Sedative-Hypnotic Agents

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**KEY POINTS**

- Benzodiazepines account for the majority of overdoses with sedative-hypnotic drugs.
- Benzodiazepines can induce cardiovascular and pulmonary toxicity, but fatalities resulting from pure benzodiazepine overdoses are rare.
- Central nervous system depression is the primary symptom of sedative-hypnotic toxicity.
- Treatment should focus on supportive care, with particular attention to airway patency and respiratory function.
- Urinary alkalinization and multiple doses of activated charcoal can enhance the elimination of phenobarbital.
- Flumazenil is a reversal agent for benzodiazepine toxicity, but it should be used cautiously, to avoid the risk of seizures.
- Other possible causes of altered mental status should always be considered.

**EPIDEMIOLOGY**

Sedative-hypnotic agents are a heterogeneous group of agents that have tranquilizing (sedative) or sleep induction (hypnotic) properties. Grouped with antipsychotics, they comprise the fourth leading class of substances reported to poison centers, and they are the leading cause of reported fatalities. These drugs are widely used in clinical settings but are also used for suicide, illicit recreational activities, and facilitation of sexual assault (“date rape”). Several high-profile deaths have been attributed to sedative-hypnotic overdoses.

Benzodiazepines have largely supplanted older agents and have become the most widely used sedative-hypnotics in clinical settings. However, given their prevalence, benzodiazepines also account for the majority of sedative-hypnotic overdoses. Flunitrazepam, sometimes referred to as “roofies,” is a potent benzodiazepine that has been popularized as a street drug of abuse and has been implicated as a date-rape drug.

Barbiturates were formerly the primary sedative-hypnotic agents used clinically. Currently, they are most often encountered as anticonvulsants, induction agents for anesthesia, and agents used for procedural sedation. Because the barbiturates have largely been replaced clinically by benzodiazepines due to safety concerns, their prevalence in overdoses has drastically decreased when compared with previous decades. The reported use of barbiturates among high school seniors experienced a slow but steady surge throughout the 1990s and reached a peak in 2005, only to experience a decline since then. Barbiturates accounted for only two single-substance deaths reported to poison centers in 2009.

Gamma-hydroxybutyrate (GHB) was synthesized in 1960 as an anesthetic agent. Although it found limited use in this arena, GHB gained widespread acceptance in the bodybuilding community in the 1990s as a purported anabolic agent. More recently, it has been used as a recreational drug for its euphoric and intoxicating effects. It has also been implicated in date rape because of its “knockout” and amnesic properties.

Several nonbenzodiazepine sedatives have been introduced for sleep induction. Examples include zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta). Cases of abuse and dependence have been reported, albeit with much less frequency compared with benzodiazepines. Nonbenzodiazepine sedatives have been implicated in cases of impaired driving.

Chloral hydrate has been used as a sedative since the nineteenth century. In the early 1900s, chloral hydrate was used maliciously, added to alcoholic drinks consumed by unwaried individuals to facilitate robberies. The drug-laced drink was referred to as a “Mickey Finn,” named after the owner of a Chicago bar who used these drinks to rob unsuspecting patrons. Currently, chloral hydrate is used primarily for procedural sedation.

Propofol is a short-acting sedative-hypnotic that has become widely used clinically for induction of anesthesia and procedural sedation. Despite its abuse potential, the literature is limited to case reports of toxicity from recreational use because of its limited availability to the general public. Most reported cases involve self-administration by medical personnel. Propofol is covered in greater detail elsewhere in this text.
BOX 155.1 Benzodiazepines

<table>
<thead>
<tr>
<th>Duration</th>
<th>Benzodiazepines</th>
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<tbody>
<tr>
<td>Short</td>
<td>Midazolam (Versed)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Triazolam (Halcion)</td>
</tr>
<tr>
<td>Long</td>
<td>Clonazepam (Klonopin)</td>
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</table>

The benzodiazepines produce central nervous system (CNS) depression through effects mediated by gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter. A specific benzodiazepine receptor exists on the GABA_\alpha_ receptor. When a benzodiazepine binds to this receptor, it subsequently promotes GABA binding to the GABA_\alpha_ receptor. Activation of the GABA_\alpha_ receptor results in influx of chloride into the neuronal cell and causes CNS inhibition. As such, benzodiazepines have anxiolytic, muscle relaxant, sedative, hypnotic, amnestic, and anticonvulsant properties.

Pure benzodiazepine overdoses cause mild to moderate CNS depression. Deep coma requiring assisted ventilation can occur, especially when a benzodiazepine is used with other sedating drugs. In severe overdoses, these agents can induce cardiovascular and pulmonary toxicity, but fatalities resulting from pure benzodiazepine overdoses are rare.

BARBITURATES

The barbiturates are often classified according to their therapeutic duration of action: ultrashort-acting, short-acting, intermediate-acting, and long-acting agents (Box 155.2). In overdoses, however, the duration of action varies with dose, rate of absorption, and rate of distribution and elimination. The ultrashort-acting and short-acting agents are highly lipid soluble and rapidly penetrate the CNS, so the onset of symptoms is also rapid. In addition, the ultrashort-acting barbiturates are more highly protein bound, have higher acid-dissociation constant (pK_a) values, and have larger volumes of distribution. Long-acting agents such as phenobarbital are metabolized more slowly in the liver, with a greater fraction of unchanged drug excreted in the kidney. These factors help explain why enhanced renal elimination through alkalinization may be more effective with phenobarbital, which also has a lower pK_a than the other barbiturates, thus making it more sensitive to alkalinization. In addition, phenobarbital undergoes enterohepatic recirculation, which makes repeated use of activated charcoal potentially advantageous.

Barbiturates are primarily CNS depressants that mediate their effect through several mechanisms. The barbiturates promote GABA binding to the GABA_\alpha_ chloride channel complex. They can also bind directly to GABA_\alpha_ chloride ion channels in the CNS, and the influx of chloride into neuronal cells leads to greater CNS inhibition. Barbiturates may also reduce specific excitatory neurotransmission.

The reticular activating system and the cerebellum appear to be the most susceptible to the depressant effects of barbiturates. Toxicity can lead to suppression of skeletal, smooth, and cardiac muscles, with resulting depressed myocardial contractility, bradycardia, vasodilation, and hypotension (Table 155.1).

GAMMA-HYDROXYBUTYRATE

GHB is a metabolite of GABA that occurs naturally in the human brain. It is highly lipophilic and rapidly absorbed, and, unlike GABA, it readily crosses the blood-brain barrier. Presentation in a coma state and subsequent rapid recovery is characteristic of GHB overdose.
These signs, symptoms, and test results should prompt the clinician to search for other causes of central nervous system depression:

- Focal neurologic deficit
- Fever
- External evidence of trauma
- Seizure activity
- QRS prolongation on electrocardiogram (seen with agents that can block myocardial sodium channels, such as tricyclic antidepressants)
- Electrolyte abnormalities
- Metabolic acidosis
- Hypoglycemia
- Dysrhythmias (except with chloral hydrate)

Mild to moderate sedative-hypnotic overdoses may manifest with a reduced level of consciousness, slurred speech, and ataxia. At high doses, sedative-hypnotic agents can cause hypothermia, hypotension, bradycardia, flaccidity, hyporeflexia, coma, and apnea. These severe symptoms are more commonly encountered in barbiturate overdoses. Patients with severe overdoses may appear to be dead, with no electroencephalographic activity.
The differential diagnosis of sedative-hypnotic toxicity includes any condition or ingestion resulting in CNS depression. Many other substances are capable of producing profound CNS depression, including alcohol and opiates. However, care should be made not to miss other, nontoxicologic causes of CNS depression. Although sedative-hypnotic toxicity resolves with just supportive care, other mimickers of sedative-hypnotic overdose may need other acute interventions. Other diagnoses that should be considered include head trauma with intracranial hemorrhage, embolic and hemorrhagic stroke, electrolyte abnormalities, hypoglycemia, hyperglycemic crisis, hypoxemia, hypothyroidism, liver or renal failure, CNS infection, seizures, and significant alterations in temperature (Table 155.2).

Diagnostic testing should be used to help exclude other causes of altered mental status. A fingerstick blood glucose determination, pulse oximetry, and cardiac monitoring may help the clinician avoid missing hypoglycemia, hypoxemia, or dysrhythmia.

Further testing to help clarify the patient’s presentation may include serum electrolytes, blood urea nitrogen, blood creatinine, serum ethanol, blood gas analysis, chest radiograph, computed tomography of the brain, cerebrospinal fluid analysis, serum transaminases, serum bilirubin, ammonia level, blood cultures, and urinalysis. If the patient is female, a urine pregnancy test is warranted. Directed quantitative serum levels of certain drugs may also be helpful; these may include acetaminophen, salicylate, lithium, and anticonvulsants.

Most institutions have a qualitative urine drug screen available, although this screen varies by institution. Most of the screens are immunoassays that detect the presence of certain drugs or metabolites in the urine. In the case of sedative-hypnotic agents, the commonly available screens usually test for benzodiazepines. The other sedative-hypnotic agents are typically not included in most urine drug screens. The typical benzodiazepine screen identifies metabolites of 1,4-benzodiazepines such as oxazepam or desmethyldiazepam. Benzodiazepines that are not metabolized or are metabolized to other compounds remain undetected. In addition, the detection cutoff may be set at a point at which the assay may not detect certain agents that can induce effects in very small amounts. A false-negative screen result may occur with

Table 155.2  Differential Diagnosis of Sedative-Hypnotic Toxidromes and Priority Actions

<table>
<thead>
<tr>
<th>DIAGNOSTIC CONSIDERATION</th>
<th>PRIORITY ACTION(S)</th>
</tr>
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<tbody>
<tr>
<td>Airway and respiratory status?</td>
<td>Provide airway protection and respiratory support as needed</td>
</tr>
<tr>
<td>Trauma?</td>
<td>If trauma is suspected, maintain spinal immobilization</td>
</tr>
<tr>
<td>Cardiovascular status?</td>
<td>Start cardiac monitoring</td>
</tr>
<tr>
<td>Hypothermia or hyperthermia?</td>
<td>Actively rewarms severely hypothermic patients</td>
</tr>
<tr>
<td>Overdose or toxicity?</td>
<td>Consider administering activated charcoal to patients with a secure airway</td>
</tr>
</tbody>
</table>

MDAC, Multiple-dose activated charcoal.
certain benzodiazepines, including alprazolam, clonazepam, and flunitrazepam. The clinician must recognize the limitations of this screen.

Quantitative benzodiazepine concentrations correlate poorly with pharmacologic or toxicologic effects and are poor predictors of clinical outcome.

A quantitative serum phenobarbital level can be helpful to document toxicity, but it is not mandatory for definitive typically management. Therapeutic concentrations of phenobarbital range between 15 and 40 mg/L. Patients with levels higher than 50 mg/L exhibit mild toxicity, whereas patients with levels higher than 100 mg/L are typically unresponsive to pain and may suffer from respiratory and cardiac depression.

**TREATMENT**

The mainstay of treatment for the patient with sedative-hypnotic overdose is supportive care, with particular attention to airway patency and respiratory status. When hypotension occurs, it should be managed with fluid resuscitation and vasopressors as needed.

Beta-blockers have been successfully used to treat cardiac dysrhythmias resulting from chloral hydrate toxicity because myocardial catecholamine sensitivity is believed to induce the dysrhythmia. Epinephrine and norepinephrine are relatively contraindicated because the myocardium may have increased sensitivity to these types of agents.

Patients who are stable after significant ingestions should receive activated charcoal as a means of preventing absorption of drugs still contained within the gastrointestinal tract. The efficacy of this procedure decays with time, so activated charcoal should be given expeditiously, ideally within the first hour after the ingestion occurred. The initial dose of activated charcoal is typically 1 g/kg. Ideally, at least a 10:1 ratio of charcoal to drug should be achieved. Given the CNS depression caused by sedative-hypnotics, careful attention should be directed to avoiding aspiration. If airway-protective reflexes are not intact, then administration of activated charcoal should be withheld unless the airway is protected by some other means.

Repeat dosing of activated charcoal has been recommended for increased clearance of certain drugs, one of which is phenobarbital. This therapeutic procedure has been referred to as multiple-dose activated charcoal (MDAC). It is thought to be helpful for phenobarbital because this drug undergoes enterohepatic circulation and is excreted back into the gut, where activated charcoal present in the intestine may bind it before it is reabsorbed distally. Phenobarbital also has physical characteristics that allow it to diffuse from the blood into the intestinal lumen. With MDAC, activated charcoal avidly binds to the phenobarbital in the intestinal lumen, a process that creates a concentration gradient into the intestine and subsequently enhances the elimination of the phenobarbital. Although MDAC has been shown to increase clearance phenobarbital, it has not been shown to improve overall clinical outcomes.

After the initial dose of activated charcoal, a reasonable dosing regimen for MDAC in adults can be accomplished by administering 25 g of activated charcoal without a cathartic every 2 hours. In pediatric patients, a dose of 0.25 g/kg every 2 hours may be used. The activated charcoal can be administered orally or through a nasogastric or orogastric tube. If a feeding pump is available, the activated charcoal can be administered continuously instead of at 2-hour intervals. Physicians must be aware that some charcoal preparations are premixed with a cathartic (usually sorbitol), and repeat doses are contraindicated because they may cause dehydration and electrolyte imbalances. A small dose of sorbitol (0.2 to 0.5 g/kg) may be given with the first dose of activated charcoal to prevent constipation. MDAC is contraindicated in patients who do not have protective airway reflexes or an otherwise secure airway. MDAC is also contraindicated in patients who have evidence of ileus or who are hemodynamically unstable.

Alkalinizing the urine with the intravenous administration of sodium bicarbonate can increase the elimination of phenobarbital. Urinary alkalinization with sodium bicarbonate to a pH of 7.5 to 8.0 can hasten the renal excretion of phenobarbital. Urinary alkalinization can be accomplished with an initial sodium bicarbonate bolus of 1 mEq/kg, followed by a continuous infusion. This infusion is made by adding 100 to 150 mEq of sodium bicarbonate to 850 mL of dextrose 5% in water and titrating it to maintain a urine pH of greater than 7.5 with an arterial pH less than 7.5. The rate must be assessed hourly to avoid excessive administration of fluid or bicarbonate, which can cause pulmonary or cerebral edema or electrolyte imbalance. Although expediting the elimination of phenobarbital from the body has theoretical benefit, no difference in clinical outcome has been shown. Alkalinization does not increase excretion of short- and medium-acting agents, which are more lipid soluble.

MDAC appears to be superior to urinary alkalinization for enhancing the elimination of phenobarbital. Performing both procedures concurrently appears to have no benefit. Urinary alkalinization may still be useful in a patient who cannot undergo MDAC.

In patients who are not responsive to standard therapeutic measures, or in patients with renal failure, hemodialysis may help eliminate long-acting barbiturates. These agents are less protein bound and less lipid soluble that the shorter-acting barbiturates, characteristics that enhance the role of hemodialysis. Fortunately, extracorporeal elimination is rarely indicated because most barbiturate overdoses resolve with supportive care alone.

Hemodialysis can enhance the elimination of chloral hydrate and its metabolites. However, supportive measures are generally effective. Hemodialysis may have a role if a patient with chloral hydrate toxicity is not responding to conservave therapy.

Flumazenil is a specific antagonist for benzodiazepines. It competitively binds at the benzodiazepine receptor, displaces benzodiazepines from the site, and inhibits GABA potentiation. Flumazenil is lipid soluble and readily crosses the blood-brain barrier to exert its effects quickly. Typically, benzodiazepine-induced sedation is reversed within a couple of minutes.

In the setting of procedural sedation, flumazenil is an excellent rescue agent for inadvertent supratherapeutic administrations of a benzodiazepine agent. Flumazenil may also be helpful in the setting of an isolated known benzodiazepine overdose. Unfortunately, this situation rarely occurs clinically. The use of flumazenil in the setting of a multiple drug overdose that includes a benzodiazepine is less clear.

Overall, for an unknown overdose, the administration of flumazenil is not indicated. Flumazenil does not antagonize...
the CNS effects of alcohol, barbiturates, tricyclic antidepressants, or narcotics. Reports have noted precipitation of seizure activity in the setting of mixed overdose or benzodiazepine dependence.26 Because supportive therapy is usually effective in benzodiazepine overdose, the benefit of flumazenil may not outweigh the risks of administration when circumstances surrounding the toxic ingestion are unclear. Flumazenil use has been described in the setting of overdose of the newer, non-benzodiazepine sedatives.27 However, supportive care is usually effective in these cases as well.

PARADOXICAL REACTIONS

Occasionally, patients who have been exposed to sedative-hypnotic agents experience a reaction that can be characterized by an increase in psychomotor activity. This has been most commonly described in benzodiazepines.28 The reactions can range from increased talkativeness and excessive movement to rage and hostility. As a whole, these reactions have been termed paradoxical because they seem counter to the sedative properties of these agents.

The mechanism of these paradoxical reactions is unclear, but some characteristics seem to increase the risk of these reactions. These characteristics include the younger and older age groups, as well as underlying psychiatric disorders. A genetic predisposition to these reactions may also exist.29 The use of flumazenil,30-32 haloperidol,33 and other agents has been described for the treatment of these reactions, with variable success. However, the mainstay of treatment should focus on supportive care. This attention to supportive care should be all that is required.

FOLLOW-UP, NEXT STEPS IN CARE, AND PATIENT EDUCATION

Patients who are symptom free from an isolated sedative-hypnotic overdose may be discharged home after a traditional 4- to 6-hour observation period. However, the events leading to the exposure may preclude discharge home. Psychiatry consultation is necessary for those patients with intentional overdoses.

Patients with prolonged sedation or other evidence of toxicity should be admitted for further observation and treatment.

Admission to a critical care setting is dictated by the severity of toxicity. Hemodynamic instability, respiratory failure, coma, severe hypothermia, and the need for hemodialysis are some indications for admission to an intensive care unit.

SUGGESTED READINGS


REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES