CHAPTER 62

Cyclic Antidepressants

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Essentials

- The onset and progression of symptoms after overdose are often quite rapid.
- The most common presenting signs are a decreased level of consciousness, sinus tachycardia, and QRS prolongation.
- QRS prolongation is the most distinctive diagnostic feature and identifies patients at highest risk of complications.
- Potentially fatal complications include hypotension, ventricular dysrhythmias, seizures, and hyperthermia.

INTRODUCTION

Antidepressant overdose is common because these drugs are often available to depressed patients who have a high suicide risk. Of the various types of antidepressants, the selective serotonin reuptake inhibitors produce a relatively benign overdose and rarely result in fatalities. In contrast, the cyclic antidepressants (CAs) and monoamine oxidase inhibitors are much more toxic and fatalities may result from their misuse. This chapter considers CA toxicity; monoamine oxidase inhibitors are discussed in Chapter 66, and selective serotonin reuptake inhibitors are discussed in Chapter 63.

PHARMACOLOGY/PATHOPHYSIOLOGY

Pharmacology

CAs are well absorbed from the gastrointestinal tract and are eliminated primarily by hepatic metabolism. There is little biliary secretion of active drug. Metabolism of CAs is by means of various cytochrome P-450 (CYP) enzymes. Hydroxylation of desipramine and imipramine is by the CYP2D6 isoenzyme. In genetically slow metabolizers (5 per cent of the population in the United States) or patients taking other drugs that inhibit or compete for this enzyme (e.g., fluoxetine, cimetidine, many antipsychotics), much longer half-lives can occur and patients can become toxic on usual doses or recover from overdose more slowly.[33] Most CAs have active metabolites; the tertiary amines (e.g., imipramine, amitriptyline) are demethylated to active secondary amines (desipramine, nortriptyline), and most CAs also undergo ring hydroxylation to active metabolites. In overdose, levels of metabolites are low and toxicity is principally due to the parent compound.[12] Distribution half-lives even with overdose are short (1–2 hr). As a result (provided that activated charcoal has been administered to terminate drug absorption), serum CA levels typically decline rapidly during the first 6 to 12 hours after presentation. The subsequent decline in serum CA levels is slower, owing to elimination half-lives for most CAs of 10 to 20 hours (50–100 hr for protriptyline).[8, 30] The elimination half-life may be prolonged with massive ingestions, owing to saturable metabolism.[21]

Pathophysiology

Physiologic effects of the CAs that contribute to their toxicity include blockade of cardiac sodium and potassium channels; blockade of α-adrenergic, cholinergic muscarinic, and histaminic receptors; and inhibition of neuronal catecholamine reuptake. Effects of these drugs on cardiac calcium channels and neuronal *N*-methyl-D-aspartate (NMDA) receptors are of less certain importance.

The most important toxic effect of the CAs is sodium channel blockade.[35] The cardiac sodium channel is responsible for cardiac cell depolarization (action potential phase 0, Fig. 62–1); its inhibition leads to slowed depolarization of individual cardiac cells. This, in turn, leads to slowing of the wave of depolarization across the myocardium. The electrocardiographic manifestation of slowed depolarization is prolongation of the QRS complex, the hallmark of CA overdose.[25] Sodium channel blockade in vitro or in animals can be partly reversed by increasing the ambient pH or sodium concentration, providing the basis for the use of hypertonic sodium bicarbonate ($NaHCO_3$) to treat some of the cardiac effects of this overdose. Conversely, QRS prolongation is aggravated by decreasing the ambient pH.[24] The mechanism of this effect is not established; but by analogy with the antidysrhythmic agent flecainide, displacement of the CA from its binding site on the sodium channel is a possibility.[28]

QRS prolongation serves as a marker for CA ingestion and the risk of adverse cardiac or central nervous system

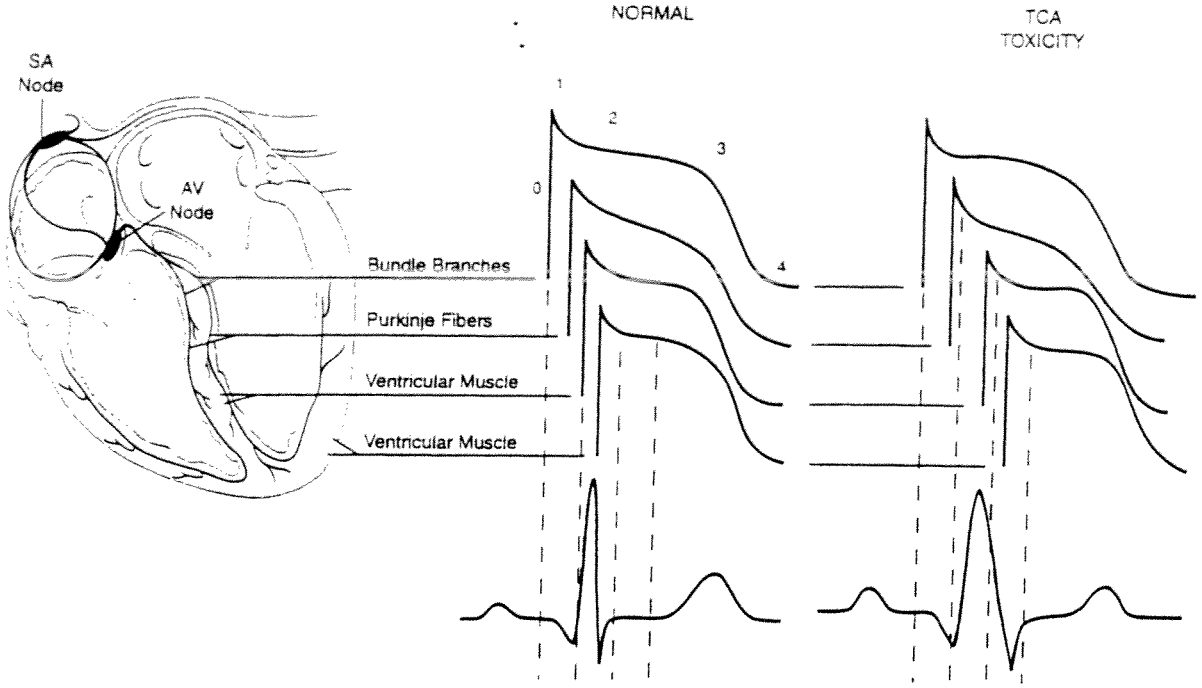

FIGURE 62–1 • Effects of CA toxicity on cardiac cell action potentials and the EKG. Depolarization of cardiac cells (phase 0 of the action potential) is due to an inward sodium current mediated by opening of the fast sodium channel. CAs in toxic doses inhibit the inward sodium current and thereby slow phase 0 depolarization of cardiac cells within the bundle branches, Purkinje fibers, and ventricular myocardium. This slowing of phase 0 depolarization is difficult to appreciate from tracings of the individual action potentials because of the rapidity of depolarization, but the net effect of slowed depolarization of individual cells is slowed conduction of the wave of depolarization from cell to cell through the His-Purkinje system and ventricular myocardium. As a result, the electrocardiographic QRS complex, which represents the wave of ventricular depolarization, is prolonged. (Redrawn and modified from Plate 11 from The Ciba Collection of Medical Illustrations, Volume 5, Section II, by Frank H. Netter, M.D.)

(CNS) events such as ventricular tachycardia or seizures.[3] This is true not just because QRS prolongation identifies patients who have ingested a substantial overdose, but also because slowed cardiac conduction is the proximate cause of much of the cardiovascular toxicity of these drugs. Slowed conduction affects the entire ventricular myocardium and conducting system but may occur nonuniformly. Greater degrees of slowing in one area relative to another provide the substrate for re-entrant dysrhythmias and is the likely mechanism by which the CAs produce ventricular tachycardia.[38] Sodium channel inhibition is also important because it is linked to myocardial contraction (excitation-contraction coupling), perhaps by regulating the intracellular sodium concentration at membrane sodium-calcium exchange sites. Agents that interfere with sodium channel opening and sodium entry into cells may therefore reduce the intracellular calcium concentration, resulting in impaired cardiac contractility and hypotension.

The CAs also block the potassium channel of cardiac cells, inhibiting the outward potassium current that contributes to repolarization.[35] This results in QT interval prolongation. Prolonged repolarization can predispose to development of torsades de pointes, but this is uncommon with CA overdose, possibly because torsades is less likely in the presence of an increased heart rate, and most patients with CA overdose have a sinus tachycardia.

Alpha-adrenergic blockade causes systemic vasodilation, which is an important contributor to hypotension.[16] Cholinergic muscarinic receptor blockade may cause an anticholinergic syndrome, including sinus tachycardia, delirium, coma, mydriasis, impaired gut motility, urinary retention, impaired sweating, and dry mucosa. Although anticholinergic potencies of therapeutic doses of CAs differ, any of these drugs may produce an anticholinergic syndrome with overdose. Histamine receptor blockade is of unclear importance, but it may contribute to coma. Seizures have been attributed to cholinergic or histaminic receptor blockade, but their mechanism is in fact unclear, and neuronal sodium channel inhibition could also contribute.

Inhibition of neuronal neurotransmitter (norepinephrine, dopamine, and serotonin) reuptake is probably important in mediating the therapeutic effects of CAs but is less relevant in overdose. The initial hypertension occasionally seen after overdose could be due to slowed norepinephrine turnover, and excessive norepinephrine could possibly also contribute to dysrhythmias, but supportive data are lacking.[15]

Hyperthermia may develop due to excessive heat production from agitation, myoclonus, or seizures, along with reduced heat dissipation from impaired sweating.[29]

CLINICAL PRESENTATION (Table 62–1)

Toxic Dose

Serious toxicity in adults is uncommon with ingestions of less than 1 g of CA, although toxicity may still be life threatening if other drugs have been co-ingested. Ingestions of more than 2 g may be fatal.

General Features

Rapid deterioration in clinical status is common with CA overdose, not because of rapid CA absorption but rather due

TABLE 62–1 • **Clinical Presentation of Cyclic Antidepressant Toxicity**

Central Nervous System
Delirium
Coma
Myoclonus
Seizures
Cardiovascular
QRS prolongation
Sinus tachycardia
First degree atrioventricular block
Rightward shift of QRS axis
Ventricular tachycardia
Hypotension
Autonomic
Decreased bowel sounds and motility
Urinary retention
Impaired sweating
Pupil size variable
Other
Hyperthermia
Acidosis or rhabdomyolysis from severe agitation or seizures

to the high doses ingested, so that absorption of even a fraction of the dose is often sufficient to produce severe toxicity.[5] Most CAs produce similar signs and symptoms with overdose (Table 62–2). Amoxapine is more likely to produce CNS toxicity, notably seizures, and very little cardiovascular toxicity.[18] Maprotiline is also more likely to produce seizures, but it may produce some cardiovascular toxicity as well. Lofepramine is a prodrug that is slowly metabolized to desipramine. Because the parent compound is not toxic, overdose tends to be relatively benign. Death from CA overdose in hospitalized patients is usually due to hypotension or ventricular dysrhythmias, because CNS toxicity is more readily managed.[2, 13] Prehospital, CNS toxicity assumes increased importance because airway compromise, impaired ventilation, or seizures may prove fatal in unattended patients.

Central Nervous System Effects

Modest doses of CAs may produce an agitated delirium. More often, the presentation is characterized by a decreased level of consciousness, often requiring airway protection and assisted ventilation.[2, 13] If seizures occur, they typically develop within the first few hours after ingestion and are generalized and brief. In patients with coexisting cardiovascular toxicity, particularly if severe, seizures may lead to rapid and marked worsening of hypotension or dysrhythmias, perhaps due to the accompanying acidosis.[10] Myoclonus is less common than seizures.

TABLE 62–2 • **Principal Overdose Toxicity of Some Cyclic Antidepressants***

Drug	Cardiovascular	Seizures
Amitriptyline	+ + +	+ + +
Nortriptyline	+ + +	+ + +
Imipramine	+ + +	+ + +
Desipramine	+ + +	+ + +
Doxepin	+ + +	+ + +
Clomipramine	+ + +	+ + +
Dothiepin	+ + +	+ + +
Protriptyline	+ + +	+ + +
Trimipramine	+ + +	+ + +
Maprotiline	+ +	+ + + +
Amoxapine	+	+ + + +
Lofepramine†	+	+

*All of the drugs listed may produce coma and anticholinergic effects with overdose.
†Lofepramine is a prodrug that is slowly metabolized to desipramine, thereby limiting its overdose toxicity.

Cardiovascular Effects

The most common cardiovascular manifestations of CA overdose are sinus tachycardia and QRS prolongation; the most important and most frequently fatal are hypotension and ventricular tachycardia. First-degree atrioventricular block is common, but higher degrees of atrioventricular block are rare.

QRS Prolongation

QRS prolongation usually takes the form of a nonspecific intraventricular conduction delay rather than a discrete bundle branch block (Fig. 62–2).[2] QRS duration is a valuable marker of risk for complications, with values of greater than

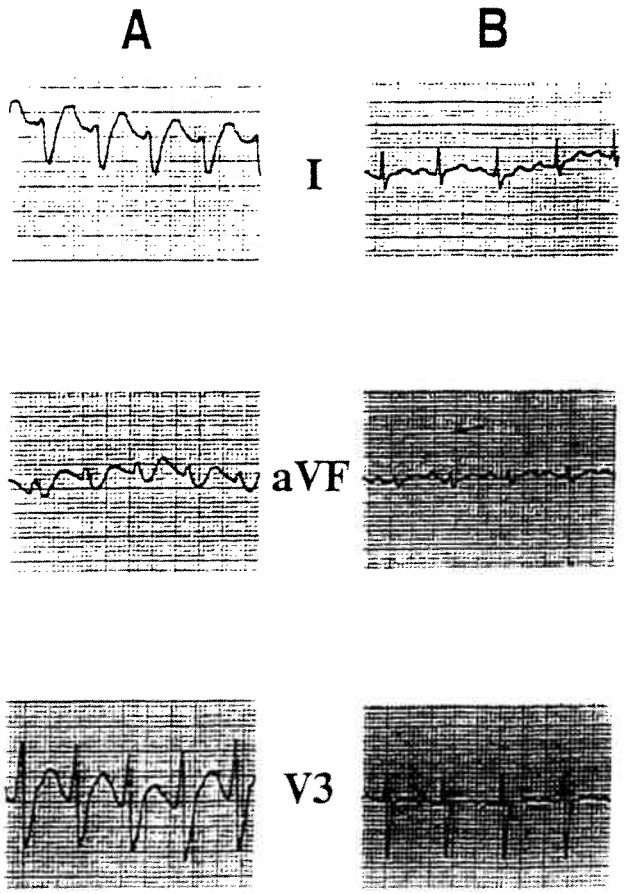

FIGURE 62–2 • EKG tracings from a patient who presented 2 hours after ingestion of imipramine. Representative leads demonstrate marked QRS prolongation (*A*). P waves are not visible, but the rhythm was demonstrated to be sinus tachycardia with intraventricular conduction delay by the gradual shortening of the QRS duration and reappearance of P waves over 36 hours (*B*).

0.16 second identifying patients at high risk for ventricular dysrhythmias or seizures.[3] Other manifestations of the conduction delay include a rightward shift of the QRS axis and the axis of the terminal 40 msec of the QRS complex and increased R wave voltage in lead aVR, but none of these markers has proven more specific or sensitive than QRS duration.[7, 18] Because sodium channel blockade is rate dependent, a rapid heart rate will exaggerate QRS prolongation.[20] QTc prolongation, often present even at therapeutic doses, is variable and of no prognostic importance.[7]

Hypotension

Hypotension often occurs in the absence of QRS prolongation, owing to vasodilation.[16, 32] If QRS prolongation is present, then impaired cardiac contractility is likely contributing as well. Tachydysrhythmias or hyperthermia may aggravate hypotension.

Dysrhythmias

Sinus tachycardia is present in more than half of patients with CA overdose and is usually of no consequence. Premature ventricular beats are rare. Ventricular tachycardia is usually monomorphic, and less commonly torsades de pointes occurs.[3, 32] Differentiating ventricular tachycardia (uncommon) from sinus tachycardia with QRS prolongation (common) may be difficult.

Other Effects

Hyperthermia may develop rapidly in patients with excessive muscular activity from agitation or seizures. Temperatures above 105°F may be fatal or result in permanent neurologic sequelae.[29] Acidosis may be caused by the same factors, as well as by hypoventilation. Pulmonary edema is common but is probably due to aspiration and hypotension rather than to a specific effect of the CAs.[31]

An anticholinergic syndrome often occurs that may include sinus tachycardia, delirium, coma, mydriasis, impaired gut motility, urinary retention, impaired sweating, and dry mucosa. However, patients need not have all of these findings, and the absence of anticholinergic effects does not rule out CA overdose.

DIFFERENTIAL DIAGNOSIS

Because CA overdose is common, it should be considered in all patients presenting with abrupt onset of delirium, seizures, a decreased level of consciousness, hypotension, or tachycardia. The most useful diagnostic marker is QRS prolongation because it is produced by relatively few other medications or conditions (Table 62–3). Detection of CAs in urine is supportive of the diagnosis, but this test is often positive even with therapeutic doses.

TABLE 62–3 • **Differential Diagnosis of Cyclic Antidepressant Toxicity: Causes of QRS Prolongation**

QRS Prolongation with Therapeutic Doses
Class IC antidysrhythmic agents: encainide, flecainide, propafenone
QRS Prolongation Primarily with Overdose
Cyclic antidepressants (except amoxapine)
Class IA antidysrhythmic agents: quinidine, procainamide, disopyramide
High-dose antipsychotics: thioridazine, chlorpromazine, mesoridazine
Antimalarials: quinine, chloroquine, hydroxychloroquine
Cocaine
Digoxin
Membrane-stabilizing β-adrenergic receptor antagonists: propranolol
Propoxyphene
Very uncommon even with overdose: diphenhydramine, lithium
Nondrug Causes
Hyperkalemia
Hypocalcemia
Ischemia
Cardiomyopathy

LABORATORY STUDIES

Alternative explanations for the patient's condition can be sought with routine screening tests, including serum electrolytes, blood urea nitrogen, glucose, and a complete blood cell count. In patients with significant cardiovascular toxicity, arterial blood gases should be measured to guide the administration of hypertonic $NaHCO_3$. Urine toxicology screens may be useful when the diagnosis is in question for detecting the presence of CAs, other drugs that prolong QRS duration (see Table 62–3), or other co-ingested drugs. A 12-lead EKG is essential to look for and follow QRS duration or dysrhythmias. A chest radiograph is useful if pulmonary edema is in question or aspiration is suspected.

Serum CA levels are not generally available in real time. Therapeutic serum levels of CAs, although established for only a few, are 50 to 250 ng/mL (of parent compound), and levels of more than 1000 ng/mL (corresponding to ingestion of more than 1 g) usually produce toxicity. Serum CA levels are not as useful as clinical markers such as QRS duration for predicting complications of CA overdose and are not usually monitored.[2, 3, 13]

TREATMENT (Table 62–4)

Because rapid deterioration is common, patients with suspected CA overdose should be closely observed with intravenous access, continuous cardiac monitoring, and frequent measurement of blood pressure and core temperature (particularly in patients who are agitated or seizing). The most important aspect of initial management is the prompt administration of activated charcoal, 1 g/kg (maximum 50 g). There is no evidence that prior gastric lavage is beneficial, and it delays the administration of activated charcoal.[4] If used, gastric lavage should probably be limited to patients seen within 1 hour of CA ingestion. Induction of emesis is contraindicated because of the risk of aspiration due to seizures or a deteriorating level of consciousness. Because the CAs have a large volume of distribution, repeated doses of activated charcoal, hemodialysis, and hemo-

TABLE 62–4 • **Treatment Essentials of Cyclic Antidepressant Toxicity***

General

Activated charcoal, 1 g/kg PO (maximum: 50 g) with sorbitol
Avoid syrup of ipecac

Coma

Protect airway, ventilate if necessary

Delirium

Diazepam, 5–10 mg, or lorazepam, 1–2 mg, intravenously if severely agitated; monitor for hyperthermia

Seizures

Diazepam, 10 mg, or lorazepam, 1–2 mg intravenously; repeat as needed
Prevent acidosis; ventilate, administer hypertonic $NaHCO_3$† intravenously, 50 mEq, if seizure prolonged

Hyperthermia

Rapid cooling; evaporation, ice water gastric lavage
Paralysis if patient persistently agitated or seizing
Monitor for acidosis, hypertonic $NaHCO_3$ intravenously, 50 mEq, if arterial pH <7.4

QRS Prolongation

<0.014 sec; observe
≥0.14 sec, or 0.11–0.14 sec and increasing or accompanied by hypotension; hypertonic $NaHCO_3$ intravenously, 50 mEq; repeat as needed until arterial pH = 7.5

Ventricular Tachycardia

Hypertonic $NaHCO_3$ intravenously, 50 mEq, as needed until arterial pH = 7.5
Lidocaine 1 mg/kg (maximum: 75 mg) over no less than 1 minute, followed by infusion of 1–3 mg/min
Overdrive pacing

Hypotension

Volume challenge: 500 mL 0.9% NaCl
If QRS is prolonged: hypertonic $NaHCO_3$ intravenously, 50 mEq; repeat as needed until arterial pH = 7.5
Dopamine, 5 μg/kg/min intravenously; increase as needed
or
Norepinephrine, 8 μg/min intravenously; increase as needed
Treat aggravating factors (ventricular tachycardia, hyperthermia, seizures) if present
Mechanical support (aortic balloon pump, cardiac bypass) for refractory hypotension

Drugs to Avoid

Class IA and IC antidysrhythmics
Physostigmine
Flumazenil

*For children younger than 12 years old, see Addendum E for pediatric drug doses.
†1 molar (mEq/mL)

perfusion all remove very little drug and are not clinically useful.

Cardiovascular Toxicity

The most effective intervention for the cardiovascular toxicity of CA overdose is hypertonic (1 molar, or 1 mEq/mL) $NaHCO_3$. In animals, $NaHCO_3$ is effective in reducing CA-induced QRS prolongation, reversing hypotension, and treating ventricular dysrhythmias.[24, 25] Human data are anecdotal but similar. $NaHCO_3$ is generally administered as intravenous boluses of 50 mEq of a 1 mEq/mL solution as needed to correct acidosis and, if toxicity persists, to raise the arterial blood pH to 7.5. It is not known if a higher pH would confer additional benefit. Hypertonic $NaHCO_3$ should not be diluted in crystalloid and administered as a continuous infusion because it will no longer be effective in raising the plasma sodium concentration.[25] Because $NaHCO_3$ is hypertonic, administration of intravenous boluses of hypertonic $NaHCO_3$ increases both the plasma pH and the plasma sodium concentration. Some animal studies suggest that increasing pH is more important, whereas others suggest that increasing the sodium concentration is the critical factor.[24, 28] In vitro studies of Purkinje fibers suggest that both are important.[35] There are no human data to address this question.

Hypertonic $NaHCO_3$ administration is indicated for patients with ventricular dysrhythmias or hypotension that has not responded to crystalloid. It is not clear whether hypertonic $NaHCO_3$ is beneficial for patients with normal blood pressure and cardiac rhythm whose only manifestation of cardiac toxicity is QRS prolongation. A common approach is to administer hypertonic $NaHCO_3$ to such patients if QRS prolongation is marked (0.14 sec or more) because of their higher risk of ventricular dysrhythmias, or if QRS duration is increasing. Routine administration of hypertonic $NaHCO_3$ is not indicated because it may lead to fluid overload, hypernatremia, or excessive alkalosis.[39]

Hyperventilation to raise blood pH has been used in patients with anecdotal benefit, and the use of hypertonic NaCl has been suggested, but clinical experience and animal data for hypertonic $NaHCO_3$ are far more extensive. Phenytoin has been used to reduce QRS duration, but proof of efficacy is lacking, and phenytoin aggravated dysrhythmias in one animal study.[6]

Hypotension

CA-induced hypotension often responds to crystalloid administration (e.g., 500 mL of 0.9 per cent saline over 15 minutes).[16, 32] If the QRS duration is prolonged, hypertonic $NaHCO_3$ can also be administered. If hypotension persists, catecholamines may be added. In animals, many catecholamines are effective and it is not clear if any one is superior.[15] Common choices are norepinephrine or dopamine.[36] Very high doses of vasopressors may be needed to overcome CA-induced α-adrenergic blockade. If time permits, the use of a pulmonary artery catheter to measure the relative contribution of vasodilation and impaired cardiac output may be useful in selecting the appropriate drug and dose.

Dysrhythmias

Sinus tachycardia rarely requires treatment. Ventricular tachycardia in animals responds to hypertonic $NaHCO_3$ or to lidocaine.[14, 24] Hypertonic $NaHCO_3$ is preferred because of its safety. If lidocaine is used, it should be infused slowly to reduce the risk of precipitating seizures. Class IA or IC antidysrhythmic agents (e.g., quinidine, procainamide, flecainide, encainide) may aggravate toxicity and should not be used. Overdrive pacing has been used anecdotally to terminate ventricular tachycardia.[27]

Central Nervous System Toxicity

Coma is treated by supportive care, including endotracheal intubation for airway protection and assisted ventilation.

Delirium can usually be managed with restraints and reassurance. Benzodiazepines may be used for agitation but can aggravate CNS depression. Seizures, if prolonged or repeated, may respond to a benzodiazepine.[11] Phenytoin has been used as a second-line drug, but efficacy data are lacking. Barbiturates were effective in an animal model (in which phenytoin was not)[1] but may aggravate hypotension. Propofol has been used in one patient.[19] Because seizures may cause acidosis, adequate ventilation should be ensured and administration of hypertonic $NaHCO_3$ considered if seizures are prolonged. Neuromuscular blockade may be considered for refractory seizures if refractory acidosis or hyperthermia occur, but it should be brief because it may mask ongoing cerebral seizure activity. Physostigmine has been used in the past for CA-induced CNS toxicity, but it is contraindicated because it may produce bradycardia or asystole even at usual therapeutic doses.[23]

Other Factors

Hyperthermia may be controlled with rapid cooling through evaporation or ice water gastric lavage. If agitation or seizures persist during hyperthermia, temporary neuromuscular blockade may be useful.

Flumazenil should not be administered to patients with overdoses involving CAs because it may precipitate seizures.[34]

Because CA toxicity is reversible, heroic measures may be justified in patients who remain viable but whose blood pressure cannot be supported pharmacologically. Such measures may be useful if they can help to support the patient while CA plasma levels fall due to tissue distribution. Survival after prolonged (3 hr) cardiopulmonary resuscitation or the use of an intra-aortic balloon pump has been reported.[37] Cardiac bypass has been of benefit in animals.[37]

DISPOSITION

Asymptomatic patients who receive activated charcoal may be observed in the emergency department with cardiac monitoring and an intravenous access for 6 hours. Those who remain free of signs or symptoms of toxicity need no further medical monitoring, and psychiatric evaluation can be obtained.[13] Patients with any signs or symptoms of CA overdose, including persistent sinus tachycardia, should be admitted. Cardiac monitoring in an intensive care unit should be continued until all signs and symptoms have resolved. If the patient's baseline QRS duration is not known, monitoring should continue until it is less than 0.10 second. If QRS duration stabilizes at more than 0.10 second, measuring the serum CA level may be helpful. Levels exceeding the therapeutic range suggest that QRS prolongation is due to residual CA toxicity, whereas levels that are therapeutic or subtherapeutic suggest that QRS prolongation simply represents the patient's baseline cardiac conduction.

SEQUELAE

Barring secondary complications such as anoxic brain damage, the acute effects of CA overdose are all reversible.

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