

Toxicology News

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GHB and Precursors (Part I): Use, Effects, Pharmacology

By Sarah Kerrigan

Gamma-hydroxybutyrate (GHB) and its metabolic precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (BDL), have gained notoriety in the popular press of late. These substances have been implicated in several celebrity overdoses and GHB has been popularized as the “date-rape drug” by the media.

GHB was first synthesized in 1960 as an orally active gamma-aminobutyric acid (GABA) analog capable of crossing the blood–brain barrier. Its ability to produce sleep and reversible coma aroused interest in the drug as a surgical anesthetic. However, its lack of analgesic effect and epileptogenic activity prevented its widespread use. Until relatively recently, GHB was widely available through health food stores, gymnasiums, fitness centers, and the Internet. In November 1990, following widespread reports of poisonings and adverse reactions, the Food and Drug Administration (FDA) designated GHB an investigational new drug and banned its distribution outside of approved clinical trials. Public awareness of its psychoactive and euphoric effects increased its popularity. This led to GHB being scheduled in more than 25 states.

In April 2000, salts and isomers of gamma-hydroxybutyric acid were placed into Schedule I of the federal Controlled Substances Act. GBL and BDL are metabolic precursors or pro-drugs of GHB. Analog laws in some states, such as California, make GBL an illicit intoxicant, but both GBL and BDL remain legal in most of the country. The emergence of new metabolic precursors and analogs compounds the regulatory, legislative, and toxicological issues surrounding GHB.

GHB is a low-potency intoxicant that, in large doses, can produce profound and life-threatening central nervous system (CNS) depression. It is

claimed to produce a variety of desirable effects, including improved athletic performance, sleep, sexual prowess, mood elevation, and euphoria. Because of these claims and the publicity surrounding GHB, it has extraordinarily diverse appeal: dietary supplements for the health conscious, euphorants for recreational drug use, and “knock-out drops” or chemical submission agents for those with more sinister, criminal intentions.

Occurrence and uses

GHB is an endogenous neuromodulator found in mammalian tissue that is structurally related to GABA. It satisfies many of the criteria for consideration as a neurotransmitter, having specific receptor sites, endogenous synthesis, and heterogeneous distribution in the CNS. Although GHB (sodium oxybate) is not currently an approved drug in the United States, it does have accepted medical uses elsewhere for anesthesia, resuscitation, treatment of sleep disorders, and treatment of substance dependence. Use of the drug within the United States is limited to FDA-approved clinical trials for the treatment of certain disorders, such as narcolepsy. GHB has been shown to decrease daytime sleepiness and episodes of cataplexy, sleep paralysis, and hypnagogic (dream-like) hallucinations in narcoleptic patients.

GHB is encountered as an odorless, colorless liquid or a hygroscopic powder (often as the sodium or potassium salt). It is frequently distributed in water bottles, mouth wash bottles, or other common household vessels. Dyes or flavorings may be added to mask the sometimes salty or soapy taste of GHB or the solvent-like aroma of GBL and BDL.

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GHB

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Doses are typically administered in “capfuls” of liquid that contain largely unknown concentrations of drug. An illicit dose of one teaspoon of powdered GHB (2.5 g) is common. GBL and BDL are most frequently encountered as diluted liquids.

Gamma-hydroxybutyric acid behaves as both an acid and an alcohol. Hydroxy-acids with a sufficient number of carbon atoms may undergo intramolecular esterification. Both gamma and delta hydroxy-acids can lose water spontaneously to form cyclic esters known as lactones. Treatment with a base rapidly cleaves the ring to produce an open-chain hydroxy-acid. This property is widely used during the clandestine manufacture of GHB.

Clandestine synthesis is common. Gamma-butyrolactone is converted into gamma-hydroxybutyrate in the presence of sodium or potassium hydroxide. Heat is not necessary but alcohol may be used to precipitate out the GHB. Conversion rates are typically 70–80% and the reaction is complete in under an hour. Care must be taken to adjust the pH to 6–7 using dilute acid prior to consumption.

GBL is a clear oily liquid that is available in hardware stores and through chemical supply houses. It is a component of many industrial cleaners, paint removers, wood cleaners, textile aids, and drilling oils. It is a solvent for polymers such as cellulose acetate, methyl methacrylate, and polystyrene and can be found in nail polish remover and glue removers. Intoxication following ingestion of GBL in “acetone-free” nail polish remover has been reported. Lactones are widely used as flavors and aromas in food, drinks, and cosmetics, and GBL has been detected in certain wines. 1,4-Butanediol is an industrial chemical and solvent used universally in the manufacture of organic chemicals. Both GBL and BDL are metabolic precursors of GHB. Gamma-butyrolactone is converted to GHB by lactonases in the blood, and 1,4-butanediol is metabolized to GHB by alcohol and acetaldehyde dehydrogenase. Because both of these substances are converted to GHB in vivo, the clinical manifestations and toxicology of these pro-drugs are identical to those of GHB.

Dietary supplements

In January 1999 the FDA issued a warning about products that contain GBL and asked companies to recall them. The FDA reported at least 55 instances of adverse health effects and one death. In 19 of these cases, consumers lost consciousness, some needing intubation or mechanical ventilation. Products such as Blue Nitro by Alpha Earth, which re-

tailed at \$64.95 for a 32 fluid-ounce bottle, contained 2.5 g GBL (“2(3H)-Furanone di-hydro”) per serving (1 fluid ounce). The manufacturer recommended the user start with small amounts (“1 tsp”) not more than every four hours and “gradually increase dose to achieve the desired effect.”

Much of the difficulty associated with identification of GHB analogs and precursors in dietary supplements is directly attributable to poor or deceptive labeling. There is no standardization or regulation for listing chemical ingredients in dietary supplements. The National Institute of Standards and Technology lists more than 30 chemical names for GBL alone (Table 1), making it particularly easy for a manufacturer to confound an unwitting consumer.

Demographics of GHB use

Popular drug culture classifies GHB as an entheogen, meaning a substance that generates god or spirit within. This term is more usually reserved for natural psychomimetics like peyote, psilocybin, or traditional hallucinogens used for shamanic inebriation. Nevertheless, widespread popularity and use of the drug transects the stereotypical socioeconomic and demographic boundaries often associated with illicit drug use.

It is claimed that GHB and its metabolic precursors can produce a wide range of beneficial effects including increased libido, restful sleep, mood enhancement, weight loss, and muscular development. GHB has been particularly popular in the bodybuilding and “rave” scenes. It has been illicitly marketed in gymnasiums and fitness centers as an alternative to anabolic steroids and as a replacement for *L*-tryptophan. Studies have indicated that GHB mediates the release of growth hormone, possibly by some cholinergic mechanism. Although GHB-induced release of growth hormone has been demonstrated in humans, there is no experimental data that links GHB to increased muscle mass or fat catabolism.

The reported euphoric and entactogenic effects of GHB have made the drug a less expensive alternative to methylenedioxymethamphetamine (MDMA, ecstasy), which may cost as much as \$40 per dose. One capful of GHB typically sells for \$5–10. The low cost, together with its perception as “low risk” or “natural,” makes GHB a gateway drug. Some of the highest rates of GHB use are reported in states where the “rave” scene is popular: Florida, New York, and California. Nationwide, however, the Drug Abuse Warning Network reports that the number of GHB-related emergency department mentions increased dramatically between 1997 and 1999 (Figure 1). Seductive and enticing claims, alluring

Table 1. Chemical Names and Common Street Names of GHB and Analogs**GHB***Chemical Names:*

4-Hydroxybutyrate; Butanoic acid, 4-Hydroxy-; Gamma-hydroxybutyrate; Sodium oxybate

Common Names:

Cherry Menth; Degreaser Plus; Lye; Easy Lay; Everclear; Fantasy; G; G-Caps; G-Riffick; Gamma-G; Gamma-OH; GBH; Geebers; Georgia Home Boy; Gib; Great Hormones at Bedtime; Liquid E; Liquid Ecstasy; Liquid X; Natural Sleep-500; Nature's Quaalude; Organic Quaalude; Salty Water; Somatomax; Scoop; Soap

GBL*Chemical Names:*Butyrolactone; 2(3H)-Furanone, dihydro-; γ -Hydroxybutyric acid cyclic ester; γ -Hydroxybutyric lactone; γ -Hydroxybutyrolactone; Butanoic acid, 4-hydroxy-, γ -lactone; Butyric acid lactone; Butyryl lactone; Dihydro-2(3H)-furanone; Tetrahydro-2-furanone; 1,4-Butanolide; 4-Butanolide; 4-Butyrolactone; 4-Deoxytetronic acid; 4-Hydroxybutanoic acid lactone; 4-Hydroxybutyric acid lactone; Dehydro-2(3H)-furanone; 1,4-Butyrolactone; α -Butyrolactone; Butyric acid, 4-hydroxy-, γ -lactone; Dihydro-2-furanone; 1,2-Butanolide; 4-Hydroxybutanoic acid, γ -lactone; γ -Lactone; 2-Oxolanone; 1-Oxacyclopentan-2-one; 2-Oxotetrahydrofuran; γ -Butanolactone*Common Names:*

Blue Nitro; Firewater; Furanone Extreme; Gamma-G; GBL; GH-Release; Insom-X; Invigorate; Jolt; Liquid Libido; Notro Vitality; Regenerize; RenewTrient; Remforce; Revivarant; Revivarant-G

BDL*Chemical Names:*

1,4-Butanediol; 1,4-Butylene glycol; 1,4-Dihydroxybutane; 1,4-Tetramethylene glycol; 1,4-BD; Butane-1,4-diol; Butanediol; Diol 14B; Sucol B; Tetramethylene glycol; Tetramethylene 1,4-Diol

Common Names:

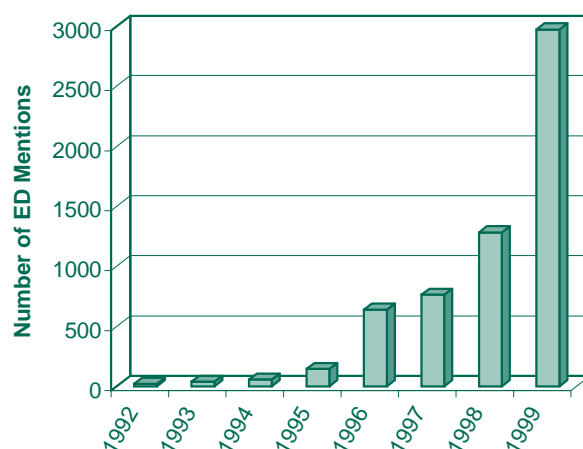
Biocopia PM; Borametz; BVM; Cherry FX Bomb; Enliven; FX; Inner G; Lemon FX Drop; NRG3; Orange FXPro G; Pine Needle Extract; Promusol; Rest-eze; Revitalize-Plus; Serenity; Somato-Pro; Thunder Nectar; Weight Belt Cleaner

names, and the use of teen icons have popularized GHB and its analogs among young people.

Analogs, precursors, and legal alternatives

Regulation of the sale and distribution of GHB has been hampered by the prompt appearance and ready availability of metabolic precursors such as GBL, BDL, and others. Numerous sites on the Internet describe the clandestine synthesis and pharmacological effects of GHB alternatives, such as 4-hydroxyvalerate (also called 4-methyl-GHB) and GHB-aldehyde. Emergence of these supposedly legal alternatives is a direct consequence of prohibition. These are typically homologues of GHB with additional carbon atoms (e.g. valeric, caproic hydroxy-acids), as well as substituted alcohols or lactones. The widespread industrial use of many of these relatively non-complex chemicals makes government regulation extremely challenging. Illicit use of GHB analogs and precursor chemicals is of growing concern from clinical, law enforcement, and legal standpoints.

The April 2000 amendment to the federal Controlled Substances Act making GBL a Schedule I chemical means that any person who imports, exports, or distributes GBL must register with the Drug

Figure 1. GHB-Related Emergency Department Episodes (Source: Drug Abuse Warning Network)

Enforcement Administration and provide required documentation. Future rulings will address the issue of a GBL threshold, to exempt legitimate use from the regulation. Until that time, all transactions involving any amount of GBL are subject to regulation by the Controlled Substances Act.

At the time of scheduling, it was recognized

that due to the pharmacological similarity and the fact that other substances are often substituted for GHB, under certain circumstances they could satisfy the definition of a controlled substance analog, making them illegal. Some states have already addressed this problem. In California, Section 11055 of the Health and Safety Code lists GHB and all immediate precursors, not limited to GBL, as Schedule II substances.

In October 2000, Orphan Medical Inc. submitted a new drug application to the FDA for Xyrem (sodium oxybate). Xyrem is proposed for the therapeutic management of cataplexy, which is estimated to affect as many as 75% of the 125,000 Americans suffering from narcolepsy. Presently, because GHB is a Schedule I substance in the federal Controlled Substance Act, its possession, manufacture, or sale is punishable by up to 20 years imprisonment. Schedule I substances are defined as those with high potential for abuse, no currently accepted medical use in the United States, and a lack of accepted safety for use under medical supervision. If the FDA approves Xyrem for the treatment of cataplexy, GHB will likely revert to a Schedule III substance with Schedule I consequences for illegal use. Internationally, GHB is a scheduled drug in both Australia and Canada.

Pharmacology of GHB

Once ingested, GBL and BDL are rapidly metabolized to GHB (Figure 2). GBL is converted to GHB *in vivo* by a rapidly acting lactonase found in blood and liver. Animal studies indicate the half-life of the conversion of GBL to GHB in plasma is approximately 1 minute. Lactonase conversion of gamma-lactones to their corresponding hydroxyacids is inhibited by ethylenediaminetetraacetate (EDTA). However, lactonization of GHB *in vivo* is reported not to occur because GBL is absent following administration of GHB. BDL is converted to GHB by alcohol dehydrogenase and aldehyde dehydrogenase via an intermediate, 4-hydroxybutanal. Because of the efficient conversion of both 1,4-butanediol and gamma-butyrolactone, their toxicological profiles are analogous to that of GHB.

GHB is readily absorbed with peak plasma concentrations occurring 20–60 minutes after oral administration. The onset of action is fairly rapid, often within 15 minutes. This is attributed to the rapid gastrointestinal absorption of the drug and penetration of the blood–brain barrier. GHB has a half-life of 0.3–1.0 hour and a volume of distribution of 0.4 L/kg. Elevated tissue concentrations of GHB were seen during co-administration of BDL and ethanol, suggesting that there might be *in vivo* com-

petition between the two for alcohol dehydrogenase. Non-linear elimination kinetics were observed in some individuals and some studies have indicated that oral absorption and elimination of GHB are capacity-limited processes. Higher doses of the drug appear to increase absorption and elimination half-lives and the time to peak plasma concentration. Less than 5% of the dose is eliminated unchanged in the urine. Approximate detection times are 6–8 hours in blood and 12 hours in urine.

A combination of GABAergic, opioid, and dopaminergic systems appear to be involved in GHB's mode of action. GHB has been reported to both stimulate and inhibit dopamine release. It behaves as a GABA-B agonist and produces a biphasic dopamine response, inhibiting dopamine release at low doses and promoting release at higher doses. The effect of GHB on the cerebral dopaminergic system is not yet completely understood. GHB has distinct neurophysiological and pharmacological actions, attributable to the activation of specific receptors that have yet to be elucidated. Radioisotope studies in animals indicate that GHB undergoes oxidative metabolism and is eliminated as carbon dioxide, through respiration. Interestingly, GHB has been shown to reduce tissue oxygenation demands, having a protective effect during periods of anoxia. The drug has also been shown to reduce intracranial pressure and increase cerebral blood flow.

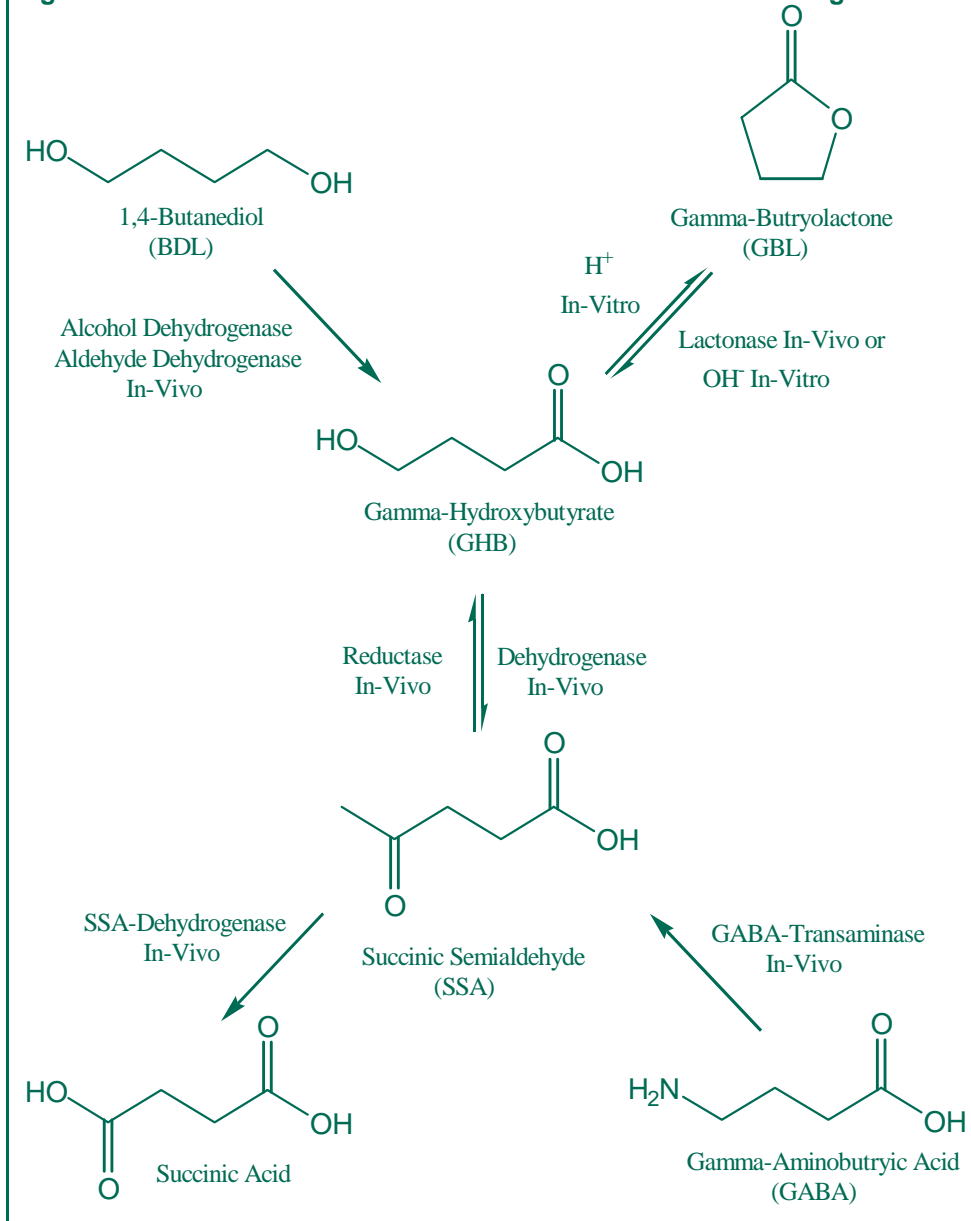
Outside of the United States, oral doses of 25–50 mg/kg have been used for the treatment of opiate and alcohol dependence. In Italy, GHB has been used clinically to treat alcoholism since 1991. GHB may control drug craving and subsequent drug use by substituting the reinforcing effects of the drug and providing an anxiolytic effect. However, its employment for the treatment of withdrawal is controversial due to its abuse liability and adverse effects.

Adverse effects

The FDA has released numerous reports and warnings conveying the adverse health consequences of GHB, GBL, and BDL. According to FDA statistics, ingestion of products containing these substances has been linked to at least 122 serious illnesses and three deaths. Although 1,4-butanediol is not a controlled substance, the FDA declared it a Class I Health Hazard, having potentially life-threatening risks. Serious adverse effects include respiratory depression, bradycardia, loss of laryngeal reflex, and coma (Table 2).

Accidental ingestion and inadvertent overdose are commonly caused by storage of GHB as a clear liquid of unknown concentration in unmarked water bottles or drinking vessels. Popular drug sites on the

Figure 2. In Vitro and In Vivo Transformations of GHB and Analogs



Concurrent use of other sedative or CNS depressant drugs, such as ethanol, opiates, benzodiazepines or neuroleptics, may potentiate the effects of GHB or its metabolic precursors. Side effects can include nausea, vomiting, bradycardia, hypotension, diarrhea, incontinence, tremor, and euphoria. Severe side effects can include ataxia, tunnel vision, hallucinations, seizure-like activity, respiratory arrest and coma. Other adverse effects include esophageal ulcers or burns following ingestion of caustic GHB solutions.

An abstinence syndrome following cessation of chronic heavy use of GHB has been documented (Table 2). Physically dependent individuals have been reported to ingest as much as 25 g of GHB per day in divided doses. Withdrawal symptoms, which often include muscle cramps, tremor, insomnia, and anxiety, usually resolve within 3–12 days without sequelae. Treatment of symptoms may include the use of propranolol, benzodiazepines, or phenothiazines.

Multiple drug use is common, and GHB is often used in combination with other intoxicants, particularly alcohol. This practice makes it difficult to determine which symptoms are attributable to GHB. In one study, of the 88 patients who received hospital treatment in San

Internet warn prospective users of the potential dangers of GHB, providing testimonials and precautionary tips for those who intend to use the drug as a recreational intoxicant.

GHB is a relatively fast-acting depressant. Within about 15 minutes of administration, drowsiness, dizziness, euphoria, nausea, visual disturbances, and unconsciousness may ensue. The duration of action is about three hours. Users may experience a pleasant euphoric or entactogenic response, together with loss of inhibitions and sedation. In contrast, combative or aggressive behavior has been observed in some individuals. Emergence delirium, characterized by myoclonic jerking, confusion, agitation, and combative behavior is usually transient (30 minutes) but may worsen with stimulation.

Table 2. Effects of GHB

Acute GHB Intoxication:

Apnea, ataxia, agitation, amnesia, bradycardia, combativeness, coma, confusion, diaphoresis, disorientation, dizziness, drowsiness, emergence delirium, euphoria, hallucinations, hypnosis, hypothermia, incontinence, loss of laryngeal reflex, miosis, nausea, nystagmus, respiratory depression, seizure-like activity, somnolence, tonic-clonic jerking, tremors, vomiting

GHB Withdrawal Syndrome:

Agitation, anxiety, combativeness, delirium, hallucinations (visual and auditory), insomnia, muscle cramps, paranoia, tachycardia, tremor

Francisco for GHB intoxication, 39% involved co-ingestion of ethanol and 28% involved another drug, most commonly amphetamine, ecstasy, cocaine, or heroin. GHB is sometimes used to ameliorate the side effects of chronic methamphetamine use.

In patients receiving treatment for GHB intoxication, about 28% had a Glasgow Coma Scale (GCS) of 3, and 33% had GCS of 4–8. Asymptomatic bradycardia was seen in 36%, hypothermia in 31%, emesis in 30%, and hypotension in only 11% of patients. Respiratory acidosis was also observed. Interactions with therapeutic drugs have been reported, including a near-fatal interaction between GHB and the HIV-1 protease inhibitors Ritonavir and Saquinavir.

Reported adverse effects following GHB intoxication are almost entirely reversed through spontaneous recovery within 2–96 hours. Long-term adverse effects were described in only two reported cases, involving delirium, visual hallucinations, and suicidal tendencies. In these cases, the symptoms persisted for as long as nine days following cessation of drug use and required psychiatric hospitalization.

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Revised SAMHSA Guidelines

The third draft of the Mandatory Guidelines for Federal Workplace Drug Testing Programs is now available at the Substance Abuse and Mental Health Services Administration's Division of Workplace Programs' website: www.health.org/workplace. The draft includes changes in cutoff concentrations, drugs tested, and scientific methods used.

Blind Quality Control Material

A list of blind quality control sources has been compiled by the Division of Workplace Programs to facilitate compliance with the U.S. Department of Health and Human Services Mandatory Guidelines. The complete list can be downloaded from: www.health.org/workplace.

Call for Contributors

The editorial board of *Clinical and Forensic Toxicology News* has broad experience, but their expertise cannot cover every aspect of this wide-ranging and fast-changing field. However, the newsletter has a talented pool of readers, many of them with unique expertise, who could contribute.

Do you have a topic you would like to share with the other readers of the newsletter? If so, let us know by sending a message to cftnews@aacc.org.

Inhalation of Volatiles is a Growing Abuse Problem

By Mark W. Linder

The inhalation of volatile substances is one of the most common cause of fatalities associated with substance abuse in adolescents (1). The intentional inhalation of volatile substances found in a variety of commercially available products, such as air fresheners, hair spray, paint thinner, and gasoline, is a growing global problem.

In 1995, 21% of high school students in the United States reported they had experimented with inhalants (2). In a study of adolescents within a juvenile correctional facility in Virginia, McGarvey et al. (3) reported that 25% of the youth had experimented with inhalant abuse and 27% self-reported as heavy users.

In a study of deaths associated with inhalant abuse in Virginia from 1987 through 1996, Bowen et al. (4) reported that the vast majority (85%) of deaths involved males and included subjects 22 years old or younger with the youngest victim being 13 years of age. In this population, the most common agent of abuse was butane, followed by chlorodifluoromethane (Freon), propane, and trichloroethane. According to Spiller and Krenzelok (5), the most common substances reported to a regional poison control center were: toluene, 36.9%; gasoline, 27.3%; butane, 5.4%; chlorodifluoromethane, 4.2%; and 1,1,1 trichloroethane, 3.6%.

In the 1999 report of the American Association of Poison Control Centers Toxic Exposure Surveillance System, abuse of inhalants was the second most common reason for unintentional deaths from intentional exposures (23%) in adolescents, second to analgesics and greater than for stimulants and street drugs (1). The most common inhalants included air fresheners (butane and isobutane propellants) and hydrocarbons. The specific agents of exposure varied and included nitrous oxide, propane, butane, chlorodifluoromethane, air freshener propellant (agent not specified), and butane/isobutane. The most common inhalant associated with acute death from exposure appears to be butane. In contrast, the most common inhalant of abuse is toluene.

Acute and chronic manifestations

Inhalants can be addictive and can result in sudden death as well as serious chronic medical problems, including central nervous system impairment, cardiotoxicity, and hepatorenal damage. Sudden death most commonly occurs from abuse of fuel

gases and results from cardiac arrhythmias leading to cardiorespiratory arrest. Interestingly, volatile substance abuse sensitizes the heart to catecholamine response and thus most sudden deaths also include a contributory stimulatory factor such as fright, exercise, or sexual activity. The acute cardiotoxic and central nervous system depressive effects of volatile substances are generally the same due to similar pharmacodynamic properties; however, the chronic manifestations of abuse vary among the substances abused and include those resulting from toxic metabolic products of certain abused volatile substances.

Chronic effects of long-term abuse of volatile substances for the most part have been difficult to appreciate due to the physiologic reserve of the adolescent abuser and the ambiguity of the specific substance of abuse in most cases. However, permanent organ damage, including damage to the heart, kidney, and liver, has been clearly associated with chronic abuse of toluene; 1,1,1 trichloroethane; and trichloroethylene.

Laboratory analysis

For clinical toxicology purposes, blood is a good specimen for supporting the diagnosis of inhalant abuse and intoxication. The majority of the volatile substances abused are detectable in whole blood within 10 hours of exposure and some have been measured after 40 hours or more (6). The recommended specimen for volatiles analysis is anti-coagulated (EDTA or Li-heparin) whole blood collected in a glass tube fitted with a cap lined with metal foil, filled as completely as possible, and maintained at 4°C (7). A few volatile substances, such as toluene, xylene, and trichloroethylene, have suitable urinary metabolites for analysis, which may permit the identification of inhalant abuse using samples collected more than 48 hours after exposure.

For forensic purposes, analysis of tissue, in particular brain, can be superior to blood because of the accumulation and slow post-mortem decay of volatile substance concentrations in these tissues.

Using headspace gas chromatography (GC) with flame ionization detection, Lee et al. reported sensitivities for detection of solvent thinner components (including toluene and ethyl acetate) of 1–2 ng/ml

Elimination Half-Lives of Abused Volatile Substances

Toluene	7.5 h
Tetrachloroethylene	2 h
1,1,1-Trichloroethane	10–12 h
Trichloroethylene	30–38 h
Xylene	20–30 h

whole blood (8). Streete et al. (9) described methods using GC with electron capture detection to identify 244 volatile compounds in whole blood or urine, with adequate sensitivity for clinical application.

In general, there is a poor relationship between blood concentration and severity of poisoning, and thus this testing serves primarily a diagnostic role. The diagnosis of volatile substance abuse has significant medical and social implications. Youth who experiment with volatile substances are not only at risk for an acute and potentially fatal outcome, even from a first experimental exposure, but are also more likely to experiment with other drugs of abuse later in life.

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