SECTION 16

Acute Intoxication and Poisoning

CHAPTER 98

Drugs and Antidotes in Acute Intoxication

George Braitberg

OBJECTIVES

This chapter will:

1. Provide an overview of drugs and antidotes in acute intoxication.
2. Highlight clinical pitfalls in the management of toxicity.
3. Identify the clinically significant toxidromes.
4. Describe the effects of sodium and potassium channel blockers.
5. Present a review of specific poisons and antidotes.
6. Review poisons that have significant effects on the kidney.

Deliberate self-poisoning, accidental poisoning, and recreational drug abuse and chemical exposure are increasing in frequency across the world. The Toxic Exposure Surveillance System (TESS) database of poison control centers of the United States reported a frequency of approximately 6.7 exposures per 1000 population in 2014.[1]

Calls from healthcare facilities regarding human exposures have increased consistently over the last 14 years (3.3% since 2000). Human exposures with more serious outcomes have increased by 4.29% since 2000.[1] Although children younger than 6 years of age were involved in 47.7% of poisoning reports, they incurred just 2.2% (26) of the recorded 1173 fatalities. Forty-six percent of poisoning fatalities occurred in persons 20 to 49 years of age. Analgesics were thought to be responsible for most of the fatalities, with the next most common cause attributable to stimulants and "street drugs." However, sedatives/hypnotics/antipsychotics have demonstrated the most rapid increase in serious outcomes over the last few years. Of all reported exposures, 16.7% of inquiries were described as intentional exposure, a majority as a result of a suspected suicide (11.2%). Therapeutic errors accounted for 12.6% of exposures. Overall, 22.3% of the patients required evaluation in a healthcare facility, of whom 3.2% were admitted to an acute inpatient bed and 4.7% to a critical care unit. Of all of the reported exposures, therapies other than decontamination were used 11.5% of the time.[1]

Although poisoning should be suspected in any patient with multisystem involvement of unknown cause until proven otherwise, the clinician also should be aware of common pitfalls in the workup of the patient with suspected or known poisoning (Box 98.1).

TOXIDROMES

In many clinical circumstances, the poison is unknown, at least initially. In these circumstances, after appropriate life support measures have been instituted, the toxic treatment paradigm is to group signs and symptoms together into a toxidrome. *Toxidrome* describes clinical presentations common to a number of toxins.

The most common toxidromes are the following:

- Anticholinergic (antimuscarinic)
- Cholinergic
- Adrenergic
- GABAergic
- Sodium and potassium channel blocker related
- Serotoninergic
- Opiate-related

Anticholinergic Toxidrome

The most common toxidrome by far is due to anticholinergic toxicity. Anticholinergic drugs continue to increase in serious exposures every year.[1]

In 2014, 10,774 exposures were reported, of which 4.2% were reported to be minor or moderate seriousness. One death was reported.[1]

Anticholinergic toxicity is defined more appropriately as antimuscarinic poisoning. It occurs when the acetylcholine postsynaptic muscarinic receptor is antagonized. This receptor is found on the parasympathetic postganglionic receptor.

BOX 98.1

Pitfalls in Clinical Management of Suspected Toxicity

- Not all patients with a presumed overdose have, in fact, overdosed. The young patient with altered state of consciousness may have suffered a primary neurologic event, and a careful neurologic examination looking for focal signs must always be part of the evaluation in such cases.
- A poisoned patient may have suffered a secondary event after the overdose or exposure (e.g., neurologic and cardiac sequelae of cocaine intoxication are well documented).
- Polypharmacy is the rule. In one study, acetaminophen was the drug most commonly implicated in overdose (54%), but polypharmacy ingestions were the next most frequent (38%).[2] In multiple-ingestion overdoses, the poisoned patient will not follow a "predictable" path of recovery, because other substances may have different time courses for the development of toxicity (e.g., a patient who has overdosed on sustained-release verapamil may not display any signs of poisoning for up to 18 hours, at a time when toxicity from other substances co-ingested may be resolving).
- Recovery may be prolonged as a result of therapeutic intervention (e.g., development of aspiration pneumonia after gastrointestinal tract decontamination).
- Poisoning may occur from routes other than oral. Dermal absorption, as in the case of organophosphate poisoning, poses a particular risk for the rescuer or healthcare worker who attends the patient, without protective clothing, before decontamination. Inhalation absorption, as with exposures involving some noxious gases (e.g., products of combustion), puts rescuer and victim at risk.
- Intravenous substance abuse has been associated with risk of infection, of which hepatitis and HIV infection are well known, but at present the leading cause of botulism in the United States is the use of contaminated needles.

HIV, Human immunodeficiency virus.

Dawson and Buckley[4] describe four mechanisms contributing to anticholinergic delirium:

1. Predominant muscarinic antagonists such as atropine, benztropine, and many plants
2. Muscarinic antagonists with other mixed effects, such as antihistamines, tricyclic antidepressants, and antipsychotics
3. Decreased acetylcholine release after carbamazepine, opiate, and clonidine ingestion
4. Decreased acetylcholine synthesis as a result of thiamine deficiency[4]

Anticholinergic toxicity can be central, peripheral, or both. Peripheral toxicity may or may not be present before central toxicity develops, and vice versa.

Characteristics of *central* anticholinergic toxicity include the following:

- Biphasic effect of central nervous system (CNS) excitation followed by depression
- Distinctive mumbling or fragmentary speech pattern
- Atypical behavior, especially inappropriate undressing
- Repetitive "picking" movements (e.g., tugging at the bedclothes or a catheter or grasping at space)
- Hallucinations, more commonly visual
- Movement disorders of an ataxic or clonic nature in some cases

Patients with severe central manifestations (e.g., hallucinations, psychoses, seizures, coma) have the highest morbidity rates.

Characteristics of *peripheral* anticholinergic syndrome, in order of onset, include the loss of ability to salivate, sweat, and lacrimate, followed by blurred vision (caused by decreased ability to accommodate and papillary mydriasis) and then an increase in heart rate and a decrease in bladder motility (leading to urinary retention). Finally, gut peristalsis is lost, leading to constipation.

An important *clinical clue* is that tachycardia with dry axillae distinguishes the anticholinergic toxidrome from the adrenergic toxidrome.

Anticholinergic syndrome can be summarized as follows:

- Mad as a hatter*
- Hot as a hare
- Blind as a bat
- Red as a beet
- Dry as a bone

Many drugs and substances cause anticholinergic toxicity. Box 98.2 provides a list of common anticholinergic agents.

Antidote Considerations: Physostigmine

Little role exists for the routine use of physostigmine in the management of a patient displaying anticholinergic toxicity. Physostigmine is an acetylcholinesterase inhibitor and, unlike neostigmine, crosses the blood-brain barrier. Thus it can increase central and peripheral levels of acetylcholine.

The clinical response to physostigmine can be dramatic, controlling agitation and reversing delirium 96% and 87%, respectively, compared with benzodiazepines, which control agitation in only 24% and have no effect on delirium.[4] The use of physostigmine is not without adverse effects, with seizure, bradycardia, and even asystole being reported when used in the management of overdose, especially in the setting of tricyclic antidepressant toxicity.[5] It is postulated that in this situation, the anticholinergic-induced tachycardia, which may be helpful in offsetting the negatively inotropic effect of sodium channel blockade, when antagonized acutely leads to cardiac or pump failure and dysrhythmia. Although physostigmine has a short half-life (minutes), the clinical effect is longer.[4] Therefore physostigmine should be used only after consultation with a toxicologist, in a setting in which full resuscitation facilities are available. Alternatives such as tacrine, donepezil, rivastigmine, and galantamine do not have sufficient evidence to support use in this setting.[4]

The dose is 2.0 mg administered intravenously in 0.5-mg aliquots, given 5 to 10 minutes apart.

Cholinergic Toxidrome

The parasympathetic nervous system has acetylcholine as its neurotransmitter at central and peripheral receptors. The central preganglionic receptor is a nicotinic receptor (Nn type). The sympathetic nervous system uses two neurotransmitters: acetylcholine acts on Nn receptors in the preganglionic central chain, and norepinephrine acts on the peripheral α and β receptors. The somatic nervous system has acetylcholine as its neurotransmitter, acting on the nicotinic Nm receptor subtype to innervate striped (skeletal) muscle.

*Hat manufacturers applied mercury to the felt of their hats and as a result developed mercury poisoning. Thus, in reality, hatters were mad for reasons other than anticholinergic poisoning.

BOX 98.2

Common Anticholinergic Agents

Antihistamines
Chlorpheniramine
Cyproheptadine
Doxylamine
Hydroxyzine
Dimenhydrinate
Diphenhydramine
Meclizine
Promethazine

Tricyclic Antidepressants
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin
Imipramine
Nortriptyline
Protriptyline

Mydriatics (Easily Systemically Absorbed)
Atropine
Cyclopentolate
Homatropine
Tropicamide

Class 1 Antiarrhythmics
Disopyramide
Plants
Atropa belladonna (deadly nightshade)
Cestrum nocturnum (night-blooming jasmine)
Datura suaveolens (angel's trumpet)
Datura stramonium (jimson weed)
Hyoscyamus niger (black henbane)
Lantana camara (red sage)
Solanum carolinensis (wild tomato)
Solanum dulcamara (bittersweet)
Mushrooms (e.g., *Amanita muscaria*)

Antipsychotics
Phenothiazines (e.g., chlorpromazine)
Clozapine
Mesoridazine
Olanzapine
Quetiapine
Thioridazine

Antiparkinsonian Drugs
Benztropine (also used to control extrapyramidal effects from the major tranquilizers)

Motion Sickness Preparations
Scopolamine patches

Muscle Relaxants
Orphenadrine (Norflex)

Others
Carbamazepine

The cholinergic toxidrome is manifested by signs of stimulation of the muscarinic and the nicotinic receptors in autonomic and somatic nervous systems.

Stimulation of the muscarinic receptors leads to the "classic" SLUDGE syndrome:

- Salivation
- Lacrimation
- Urination
- Diarrhea
- Gastrointestinal cramps
- Emesis

In addition, muscarinic cholinergic stimulation leads to bronchoconstriction and bronchorrhea.

Stimulation of central nicotinic receptors affects sympathetic and parasympathetic neurons. This causes a release of norepinephrine and acetylcholine. An initial excitation phase, manifested by tachycardia and hypertension, may occur as a result of sympathetic nervous system stimulation. After the initial stimulation, however, prolonged ganglionic blockade and adrenal suppression occur (nicotinic receptors also are located in the adrenal medulla). At this point, hypotension and bradycardia predominate. Nicotinic receptor stimulation in the brain leads to altered mental status, with confusion, agitation, restlessness, and vomiting. This may be followed by onset of seizure and neurologic depression with coma.

Acetylcholinergic stimulation of Nm receptors on skeletal muscle causes initial excitation, with fasciculation and tonic clonic jerks, followed by blockade and muscle weakness. Hypotonia, decreased tendon reflexes, and motor paralysis sequentially occur.

Agents that cause a cholinergic toxidrome can be divided into two main groups, according to their mechanism of action:

- Direct nicotinic receptor stimulation plant alkaloids such as nicotine and coniine (found in poison hemlock), nicotine-based insecticides, cigarette butts (at least three whole butts in a young child)
- Increased acetylcholine levels, organophosphates, and carbamates

Organophosphates

Organophosphates are agricultural insecticides. These agents inhibit the enzyme acetylcholinesterase, which is responsible for the degradation of acetylcholine. The organophosphate binds to the enzyme, causing it to undergo a conformational change at its binding site to acetylcholine. If the organophosphate does not leave the acetylcholinesterase enzyme within 24 to 48 hours, it is bound irreversibly to the enzyme, which is permanently inactivated; this process is called "aging." Recovery from poisoning occurs only with resynthesis of new enzyme, a process that takes several weeks. The treatment of organophosphate poisoning is twofold:

1. Symptomatic treatment with atropine to overcome muscarinic stimulation by acetylcholine. The dose given is that sufficient to "atropinize" the patient—to abolish signs and symptoms (see later).
2. Reactivation of acetylcholinesterase with an oxime such as pralidoxime. Oximes cleave the organophosphate from acetylcholinesterase and bind circulating free organophosphate. In addition, pralidoxime displays antimuscarinic properties of its own. Because of the aging of the organophosphate-acetylcholinesterase complex, the earlier oximes are administered, the earlier acetylcholinesterase can be re-formed. Resolution of symptoms and a rising acetylcholinesterase level indicate response to therapy.

In military or disaster scenarios, atropine and an oxime are combined in "autoinjectors." Pralidoxime is discussed here, but in other parts of the world, including the United States, other oximes are used, the most frequent being obidoxime. Oxime effectiveness and dosing have been the subject of much discussion because of the lack of randomized trials evaluating organophosphate treatment. A recently

published article by Pawar et al. showed that higher-dose continuous infusion of pralidoxime iodide (1 g/hr of pralidoxime for 48 hours) was superior to intermittent dosing (a bolus of 1 g/hr every 4 hours).[6]

Antidote Considerations

ATROPINE. Atropine is a physiologic antidote to the muscarinic features of organophosphate toxicity, acting to competitively inhibit acetylcholine at muscarinic receptors but with no effect at ganglionic or neuromuscular nicotinic receptors. It also may be useful in carbamate toxicity, which may be clinically indistinguishable from organophosphate toxicity.

The *dose* is 2 mg (0.05 mg/kg in children), repeated at 10- to 30-minute intervals until drying of excessive secretions occurs. There is no upper limit of dose in the treatment of a severe organophosphate poisoning. Severe toxicity may require extremely large doses to achieve atropinization (up to 1000 mg/24 hours has been used). An atropine infusion at 5 to 20 mg/hr may be required. Pupillary dilatation and tachycardia are not reliable therapeutic end points. Normalization of peripheral vascular resistance may be a better end point but is not normally measurable outside an ICU environment. Atropine may be useful in the treatment of hypotension without bradycardia. In the randomized controlled trial, the atropine was administered as a 1.8- to 3.0-mg bolus on admission, followed by an infusion with intermittent boluses to achieve control of secretions from the tracheobronchial tree, return pupils to their normal size, and stabilize the pulse rate at between 80 and 100 beats per minute.[6]

Adverse reactions to atropine may include the following:

- Ventricular arrhythmias may occur if adequate tissue oxygenation is not achieved before the use of atropine.
- Atropine excess may cause anticholinergic symptoms: mydriasis, tachycardia, hyperpyrexia, ileus, delirium, facial flushing, urinary retention, drying of secretions.

PRALIDOXIME. The dosage is 1 to 2 g (25 to 50 mg/kg in children) given over 30 minutes, followed by an infusion of 200 to 500 mg/hr. Infusions usually must be continued for at least 48 hours in significant exposures. The dose should be reduced in the presence of renal failure.

Adverse reactions reported after pralidoxime iodide injection include dizziness, blurred vision, diplopia and impaired accommodation, headache, drowsiness, nausea, tachycardia, hyperventilation, and muscular weakness, but it is very difficult to differentiate the toxic effects produced by the organophosphate compounds from those of the drug. When atropine and pralidoxime iodide injection are used together, the signs of atropinization may occur earlier than may be expected when atropine is used alone, and less atropine may be required.[6] Excitement and manic behavior occurring immediately after recovery of consciousness have been reported in several instances. However, similar behavior has been described in cases of organophosphate poisoning that were not treated with pralidoxime iodide injection.[7]

Recent studies have cast doubt on the efficacy of pralidoxime in the treatment of organophosphate poisoning. A randomized double-blind placebo-controlled trial comparing pralidoxime to saline showed no difference in mortality (28% vs. 26%) or length of ICU stay.[8] A previous study by Eddleston[9] reported that despite showing a reactivation of red blood cell acetylcholinesterase in the pralidoxime-treated group, there was increased case fatality mortality (although not statistically significant) in those treated with pralidoxime. At the time of publication there has been no change to the World Health Organization recommendations pralidoxime regime.

BOX 98.3

Common Causes of the Adrenergic Toxidrome

Recreational drugs
- Cocaine
- Amphetamines and other "designer drugs"[a]—"ecstasy" (3,4-methylenedioxymethamphetamine [MDMA]); 3,4- methylenedioxyamphetamine (MDA); 3,4- methylenedioxyethylamphetamine (MDEA); paramethoxyamphetamine (PMA); methamphetamine

β_1-Adrenergic agents
- Salbutamol
- Theophylline

Inotropic agents
- Norepinephrine
- Epinephrine
- Isoproterenol

Over-the-counter cough and cold preparations and nasal decongestants
- Phenylpropanolamine
- Pseudoephedrine

Amphetamine-like agents prescribed for ADD or weight loss
- Methylphenidate
- Dextroamphetamine

Psychostimulants

[a]Up to 80% of ecstasy tablets sold in Australia are actually methamphetamine.
ADD, Attention deficit disorder.

Adrenergic Toxidrome

Box 98.3 lists common causes of the adrenergic toxidrome. The adrenergic toxidrome is caused by sympathomimetic agents. Neurologic manifestations include hyperthermia, agitation, seizures, and coma. Cardiovascular effects include tachycardia, hypertension, peripheral vasoconstriction, arrhythmias, and myocardial infarction. Metabolic disturbances from increased circulating catecholamines cause elevation of glucose levels and the white blood cell count. Hypokalemia in the absence of vomiting usually does not require correction, because the cause is not a potassium deficit but rather an intracellular shift, which will settle as the toxidrome abates. Other signs and symptoms include bronchodilation, nausea, and vomiting; diaphoresis and rhabdomyolysis also may occur.

No specific antidotes are available. Management consists of lowering body temperature and blood pressure and achieving central sedation, usually with a benzodiazepine and other supportive measures. Hypertension requiring pharmacologic intervention is treated with a specific alpha blocker or smooth muscle antihypertensive (e.g., hydralazine or sodium nitroprusside). Beta blockers have the potential to precipitate a vasoconstriction crisis by unopposed alpha stimulation.[10] If the patient exhibits psychosis in the setting of amphetamine or cocaine toxicity without significant cardiovascular toxicity, an agent such as haloperidol may improve the patient's mental status by means of dopamine antagonism. Phenothiazines such as chlorpromazine should be avoided because they lower the seizure threshold and may exacerbate hyperthermia because of anticholinergic activity. "Ecstasy" (i.e., 3,4-methylenedioxymethamphetamine

[MDMA]) poisoning may respond to antiserotoninergic medication such as cyproheptadine (see later).[11]

Note About Recreational Drugs

The 2015 National Institute on Drug Abuse Survey on the prevalence of use of various recreational substances reported that between the ages of 12 to 17, 28.4% used alcohol in the past year, 8.1% cigarettes, 17.5% some form of illicit drug consisting of cocaine (0.6%), hallucinogens (2.1%), and LSD (1%). Amphetamine derivatives MDMA, methamphetamines, and others were used by 2.1% within the past year. In the over 18 age group, this increased to 14.5%.[12]

Methamphetamines are produced by reduction of ephedrine or pseudoephedrine, found in decongestants and other household products, making them relatively simple drugs to produce.

Psychostimulants cause an overall increase in the amount of monoamine neurotransmitters—norepinephrine, dopamine, and serotonin—by increasing their release and blocking reuptake. Amphetamines, MDMA, and cocaine have the greatest effect on norepinephrine, serotonin, and dopamine, respectively.[13] Ecstasy primarily increases serotonergic activity, whereas methamphetamine primarily increases adrenergic activity. Cocaine also blocks fast sodium channels, causing local anesthetic and proarrhythmic effects.

A majority of ecstasy users do not experience adverse events that precipitate a hospital visit. Serious complications are rare and partly dependent on individual susceptibility and circumstances. The common adverse acute physiologic and psychologic effects that psychostimulants elicit constitute an exaggerated "fight or flight" response.

Extreme dehydration and water intoxication have been associated with MDMA toxicity. Dehydration is due to a lack of awareness of thirst in the setting of extreme physical activity. Water intoxication can be a consequence of increased antidiuretic hormone secretion and consumption of too much water (to prevent dehydration), leading to complications associated with hyponatremia. Cardiac ischemia can occur with any of these drugs but is particularly associated with cocaine. It is due to a combination of increased myocardial demand, coronary vasoconstriction, and increased thromboxane A_2 activity and thrombus formation.[14]

The most commonly repeated findings in studies of MDMA, methamphetamine, and cocaine use have been problems in the area of learning and memory. Animal and human studies have yielded evidence of neurotoxicity, but whether this is permanent and irreversible after chronic use in humans is inconclusive. However, the evidence for neurotoxicity continues to accumulate.[15]

GABAergic Toxidrome

γ-Aminobutyric acid (GABA) is a naturally occurring inhibitory neurotransmitter located in the CNS. The other important inhibitory neurotransmitter, glycine, is situated centrally and peripherally, where it is involved in inhibitory stimuli to tendon stretch reflexes. This peripheral action is demonstrated in strychnine poisoning, in which glycine receptors are inhibited by strychnine, leading to abnormal muscle activity and painful spasms in affected patients, who retain a normal mental status.[16]

The GABAergic toxidrome refers to the effects of stimulation of the $GABA_A$ receptor. The $GABA_A$ receptor is a chloride ion receptor complex that causes chloride ions to enter the nerve cell, causing hyperpolarization on stimulation. This action produces inhibitory neurotransmission. Antagonism of the $GABA_A$ receptor causes excitation.[16]

Most CNS depressants work by enhancing $GABA_A$ neurotransmission. Benzodiazepines and barbiturates, anticonvulsants such as valproate, and to some degree, carbamazepine, general anesthetics, and ethanol are some examples. All of these agents must bind to GABA to produce their neuroinhibitory effect. In isoniazid overdose, in which GABA formation has been stopped, seizures are refractory to control with GABA-dependent anticonvulsants, such as barbiturates and benzodiazepines.[17]

Antagonists of the $GABA_A$ receptor include toxins such as chlordane, an organochlorine pesticide, and lindane, used in the treatment of lice. High-dose penicillin, used in animal models to induce seizures, antagonizes the receptor, as does the administration of ciprofloxacin. All of these agents may precipitate seizures.[16]

Antidote Considerations: Flumazenil

Flumazenil is a benzodiazepine antagonist that binds to the benzodiazepine receptor, displacing other benzodiazepine agonists, without neuroinhibitory effects.[18,19] Thus it antagonizes the neuronal depression caused by GABA stimulation at the $GABA_A$ receptor. The routine use of flumazenil in the management of benzodiazepine overdose is not recommended, because withdrawal seizures may be precipitated in patients who are chronically dependent on benzodiazepines, or in those who are not, the abrupt reversal of benzodiazepines may unmask the effect of an excitatory drug taken as a co-ingestant (e.g., tricyclic antidepressants), also with the potential for causing seizures. A recent meta-analysis of adverse events associated with the use of flumazenil reported a risk ratio of 2.85 (compared with placebo), increasing to 3.81 when only serious adverse events were included.[20] A further consideration is the relatively high safety index (toxic-to-therapeutic dose ratio) of benzodiazepines.[16]

Sodium and Potassium Channel—Blocking Agents

Sodium Channel

In addition to the class I antiarrhythmic agents, numerous other drugs, including tricyclic antidepressants, amantadine, carbamazepine, antihistamines (e.g., diphenhydramine), beta blockers (propranolol, acebutolol, and oxprenolol), cocaine, and propoxyphene, have sodium channel–blocking properties. Many other drugs can cause sodium channel blockade when taken in overdose. Tricyclic antidepressants such as imipramine exert cardiovascular toxicity through their anticholinergic effects and ion channel–blocking effects in cardiac muscle.[21] Class Ic agents are the most potent sodium channel blockers but do not affect potassium channels; therefore these agents cause QRS prolongation without QT prolongation on the electrocardiographic tracing.[22] Bicarbonate is considered by most toxicologists to be the treatment of choice for cardiac toxicity in the setting of sodium channel–blocker poisoning. In Europe, hypertonic sodium lactate is used in place of bicarbonate. Both agents overcome sodium channel blockade by mass effect and by increasing serum pH, which inhibits binding of at least some sodium channel blockers to sodium channels. Serum alkalinization has been shown to be of benefit in reversing

toxicity from tricyclic antidepressants, cocaine, quinidine, flecainide, procainamide, mexiletine, and bupivacaine.[21,23–28]

Potassium Channel

The QT interval is an electrocardiographic measure that includes depolarization and repolarization. It begins with the onset of ventricular depolarization (Q wave) and ends with completion of repolarization (T wave). Because the QT interval shortens with increasing heart rates, it usually is corrected for heart rate (QTc). Depolarization of ventricular cells is the result of a rapid influx of sodium ions through selective sodium channels, and its duration is measured by the QRS interval. Repolarization involves calcium, sodium, and several potassium channels, but potassium channels play the pivotal role in drug-induced torsades de pointes (TdP). The potassium channel most often involved in drug-induced QT syndromes is the potassium rectifier (I_{Kr}) channel. Drugs blocking the I_{Kr} channel can induce TdP and sudden death in apparently healthy adults and after poisoning.[29,30] Although most drugs that block I_{Kr} result in QT prolongation, which is a requisite for TdP, QT prolongation is not sufficient to result in TdP. Indeed, amiodarone usually results in significant QT prolongation, but TdP from amiodarone is exceedingly rare. Heterogeneity of repolarization across cell types within ventricular myocardium is being recognized increasingly as one explanation for the lack of direct correlation between QT prolongation and proarrhythmia.[31]

Prolonged QTc interval has been associated with the risk of sudden death in epidemiologic studies.[32,33] Measuring QTc is problematic. Onthong et al. surveyed medical toxicologists across the United States and found different measurement practices leading to different results.[34] An alternative is to use the QT normogram, which uses area under the curve, adjusting for heart rate and when evaluated in case of drug-induced TdP was found to be highly sensitive and specific (Fig. 98.1).[35]

Agents that produce QT prolongation in therapeutic and toxic doses are listed in Box 98.4.[36–38]

In 1991 Mehtonen et al.[39] reviewed all medicolegal autopsies (coroners' cases) in Finland. Analyzing 24,158 cases, they found 49 sudden unexpected deaths among apparently healthy adults taking antipsychotic medication. Of these 49 deaths, 46 involved a phenothiazine, primarily thioridazine (28 of the 46 cases). Berling and Isbister[40] identified increased likelihood of torsades de pointes (TdP) with amisulpride. Although sudden unexpected death occurs almost twice as often (relative risk, 2.39; 95% confidence interval [CI], 1.77 to 3.22) in populations receiving antipsychotics as in normal populations, nevertheless only 10 to 15 such events occur in 10,000 person-years of observation.[41,42]

Treatment

QT prolongation is associated with an increased arrhythmogenic risk, in particular, TdP. Although rare, it is reported to be fatal in about 20% of cases.[40] Although prolonged QTc after drug exposure may place the patient at greater risk of arrhythmia, it is important to realize that TdP can occur with a narrow QTc as well.[43] Although the evidence for treatment is based on case reports and in vivo experiments, the general consensus is to treat drug-induced TdP with magnesium sulfate given as a bolus (2 to 5 g over 60 seconds), to decrease the amplitude of early afterdepolarizations and suppress triggered rhythms. Treatment for patients with electrocardiographic evidence of prolonged QTc, particularly in the presence of any arrhythmia (e.g., bigeminy), has even less evidence base, but the current practice is to administer a slower infusion of magnesium.[44]

Serotonin Syndrome

The diagnosis of serotonin toxicity is based on clinical findings. Although several diagnostic criteria have been developed, the decision rules described in Fig. 98.2, originated by Boyer and Shannon,[45] are more sensitive (84% vs. 75%) and specific (97% vs. 96%) for diagnosing the syndrome. Clonus (inducible, spontaneous, and ocular) is a highly specific feature for establishing the diagnosis. Clinicians always should be aware that hyperthermia and hypertonicity occur in life-threatening cases, but muscle rigidity may mask the highly distinguishing

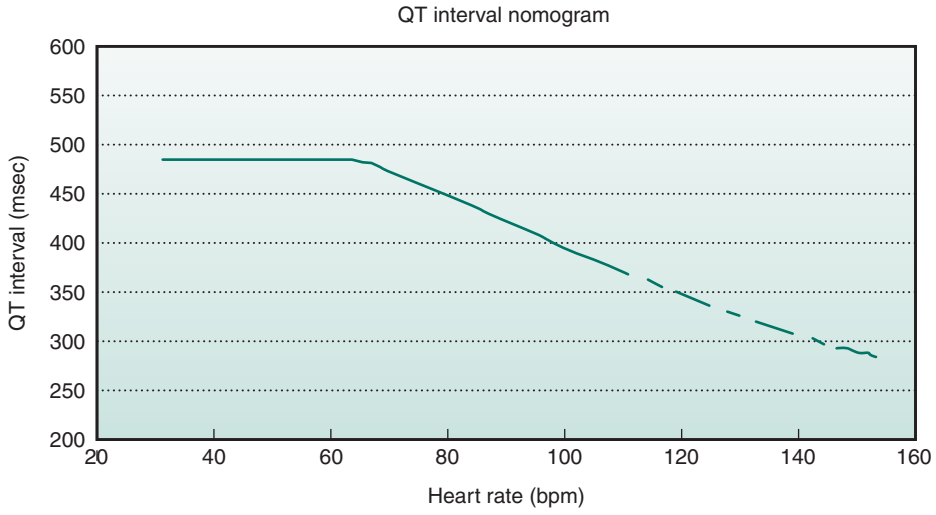

FIGURE 98.1 QT normogram. (Reproduced from Chan A, Isbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. *QJM*. 2007; 100:609–615.)

BOX 98.4

Drugs or Conditions That Cause Prolonged QTc Interval

Antihistamines
Diphenhydramine
Astemizole
Terfenadine
Cetirizine

Antidepressants
Citalopram
Escitalopram
Fluoxetine

Tricyclic Antidepressants
Bupropion
Lithium
Moclobemide

Antipsychotic Medications
Olanzapine
Risperidone
Quetiapine
Thioridazine
Haloperidol
Droperidol
Ziprasidone
Chlorpromazine
Mesoridazine
Amisulpride

Cardiac Drugs
Class 3 and class 1a antiarrhythmics

Antibiotics
Erythromycin
Clarithromycin
Pentamidine
Chloroquine

Metabolic Disturbances
Hypokalemia
Hypomagnesemia
Hypocalcemia

Other Drugs and Toxins
Carbamazepine
Cisapride
Organophosphates
Methadone
Levomethadyl
Arsenic
Carbon monoxide
Fluoride

Modified from Proudfoot AT, Donovan JW. Diagnosis of poisoning. In Brent J, Wallace KL, Burkhart KK, et al, eds. *Critical Care Toxicology. Diagnosis and Management of the Critically Poisoned Patient.* Philadelphia: Mosby; 2005:225–238.

findings of clonus and hyperreflexia, thereby clouding the diagnosis.

Treatment is essentially supportive, with intravenous hydration and close monitoring. Removal of the precipitating drug(s) and managing agitation, autonomic instability, and hyperthermia are essential. The administration of a 5-hydroxytryptamine type 2A ($HT_{[2A]}$) antagonist should be considered (see later).

The intensity of therapy depends on the severity of illness. Mild cases (e.g., with hyperreflexia and tremor but no fever) usually can be managed with supportive care and treatment with benzodiazepines. Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-$HT_{(2A)}$ antagonists. Hyperthermic patients (with body temperature higher than 41.1°C) are severely ill and should receive the aforementioned therapies and also should undergo immediate sedation, neuromuscular paralysis, and orotracheal intubation.[46] Moderately affected patients may display restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), and rapid eye movement (REM) sleep behavior disorder.[47]

Control of agitation with benzodiazepines is essential in the management of the serotonin toxicity, regardless of its severity. Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.[46,48] Physical restraints are ill advised in any drug-induced agitated state and may contribute to the risk of death by enforcing the isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.[49] If physical restraints are used initially, they must be replaced rapidly with chemical sedation.

Pharmacologically directed therapy involves the administration of a 5-$HT_{(2A)}$ antagonist. Cyproheptadine currently is recommended, although its efficacy has not been established rigorously. Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85% to 95% of serotonin receptors.[50] In general, an initial dose of 8 to 12 mg of cyproheptadine is recommended. Maintenance dosing involves the administration of 8 mg of cyproheptadine every 6 hours. Cyproheptadine is available only in oral form, but tablets may be crushed and administered by nasogastric tube.[45] Atypical antipsychotic agents with 5-$HT_{(2A)}$ antagonist activity may be beneficial in treating serotonin syndrome. The sublingual administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.[51] If a parenteral agent is needed, the intramuscular administration of 50 to 100 mg of chlorpromazine may be considered.[46] Care should be taken, however, with use of this drug in patients with hypotension, or those in whom the neuroleptic malignant syndrome is a possibility, because the drug potentially may exacerbate these conditions.[45]

Control of autonomic instability involves stabilization of fluctuating pulse and blood pressure. Hypotension arising from monoamine oxidase (MAO) inhibitor interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, epinephrine). Direct agonists do not require intracellular metabolism to generate a vasoactive amine, as distinct from indirect agents such as dopamine, which must be metabolized to epinephrine and norepinephrine by way of MAO. When inhibited, however, MAO cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue.

Other therapies for serotonin toxicity, including propranolol, bromocriptine, and dantrolene regimens, have not been shown to decrease morbidity and mortality rates.[45,52]

Opiate Toxidrome

Opiate refers to a substance that originates from opium, derived from the latex of the capsule of the opium plant, *Papaver somniferum*. *Opioid* is the term used for analogue substances with an effect similar to that of morphine. Opioids are ligands on opioid receptors that possess intrinsic activity. Overdose generally manifests with the classic triad of CNS depression, respiratory depression, and pinpoint

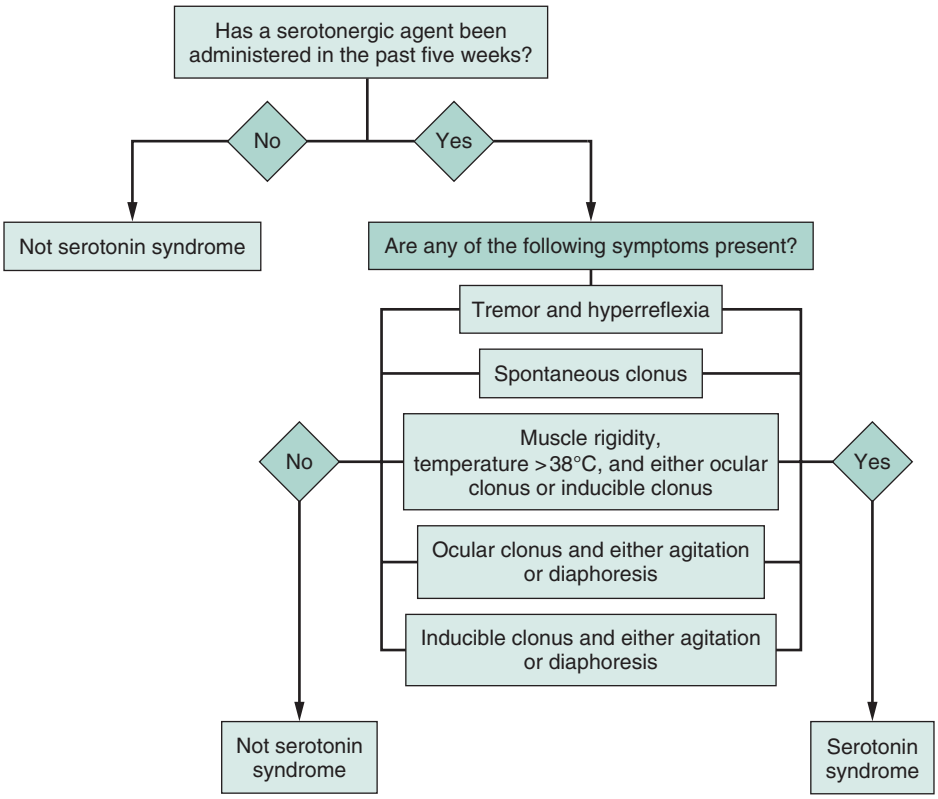

FIGURE 98.2 Algorithm for diagnosis of serotonin syndrome. (Redrawn from Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112–1120.)

(myopic), sluggishly reactive pupils. The cause of acute lung injury, formerly called "noncardiogenic pulmonary edema," is not clearly understood but is likely to be multifactorial. Naloxone administration causing a catecholamine surge may be a contributing factor.[53]

Typically in their late 20s or early 30s, heroin overdose victims are likely to have a long heroin-using career, be opioid dependent and regular users, prefer the intravenous route, have high levels of treatment contact but not be currently in treatment, and have a criminal history. Research indicates that nonfatal acute opioid overdose is a remarkably common experience among heroin users[54]; however, in multiple logistic regression analyses, age, hospital admission, suicidal intent, principal poisoning, and type of opiate were statistically significant predictors of death.[55] The risk of death from use or misuse of prescription opioids such as oxycodone has been highlighted recently in the lay and medical literature. Serious toxicity from prescription opioids has risen over the last two decades in parallel with an increase in opioid prescribing to manage acute and chronic pain. The increase in Veteran Health Administration (VHA) patients has almost doubled to 33.4% from 2004 to 2014.[56] Of the 1105 pharmaceutical substances causing death in the 2014 American Association of Poison Control Centers *National Poison Data System*, hydrocodone or oxycodone were implicated in 79 cases (7.2%) compared with heroin (67 deaths) and all amphetamines derivatives (66 deaths).[1]

Other opiates, such as methadone, codeine, and diphenoxylate, which are also long-acting, must be administered with care, especially in patients at the extremes of age or those with renal or hepatic impairment.

Antidote Considerations: Naloxone

Two important early studies demonstrated the efficacy of naloxone in reversing opiate poisoning. Evans et al.[57] reported a study in which naloxone (0.4 to 1.2 mg given intravenously) resulted in recovery of consciousness within 1 to 2 minutes in nine patients with a history of opiate ingestion. This was associated with improvement in respiratory function in the six patients in whom this could be assessed by measurement of minute volume and respiratory rate. This rapid and clear benefit of therapy also was reported by Buchner et al. in 1972,[58] who studied the effects of naloxone (0.005 to 0.01 mg/kg) in 10 children with methadone poisoning.

The *recommended dose* of naloxone for a 70-kg adult is 0.2 to 0.4 mg given intravenously, for a maximum dose of 10 mg, and titrated to response. A high incidence (45%) of adverse events was reported during out-of-hospital naloxone administration. It is likely that the observed events represented mainly opioid withdrawal effects caused by naloxone. They also could be related to hypoxia and to the extensive use of heroin in combination with other agents. Most events were not serious.[59]

SPECIFIC POISONS AND ANTIDOTES

Acetaminophen

Acetaminophen (paracetamol) is one of the most common drugs taken in overdose. It is easily accessible and requires

no prescription. Acetaminophen causes liver toxicity. Toxic levels are more likely to occur with ingestions over 150 mg/kg. Acetaminophen is metabolized by three mechanisms in the liver. A major portion of the drug is conjugated to glucuronide or sulfate (the latter is of decreasing importance with age but is extremely important in pediatric ingestions). A small amount is metabolized by the P-450 enzyme system to a potentially toxic intermediate (4%) *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This intermediate is metabolized by glutathione to a nontoxic mercaptopurine product. Only when an excessive amount of acetaminophen has been ingested is this pathway of any importance. In the face of an overdose, however, glutathione can be used up, and when levels fall below 30% of normal, glutathione can no longer detoxify the acetaminophen intermediate, so toxicity develops.[60]

Because P-450 distribution is confined primarily to the centrilobular area of the liver, the characteristic histopathologic change seen in acetaminophen-induced liver injury is centrilobular necrosis. Very rarely, renal impairment or mental status changes and acidosis may develop in the presence of a massive overdose. Without treatment, patients experience nausea and vomiting. Within 24 hours, they will show an elevation in the international normalized ratio (INR). At 36 to 48 hours after ingestion, they will demonstrate an elevation in liver transaminases, followed by a rise in bilirubin levels. Frank liver failure occurs 5 to 7 days after the ingestion.

Treatment

The management of acetaminophen poisoning is determined by the drug level measured at least 4 hours after ingestion (after distribution has occurred). A nomogram plots the level against the probability of liver damage. A 4-hour level of 1000 mmol/L is an indication to begin treatment with *N*-acetylcysteine (NAC). If the level is above the line for the time after ingestion, antidotal therapy with *N*-acetylcysteine is indicated. If the level falls below the line, and the history of time of ingestion is accurate, then antidotal treatment is not required. The nomogram is adjusted down (by 30%) for patients with glutathione deficiency states. All patients who are seen within 1 hour of an acetaminophen overdose should be given activated charcoal if their airway is secure. If the patient can be given *N*-acetylcysteine within 8 hours after ingestion, then liver damage despite a high blood level is highly unlikely.

N-acetylcysteine acts by donating a sulfhydryl group to detoxify the P-450–formed intermediate. It also replenishes glutathione stores. People at risk for acetaminophen toxicity are those with lowered glutathione stores, including alcoholic persons and those on medication that increases P-450 activity, such as phenobarbital.

There is *no* time at which *N*-acetylcysteine *cannot* be given. Early reports, especially from the United Kingdom, suggested that *N*-acetylcysteine was of no benefit if given 16 hours after ingestion. This suggestion has proved to be false, and in more recent studies, even patients with fulminant hepatic failure from acetaminophen ingestion have benefited from the administration of *N*-acetylcysteine.[61] In fact, one school of thought advocates the use of *N*-acetylcysteine for any cause of liver failure, in accordance with the rationale that restored glutathione stores are helpful in combating oxidant stress on liver that has failed from any cause. Animal studies have shown that *N*-acetylcysteine may improve the survival of isolated perfused rat livers and may improve liver function in pigs.[62,63] The use of *N*-acetylcysteine in orthotopic liver transplantation had modest but not statistically significant hemodynamic effects in a study of 50 patients with chronic end-stage liver disease.[64]

In a recent study, Kerr et al.[65] showed no difference in anaphylactoid reaction rate when the initial bolus injection was given in 60 minutes rather than 15 minutes. (However, a trend toward decreased anaphylactoid reactions in the slower infusion group was demonstrated, with a 4% absolute risk reduction in the 60-minute group.) The lack of statistical difference has since been supported in a smaller retrospective study.[66] The rate of adverse reactions to intravenous *N*-acetylcysteine is quoted variously between 6% and 45%.[65–67] Merl et al.[66] found the most common adverse reaction to be flushing (noted in 14 patients [6%]), with urticaria (in 13 [5%]), bronchospasm (in 9 [4%]), and pruritus (in 3 [1.2%]) also reported. Patients were more likely to have an adverse reaction if they had not received *N*-acetylcysteine previously (10% vs. 20%) and if the initial infusion was administered within 15 minutes (45% vs. 28%), but neither factor reached statistical significance.

The anaphylactoid reaction seen in *N*-acetylcysteine administration is dose- and dose-rate—dependent. Because this reaction does not represent mast cell degranulation, if a rash or wheeze develops, the infusion should be stopped, antihistamines with or without steroids should be administered, and when the symptoms abate, the infusion should be restarted cautiously.

The *loading dose* of *N*-acetylcysteine is 150 mg/kg in 200 mL of 5% dextrose given over 15 minutes to 1 hour (note alteration from conventional recommendation of 15 minutes). Then 50 mg/kg in 500 mL of 5% dextrose is given over 4 hours, followed by 100 mg/kg in 1000 mL of 5% dextrose over 16 hours.

A recently published position statement from the American College of Medical Toxicology addressed the duration of antidote treatment. Although acetaminophen has an elimination half-life of 21 hours, hepatic injury as a consequence of toxicity may impair metabolism and the usual 21- hour NAC protocol may be insufficient. The half-life may be further increased in large ingestions or co-ingestants that may decrease gut peristalsis.[68] Hence the AMCT recommendation is to continue NAC infusion until all the following criteria are present:

- Undetectable acetaminophen levels
- Improving hepatic aminotransferases
- Improving prognostic markers (e.g., creatinine, lactate, INR, pH, and phosphate)

Ethylene Glycol

In the 2014 American Association of Poison Control Centers (AAPC) report[1] fomepizole, the alcohol dehydrogenase antagonist used in the treatment of ethylene glycol poisoning, was reported to be used 2034 times, representing 0.1% of all human exposures. The ingested amount of ethylene glycol required to produce toxicity in animals is approximately 1 to 1.5 mL/kg.[69] Glyoxylic and glycolic acid are the major toxins formed by the metabolism of ethylene glycol, but the parent compound is not measured readily, nor are these metabolites. Acid-base measurement and calculated osmolar gap often are used as indirect indicators of ethylene glycol toxicity, but the sensitivity and specificity of these measures is dependent on time from ingestion. Late presenters may have low or immeasurable concentrations of unchanged ethylene glycol and a consequently normal osmolar gap (less than 10 mOsm/kg).[70] In a survey of US teaching hospitals, only 25% performed analysis of

ethylene glycol on site, with a median turnaround time of 42 hours reported for off-site results.[71]

Clinical Manifestations

CNS depression is most severe within 6 to 12 hours after ingestion, when the acidic metabolites reach maximal concentration. Pneumonitis, pulmonary edema, and acute lung injury also have been reported.[72] Renal involvement becomes apparent 24 to 72 hours later as the metabolites of ethylene glycol, notably glycolic acid, accumulate.[73] If untreated, ethylene glycol toxicity may be fatal within 24 to 36 hours (Boxes 98.5 and 98.6).

Laboratory Findings

Confirmatory quantitative levels (by gas chromatography) for toxic alcohols such as ethylene glycol levels are not available on site at most hospitals. Colorimetric qualitative enzymatic assays are commercially available but not routinely used. Therefore indirect tests are required. These include elevated osmolar gap calculation, elevated anion gap, metabolic acidosis, and a routine serum electrolyte panel to include a measure of carbon dioxide content. Note early in the postingestion period an increased osmole gap with a normal anion gap can occur before any significant formation of glyoxylic acid. Crystalluria (calcium oxylate) may be present, but its absence does not exclude ethylene glycol toxicity. Crystals may look like "folded envelopes" if formed as calcium oxylate dehydrate or needlelike as calcium oxylate monohydrate.[74]

BOX 98.5

Recommended Biochemical Tests for Screening Patients With Suspected Toxicity in Small, Rural, or Remote Hospitals

- Arterial blood gases
- Electrolytes
- Anion gap
- Serum osmolality
- Urine oxalate crystals
- Lactate analysis
- Serum creatinine

In larger toxicology centers, testing should include all of the above and ethylene glycol confirmatory test and screening and quantification of glycolic acid on a 24-hour basis (<2-hour turnaround time).
Modified from Fraser AD. Clinical toxicologic implications of ethylene glycol and glycolic acid poisoning. *Ther Drug Monit.* 2002;24:232–238.

BOX 98.6

AACT Criteria for Treatment of Ethylene Glycol Poisoning With an Antidote

Plasma ethylene glycol level >20 mg/dL (3 mmol/L)
Or
Documented recent history of ingestion of ethylene glycol with an osmolar gap >10 mOsmol/kg
Or
Strong suspicion of poisoning and at least two of the following:
- Arterial pH < 7.3
- Serum bicarbonate <20 mEq/L (20 mmol/L)
- Osmolar gap >10 mOsmol/kg
- Urinary oxalate crystals present

Modified from Barceloux DG, Krenzelok EP, Olsen K, et al. American Academy Practice Guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol.* 1999;37:537–560.
AACT, American Academy of Clinical Toxicology.

Treatment

FOMEPIZOLE. The loading dose is 15 mg/kg, with a maintenance dose 10 mg/kg every 12 hours for 4 doses followed by 15 mg/kg every 12 hours until ethylene glycol levels fall below 20 mg/dL (3 mmol/L). A separate treatment regime is used for the administration of fomepizole during hemodialysis.[75]

ETHANOL INFUSION. Intravenous ethanol (10% diluted in 5% dextrose) is given as a loading dose of 10 mL/kg over 30 minutes, followed by an infusion of 1.4 to 2.0 mL/kg per hour. Ethanol acts as an alternative substrate for alcohol dehydrogenase.

HEMODIALYSIS. American Academy of Clinical Toxicology (AACT) guidelines for hemodialysis in the setting of ethylene glycol poisoning include deteriorating vital signs despite intensive care support, significant metabolic acidosis (pH < 7.25), and renal failure or electrolyte imbalances unresponsive to conventional therapy.[69] Glycolic acid has a half-life of up to 18 hours, which is reduced by a factor of 6 with hemodialysis.[76]

OTHER AGENTS. Pyridoxine (50 to 100 mg every 6 hours) and thiamine (100 mg daily) help promote the metabolism of intermediate byproducts to nontoxic metabolites.

Hypoglycemia Secondary to Sulfonylureas and Other Long-Acting Diabetic Medications

Sulfonylureas are responsible for 4000 poisoning exposures each year.[77] These medications can produce toxicity after a single tablet ingestion in children.[78] By binding to the sulfonylurea receptor on the beta cell of the pancreas, they promote the release of insulin. In people without diabetes, this excess insulin can lead to prolonged hypoglycemia.

Treatment

The mainstay of treatment is dextrose replacement, often at high infusion rates or concentrations. Octreotide is a long-acting synthetic octapeptide analogue of somatostatin and has been used to treat a variety of endocrine problems and esophageal variceal bleeding. In the hyperinsulinemic state after a sulfonylurea overdose, octreotide inhibits further insulin release from pancreatic beta cells. In human studies, octreotide decreases the number of hypoglycemic episodes and the required duration of dextrose therapy.[79,80] Octreotide is given by infusion at 50 µg/kg per dose, divided, every 6 to 8 hours.

Cyanide

Cyanide is a metabolic poison. Although the precise in vivo action of cyanide has yet to be determined, it is thought that its major effect is due to binding with the ferric ion (Fe^{3+}) in cytochrome oxidase, the last cytochrome in the respiratory chain causing inhibition of oxidative phosphorylation. The major pathway of endogenous detoxification is

the conversion of cyanide by sulfurtransferase to thiocyanate. In the presence of excess cyanide, the rate-limiting step is an adequate supply of sulphane sulphur, which can be supplied by thiosulphate.[81] As a result of this action, the clinical signs and symptoms of acute cyanide poisoning reflect gross metabolic disruption. As a consequence of inhibition of oxidative phosphorylation, there is a net accumulation of hydrogen ions and a change in the nicotinamide adenine dinucleotide (NAD)/NADH ratio, with greatly increased lactic acid production.[82] MRI may show damage to the basal ganglia.[81]

Clinical Manifestations

CNS signs and symptoms, in order of increasing severity of cyanide exposure, include headache, anxiety, disorientation, lethargy, seizures, respiratory depression, CNS depression, and, finally, cerebral death.

Respiratory manifestations include initial tachypnea, which gives way to respiratory depression as CNS depression emerges.

Cardiovascular signs and symptoms include hypertension, usually followed by hypotension, tachycardia followed by bradycardia, and the development of a variety of arrhythmias, including atrioventricular block. Systemic vascular resistance usually is decreased, and cardiac output usually is increased. The arteriovenous oxygen difference, a measure of oxygen extraction, is decreased. In the event of cardiovascular collapse, bright red skin or blood will not be a feature (with decreased oxygen consumption) in patients in whom significant myocardial, respiratory, or CNS depression already has occurred. In these situations, the patient will appear cyanotic. Cyanosis also may "appear" after treatment with amyl nitrite and induction of methemoglobinemia.[83,84]

Treatment

Cyanide poisoning is treated differently in different parts of the world. The treatment approach will differ according to whether cyanide is to be directly chelated with a cobalt-containing moiety (dicobalt edetate 300 mg and hydroxocobalamin 2.5 to 5 g as an initial dose) or whether the cyanide is provided with an alternative ferric ion source, thereby competitively removing it from the cytochrome, using a cyanide antidote kit containing amyl nitrite perles, sodium nitrite 10 mL (30 mg/mL), and sodium thiosulfate, 50 mL (250 mg/mL). The rationale for use of the cyanide antidote kit is that the nitrites produce methemoglobin (ferric hemoglobin) to which the cyanide combines to form cyanmethemoglobin, releasing the cyanide from the cytochrome. The addition of sodium thiosulfate converts the cyanide to thiocyanate, which is excreted renally, while the iron in the hemoglobin is restored to the ferrous state.

Currently the only labeled antidote available in Australia is dicobalt edetate, known as Kelocyanor. A major consideration is that administration of Kelocyanor is associated with a high rate of allergic reactions, particularly in the nonpoisoned patient. The cyanide antidote kit may be unsuitable for use in patients with carboxyhemoglobin poisoning. It has been shown that the mean peak amount of methemoglobin levels achieved after the administration of 300 mg of sodium nitrite is 10.5%.[85] This amount is below levels expected to affect significant exposure to carbon monoxide alone. Nevertheless, in the presence of coexisting carboxyhemoglobin poisoning and the reduced aerobic metabolism of cyanide toxicity, methemoglobin represents a potential (as yet undetermined) insult. Thus the decision to use the kit presents a dilemma in the management of victims of potential smoke inhalation.

Hydroxocobalamin is a therapeutic agent with few side effects that can be given safely to nontoxic patients and is currently in use in Europe. A paucity of scientific data is available comparing the efficacy of hydroxocobalamin and dicobalt edetate, thereby precluding any definitive conclusion about which antidote is best. More is known about the fate of hydroxocobalamin in humans and its safety. In the emergency situation, hydroxocobalamin appears to offer a greater margin of safety. Hydroxocobalamin is recognized as an efficacious, safe, and easily administered cyanide antidote.[86,87]

Because of its extremely low adverse effect profile, hydroxocobalamin is ideal for out-of-hospital use in suspected cyanide intoxication. It has been recommended recently as the antidote of choice in the event of a cyanide chemical disaster to prevent needless morbidity and mortality.[88] The combination of hydroxocobalamin and thiosulfate has been reported to provide effective treatment for patients with extremely high levels of cyanide poisoning, and this combination is to be recommended.[89]

Heavy Metals

A variety of heavy metals have been taken (or given) as poison, deliberately and accidentally. Common poisons include lead, arsenic, mercury, copper, and thallium. Although an exhaustive list of potential poisons is beyond the scope of this chapter, each of the available antidotes, dimercaprol (British anti-Lewisite [BAL]), dimercaptosuccinic acid (DMSA) (i.e., succimer), 2,3-dimercaptopropane-1-sulfonic acid (DMPS), and calcium edetate (calcium disodium ethylenediaminetetraacetic acid [EDTA]), is discussed next.

Treatment

DIMERCAPROL. Dimercaprol was developed during World War II as an antidote to the war gas Lewisite. Based on observations that arsenoxide drugs acted on thiol groups, and that these reactions could be mitigated by sulfhydryl groups, BAL was found to be an effective treatment for the severe reactions associated with organoarsenical antibiotics used in the treatment of syphilis.[90] Subsequently, BAL was found to be effective in the treatment of mercury poisoning as well.[91] Dimercaprol is an oily, colorless solution that has a peanut odor associated with the peanut oil vesicant in which it is dissolved. It forms 1:1 or 1:2 complexes with several metals and then promotes urinary excretion of the metal.

FDA-labeled indications are as follows:

- Arsenic toxicity (mild)
- Arsenic toxicity (severe)
- Gold toxicity (mild)
- Gold toxicity (severe)
- Lead poisoning (mild)—when used concomitantly with edetate calcium disodium injection
- Lead poisoning (severe)—when used concomitantly with edetate calcium disodium injection
- Mercury toxicity—effective for acute poisoning by mercury salts if therapy starts within 1 to 2 hours after ingestion; not very effective for chronic mercury poisoning

BOX 98.7

Dosages for Dimercaprol

- **Arsenic toxicity—mild:** 2.5 mg/kg IM 4 times per day for 2 days, 2 times on day 3, then once daily for 10 days or recovery
- **Arsenic toxicity—severe:** 3 mg/kg IM every 4 hr for 2 days, 4 times on day 3, then twice daily for 10 days or recovery
- **Gold toxicity—mild:** 2.5 mg/kg IM 4 times per day for 2 days, 2 times on day 3, then once daily for 10 days or recovery
- **Gold toxicity—severe:** 3 mg/kg IM every 4 hr for 2 days, 4 times on day 3, then twice daily for 10 days or recovery
- **Lead poisoning—mild:** 4 mg/kg IM for initial dose, then 3 mg/kg every 4 hr for 2 to 7 days in combination with edetate calcium disodium injection at separate injection site
- **Lead poisoning—severe:** 4 mg/kg IM every 4 hr for 2 to 7 days in combination with edetate calcium disodium injection at separate injection site
- **Mercury toxicity:** 5 mg/kg IM for 1 day, followed by 2.5 mg/kg 1 or 2 times daily for 10 days

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The major concern with BAL is the required method of administration and the theoretical possibility of mobilization of metal with redistribution to the brain, seen in animal models.[92] BAL is given as deep intramuscular injections (by spinal needle), with dose and frequency dependent on the type of metal poisoning, as evident in Box 98.7.[93]

Adverse reactions are dose dependent and include transient hypertension, tachycardia, gastrointestinal effects, salivation, and muscular aches and pains. CNS effects include headache, paresthesia, tremor, and seizures at high doses.[94] Dermatitis is common, and the formation of a sterile abscess at the injection site has been reported.[95]

Contraindications include the following:

- Acute renal insufficiency that develops during therapy (in such cases, use at a reduced dosage with extreme caution or discontinuation of therapy is recommended)
- Hepatic insufficiency except in postarsenical jaundice
- Iron, cadmium, or selenium poisoning (more toxic in complex with dimercaprol)[96,97]

Use in copper, silver, and tellurium intoxications is limited.

Calcium Edetate

In 1950 calcium edetate (calcium disodium EDTA) was used for the treatment of hypercalcemia and in 1952 first was reported to be used in the treatment of lead poisoning.[98] EDTA acts to reduce blood concentrations and depot stores of lead. The calcium is replaced by divalent and trivalent metals, especially any available lead, to form stable, soluble complexes that are excreted readily. EDTA also will complex with zinc, and during therapy, serum zinc levels decline by 60% to 70%, returning to normal at the cessation of treatment.[99]

FDA-labeled indications are as follows:

- Lead poisoning, acute—to reduce blood levels and depot stores of lead
- Lead poisoning, chronic—to reduce blood levels and depot stores of lead
- Toxic encephalopathy resulting from lead—to reduce blood levels and depot stores of lead

Contraindications include the following:

- Anuria or active renal disease
- Hepatitis

Adverse effects with EDTA may include injection site pain, nausea, vomiting, myalgia, headache, and hypotension. Fever, thrombophlebitis, hypersensitivity reactions, and nephrotoxicity are said to occur relatively frequently.

The preferred route of administration is continuous intravenous infusion, rather than intermittent intramuscular injections. The dose for adults with severe lead poisoning is 2 to 4 g per 24 hours.

Succimer Dimercaptosuccinate (DMSA)

Orally active succimer is a heavy metal–chelating agent that forms stable, water-soluble complexes with lead and consequently increases the urinary excretion of lead.

The FDA-labeled indication for this agent is lead poisoning, but succimer chelates other heavy metals such as arsenic and mercury. In a study of the relative effectiveness or therapeutic index of the various dimercapto compounds in protecting mice from the lethal effects of a 99% lethal dose (LD99) of sodium arsenite, Aposhian et al.[100] found that DMSA is more effective than DMPS, DMPA, and BAL, with relative efficacy of 42:14:4:1, respectively. In addition, unlike in BAL, DMPS, DMPA, and DMSA will not increase the arsenic content of the brain of rabbits injected with sodium arsenite.[100]

The dose is 30 mg/kg daily for 5 days, followed by 20 mg/kg daily for 14 days.

Hypersensitivity is a contraindication to use of succimer. Reported adverse events include rash (occurring in approximately 4% of exposed people), diarrhea, loss of appetite, nausea, vomiting, abnormalities on liver function tests, and neutropenia.[101]

Monitoring of the following is recommended with use of this agent:

- Blood lead levels at least once weekly after therapy until the patient is stable
- Complete blood count (including white cell count with differential and direct platelet counts), before and weekly during treatment
- Measurement of serum transaminases before and weekly during treatment

2,3-Dimercaptopropane-1-Sulfonic Acid (Unithiol)

Unithiol is a chelator structurally related to dimercaprol. It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds. It also has been used in poisoning with chromium or cadmium, although its efficacy in such cases is not established.

Unithiol is administered orally in a dose of 100 mg given three or four times daily in chronic poisoning. It also may be given parenterally in patients with severe toxicity; a suggested intravenous dose is 3 to 5 mg/kg every 4 hours, reducing the frequency or changing to oral therapy after 1 to 2 days.[102]

ARSENIC POISONING. Complete recovery, without renal or neurologic sequelae, has been reported after the use of unithiol in patients with potentially lethal acute arsenic poisoning.[103,104] Increased urinary arsenic excretion, with some reduction in clinical signs and symptoms, also has been reported with unithiol in chronic arsenic toxicity.[105,106]

LEAD POISONING. Unithiol may be used in lead poisoning, although other chelators generally are preferred. In a study of 12 children, unithiol reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.[107]

MERCURY POISONING. Unithiol is used in poisoning with mercury and mercury salts and has been administered by various routes. In seven patients with poisoning resulting from mercury vapor or mercuric oxide, unithiol 100 mg, given twice daily by mouth for up to 15 days, was found to enhance urinary elimination of mercury.[108] The urinary elimination of copper and zinc also was increased in most patients; skin rashes developed in two patients. A dose of 5 mg/kg given intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[109] Unithiol also has been used with hemofiltration in patients with inorganic mercury poisoning and acute renal failure.[110,111]

WILSON DISEASE. Unithiol 200 mg twice daily was used successfully to maintain cupruresis in a 13-year-old boy with Wilson disease after systemic lupus developed during treatment with penicillamine and trientine dihydrochloride. Unithiol was started in two similar patients, but both withdrew from treatment, one because of fever and a fall in leukocyte count after a test dose and the other because of intense nausea and taste impairment.[112]

ADVERSE EFFECTS. Rash and pruritus have been reported in patients receiving unithiol (200 to 300 mg/day).[108,113] Nausea has been reported after use of unithiol.[112–114] Elevated liver enzymes occurred in a patient receiving unithiol 400 mg/day. Leukopenia and fever have been reported in a patient after a test dose of unithiol.[109] An allergic reaction with bronchospasm occurred in a patient after intravenous administration of unithiol 2 mg/kg; however, treatment was not necessary.[115] Headache has been reported in patients receiving unithiol (300 to 400 mg/day).[113,114] Bronchospasm occurred in a patient after intravenous administration of unithiol 2 mg/kg; treatment was not necessary.[115]

Digoxin

It was estimated in 2010 that there were more than 33.5 million people who had atrial fibrillation worldwide.[133]

For those toxins with a high volume of distribution (V_d), a potential for enhancing removal of absorbed drug is recognized. The best illustration of such therapy is for digoxin overdose. Digoxin has a high V_d and in toxic doses causes a multitude of cardiac dysrhythmias and is responsible for considerable morbidity and mortality.

Treatment: Digoxin-Fab$_2$ Fragments (Digibind or Digitab)

If an ingested toxin can be seen as a foreign agent, like an invading microbe, then the use of immunotherapy to combat the "invasion" was a logical concept. Antidigoxin antibodies raised in sheep have been available for some years; administration of such antibodies is now the standard of care in the treatment of digoxin toxicity. The antibodies use only the Fab fragment of the antibody so that they have a low likelihood of producing an anaphylactic reaction on administration but carry the important antibody-binding site.

Fab fragments should be administered to severely cardiac glycoside—intoxicated patients who fail to respond to immediately available conventional therapy. Severe cardiac toxicity includes ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation), progressive bradyarrhythmias (severe sinus bradycardia), or second- or third-degree heart block not responsive to atropine. Use of Digibind should be *considered* in adults who have ingested more than 10 mL of digoxin or children who ingested more than 4 mL of digoxin, in patients with a postdistribution serum concentration greater than 10 ng/mL (6 to 8 hours after ingestion), or in those patients with progressive elevation of serum potassium concentration associated with an ingestion of digoxin.

The dose of Digibind varies according to the amount of digoxin to be neutralized. Typically the aim is to bind half or the entire estimated digoxin body load.[116]

A 76-mg dose of digoxin—immune Fab will neutralize approximately 1 mg of digoxin or digitoxin. The following dosing calculations and principles are used:

1. Digibind dose (number of vials) = body load (mg)/0.5 (mg/vial), *or*
2. Dose calculated from serum level: Digibind dose (number of vials) = (serum digoxin concentration [ng/mL] × patient's weight [kg])/100.
3. If the estimated amount ingested or digitalis serum concentration is not available, 20 vials (760 mg) can be administered.
4. Four to six vials (152 mg to 228 mg) will be adequate to treat 90% to 95% of cases of chronic digoxin toxicity.[117]

Digibind is administered intravenously over 30 minutes, infused through a 0.22-μg filter. Intraosseous administration is *not* recommended. Earliest-possible administration is recommended in life-threatening intoxication.[117] A bolus injection can be given if cardiac arrest is imminent.

According to a recent study, only one or two vials are required to neutralize all the digoxin, although the clinical response to neutralization were modest.[116] This may be due to other comorbidities in patients presenting with chronic toxicity.

After therapy, free digoxin levels rebound, peaking approximately 3 to 24 hours after Fab administration in patients with normal renal function; then a slow, steady decline in free digoxin occurs at a rate dependent on Fab and renal and nonrenal routes of elimination.[118]

Adverse reactions have been reported with use of Fab fragment therapy. Congestive heart failure and low cardiac output states may be exacerbated by withdrawal of the inotropic effects of digitalis. Reactivation of ATPase may lead to hypokalemia. Withdrawal of the effects of digitalis on the atrioventricular node may result in the development of a rapid ventricular response in patients with atrial fibrillation.[119] Digoxin-Fab fragments should be used with caution in patients with severe renal failure. The use of Fab therapy in a patient with renal disease is considered as effective as in patients with normal renal function, although the increased risk of rebound digoxin toxicity mandates a longer period of observation. In patients with kidney failure, neither digoxin nor Fab can be removed efficiently from the systemic circulation by hemodialysis or continuous arteriovenous hemofiltration.[120]

Other Immunotoxicologic Therapies

No other antibodies (other than antivenoms) are available for clinical use in Australia at the present time. However, antibodies to the antimetabolite colchicine have been developed and used in a patient. Although colchicine poisoning is not especially common, it does appear to meet most of the requirements for a Fab antidote, because the usual ingested amount is small and colchicine is extremely toxic, with a high mortality rate from progressive hemodynamic collapse. The use of a Fab antidote for human colchicine poisoning was reported in a young woman who took a large overdose in a suicide attempt. Subsequently, progressive severe cardiopulmonary compromise resistant to fluid administration and inotrope infusion developed, but she improved rapidly with administration of goat-derived colchicine-specific Fab fragments.[121]

Fab therapy for cyclic antidepressant toxicity in experimental use has reduced lethality, but such intoxications are not ideal for an immunologic antidote because ingested amounts typically are large; thus the required Fab dose for human poisoning is very large.[122–124] Experimental antibodies specific for other intoxicants including phencyclidine,[125] the herbicide paraquat,[126] amanitin,[127] and tetrodotoxin[128] also have been reported, but clinical experience is lacking for these agents.

SOME RENAL CONSIDERATIONS

Acute renal toxicity from poisoning or overdose can be due to organ-specific injury or be part of a generalized multiorgan pattern. The unusual susceptibility of the kidney to toxic injury stems from its function of regulating the volume and composition of body fluids. The physiologic role of the kidneys in filtration, concentration, excretion, and secretion directly affects how toxins and poisons are handled. Lithium, for example, almost exclusively eliminated in the urine (98%), can reach toxic levels in conditions that alter kidney function. Drug interactions, acute intercurrent medical illness, low-salt diet, dehydration and volume depletion, cardiac failure, thiazide diuretics, and concurrent use of nonsteroidal anti-inflammatory medication can predispose patients to develop acute or acute-on-chronic lithium poisoning, without having a direct tubulotoxic effect. By contrast, ethylene glycol causes renal toxicity by elaboration of a toxic metabolite glycolic acid, which in isolated rodent proximal tubule cells causes direct cellular damage.[73] The inherent toxicity of unmetabolized ethylene glycol is low compared with its many metabolites, and this knowledge has driven the treatment of toxicity, including the introduction of the antidote fomepizole, an alcohol dehydrogenase inhibitor that blocks the metabolism of ethylene glycol and slows the metabolism.

In salicylate toxicity, for example, the normal mechanisms for handling the poison are exceeded (zero-order kinetics), and renal excretion becomes time dependent, renal absorption is pH-dependent, renal toxicity is direct and indirect, and a major treatment modality involves manipulation of kidney processes.

Normally salicylate undergoes glomerular filtration and tubular secretion. At therapeutic doses, the metabolic pathways for salicylates become saturated. Renal excretion is therefore very important in the elimination of salicylate at therapeutic and toxic levels. Only the unbound fraction of salicylate is available for glomerular filtration, but in toxicity, this portion increases. Salicylate is reabsorbed at the proximal convoluted tubules (PCTs). This latter process depends on urine flow rate and urine pH, and in an acid environment, salicylate is maximally nonionized, facilitating transfer across cell membranes and therefore PCT reabsorption.

The mechanism by which aspirin exerts its toxicity is complex and not fully understood. Recognized effects, however, include direct respiratory center stimulation, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, inhibition of amino acid metabolism, stimulation of glyconeogenesis and lipid metabolism, and increased tissue glycolysis. In addition, interference with hemostatic mechanisms also is seen. Together, these features contribute to the total picture of aspirin poisoning.[129]

Renal toxicity may be explained either by a reduction in renal blood flow or as a result of direct nephrotoxicity. Typically it is thought salicylates acutely inhibit prostaglandin synthesis, resulting in vasoconstriction and reduced renal blood flow and glomerular filtration.[130] The resultant oliguria is exacerbated by the presence of dehydration. Preexisting renal disease may predispose affected patients to the development of renal impairment.[131] Other toxic manifestations include pulmonary edema and fluid retention from inappropriate antidiuretic hormone secretion, hypernatremia, and hypokalemia. The presence of a significant acidemia may result in a normal serum K^+ level but mask a true total body potassium deficiency.

Although acid-base disturbance is one of the most common manifestations of salicylate toxicity, toxicity itself is influenced by serum and urinary acid-base balance. Because biliary elimination of salicylate is minimal,[132] the renal handling of salicylate after poisoning is highly relevant to clinical management. To prevent CNS penetration and promote urinary excretion, the serum and urine of the patient should be alkalinized to shift the salicylate moiety to the ionic form. Chapman and Proudfoot[133] described patients in four categories of acid-base disturbance, with mixed respiratory alkalosis and metabolic acidosis or respiratory alkalosis alone predominating in 61% and 19% of patients, respectively. The arterial pH, rather than the class of acid-base disturbance, was of greater value in determining clinical severity and mortality. Reabsorption of salicylate by the kidney is pH dependent.

CONCLUSION

Paracelsus, the father of toxicology, wrote: "All things are poison and nothing is without poison, only the dose permits something not to be poisonous." The potential source matter for a chapter on drugs and antidotes is therefore as extensive as a pharmacopedia. Accordingly, many toxins, including plant and animal toxins and mushrooms to any great degree, have been omitted here, with the focus on the common and the challenging and with a renal perspective. The reader is encouraged to consult textbooks of toxicology for a broader review.

Key Points

1. Identification of toxidromes enables the clinician to identify the type of poisoning and initial treatment even if the identity of the substance is unknown.

2. The most common toxidrome is from anticholinergic poisoning.
3. Consideration of antidotal therapy is limited to specific toxins. Supportive care is the mainstay of treatment.
4. Antidotal therapy depends on the pharmacokinetic (toxicokinetic) properties of the poison.
5. Although poisoning is part of the differential diagnosis in all cases of poorly defined illness, consideration of nontoxic causes, such as head or environmental trauma, which may occur concomitantly, is vital to ensure that treatable conditions are not overlooked.

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