in all cases.[104] Two of the most likely mechanisms for causing a hepatotoxic reaction are immune-mediated reaction or injury secondary to hyperthermia.[119] Hepatotoxic reaction arising from drug impurities or MDMA metabolites is also possible. Liver transplantation has been required because of hepatic damage associated with MDMA use.[118]

Psychopathology

A psychotic syndrome characterized by delusions, usually of the persecutory type, may be caused by MDMA. Other nonpsychotic conditions include visual phenomena, depersonalization and derealization, panic attacks, and depression. Persons who display such symptoms may have at least one first-degree relative with a history of psychiatric illness and be predisposed to have psychiatric symptoms.[120] Anxiety attacks, persistent insomnia, rage reactions, and psychosis (especially at higher doses) have occurred after MDMA use, although in most cases the premorbid psychiatric status of these patients was not known.[11] Compared with control subjects who do not take MDMA, those who frequently take MDMA have significantly higher scores on scales used to assess somatization, obsessionality, anxiety, hostility, phobic-anxiety, paranoid ideation, psychoticism, poor appetite, and restless or disturbed sleep. They also showed greater impulsiveness.[121]

Death

Conditions commonly contributing to death due to MDMA include dehydration, hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, acute renal failure, tachycardia and other cardiac arrhythmias, and convulsions.[93, 122] In other fatal cases involving MDMA, necrosis of the liver and heart were found at autopsy as were various injuries to the brain such as focal hemorrhages and severe cerebral edema consistent with water intoxication.[104]

Treatment

The diagnosis of acute toxic reaction to MDMA is made based on the history and clinical features of intoxication. Initial examination should include blood chemistry analysis, complete blood count, liver function tests, cardiac enzyme and creatine kinase measurements, and a urine toxicology screen. Quantitative serum levels do not correlate well with severity of symptoms and are not generally available.[94] A complete history and physical examination should be performed, and the patient should be assessed for hypertensive crisis or life-threatening arrhythmias. An electrocardiogram for chest pain or a computed tomographic (CT) scan of the brain for persistent mental status changes should be obtained.[123, 124] Amphetamines and related drugs (i.e., methamphetamine, MDMA) can be detected in the urine, but there is a high degree of cross-reactivity between amphetamine derivatives and adrenergic amines. Therefore, confirmatory testing usually is required.[94]

Resuscitation

There is no antidote for MDMA intoxication, and in general, recommended treatment of MDMA overdose is similar to the treatment of amphetamine or methamphetamine overdose. The first priority should be maintaining the airway, breathing, and circulation.[123, 124] Treatment will then be aimed at reducing various symptoms, including hyperthermia, agitation, cardiovascular and cerebrovascular incidents, neuroendocrine abnormalities, and neurologic problems.

Decontamination and Elimination

Decontamination of the gastrointestinal tract with lavage, activated charcoal, and cathartic techniques has been used. Induction of emesis is not appropriate because of the potential for CNS depression and seizures.[94] Because approximately 50–70%[15, 16] of MDMA is recovered in the urine, renal failure would significantly decrease the elimination of MDMA from the body, so maintaining adequate hydration is essential. Because MDMA is a weak base and a significant proportion is eliminated in the urine, acidifying the urine is likely to be an effective means of increasing renal elimination, but it may precipitate acute renal failure in patients with myoglobinuria and is not recommended.[94]

Hyperthermia

Although fatalities may be due to many different causes, hyperthermia is probably the single most important condition to treat because it may lead to further severe complications, such as rhabdomyolysis and DIC.[125] Mortality has been correlated to both the extent of hyperthermia and the duration, and active cooling measures are indicated in cases of MDMA-induced hyperthermia (see Supportive Care section).[99] It is important to control agitation to limit further heat production.[126] Neuromuscular blockers, such as pancuronium, have been given, but their use requires ventilation and endotracheal intubation.[94]

Dantrolene sodium, a drug that is indicated for the treatment of malignant hyperthermia and that inhibits the release of calcium from the sarcoplasmic reticulum, is recommended by many clinicians to treat hyperthermia secondary to MDMA use.[93, 95, 96, 99, 127–132] Speculative hypotheses notwithstanding, the use of dantrolene for the treatment of MDMA intoxication remains controversial. The efficacy of dantrolene in treating this condition has been questioned, as some patients have improved with supportive care only[133] and some clinicians assert that there is insufficient evidence to recommend dantrolene in cases of MDMA acute toxic reaction.[134–136]

To determine if MDMA caused an increase of calcium within the muscle, which would suggest that an inhibitor of calcium release in skeletal muscle, such as dantrolene, might be efficacious in treating MDMA intoxication, in vitro experiments using human muscle subjected to halothane and caffeine contracture tests were performed (used to test for susceptibility to malignant hyperthermia). It was hypothesized that if MDMA raised the calcium levels within the muscle, then dantrolene should be effective in treating MDMA acute toxic reaction, since it is

effective in treating malignant hyperthermia. The results indicated that the hyperthermia from MDMA intoxication is associated with an elevation in the myoplasmic calcium concentrations, similar to that seen in malignant hyperthermia, which suggests that dantrolene might be a helpful agent in treating MDMA-induced hyperthermia.[137] It has been argued that MDMA-induced hyperthermia results from augmentation of central serotonin, and since dantrolene has no central activity (inhibits calcium peripherally in the skeletal muscle), it should not be effective. Therefore, a non-depolarizing neuromuscular blocker may be just as effective in treating MDMA acute toxic reaction.[92] As stated previously, however, ventilation and intubation may be required.[94] Although, there are not sufficient data in humans to confirm that the hyperpyrexia associated with MDMA is a centrally mediated effect, the use of dantrolene should not be precluded because it does appear to reduce pyrexia secondary to exertional heatstroke.[138] It is hypothesized that the unpredictable hyperthermia associated with MDMA may result from an underlying metabolic myopathy, similar to that seen with exertional heatstroke, and associated with a skeletal muscle abnormality similar to malignant hyperthermia.[139]

Cardiovascular Treatment

Tachycardia without hemodynamic compromise does not need to be treated. Sedative dosages of benzodiazepines may be helpful by reducing blood pressure and heart rate, which may reduce myocardial oxygen demand.[140] β-Blockers should be avoided when treating stimulant-induced hypertension because this may result in unopposed α-adrenergic vasoconstriction. Hypertension can be treated with an α-blocker such as phentolamine or with a direct-acting vasodilator such as nitroprusside.[94, 123] Another option is the use of a β-blocker concurrently with phentolamine.[126] Myocardial ischemia caused by stimulants should be treated with oxygen, aspirin, and benzodiazepines. If these options do not reverse the ischemia, then vasodilators or phentolamine should be given.[102] Arterial spasm may be treated with sublingual or intravenous nitroglycerin.[94] Arrhythmias should be treated according to advanced cardiac life support guidelines.[123, 126] Thrombolytic agents have been given safely to patients with stimulant-induced myocardial infarction.[140]

Cerebrovascular Treatment

Patients with altered mental status, lethargy, or obtundation should undergo CT of the brain because of the risk for intracranial hemorrhage and infarct.[123] In patients with nontraumatic intracranial hemorrhage, arteriography should be performed and a thorough history of the use of illicit substances should be evaluated.[105]

Neurologic Treatment

Patients who are agitated may require treatment with a benzodiazepine, such as diazepam, lorazepam, or midazolam.[94, 123] It is very important to control agitation as this may decrease further heat production.[126] Some of the conditions associated with MDMA acute toxic reaction (mental status changes, hyperthermia, autonomic instability, increased motor restlessness, myoclonus, elevated creatine kinase level, diaphoresis, and death due to renal failure) are similar to the findings in both neuroleptic malignant syndrome and serotonin syndrome.[91, 127] Pharmacologic treatments effective in these syndromes are recommended by some clinicians,[127] including methysergide maleate (nonspecific serotonin antagonist),[141] β-blockers (5-HT$_{1A}$ antagonists),[142] or bromocriptine (a dopamine agonist).[143] However, none of these drugs has been prospectively evaluated for the treatment of MDMA acute toxic reaction.

Caution may be warranted in using antipsychotic agents when treating MDMA intoxication. Antipsychotics decrease the seizure threshold, and blocking dopamine receptors may affect the thermoregulatory system leading to hyperthermia or exacerbation of existing hyperthermia. In addition, SSRIs may further increase serotonergic transmission by blocking the reuptake of synaptic serotonin, possibly raising the risk for development of the serotonin syndrome or aggravating already existing hyperthermia.[144]

Hepatotoxicity

Owing to the risk for hepatotoxicity, it would be prudent to monitor liver function in persons suspected of taking MDMA,[119] and any person with unexplained jaundice or hepatomegaly should be screened for a history of MDMA use.[93] Treatment will be primarily supportive (see Supportive Care section). If severe hepatic necrosis has occurred, transplantation may be the only option[101] and has been performed successfully in patients with acute liver failure due to MDMA use.[118]

Supportive Care

Supportive therapy includes rehydration with intravenous fluids and lowering the temperature of the patient with use of cooling blankets or ice baths.[143] In some cases, lowering the body temperature may require infusion of cold intravenous fluids or peritoneal lavage with cool dialysate.[92] Crystalloids may be given to help treat both the profuse sweating that often accompanies MDMA acute toxic reaction as well as prophylaxis against acute renal failure secondary to rhabdomyolysis and myoglobinuria.[95] Furthermore, judicious fluid support may help with symptoms of hepatotoxicity as it may increase liver blood flow and prevent further hepatic damage.[119]

Summary

The use of MDMA is on the rise, especially over the last couple of years. Although it causes pleasant sensations, MDMA can be a very dangerous drug when used recreationally. Particularly severe adverse reactions include hyperthermia, rhabdomyolysis, DIC, renal failure, cardiac complications, intracranial hemorrhage, and hepatotoxicity. The long-term neurotoxic effects, particularly in the serotonergic system, of MDMA have not been fully elucidated. It is imperative that clinicians be familiar with the symptoms and treatment options for acute toxic reaction to MDMA.

GHB

History

γ-Hydroxybutyric acid (GHB) is a CNS depressant that has become increasingly popular as a drug of abuse over the last 10 years. Many names are used for GHB such as sodium oxybate, sodium oxybutyrate, γ-hydroxybutyrate sodium, γ-OH, 4-hydroxy butyrate, and γ-hydrate, as well as others. Names used on the street include Liquid Ecstasy, Liquid X, Liquid E, Georgia Home Boy, Grievous Bodily Harm, G-Riffick, Soap, Scoop, Salty Water, Somatomax, and Organic Quaalude. In the 1960s, a French researcher synthesized GHB in an attempt to create a γ-aminobutyric acid (GABA) analog that would, unlike GABA, cross the blood-brain barrier.[145] Somewhat simultaneously, in 1963, GHB was found to be a naturally occurring metabolite in the human brain.[146] The first accepted medical application of GHB was for intravenous induction of anesthesia.[145] However, its use was limited due to the high frequency of vomiting,[147] seizure-like activity in animals,[148, 149] and inability to produce analgesia.[150] In the 1970s, GHB was recommended for narcolepsy because it increases slow-wave sleep and consolidates sleep at night, therefore decreasing sleep during the day.[151] In the 1980s, GHB was commonly sold over-the-counter in health food stores where it was alleged to increase the effect of growth hormone.[152] In the late 1980s and early 1990s, GHB was advocated for the treatment of alcohol dependence[153] and opiate withdrawal.[154] During the same time period, GHB was illicitly advertised as a hypnotic to replace tryptophan, which had been removed from the market due to its connection with eosinophilia-myalgia syndrome.[155] Since 1990, an increasing number of cases of both abuse and toxic reaction has been noted, and in 1997 GHB was labeled a "date rape" drug by the press.[156] In March 2000, GHB became a schedule I controlled substance in the U.S.[157]

Availability

Most of the GHB available in the U.S. is manufactured clandestinely. Many Internet sites and books that describe the process of making GHB are available.[158] Commonly offered for sale on Internet sites, GHB kits provide the chemicals and recipes used to produce GHB.[159, 160] Currently, GHB is only legally available in the U.S. for the investigational treatment of narcolepsy. The drug is synthesized by using a combination of sodium hydroxide and γ-butyrolactone (GBL; another commonly abused drug). Because sodium hydroxide is very caustic, severe toxic reactions may result if GHB is manufactured improperly. The drug GHB is available as a powder or a colorless, odorless liquid with a salty or soapy taste. Its taste can easily be masked by adding it to flavored beverages. As GHB is colorless and odorless, and because small quantities are required to achieve a desired effect, GHB has been used as a date rape drug. The amnesia produced by GHB often makes victims unable to serve as valid witnesses.

Pharmacokinetics

Pharmacokinetic Parameters

The pharmacokinetics of GHB are nonlinear in humans over the therapeutic dosage range.[161–164] The drug is rapidly absorbed orally,[165] with an onset of action within 15 minutes.[166] In the rat,

oral bioavailability is 52–65%.[167] In humans, the free fraction of GHB in plasma has been shown to be 0.99, indicating a lack of significant plasma protein binding.[161] The half-life of GHB is 22–28 minutes after an oral dose of GHB 25 mg/kg;[161, 162] the half-life is slightly longer with higher doses. In one study, GHB exhibited a longer half-life of 53 minutes in patients with narcolepsy after dosages of GHB 3.0 g twice/night, administered 4 hours apart.[163] At lower doses of 25 mg/kg, the T_{max} of GHB is approximately 30 minutes. After higher doses of 50 mg/kg, the T_{max} occurs around 45 minutes.[161, 162] As the dose of GHB increases by a factor of four from 12.5 to 50 mg/kg, the AUC increases by a factor approaching seven. In addition, the C_{max} increases, but not to the degree expected in relation to the increase in AUC and the decrease in oral clearance. The oral clearance is halved from 14 to 7 ml/minute/kg when the dose is increased from 12.5 to 50 mg/kg, respectively.

Two suggested mechanisms for this nonlinearity include the saturation of one of the metabolic pathways of GHB or the capacity-limited absorption of GHB.[161] The capacity-limited absorption would explain the relatively small increase in C_{max} with increasing dose, relative to the decrease in oral clearance. It is possible that several mechanisms operate concurrently, explaining the pharmacokinetic profile of GHB. In one investigation,[162] four of the five subjects exhibiting linear kinetics had normal liver function test results, whereas all of the subjects who displayed nonlinear kinetics (capacity-limited elimination) had elevated values for some of their liver function tests. In the subjects displaying nonlinear kinetics, a doubling of the dose resulted in a dispropor-tionate 3-fold increase in the AUC from approximately 3500 to approximately 10,800 µg/ml/minute. The appearance of nonlinearity was found only in the patients who had abnormal liver function values. The authors suggest a relationship between liver function and saturation of the elimination pathway for GHB. In addition, when the dose was increased from 25 mg/kg to 50 mg/kg, there were proportional changes in C_{max}, accompanied by dispropor-tionate increases in AUC.

Metabolism and Synthesis

The biosynthetic pathway and metabolic degradation of GHB occurs in brain tissue by means of multiple cytosolic and mitochondrial enzymes. γ-Hydroxybutyrate is a natural product of GABA metabolism by way of the intermediate compound, succinic semialdehyde (SSA). The neurotransmitter GABA appears to be the major precursor for SSA, from which GHB is synthesized. In early investigations, it was shown that GABA underwent transamination to SSA,[168] that the enzymatic reduction of SSA to GHB occurred in mammalian brain in vitro,[169] and that [³H]GABA was converted to GHB in the rat brain in vivo.[170] The finding that GABA is a precursor of GHB was confirmed by other investigators.[171] The NADPH-dependent enzyme SSA reductase is responsible for the conversion of SSA to GHB (Figure 4).[171] γ-Hydroxybutyrate is oxidized into SSA by means of GHB dehydro-genase and GHB-oxoacid transhydrogenase.[172] The SSA is further metabolized to succinate, which then enters the Krebs cycle.[173]

Elimination

Less than 2% of GHB is eliminated unchanged in the urine.[162, 164] Owing to the short half-life, there is no accumulation of GHB with repeated dosing and GHB doses of up to 100 mg/kg are no longer detectable in the blood from 2–8 hours or in the urine after 8–12 hours.[162, 165] The variability of these findings may depend on the sensitivity of the assay used, or it may be due to interindividual variability. In summary, it has been suggested that regardless of the dose given, the elimination of GHB is so rapid, even in those with compromised liver function, that the drug is completely eliminated within 4–6 hours after ingestion.[162]

Pharmacology

Receptor Biochemistry

The exact mechanism of GHB action in the CNS has not been determined, but GHB is structurally related to GABA (Figure 4), which is a precursor in GHB formation.[170] Much debate exists regarding whether GHB has neuro-transmitter or neuromodulatory roles,[174–177] because GHB has high-affinity brain receptors and undergoes synthesis, release, uptake, and degradation within the CNS.[174, 175] The exact location of the biosynthetic pathway of GHB inside the cell (cytosol vs mitochondria) has not been fully established.[178] The neurotransmitter GABA is transaminated by GABA amino-transferase to form SSA, which is either further metabolized into succinic acid or reduced to

form GHB by the enzyme SSA reductase, a NADPH-dependent enzyme.[171, 173] The highest concentrations of GHB in the brain are found in the substantia nigra[179] and hypothalamus, whereas the highest turnover rate of GHB occurs in the hippocampus.[180] The uptake of GHB appears to be the highest in the striatum,[181, 182] and this uptake is dependent on a specific sodium-dependent active transport system for GHB.[181] In addition to being found in the CNS, GHB is found in the kidney, heart, skeletal muscle, and brown fat.[183]

γ-Hydroxybutyrate appears to have affinity for two receptor sites in the CNS. It binds to GHB receptors, which may be linked to cyclic guanosine 3′5′-monophosphate and inositol phosphate intracellular pathways[184, 185] and are most numerous in the hippocampus and cortex.[186] It also binds to $GABA_B$ receptors,[187, 188] but not to $GABA_A$ receptors.[189] The relevance of this remains unknown but suggests that some of the pharmacologic actions of GHB are mediated by the $GABA_B$ receptor.

The drug GHB alters dopaminergic activity, in some cases increasing and in others decreasing the amount of dopamine released.[178] The systemic administration of GHB to animals results in increased dopamine accumulation in the extrapyramidal system of the brain, which reaches its highest values 1–2 hours after injection, without parallel increases in serotonin or norepinephrine.[190] The administration of α-methyltyrosine, which blocks the activity of tyrosine hydroxylase, almost completely blocks the rise in brain dopamine induced by GHB, which occurred within 1 hour in control mice. Therefore, GHB mediates the accumulation of dopamine by increasing the activity of tyrosine hydroxylase.[191] In addition, GHB may inhibit the release of newly synthesized dopamine[192] and decrease the firing rate of dopaminergic neurons in the substantia nigra with maximal inhibition within 8 minutes.[179] The end result seems to be a tissue accumulation of dopamine in the brain,[175] which is supported by results of the short-term studies described above. Dopamine release in the
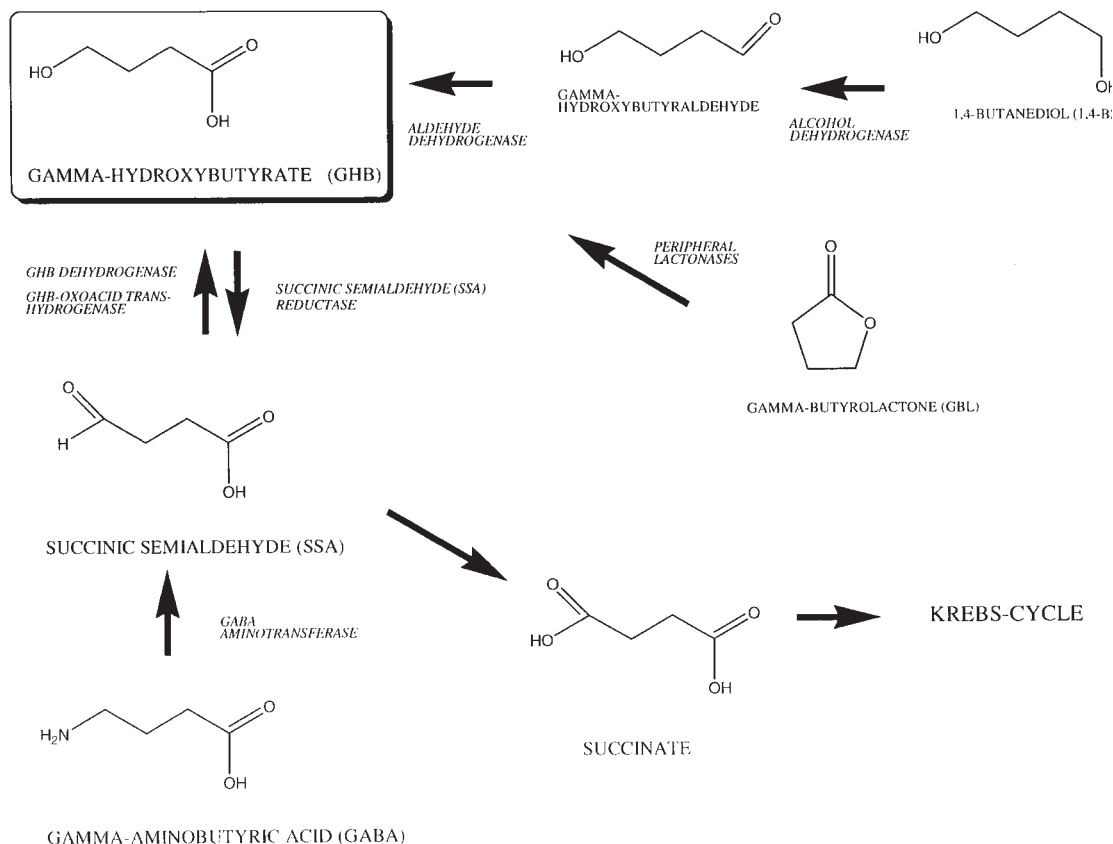

Figure 4. Mechanism of GHB elimination. γ-Butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are converted in the body to GHB.

striatum may be accompanied by the release of endogenous opioids.[193] The exact interactions between GHB and the opioid system are not fully understood, but the administration of naloxone or nalorphine, opioid receptor antagonists, blocks some of the effects of GHB.[193, 194]

Dose-Related Effects

The primary dose-related effects of GHB are related to CNS depression. At 10 mg/kg, GHB is capable of producing amnesia[195] and hypotonia of the skeletal muscles[196, 197] resulting from the depression of neurons in the spinal cord.[166] At 20–30 mg/kg, GHB promotes a normal sequence of rapid eye movement (REM) and non-REM (slow-wave) sleep, which lasts from 2–3 hours.[151, 198] At 40–50 mg/kg intravenously, GHB produces a state of somnolence, which appears within 5–15 minutes, and an oral dose of approximately the same amount will produce similar results.[166] Anesthesia is associated with doses of 50 mg/kg,[164, 166, 199] and doses higher than 50 mg/kg have been associated with profound coma,[199] as well as decreased cardiac output, respiratory depression, and seizures. These effects are more pronounced with the coingestion of CNS depressants, particularly ethanol.[155] Larger doses of 60–70 mg/kg produce a state of unarousable coma that lasts about 1–2 hours.[166] The investigators who initially discovered that GHB was a natural metabolite of the brain reported that GHB 100 mg/kg administered intravenously produced sleep that begins within 15 minutes of administration and lasts about 1.5–2 hours.[146]

Serum Concentrations

Oral ingestion of GHB 75–100 mg/kg in humans results in peak blood levels of approximately 90–100 µg/ml at 1–2 hours after ingestion.[165] Intravenous administration of GHB 50 and 165 mg/kg results in peak blood levels that reach 180 and 412 µg/ml, respectively. The mean blood GHB level at the commonly used dose of 100 mg/kg is 304 µg/ml.[164] When the blood GHB levels exceed 258 µg/ml, subjects fall into a state of deep sleep, characterized by nonresponse to various stimuli such as touch, pinprick, deep pressure, skin preparations, or vaginal examinations, although there is still reflex response to surgical incision. During this stage of deep sleep, blinking stops and the eyes remain central and fixed with small pupils. A moderate level of sleep is associated with blood GHB levels ranging from 155–258 µg/ml. This moderate stage of sleep is characterized by spontaneous blinking and responses to deep pressure. Blood GHB levels ranging from 52–155 µg/ml are associated with a light sleep characterized by spontaneous movements and occasional opening of the eyes. When the blood GHB levels decrease below 52 µg/ml, subjects wake up.[164]

Abuse Potential and Intoxication

Factors that seem to contribute to the abuse potential of GHB include its intoxicating effects, its purported anabolic effects, its hypnotic effects, and its ability to incapacitate women for purposes of sexual assault.[157, 200, 201] One of the main reasons GHB became a popular drug of abuse is its ability to produce a "high."[155, 202] Those who take GHB describe it as producing a state of relaxation and tranquility accompanied by feelings of calmness, mild euphoria, a tendency to verbalize, mild numbing, and pleasant disinhibition. Despite these positive feelings attributed to the use of GHB, the dose-response curve for GHB has been described as being remarkably steep. Therefore, as the dose of GHB is increased, a steep increase in adverse effects may occur.[143] The effects of GHB have been described as being similar to those of alcohol, and the two agents may act synergistically, further increasing the risk for intoxication or overdose.[203]

Cardiovascular Effects

Moderate bradycardia appears after the administration of GHB[204, 205] and is likely due to central vagal activity.[166] In addition to bradycardia, GHB reduces stroke volume as well as cardiac output, which reaches a nadir around 30 minutes after ingestion. Atropine reverses the decreases in both heart rate and stroke volume.[205] The autonomic centers are fully active during GHB-induced coma, and surgical stimuli result in a cardiovascular response, such as tachycardia, hypertension, and raised cardiac output.[150, 166, 204]

Respiration

Respiratory rate is often reduced, but this is usually accompanied by an increase in tidal volume.[150, 204] The drug GHB also produces a slowing and deepening of respiration sometimes leading to a Cheyne-Stokes pattern.[166, 204]

Neuroendocrine Effects

In an early study that stimulated much interest

in the use of GHB by the bodybuilding population, intravenous administration of GHB 2.5 g significantly increased plasma growth hormone levels, which peaked at 60 minutes.[152] In a more recent study, after bedtime oral ingestion of GHB 2.5, 3.0, and 3.5 g, a significant increase occurred in the normal secretory pulse of growth hormone during the first 2 hours after sleep onset. The authors suggest that agents such as GHB may increase the release of growth hormone by increasing slow-wave sleep, because there is a large pulse in growth hormone secretion during the first stage of slow-wave sleep more than 90% of the time.[206]

Sedation and Anesthesia

The principal actions of GHB have not been fully elucidated. However, the results of early investigations suggest that GHB appears to act on the cerebral cortex with little or no depression of the reticular activating system.[150] Some authors speculate that there is depression of the limbic hippocampal structures[166] and subcortical centers.[199] The anesthetic effects of GHB are primarily hypnotic[204] as GHB provides little or no analgesia.[150, 204] The transition from wakefulness is described as being a sudden shift from responsivity to unconsciousness.[199]

Sleep Physiology

The drug GHB stimulates slow-wave sleep.[199, 207–210] It does not appear to suppress REM sleep[207, 209] and may even decrease fragmentation of REM sleep.[208] It appears to increase "slow" sleep as evidenced by a slow synchronized electroencephalographic recording.[199] In addition, GHB increases slow-wave sleep (stages 3 and 4), whereas light sleep (stage 1) is decreased, and the frequency of awakenings is reduced.[210] In healthy subjects, under double-blind conditions, single oral doses of GHB 2.25 g significantly increased the time spent in slow-wave sleep, while sacrificing stage 1 sleep and significantly decreasing slow-wave sleep latency. The efficiency of REM sleep is increased, but the REM latency and time spent in REM sleep do not change.[211]

Therapeutic Applications

Most of the therapeutic applications of GHB result from its sedative and hypnotic effects on the CNS. There are no currently accepted medical applications for GHB in the U.S., although it is being evaluated for the symptoms

of narcolepsy.[157] However, GHB has been extensively administered and studied for a variety of indications in other countries.

Sedation and Anesthesia

The first clinical application of GHB was as a hypnotic anesthetic agent.[145] It is still given for sedation and anesthesia in Germany, where it is considered safe and effective as long as the doses given are limited to the clinical needs.[212] In doses of 10–20 mg/kg, GHB demonstrates hemodynamic stability and lack of severe respiratory depression, while control and recovery are acceptable for clinical purposes.[213] However, bradycardia, hypotension, arrhythmias, and severe respiratory depression have been reported during GHB intoxication (see Adverse Effects section).

Cellular and Cerebral Protection

γ-Hydroxybutyrate may be an endogenous inhibitor of energy metabolism, protecting tissues when energy supplies are low. Evidence suggests that GHB reduces cellular activity, while depressing the utilization of glucose as well as other energy substrates. This may result in tissues being less sensitive to the damaging effects of anoxia or during periods of excessive metabolic demand. Therefore, the natural function of GHB may include a role as a tissue protective substance.[214] γ-Hydroxybutyrate reduces tissue oxygenation demands and protects cells during hypoxic states, which has been demonstrated in both human and animal studies as well as in various organ systems. It exerts a protective effect and reduces cellular damage during sepsis, hemorrhagic shock, great vessel or coronary artery occlusion, stroke, organ transplantation, and myocardial infarction. In addition, in humans with brain tumors, GHB decreases intracranial pressure and increases cerebral blood flow. A thorough review of these topics involving the cellular protective effects and cerebral protective effects of GHB, as well as various applications for GHB in anesthesia, has been published.[215]

Narcolepsy and Insomnia

Owing to the ability of GHB to increase slow-wave sleep and facilitate REM sleep efficiency, GHB may improve nighttime sleep and therefore improve alertness during the day, which could alleviate some of the symptoms of narcolepsy.[151, 208–210, 216] In addition, administration of GHB to

patients with narcolepsy revealed significant improvements in sleep attacks, daytime drowsiness, cataplexy, hypnogogic hallucinations, and sleep paralysis.[209, 217] Because GHB is a CNS depressant, it has been investigated for treating the symptoms of insomnia,[165, 207] and in one investigation it was rated by the subjects as being an "excellent hypnotic."[165] However, when being used as a hypnotic, an oral dose of GHB 100 mg/kg resulted in frequent awakenings at either 1.5 or 4–5 hours after ingestion, which accounted for 14 of the 25 adverse effects reported in this dose group.[165] Furthermore, GHB reportedly produced sleep paralysis, sleep walking, and cataplexy.[151]

Alcohol and Opiate Withdrawal

The drug GHB 50 mg/kg/day has been given orally to treat the symptoms of acute alcohol withdrawal and to facilitate both short- and long-term abstinence from alcohol. It also was given to treat opiate withdrawal, often in higher dosages of 50–300 mg/kg/day. These applications of GHB were discussed extensively in a recent review of this topic during a symposium hosted by the Italian Society on Biological Psychiatry.[218] Despite a possible benefit of taking GHB for these conditions, craving for GHB developed during these trials, with some subjects increasing their dosage up to 6-7 times the recommended levels.[219]

Anabolism

Although GHB is commonly taken for its proposed anabolic effects (related to the ability of GHB to stimulate the release of growth hormone), especially by the bodybuilding community,[152, 206, 220] no definitive evidence exists that it increases muscle mass or fat catabolism. In addition, in patients with chronic alcoholism, long-term administration of GHB did not affect muscular mass.[221]

Adverse Effects and Acute Toxic Reactions

Acute Syndrome

The Centers for Disease Control and Prevention (CDC) released two reports describing the toxic effects of GHB.[155, 222] These reports document over 120 poisonings and one fatality in individuals from various regions of the U.S. who became ill secondary to taking GHB. The usual course of illness was very similar from case to case. Approximately 15–60 minutes after

ingestion, one or more of the following symptoms occurred: vomiting, drowsiness, soporific state, hypotonia, or vertigo. Depending on the dosage taken and concurrent use of other CNS depressants, such as alcohol, any of the following occurred as well: loss of consciousness, respiratory depression, tremors, myoclonus, seizure-like activity, bradycardia, hypotension, or respiratory arrest. In many of these cases, the symptoms spontaneously resolved within 2–96 hours.[155, 222] As a result of the increased rate of GHB abuse since the first CDC report in 1990, the number of acute intoxications due to GHB has increased.[158, 160, 200, 202, 222–235] Some of the more common and better documented conditions that appear in various reports include coma, respiratory depression, seizure-like activity (uncontrollable or unusual movements), bradycardia, drowsiness or dizziness, confusion, amnesia, headache, nausea, vomiting, mild hypothermia, acidosis, and psychiatric complications (e.g., agitation, delirium).

Since 1992, the DEA has documented over 9600 adverse reactions, overdoses, and other cases reported by various law enforcement agencies, poison control centers, and hospitals in 46 states.[157] The Food and Drug Administration has issued warnings to inform consumers about the dangers of ingesting two potentially dangerous GHB precursors, γ-butyrolactone (GBL) and 1,4 butanediol (BD), which are converted to GHB in the body.[236, 237] The doses of GHB that elicit adverse effects vary greatly from report to report and range from 0.25 teaspoon (1.25 ml) to 4 tablespoons (60 ml)[200] up to 16 ounces (480 ml).[223] However, GHB often is produced in clandestine laboratories, resulting in preparations with a wide range of purity and strength. Therefore, the quantities reported to be ingested in cases of acute intoxications may not be that informative. A 99% pure sample of GHB weighs 2.8 g/level teaspoon (5 ml).[200] However, 40 ml of clandestinely produced GHB may weigh from 3–20 g.[224] One aspect of GHB that makes it dangerous is that the response to oral ingestion seems to vary within the same patient as well as between patients.

The adverse effects described in the following sections were found in experimental investigations and in reports of intoxications. The drug GHB affects the CNS, cardiovascular system, and respiratory system but does not have a toxic effect on the kidneys or the liver.[151, 166]

CNS Effects

Drowsiness and dizziness induced by GHB are reported frequently in both investigational and toxicity reports. Subjects receiving oral doses of GHB 25–50 mg/kg in a controlled study complained of dizziness and drowsiness.[161] Other common CNS adverse effects include vertigo and headache.[165] More serious CNS depression during intoxication with GHB commonly occurs. Numerous reports of intoxication with GHB describe patients who present with Glasgow Coma Scale (GCS) scores as low as 3–5.[224–231] Recovery appears to be inversely related to GCS score, with a lower GCS score resulting in a longer time to recover.[228] Coma induced by GHB usually appears rapidly after ingestion, followed by a rapid and apparent full recovery. Often in the cases of intoxication, the unconsciousness will resolve within 6–7 hours.[200, 223, 225–230, 232] One of the distinctively characteristic aspects of GHB intoxication is the rapid recovery, which is often uneventful and may create a false sense of security in the user.[223]

Cardiovascular Effects

Bradycardia has occurred when GHB was given for anesthesia[150, 166, 204] as well as in overdose situations.[200, 222, 224, 228, 231] In a retrospective review of GHB intoxication, 36% of patients had pulse rates defined as bradycardia (heart rate < 55 beats/minute) and one patient required a single dose of atropine for a heart rate of 24 beats/minute.[228] In the same case series, 10 patients had hypotension (systolic blood pressure ≤ 90 mm Hg) at presentation. Six of the patients with hypotension also had concurrent bradycardia, and in all six cases alcohol and/or another drug of abuse were present. In another case series of seven patients, the authors reported that five patients developed U waves on their electro-cardiograms after GHB exposure, although none of them was significantly hypokalemic. Three of these five patients had significant abnormalities that included first-degree heart block, right bundle branch block, and ventricular ectopy.[233]

Respiratory System

Respiratory depression, difficulty breathing, and apnea have been reported after the administration of GHB.[155, 166, 200, 202, 222, 224, 228, 231, 233, 235] The respiratory depression may be very severe, and in some cases the respiratory rate may drop to as low as four breaths/minute.[224, 231] Abnormal patterns of breathing such as Cheyne-Stokes breathing may result.[204]

Psychopathology

Under the influence of GHB, some individuals may become hostile, belligerent, and agitated.[223, 225] Patients display loss of consciousness and are extremely combative when stimulated, despite profound respiratory depression. Furthermore, they may require physical restraints to protect themselves and hospital personnel.[233] Psychiatric complications such as delirium, paranoia, depression, and hallucinations have been reported in a small number of patients.[158, 234]

Ocular Effects

During intoxication with GHB, the pupils have been described as being miotic and sluggishly reactive to light,[225] and during coma induced by GHB the eyes have been found to be miotic and unresponsive to light.[199]

Acidosis

Mild acute respiratory acidosis is a common finding when GHB has been used as an anesthetic, as well as when it has been abused.[228, 233] In one review, 93% of patients had a pH less than 7.40, and 30% had a pH less than 7.30. In addition, 70% of patients had a partial pressure of carbon dioxide of 45 mm Hg or greater.[228]

Gastrointestinal System

A high frequency of vomiting is associated with the use of GHB,[147, 238] especially during induction and on emergence from intravenously induced anesthesia.[166, 238] In an early investigation, 52% of patients receiving GHB for anesthesia experienced nausea or vomiting.[204] According to one case series, vomiting was also very common and occurred in 30% of 88 cases of GHB intoxication. It typically occurred as the patients were regaining consciousness.[228] In another review of 78 cases of GHB overdose, vomiting was reported in 22% of the cases.[229]

Body Temperature

Although hypothermia has not been a universal finding during GHB intoxication,[233] mild hypothermia has been observed in patients after a GHB overdose.[223, 225, 227, 228] In one study of 70 patients, 31% had an initial body temperature of less than 35°C, and the mean body temperature was 35.8 ± 1.1°C.[228] In an additional small series of five patients, hypothermia was reported in three patients, with the lowest temperature being 32.8°C.[227]

Movements

There have been many reports of unusual, random clonic movements and uncontrollable shaking associated with GHB use.[150, 155, 166, 200, 202, 225, 227, 229, 234, 235] In anesthesia studies, abnormal movements occurred during induction with GHB but were not accompanied by any seizure-like electroencephalographic tracings and could be reduced by administering a phenothiazine drug.[150] Administration of GHB will not necessarily result in abnormal epileptiform electroencephalographic changes[212] or seizure-like activity.[228]

Miscellaneous

Cold and heavy extremities have been reported after oral ingestion of GHB 50 mg/kg.[165] Diaphoresis was reported in 35% of the 78 cases of GHB overdose in one investigation.[229] Home brewing of GHB, often from kits sold on Internet sites or from mail order sources, can lead to various adverse effects due to improper manufacturing of GHB. The manufacture of GHB involves the mixture of γ-butyrolactone and the alkaline substance, sodium hydroxide. The inappropriate manufacture of GHB may lead to a very alkaline mixture, resulting in esophageal damage.[239] In New York, a 20-year-old man aspirated during vomiting, resulting in damage to his lung tissue that was attributed to the mixture of gastric contents containing sodium hydroxide.[222] Hematuria has also occurred after the ingestion of improperly manufactured GHB. Home-brewed GHB was being made with swimming pool chlorine tablets instead of the required sodium hydroxide.[159]

Withdrawal and Tolerance

Data gathered by the DEA indicate that those who take GHB have exhibited chronic self-administration, compulsive abuse regardless of adverse consequences, as well as drug-seeking behaviors. These data suggest individuals may become psychologically dependent on GHB.[157] Physical dependence may develop, with a withdrawal syndrome occurring on abrupt discontinuation.[157, 201, 240–242] Tolerance to the effects of GHB results in an increase in dosage and a withdrawal syndrome on cessation of GHB ingestion.[201, 241–243] The withdrawal syndrome is characterized by insomnia, tremor, and anxiety that may last approximately 1 week.[201] In addition, more severe symptoms have been reported, including confusion, hallucinations, delirium, and autonomic stimulation with tachycardia. The symptoms of withdrawal may begin within 1–6 hours after the last dose of GHB and may last from 5–15 days.[242]

One case of Wernicke-Korsakoff syndrome has been attributed to the use of GHB.[244] According to the authors, the patient had not imbibed alcohol for several months before admission, although there was no mention of an ethanol screen. The patient presented with the classic triad of symptoms of Wernicke-Korsakoff syndrome: global confusion, sixth nerve palsies, and ataxic gait. In addition, paranoid delusions and hallucinations were present. According to the authors, the atypical mental features represented GHB withdrawal and were similar, in part, to delirium tremens without the serious autonomic dysfunction. The patient's symptoms resolved quickly with thiamine treatment, with the eye movement abnormalities resolving rapidly, followed by resolution of the abnormal gait and mentation.[244] The clinical picture of GHB withdrawal appears to range from anxiety, tremor, and insomnia to more severe symptoms such as disorientation, paranoia, hallucinations, tachycardia, and possibly extraocular motor impairment.

Death

Fatalities have been associated with GHB use.[157, 222, 245–247] The DEA has collected investigative, toxicology, and autopsy reports from cases in which GHB was found in biological samples of the deceased. Since 1990, the DEA reports that they are aware of 68 deaths associated with the use of GHB, most of which have occurred in the last 4 years. Details of the cases are not given.[157] In an article discussing pre- and postmortem GHB blood and urine levels, the authors refer to four fatalities attributed to the use of GHB.[246] Three of the fatalities had postmortem blood GHB levels ranging from 52–121 mg/L. In a series of forensic samples submitted for laboratory analysis, blood GHB levels ranging from 3.2–168 mg/L were found in 15 of 20 autopsy specimens, although the deaths were not thought to be GHB related. Furthermore, GHB was not found in samples from living subjects who did not take GHB. Because of these findings, the authors suggest that GHB may be a natural product of postmortem decomposition occurring in blood.[246] Other investigators suggest that the magnitude of GHB levels found in many fatality cases is too significant to be attributed to postmortem decomposition.[247]

Treatment

Resuscitation

The mainstay of treatment for GHB intoxication is protection of the airway and assisted ventilation if needed. Intubation, to protect the airway, is a common treatment procedure during GHB intoxication, and assisted ventilation may be required in some cases.[233, 248]

Laboratory monitoring should include serum electrolytes and blood glucose levels in symptomatic patients, and additional monitoring, such as pulse oximetry and arterial blood gases, in patients with respiratory depression. Because of the increased prevalence of GHB abuse, it should be considered as a causal agent in any patient with coma of unknown origin at presentation. Since GHB is rapidly cleared from the body, it is often difficult to confirm the definite use of GHB. Furthermore, GHB will be missed by many conventional first-line urine drug screens,[249] and analysis with gas chromatography mass spectrometry is required for detection and quantification.[250] Therefore, a history from the patient, or others who witnessed the GHB use, may be important diagnostic information. However, because GHB has amnestic properties, the patient may not be able to provide a very reliable history. Some suggest that a history of bodybuilding or athletic physique may aid in the diagnosis of GHB abuse,[158, 226] as this drug is commonly used in this patient population.

Decontamination and Elimination

The roles of gastric lavage and activated charcoal have been questioned as the volumes of GHB are very small and GHB is rapidly absorbed from the gut,[251] but these treatments may be helpful when GHB is coingested with other drugs of abuse. Activated charcoal may be of benefit for recent, large ingestions of GHB.[252] Induction of emesis is not recommended because the CNS depression and diminished gag reflex may lead to pulmonary aspiration.[252]

Neurologic Treatment

Because many of the symptoms of GHB intoxication are so rapidly reversed, it is difficult to determine if purported helpful pharmacologic treatments have been successful or if the GHB intoxication has simply worn off. In clinical cases of GHB intoxication, both naloxone and flumazenil have been found to be of no benefit in reversing unconsciousness.[155, 200, 223–225, 230, 231, 233, 234]

Owing to the association between GHB and absence epilepsy in animals, various anticonvulsant agents have been used as GHB-reversal agents, but there are no data in the literature indicating that any of these agents have been useful in experimental or clinical situations in humans. Monitoring neurologic function and applying GCS scores are essential. Patients with an initial GCS of 8 or less may have a more serious clinical course, requiring a longer recovery time, so they should be monitored very closely.[228] It has been suggested that if a patient has stable mental status and vital signs after 6 hours of observation in the emergency department, he or she could be discharged unless there is some other indication for hospital admission.[233]

Case reports[231] and clinical trials[253–255] indicate that neostigmine or physostigmine may be helpful in the treatment of the symptoms of GHB intoxication. Physostigmine is given clinically to reverse the toxic CNS effects caused by anticholinergic agents. Three trials in humans undergoing GHB anesthesia have evaluated the use of physostigmine or neostigmine as reversal agents.[253–255] Two of these studies included the use of a neuromuscular blocker in addition to GHB, which complicate the results. In one study, effective reversal of GHB-induced sedation occurred after the administration of physostigmine alone, given intravenously as 2-mg single or repeated doses.[253]

Cardiovascular Treatment

Symptomatic bradycardia associated with GHB intoxication should be treated with atropine.[230, 233] However, although a single case report indicated that atropine was successful in treating a case of severe bradycardia,[228] this approach has not been adequately evaluated.

Withdrawal

Benzodiazepines may be given to treat the GHB withdrawal syndrome.[252] In one reported case, the withdrawal symptoms were so severe that, over a 9-day detoxification period, the patient received propranolol, benzodiazepines, and phenothiazines for paranoia, agitation, and delirium.[241] In another report, the patient displayed agitation, hallucinations, tachycardia, and elevated blood pressure after the cessation of GHB. Over the course of this patient's treatment, he received lorazepam 507 mg and diazepam 120

mg for agitation over a 90-hour period.[243] Although benzodiazepines and other agents have been given to treat the signs and symptoms of GHB withdrawal, no standard treatment protocol exists.

Supportive Care

The treatment of GHB intoxication is mainly supportive because no specific GHB antidote has been proved effective in humans. Because of reduced respiratory function, the patient may require intubation or mechanical ventilation. As vomiting is a common symptom of GHB intoxication, airway protection becomes even more important to avoid the risk of aspiration. The improper manufacture of GHB can lead to a mixture of GHB and sodium hydroxide, which is very caustic and, if aspirated, is likely to cause severe damage to the lung tissue. Therefore, it is important to maintain the airway and establish intravenous access.

Conclusion

The use of MDMA and GHB has risen dramatically over the last couple of years. Evidence indicates that MDMA is toxic to serotonergic neurons in animals. Further evidence indicates that MDMA may be a neurotoxin in humans as well.

The drug MDMA is the most popular of the club drugs and continues to gain popularity despite adverse effects that have been associated with it, such as agitation, tachycardia, hypertension, dilated pupils, trismus, bruxism, sweating, hyperthermia, DIC, rhabdomyolysis, and acute renal failure. Hyperthermia appears to be the most serious complication, sometimes leading to a cascade of events including DIC, rhabdomyolysis, and acute renal failure.

No standard protocols exist for treating MDMA intoxication. However, the most important techniques include lowering the body temperature and maintaining adequate hydration to avoid acute renal failure due to rhabdomyolysis and myoglobinuria. The cases of hyponatremia associated with MDMA that have resulted in seizures, coma, and cerebral edema indicate that it is extremely important to avoid overhydration of the patient during treatment.

The use of GHB, although not as popular as MDMA, is also a significant problem. It is used for its sedating, intoxicating, and alleged bodybuilding properties. In addition, in recent years, GHB has been used to facilitate sexual assault and has been labeled a "date rape" drug by the press. Regardless of the initial motive for using GHB, it is a dangerous substance when used outside of a controlled setting. It may cause acute toxic reactions and possibly physical dependence, especially if used at high doses for a prolonged period of time. Acute symptoms of a GHB toxic reaction include coma (often with a GCS score < 8), respiratory depression, seizure-like activity, bradycardia, drowsiness, confusion, amnesia, nausea, vomiting, mild hypothermia, acidosis, and psychiatric complications. Symptoms associated with acute withdrawal in those who are physically dependent range from anxiety, tremor, and insomnia in milder cases, to confusion, delirium, and hallucinations in more severe cases.

No standard treatment protocols exist for GHB intoxication or withdrawal. However, physostigmine has been suggested as a possible treatment option to reduce the CNS and respiratory depression induced by GHB. Atropine may be beneficial in cases of severe bradycardia. Benzodiazepines are commonly given for GHB withdrawal symptoms; although, to our knowledge no prospective studies have evaluated their use for this indication.

Because of the increasing popularity of club drugs and their dangerous adverse effects, health care professionals must be familiar with these substances. Early identification and treatment of symptoms associated with these agents is of paramount importance. No standard treatment protocols exist for the intoxication syndromes associated with MDMA or GHB, and supportive care is currently the standard of treatment. Pharmacologic treatments have been given successfully for treating the symptoms associated with MDMA and GHB toxic reactions. However, larger clinical trials evaluating the use of pharmacotherapy during intoxication with, or withdrawal from, either of these agents are lacking. A knowledge of the expected adverse effects and the course and duration of intoxication or withdrawal will help health care providers to identify and treat the consequences of MDMA or GHB abuse.

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