Part 10.2: Toxicology in ECC

Poisoning is an infrequent cause of cardiac arrest in older patients, but it is a leading cause of cardiac arrest in victims <40 years of age.[1–4] When a patient with poisoning is in cardiac arrest or near-arrest, immediate support of airway, breathing, and circulation is essential. Urgent consultation with a medical toxicologist or certified regional poison center is recommended[5,6] because standard guidelines for emergency cardiovascular care may not be optimal in the management of acute poisoning and overdose.

This section presents recommendations for the care of the patient with a toxicologic problem. Some recommendations are evidence-based, but most toxicology research in this area consists primarily of small case series (LOE 5), case reports, and animal studies (LOE 6). Hence many of these recommendations are based on expert consensus, and further research is needed to validate them.

Clinicians may see a patient with a history of ingestion of an unknown substance. In such cases the clinician must be familiar with common toxidromes and their therapies. To assist during such encounters, Table 1 lists drug-induced cardiovascular emergencies or altered vital signs, potential therapies to consider, and interventions that should be used with caution.

Clinicians may also encounter patients with a history of known ingestion. Then the clinician must anticipate the complications from that substance and be prepared to treat them. Table 2 lists potentially cardiotoxic drugs, signs of toxicity, and therapy to consider.

Drug-Induced Emergencies: Prearrest

Airway and Respiratory Management

Poisoned patients may deteriorate rapidly. Providers must assess and frequently reassess airway, breathing, and circulation and support them as needed. Although consultation with a poison control center or toxicologist may be needed to identify a particular toxin or antidote, the first priority of care is support of airway, breathing, and circulation. In patients who are obtunded or comatose, perform rapid sequence intubation before gastric lavage to decrease the risk of aspiration. Gastric lavage is recommended only for patients who have ingested a potentially lethal amount of a drug or toxin and present within 1 hour of ingestion.[7]

Reversal of benzodiazepine intoxication with flumazenil is associated with significant toxicity in patients with benzodiazepine dependence[8–12] or coingestion of proconvulsant medications such as tricyclic antidepressants. But it may be useful to reverse excessive sedation when benzodiazepines are used for procedural sedation.[13] Thus, the routine use of flumazenil in "coma cocktail" protocols is not recommended.

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Opiate Poisoning

Opiate poisoning commonly causes respiratory depression followed by respiratory insufficiency or arrest. Heroin overdose may cause respiratory depression, and it frequently causes pulmonary edema. The respiratory effects of opioids are rapidly reversed by the opiate antagonist naloxone.

In the hospital setting the administration of naloxone for acute opioid exposure has been successful without prior ventilation (LOE: 4[14,15]; 5[16,17]; 7[18]) if the airway was maintained and high-flow oxygen administered and the patient was otherwise healthy with no chronic opioid addiction and no cardiovascular disease. In the out-of-hospital setting, however, the evidence indicates fewer adverse events when emergency medical services (EMS) system personnel provide ventilation (ie, provide positive-pressure ventilation with bag and mask) before administration of naloxone to all patients with opioid-induced respiratory depression (LOE 5[19–21] in adults, extrapolated from pediatric cases [LOE 7[22,23]; LOE 8]).[24] The adverse effects seen in patients receiving naloxone prior to ventilation may be due to the underlying cardiovascular disorders or chronic epileptic conditions, and thus the hazards of naloxone might be overstated in some cases.

As a general practice for the treatment of suspected opiate overdose, providers should try to support ventilation before administration of naloxone. Naloxone may be administered before intubation (ie, with bag and mask), however, because significant complications after administration of naloxone are uncommon and effective reversal of opiate-induced respiratory depression may make intubation unnecessary. Naloxone can be administered by the intravenous (IV), intramuscular (IM), intranasal, or subcutaneous (SC) routes. IV is preferred. If the patient is already intubated and vascular access is not available, naloxone may be administered by the endotracheal route, although a slightly higher dose may be needed than that administered by other routes. There is only anecdotal (case report) support for endotracheal administration of naloxone for opioid overdose; intravenous and other routes (SC, IM) are preferred to the endotracheal route.

The duration of action of naloxone is approximately 45 to 70 minutes, but respiratory depression may persist for 4 to 5 hours with opiate ingestion or overdose. Thus, the clinical effects of naloxone may not last as long as those of a significant opioid overdose, and repeat doses of naloxone may be needed. The end points of opiate reversal are adequate airway reflexes and ventilation, not complete arousal.

Acute withdrawal from opiates produces a state of sympathetic excess and severe agitation. Pulmonary edema and ventricular arrhythmias are less common complications. Naloxone reversal of opiate intoxication should be used with caution in patients who are suspected of being opiate-dependent, especially if they have cardiovascular disease.

In the emergency setting the recommended adult dose range is 0.4 mg to 2 mg IV or 0.4 mg to 0.8 mg IM or SC, repeated as needed. Some opiate overdoses may require

TABLE 1. Drug-Induced Cardiovascular Emergencies or Altered Vital Signs*: Therapies to Consider† and Contraindicated Interventions

Drug-Induced Cardiovascular Emergency or Altered Vital Signs*	Therapies to Consider†	Contraindicated Interventions (or Use With Caution)
Bradycardia	• Pacemaker (transcutaneous or transvenous) • Toxic drug—*calcium channel blocker:* epinephrine, calcium salt? glucose/insulin? glucagon? NS (if hypotensive) • Toxic drug—*β-blocker:* NS, epinephrine, calcium salt? glucose/insulin? glucagon?	• Atropine (seldom helpful except for cholinesterase inhibitor poisonings) • Isoproterenol if hypotensive • Prophylactic transvenous pacing
Tachycardia	• Toxic drug—*sympathomimetics:* benzodiazepines, lidocaine, sodium bicarbonate, nitroglycerin, nitroprusside, labetalol • Toxic drug—*tricyclic antidepressants:* sodium bicarbonate, hyperventilation, NS, magnesium sulfate, lidocaine • Toxic drug—*anticholinergics:* physostigmine	• β-Blockers (not generally useful in drug-induced tachycardia) • Do not use propranolol for cocaine intoxication • Cardioversion (rarely indicated) • Adenosine (rarely indicated) • Calcium channel blockers (rarely indicated) • Physostigmine for TCA overdose
Impaired conduction/ventricular arrhythmias	• Sodium bicarbonate • Lidocaine	• If TCA overdose: amiodarone or type I_{VW} antiarrhythmics (eg, procainamide)
Hypertensive emergencies	• Toxic drug—*sympathomimetics:* benzodiazepines, lidocaine, sodium bicarbonate, nitroglycerin, nitroprusside, phentolamine	• β-Blockers
Acute coronary syndrome	• Benzodiazepines • Lidocaine • Sodium bicarbonate • Nitroglycerin • Aspirin, heparin • Base reperfusion strategy on cardiac catheterization data	• β-Blockers
Shock	• Toxic drug—*calcium channel blocker:* NS, epinephrine, norepinephrine, dopamine, calcium salt? glucose/insulin? glucagon? • Toxic drug—*β-blocker:* NS, epinephrine, norepinephrine, dopamine, calcium salt? glucose/insulin? glucagon? • If refractory to *maximal* medical therapy: consider circulatory assist devices	• Isoproterenol • Avoid calcium salts if digoxin toxicity is suspected
Acute cholinergic syndrome	• Atropine • Pralidoxime/obidoxime	• Succinylcholine
Acute anticholinergic syndrome	• Benzodiazepine • Physostigmine (not for TCA overdose)	• Antipsychotics • Other anticholinergic agents
Opioid poisoning	• Assisted ventilation • Naloxone • Tracheal intubation	• Do not use naloxone for meperidine-induced seizures

*Unless stated otherwise, listed alterations of vital signs (bradycardia, tachycardia, tachypnea) are "hemodynamically significant."
†*Therapies to consider* should be based on specific indications. Therapies followed by "?" are *Class Indeterminate*.
NS indicates normal saline; TCA, tricyclic antidepressant; and VW, Vaughan Williams.

titration to a total naloxone dose of 6 to 10 mg over a short period. For the patient with chronic opioid addiction, use smaller dose and titrate slowly to minimize adverse cardiovascular effects and withdrawal symptoms. There is no good evidence to suggest that naloxone improves outcome in the patient with an opioid-induced cardiac arrest. Thus, once arrest has occurred, normal guidelines for advanced cardiovascular life support (ACLS) should be followed, with airway control coming before use of naloxone (Class IIa).[19–21]

Drug-Induced Hemodynamically Significant Bradycardia

Hemodynamically significant bradycardia from poisoning or drug overdose may be refractory to standard ACLS protocols because some toxins bind receptors or produce direct cellular toxicity. In these cases specific antidote therapy may be needed.

Administration of atropine may be lifesaving in organophosphate, carbamate, or nerve agent poisoning (LOE 4).[25] Atropine may be administered in an initial dose of 2 to 4 mg

TABLE 2. Potentially Cardiotoxic Drugs: Cardiopulmonary Signs* of Toxicity and Therapy to Consider†

Potentially Toxic Drugs: by Type of Agent	Cardiopulmonary Signs* of Toxicity	Therapy to Consider†
Stimulants (sympathomimetics) • Amphetamines • Methamphetamines • Cocaine • Phencyclidine (PCP) • Ephedrine	• Tachycardia • Supraventricular arrhythmias • Ventricular arrhythmias • Impaired conduction • Hypertensive crises • Acute coronary syndromes • Shock • Cardiac arrest	• Benzodiazepines • Lidocaine • Sodium bicarbonate (for cocaine-related ventricular arrhythmias) • Nitroglycerin • Nitroprusside • Reperfusion strategy based on cardiac catheterization data • Phentolamine (α_1-adrenergic blocker) • β-Blockers relatively contraindicated (do not use propranolol for cocaine intoxication)
Calcium channel blockers • Verapamil • Nifedipine (and other dihydropyridines) • Diltiazem	• Bradycardia • Impaired conduction • Shock • Cardiac arrest	• NS boluses (0.5 to 1 L) • Epinephrine IV; or other α/β-agonists • Pacemakers • Circulatory assist devices? • Calcium infusions • Glucose/insulin infusion? • Glucagon
β-Adrenergic receptor antagonists • Propranolol • Atenolol • Sotalol • Metropolol	• Bradycardia • Impaired conduction • Shock • Cardiac arrest	• NS boluses (0.5 to 1 L) • Epinephrine IV; or other α/β-agonists • Pacemakers • Circulatory assist devices? • Calcium infusions? • Glucose/insulin infusion? • Glucagon
Tricyclic antidepressants • Amitriptyline • Desipramine • Nortriptyline • Imipramine	• Tachycardia • Bradycardia • Ventricular arrhythmias • Impaired conduction • Shock • Cardiac arrest	• Sodium bicarbonate • Hyperventilation • NS boluses (0.5 to 1 L) • Magnesium sulfate • Lidocaine • Epinephrine IV; or other α/β-agonists
Cardiac glycosides • Digoxin • Digitoxin • Foxglove • Oleander	• Bradycardia • Supraventricular arrhythmias • Ventricular arrhythmias • Impaired conduction • Shock • Cardiac arrest	• Restore total body K^+, Mg^{++} • Restore intravascular volume • Digoxin-specific antibodies (Fab fragments: *Digibind* or *DigiFab*) • Atropine • Pacemakers (use caution and monitor for ventricular arrhythmias) • Lidocaine • Phenytoin?
Anticholinergics • Diphenhydramine • Doxylamine	• Tachycardia • Supraventricular arrhythmias • Ventricular arrhythmias • Impaired conduction • Shock, cardiac arrest	• Physostigmine
Cholinergics • Carbamates • Nerve agents • Organophosphates	• Bradycardia • Ventricular arrhythmias • Impaired conduction, shock • Pulmonary edema • Bronchospasm • Cardiac arrest	• Atropine • Decontamination • Pralidoxime • Obidoxime
Opioids • Heroin • Fentanyl • Methadone • Morphine	• Hypoventilation (slow and shallow respirations, apnea) • Bradycardia • Hypotension • Miosis (pupil constriction)	• Assisted ventilation • Naloxone • Tracheal intubation • Nalmefene
Isoniazid	• Lactic acidosis with/without seizures • Tachycardia or bradycardia • Shock, cardiac arrest	• Pyridoxine (vitamin B_6)—large doses may be needed (ie, 1 g pyridoxine/g of ingested isoniazid)
Sodium channel blockers (Class I_{vw} antiarrhythmics) • Procainamide • Disopyramide • Lidocaine • Propafenone • Flecainide	• Bradycardia • Ventricular arrhythmias • Impaired conduction • Seizures • Shock, cardiac arrest	• Sodium bicarbonate • Pacemakers • α- and β-agonist • Lidocaine (not for lidocaine overdose) • Hypertonic saline

*Unless stated otherwise, listed alterations of vital signs (bradycardia, tachycardia, tachypnea) are "hemodynamically significant."
†Specific *therapy to consider* should be based on specific indications. Therapies followed by "?" are *Class Indeterminate*.

for bradycardia resulting from acetylcholinesterase-inhibiting agents, and large total doses may be required. Providers should notify the pharmacy to obtain a large amount (eg, 20 to 40 mg or higher) of atropine for use if needed.

Isoproterenol is contraindicated in acetylcholinesterase-induced bradycardias, although it may be useful at high doses in refractory bradycardia induced by β-antagonist receptor blockade. Heart block and ventricular arrhythmias associated with digoxin or digitalis glycoside poisoning may be effectively treated with digoxin-specific antibody fragment therapy (LOE 5).[26] Antibody-specific therapy may also be effective in poisoning caused by plants and Chinese herbal medications containing digitalis glycosides (LOE 2, 8[27,28]; LOE 5[26]). Transcutaneous pacing may be effective in mild to moderate hemodynamically significant bradycardia associated with poisoning and overdose.

Drug-Induced Hemodynamically Significant Tachycardia

Drug-induced hemodynamically significant tachycardia may cause myocardial ischemia, myocardial infarction, or ventricular arrhythmias and may lead to high-output heart failure and shock. Adenosine and synchronized cardioversion are unlikely to be of benefit in this context given the ongoing presence of a toxin. Some drug-induced tachyarrhythmias, however, may be successfully treated with adenosine (LOE 5).[29] In patients with borderline hypotension, diltiazem and verapamil are contraindicated because they may further lower blood pressure.

Benzodiazepines such as diazepam or lorazepam are safe and effective in patients with drug-induced hemodynamically significant tachycardia resulting from sympathomimetic agents. When large quantities of benzodiazepines are used to treat poisoning or overdose, providers must closely monitor the patient's level of consciousness, ventilatory effort, and respiratory function because the sedative effects of the benzodiazepines may produce respiratory depression and loss of protective airway reflexes.

Physostigmine is a specific antidote that may be preferable for drug-induced hemodynamically significant tachycardia and central anticholinergic syndrome caused by pure anticholinergic poisoning.[30] Physostigmine must be used with caution because it can produce symptoms of cholinergic crisis such as copious tracheobronchial secretions (frequent suctioning will be required), seizures, bradycardia, and even asystole if given in excessive doses or given too rapidly. Often patients with anticholinergic intoxication can be managed with benzodiazepines alone, but at least one clinical study suggested that physostigmine used appropriately may offer superior results (LOE 4).[30] Physostigmine should not be administered for anticholinergic symptoms associated with tricyclic antidepressant overdose. Consultation with a medical toxicologist or regional poison center is recommended.

Drug-Induced Hypertensive Emergencies

Benzodiazepines are the drug class of choice for treatment of drug-induced hypertension because they decrease the effects of endogenous catecholamine release. Hypotension may follow drug-induced hypertension, and aggressive control of blood pressure may not be warranted. Thus, short-acting antihypertensive agents, such as nitroprusside, are preferred in patients who are refractory to benzodiazepine therapy. Nonselective β-antagonist receptor blocking agents, such as propranolol, are contraindicated in poisoning by sympathomimetic agents. Blockade of β-receptors with unopposed α-receptor stimulation may worsen hypertension.[31] Labetalol, a mixed α- and β-receptor antagonist, may be used with caution as third-line therapy in patients with refractory drug-induced hypertension.

Drug-Induced Acute Coronary Syndromes

Acute coronary syndromes (ACS) can develop in patients with cocaine overdose. ACS results from coronary artery vasoconstriction with resultant coronary ischemia that is exacerbated by tachycardia and hypertension associated with excess sympathetic nervous system stimulation.

Fibrinolytics are thought to have a higher risk-to-benefit ratio when used in the context of drug-induced ACS, particularly in the presence of severe hypertension, so they should be used with caution if at all.[32] Intracoronary administration of fibrinolytics or coronary vasodilators is preferred to peripheral administration.

Cardiac catheterization studies in cocaine overdose have shown that nitroglycerin and phentolamine reverse cocaine-induced vasoconstriction. Labetalol has no significant effect, and propranolol worsens it.[33–36] Therefore, nitroglycerin and benzodiazepines are first-line agents, phentolamine is a second-line agent, and propranolol is contraindicated for cocaine-induced ACS. Although labetalol has been reported to be effective in isolated cases of cocaine toxicity,[37,38] use of this agent is controversial because it blocks the peripheral signs of drug-induced sympathetic excess without affecting central nervous system effects such as seizures. Esmolol and metoprolol may induce hypotension.[39]

Drug-Induced Ventricular Tachycardia and Ventricular Fibrillation

When a patient develops sudden conversion to a wide-complex rhythm with hypotension, drug-induced ventricular tachycardia (VT) is likely and cardioversion is indicated. If the patient is unstable and polymorphic VT is present, use high-energy unsynchronized shocks (defibrillation doses).

Use of antiarrhythmics is indicated in cases of hemodynamically stable drug-induced VT. Lidocaine is the antiarrhythmic of choice in most cases of drug-induced monomorphic VT. Types I_A and I_C and other antiarrhythmics that block the fast sodium channel (eg, sotalol) are contraindicated in cases of poisoning with tricyclic antidepressants or other fast sodium channel blockers because of the risk of synergistic toxicity. The efficacy and safety of phenytoin for tricyclic antidepressant poisoning has been questioned and is no longer recommended.[40,41] Magnesium has beneficial effects in certain cases of drug-induced VT (LOE 5[42]), but it may also aggravate drug-induced hypotension.[43,44]

Torsades de pointes can occur with either therapeutic or toxic exposure to many drugs. Administration of magnesium is recommended for patients with torsades de pointes even

when the serum magnesium concentration is normal (Class IIa). Summary of therapy:

- Correction of hypoxia, hypokalemia, and hypomagnesemia is critical.
- The effectiveness of lidocaine in treatment of torsades de pointes has not been demonstrated.
- Electrical overdrive pacing at rates of 100 to 120 beats per minute may terminate torsades de pointes.
- Pharmacologic overdrive pacing with isoproterenol may be effective (LOE 8).[45]
- Some toxicologists recommend potassium supplementation even when the serum potassium is normal.

High level studies have not established the safety and efficacy of any of these recommended therapies for drug-induced polymorphic VT (Class Indeterminate).

Drug-Induced Impaired Conduction

Hypertonic saline and systemic alkalinization may prevent or terminate VT secondary to poisoning from sodium channel blocking agents (eg, procainamide, flecainide) and tricyclic antidepressants (LOE 5).[46,47] Sodium bicarbonate provides hypertonic saline and induces systemic alkalinization; hypertonic saline alone may be effective in treating the impaired conduction associated with these agents.[48] When sodium bicarbonate is used to treat arrhythmias and hypotension, the goal of alkalinization is to maintain an arterial pH of 7.45 to 7.55 with repeated boluses of 1 to 2 mEq/kg of sodium bicarbonate. Although no study has investigated the optimal target pH with bicarbonate therapy, this pH range has been commonly accepted and seems reasonable. A maintenance infusion of 150 mEq/L of sodium bicarbonate plus 30 mEq KCl/L in D_5W is recommended (Class IIa). Boluses of sodium bicarbonate are used without prior determination of serum pH for acute decompensation if the QRS duration is $>$100 milliseconds or if hypotension develops.

There is insufficient evidence to recommend for or against the use of sodium bicarbonate in adults with calcium channel blocker overdose (Class Indeterminate). Calcium channel antagonist and β-adrenergic antagonist overdose may lead to seriously impaired conduction. These patients may require chronotropic adrenergic agents such as epinephrine, use of glucagon in high doses (although the data to support this is inadequate and primarily limited to animal studies),[49] or possibly pacing.[50]

Drug-Induced Shock

Drug-induced shock may produce a decrease in intravascular volume, a decrease in systemic vascular resistance (SVR), diminished myocardial contractility, or a combination of these factors. In addition, drugs can disable normal compensatory mechanisms. It is these combined aspects of cardiovascular dysfunction that render drug-induced shock refractory to many standard therapies.

Drug-Induced Hypovolemic Shock

Overdose of some drugs or chemicals (eg, zinc salts) can cause excessive fluid loss through the gastrointestinal tract, resulting in pure hypovolemia. Drug-induced shock, however, typically includes cardiovascular dysfunction with decreased myocardial contractility and low SVR that requires a combination of volume therapy and myocardial support. Initial treatment will require a fluid challenge to correct relative hypovolemia and optimize preload. In cardiotoxic poisoning congestive heart failure may limit tolerance of, and response to, fluid administration. Central hemodynamic monitoring with a pulmonary artery catheter may be required to titrate therapy.

Patients unresponsive to fluid loading may require inotrope or vasopressor support, or both. Dopamine is often the recommended initial agent. However, drug-induced shock following overdose of some drugs (eg, calcium channel blockers) will require administration and titration of a variety of cardiovascular medications.

Drug-Induced Distributive Shock

Distributive shock is associated with normal or even high cardiac output and low SVR. Treatment with α-adrenergic drugs such as norepinephrine or phenylephrine may be needed. Case reports suggest that vasopressin may also be useful.[51] More powerful vasoconstrictors such as endothelin are not yet available in the United States and have not been well studied. Watch for the development of ventricular arrhythmias with the use of these agents. **Caution:** Avoid dobutamine and isoproterenol, which may worsen hypotension by further decreasing SVR.

Drug-Induced Cardiogenic Shock

Drug-induced cardiogenic shock is associated with low cardiac output and high SVR. Cardiac ischemia may also be present in these patients. In addition to volume titration and use of sympathomimetic drugs such as dobutamine, inotropic support may be provided by agents such as inamrinone, calcium, glucagon, insulin, or even isoproterenol, depending on the toxic agent(s) identified.[52,53] Concurrent vasopressor therapy is often required.[54]

Drug-Induced Cardiac Arrest

Cardioversion/Defibrillation

Electric defibrillation is appropriate for pulseless patients with drug-induced VT or ventricular fibrillation (VF) and also for unstable patients with polymorphic VT. In cases of sympathomimetic poisoning with refractory VF, increase the interval between doses of epinephrine and use only standard dosing. Propranolol is contraindicated in cocaine overdose. It was thought to be contraindicated in sympathomimetic poisoning, but there are some case reports suggesting that it may be useful in the treatment of ephedrine and pseudoephedrine overdose.[55]

Prolonged CPR and Resuscitation

More prolonged CPR and resuscitation may be warranted in patients with poisoning or overdose, especially those with calcium channel blocker poisoning (LOE 5).[56] In cases of severe poisoning, recovery with good neurologic outcomes has been reported in patients who received prolonged CPR (eg, 3 to 5 hours).[52,53] Cardiopulmonary bypass (extracorporeal membrane oxygenation) has been used successfully in resuscitation of patients with severe poisoning.[57]

Summary

Use of standard ACLS protocols for all patients who are critically poisoned may not result in an optimal outcome. Care of patients with severe poisoning can be enhanced by consultation with a medical toxicologist or regional poison center. Alternative approaches that may be effective in severely poisoned patients include

- Higher doses of medication than those in standard protocols
- Nonstandard drug therapies, including inamrinone, calcium chloride, glucagon, insulin, labetalol, phenylephrine, physostigmine, and sodium bicarbonate
- Use of specific antagonists or antidotes
- Heroic measures, such as prolonged CPR and possible use of circulatory assist devices such as extracorporeal membrane oxygenation

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