Chapter 53

PHARMACEUTICAL TOXINS & ANTIDOTES

There is little doubt that pharmaceutical mishaps are a source of considerable morbidity and even mortality. Adverse drug reactions are responsible for up to 7% of hospital admissions, and 20% of ICU admissions (1,2). Once in the hospital, 7% of patients experience a severe adverse drug reaction (3). The average ICU patient receives 6 to 9 different medications daily and 8 to 12 different medications during the ICU stay (4). Therefore, the ICU is a fertile environment for pharmaceutical misadventures.
This chapter describes the clinical toxicity associated with the pharmaceutical agents listed below, and the treatment of each with specific antidotes (shown in parentheses). Included are toxic drug ingestions that prompt admission to the ICU and toxic drug reactions that surface after admission to the ICU.

Acetaminophen (N-acetylcysteine)
Benzodiazepines (flumazenil)
Beta-Blockers (glucagon)
Calcium antagonists (calcium, glucagon)
Opioids (naloxone)

ACETAMINOPHEN

Acetaminophen is a ubiquitous analgesic-antipyretic agent that is included in over 600 commercial drug preparations. **It** is also a hepatotoxin, and is the leading cause of toxic drug ingestion and acute liver failure in

the United States (5,6). The general public seems unaware of acetaminophen's toxic potential, and almost one-third of overdoses are unintentional, occurring in people who are using the drug for pain relief (7).

Toxic Mechanism

The toxicity of acetaminophen is related to its metabolism, which is shown in Figure 53.1. The bulk of acetaminophen metabolism involves the formation of sulfate and glucuronide conjugates in the liver, which are then excreted in the urine (8,9). Approximately 5 to 15% of the metabolism involves formation of a highly reactive intermediate that promotes oxidant injury in hepatic parenchymal cells. This toxic metabolite is normally removed by conjugation with glutathione, an intracellular antioxidant. Large doses of acetaminophen saturate the conjugation pathways and spill over into the glutathione pathway to deplete glutathione reserves. When hepatic glutathione stores fall to 30% of normal, the toxic

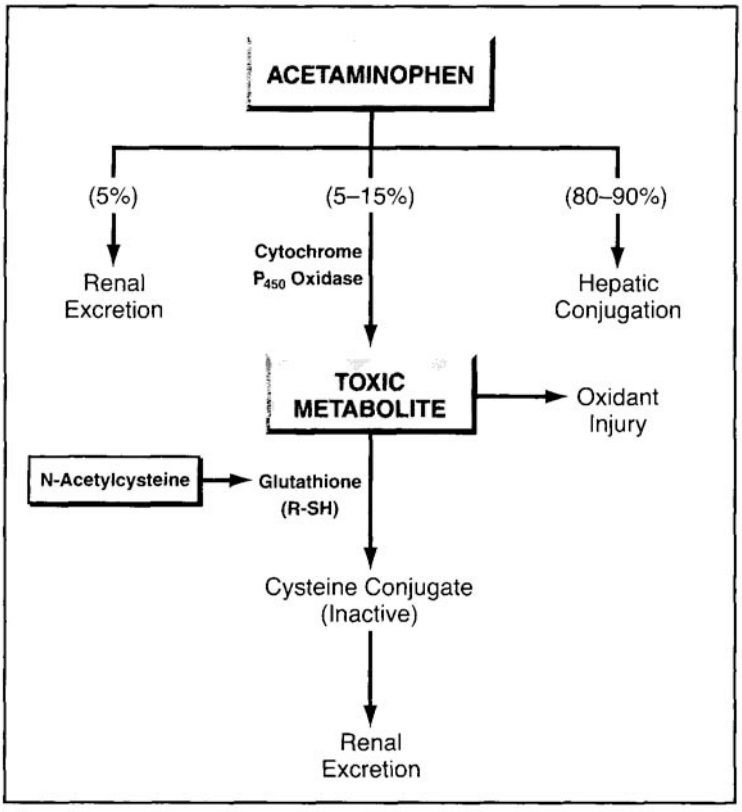

FIGURE 53.1 The hepatic metabolism of acetaminophen and the mechanism of action of N-acetylcysteine.

acetaminophen metabolite can accumulate and promote widespread hepatocellular damage (9).

Clinical Presentation

The period following acetaminophen overdose is divided into four stages of toxicity (8,10,11). In the initial stage (the first 24 hours), symptoms are either absent or non-specific (e.g., nausea), and no laboratory evidence of hepatic injury exists. In patients who develop hepatotoxicity, a second stage (24-72 hours after drug ingestion) occurs where clinical manifestations continue to be minimal or absent, but laboratory evidence of hepatic injury begins to appear. Elevated aspartate aminotranferase (AST) is the most sensitive marker of acetaminophen toxicity; the rise of AST precedes the hepatic dysfunction, and peak levels are reached at 72-96 hours. In advanced cases of hepatic injury, a third stage follows (after 72-96 hours) that is characterized by clinical and laboratory evidence of progressive hepatic injury and hepatic insufficiency (e.g., encephalopathy, coagulopathy) occasionally combined with renal insufficiency. Death from hepatic Injury usually occurs within 3 to 5 days. Patients who survive often recover completely, although recovery can be prolonged.

Diagnosis

In most cases of acetaminophen overdose, the initial presentation occurs within 24 hours after drug ingestion, when there are no manifestations of hepatic injury. The principal task at this time is to identify those who are likely to develop hepatotoxicity. Two variables can have prognostic value.

Ingested Dose

Determining the risk of hepatotoxicity from the ingested dose is problematic because: 1) The minimum toxic dose can vary in individual patients, and is somewhere between 7.5-15 grams in an average sized adult (8-10), 2) The ingested dose is often difficult to determine accurately, and 3) Several conditions can increase the susceptibility to acetaminophen hepatotoxicity, including: glutathione depletion (e.g., malnutrition), isoniazid, and chronic ethanol ingestion (6,7,9). For these reasons, plasma acetaminophen levels should be used to assess the risk of hepatotoxicity.

Plasma Drug Levels

Plasma acetaminophen levels obtained from 4 to 24 hours after drug ingestion can be used to predict the risk of hepatotoxicity using the nomogram in Figure 53.2 (9). If the plasma level is in the high-risk region of the nomogram, the risk of developing hepatotoxicity is 60% or higher, and antidote therapy is warranted. The risk of hepatotoxicity is only 1 to 3% in the low-risk region of the nomogram, and this does not warrant antidote therapy (9).

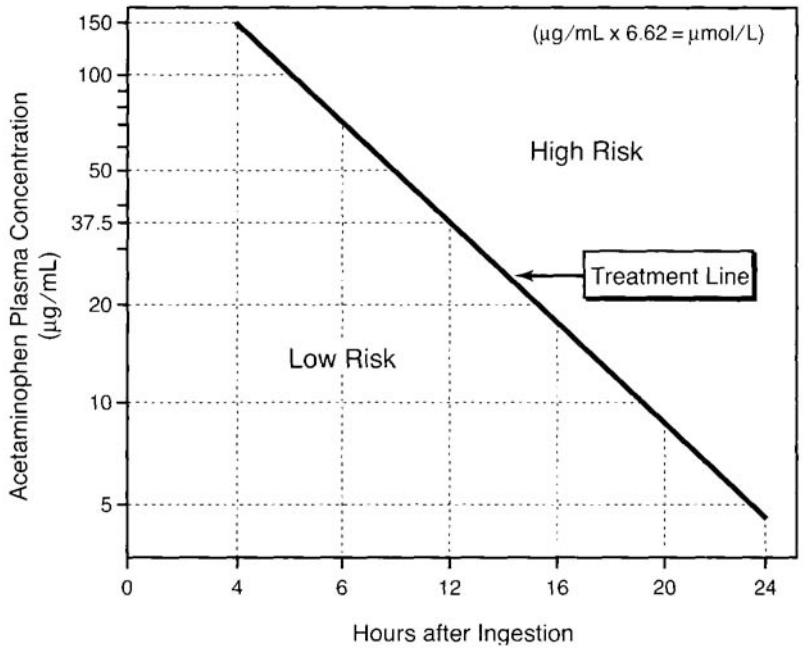

FIGURE 53.2 Nomogram for predicting the risk of hepatotoxicity using plasma acetaminophen levels obtained between 4 and 24 hours after ingestion. A plasma level that falls on or above the treatment line is an indication to begin antidotal therapy with N-acetylcysteine. From Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 2002;40:3–20.

N-Acetylcysteine

The goal of antidote therapy for acetaminophen overdose is to limit accumulation of the toxic metabolite and prevent hepatocellular damage. Since glutathione does not readily cross cell membram's, the administration of exogenous glutathione is not well suited for this task. N-acetylcysteine (NAC) is a glutathione analogue that can cross cell membranes and act as an intracellular glutathione surrogate (12). As shown in Figure 53.1, NAC contains a sulfhydryl group that allows it to act as a reducing agent and inactivate the toxic acetaminophen metabolite.

Timing

NAC is indicated only when therapy can be started within 24 hours after acetaminophen overdose (13). Protection is most effective when NAC is started in the first 8 hours after ingestion (8.10,14,15), so avoiding treatment delays is necessary to ensuring optimal protection. In some circumstances, NAC can be protective when given 24-36 hours after drug ingestion (16), but consensus opinion is not to extend the 24 hour treatment window.

TABLE 53.1 Treatment of Acetaminophen Overdose with N-Acetylcysteine (NAC)

Intravenous Regimen*
Use 20% NAC (200 mg/mL) for each of the doses below and infuse in
1. 150 mg/kg in 200 mL D5W over 60 min
2. 50 mg/kg in 500 mL D5W *over* 4 h
3. 100 mg/kg in 1000 mL D5W *over* 16 h
Total dose: 300 mg/kg over 21 h
Oral Regiment
Use 10% NAC (100 mg/mL) and dilute 2:1 in water or juice 10 make a 5% solution (50 mg/mL).
Initial dose: 140 mg/kg
Maintenance dosage: 70 mg/kg *every* 4 h for 17 doses
Total dose: 1330 mg/kg over 72 h

'From Cumberland Pharmaceulicals. Acetadote Package Insert. 2006.
tFrom Smilkslein MJ, Knapp GL, Kulig KW, el al. Efficacy of oral N-treatment of acetaminophen overdose. New Engl J Med 1988;319:1557-1562.

Therapeutic Regimens
NAC can be given intravenously or orally using the dosing regimens shown in Table 53.1. Even though there is no direct comparison of these two approaches, they are considered equally effective (17,18). The intravenous route is preferred because it is the most reliable mode of drug delivery, and because oral ingestion of NAC can be problematic (see next section). (15).

Adverse Reactions
Intravenous NAC can cause troublesome anaphylactoid reactions, which are uncommon but can be severe (in 1 % of treatments) (19,20). The sulfur content of NAC gives the liquid drug preparation a very disagreeable taste (often described as rotten eggs). As a result, oral administration of NAC frequently incite5 vomiting, and a nasogastric tube is sometimes required to administer therapy. The oral regimen of NAC is also associated with a dose-dependent diarrhea that appears in about half the patients who complete the 72-hr regimen (21). This resolves with continued therapy in over 90% of cases.

Activated Charcoal
Acetaminophen is completely absorbed from the gastrointestinal tract in the first few hours after drug ingestion (10). Therefore, activated charcoal (1 g/kg body weight) is recommended only in the first 4 hours after acetaminophen *overdose* (10,22). Although charcoal can also adsorb N-acetylcysteine, this interaction is probably not significant (10).

BENZODIAZEPINES

Benzodiazepines are the second most frequently overdosed prescription drugs in the United States, and are second only to analgesics as the leading cause of medication-related death (5). Benzodiazepine-related fatalities almost always involve other respiratory depressants (23). Admissions for drug overdose are not the only source of benzodiazepine toxicity in the ICU. Surveys reveal that roughly 50% of ICU patients receive benzodiazepines for sedation (24), and adverse reactions to benzodiazepine sedation is likely to be a significant source of clinical toxicity. The use of benzodiazepines for sedation in the ICU is described in Chapter 49.

Clinical Toxicity

Benzodiazepines produce a dose-dependent depression in the level of consciousness, but there is usually no respiratory or cardiovascular depression. However, there are several factors in the ICU that predispose to respiratory and cardiovascular depression from benzodiazepines. These include advanced age of the patients, combined therapy with opioid analgesics, and drug accumulation from prolonged drug therapy (see Chapter 49 for a description of benzodiazepine accumulation).

Flumazenil

Flumazenil is a benzodiazepine antagonist that binds to benzodiazepine receptors in the central nervous system but does not exert any agonist actions (25,26). This agent is most effective in reversing the sedative effects of the benzodiazepines, but is inconsistent in reversing benzodiazepineinduced respiratory depression (27,28). Flumazenil can also improve the sensorium in hepatic encephalopathy (29) and ethanol intoxication (30), but the doses required are large (5 mg) and potentially hazardous.

Drug Administration

Flumazenil is given as an intravenous bolus. The initial dose is 0.2 mg, and this can be repeated at 1 to 6 minute intervals if necessary to a cumulative dose of 1.0 mg. The response is rapid, with onset in 1-2 minutes, peak effect at 6-10 minutes, and duration of approximately one hour (25, 31). Since flumazenil has a shorter duration of action than the benzodiazepines, resedation is common after 30-60 minutes. Because of the risk for resedation, the initial bolus dose of flumazenil is often followed by a continuous infusion at 0.3-0.4 mg/hr (31).

Adverse Reactions

Flumazenil produces few undesirable side effects (25,26,32,33). It can precipitate a benzodiazepine withdrawal syndrome in patients with a long-standing history of benzodiazepine use, but this is uncommon (32). Flumazenil can also precipitate seizures in patients receiving

benzodiazepines for seizure control, and in mixed overdoses involving tricyclic antidepressants (34).

Clinical Uses

Because of the benign nature of benzodiazepine toxicity, flumazenil is a treatment in search of an illness. The principal use of flumazenil is in patients with known or suspected benzodiazepine overdose, but only when a mixed overdose involving tricyclic antidepressants is not suspected, and only in patients who are not receiving benzodiazepines for control of seizures. Flumazenil has even fewer uses in the ICU. Although flumazenil can reverse oversedation with benzodiazepines in ventilator-dependent patients (31), the hazards of oversedation are minimal in patients receiving ventilatory support. Flumazenil has been reported to hasten weaning from mechanical ventilation (35), but this application seems limited by the lack of respiratory depression when the benzodiazepine dose is not excessive.

Beta-RECEPTOR ANTAGONISTS

According to the 2004 annual report of the Toxic Exposure Surveillance System, there were 8,186 Beta-blocker overdoses treated in a health care facility resulting in 481 major adverse outcomes and 25 mortalities (5). Intentional overdose is not the only source of Beta-blocker toxicity in the ICU. At present, 15 different Beta-blockers are approved for use in the United States (36). BETA-Blockers are used to manage several conditions in the ICU, including hypertension, narrow-complex tachycardias, unstable angina, and acute myocardial infarction, and these uses create an additional source of Beta-blocker toxicity. The Beta-receptor antagonists used most frequently in the ICU are shown in Table 53.2.

Clinical Toxicity

The manifestations of beta-receptor blockade arise primarily from the cardiovascular system and the central nervous system (36-38).

TABLE 53.2 Comparison of Intravenous Beta-Receptor Antagonists

Antagonist	Target Receptors	Relative Potency	Intravenous Dosage	Lipid Solubility	Metabolism
Propranolol	All Beta	1	1-10 mg	+++	Hepatic
Metoprolol	Beta 1	1	5-15 mg	+	Hepatic
Atenolol	Beta 1	1	5-10 mg	0	Renal
Timolol	All Beta	6	0.3-1 mg	+	Hepatic/Renal
Labetalol	alpha, all Beta	0.3	2 mg/kg	++	Renal
Esmolol	All Beta	0.06	0.5-1 mg/kg 0.1-0.3 mg/kglmin	0	Plasma

Cardiovascular Toxicity
The most common manifestations of Beta-blocker toxicity are bradycardia and hypotension (36-38). The bradycardia is usually sinus in origin, and is well tolerated. The hypotension can be due to peripheral vasodilatation (renin blockade), or a decrease in cardiac output (beta receptor blockade). Hypotension that is sudden in onset is usually a retlection of a decrease in cardiac output and is an ominous sign.
Especially in overdose, the Beta-blockers can exert a membranestabilizing (quinidine-like) effect that inhibits fast sodium channels, prolongs atrioventricular (AV) conduction (causing heart block), and can impair myocardial contractility (causing refractory hypotension) (39,40). Membrane-stabilizing activity is greatest for propranolol, less for metoprolol and labetalol, and is not important for timolol and atenolol (39). When a lipophilic agent with membrane stabilizing properties (e.g., propranolol) crosses the blood brain barrier, neurotoxicity can be especially severe (36).

Neurotoxicity
Most Beta-blockers are lipid soluble to some degree and thus have a tendency to accumulate in lipid-rich organs like the central nervous system. As a result, Beta-blocker overdose is often accompanied by lethargy, depressed consciousness, and generalized seizures. The latter manifestation is more prevalent than suspected, and has been reported in 60% of overdoses with propranolol (38). Like the prolonged AV conduction, the neurological manifestations are not the result of Beta-receptor blockade and are likely related to membrane stabilizing activity. Thus, seizures are most frequently observed in association with propranolol overdose (usually in excess of 1.5 grams) (41).

Glucagon
The cardiovascular depression from Beta-receptor blockade (especially those agents with intrinsic membrane stabilizing effects) can be resistant to conventional therapy with atropine (1 mg IV), isoproterenol (0.1-0.2 mg/ min titrated to effect), and transvenous ventricular pacing (37,42). The regulatory hormone glucagon is the agent of choice for reversing the cardiovascular depression in Beta-receptor blockade. The actions of glucagon in Beta-blocker overdose are explained below.

Mechanism of Action
The diagram in Figure 53.3 shows the chain of events responsible for the positive inotropic actions of beta receptor activation in the heart. The 13receptor is functionally linked (via specialized G proteins) to the adenyl cyclase enzyme on the inner surface of the cell membrane. Activation of the receptor-enzyme complex results in the hydrolysis of adenosine triphosphate (ATP) to form cyclic adenosine mono phosphate (cyclic AMP). The cyclic AMP then activates a protein kinase that promotes the inward movement of calcium through the cell membrane. The influx of

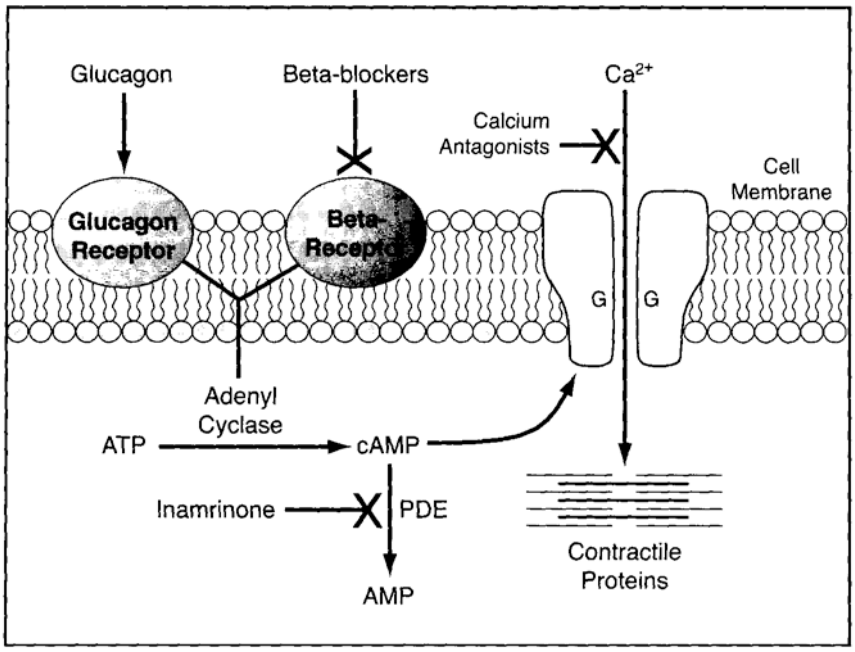

FIGURE 53.3 The mechanism of action of drugs that affect the strength of cardiac contraction. Abbreviations: ATP: adenosine triphosphate, cAMP: cyclic adenosine monophosphate, PDE: phosphodiesterase, AMP: adenosine monophosphate.

calcium promotes interactions between contractile proteins and thereby augments the strength of cardiac contraction.
The diagram in Figure 53.3 also shows that glucagon can activate adenyl cyclase through a membrane receptor that is distinct from the 13receptor. This allows glucagon to mimic the positive inotropic effects of Beta-receptor activation when the Beta-receptors are quiescent.

Indications
Glucagon is indicated for the treatment of hypotension and *symptomatic* bradycardia associated with toxic exposure to Beta-blockers (see Table 53.3). When used in the appropriate doses, glucagon will elicit a favorable response in 90% of patients (37). Glucagon is *not* indicated for reversing the prolonged AV conduction or neurological abnormalities in Beta-blocker overdose because these effects are not mediated by Beta-receptor blockade.

Dosing Recommendations
The effective dose of glucagon can vary in individual patients, but a bolus dose of 3 to 5 mg IV should be effective in most adults (37,38,43). The initial dose is 3 mg (or 0.05 mg/kg), and this can be followed by a second dose of 5 mg (or 0.07 mg/kg) if necessary. The response to glucagon is most pronounced when the plasma ionized calcium is normal (44).

TABLE 53.3 Antidote Therapy with Glucagon

Indications:

For toxic exposure to [j-blockers or calcium channel blockers accompanied by

a) Symptomatic bradycardia or

b) Hypotension

Preparation:

Supplied as a powder (1 mg). Reconstitute with supplied 1 mL bottle of diluent (Glucagon, Eli Lilly) or sterile water (Glucagen *Novo* Nordisk) to a of 1 mg/mL.

Administration:

Initial dose: 50 μg/kg (or 3 mg) IV over 1 min, then 70 μg/kg (or 5 mg) if necessary.
Infusion: 70 μg/kg/h (or 5 mg/h)

The effects of glucagon can be short-lived (5 minutes), and so a favorable response should be followed by a continuous infusion (5 mg/hr).

Adverse Effects

Nausea and vomiting are common at glucagon doses above 5 mg/hr. Mild hyperglycemia is common, and is due to glucagon-induced glycogenolysis and gluconeogenesis. The insulin response to the hyperglycemia can drive potassium into cells and promote hypokalemia. Finally, glucagon stimulates catecholamine release from the adrenal medulla, and this can raise the blood pressure in hypertensive patients. This hypertensive response is exaggerated in pheochromocytoma, so glucagon is contraindicated in patients with pheochromocytoma.

CALCIUM ANTAGONISTS

Calcium blockers are among the five most frequently reported (and most lethal) toxic ingestions in the United States in 2004 (5,45). At present, 10 different calcium channel blockers are available in the US (36); however, the three original calcium antagonists (verapamil, nifedipine, and diltiazem) are responsible for most of the clinical experience with calcium antagonist toxicity.

Mechanisms

Calcium

Calcium has a profound influence on the electrical and mechanical performance of smooth muscle. Its role in the contraction of cardiac smooth muscle is shown in Figure 53.3. The inward movement of calcium across the cell membrane (triggered by depolarization of the cell membrane or by activation of the cyclic AMP pathway) promotes the interaction

between contractile proteins that ultimately determines the strength of muscle contraction. Although not shown in the figure, calcium influx triggers calcium release from the sarcoplasmic reticulum, which is the primary source of calcium that produces muscle contraction). This process from membrane depolarization to muscle contraction is called excitation-contraction coupling (46).

Calcium also participates in the propagation of electrical impulses in smooth muscle. The depolarization-triggered inward movement of calcium facilitates the propagation of electrical impulses in cardiac muscle, and speeds conduction through the atrioventricular (AV) node.

The calcium antagonists block the inward movement of calcium across smooth muscle membranes, but not across the sarcoplasmic reticulum. This can result in any of the following: negative inotropic and chronotropic effects, prolonged atrioventricular conduction (negative dromotropic effect), decreased arrhythmogenicity, vascular dilatation, and bronchial dilatation. The individual calcium antagonists differ in their ability to elicit these responses, as described below.

Clinical Toxicity

The toxic manifestations of the three most popular calcium antagonists (verapamil, nifedipine, and diltiazem) are shown in Table 53.4 (47). Verapamil is most likely to produce hypotension and prolonged AV conduction. Verapamil is only a weak vasodilator and the hypotension is due to a decrease in cardiac output (negative inotropic effect) without compensatory vasoconstriction. Nifedipine is predominantly a vasodilator (hence the high incidence of reflex tachycardia) and has little influence on AV conduction. Diltiazem. is similar to verapamil in its ability to prolong AV conduction, but it causes less cardiac depression than verapamil and less vasodilatation than nifedipine.

Noncardiovascularmanifestations of calcium blocker toxicity include lethargy and depressed consciousness (most common), generalized seizures, and hyperglycemia (caused by inhibition of insulin release, which is calcium-dependent) (47,48).

TABLE 53.4 Clinical Features Associated with Overdose of Specific Calcium Antagonists

	Incidence (%)		
Clinical Manifestation	Verapamil	Nifediplne	Diltiazem
Hypotension	53	32	38
Sinus tachycardi,a	23	57	26
Sinus bradycardia	29	14	29
Prolonged AV condition	55	18	29

From Ramoska EA, Spiller HA, Winter M, et al. A one-year evaluation of blocker overdoses: toxicity and treatment. Ann Emerg Med

TABLE 53.5 Antidote Therapy with Intravenous Calcium

Characteristics	10% Calcium Chloride	10% Calcium Gluconate
Unit *volume*	10 mL per ampule	10 mL per ampule
Calcium conlent	1.36 mEq/mL	0.46 mEq/mL
Dose to *prevent* calcium channel blockage	3 mL	10 mL
Dose to *reverse* calcium channel blockage	13.6 mEq (10 mL)	13.8 mEq (30 mL)

Treatment

There are two approaches to calcium channel blockade (37). The first involves the administration of calcium to antagonize the blockade on the outer surface of the cell membrane. The second involves the use of drugs that activate the cyclic AMP pathway, which antagonizes the blockade from the inner surface of the cell membrane.

Intravenous Calcium

Intravenous calcium is the traditional first-line therapy for reversing calcium channel blockade, and elicits favorable responses in 35 to 75% of cases (47-49) resulting in improved inotropy, conduction disorders, and hypotension (45). As described in Chapter 35, there are two calcium salts for intravenous use (calcium chloride and calcium gluconate), and equivalent weights of each salt do not contain equivalent amounts of elemental calcium. This is shown in Table 53.5. One gram of 10% calcium chloride contains roughly three times more elemental calcium than one gram of 10% calcium gluconate. Therefore, ordering calcium without identifying the calcium salt, is inappropriate.

Although the calcium dose varies widely in clinical reports, calcium is most effective when given in doses that will increase the serum calcium level (48). The dose of calcium for reversing calcium channel blockade shown in Table 53.5 should raise the serum calcium level. The response to calcium may last only 10 to 15 minutes, so the initial response to calcium should be followed by a continuous infusion at 0.3 to 0.7 mEq/ kg/hr (37,45). Calcium infusions are *not* recommended for patients being treated with digitalis.

Atropine

Atropine is the agent of choice to reverse significant bradycardia due to calcium channel blocker overdose, but it is not effective in severe cases of toxicity. The effect of atropine is enhanced by prior administration of calcium; therefore, calcium should be given before atropine (50). The dose of atropine is 0.5-1 mg given intravenously every 2-3 minutes up to a maximum of 3 mg (45).

Catecholamines
A variety of catecholamines have been used clinically to antagonize calcium channel blockade (e.g., epinephrine, norepinephrine, dopamine) but no single agent has proven to be effective on a consistent basis and the dosage requirements may be in the high range (45).
Preventive Therapy
Hypotension is a common complication of therapy with intravenous verapamil for supraventricular tachyarrhythmias. Pretreatment with 3 mL of 10% calcium chloride or 10 mL of 10% calcium gluconate (4.6 mEq calcium) is effective in preventing verapamil-induced hypotension in most cases (see Table 53.5) (49).

OPIOIDS

The opioids are common offenders in overdoses involving illicit street drugs, and the opioid analgesic morphine is the most common cause of toxic drug reactions in hospitalized patients (51). The adverse side effects of the opioid analgesics are described in Chapter 49. The following description will focus on the treatment of opioid intoxication with the opioid antagonist naloxone.

Naloxone
Naloxone is a pure opioid antagonist that binds to endogenous opioid receptors but does not elicit any agonist responses. **It** is most effective in blocking *μ*-receptors (primarily responsible for analgesia, sedation, and respiratory depression) and less effective in blocking K-receptors and a-receptors (52,53).

Routes oj Administration
Naloxone (0.4 mg/ml or 1 *mg/ml)* is usually given intravenously (onset 2-3 minutes) or intramuscularly (onset 15 minutes) (52,54), but can also be given endotracheally (55), or by intralingual injection (56,57).

Dosing Recommendations
In opioid overdose, reversal of the sedation usually requires smaller doses of naloxone than reversal of the respiratory depression.

DEPRESSED MENTAL STATE. For patients with a depressed sensorium but no respiratory depression, the initial dose of naloxone should be 0.4 mg IV push. This can be repeated in 2 minutes, if necessary. A total dose of 0.8 mg should be effective if the mental status changes are caused by an opioid derivative (32). In patients with known opioid dependency, the bolus dose of naloxone should be reduced to 0.1 or 0.2 mg (32).

RESPIRATORY DEPRESSION. For patients who have evidence of respiratory depression (e.g., respiratory rate less than 12 breaths/min), the initial dose of naloxone should be 2 mg IV push. This dose is repeated every 2 minutes if necessary, to a total dose of 10 mg (32).
The effects of naloxone last about 60 to 90 minutes, which is less than the duration of action of most opioids. Therefore, a favorable response to naloxone should be followed by repeat doses at one-hour intervals, or by a continuous infusion. For a continuous naloxone infusion, the hourly dose of naloxone should be two-thirds of the effective bolus dose (diluted in 250 or 500 mL of isotonic saline and infused over 6 hours) (58). To achieve steady-state drug levels in the early infusion period, a second bolus of naloxone (at one-half the original bolus dose) is given 30 minutes after the infusion is started. The duration of treatment varies (according to the drug and the dose ingested), but averages 10 hours (32).

Empiric Therapy
Patients with a depressed mental state of undetermined etiology are often given naloxone (0.8-2 mg IV push) as empiric therapy. This practice has been questioned, because it elicits a favorable response in fewer than 5% of cases (59). An alternative approach has been proposed where empiric naloxone is indicated only for patients with pinpoint pupils who have circumstantial evidence of opioid abuse (e.g., needle tracks) (32,59). When naloxone is used in this manner, a favorable response is expected in approximately 90% of the patients (59).

Adverse Reactions
Naloxone has few side effects. The most common adverse reaction is the opioid withdrawal syndrome (anxiety, abdominal cramps, vomiting, and piloerection). There are case reports of acute pulmonary edema (most in the early postoperative period) and generalized seizures following naloxone administration (32), but these complications are rare.

A FINALWORD
The drug that deserves the most attention in this chapter is acetaminophen, which is now the leading cause of acute liver failure in the United States and Great Britain (where it is called paracetamol). The general public seems unaware of the toxic potential of this drug, which is why one of every three overdoses is unintentional. When presented with a possible acetaminophen overdose, remember that the effectiveness of the antidote, N-acety1cysteine (NAC), is time-dependent, even within the 24-hour treatment window, so don't delay in starting therapy when it is indicated by the nomogram in Figure 53.2. The recent approval of the intravenous NAC regimen represents a real advance in treatment because patient compliance with the oral regimen is poor due to the foul taste of NAC.
Acetaminophen became popular in the 1970s because of concerns about the toxicity of aspirin, arid it looks like we replaced a mouse with a gorilla.

References