CHAPTER 74
SEDATIVE-HYPNOTICS

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Sedative-hypnotics are xenobiotics that limit excitability (sedation), and/or induce drowsiness and sleep (hypnosis). *Anxiolytics* (formerly known as *tranquilizers*) are medications prescribed for their sedative-hypnotic properties. There are many different types of medications used to induce anxiolysis or sleep. This chapter focuses primarily on pharmaceuticals prescribed for their sedative-hypnotic effects, many of which interact with the γ-aminobutyric acid-A ($GABA_A$) receptor (Table 74–1). Specific sedative-hypnotics such as ethanol and γ-hydroxybutyric acid are discussed in more depth in their respective chapters (Chaps. 77 and 80).

HISTORY AND EPIDEMIOLOGY

Mythology of ancient cultures is replete with stories of xenobiotics that cause sleep or unconsciousness (Chap. 1). Symptomatic overdoses of sedative-hypnotics were described in the medical literature soon after the commercial introduction of bromide preparations in 1853. Other commercial xenobiotics that subsequently were developed include chloral hydrate, paraldehyde, sulfonyl, and urethane.

The barbiturates were introduced in 1903 and quickly supplanted the older xenobiotics. This class of medications dominated the sedative-hypnotic market for the first half of the 20th century. Unfortunately, because they have a narrow therapeutic-to-toxic ratio and substantial potential for abuse, they quickly became a major health problem. By the 1950s, barbiturates were frequently implicated in overdoses and were responsible for the majority of drug-related suicides. As fatalities from barbiturates increased, attention shifted toward preventing their abuse and finding less toxic alternatives.[19] The "safer" drugs of that era included methyprylon, glutethimide, ethchlorvynol, bromides, and methaqualone. Unfortunately, many of these sedative hypnotics also had significant undesirable effects. After the introduction of benzodiazepines in the early 1960s, barbiturates and the other alternatives were quickly replaced as commonly used sedatives in the United States.

Intentional and unintentional overdoses with sedative-hypnotics occur frequently. According to the American Association of Poison Control Centers, sedative-hypnotics is consistently one of the top five classes of xenobiotics associated with overdose fatalities (see Chap. 135). With the ubiquitous worldwide use of sedative-hypnotics, they may be associated with a substantially higher number of overdoses and deaths than are officially reported. For example, a recent report described benzodiazepines as being increasingly used in drug-facilitated thefts outside the United States.[75]

Chlordiazepoxide, the first commercially available benzodiazepine, initially was marketed in 1960. Since then, more than 50 benzodiazepines have been marketed, and more are being developed. Compared with barbiturate overdoses, overdoses of benzodiazepines alone account for relatively few deaths.[37] Most deaths associated with benzodiazepines result from mixed overdoses with other centrally acting respiratory depressants.[46]

Benzodiazepines remain the most popular prescribed anxiolytics. However, the recently introduced hypnotics zolpidem, zaleplon, zopiclone, and eszopiclone have replaced benzodiazepines as the most commonly prescribed pharmaceutical sleep aids. Melatonin and ramelteon are emerging as popular sleep aids whose effects are mediated through melatonin receptor subtypes MT-1 and MT-2 specifically.[107,112,127] Dexmedetomidine, a central α_2-adrenergic agonist, is now increasingly used in the hospital setting for short-term sedation.[5,111]

PHARMACODYNAMICS/TOXICODYNAMICS

All sedative-hypnotics induce central nervous system (CNS) depression. Most clinically effective sedative-hypnotics produce their physiologic effects by enhancing the function of GABA-mediated chloride channels via agonism at the $GABA_A$ receptor. These receptors are the primary mediators of inhibitory neurotransmission in the brain (see Chap. 13). The $GABA_A$ receptor is a pentameric structure composed of varying polypeptide subunits associated with a chloride channel on the postsynaptic membrane. These subunits are classified into families (α, β, γ, etc.). Variations in the five subunits of the GABA receptor confer the potency of its sedative, anxiolytic, hypnotic, amnestic, and muscle relaxing properties. The most common $GABA_A$ receptor in the brain is composed of $\alpha_1\beta_2\gamma_2$ subunits. Almost all sedative-hypnotics bind to $GABA_A$ receptors containing the α_1 subunit. One exception may be etomidate, which has been shown to produce sedation at the β_2 unit and anesthesia at the β_3 subunit.[24,91,104,150] Low doses of benzodiazepines will be effective only at $GABA_A$ receptors with the γ_2 subunit. Even within classes of sedative-hypnotics, there will be varying affinities for differing subunits of the GABA receptor.[30,79]

Many sedative-hypnotics also act at receptors other than the $GABA_A$ receptor. Trichloroethanol and propofol, also inhibit glutamate-mediated *N*-methyl-D-aspartate (NMDA) receptors, thereby inhibiting excitatory neurotransmission.[26,99,116] Some benzodiazepines may also inhibit adenosine metabolism and reuptake, thereby potentiating both A_1-adenosine (negative dromotropy) and A_2-adenosine (coronary vasodilation) receptor-mediated effects.[87,124] Benzodiazepines also interact with specific benzodiazepine receptors that are not associated with the GABA receptor. These receptors have been labeled ω receptors. Benzodiazepines can also interact with serotonergic pathways. For example, diazepam modulates morphine analgesia via interactions with serotonin receptors. In addition, the anxiolytic effects of clonazepam can be partially explained by upregulation of serotonergic receptors, specifically 5-HT_1 and 5-HT_2.[8,88,157] Newer sleep aids, such as melatonin and ramelteon, do not appear to act at the $GABA_A$ receptor. Instead, they are agonists at melatonin receptor subtypes MT-1 and MT-2 in the suprachiasmatic nucleus of the brain.[127] Dexmedetomidine, a central α_2-adrenergic agonist similar to clonidine, induces a state of "cooperative sedation."[136]

PHARMACOKINETICS/TOXICOKINETICS

Most sedative-hypnotics are rapidly absorbed via the gastrointestinal (GI) tract, with the rate-limiting step consisting of dissolution and dispersion of the xenobiotic. Barbiturates and benzodiazepines are primarily absorbed in the small intestine. Clinical effects are determined by their relative ability to penetrate the blood–brain barrier. Drugs that are highly lipophilic penetrate most rapidly. The ultrashort-acting barbiturates are clinically active in the most vascular parts of the brain (gray matter first), with sleep occurring within 30 seconds of administration. Table 74–1 lists individual sedative-hypnotics and some of their pharmacokinetic properties.

TABLE 74–1. Pharmacology of Sedative-Hypnotics

	Equipotent Dosing Oral Dose (mg)[a]	$t_{1/2}$ (min.)	Protein Binding (%)	V_d (L/kg)	Active Metabolite Important
Benzodiazepines					
Agents with full agonist activity at the benzodiazepine site					
Alprazolam (Xanax)	1.0	10–14	80	0.8	No
Chlordiazepoxide (Librium)	50	5–15	96	0.3	Yes
Clorazepate (Tranxene)	15	97	0.9	Yes	
Clonazepam (Klonopin)	0.5	18–50	85.4	Unclear	Yes
Diazepam (Valium)	10	20–70	98.7	1.1	Yes
Estazolam (ProSom)	2.0	8–31	93	0.5	No
Flunitrazepam[b] (Rohypnol)	1.0	16–35	80	1.0–1.4	Yes
Flurazepam (Dalmane)	30	2.3	97.2	3.4	Yes
Lorazepam (Ativan)	2.0	9–19	90	1–1.3	None
Midazolam (Versed)	–	3–8	95	0.8–2	Yes
Oxazepam (Serax)	30	5–15	Unclear	Unclear	No
Temazepam (Restoril)	30	10–16	97	0.75–1.37	No
Triazolam (Halcion)	0.25	1.5–5.5	90	0.7–1.5	Yes
Nonbenzodiazepines active mainly at the type I (ω_1) benzodiazepine site					
Eszoplicone (Lunesta)	?	6	55	1.3	No
Zaleplon (Sonata)	20	1.0	92	0.54	No
Zolpidem (Ambien)	20	1.7	92	0.5	No
Barbiturates					
Amobarbital (Amytal)	–	8–42	Unclear	Unclear	Unclear
Aprobarbital[b] (Alurate)	–	14–34	Unclear	Unclear	Unclear
Butabarbital (Butisol)	–	34–42	Unclear	Unclear	Unclear
Barbital[b]	–	6–12	25	Unclear	Unclear
Mephobarbital (Mebaral)	–	5–6	40–60	Unclear	Yes
Methohexital (Brevital)	–	3–6	73	2.2	Unclear
Pentobarbital (Nembutal)	100	15–48	45–70	0.5–1.0	Unclear
Phenobarbital (Luminal)	30	80–120	50	0.5–0.6	No
Primidone (Mysoline)	–	3.3–22.4	19	Unclear	Yes
Secobarbital (Seconal)	–	15–40	52–57	Unclear	Unclear
Thiopental (Pentothal)	–	6–46	72–86	1.4–6.7	Unclear
Other					
Chloral hydrate (Aquachloral)	NA	4.0–9.5	35–40	0.6–1.6	Yes
Ethchlorvynol[b] (Placidyl)	NA	10–25	30–40	4	Unclear
Etomidate (Amidate)	NA	2.9–5.3	98	2.5–4.5	Unclear
Glutethimide[b] (Doriden)	NA	5–22	47–59	2.7	Unclear
Methyprylon[b] (Nodular)	NA	3–6	60	0.97	Unclear
Meprobamate[b] (Miltown)	NA	6–17	20	0.75	Unclear
Methaqualone[b] (Quaalude)	NA	19	80–90	5.8–6.0	Yes
Paraldehyde[b] (Paral)	NA	7	Unclear	0.9	Unclear
Propofol (Diprivan)	NA	4–23	98	2–10	No
Ramelteon (Rozerem)	NA	1–2.6	82	High	Yes
Dexmedetomidine (Precedex)	NA	2	94	1.5	No

NA = not applicable comparison.

[a]This table is an approximation of equipotent doses of xenobiotics affecting the benzodiazepine receptor and several barbiturates. All of the full agonist benzodiazepines have similar amnestic, anxiolytic, sedative, and hypnotic effects. These effects are a reflection of dose and serum concentration. There can be significant variation of these effects according to age and gender.

[b]Not presently available in the United States.

After initial distribution, many of the sedative-hypnotics undergo a redistribution phase as they are dispersed to other body tissues, specifically fat. Xenobiotics that are redistributed, such as the lipophilic (ultrashort-acting) barbiturates and some of the benzodiazepines (diazepam, midazolam), may have a brief clinical effect as the early peak concentrations in the brain rapidly decline. The clinical activity of many of them after single doses is determined by their rapid distribution and redistribution (alpha phase) and not by their elimination (beta phase) (see Chap. 8).

Many of the sedative-hypnotics are metabolized to pharmacologically active intermediates. This is particularly true for chloral hydrate and some of the benzodiazepines. Benzodiazepines can be demethylated, hydroxylated, or conjugated with glucuronide in the liver. Glucuronidation results in the production of inactive metabolites. Benzodiazepines, such as diazepam, are demethylated which produces active intermediates with a more prolonged therapeutic half-life than the parent compound. Because of the individual pharmacokinetics of sedative-hypnotics and the production of active metabolites, there is often little correlation between the therapeutic and biologic half-lives.

The majority of sedative-hypnotics, such as the highly lipid-soluble barbiturates and the benzodiazepines, are highly protein bound. These drugs are poorly filtered by the kidneys. Elimination occurs principally by hepatic metabolism. Chloral hydrate and meprobamate are notable exceptions. Xenobiotics with a low lipid-to-water partition coefficient, such as meprobamate and the longer-acting barbiturates, are poorly protein bound and more subject to renal excretion. Phenobarbital is a classic example of a drug whose elimination can be enhanced through alkalinization. Most other sedative-hypnotics are not amenable to urinary pH manipulation.

Overdoses of combinations of sedative-hypnotics enhance toxicity through synergistic effects. For example, both barbiturates and benzodiazepines act on the $GABA_A$ receptor, but barbiturates prolong the opening of the chloride ionophore, whereas benzodiazepines increase the frequency of ionophore opening.[128] Various sedative-hypnotics may increase the affinity of another xenobiotic at its respective binding site. For example, pentobarbital increases the affinity of γ-hydroxybutyrate (GHB) for its non-GABA binding site.[130] Propofol potentiates the effect of pentobarbital on chloride influx at the GABA receptor.[142] Propofol also increases the affinity and decreases the rate of dissociation of benzodiazepines from their site on the GABA receptor.[18,106] These actions increase the clinical effect of each xenobiotic and may lead to deeper CNS and respiratory depression.

Another mechanism of synergistic toxicity occurs via alteration of metabolism. The combination of ethanol and chloral hydrate, historically known as a "Mickey Finn," has additive CNS depressant effects. Chloral hydrate competes for alcohol and aldehyde dehydrogenases, thereby prolonging the half-life of ethanol. The metabolism of ethanol generates the reduced form of nicotinamide adenine dinucleotide (NADH), which is a cofactor for the metabolism of choral hydrate to trichloroethanol, an active metabolite. Finally, ethanol inhibits the conjugation of trichloroethanol, which in turn inhibits the oxidation of ethanol (Fig. 74–1).[16,80,121,122] The end result of these synergistic pharmacokinetic interactions is enhanced CNS depression.

Multiple drug–drug interactions can occur that may prolong the half-life of many sedative-hypnotics and significantly increase their potency or duration of action. The half-life of midazolam, which undergoes hepatic metabolism via cytochrome CYP3A4, can change dramatically in the presence of certain drugs that compete for its metabolism, or that induce or inhibit CYP3A4.[94,145] For example, the half-life of midazolam rises 400-fold when coadministered with itraconazole.[7] Various receptor and metabolic enzyme alterations resulting in upregulation or downregulation may occur in the setting of acute or chronic exposure to certain sedative-hypnotics.

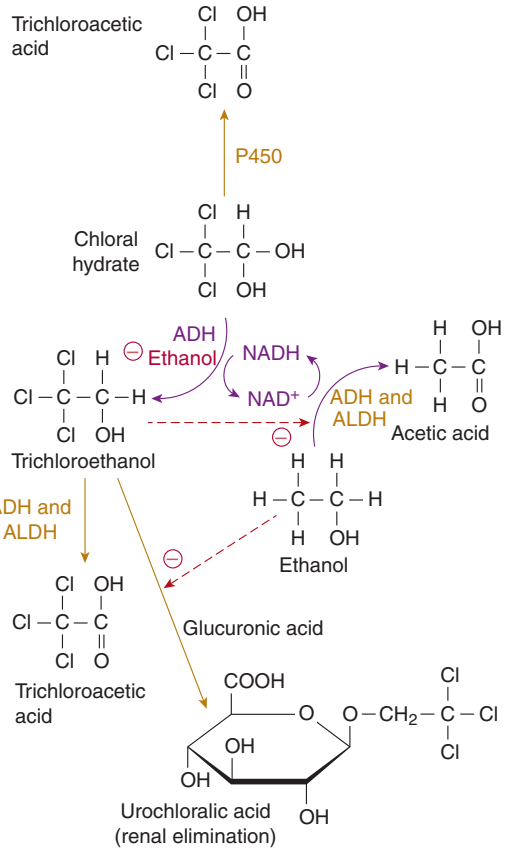


FIGURE 74–1. Metabolism of chloral hydrate and ethanol, demonstrating the interactions between chloral hydrate and ethanol metabolism. Note the inhibitory effects (dotted lines) of ethanol on trichloroethanol metabolism and the converse.

TOLERANCE/WITHDRAWAL

Ingestions of relatively large doses of sedative-hypnotics may not have predictable effects in patients who chronically use them. This is due to *tolerance*, defined as the progressive diminution of effect of a particular drug with repeated administrations that results in a need for greater doses to achieve the same effect. Tolerance occurs when adaptive neural and receptor changes (plasticity) occur after repeated exposures. These changes include a decrease in the number of receptors (downregulation), reduction of firing of receptors (receptor desensitization), structural changes in receptors (receptor shift), or reduction of coupling of sedative-hypnotics and their respective $GABA_A$ related receptor site (see Chap. 14). Tolerance can also be secondary to pharmacokinetic factors. However, in the majority of cases, tolerance to sedative-hypnotics is caused by pharmacodynamic changes such as receptor downregulation.[129]

Cross-tolerance readily exists among the sedative-hypnotics. For example, chronic use of benzodiazepines not only decreases the activity of the benzodiazepine site on the GABA receptor but also decreases the binding affinity of the barbiturate sites.[3,55] Many sedative-hypnotics are also associated with drug dependence after chronic exposure. Some of these, classically the barbiturates, benzodiazepines, and ethanol, are associated with characteristic potentially life-threatening withdrawal syndromes.

CLINICAL MANIFESTATIONS

Patients with sedative-hypnotic overdoses may exhibit slurred speech, ataxia, and incoordination. Larger doses result in stupor or coma. In most instances, respiratory depression parallels CNS depression. However, not all sedative-hypnotics cause significant hypoventilation. Oral overdoses of benzodiazepines alone may lead to sedation and hypnosis, but rarely life-threatening hypoventilation. Typically, the patient may appear comatose but have relatively normal vital signs. In contrast, large intravenous doses of benzodiazepines may lead to potentially life-threatening respiratory depression. Single overdoses of zolpidem and its congeners have not been shown to cause life-threatening respiratory depression in adults.[40]

Although the physical examination is rarely specific for a particular sedative-hypnotic, it can sometimes offer clues of exposure based on certain physical and clinical findings (Table 74–2). Hypothermia has been described with most of the sedative-hypnotics but may be more pronounced with barbiturates.[56,113] Barbiturates may cause fixed drug eruptions that often are bullous and appear over pressure-point areas. Although classically referred to as "barbiturate blisters," this phenomenon is not specific to barbiturates and has been documented with other CNS depressants, including carbon monoxide, methadone, imipramine, glutethimide, and benzodiazepines. Methaqualone can cause muscular rigidity and clonus.[1] Glutethimide can result in anticholinergic signs and symptoms.[47] Chloral hydrate use may result in vomiting, gastritis, and cardiac dysrhythmias.[45,71,92,149] Meprobamate overdoses may present with significant hypotension due to myocardial depression.[21]

Large or prolonged intravenous doses of sedative-hypnotics may also be associated with toxicities due to their diluents. Propylene glycol is a classic example of a diluent that may accumulate with prolonged infusions of certain medications such as lorazepam. Rapid infusions of propylene glycol may induce hypotension. Accumulated amounts of propylene glycol may lead to metabolic acidosis and a hyperosmolar state with elevated serum lactate concentrations.[68,72,78,105,146] In one study, two-thirds of critical care patients given high doses of lorazepam (0.16 mg/kg/h) for more than 48 hours had significant accumulations of propylene glycol as manifested by hyperosmolar anion gap metabolic acidosis[6] (see Chap. 55).

TABLE 74–2. Clinical Findings of Sedative-Hypnotic Overdose

Clinical Signs	Sedative-Hypnotics
Hypothermia	Barbiturates, bromides, ethchlorvynol
Unique odors	Chloral hydrate (*pear*), ethchlorvynol (*new vinyl shower curtain*)
Cardiotoxicity	
Myocardial depression	Meprobamate
Dysrhythmias	Chloral hydrate
Muscular twitching	GHB, methaqualone, propofol, etomidate
Acneiform rash	Bromides
Fluctuating coma	Glutethimide, meprobamate
GI hemorrhage	Chloral hydrate, methaqualone
Discolored urine	Propofol (green/pink)
Anticholinergic signs	Glutethimide

DIAGNOSTIC TESTING

When overdose is a primary concern in the undifferentiated comatose patient without a clear history laboratory testing, including electrolytes, liver enzymes, thyroid function tests, blood urea nitrogen (BUN), creatinine, glucose, venous or arterial blood gas analysis, and cerebrospinal fluid analysis, may be useful to exclude metabolic abnormalities. With any suspected intentional overdose, a serum acetaminophen concentration should be obtained. Diagnostic imaging studies, such as head CT scans, may be warranted on a case-by-case basis.

Routine laboratory screening for "drugs of abuse" generally is not helpful in the management of undifferentiated comatose adult patients, although screening may be useful for epidemiologic purposes in a particular community. These tests vary in type, sensitivity, and specificity. Furthermore, many sedative-hypnotics are not included on standard screening tests for drugs of abuse. For example, a typical benzodiazepine urine screen identifies metabolites of 1,4-benzodiazepines, such as oxazepam or desmethyldiazepam. Many benzodiazepines that are metabolized to alternative compounds remain undetected and thus may exhibit a false-negative result on the benzodiazepine screening assay. Benzodiazepines that are 7-amino analogs, such as clonazepam and flunitrazepam, may not be detected because they do not have a metabolite with a 1,4-benzodiazepine structure. Alprazolam and triazolam are not detected because they undergo minimal metabolism.[33]

Specific concentrations of xenobiotics such as ethanol or phenobarbital may be helpful to confirm or disprove exposure. However, specific concentrations of most other sedative-hypnotics are not routinely performed in hospital laboratories. Abdominal radiographs may detect chloral hydrate in the gastrointestinal tract because of its potential radiopacity (see Chap. 5). Although immediate identification of a particular sedative-hypnotic may be helpful in predicting the length of toxicity, it rarely affects the acute management of the patient. One exception is phenobarbital, for which urinary alkalinization and MDAC may enhance elimination.[39,102]

MANAGEMENT

Death secondary to sedative-hypnotic overdose usually results from cardiorespiratory collapse. Careful attention should focus on monitoring and maintaining adequate airway, oxygenation, and hemodynamic support. Supplemental oxygen, respiratory support, and prevention of aspiration are the cornerstones of treatment. Hemodynamic instability, although often a secondary or a delayed manifestation of sedative-hypnotic poisoning, should be treated initially with volume expansion. Historically, analeptics and other nonspecific arousal xenobiotics (see Chap. 1) were used, but their use is no longer recommended. With good supportive care and adequate early airway/respiratory support as needed, patients with sedative-hypnotic overdoses should eventually recover. Patients with meprobamate and chloral hydrate overdoses, however, may present with both respiratory depression and cardiac toxicity. Meprobamate toxicity may be associated with myocardial depression and significant hypotension, often resistant to standard intravenous fluid resuscitation.[21] Chloral hydrate cardiotoxic effects include lethal ventricular dysrhythmias, resulting from its active halogenated metabolite trichloroethanol. In the setting of cardiac dysrhythmias from chloral hydrate, judicious use of β-adrenergic antagonists is recommended.[15,45,158]

The use of gastrointestinal decontamination should be decided on a case-by-case basis. The benefits of activated charcoal (AC) must be balanced with the risks of its aspiration and subsequent potential for pulmonary toxicity. The use of AC should be determined judiciously

based upon a patient's current mental status, potential for further deterioration, the xenobiotic(s) ingested if known, and the expected clinical course. Phenobarbital overdose is one particular scenario in which multiple-dose AC (MDAC) may be considered. MDAC increases phenobarbital elimination by 50%–80%.[9,10,14] However, in the only controlled study, no difference could be demonstrated in outcome measures (time to extubation and length of hospitalization) in intubated, phenobarbital-poisoned patients who were randomized to single-dose activated charcoal versus MDAC.[101] Although inconclusive, after ensuring an adequately protected airway, activated charcoal may have potential benefits in certain situations (Antidotes in Depth A2: Activated Charcoal).

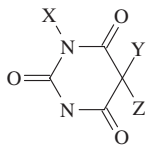
Although the efficacy of delayed orogastric lavage is controversial, orogastric lavage may be considered in overdoses with xenobiotics that slow GI motility or that are known to develop concretions, specifically phenobarbital and meprobamate,[21,59,119] Orogastric lavage in the setting of oral benzodiazepine overdoses alone is not recommended, as the benefits of lavage are minimal compared to the significant risks of aspiration. The use of orogastric lavage in sedative-hypnotic overdose should always be done cautiously as outlined in Chap. 7. No antidote counteracts all sedative-hypnotic overdoses. Flumazenil, a competitive benzodiazepine antagonist, rapidly reverses the sedative effects of benzodiazepines as well as zolpidem and its congeners.[30,73,156] However, flumazenil has been documented to precipitate life-threatening benzodiazepine withdrawal in benzodiazepine-dependent patients and precipitate seizures, especially in patients who have overdosed on tricyclic antidepressants[41,132,133] (see Antidotes in Depth A23: Flumazenil).

Patients with sedative-hypnotic overdoses rarely require invasive therapy other than respiratory support. Hemodialysis may be considered in patients with chloral hydrate overdoses who develop life-threatening cardiac manifestations or in patients who ingest extremely large quantities of phenobarbital and meprobamate who might require prolonged intubation.

Because the lethality of sedative-hypnotics is associated with their ability to cause respiratory depression, asymptomatic patients can be downgraded to a lower level of care after a period of observation with no signs of respiratory depression. Patients with symptomatic overdoses of long-acting sedative hypnotics, such as meprobamate and clonazepam, or drugs that can have significant enterohepatic circulation, such as glutethimide, may require 24 hours of observation (see Chap. 10). Patients with mixed overdoses of various sedative-hypnotics and CNS depressants also warrant closer observation for respiratory depression due to synergistic respiratory depressant effects.

SPECIFIC SEDATIVE-HYPNOTICS

BARBITURATES



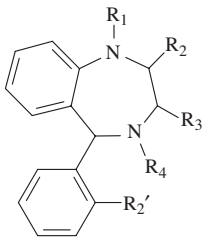
Barbital became the first commercially available barbiturate in 1903. Although many other barbiturates were subsequently developed, their popularity has greatly waned since the introduction of benzodiazepines. Barbiturates are derivatives of barbituric acid (2,4,6-trioxo-hexahydropyrimidine), which itself has no CNS depressant properties. The addition of various side chains influence pharmacologic properties. Barbiturates with long side chains tend to have increased lipophilicity, potency, and slower rates of elimination. However, the observed clinical effects also depend on absorption, redistribution, and the presence of active metabolites. For this reason, the duration of action of barbiturates (like those of benzodiazepines) does not correlate well with their biologic half-lives.

Oral barbiturates are preferentially absorbed in the small intestine and are eliminated by both hepatic and renal mechanisms. Longer-acting barbiturates tend to be more lipid soluble, more protein bound, have a high pK_a, and are metabolized almost completely by the liver. Renal excretion of unchanged drug is significant for phenobarbital, a long-acting barbiturate with a relatively low pK_a (7.24). Alkalinizing the urine with sodium bicarbonate to a urinary pH of 7.5–8.0 can increase the amount of phenobarbital excreted by 5- to 10-fold. This procedure is not effective for the short-acting barbiturates because they have higher pK_a values, are more protein bound, and are primarily metabolized by the liver with very little unchanged drug excreted by the kidneys (see Chap. 9).

Barbiturates (especially the shorter-acting barbiturates) can accelerate their own hepatic metabolism by cytochrome P450 enzyme autoinduction. Phenobarbital is a nonselective inducer of hepatic cytochromes, the greatest effects being on CYP2B1, CYP2B2, and CYP2B10, although CYP3A4 is also affected.[65,93,115,126,143] Not surprisingly, a variety of interactions are reported following the use of barbiturates. Clinically significant interactions as a result of enzyme induction lead to increased metabolism of β-adrenergic antagonists, corticosteroids, doxycycline, estrogens, phenothiazines, quinidine, theophylline, and many other xenobiotics.

Similar to other sedative-hypnotics, patients with significant barbiturate overdoses present with CNS and respiratory depression. Hypothermia and cutaneous bullae ("barb blisters") are often present. These two signs are also described for other patients with sedative-hypnotic overdoses, but they may be more pronounced with barbiturates.[11,32] Early deaths caused by barbiturate ingestions result from respiratory arrest and cardiovascular collapse. Delayed deaths result from acute renal failure, pneumonia, acute lung injury, cerebral edema, and multiorgan system failure as a result of prolonged cardiorespiratory depression.[2,48]

BENZODIAZEPINES



The commercial use of benzodiazepines began with the introduction of chlordiazepoxide for anxiety in 1961 and diazepam for seizures in 1963. Benzodiazepines are used principally as sedatives and anxiolytics. Clonazepam is the only benzodiazepine approved for use as a chronic anticonvulsant. Benzodiazepines may rarely cause paradoxical psychological effects, including nightmares, delirium, psychosis, and transient global amnesia.[12,13,34,86] The incidence and intensity of CNS adverse events increases with age.[81]

Similar to barbiturates, various benzodiazepine side chains influence potency, duration of action, metabolites, and rate of elimination. Most benzodiazepines are highly protein bound and lipophilic. They

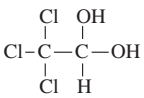
passively diffuse into the CNS, their main site of action. Because of their lipophilicity, benzodiazepines are extensively metabolized via oxidation and conjugation in the liver prior to their renal elimination.

Benzodiazepines bind nonselectively to "central" benzodiazepine receptors within the brain, termed ω_1 and ω_2. ω_1 receptors are located throughout the brain and contain the $GABA_A$ α_1 subunit.[30] They are hypothesized to affect anxiety, sleep, and amnesia. ω_2 receptors are concentrated predominantly in the hippocampus, striatum, and the spinal cord. They are hypothesized to affect muscle relaxation, cognition, memory, and dependence. Peripheral benzodiazepine receptors ω_3 are found throughout the body, with the greatest concentrations in steroid-producing cells in the adrenal gland, anterior pituitary gland, and reproductive organs (Antidote in Depth A24: Benzodiazepines).

One unique property of the benzodiazepines is their relative safety even after substantial ingestion, which probably results from their GABA receptor properties.[30,95] Unlike many other sedative-hypnotics, benzodiazepines do not open GABA channels independently at high concentrations. Benzodiazepines are not known to cause any specific systemic injury, and their long-term use is not associated with specific organ toxicity. Deaths resulting from benzodiazepine ingestions alone are extremely rare. Most often deaths are secondary to a combination of alcohol or other sedative-hypnotics.[46,123] Supportive care is the mainstay of treatment.

Tolerance to the sedative effects of benzodiazepines occurs more rapidly than does tolerance to the antianxiety effects.[74,110] Abrupt discontinuation following long-term use of benzodiazepines may precipitate benzodiazepine withdrawal, which is characterized by autonomic instability, changes in perception, paresthesias, headaches, tremors, and seizures. Withdrawal from benzodiazepines is common, manifested by almost one-third of long-term users.[66] Alprazolam and lorazepam are associated with more severe withdrawal syndromes compared with chlordiazepoxide and diazepam.[66,67] This is likely due to the fact that both chlordiazepoxide and diazepam have active metabolites. Withdrawal may also occur when a chronic user of a particular benzodiazepine is switched to another benzodiazepine with different receptor activity.[76]

CHLORAL HYDRATE

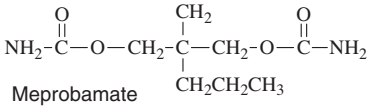


Chloral hydrate, first introduced in 1832, belongs to one of the oldest classes of pharmaceutical hypnotics, the chloral derivatives. Although still used fairly commonly in children, its use has substantially decreased. Chloral hydrate is well absorbed but is irritating to the GI tract. It has a wide tissue distribution, rapid onset of action, and rapid hepatic metabolism by alcohol and aldehyde dehydrogenases. Trichloroethanol is a lipid soluble, active metabolite that is responsible for the hypnotic effects of chloral hydrate. It has a plasma half-life of 4–12 hours and is metabolized to inactive trichloroacetic acid by alcohol dehydrogenases. It is also conjugated with glucuronide and excreted by the kidney as urochloralic acid. Less than 10% of trichloroethanol is excreted unchanged.

Metabolic rates in children vary widely because of variable development and function of hepatic enzymes, in particular glucuronidation.[16,80] The elimination half-life of chloral hydrate and triculoroethanol is markedly increased in children younger than 2 years. This may be especially of concern in neonates and in infants exposed to repetitive doses.

Acute chloral hydrate poisoning is unique compared with that of other sedative-hypnotics. Cardiac dysrhythmias are believed to be the major cause of death.[45] Chloral hydrate and its metabolites reduce myocardial contractility, shorten the refractory period, and increase myocardial sensitivity to catecholamines.[17,18,26,158] Persistent cardiac dysrhythmias (ventricular fibrillation, ventricular tachycardia, torsades de pointes) are common terminal events.[45] Standard antidysrhythmics often are ineffective, and β-adrenergic antagonists are considered the treatment of choice.[15,17,70,163] In addition to cardiotoxicity, chloral hydrate toxicity may cause vomiting, hemorrhagic gastritis, and rarely gastric and intestinal necrosis, leading to perforation and esophagitis with stricture formation.[71,92] Chloral hydrate is radiopaque and may be detected on radiographs; however, a negative radiograph should not be used to exclude chloral hydrate ingestion. Few hospital-based laboratories have the ability to rapidly detect chloral hydrate or its metabolites.

MEPROBAMATE/CARISOPRODOL



Meprobamate

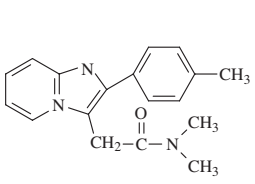
Meprobamate was introduced in 1950 and was used for its muscle-relaxant and anxiolytic characteristics. Carisoprodol, which was introduced in 1955, is metabolized to meprobamate. Both drugs have pharmacologic effects on the $GABA_A$ receptor similar to those of the barbiturates. Like barbiturates, meprobamate can directly open the GABA-mediated chloride channel and may inhibit NMDA receptor currents.[108] Both are rapidly absorbed from the GI tract. Meprobamate is metabolized in the liver to inactive hydroxylated and glucuronidated metabolites that are excreted almost exclusively by the kidney. Of all the nonbarbiturate tranquilizers, meprobamate most likely will produce euphoria.[57,58] Unlike most sedative-hypnotics, meprobamate has been reported to cause profound hypotension from myocardial depression.[21] Large masses or bezoars of pills have been noted in the stomach at autopsy after large meprobamate ingestions.[119] Orogastric lavage with a large-bore tube and MDAC may be indicated for significant meprobamate ingestion; however, the potential benefits of orogastric lavage must be weighed against the risks of aspiration. Whole-bowel irrigation may be helpful if multiple pills or small concretions are noted. It is important to note that patients can experience recurrent toxic manifestations as a result of concretion formation with delayed drug release and absorption. Careful monitoring of the clinical course is essential even after the patient shows initial improvement because recurrent and cyclical CNS depression may occur.[119]

BROMIDES

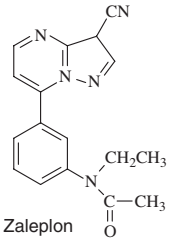
Bromides have been used in the past as "nerve tonics," headache remedies, and anticonvulsants. Although medicinal bromides have largely disappeared from the US pharmaceutical market, bromide toxicity still occurs through the availability of bromide salts of common drugs, such as dextromethorphan.[89] Poisoning also may occur in immigrants and travelers from other countries where bromides are still therapeutically used.[38] An epidemic of more than 400 cases of mass bromide poisoning occurred in the Cacuaco municipality of Luanda Province, Angola in 2007. According to a World Health Organization report, the etiology of the bromide exposure in these cases was believed to be table salt contaminated with sodium bromide. Although the majority of persons affected were children, no actual deaths were attributed to bromide poisoning in this epidemic.[159]

Bromides tend to have long half-lives and toxicity typically occurs over time as concentrations accumulate in tissue. Bromide and chloride ions have a similar distribution pattern in the extracellular fluid. It is postulated that because the bromide ion moves across membranes slightly more rapidly than the chloride ion, it is more quickly reabsorbed in the tubules from the glomerular filtrate than the chloride ion. Although osmolar equilibrium persists, CNS function is progressively impaired by a poorly understood mechanism, with resulting inappropriateness of behavior, headache, apathy, irritability, confusion, muscle weakness, anorexia, weight loss, thickened speech, psychotic behavior, tremulousness, ataxia, and eventually coma.[20,164] Delusions and hallucinations can occur. Bromide can lead to hypertension, increased intracranial pressure, and papilledema. Chronic use of bromides can also lead to dermatologic changes, with the hallmark characteristic of a facial acneiform rash.[53,141] Toxicity with bromides during pregnancy may lead to accumulation of bromide in the fetus.[100] A spurious laboratory result of hyperchloremia with decreased anion gap may result from bromide's interference with the chloride assay on older analyzers[161] (Chap. 16). Thus an isolated elevated serum chloride concentration with neurologic symptoms should raise suspicion of possible bromide poisoning.

ZOLPIDEM/ZALEPLON/ZOPICLONE/ESZOPICLONE



Zolpidem



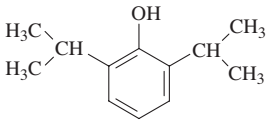
Zaleplon

These oral xenobiotics have supplanted benzodiazepines as the most commonly prescribed sleep aid medications.[35] Although they are structurally unrelated to the benzodiazepines, they bind preferentially to the ω_1 benzodiazepine receptor subtype in the brain, specifically the $GABA_A$ α_1 subunit.[30] They have a lower affinity for ω_2 receptors than benzodiazepines, therefore they have potent hypnotic effects with less potential for dependence.[30,52] Each of these xenobiotics has a relatively short half-life (≤6 hours), with zaleplon exhibiting the shortest half-life (1 hour). Unlike benzodiazepines that prolong the first two stages of sleep and shorten stages 3 and 4 of rapid eye movement (REM) sleep, zolpidem and its congeners all decrease sleep latency with little effect on sleep architecture. Because of their receptor selectivity, they appear to have minimal effect at other sites on the GABA receptor that mediate anxiolytic, anticonvulsant, or muscle-relaxant effects.[69,151]

They are hepatically metabolized by various CYP450 enzymes. Zolpidem is mainly metabolized by CYP3A4. Zaleplon is primarily metabolized by aldehyde oxidase, but CYP3A4 is also involved in parent compound oxidation. Zopiclone is primarily metabolized by CYP3A4 and CYP2C8, whereas eszopiclone is metabolized mainly by CYP3A4 and CYP2E1. Various pharmacokinetic interactions with inhibitors or inducers of CYP450 enzymes and these medications have been reported.[51]

In isolated overdoses, drowsiness and CNS depression are common. However, prolonged coma with respiratory depression is exceptionally rare. Isolated overdoses usually manifest with depressed level of consciousness without respiratory depression. For example, even at 40 times the therapeutic dose of zolpidem, no biologic or electrocardiographic abnormalities were reported.[40] Tolerance to zolpidem and its congeners has also been described. Withdrawal has been reported after abrupt discontinuation following chronic use but typically is mild.[50,155] Flumazenil may reverse the hypnotic or cognitive effects of these agents.[73,156] Deaths have resulted when zolpidem was taken in large amounts with other CNS depressants (Antidote in Depth A23 Flumazenil).[40]

PROPOFOL



Propofol is a rapidly acting intravenous sedative-hypnotic that is a postsynaptic $GABA_A$ agonist and also induces presynaptic release of GABA.[117] Propofol is also an antagonist at NMDA receptors.[63,64,131] In addition, propofol also interacts with dopamine, promotes nigral dopamine release possibly via $GABA_B$ receptors,[96,120] and has partial agonist properties at dopamine (D_2) receptors.[118] Propofol is used for procedural sedation and either induction or maintenance of general anesthesia. It is highly lipid soluble, so it crosses the blood–brain barrier rapidly. The onset of anesthesia usually occurs in less than 1 minute. The duration of action after short-term dosing is usually less than 8 minutes due to its rapid redistribution from the CNS.

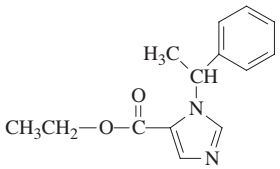
Propofol use is associated with various adverse effects. Acutely, propofol causes dose-related respiratory depression. Propofol may decrease systemic arterial pressure and cause myocardial depression. Although short-term use of propofol does not typically cause dysrhythmias or myocardial ischemia, atropine-sensitive bradydysrhythmias have been noted, specifically sinus bradycardia and Mobitz type I atrioventricular block.[140,154,162] Short-term use of propofol in the perioperative setting is associated with a myoclonic syndrome manifesting as opisthotonus, myoclonus, and sometimes myoclonic seizure like activity.[82,90]

Prolonged propofol infusions for more than 48 hours at rates of 4–5 mg/kg/h or greater are associated with a life-threatening *propofol-infusion syndrome* (PIS) involving metabolic acidosis, cardiac dysrhythmias, and skeletal muscle injury.[61] The clinical signs of PIS often begin with the development of a new right bundle branch block and ST segment convex elevations in the electrocardiogram precordial leads.[60] Predisposing factors to the development of PIS include young age, severe brain injury (especially in the setting of trauma), respiratory compromise, concurrent exogenous administration of catecholamines or glucocorticoids, inadequate carbohydrate intake, and undiagnosed mitochondrial myopathy. Some authors propose a "priming" and "triggering" mechanism for PIS with endogenous glucocorticoids, catecholamines, and possibly cytokines as "priming" agents, and exogenous catecholamines and glucocorticoids in the setting of high-dose propofol infusion as "triggering" stimuli.[147] Propofol is suggested to induce disruption of mitochondrial free fatty acid utilization and metabolism, causing a syndrome of energy imbalance and myonecrosis similar to other mitochondrial myopathies.[22,125,148] Case reports associate propofol with metabolic acidosis with elevated lactate concentration and fatal myocardial failure in children and young adults; however, it has been reported in older adults as well.[98] Cases of metabolic acidosis may be associated with an inborn disorder of acylcarnitine metabolism.[160] Caution is advised when prolonged propofol infusions are used in any patient, especially children, as they may have a previously undiagnosed myopathy that would cause them to be at increased risk for PIS. Despite

the increasing number of reports of PIS in the literature, a direct cause-and-effect relationship remains to be fully elucidated.

The unique nature of propofol's carrier base, a milky soybean emulsion formulation, is associated with multiple adverse events. It is a fertile medium for many organisms, such as enterococcal, pseudomonal, staphylococcal, streptococcal, and candidal strains. In 1990, the Centers for Disease Control and Prevention (CDC) reported an outbreak of *Staphylococcus aureus* associated with contaminated propofol. This carrier base also impairs macrophage function,[22] causes hypertriglyceridemia[33,55,67,76] and histamine-mediated anaphylactoid reactions,[31,62,148] and impairs platelet and coagulation function.[4,29]

ETOMIDATE



Etomidate is an intravenous nonbarbiturate, hypnotic primarily used as an anesthesia induction agent. It is active at the $GABA_A$ receptor, specifically the β_2 and β_3 subunits.[91,104] Only the intravenous formulation is available in the United States. The onset of action is less than 1 minute and its duration of action is less than 5 minutes.

Etomidate is commercially available as a 2 mg/mL solution in a 35% propylene glycol solution. Propylene glycol toxicity from prolonged etomidate infusions is implicated in the development of hyperosmolar metabolic acidosis.[78,144,146] Etomidate has minimal effect on cardiac function, but rare cases of hypotension are reported.[42–44,135] Etomidate has both proconvulsant and anticonvulsant properties.[25,103] Involuntary muscle movements are common during induction, and may be caused by etomidate interaction with glycine receptors at the spinal cord level.[27,84,85]

Etomidate depresses adrenal production of cortisol and aldosterone and has thus been associated with adrenocortical suppression, usually after prolonged infusions.[117,152,153] One prospective randomized trial demonstrated chemical adrenal suppression with decreased serum cortisol levels and decreased responses to ACTH stimulation in trauma patients even after receiving single-dose etomidate.[54] The authors postulate that this may have been associated with prolonged duration of hospital and ICU stays, as well as prolonged ventilator requirements. Other authors question the clinical significance of adrenal suppression from single-dose etomidate administration.[137]

DEXMEDETOMIDINE

Dexmedetomidine is a central α_2 adrenergic agonist that decreases central presynaptic catecholamine release, primarily in the locus coeruleus. It was approved by the FDA in 1999 for short-term use in the critical care setting. It has a terminal half-life of 1.8 hours and its volume of distribution is less than 1 L/kg. When dexmedetomidine is used to help wean patients from ventilators, a better level of desired sedation is achieved with less associated delirium.[97,136] It is also used for procedural sedation in certain settings such as interventional radiology procedures and awake fiberoptic intubations. In addition, other authors have described lesser opioid requirements in postoperative patients sedated with dexmedetomidine, compared with propofol. Individual case reports also document the use of dexmedetomidine in benzodiazepine, opioid, or ethanol withdrawal.[28,36,114,138,139]

Dexmedetomidine has no effect at the GABA receptor, and unlike other sedative-hypnotics, it is not associated with significant respiratory depression. Although mechanistically similar to clonidine, dexmedetomidine does not appear to cause as much respiratory depression as clonidine. Dexmedetomidine is said to induce a state of "cooperative sedation," in which a patient is sedated but yet able to interact with health-care providers. Dexmedetomidine may also have analgesic effects.[23]

Dexmedetomidine is currently approved for use only for less than 24 hours, as safety trials have not yet explored its use beyond 24 hours. Unlike clonidine, rebound hypertension and tachycardia have not been described upon cessation of dexmedetomidine. Because dexmedetomidine decreases central sympathetic outflow, its use should probably be avoided in patients whose clinical stability is dependent on high resting sympathetic tone. The most common adverse effects from its use are nausea, dry mouth, bradycardia, and varying effects on blood pressure (usually hypertension followed by hypotension). Slowing of the continuous infusion may help to prevent or lessen the hypotensive effects.[23]

RAMELTEON/MELATONIN

Ramelteon is a synthetic melatonin-analog that is FDA approved for the treatment of chronic insomnia. Ramelteon has been proposed to decrease both latency to sleep induction and length of persistent sleep.[127] Melatonin (*N*-acetyl-5-methoxytryptamine) and melatonin-containing products are sold as dietary supplements. Melatonin is naturally synthesized from tryptophan by the enzyme 5-hydroxyindole-*O*-methyltransferase, primarily within the pineal gland in humans. Melatonin and ramelteon both act as agonists at MT-1 and MT-2 receptors, which are G protein–coupled receptors mainly located in the suprachiasmatic nucleus of the brain.[127] Ramelteon is specific for MT-1 and MT-2 receptors, whereas melatonin is active at other melatonin receptors that are likely not involved in sleep. MT-1 receptors appear to be involved in sleep induction, whereas MT-2 receptors are involved in regulation of the circadian sleep-wake cycle in humans.[134]

Ramelteon is administered as an oral medication that is rapidly absorbed but undergoes significant first-pass metabolism. Ramelteon is metabolized primarily by CYP1A2 hepatic isoenzyme. The half-life of ramelteon with therapeutic use is roughly 1.5 hours.

Adverse effects of ramelteon are often mild, and usually include dizziness, fatigue, headache. The endocrine effects of long-term exposure to ramelteon seem to be limited to subclinical increases in serum prolactin concentration in women, and do not appear to affect adrenal or thyroid function.[109] In addition, ramelteon has a low abuse potential and does not appear to be associated with a withdrawal syndrome or with rebound insomnia.[49,77,83] As of yet, there are no reported cases of significant toxicity from ramelteon overdose.

SUMMARY

Sedative-hypnotics encompass a wide range of xenobiotics with varying mechanisms of action. Patients with sedative-hypnotic overdoses often present with the primary manifestation of CNS depression; however, death typically results from respiratory depression and subsequent cardiovascular collapse in the setting of concurrent co-ingestion of other CNS depressants. Careful monitoring, airway protection, and good supportive care are the cornerstones of treatment. Specific antidotes such as flumazenil and treatments such as hemodialysis are rarely indicated.

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