

## CHAPTER 165

# SEDATIVE HYPNOTICS

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## BARBITURATES

### Perspective

Barbiturates are discussed in do-it-yourself suicide manuals and were implicated in the high-profile deaths of Marilyn Monroe, Jimi Hendrix, Abbie Hoffman, and Margaux Hemingway as well as in the mass suicide of 39 members of the Heaven's Gate cult in 1997. Although barbiturates are still useful for seizure disorders, they rarely are prescribed as sedatives, with the availability of safer alternatives, such as benzodiazepines. Mortality from barbiturate poisoning declined from approximately 1500 deaths per year in the 1950s to only two fatalities in 2009.<sup>1</sup>

Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening. Whereas tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.

### Principles of Disease

Barbiturates depress the activity of all excitable cells, especially those in the central nervous system (CNS), by enhancing the activity of  $\gamma$ -aminobutyric acid (GABA), the major central inhibitor. In acute overdose, barbiturates decrease neural transmission in autonomic ganglia, the myocardium, and the gastrointestinal tract and also inhibit the response to acetylcholine at the neuromuscular junction.

The GABA<sub>A</sub> receptor is a protein complex found on postsynaptic membranes in the CNS. Structurally, it consists of several distinct receptor sites surrounding a chloride ion (Cl<sup>-</sup>) channel (Fig. 165-1). GABA opens the chloride channel. The resulting flow of Cl<sup>-</sup> into the cell increases the negative resting potential, hyperpolarizing and stabilizing the membrane. There are separate receptor sites for barbiturates and for benzodiazepines and a third site that binds GABA, ethanol, and meprobamate. Although barbiturates and ethanol can directly increase Cl<sup>-</sup> conductance, benzodiazepines require the presence of GABA to affect Cl<sup>-</sup> flow, which may account for the relative safety of benzodiazepines in comparison with barbiturates.

Barbiturates produce dose-related depressive effects ranging from mild sedation to coma and fatal respiratory arrest. In the early stages of intoxication, some patients experience euphoria. Barbiturates have no analgesic effect and can paradoxically increase the reaction to pain at low doses.

Barbiturates act directly on the medulla to produce respiratory depression. In therapeutic doses, this respiratory depression mimics that of normal sleep. Starting with doses approximately

three times therapeutic, the neurogenic, chemical, and hypoxic respiratory drives are progressively suppressed. Because airway reflexes are not inhibited until general anesthesia is achieved, laryngospasm can occur at low doses.

Therapeutic oral doses of barbiturates produce only mild decreases in pulse and blood pressure, similar to sleep. With toxic doses, more significant hypotension occurs from direct depression of the myocardium along with pooling of blood in a dilated venous system. Peripheral vascular resistance is usually normal or increased, but barbiturates interfere with autonomic reflexes, which then do not adequately compensate for the myocardial depression and decreased venous return. Barbiturates can precipitate severe hypotension in patients whose compensatory reflexes are already maximally stimulated, such as those with heart failure or hypovolemic shock. Barbiturates also decrease cerebral blood flow and intracerebral pressure. Although hypnotic doses of barbiturates do not affect gastric emptying, higher doses can decrease gastrointestinal smooth muscle tone and peristaltic contractions and delay gastric emptying.

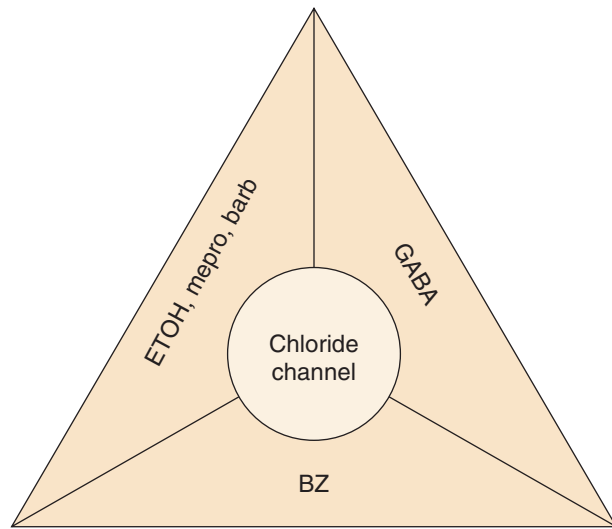
Barbiturates are classified according to their onset and duration of action (Box 165-1): ultra-short acting (onset immediate after intravenous dose, duration minutes), short acting (onset 10-15 minutes after oral dose, duration 6-8 hours), intermediate acting (onset 45-60 minutes, duration 10-12 hours), and long acting (onset 1 hour, duration 10-12 hours). Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. Short- and intermediate-acting preparations are almost completely metabolized to inactive metabolites in the liver, whereas 25% of a phenobarbital (long-acting) dose is excreted unchanged through the kidney. Because phenobarbital is a weak acid (pK<sub>a</sub> 7.2), alkalinization of the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance. Short- and intermediate-acting barbiturates are not significantly affected by pH changes in this range.

Barbiturates cross the placenta, with fetal levels approaching those of the mother. They are also excreted in low concentration in breast milk. Use during pregnancy is associated with birth defects (category D).

### Clinical Features

Mild barbiturate toxicity mimics ethanol intoxication. It is manifested with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, and impaired cognition.

In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. Although pupils are usually normal or small and reactive, concomitant hypoxia can cause pupils to be fixed and dilated. Corneal and gag reflexes may



**Figure 165-1.** The  $\gamma$ -aminobutyric acid (GABA) receptor complex. BZ, benzodiazepine binding site; GABA, GABA binding site; ETOH, mepro, barb, binding sites for ethanol, meprobamate, and barbiturates, respectively.

### Box 165-1 Barbiturates

#### Ultrashort Acting

Methohexital (Brevital)  
Thiopental (Pentothal)

#### Short and Intermediate Acting

Pentobarbital (Nembutal)  
Secobarbital (Seconal)  
Amobarbital (Amytal)  
Aprobarbital (Alurate)  
Butobarbital (Butisol)  
Butalbital (Fiorinal)

#### Long Acting

Phenobarbital (Solfoton, Luminal)  
Mephobarbital (Mebaral)

be diminished or absent, muscle tone flaccid, and deep tendon reflexes diminished or absent. Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose from barbiturate intoxication. These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma. A fluctuating level of consciousness is commonly seen. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise.

The life threat in severe barbiturate toxicity is respiratory depression. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, and pulse oximetry or capnography may be needed to detect the ventilation compromise.

Hypotension is common in patients with severe intoxication, along with a normal or increased heart rate. Barbiturate overdose is associated with noncardiogenic pulmonary edema. Altered pulmonary capillary permeability can be caused by hypoperfusion, hypoxia, or a direct effect of the drug. Pneumonia may be delayed.

Barbiturate withdrawal syndrome includes tremors, hallucinations, seizures, and delirium (similar to the delirium tremens

of ethanol withdrawal). However, severe withdrawal occurs only after dependence on short- or intermediate-acting barbiturates (e.g., pentobarbital, secobarbital, amobarbital, or butalbital). Because these drugs are not commonly used, this syndrome is now very rare.

### Diagnostic Strategies

The therapeutic level of phenobarbital is 15 to 40  $\mu\text{g/mL}$  (65–172  $\mu\text{mol/L}$ ). A serum level greater than 50  $\mu\text{g/mL}$  can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80  $\mu\text{g/mL}$  are potentially fatal. Serial phenobarbital levels can monitor effectiveness of treatment. Other than phenobarbital, barbiturates have high volumes of distribution, so serum levels do not accurately reflect CNS concentrations or correlate with clinical severity. A positive urine screen establishes only exposure to a barbiturate but does not prove that the drug is present in toxic amounts and should not be relied on to explain decreased mental status.

Chest radiographs can detect noncardiogenic pulmonary edema or pneumonia. Computed tomography of the head may be helpful in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis to detect other causes of stupor and coma.

Because the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared “brain dead” if barbiturates are present at therapeutic levels or higher.

### Management

Because barbiturates have no specific antidote, the key to management of these patients is supportive care, particularly with respect to the cardiovascular and respiratory systems. Severely intoxicated patients are unable to protect their airway and have decreased ventilatory drive. Supplemental oxygen may suffice for patients with mild to moderate overdose, but intubation is often required. Long-term induced paralysis is rarely necessary, and additional sedation usually is unnecessary for mechanical ventilation. Careful fluid replacement should maintain a systolic blood pressure above 90 mm Hg and adequate urine output. Patients should be monitored for fluid overload and pulmonary edema. Active warming should be initiated if the rectal temperature is below 30° C.

### Gastrointestinal Decontamination and Enhanced Elimination

Gastric emptying by lavage is not indicated. For large overdoses, there is evidence that clearance of phenobarbital is markedly increased with multidose activated charcoal (MDAC).<sup>2</sup> One dosage for MDAC is 25 g every 2 hours in an adult; the pediatric dose is 0.5 g/kg every 2 hours. If vomiting occurs, a smaller dose or antiemetics should be used. MDAC can also be administered slowly through a nasogastric tube. Contraindications to MDAC include an unprotected airway and gastrointestinal obstruction or perforation. Decreased peristalsis can result in constipation with MDAC and is a relative contraindication to MDAC.<sup>2</sup> Although MDAC may shorten the duration of the intoxication, there is no evidence for improved outcome over supportive care, and supportive care without administration of activated charcoal is also an acceptable approach.

Although alkalinization of the urine with sodium bicarbonate has been recommended in the past, a nonrandomized study suggested that MDAC alone is most effective at increasing the drug's clearance.<sup>3</sup> The authors of that study hypothesize that alkalinization may interfere with the ability of the drug to diffuse across intestinal mucosa from the blood into the gut. A recent

comprehensive review concluded that there is no role for urine alkalinization in acute barbiturate poisoning.<sup>4</sup>

Hemodialysis is rarely needed but may increase clearance of phenobarbital in the presence of renal or cardiac failure, acid-base or electrolyte abnormalities, unstable cardiorespiratory status, or inadequate response to less invasive measures. Because phenobarbital is 40 to 60% protein bound, hemoperfusion was advocated over hemodialysis; however, newer high-efficiency dialyzers using high blood flow rates provide drug clearance greater than that achieved by hemoperfusion.<sup>5</sup> Unfortunately, there are insufficient data to determine the true risk-benefit ratio of hemodialysis in acute barbiturate overdose.<sup>4</sup>

## Disposition

An asymptomatic patient who arrives in the emergency department (ED) after ingesting barbiturates should be observed for 6 hours after ingestion for mental status changes, slurred speech, ataxia, hypotension, and respiratory depression. Symptoms generally occur within 1 hour of ingestion. Patients who remain asymptomatic and have no significant complicating coingestants or medical problems can be discharged or referred for psychiatric care. Patients who are still symptomatic after 6 hours should be admitted for observation and supportive care.

## BENZODIAZEPINES

### Perspective

Before 1950, treatment options for anxiety were limited. Whereas meprobamate, first synthesized in 1950, ultimately proved no safer than the barbiturates, its commercial success inspired the development of other nonbarbiturate anxiolytics. With chlordiazepoxide in 1960 and diazepam in 1963, benzodiazepines emerged as the principal agents for the treatment of anxiety. Cardiac effects and fatalities from pure benzodiazepine overdose are rare, and respiratory depression is less than with barbiturates. In addition, drug-drug interactions involving benzodiazepines are uncommon.

Benzodiazepines remain among the most widely prescribed class of drugs (Table 165-1) and are the most common

prescription drugs used in suicide attempts. Fortunately, most benzodiazepine overdoses follow a relatively benign clinical course. Children make up 10% of benzodiazepine overdose cases.

## Principles of Disease

Benzodiazepines produce sedative, hypnotic, anxiolytic, and anti-convulsant effects by enhancing the inhibitory actions of GABA. Binding of a benzodiazepine to a specific benzodiazepine receptor potentiates GABA effects on the chloride channel at the GABA<sub>A</sub> receptor, increasing intracellular flux of chloride ions and hyperpolarizing the cell. The net effect is a diminished ability of the nerve cell to initiate an action potential, inhibiting neural transmission.

Three unique benzodiazepine receptors exist, distributed variably throughout the central and peripheral nervous systems. Classic benzodiazepines are nonselective, producing a broad range of clinical effects. Newer benzodiazepines interact selectively with a single receptor subtype to achieve a desired result, such as sedation, while minimizing unwanted effects.

## Pharmacokinetics

Benzodiazepines are rapidly absorbed orally. Intramuscular use of chlordiazepoxide and diazepam is limited by erratic absorption, but lorazepam and midazolam are predictably absorbed after intramuscular injection. After absorption, benzodiazepines distribute readily and rapidly penetrate the blood-brain barrier. In plasma, benzodiazepines are highly protein bound.<sup>6</sup>

All benzodiazepines are metabolized in the liver. Oxazepam, temazepam, and lorazepam are directly conjugated to an inactive, water-soluble glucuronide metabolite that is excreted by the kidney. Other benzodiazepines must first be converted by the hepatic cytochrome P<sub>450</sub> system. Chlordiazepoxide, diazepam, flurazepam, and clorazepate are metabolized to active derivatives that are then slowly conjugated and excreted. The long elimination half-lives of these intermediates can cause accumulation in the body with repeated dosing. Triazolam, alprazolam, and midazolam are converted to hydroxylated intermediates that are active, but because they are so rapidly conjugated and excreted, they do not contribute significantly to the drug's overall effect.<sup>6</sup>

**Table 165-1** Benzodiazepines

NAME	USUAL DOSE	ORAL PEAK (hr)	HALF-LIFE (hr)	PARENT METABOLITE ACTIVITY
Alprazolam (Xanax)	0.25-0.5 mg	1-2	6-27	Inactive
Chlordiazepoxide(Librium)	5-25 mg	0.5-4	5-30	Active
Clonazepam (Klonopin)	0.25-0.5 mg	1-2	18-50	Inactive
Clorazepate (Tranxene)	7.5-15 mg	1-2	1-3	Active
Diazepam (Valium)	2-10 mg	0.5-1	20-50	Active
Estazolam (ProSom)	1-2 mg	2	8-28	Inactive
Flurazepam (Dalmane)	15-30 mg	0.5-1	2-3	Active
Halazepam (Paxipam)	20-40 mg	1-3	14	Active
Lorazepam (Ativan)	0.5-2 mg	2-4	10-20	Inactive
Midazolam (Versed)	0.025-0.1 mg/kg	1-2	1.5-3	Active
Oxazepam (Serax)	10-30 mg	2-4	5-20	Inactive
Quazepam (Doral)	7.5-15 mg	2	39-41	Active
Temazepam (Restoril)	7.5-30 mg	1-2	3-19	Inactive
Triazolam (Halcion)	0.125-0.25 mg	1-2	1.5-5.5	Inactive

Cytochrome P<sub>450</sub> processes may be significantly impaired in elderly patients or those with liver disease, leading to prolonged elimination of some benzodiazepines. Coingestion of drugs that also undergo cytochrome P<sub>450</sub> metabolism (e.g., cimetidine, ethanol) also prolongs the half-lives of these benzodiazepines, but the clinical significance of these interactions is unclear.<sup>7</sup>

## Clinical Features

CNS depression is common in patients with benzodiazepine poisoning and ranges from mild drowsiness to coma. Respiratory depression is due mainly to upper airway obstruction and increased upper airway resistance from loss of muscle tone rather than central apnea. Significant respiratory depression is rare but can be seen with large oral overdoses or during intravenous conscious sedation, particularly when the benzodiazepine is combined with an opioid such as fentanyl.<sup>7</sup> Hypotension is uncommon. Other potential complications include aspiration pneumonia and pressure necrosis of skin and muscles.

Most children have symptoms within 4 hours of benzodiazepine ingestion. Ataxia is the most common sign of toxicity, occurring in 90% of patients. Respiratory depression occurs in less than 10% of pediatric cases, and hypotension has not been reported.

Prolonged or high-dose infusions of certain benzodiazepine preparations have been associated with the development of lactic acidosis. Metabolism of the propylene glycol diluent in diazepam and lorazepam intravenous solutions by alcohol dehydrogenase produces lactate, which can accumulate and cause acidosis severe enough to require intervention. Patients with renal or hepatic insufficiency are at increased risk for this complication.<sup>8</sup>

## Diagnostic Strategies

Any patient with altered mental status should have a blood glucose level rapidly determined. Qualitative immunoassays for benzodiazepines in urine are available but do not aid management decisions. Most of these tests detect only benzodiazepines that are metabolized to oxazepam glucuronide; therefore, clonazepam, lorazepam, midazolam, and alprazolam are not detected on many urine drug screens.<sup>9</sup> Serum drug concentrations are not routinely available and do not correlate with clinical severity. A lack of alcohol odor or a negative breathalyzer or blood ethanol test result suggests benzodiazepine or another sedative as a possible cause.

The benzodiazepine antagonist flumazenil should not be routinely administered to patients with coma of unknown origin or suspected benzodiazepine overdose, either for diagnostic or for therapeutic purposes.<sup>10</sup> Any possibility of concomitant tricyclic overdose contraindicates flumazenil use.

## Differential Considerations

Benzodiazepine overdose is usually suspected or diagnosed because of the clinical presentation. Many patients are arousable and can provide supporting information. Atypical or focal findings suggest the presence of other conditions. Profound coma or cardiopulmonary instability is rare with pure benzodiazepine overdose and should prompt the search for a coingestant. Nontoxicologic causes of CNS depression should also be considered.

## Management

### General

Initial stabilization, including endotracheal intubation, should not be delayed by the administration of an antidote. Most benzodiazepine overdoses can be managed expectantly. Activated charcoal is generally not beneficial in overdose.<sup>11</sup> MDAC, hemodialysis,

### Box 165-2 Use of Flumazenil

#### Indications

Isolated benzodiazepine overdose in nonhabituated user (e.g., accidental pediatric exposure)  
Reversal of conscious sedation

#### Absolute Contraindications

Suspected coingestant that lowers seizure threshold (e.g., tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate)  
Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)  
Concurrent sedative-hypnotic withdrawal  
Seizure activity or myoclonus  
Hypersensitivity to flumazenil or benzodiazepines  
Patient with neuromuscular blockade

#### Relative Contraindications

Chronic benzodiazepine use, not taken for control of life-threatening condition  
Known seizure disorder not treated with benzodiazepines  
Head injury  
Panic attacks  
Chronic alcoholism

and whole-bowel irrigation are not effective in benzodiazepine overdose.

### Antidote

Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and confirmed benzodiazepine overdose, but it is not recommended for the routine reversal of sedative overdose in the ED. Although theoretic benefits of flumazenil use include cost savings and avoidance of procedures and tests such as endotracheal intubation and lumbar puncture, several studies have not been able to demonstrate an actual benefit.<sup>12</sup> Seizures and cardiac dysrhythmias can occur after flumazenil administration, and fatalities have been reported. Flumazenil use can precipitate acute withdrawal in patients who are dependent on benzodiazepines. Similarly, this antidote is hazardous when it is given to patients who have coingested seizure-causing drugs (such as cocaine or a tricyclic antidepressant) because of loss of the benzodiazepine's protective anticonvulsant properties. Coingestants that cause dysrhythmias, such as carbamazepine and chloral hydrate, may increase the likelihood of cardiac effects. Other risk factors are summarized in Box 165-2. One study found that 12% of patients receiving flumazenil after known pure or mixed benzodiazepine overdose actually had a contraindication to its use.<sup>13</sup>

The initial adult dose of flumazenil is 0.2 mg given intravenously during 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2-mg doses at 1-minute intervals to a total of 1 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (0.7-1.3 hours), re-sedation occurs in up to 65% of patients and requires either redosing or continuous infusion (0.25-1.0 mg/hr).

In summary, benzodiazepine overdose requires primarily supportive care (including, in some cases, intubation). Flumazenil may precipitate seizures or acute withdrawal and should be used only in highly selected cases, such as small children with accidental poisoning or for accidental overdose of benzodiazepines during procedural sedation. When flumazenil is used, careful monitoring



**Box 165-3 Benzodiazepine Withdrawal Symptoms****Nonspecific**

Anxiety, depression, insomnia, tremor, tachycardia, sweating

**Severe (rare)**

Visual hallucinations, delirium, seizures

is necessary because of the risk for recurrent respiratory depression or re sedation. Use of flumazenil has not consistently altered outcome, complication rate, number of costly procedures performed, or duration of hospital stay in ED patients.<sup>13</sup>

**Disposition**

Patients remaining asymptomatic after 4 to 6 hours of ED observation may be medically cleared. For cases of deliberate overdose, appropriate psychiatric consultation should be obtained.

**Benzodiazepine Withdrawal Syndrome**

Abrupt discontinuation of a benzodiazepine in a chronic user results in a characteristic constellation of symptoms similar to ethanol withdrawal (Box 165-3). Risk for withdrawal is a function of both the dose of benzodiazepine and the duration of its use. Continuous treatment for more than 4 months is generally required before a patient is at risk for withdrawal. With abrupt discontinuation of a benzodiazepine, the most severe withdrawal symptoms are expected within several days to a week.<sup>14</sup> Use of flumazenil can precipitate immediate withdrawal symptoms. Treatment of withdrawal consists of restarting of benzodiazepines.

**FLUNITRAZEPAM**

Flunitrazepam (Rohypnol) has been used in Europe, Asia, and Latin America for insomnia and preoperative sedation since 1975. Although it has never been manufactured or sold in the United States, flunitrazepam has been suggested in many “date rape” incidents. Flunitrazepam has been an active agent in the illicit drug market, where it is used to alter the effects of other drugs, including heroin and cocaine.<sup>15</sup>

Flunitrazepam has 10 times more affinity than diazepam for certain benzodiazepine receptors. CNS depression occurs within 30 minutes. The drug is most frequently ingested with alcohol, producing additional disinhibition and amnesia. Despite marked CNS depression, patients can usually be aroused with noxious stimuli. The half-life of the drug is 16 to 35 hours, but coma can be prolonged for up to 48 hours.<sup>15</sup> Flunitrazepam is easily obtained outside the United States. The drug is not detected on routine urine drug screens, but if it is needed as evidence, urine should be refrigerated or frozen and the local or state police crime laboratory contacted to arrange specific testing. Metabolites of flunitrazepam are detected in the urine up to 72 hours after exposure.

**BUSPIRONE**

Bupirone (BuSpar) has been used for generalized anxiety since 1986. Unlike benzodiazepines, bupirone does not have any effect on GABA but is a partial serotonin (5-HT<sub>1A</sub>) agonist. To a lesser extent, it also antagonizes dopamine (D<sub>2</sub>) receptors. Bupirone has no hypnotic, anticonvulsant, or muscle relaxant effects.

Bupirone has several advantages over benzodiazepines. The drug causes minimal CNS depression, even in combination with

ethanol. Dosage adjustment is not needed for elderly patients. A withdrawal state after discontinuation has not been reported. Only one case of isolated bupirone overdose has been published. That patient was lethargic and had a tonic-clonic seizure but recovered fully.<sup>16</sup>

**ZOLPIDEM AND ZALEPLON**

Zolpidem (Ambien) and zaleplon (Sonata) differ in structure from both the benzodiazepines and bupirone, and neither is detected on a benzodiazepine toxicology screen. They act selectively at a specific benzodiazepine receptor, producing sedation without many of the side effects seen with benzodiazepines. They have modest anxiolytic, muscle relaxant, and anticonvulsant properties. Significant drug interactions are rare. Compared with zolpidem, zaleplon causes less memory loss and sedation at therapeutic doses and is more rapidly eliminated.<sup>17</sup> Transient visual disturbances, transient global amnesia, and hallucinations can occur in patients with normal levels of consciousness with both zolpidem and zaleplon.<sup>17-19</sup> Abuse of zolpidem is limited by vomiting, which may occur after a supratherapeutic dose. Both zolpidem and zaleplon are rapidly eliminated and lack active metabolites.<sup>20</sup> In 2005, a controlled-release formulation of zolpidem (Ambien CR) became available. The dual-layered tablet releases an immediate dose of zolpidem, followed by a slow, extended release from the inner layer to maintain plasma zolpidem concentrations. Clinical experience thus far suggests that overdoses with the controlled-release formulation mirror those of the immediate-release preparation, with only small differences in the likelihood of drowsiness, hallucinations, and ataxia.<sup>21</sup>

Patients with zolpidem overdose do well with supportive care alone. Fatalities from isolated zolpidem overdose are rare. All published cases have involved individuals found dead at home and have been associated with coingestants, particularly other sedative-hypnotics or antipsychotics.<sup>22</sup> Drowsiness is by far the most common symptom. Coma and respiratory failure are rare, despite overdoses of up to 40 times the normal dose, although intubation may be required, particularly if there are coingestants. Zolpidem overdose in children follows a similarly benign course. Drowsiness, ataxia, and hallucinations generally resolve within 10 hours.<sup>23</sup>

Overdose information for zaleplon is limited. In one case series, patients had CNS depression and mild hypotension. Arousal was temporally associated with flumazenil use in one patient.<sup>24</sup> The only published fatality involved a mixed drug overdose including unknown quantities of zaleplon and butalbital, with postmortem serum zaleplon concentration 40 times greater than therapeutic.<sup>25</sup> Adverse effects with therapeutic use include headache, anterograde amnesia, and transient visual hallucinations.<sup>20</sup> The blue-green discoloration of gastric contents, mouth, and urine after zaleplon overdose is attributed to the indigo carmine dye present in zaleplon's capsule shell.<sup>26</sup>

**ESZOPICLONE**

Eszopiclone (Lunesta) has been marketed in the United States since 2005 for treatment of insomnia. It is the S-isomer of racemic zopiclone, which has been used for decades outside the United States. Eszopiclone has a structure unrelated to that of benzodiazepines, barbiturates, zolpidem, and zaleplon.<sup>27-30</sup>

The mechanism of eszopiclone's action is not completely described but may involve a specific GABA<sub>A</sub> receptor close to or coupled with the benzodiazepine receptor.<sup>27-29</sup> Eszopiclone is rapidly absorbed, with a peak serum level at 1 hour and a half-life of 6 hours. It is metabolized in the liver to minimally active metabolites. The usual bedtime dose is 3 mg. It is recommended that elderly patients and those with hepatic insufficiency be treated with a lower (1 mg) dose.

Adverse effects with therapeutic use of eszopiclone include drowsiness, dizziness, dry mouth, unpleasant taste, nausea, and vomiting. Auditory and visual hallucinations have been reported.<sup>31</sup> Experience with eszopiclone overdose is limited. The key to treatment is good supportive care. CNS depression may be prolonged and pronounced in elderly patients.<sup>32</sup> A retrospective case review described 525 eszopiclone ingestions, but 259 of these patients had also ingested other drugs or chemicals.<sup>28</sup> The ingestions involved eszopiclone doses up to 210 mg and had mild to moderate symptoms at most. Two deaths occurred, both involving significant coingestants. A single case report described a 52-year-old man who had coronary vasospasm and a ventricular fibrillation arrest after ingestion of 45 to 60 mg of eszopiclone.<sup>30</sup> However, the arrest occurred approximately 20 hours after ingestion, and it is unclear what role, if any, eszopiclone played in causing the arrest.

## CHLORAL HYDRATE

### Perspective

Chloral hydrate has a low therapeutic ratio and can produce significant, potentially fatal toxicity. Whereas chloral hydrate use is rare today, it is still occasionally prescribed as a sedative in the elderly and for sedation in children undergoing medical procedures. The hypnotic oral adult dose is 0.5 to 1.0 g. The toxic oral dose in adults is approximately 10 g and may be as little as 1.5 g in a child.<sup>33</sup>

The toxic effects of chloral hydrate include CNS depression, gastrointestinal irritation, cardiovascular instability, hepatitis, and proteinuria.<sup>34,35</sup> The primary active metabolite of chloral hydrate, trichloroethanol, has a barbiturate-like effect on GABA<sub>A</sub> receptors and is responsible for most of the CNS depression seen with significant overdose.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and almost immediately metabolized to trichloroethanol by the enzyme alcohol dehydrogenase. Onset of action is 20 to 30 minutes.<sup>36</sup> Trichloroethanol is long acting, and its half-life can be significantly prolonged after overdose as metabolic pathways become saturated.

Chloral hydrate and ethanol in combination (the “Mickey Finn”) potentiate each other’s action to produce rapid loss of consciousness. Chloral hydrate increases the half-life of ethanol by competitively inhibiting the enzyme alcohol dehydrogenase, and the metabolism of ethanol generates NADH, a cofactor for the conversion of chloral hydrate to trichloroethanol.

### Clinical Features

Chloral hydrate toxicity causes CNS and respiratory depression, gastrointestinal irritation, cardiovascular instability, and dysrhythmias.<sup>34,35</sup> The combination of deep coma and cardiac dysrhythmia without hypoxia is characteristic of severe cases.

Mild chloral hydrate toxicity can mimic ethanol or barbiturate overdose, with drowsiness, ataxia, and lethargy. A pear-like odor to the patient’s breath or gastric contents may suggest the diagnosis. More severe toxicity includes miosis, muscle flaccidity, diminished deep tendon reflexes, hypoventilation, hypotension, and hypothermia.<sup>33</sup> Chloral hydrate is corrosive and causes nausea, vomiting, esophagitis, hemorrhagic gastritis, and, more rarely, gastrointestinal perforation or necrosis.<sup>33</sup> Transient hepatic or renal dysfunction can also occur.

Dysrhythmias from chloral hydrate toxicity can be fatal. Chloral hydrate decreases myocardial contractility, shortens the cardiac refractory period, and increases the sensitivity of myocardium to catecholamines. Dysrhythmias include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, multifocal premature ventricular contractions, torsades de pointes, ventricular

fibrillation, and asystole.<sup>36</sup> Hypotension results from inhibition of central neurovascular regulatory centers and impaired myocardial contractility.

### Management

The key to management is support of cardiorespiratory function. Intubation may be required for airway protection or to support ventilation and oxygenation. Avoid naloxone or flumazenil, which may precipitate ventricular dysrhythmias.<sup>33</sup> Because chloral hydrate, like other chlorinated hydrocarbons, sensitizes myocardium to catecholamines, epinephrine and norepinephrine should also be avoided. Standard antidysrhythmic agents, such as lidocaine, do not appear effective against chloral hydrate-induced cardiac ectopy. The treatment of choice is a beta-blocker.<sup>37</sup> Intravenous propranolol can be given in adult doses of 0.5 mg until ectopy is suppressed, followed by an infusion of 1 to 2 mg/hr, titrated to a heart rate of 80 to 100 beats/minute. A short-acting agent such as esmolol can also be used. Torsades de pointes should be treated with intravenous magnesium or overdrive pacing. Type I antidysrhythmic agents such as quinidine should be avoided. Unstable patients not responding to conservative therapy can be treated with hemoperfusion or hemodialysis.<sup>33</sup>

## OVER-THE-COUNTER SLEEP AIDS

### Perspective

Over-the-counter (OTC) sleep aids currently available in the United States contain either diphenhydramine or doxylamine. Many preparations also contain acetaminophen or aspirin, added to achieve nighttime pain relief. The availability and frequent use of these agents may explain why overdose is so common.

### Principles of Disease

Diphenhydramine and doxylamine are antihistamines that also have hypnotic, anticholinergic, and weak local anesthetic properties. They act as competitive antagonists of H<sub>1</sub> histamine receptors and cause sedation by inhibiting the actions of acetylcholine on muscarinic receptors in the CNS.

The pharmacokinetic profiles of diphenhydramine and doxylamine are similar. Both are rapidly absorbed, with peak plasma levels occurring at 1 to 2 hours after administration. In the systemic circulation, they are highly protein bound, with large volumes of distribution. Extensive metabolism occurs in the liver by the cytochrome P<sub>450</sub> system. The elimination half-life is 4 hours for diphenhydramine and 9 hours for doxylamine.

### Clinical Features

Impaired consciousness is the most frequent finding with diphenhydramine overdose. Somnolence, psychotic behavior, and agitation are common. Seizures can occur. Anticholinergic effects may be apparent, as noted in Chapter 150. Cardiovascular effects include sodium-channel blockade and wide-complex tachycardia.<sup>38</sup> Apart from a lower incidence of psychosis, doxylamine has toxicity similar to that of diphenhydramine. Seizures and rhabdomyolysis may occur with severe toxicity. Serious cardiotoxicity is rare. Doxylamine toxicity has been reported to cause false-positive results on some immunoassay-based drug screens for methadone and phencyclidine.<sup>39</sup>

### Diagnostic Strategies

Some comprehensive urine drug immunoassays will detect diphenhydramine. Quantitative serum levels of diphenhydramine

**Box 165-4**  $\gamma$ -Hydroxybutyrate Street Names

GHB	Liquid ecstasy
Grievous bodily harm	Liquid G
GBH	Somatomax
Georgia home boy	Soap
Gib	Salty water
Natural sleep-500	Scoop
Gamma-OH	Sodium oxybate
Gamma hydrate	Easy lay
Liquid X	Cherry menth
Organic quaalude	Fantasy
Liquid E	G-Riffick

**Box 165-5**  $\gamma$ -Butyrolactone Street Names

Blue Nitro	Nitro
Blue Nitro Vitality	NRG3
Enliven	Remforce
Fire Water	RenewTrient
Gamma G	Revitalize Plus
GH Revitalizer	Revivart
GHRE (growth hormone release extract)	SomatoPro
	Verve 5.0

or doxylamine are neither routinely available nor clinically useful. Serum acetaminophen and salicylate concentrations should be measured in patients with OTC sleep aid overdoses because many preparations contain both a hypnotic and an analgesic. Measurement of serum creatine kinase and urinary myoglobin may help detect myoglobinuria.

### Management

Management of mild to moderate toxicity from OTC sleep aid overdose is generally supportive. Specific details of anticholinergic toxicity are discussed in Chapter 150.

### Disposition

Patients with minor sedation or anticholinergic effects that are resolving or who remain asymptomatic after a 4-hour observation period can be medically cleared. If the ingestion was a suicide attempt or gesture, psychiatric evaluation is indicated. Other patients require inpatient observation in a monitored setting.

## $\gamma$ -HYDROXYBUTYRATE

### Perspective

Originally synthesized in the 1960s as an anesthetic,  $\gamma$ -hydroxybutyrate (GHB) was later discovered to be a naturally occurring metabolite of GABA. Since 1970, GHB has been used to treat narcolepsy, alcohol addiction, and opiate withdrawal.<sup>40</sup>

A 1977 report that GHB may enhance effects of steroids and increase release of growth hormone resulted in marketing of the agent as a “natural” aid for increasing muscle mass. Numerous reports of adverse effects followed. In 1989, the U.S. Food and Drug Administration (FDA) called for a voluntary withdrawal of the drug from store shelves. Its sale and manufacture were banned in 1990; however, illicit use of GHB increased, along with its precursors  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD) (Box 165-4).<sup>41</sup> The Hillary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 made GHB a schedule I controlled substance. In 2005, GHB was approved by the FDA for the treatment of narcolepsy under the trade name Xyrem (sodium oxybate, 0.5 mg/mL) as a schedule III drug.

GHB remains a popular drug of abuse.<sup>42</sup> Some individuals take GHB for its purported muscle-building and fat-burning actions, others for its psychoactive effects. The drug’s euphoria-producing properties make it popular at “raves” (large, crowded youth parties with energetic dancing to rhythmic music for many hours).<sup>43</sup> Self-treatment of insomnia with GHB has been reported and can cause dependence.<sup>44</sup> CNS depression, amnesia, and disinhibition caused by mixing of GHB with ethanol make this combination a potential agent in “date rape” situations.<sup>45,46</sup> A recent review of 226

GHB-associated deaths revealed that calls for medical assistance were often delayed or absent because of the false belief that victims need only “sleep off” their intoxications. Death occurs most often in the prehospital setting, both directly and by increasing the risk for fatal accidents. In this series, GHB was the sole intoxicant in 35% of deaths, underlining the lethal potential of the drug and its congeners.<sup>47</sup>

Chemical precursors to GHB are also commonly abused. GBL is rapidly converted to GHB by plasma lactonases. 1,4-BD is metabolized to  $\gamma$ -hydroxybutyraldehyde by the enzyme alcohol dehydrogenase and then to GHB by aldehyde dehydrogenase.<sup>48,49</sup>

### Principles of Disease

GHB binds to specific GHB receptors and at high concentrations to GABA<sub>B</sub> receptors.<sup>50</sup> The complex interaction between these two receptors may explain the sometimes paradoxical manifestations of GHB toxicity of somnolence alternating with agitation. Through its action on the GABA<sub>B</sub> receptor, GHB decreases release of dopamine.<sup>51,52</sup>

As underground laboratories often synthesize liquid GHB by mixing and heating butyrolactone and sodium hydroxide, careless preparation can result in residual unreacted base, causing significant caustic injury when the liquid is ingested.<sup>41</sup>

GHB is lipophilic and rapidly absorbed. Onset of symptoms occurs within 15 to 30 minutes, and peak plasma levels are reached within 20 to 60 minutes. Unlike GABA, GHB readily crosses the blood-brain barrier. The half-life of GHB is 27 minutes but may increase at high doses.

GBL is an industrial solvent that is rapidly absorbed after ingestion and metabolized within minutes to GHB by peripheral and hepatic lactonases.<sup>41</sup> Before conversion to GHB, GBL itself is inactive and has no sedating effects.<sup>40</sup> It produces a clinical syndrome similar to that of GHB ingestion, but its effects are greater and more prolonged. In fact, after ingestion, GBL is more efficient at delivery of GHB to the CNS than GHB itself is.<sup>53</sup> GBL is available under a number of street names (Box 165-5).

1,4-BD is converted after ingestion to GHB by the enzyme alcohol dehydrogenase.<sup>49</sup> Like GBL, it is used as an industrial solvent. Unlike GBL, 1,4-BD itself has sedative-hypnotic effects. Clinical findings are similar to those of GHB. When 1,4-BD and ethanol are ingested together, ethanol acts as a competitive inhibitor of alcohol dehydrogenase, so the toxic effects of 1,4-BD are delayed and prolonged, and the risk of death is increased.<sup>49</sup> 1,4-BD is available under a number of street names (Box 165-6).

In 2007, a children’s toy marketed under the names Aqua Dots and Bindeez Beads was contaminated when 1,4-BD was substituted for a more expensive industrial solvent during the manufacturing process. The toy consisted of tiny brightly colored spheres that were readily ingested by toddlers, causing decreased levels of consciousness, coma, or apparent seizures.<sup>54</sup>

**Box 165-6 1,4-Butanediol Street Names**

Blue Raine	Revitalize Plus
Dream On	Serenity
Fubar	SomatoPro
Inner G	Thunder nectar
Pine needle extract	Weight belt cleaner
Pine needle oil	Zen
ReJuv@Nite	

**Clinical Features**

Diagnosis of GHB intoxication is based on the history and clinical course. Rapid recovery from coma, or periods of agitation alternating with periods of decreased level of consciousness, is characteristic. Hypothermia may occur.<sup>43</sup> In the presence of coma, bradycardia with or without hypotension may be seen and can respond to stimulation alone.<sup>43</sup> Miosis with or without nystagmus may be seen. Emesis occurs in 50% of cases.<sup>43</sup> Apparent seizure activity may actually represent random myoclonic movements of the face and extremities. Severity is dependent on the dose and the concurrent use of alcohol or other psychoactive drugs.<sup>44</sup>

**Diagnostic Strategies**

GHB is not detected on urine toxicology screens. If laboratory confirmation is required, specimens must be collected early and sent for gas chromatography–mass spectroscopy. The drug may be detected in urine up to 12 hours after ingestion.<sup>55</sup>

Poisoning with other sedative-hypnotics can produce a similar clinical picture. Unique to GHB, however, is the relatively rapid resolution of symptoms. In the absence of a coingestant such as ethanol, most patients will awaken within 3 to 4 hours. Nearly all patients recover fully within 8 hours. Prolonged coma should prompt a search for another cause. Cardiac effects and refractory seizures are rare and suggest the presence of other agents.

**Management**

Because of the high incidence of emesis with GHB overdose, intubation for airway protection should be seriously considered in patients with significant CNS depression. Bradycardia unresponsive to stimulation can be treated with atropine. Treatment of isolated GHB ingestion is supportive. Although some authors suggest physostigmine to reverse GHB-induced coma, the efficacy and safety of this intervention have not been demonstrated, and physostigmine is not indicated or recommended.<sup>48,56,57</sup>

**Withdrawal**

Patients who suddenly stop GHB or its precursors after chronic, frequent use can experience a severe and potentially life-threatening withdrawal syndrome.<sup>50,58,59</sup> Because of the short half-life of GHB, symptoms of withdrawal begin within several hours of the last dose. The typical patient will have been using these products for

weeks or years, every 1 to 3 hours around-the-clock, to avoid withdrawal symptoms.

Mild withdrawal is manifested with anxiety, tremor, and insomnia. This can progress to confusion, delirium, overt psychosis, paranoid ideation, hallucinations (visual, aural, or tactile), and autonomic instability. Diagnosis relies on a history of symptoms beginning after abrupt cessation of use of these products. The differential diagnosis includes withdrawal from other sedatives or hypnotics, delirium tremens, sympathomimetic toxicity, serotonin syndrome, neuroleptic malignant syndrome, CNS infection, and thyroid storm.

Initial treatment begins with high-dose benzodiazepines. However, GHB withdrawal may involve depleted levels of GABA.<sup>58</sup> Because the effect of benzodiazepines requires the presence of GABA, they may not be effective in control of GHB withdrawal. Barbiturates, such as pentobarbital, which do not need GABA to be effective, are often required in cases of severe intoxication.<sup>60</sup>

These patients often require intensive care admission for aggressive sedation and to monitor fluctuating vital signs. Rhabdomyolysis and severe hyperthermia should be ruled out. Deaths have been reported, sometimes many days after presentation and after apparent improvement.<sup>58</sup>

**Disposition**

Because of GHB's short half-life, symptoms often resolve while the patient is still in the ED. The patient generally regains consciousness spontaneously. No delayed toxicity is expected. Patients should be counseled about the seriousness of GHB intoxication.<sup>47</sup>

**KEY CONCEPTS**

- Barbiturate intoxication is rare and most patients recover with observation and meticulous supportive care. Most will not require hemodialysis.
- A urine toxicology screen positive for barbiturates does not prove that the drug caused the patient's clinical condition. Serum barbiturate levels confirm the diagnosis but do not correlate with depth of coma or clinical outcome.
- Flumazenil is not needed in most benzodiazepine overdoses. Because it can precipitate seizures, it should not be used in patients who are regular benzodiazepine users. If flumazenil is used, patients should be monitored closely for recurrent respiratory depression and for re sedation.
- Chloral hydrate–induced dysrhythmia should be treated with a beta-blocker.
- Endotracheal intubation to protect against emesis and respiratory depression should be strongly considered for patients with GHB overdose and significant CNS depression.
- Withdrawal from GHB or its precursors can be manifested with anxiety, tremor, and insomnia but can progress to a severe syndrome characterized by delirium and autonomic instability. Management of this syndrome often requires high-dose benzodiazepines or barbiturates.

*The references for this chapter can be found online by accessing the accompanying Expert Consult website.*



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