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Cardiotoxins: A Systematic Approach to the Evaluation and Management of Patients with Life-Threatening Manifestations of Drug-Induced Cardiotoxicity

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The diagnosis and management of patients with manifestations of drug-induced cardiotoxicity is challenging for even the most experienced emergency physician.

Manifestations of cardiotoxicity are wide and varied, and include bradycardia, QTc prolongation, and life-threatening cardiac dysrhythmias. Although when taken appropriately, in recommended doses, most cardiac agents are safe, susceptible patients, especially those with underlying cardiac abnormalities and/or conduction disturbances, may manifest cardiotoxicity at normal therapeutic doses. When ingested at higher doses in the setting of drug overdose, these agents can produce serious consequences that require precise diagnosis and immediate action. While advanced cardiac life support (ACLS) protocols represent the foundation of management, a number of targeted, pharmacotherapeutic interventions are available that will optimize patient outcomes.[1]

The following report reviews the pathophysiology and clinical manifestations of cardiotoxins to provide the front-line practitioners with evidence-based protocols for managing patients with life-threatening toxicity.

—The Editor

The purpose of this report is to group together agents with similar cardiotoxic effects, review their pharmacologic actions, and discuss the current recommended treatment options of each class. The five main categories reviewed will include: calcium channel blockers, beta-blockers, sodium channel blockers, potassium-efflux blockers, and sodium-potassium adenosine triphosphatase (ATPase) blockers.

Epidemiology

Emergency physicians routinely evaluate and manage poisoned patients. In 2001, more than 2 million human exposure cases were reported to poison centers throughout the United States.[2] Of those cases, 22 % (498,524) were treated in a health care facility, with the majority of those cases evaluated in the emergency department (ED). Cardiovascular drugs were listed as the 11th most frequently encountered exposure in adults and the fifth leading cause of poisoning deaths.

Cardiac Physiology

The myocardial cell membrane in its resting state is impermeable to Na^+. (*See Figure 1.*) The Na^+-K^+ ATPase actively pumps three sodium ions out of cardiac cells while pumping in two potassium ions to maintain a negative electric potential in the myocyte of approximately -90 mV (phase 4). Depolarization of the cardiac cell membrane is due to the rapid opening of Na^+ channels and the subsequent massive Na^+ influx (phase 0). This Na^+ influx causes the rapid upstroke of the cardiac action potential as it is conducted through the ventricles and is directly responsible for the QRS interval of the electrocardiogram (ECG). The peak of the action potential is marked by the closure of Na^+ channels and the activation of potassium efflux channels (phase 1). Calcium influx then occurs, allowing for a plateau in the action potential (phase 2) and continued myocardial contraction. The cardiac cycle ends with closure of the calcium channels and activation of potassium efflux channels, causing the potential again to approach -90 mV (phase 3). It is this potassium efflux from the myocardial cell that primarily is responsible for the QT interval of the ECG.

General Management of Cardiac Toxins

All patients who present with toxicity or potential toxicity following ingestion of cardiotoxins should be managed aggressively. The patient's airway should be patent and adequate ventilation assured. If necessary, endotracheal intubation should be performed. Too often, physicians are lulled into a false sense of security when a patient's oxygen saturation is adequate on high flow oxygen. If the patient has either inadequate ventilation or a poor gag reflex, then the patient may be at risk for subsequent CO_2 narcosis with worsening acidosis or aspiration. Because laryngoscopy has been reported to induce a vagal response, the physician may consider administration of atropine in the bradycardic patient prior to intubation. The initial treatment of hypotension consists of intravenous fluids. Close monitoring of the patient's pulmonary exam should be performed to assure that pulmonary edema does not develop as fluids are infused. The health care providers should place the patient on continuous cardiac monitoring with pulse oximetry and make frequent neurological checks. Placement of a urinary catheter should be considered early in the care of symptomatic patients to monitor urinary output, as this is one of the best indicators of adequate perfusion. In all patients with altered mental status, the patient's glucose should be checked. These patients should receive a large-bore peripheral intravenous line, and all critically ill patients should have a second line placed either peripherally or centrally. If the patient is a potential candidate for an intravenous pacemaker, a central line should be placed preferentially in the right internal jugular.

Gastrointestinal decontamination should be considered only after initial supportive care has been provided and airway control has been assured. Activated charcoal (1 g/kg) may be administered. Because many cardiotoxins have sustained release preparations, multidose charcoal administration (1 g/kg first dose and then ½ g/kg q 4 hours) should be considered along with whole bowel irrigation (polyethylene glycol with electrolytes at 500 mL/hr for children and 2 L/hr for adults). Syrup of ipecac should not be administered in the ED and is contraindicated after overdose with the agents listed in this paper due to the potential for

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Figure 1. Cardiac Action Potential with Corresponding ECG Tracing

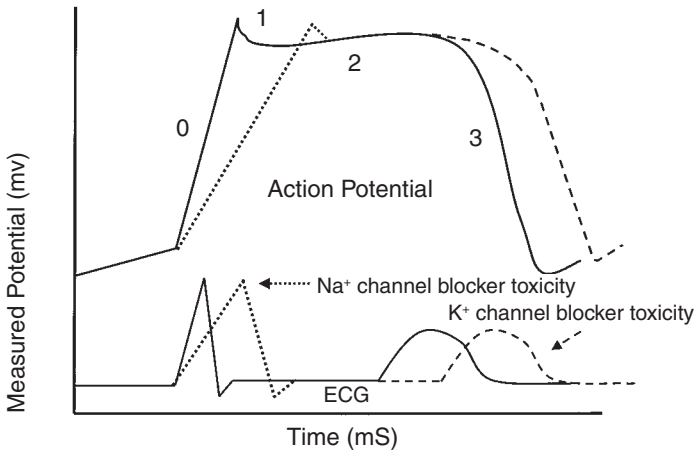


Table 1. Calcium Channel Blocking Agents

DIHYDROPYRIDINES
• Nicardipine
• Nifedipine
• Isradipine
• Amlodipine
• Felodipine
• Nimodipine
PHENYLALKYLAMINE
• Verapamil
BENZOTHIAZEPINE
• Diltiazem
DIARYLAMINOPROPYLAMINE ETHER
• Bepridil

rapid clinical deterioration. Gastric lavage has not been shown to change outcome after overdose of these agents and can induce an unwanted vagal response.[3]

Calcium Channel Blocker Toxicity

Definition. There are nine cardiac calcium channel blockers that have been approved for clinical use in the United States. These nine are found within four classes of compounds. (*See Table 1.*) During the past decade, the number of exposures to these agents has increased dramatically as these drugs have become available on the market. In 2001, calcium channel blockers accounted for 40% of all the deaths due to cardiovascular drugs reported to the American Association of Poison Control Centers (AAPCC).[2]

Pathophysiology. All cardiac calcium channel blockers inhibit the voltage-sensitive L-type calcium channel within the cell membrane.[4] This channel resides both in heart and smooth muscle cell membranes. The inhibition of this channel prevents movement of calcium from extracellular sites through the cell membrane to intracellular sites. The inhibition of calcium influx in pacemaker cells and within the conduction system results in slowing of conduction and potential heart blocks (1st-3rd degree), bradycardia, and junctional and ventricular escape rhythms. (*See Figure 2.*) Decreased intracellular calcium within the myocardial cells results in decreased contractility and decreased cardiac output. Blockade of calcium influx within the vascular smooth muscle cells results in vasodilation. Decreased cardiac output coupled with vasodilation may result in profound hypotension. The dihydropyridine class of drugs tends to have a higher affinity for the peripheral vascular smooth muscle cells and have less effect on the cardiac calcium channels. As a result, the dihydropyridine class of agents more often is associated with hypotension with the possibility of reflex tachycardia. Verapamil and diltiazem, on the other hand, have strong affinity for both cardiac and vascular calcium channels and, subsequently, the combination of hypotension with bradycardia may be seen.

The calcium channel blockers also have been associated with profound hyperglycemia refractory to standard doses of insulin.[5] Though the exact etiology of this effect is unclear, both the blockade of insulin release and the blockade of peripheral insulin receptors have been suggested as possible mechanisms.[6] This hyperglycemic effect has been seen in both verapamil and diltiazem poisoning, but it is not well demonstrated in the dihydroperidine class of calcium channel blockers.

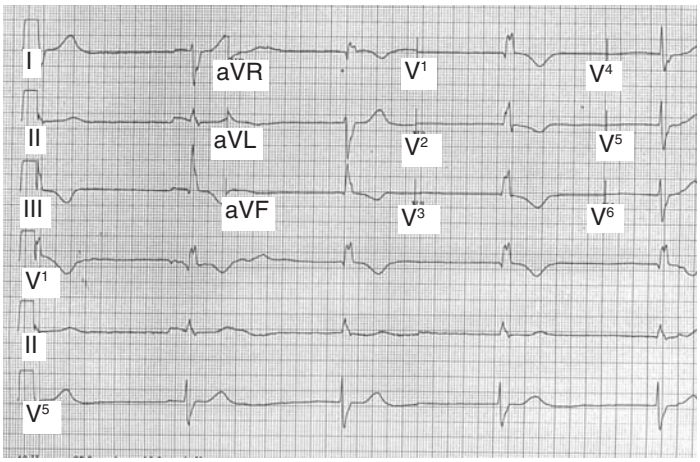
In both animal models and human case series, calcium channel blockers also have been associated with cardiac sodium channel blockade.[5,7] This results in a delay of phase 0 of depolarization, subsequent QRS prolongation, and further potential for dysrhythmias (see the "Sodium Channel Blocker Toxicity" section below).

Clinical Features. Hypotension is the most common sign associated with toxicity from a calcium channel blocker. This sign initially may be subtle, with the patient simply complaining of feeling lightheaded or dizzy, especially upon standing. Depending on the agent ingested, reflex tachycardia may not be seen. As levels of calcium channel blocker increase, the patient may develop marked hypotension, various heart blocks, bradydysrhythmias, pulmonary edema, acute mental status changes, syncope, asystole, and death. Hypoperfusion may result in ischemia in patients with pre-existing atherosclerotic vascular disease. Patients may develop myocardial infarction, mesenteric ischemia, seizures, renal failure, strokes, and lactic acidosis.

Diagnostic Studies. Patients suspected of having calcium channel blocker toxicity should have an ECG performed and appropriate laboratory values drawn. Acute toxicity may be associated with hyperglycemia, and a rapid glucose check should be obtained. A chest x-ray should be performed on any patient with suspected pulmonary edema. Serum levels of calcium channel blockers cannot be obtained in a timely manner and are not useful in the initial management of the overdose.

Management. A symptomatic acute calcium channel blocker overdose can be one of the most challenging poisonings encountered by a physician. The initial management of all patients presenting after an acute overdose of a calcium channel blocker or presenting with significant toxicity should be treated as discussed in the above section entitled "General Management of Cardiac Toxins."

Figure 2. Junctional Escape Rhythm Following Verapamil Overdose



Calcium channel blockers are prone to development of pulmonary edema, and frequent lung reassessments should be made.[8] Specific pharmacological therapy includes the possible use of atropine, calcium, glucagon, insulin, and/or various catecholamines.

Atropine. Atropine may be considered in an attempt to reverse bradycardia at doses of 1-2 mg intravenous (0.02 mg/kg in children, minimum of 0.10 mg and a maximum of 1 mg). In calcium channel blocker intoxications, atropine may be ineffective at reversing bradycardia, and the clinician should not be surprised to see a lack of response to this agent.[9]

Calcium. In symptomatic calcium channel blocker poisonings, intravenous calcium should be considered early in the care. The exact mechanism is unknown, but a calcium infusion certainly will increase extracellular calcium, thereby increasing the concentration gradient across the cell membrane. This gradient probably drives more calcium intracellular when unblocked calcium channels open. Either calcium gluconate or calcium chloride may be infused through peripheral line access. Recall that 10 mL of 10% calcium gluconate (93 mg Ca^{2+} or 4.6 mEq Ca^{2+}) provides less bioavailable calcium than 10 mL of 10% calcium chloride (272 mg Ca^{2+} or 13.6 mEq Ca^{2+}). However, calcium chloride has been reported to cause marked tissue necrosis if it extravasates while being infused through peripheral venous access, so it is best administered through a central venous line. The exact infusion doses of calcium and targeted calcium level have not been well delineated.[10] An initial dose of 10 cc of 10% calcium chloride or 1 g (20 mg/kg or up to 1 g in children), or the equivalent dose of calcium gluconate, administered intravenously, is appropriate. This dose may be repeated and titrated to clinical effect. It is a reasonable approach to infuse calcium to increase the ionized calcium 2-5 times the patient's baseline. However, increasing the patient's ionized calcium may lead to further sedation, nausea, and vomiting. To assure adequate ventilation and gag reflex, frequent neurological examinations of patients receiving calcium infusions are especially imperative if the patient is not intubated.

Glucagon. Glucagon may be beneficial in the management of the calcium channel blocker overdose.[11,12] Glucagon raises intracellular cyclic adenosine monophosphate (cAMP) concentrations that in turn open calcium channels. A starting dose of 2-5 mg (50 mcg/kg in children) of intravenous glucagon (diluted in 10 cc normal saline [NS] and infused over 1-2 minutes) should be considered. This dose can be repeated. If the patient responds to the initial glucagon dose, then a glucagon infusion at 5 mg/hr (50 mcg/kg/hr in children) should be started. Glucagon doses this high may induce emesis that could lead to aspiration in the sedate, non-intubated patient. When mixing glucagon, use NS and avoid using the glucagon package diluent. The package diluent contains 0.2% phenol and hypothetically could result in toxicity at doses this high.

Catecholamines. The role of the catecholamines is unclear. Catecholamine infusions may be considered after the above therapies fail to give adequate response. Both epinephrine and norepinephrine have been used in the management of calcium channel blocker toxicity with mixed success. Care should be exercised, as these agents may result in exacerbation of pulmonary edema, ischemic vascular disease, and renal failure. Dopamine also should be infused with caution due to its poor direct effects on adrenergic receptors compared to epinephrine and norepinephrine. Dobutamine, a direct beta-1 adrenergic agonist, may be of benefit, but adequate studies of its effect in calcium channel blocker toxicity are lacking.

Insulin. High-dose insulin drips have been advocated in calcium channel blocker overdose, especially in the management of both verapamil and diltiazem poisoning. Experimental models suggest a superior effect of this therapy in the canine model compared to other therapies.[13] Human case reports also suggest the efficacy of these drips.[5,14,15] The optimal dose of insulin is unclear.[16] Insulin infusions can be initiated at 0.2 U/kg/hr and titrated upward every hour to euglycemic effect and hemodynamic effect. Supplemental glucose may be necessary to maintain euglycemia. Drips exceeding 100 units per hour have been performed to achieve euglycemia. Serum glucose and potassium levels should be monitored closely during therapy.

Sodium Bicarbonate. Recently, sodium bicarbonate (SB) infusions have been advocated in the management of calcium channel blocker toxicity.[5,7] Patients with prolonged QRS (> 100 ms), acidosis, or persistent hypotension despite the above methods should be considered candidates for a trial of SB in doses noted in the section titled "Sodium Channel Blockers."

Other Therapies. Pacemakers, intra-aortic balloon pump, and cardiopulmonary bypass all may be considered in cases not responding to pharmacological therapy. Vasopressin recently has been reported to reverse hypotension resulting from specific overdoses, but there are no human or animal reports of its use in calcium channel blocker toxicity. None of the calcium channel blockers are amendable to hemodialysis or hemoperfusion due to their large size, high protein binding, and/or large volume of distribution.

Disposition. Asymptomatic calcium channel blocker overdose patients with normal ECGs and ingestions of non-sustained release products may be observed in the ED for eight hours. If they remain asymptomatic and the ECG remains unchanged, they may be discharged to a non-monitored setting. Any asymptomatic patient acutely overdosing on a sustained release product should

Table 2. Beta-Blocking Drugs

Acebutolol	Esmolol	Pindolol
Atenolol	Labetalol	Propranolol
Betaxolol	Metoprolol	Sotalol
Bisoprolol	Nadolol	Timolol
Carvedilol		

be admitted to a monitored bed for 24 hours of observation. Any symptomatic calcium channel blocker patient should be admitted to a monitored setting until complete resolution of symptoms occurs. Care should be exercised in patients with apparent improvement but who remain symptomatic following calcium channel blocker overdose, as sudden asystole has been reported hours following stabilization and apparent improvement.

Beta-Blocker Toxicity

Definition. Beta-adrenergic receptor antagonists increasingly are used due to their efficacy in the treatment of hypertension, ischemic heart disease, and arrhythmias. There currently are numerous beta-blockers available. (*See Table 2.*) These agents share the mechanism of competitive beta-adrenergic receptor antagonism. Some of these agents have equal affinity for beta-1 and beta-2 receptors (propranolol), while others are selective and have greater beta-1 than beta-2 receptor blocking activity (metoprolol). Some agents also block other receptors such as alpha-adrenergic receptors (labetalol), cardiac sodium channels (propranolol), and cardiac potassium efflux channels (sotalol).[17]

Pathophysiology. Beta-blockers competitively inhibit the beta-adrenergic receptor. Inhibition of beta-1 receptors results in a decrease in the force and rate of myocardial contraction, a decrease in AV node conduction velocity, and a decrease in renin secretion. Inhibition of beta-2 receptors results in a decrease in glycogenolysis, decrease in gluconeogenesis, and decrease in relaxation of smooth muscles in blood vessels, bronchi, and the gastrointestinal tract.

Clinical Features. In acute overdose, the most pronounced effect of beta-blockers is on the cardiovascular system.[12] Bradycardia, heart blocks, and hypotension are the hallmarks of significant beta-blocker toxicity.[18] Dyspnea may occur and may be the result of congestive heart failure or bronchospasm. Changes in mental status, seizures, and coma have been reported and typically are associated with coexisting cardiovascular effects and hypoperfusion. Hypoglycemia may occur and should be considered in those patients with altered mental status or seizures, especially young children.

Diagnostic Studies. Patients suspected of having beta-blocker toxicity should have an ECG performed and appropriate laboratory values drawn. Acute toxicity may be associated with hypoglycemia, and a rapid glucose check should be obtained in any patient presenting with acute mental status changes. Serum levels of beta-blocker cannot be obtained in a timely manner and are not of clinical utility. A chest x-ray should be obtained in any patient with suspected pulmonary edema.

Management. The initial management of all patients who present after an acute overdose of a beta-blocker or with significant toxicity should be treated as discussed in the above section on "General Management of Cardiac Toxins." Specific pharmacological therapy may include atropine, glucagon, calcium, insulin, and/or various catecholamines.[19]

Atropine. Atropine may be considered in an attempt to reverse bradycardia at doses of 1-2 mg intravenous (0.02 mg/kg in children, minimum of 0.10 mg and a maximum of 1 mg). In beta-blocker toxicity, atropine has been shown to have poor effect in reversing bradycardia and increasing blood pressure.

Glucagon. Glucagon infusion should be considered in symptomatic beta-blocker toxic patients.[12] Beta-adrenergic stimulation raises intracellular cAMP concentrations that in turn regulate ion channels. When beta-adrenergic receptors are inhibited, intracellular cAMP levels decrease. Glucagon increases intacellular cAMP through non-adrenergic pathways.[20] A starting dose of 2-5 mg (50 mcg/kg in children) of intravenous glucagon (diluted in 10 cc NS and infused over 1-2 minutes) should be considered. This dose can be repeated. If the patient responds to the initial glucagon dose, then a glucagon infusion at 5 mg/hr (50 mcg/kg/hr in children) should be started. For further information on glucagon therapy, see the section on "Calcium Channel Blocker Toxicity."

Calcium. Calcium has been shown to have efficacy at reversing the hypotensive effects of beta-blocker toxicity in both animal models and human case reports.[12,21] Dosing of calcium should be performed at the doses noted in the calcium channel blocker section.

Catecholamines. Catecholamine infusions may be considered after the above therapies fail to give adequate response. Both epinephrine and norepinephrine have been used in the management of beta-blocker toxicity. Care should be exercised, as these agents may result in exacerbation of pulmonary edema, ischemic vascular disease, and renal failure. Dopamine also should be infused with caution. Recall that dopamine at low concentrations (1-5 mcg/kg/min) affects dopamine receptors in renal, mesenteric, and coronary beds, leading to vasodilation. At somewhat higher concentrations (5-10 mcg/kg/min), dopamine exerts positive ionotropic effects by acting on beta-1 adrenergic receptors. It is not until dopamine is infused at high concentrations (greater than 10 mcg/kg/min), that dopamine affects alpha-1 adrenergic receptors and leads to vasoconstriction and elevated blood pressure. Unlike the direct alpha-1 adrenergic agonist activity of epinephrine and norepinephrine, dopamine does not have significant direct activity and instead induces norepinephrine release at the alpha-1 adrenergic receptor. Dobutamine, a direct beta-1 adrenergic agonist, may be of benefit, but adequate studies of its effect in beta-blocker toxicity are lacking. Isoproterenol is a potent, non-selective beta-adrenergic agonist. The literature has reported mixed results with its use and it also should be considered only after the above therapy has failed.

Insulin. Insulin infusions have been advocated for beta-blocker toxicity based on an animal model.[22] The exact mechanism of this therapy is unclear, but it is thought to be secondary to increased myocardial glucose utilization resulting from the high-

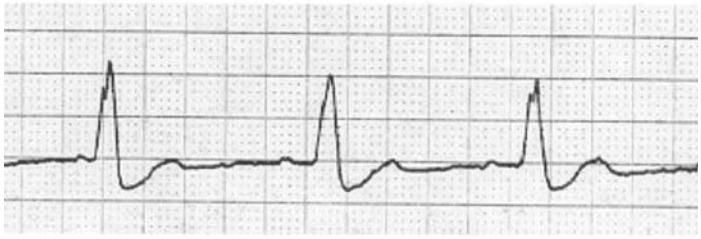
Table 3. Sodium Channel Blocking Drugs

AMANTADINE
CARBAMAZEPINE
CHLOROQUINE
CLASS IA ANTIARRHYTHMICS
• Disopyramide
• Quinidine
• Procainamide
CLASS IC ANTIARRHYTHMICS
• Encainide
• Flecainide
• Propafenone
COCAINE
TRICYCLIC ANTIDEPRESSANTS
• Amitriptyline
• Amoxapine
• Desipramine
• Doxepin
• Imipramine
• Nortriptyline
• Maprotiline
DILTIAZEM
DIPHENHYDRAMINE
HYDROXYCHLOROQUINE
LOXAPINE
ORPHENADRINE
PHENOTHIAZINES
• Medoridazine
• Thioridazine
PROPRANOLOL
PROPOXYPHENE
QUININE
VERAPAMIL

dose insulin drips. Infusions of insulin at 0.5 U/kg/hr along with glucose infusions have been advocated by some clinical studies where the other above methods have failed. Care should be taken to closely monitor blood glucose levels during these infusions.

Other Therapies. The phosphodiesterase inhibitors amrinone and milrinone increase cAMP concentrations and, therefore, theoretically would be useful in beta-blocker toxicity. Current animal models have demonstrated mixed results with use of these agents in beta-blocker toxicity.[23,24] Pacemaker insertion, balloon pump, and bypass all may be considered in cases not responding to pharmacological therapy. Extracorporeal removal has been reported with specific beta-blockers with small volumes of distribution and low protein binding (atenolol, nadolol, and acebutolol), but it is technically difficult if there is coexisting hypotension. Vasopressin recently has been reported to reverse hypotension on specific overdoses, but there are no human or animal reports of its use in beta-blocker toxicity.

Figure 3. Marked QRS Widening Following Propoxyphene Overdose



Disposition. Asymptomatic beta-blocker overdose patients with normal ECGs and ingestions of a non-sustained release beta-blocker may be observed in the ED for six hours.[25] If they remain asymptomatic and the ECG remains unchanged, they may be discharged to a non-monitored setting. Any asymptomatic patient acutely overdosing on a sustained release beta-blocker or on sotalol should be admitted to a monitored bed for 24 hours of observation. Any symptomatic beta-blocker toxic patient should be admitted to a monitored setting until complete resolution of symptoms occurs.

Sodium Channel Blocker Toxicity

Definition. The ability of drugs to block cardiac Na^+ channels has been well described in numerous previous literature reports, with Kolecki and Curry publishing an excellent review of these agents in 1997.[26] This Na^+ channel blockade activity has been described as a membrane stabilizing effect, a local anesthetic effect, or a quinidine-like effect. All the agents listed in Table 3 are similar in that they may induce myocardial Na^+ channel blockade and may respond to SB therapy.

Pathophysiology. Cardiac voltage-gated sodium channels reside in the cell membrane and open in response to depolarization of the cell. The Na^+ channel blockers bind to the transmembrane Na^+ channels and decrease the number available for depolarization. This creates a delay of Na^+ entry into the cardiac myocyte during phase 0 of depolarization. As a result, the upslope of depolarization is slowed and the QRS complex widens. (*See Figure 1.*)

Clinical Features. Myocardial Na^+ channel blocking drugs comprise a diverse group of pharmaceutical agents. As a result, patients poisoned with these agents will have a variety of clinical presentations. For example, cyclic antidepressants, propoxyphene, and cocaine may result in anticholinergic, opioid, and sympathomimetic syndromes, respectively. In addition, these agents may affect not only the myocardial Na^+ channels, but also other myocardial ion channels, such as the calcium influx and potassium efflux channels. This may result in ECG changes and rhythm disturbances not related entirely to the drug's Na^+ channel blocking activity.

Sodium channel blockers result in widening of the QRS complex. (*See Figure 3.*)[27] In some cases, the QRS complexes may take the pattern of recognized bundle-branch blocks. In the most severe cases, the QRS prolongation becomes so profound that it is difficult to distinguish between ventricular and supraventricular rhythms.[28] Continued prolongation of the QRS may result in a

Figure 4. Sine Wave Pattern Following Hydroxychloroquine Overdose

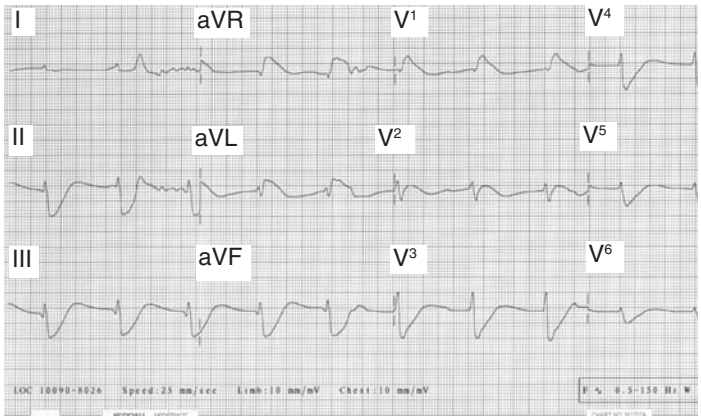
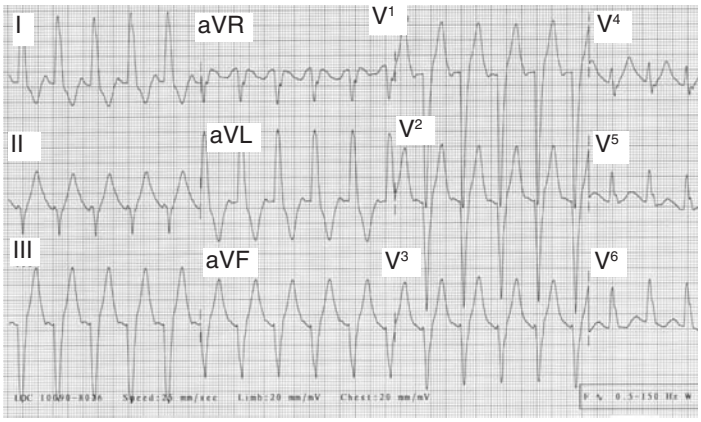


Figure 5a. Wide Complex Dysrhythmia Following Diphenhydramine Overdose



sine wave pattern (*see Figure 4*) and eventual asystole. Sodium channel blockers also may induce a monomorphic ventricular tachycardia. It has been theorized that the Na^+ channel blockers can cause slowed intraventricular conduction, unidirectional block, the development of a re-entrant circuit, and a resulting ventricular tachycardia. (*See Figure 5a.*) This then can degenerate into ventricular fibrillation. Because many of the Na^+ channel blocking agents also are anticholinergic or sympathomimetic agents, bradydysrhythmias are rare. However, the Na^+ channel blocking agents can affect cardiac pacemaker cells. Bradycardia may occur due to slowed depolarization of pacemaker cells that depend upon entry of Na^+. In Na^+ channel blocker poisoning by anticholinergic and sympathomimetic drugs, the combination of a wide QRS complex and bradycardia is an ominous sign and may indicate that the Na^+ channel blockade is so profound that a tachycardia cannot be mounted in response to muscarinic antagonism or adrenergic agonism.

Diagnostic Studies. Patients suspected of having toxicity due to a Na^+ channel-blocking agent must have an ECG performed and their interval indices should be scrutinized.[27] Appropriate laboratory values should be obtained. Specific drug levels are not helpful in the initial management of these poisonings and poorly correlate with ECG findings.

Management. The initial management of all patients presenting after an acute overdose of Na^+ channel-blocking agents or presenting with significant toxicity from these agents should be treated as discussed in the above section on "General Management of Cardiac Toxins." Specific pharmacological therapy may include SB infusion.

Sodium Bicarbonate. The management of Na^+ channel-blocking agents consists of administration sodium and/or alkalinizing the patient.[29] Infusion of SB either by intermittent bolus or by continuous infusion has been advocated. Hypertonic sodium infusion also has been advocated. The indications for SB infusion include a QRS duration of greater than 100 ms, persistent hypotension despite adequate hydration, and dysrhythmias. An ampule of SB contains 50 mEq of sodium and multiple doses may be necessary to achieve clinical improvement in the patient. Start an infusion by adding three ampules of SB to 1 liter of D5W and infuse at two times maintenance. Consider adding potassium (40 mEq to a liter of D5W) to the SB drip to prevent the development of hypokalemia (due to the excretion of potassium in exchange for hydrogen ions as the kidneys attempt to correct the alkalosis). The infusion then can be adjusted as necessary to decrease QRS duration and improve clinical outcome. The exact mechanism of SB therapy is unknown. SB infusions certainly will increase extracellular sodium, thereby increasing the concentration gradient across the cell membrane and probably driving sodium intracellular when unblocked sodium channels open. The benefit of alkalosis has been well demonstrated, but the mechanism is poorly understood. During infusions of SB, close monitoring of electrolyte, pH, and fluid balance should be performed. (*See Figure 5b.*)

Other Therapy. Hyperventilation has been shown to be effective in reversing sodium channel blocking activity, probably due to the respiratory alkalosis induced. Lidocaine has been suggested in the treatment of ventricular dysrhythmias, though clear evidence is lacking. Class IA and IC antiarhythmics should be avoided due to their ability to block cardiac sodium channels.

Disposition. Any symptomatic patient who has ingested a potential Na^+ channel-blocking agent should be admitted and observed in a monitored setting. In the asymptomatic patient who has ingested a Na^+ channel-blocking agent, the length of observation will vary. For example, a patient who has ingested amitriptyline should be observed for a minimum of six hours, and if that person remains asymptomatic and develops no ECG changes during that time period, then the patient can be discharged. Other poisonings, such as diphenhydramine, can be discharged if asymptomatic after a four-hour observation period.

Potassium Efflux Blocker Toxicity

Definition. Potassium efflux-blocking agents competitively inhibit cellular potassium efflux during cellular repolarization. (*See Figure 1.*) This results in a delay in repolarization corresponding with an increase in the QT interval. (*See Figure 6.*)[30] This may place the patient at risk for polymorphic ventricular tachycardia or torsades de pointes.[31] Some drugs, such as sotalol, are prescribed specifically for this mechanism.[32] Other medications possess this activity as an unwelcome side effect at therapeutic

Figure 5b. Same Patient as in 5a Following Multiple Doses of Sodium Bicarbonate

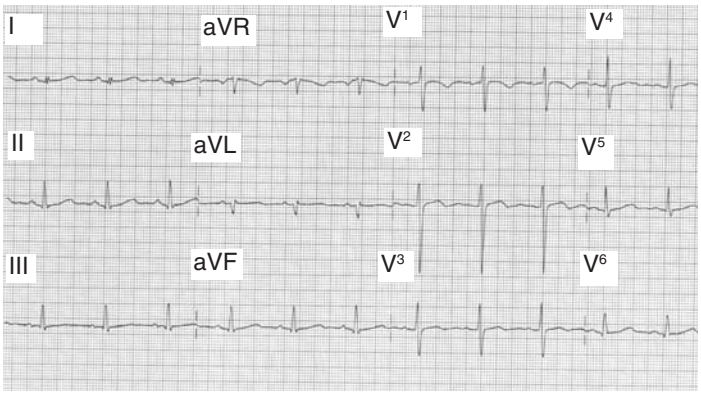
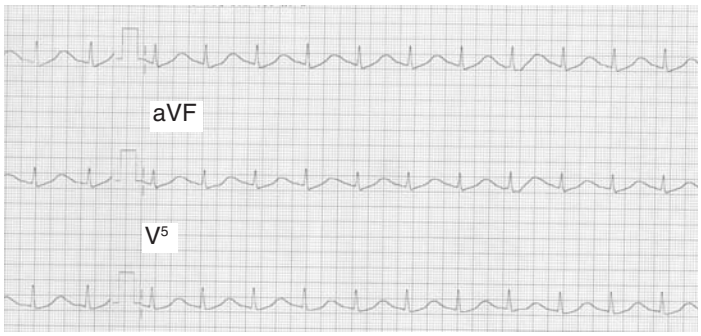


Figure 6. Prolongation of the QT Interval Following Hydroxychloroquine Overdose



doses. A number of medications, such as cisapride and terfenadine, have been removed from the U.S. market due to reports of torsades de pointes and sudden death in patients taking these drugs.[33,34] Other medications rarely have been reported to cause QT prolongation except when taken in massive overdose. A complete listing of the reported agents associated with QT prolongation are noted in Table 4.[35] Other etiologies of prolongation of the QT interval include: congenital long QT syndrome, hypokalemia, hypomagnesemia, hypocalcemia, myocardial ischemia, neurological catastrophes, and hypothyroidism.[36]

Pathophysiology. The primary problem with K^+ efflux channel-blocking drugs is that they prolong cardiac action potentials, which lead to torsades de pointes.[37] Patients at increased risk are those who have familial QT prolongation or electrolye abnormalities, or those who take multiple agents with K^+ efflux channel-blocking activity or drugs that inhibit the metabolism of K^+ efflux channel-blocking agents, resulting in the build-up to toxic levels.

Clinical Features. Syncope may be associated with drug-induced QT prolongation. Palpitations, dyspnea, and sudden death also may be associated with QT prolongation. After acute overdose, the presenting signs and symptoms may not be related to the cardiac effects, but rather to other mechanisms of those drugs.

Diagnostic Studies. Patients suspected of having toxicity due to a K^+ efflux channel-blocker should have an ECG performed and appropriate laboratory values drawn to rule out coexisting electrolyte abnormalities. If thyroid disorder is suspected, thyroid function studies also should be performed.

Management. If a patient has a prolonged QT interval due to a K^+ efflux-blocking agent, therapy should focus on immediate withdrawal of the potential cause and correction of any coexisting hypoxia or electrolyte abnormalities. All patients initially should be treated as discussed in the above section titled "General Management of Cardiac Toxins."

Magnesium. Intravenous magnesium sulfate is an effective and benign intervention to suppress occurrence of dysrhythmias associated with QT prolongation, even though Mg^{++} does not typically result in shortening of the interval itself.[36] A starting dose of 2 g in 10 mL D5W can be given intravenously and titrated to effect.

Overdrive Pacing. In patients with intermittent runs of torsades not responsive to magnesium therapy, electrical overdrive pacing should be considered.[39] Pacing at rates up to 100-120 bpm often is effective at terminating torsades de pointes.

Cardioversion. In the presence of a nonperfusing rhythm, such as ventricular fibrillation, pulseless ventricular tachycardia, or torsades de pointes, unsynchronized electrical defibrillation should be performed.

Disposition. Patients with newly diagnosed prolongation of their QT interval or torsades de pointes should be admitted to a monitored setting. Symptomatic patients who have ingested these agents also should be admitted to a monitored setting.

Sodium-Potassium ATPase Blocker Toxicity

Definition. Cardiac glycosides are agents that inhibit the sodium-potassium adenosine triphosphate (Na^+-K^+ ATPase) pump. Digoxin is the most widely encountered cardiac glycoside, but numerous other similar-acting agents also exist. (*See Table 5.*) Digoxin historically has been administered to treat supraventricular tachydysrhythmias and congestive heart failure, but its use has been decreasing as newer agents have been developed. Ingestion of specific plants and contaminated herbal products also has been associated with cardiac glycoside toxicity.[40]

Pathophysiology. The cardiac glycosides inhibit active transport of Na^+ and K^+ across cell membranes by inhibiting the Na^+-K^+ ATPase. This results in an increase in both extracellular K^+ and intracellular Na^+. An increased intracellular Na^+ results in a reduced transmembrane Na^+ gradient and subsequent increased activity of the Na^+-Ca^+ exchanger. Intracellular calcium rises, which augments myofibril activity in cardiac myocytes and causes a positive inotropic action. The cardiac glycosides also increase vagal tone, leading to a direct AV depression and conduction disturbances.

Clinical Features. Cardiac glycoside toxicity may result in a wide array of dysrhythmias.[41] Excitant activity (atrial, junctional, and ventricular premature beats and tachydysrhythmias), suppressant activity (i.e., sinus bradycardia, bundle-branch blocks, and first-, second-, and third-degree blocks), and combination of excitant and suppressant activity (atrial tachycardia with atrioventricular block and second-degree block with junctional premature beats) all may be seen. (*See Figure 7.*) The most common

Table 4. Potassium Efflux Channel-Blocking Drugs

ANTIHISTAMINES
- Astemizole
- Diphenhydramine
- Terfenadine

ANTIPSYCHOTICS
- Haloperidol
- Phenothiazines
- Quetiapine
- Risperidone
- Ziprasidone

CHLOROQUINE

CISAPRIDE

CLASS IA ANTIARRHYTHMICS
- Disopyramide
- Quinidine
- Procainamide

CLASS IC ANTIARRHYTHMICS
- Encainide
- Flecainide
- Propafenone

CLASS III ANTIARRHYTHMICS
- Amiodarone
- Ibutilide
- Sotalol

TRICYCLIC ANTIDEPRESSANTS
- Amitriptyline
- Amoxapine
- Desipramine
- Doxepin
- Imipramine
- Nortriptyline
- Maprotiline

DROPERIDOL

ERYTHROMYCIN

HYDROXYCHLOROQUINE

PENTAMIDINE

QUININE

VENLAFAXINE

toxicity-related dysrhythmia is frequent premature ventricular beats. Bidirectional ventricular tachycardia is stated to be specific for digitalis toxicity but rarely is seen.

In addition to the cardiac manifestations, non-cardiac signs and symptoms may occur in cardiac glycoside toxicity and vary widely depending on whether the toxicity is acute or chronic. Acute toxicity may have few initial signs and symptoms prior to cardiac instability. Chronic toxicity, on the other hand, may have multiple signs and symptoms, including anorexia, nausea, vomiting, headache, fatigue, depression, dizziness, confusion, memory loss, delirium, hallucinations, and visual disturbances such as seeing yellow halos around objects (xanthopsia). Not uncommonly, chronic digoxin intoxication may be misdiagnosed as a more common illness, such as influenza or gastroenteritis.

Diagnostic Studies. Patients suspected of having cardiac glycoside toxicity should have an ECG performed and electrolytes obtained. Acute toxicity most closely correlates with hyperkalemia, as the Na^+-K^+-ATPase is inhibited and extracellular K^+ rises. In chronic toxicity, hyperkalemia may not be seen. This is due to the slow rise in K^+, allowing the kidneys to correct the imbalance. Many of those patients on chronic digoxin therapy also are taking diuretics that further promote potassium excretion. Chronic toxicity associated with renal failure may result in hyperkalemia due to the kidneys' inability to compensate.

A serum digoxin level should be obtained; therapeutic levels are 0.5-2.0 ng/mL. Serum digoxin levels should be interpreted with caution. In acute exposure, digoxin is absorbed into the plasma and then slowly redistributes into the tissues. As a result, high acute digoxin levels are not always associated with toxicity. Levels greater that 10 ng/mL at any time may be associated with significant toxicity, and treatment with digoxin-specific Fab should be considered. Other cardiac glycosides can cross-react with the digoxin assay, though the degree of this cross-reactivity varies. A false-positive assay may result in the presence of digoxin-like immunoreactive substance seen in neonates, pregnancy, renal insufficiency, liver disease, congestive heart failure, acromegaly, and stress.

Management. Cardiac glycoside toxicity should be considered in any patient taking digoxin and presenting with new-onset dysrhythmias, gastrointestinal complaints, or altered mental status. Meticulous attention to supportive care and a search for easily correctable conditions, such as hypoxia, hypovolemia, and electrolyte disturbances, are top priorities. All patients should be treated as discussed in the above section on "General Management of Cardiac Toxins."

In cardiac glycoside-poisoned patients, Fab fragments are the first-line therapy in patients with symptomatic cardiac dysrhythmias.[41] Since cardiac glycoside-enhanced vagal activity is reversed by atropine sulfate, this agent has been used successfully in patients exhibiting AV block. Cardiac pacing has been advocated for bradydysrhythmias unresponsive to atropine, but care should be exercised as the pacing wire itself may induce ventricular fibrillation.

The classic treatment for ventricular dysrhythmias is phenytoin, as it increases the ventricular fibrillation threshold in the myocardium and enhances conduction through the AV node. Lidocaine has been advocated for treatment of ventricular dysrhythmias due to digitalis toxicity, although it does not affect AV nodal conduction. Amiodarone was reported to be effective in

Table 5. Sodium Potassium ATPase Blocking Agents

Digoxin	Lily of the valley
Digitoxin	Oleander
Foxglove	Red squill

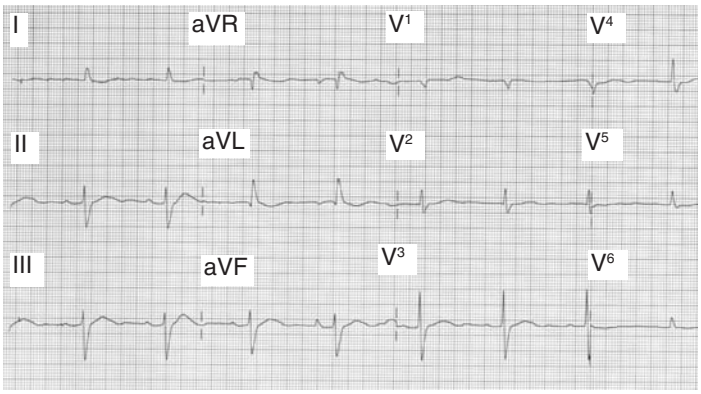
two cases refractory to other antiarrhythmics. Quinidine and procainamide are contraindicated in digitalis toxicity because they depress AV nodal conduction and may worsen cardiac toxicity. Electrical cardioversion of the digitalis-toxic patient must be performed with extreme caution and considered only as a last resort. A low energy setting (e.g., 10-25 W-sec) should be used and preparations made to treat potential ventricular fibrillation.

Potassium. Supplemental potassium may be beneficial in chronic digitalis toxicity when diuretic-induced hypokalemia is a factor. It should be given cautiously, as renal failure may be the cause of chronic digitalis toxicity. The acutely poisoned patient should not routinely receive potassium because hyperkalemia is common. Patients with acute cardiac glycoside poisoning who exhibit hyperkalemia may be treated with intravenous glucose, insulin, and SB or continuous inhaled beta agents such as albuterol (if no tachydysrhythmia or ectopy), although these therapies may be ineffective. The exchange resin sodium polystyrene sulfonate also should be considered. However, the increased serum potassium level reflects a change in potassium distribution and not an increase in total body potassium stores. Hence, use of agents such as exchange resins may lead to total body potassium depletion and subsequent problems once the digitalis toxicity has abated. There is a theoretical concern that treating cardiac glycoside-induced hyperkalemia with intravenous calcium may enhance digitalis cardiac toxicity and should be avoided.

Magnesium. Hypomagnesemia has been reported in a significant number of patients with chronic cardiac glycoside toxicity. Intravenous administration of magnesium has been shown to counteract ventricular irritability from digitalis toxicity.[42] The recommended dose of magnesium for malignant ventricular dysrhythmias is 2-4 g (10-20 mL of a 20% solution) given intravenously over one minute. It should be infused more slowly in patients with ectopy who are hemodynamically stable. Magnesium also may be helpful in treating hyperkalemia. It should be used with extreme caution in renal failure patients.

Digoxin-Specific Fab. A milestone in the treatment of cardiac glycoside poisoning was the development of drug-specific antibodies. Digoxin-specific Fab fragments (Digibind or DigiTab) are antibody fragments produced by enzymatic cleavage of sheep immunoglobulin (IgG) antibodies to digoxin. Fab fragments can reverse digitalis-induced dysrhythmias, conduction disturbances, myocardial depression, and hyperkalemia in severely poisoned patients. Most patients have an initial response to cardiac glycoside toxic dysrhythmias within 30 minutes of Fab administration, and those who responded had complete resolution by four hours. Animal studies and case reports have demonstrated the efficacy of Fab fragments to the cardiac glycoside contained in plants.

Figure 7. Chronic Digoxin Toxicity with Sinus Bradycardia, 1st Degree AV Block, and Intraventricular Conduction Delay



Adverse reactions to Fab administration have been few and include rare but mild hypersensitivity reactions, precipitous drops in serum potassium, and supraventricular tachydysrhythmias previously controlled by digoxin.

Fab fragment therapy should be administered for the following indications: 1) potassium greater than 5.0 mEq/L following acute ingestion; 2) serum digoxin concentration greater than 10 ng/mL; and 3) patients with potentially life-threatening dysrhythmias. Often, chronically poisoned patients can be managed by discontinuing digoxin and closely observing them. However, the threshold for treatment with Fab should be lower in chronically poisoned patients with signs of cardiac toxicity or who have chronic pulmonary disease, hypokalemia, hypothyroidism, renal insufficiency, or underlying cardiac disease.[43] If patients are managed conservatively, the Fab dose to be administered should be calculated and the Fab fragments made available at the bedside while the patient is monitored for worsening toxicity.

Although serum digoxin levels should not be the sole factor in determining the need to administer Fab, dosage calculations for Fab are based on the serum digoxin level or estimated body load of digoxin. It is assumed that equimolar doses of antibody fragments are required to achieve neutralization. Forty milligrams of Fab (one vial) will bind 0.6 mg of digoxin. A severely toxic patient in whom the quantity ingested acutely is unknown should be given 5-10 vials at a time, and the clinical response should be observed. If cardiac arrest is imminent or has occurred, the dose can be given as a bolus. Otherwise, it should be infused over 30 minutes. In contrast, patients with chronic therapeutic overdose often have only mildly elevated digoxin levels and respond to one to two vials of Fab. The recommended dose for a given patient can be determined using the tables in the package insert or by contacting a regional poison center or toxicology consultant.

Free digoxin levels are decreased to zero within one minute of Fab fragment administration, but total serum digoxin levels markedly are increased. Since most assay methods measure both bound and free digoxin (total), very high digoxin levels are seen after Fab fragment therapy, but they have no correlation with toxicity. Serum levels may be unreliable for several days after Fab

treatment. The digoxin-Fab complex is excreted in the urine and in patients with renal failure, elimination of the digoxin-Fab complex is prolonged and free digoxin levels gradually increase over hours after Fab administration. Rebound cardiac glycoside toxicity is rare but has been reported. Hemodialysis does not enhance elimination of digoxin-Fab complex.

Disposition. All patients who receive Fab fragments require continued monitoring in an intensive care unit for at least 24 hours. For the chronically poisoned elderly patient, modifying the outpatient treatment regimen by discontinuing the use of a cardiac glycoside or providing a more reliable method of drug administration with close clinical follow-up may avert further toxic episodes.

Conclusion

There are numerous agents that can result in human cardiotoxicity. The management of the toxicity of each should follow a rational approach as outlined above.

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Physician CME Questions

131. Which of the following drugs is associated with cardiac sodium channel blockade?
    A. Nicardipine
    B. Esmolol
    C. Hydroxychloroquine
    D. Digoxin
    E. Pentamidine

132. In regards to the ECG, which of the following corresponds with phase 0 of depolarization?
    A. QRS interval
    B. QT interval
    C. PR interval
    D. T wave

133. Calcium channel blocker toxicity is associated with which dysrhythmia?
    A. Supraventricular tachycardia
    B. Atrial fibrillation
    C. Atrial flutter
    D. Junctional escape rhythms

134. Cardiac glycoside toxicity may produce both excitant and/or suppressant dysrhythmias.
    A. True
    B. False

135. Which of the following therapies can be used for the initial treatment of QT prolongation due to a potassium efflux-blocking drug?
    A. Sodium bicarbonate
    B. Glucagon
    C. Insulin
    D. Epinephrine
    E. Magnesium sulfate

136. Overdrive pacing is used for the treatment of which condition?
    A. Atrial fibrillation
    B. Atrial flutter
    C. Torsades de pointes
    D. QRS prolongation

137. In acute digoxin toxicity, which of the following is an indication for digoxin-specific Fab?
    A. Potassium of 6.5
    B. Atrial flutter
    C. Sinus tachycardia
    D. Sodium of 129
    E. QRS of 100 ms

138. Which of the following cardiotoxins is associated with torsades de pointes?
    A. Diltiazem
    B. Atenolol
    C. Carbamazepine
    D. Digoxin
    E. Phenothiazines

139. The hallmarks of significant beta-blocker toxicity are bradycardia, heart blocks, and hypotension.
    A. True
    B. False

140. All patients who receive Fab fragments require continued monitoring in an intensive care unit for at least 24 hours.
    A. True
    B. False

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that is provided in this issue and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

In Future Issues: **Infectious Complications of Injection Drug Use**

CME Answers

131. C	136. C
132. A	137. A
133. D	138. E
134. A	139. A
135. E	140. A

Emergency Medicine Reports
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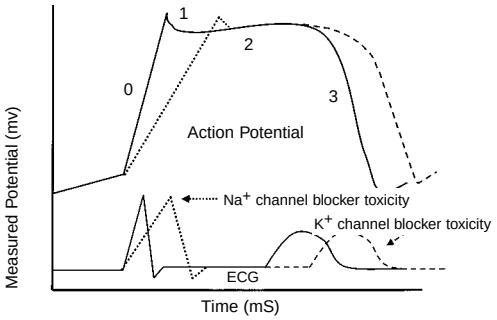
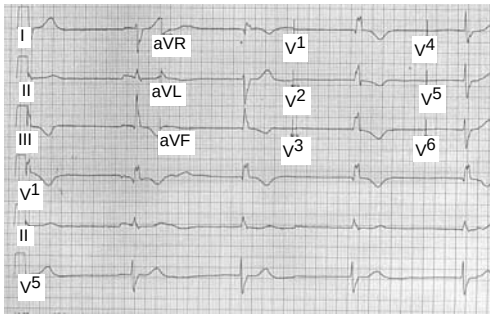
Cardiotoxins

Cardiac Action Potential with Corresponding ECG Tracing



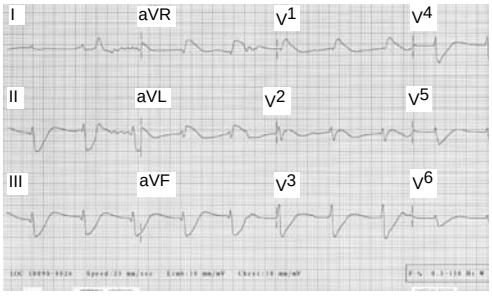
Junctional Escape Rhythm Following Verapamil Overdose



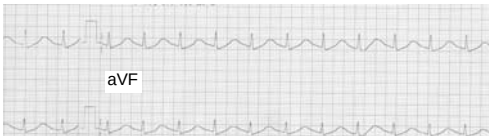
Beta-Blocking Drugs

Acebutolol	Esmolol	Pindolol
Atenolol	Labetalol	Propranolol
Betaxolol	Metoprolol	Sotalol
Bisoprolol	Nadolol	Timolol
Carvedilol		

Sine Wave Pattern Following Hydroxychloroquine Overdose



Prolongation of the QT Interval Following Hydroxychloroquine Overdose



Calcium Channel Blocking Agents

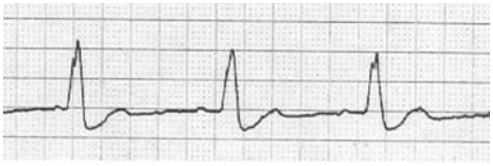
DIHYDROPYRIDINES
- Nicardipine
- Nifedipine
- Isradipine
- Amlodipine
- Felodipine
- Nimodipine

PHENYLALKYLAMINE
- Verapamil

BENZOTHIAZEPINE
- Diltiazem

DIARYLAMINOPROPYLAMINE ETHER
- Bepridil

Marked QRS Widening Following Propoxyphene Overdose



Sodium Channel Blocking Drugs

AMANTADINE

CARBAMAZEPINE

CHLOROQUINE

CLASS IA ANTIARRHYTHMICS
- Disopyramide
- Quinidine
- Procainamide

CLASS IC ANTIARRHYTHMICS
- Encainide
- Flecainide
- Propafenone

COCAINE

TRICYCLIC ANTIDEPRESSANTS
- Amitriptyline
- Amoxapine
- Desipramine
- Doxepin
- Imipramine
- Nortriptyline
- Maprotiline

DILTIAZEM

DIPHENHYDRAMINE

HYDROXYCHLOROQUINE

LOXAPINE

ORPHENADRINE

PHENOTHIAZINES
- Medoridazine
- Thioridazine

PROPRANOLOL

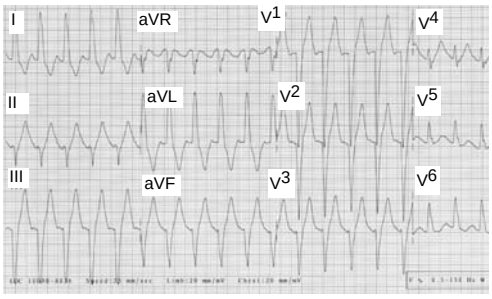
PROPOXYPHENE

QUININE

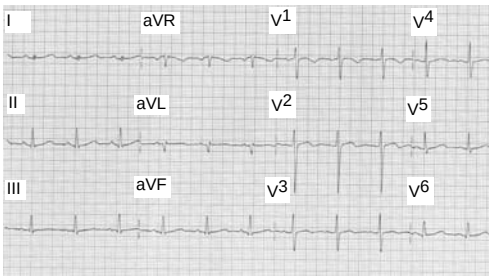
VERAPAMIL

Chronic Digoxin Toxicity with Sinus Bradycardia, 1st Degree AV Block, and Intraventricular Conduction Delay

Wide Complex Dysrhythmia Following Diphenhydramine Overdose



Same Patient as in Figure at Left After Multiple Doses of Sodium Bicarbonate



Potassium Efflux Channel Blocking Drugs

ANTIHISTAMINES
- Astemizole
- Diphenhydramine
- Terfenadine

ANTIPSYCHOTICS
- Haloperidol
- Phenothiazines
- Quetiapine
- Risperidone
- Ziprasidone

CHLOROQUINE

CISAPRIDE

CLASS IA ANTIARRHYTHMICS
- Disopyramide
- Quinidine
- Procainamide

CLASS IC ANTIARRHYTHMICS
- Encainide
- Flecainide
- Propafenone

CLASS III ANTIARRHYTHMICS
- Amiodarone
- Ibutilide
- Sotalol

TRICYCLIC ANTIDEPRESSANTS
- Amitriptyline
- Amoxapine
- Desipramine
- Doxepin
- Imipramine
- Nortriptyline
- Maprotiline

DROPERIDOL

ERYTHROMYCIN

HYDROXYCHLOROQUINE

PENTAMIDINE

QUININE

VENLAFAXINE

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Emergency Medicine Specialty Reports

Supplement 539Z **June 2003**

Abuse of the child is a social blight that has been present since the beginning of recorded history, and unfortunately, is still very present in the 21st century. Child abuse can be difficult to recognize, especially in the often chaotic environment of the emergency department (ED). An astute knowledge of the presenting signs and symptoms of child abuse is necessary, as an accurate history may be difficult to discern. Emergency physicians must maintain an index of suspicion for abuse, especially when the mechanism or pattern of a childhood injury is cryptic or out of place. As the leaders of the community and medical safety net that is the ED, emergency physicians play a unique role in detecting, treating, and preventing child abuse. This issue of Emergency Medicine Specialty Reports *provides an update on the patterns, diagnosis, and treatment of physical child abuse injuries.*

—The Editor

Physical Abuse of Children: Epidemiology of Child Abuse in the United States

Cutaneous Injuries, Fractures, and Abusive Head Trauma

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Introduction

Child abuse is a pervasive problem in the United States. The central premise of child abuse is that a child's caregiver, such as a parent, guardian, or foster parent, fails to provide for that child's health and well-being, either through acts of omission or commission. Such acts can lead to harmful effects on the child's health, development, and psychological well-being. The Child Abuse Prevention and Treatment Act (P.L. 93-247), which Congress passed in 1974, states that child abuse can be defined as the following:

"The physical or mental injury, sexual abuse, negligent treatment or maltreatment of a child under the age of 18 by a person who is responsible for the child's welfare under circumstances which indicate that the child's health and welfare is harmed or threatened thereby."

By 1968, mandated reporting laws were passed in all 50 states of the United States. A mandated reporter is an individual who is routinely responsible for a child's health or well-being, and includes teachers, day care workers, medical personnel, and law enforcement professionals. Such individuals are required to report cases of suspected child abuse to child protective service agencies. A mandated reporter needs reasonable suspicion, not proof, of child abuse to make a report, and such individuals are protected from litigation for libel in nearly all states. In fact, a mandated reporter may be prosecuted for failing to report suspected child abuse in some states.

Epidemiology

In 2000, an estimated 3 million children were reported to child protective service agencies for suspected abuse or neglect.[1] Families who are most likely to be reported to child protective service agencies are those with a history of substance abuse; domestic violence; socioeconomic constraints, such as poverty, inadequate housing, and unemployment; and poor parenting skills, such as young parental age, mental health problems, and unrealistic expectations of a child's development. There also may be racial disparities in reports of suspected child abuse. One study found that young minority children with fractures that ultimately were determined to be accidental were three times more likely to be reported for suspected abuse than Caucasian children.[2]

Of these reports of suspected child abuse, 32%, or 879, 000, were substantiated as cases of child abuse or neglect. Of these substantiated cases, 63% were due to neglect, 19% were due to physical abuse, 10% were due to sexual abuse, and 8% were from emotional maltreatment. In 2000, 1200 children died from

child abuse or neglect. Eighty-five percent of these deaths were in children younger than 6 years of age.

Unfortunately, there are numerous ways in which children are maltreated. This article will focus on the most frequent manifestations of physical abuse, such as bruises, burns, fractures, and abusive head trauma, which also is known as Shaken Baby Syndrome.

Cutaneous Manifestations of Physical Abuse

Bruises. Bruises are the most common injury in abused children, and are a common accidental injury of childhood. There are several historical and physical features that help to distinguish between accidental and abusive bruises, but still there may be considerable overlap. An understanding of the pathophysiology of bruises may be useful to aid in this distinction.

Pathophysiology. A bruise occurs when there is an impact to the skin surface, which results in disruption of underlying capillaries, leading to extravasation of blood into the dermis. The location of the impact and the complexion of the child's skin can contribute to a bruise's appearance. Bruises in locations on the body where the supporting tissue is areolar, such as the genitalia and periorbital regions, may appear immediately. Bruises in areas of significant muscle mass, such as the thigh, may not appear until days later, after extravasated blood has traversed the quadriceps or hamstring muscles to reach the dermis. A child's complexion may affect the appearance of a bruise, as children with darker complexions may not be noted to have bruising unless the skin is inspected very closely.

It previously was thought bruises undergo a predictable sequence of color changes during healing, but this premise recently has been challenged.[3] Many of the initial studies evaluating the change in color sequence of bruises were performed in adult cadaver models, and the applicability of these results to living children has been questioned. Stephenson and Bialas performed a prospective analysis of the evolution of color changes in children with bruises.[4] They recorded the color of bruises in children who were admitted to an inpatient pediatric unit with accidental trauma. These researchers noted that red was apparent in bruises up to one week after injury, yellow was seen in bruises that were 1-12 days old and green was not present in injuries fewer than 2 days old. Many of the tables regarding the age estimation of bruises printed in textbooks have been adapted from Wilson, who recognized the imprecise nature of dating bruises and recommended that practitioners refrain from stating the precise age of a bruise.[5]

History and Physical Examination. The location of bruises on a child is helpful in determining whether the mechanism is accidental or inflicted. Typically, children who are not ambulatory rarely have bruises, as their activity does not predispose them to falls unless they are left unattended. A 1999 study prospectively evaluated 973 young children who received care in several pediatric practices and found that bruises rarely were encountered in preambulatory children who presented for routine well-child visits.[6] Ambulatory children, such as toddlers, frequently have bruises on areas of bony prominences, such as the forehead, knees, and elbows, as these are the regions that first are impacted during a fall. However, there are regions of the body that are well protected in normal household falls, such as the neck, groin, and inner aspects of the thighs. A history that does not include impact to these regions during a fall should raise the suspicion of inflicted injury.

Bruises that consist of certain highly defined patterns are suggestive of inflicted injury. Frequently, the pattern of the bruise conforms to the implement that was used to strike the child. Implements commonly used include the hand, belts, cords, ropes, and rulers. Cords, belts, and ropes can be looped, leading to U-shaped bruises. Rigid, linear objects, such as rulers or cooking utensils, result in linear bruises. (*See Figure 1.*) If the implement is applied to the child with high velocity, there may be a negative image of the implement, with skin that is not bruised outlined by a fine rim of petechiae that conforms to the shape of the implement.[7]

Bite marks lead to a highly distinctive pattern of bruises. They may appear as an arched pattern of individual tooth prints that conform to the central and lateral incisors and to the canines. Forensic dentistry may be helpful to aid in the identification of the perpetrator based on the pattern of the bite injury. The typical distance between the mandibular canines in children is approximately 2.5 cm, while in adults this distance usually is greater than 3 cm.[8] This distance between the canines should be used only as an estimate, as it may increase only 5 mm between childhood and adulthood.[7] If bites are recent and the child has not

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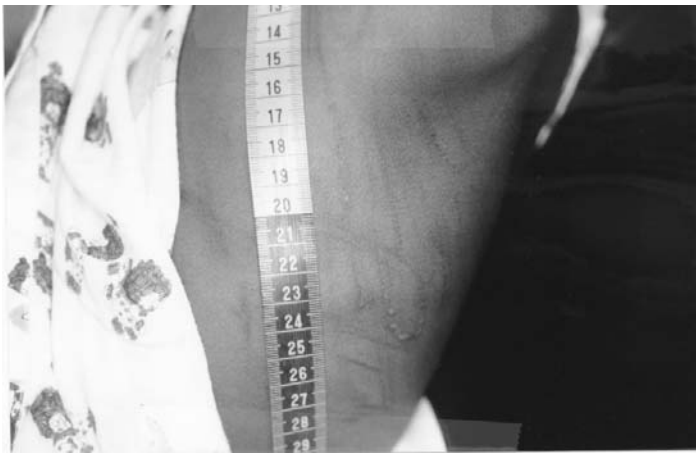
Figure 1. Linear and Looped Bruises



Linear and looped bruises appear on the upper extremity in a 10-year-old boy.

bathed, he can be swabbed with a saline-soaked cotton swab and sent for DNA markers that potentially could identify the perpetrator. Dental impressions also can be taken from alleged perpetrators and compared to the bite mark itself.

Children may be restrained during beatings, leading to bruises around the extremities. If the child is restrained by being held about the extremities with the hands of the perpetrator, there may be isolated, circular bruises of the volar and dorsal surfaces of the arms and legs. If ligatures are used, there may be circumferential, linear bruises around the ankles or upper arms, occasionally accompanied by abrasions and lacerations if the ligature was applied tightly.

Conditions that May Be Confused with Inflicted Bruises. Some conditions may be confused with inflicted bruises. Several religious or folk medicine practices from Southeast Asia may result in a distinctive pattern of bruising.[7] One is coin-rubbing, or Cao Gaio, which causes petechial bruising over the paraspinal region of the back. A coin is dipped in hot oil and rubbed vigorously over the child's back as treatment for medical illness. A second healing method involves heating a glass and applying it to the skin; when removed, there can be circular petechial bruises. While these practices result in injury, the caregiver's intent was to treat the underlying medical condition.

Mongolian spots are a congenital variation in skin color, most frequently seen in infants and children with darkly pigmented skin. They most commonly appear as slate-blue or brown-black macules on the sacrum, but also can be present on the lower extremities or forehead. Unlike bruises, there is no accompanying tenderness or edema. They fade over a period of months to years, and easily are distinguished from bruises due to the long period over which they resolve.

Other medical conditions associated with increased skin fragility and subsequent bruising include connective tissue disorders such as osteogenesis imperfecta and Ehlers-Danlos syndrome. Children with these disorders tend to have hypermobility of the joints and skin laxity. Systemic disorders associated with diminished coagulation, such Immune Thrombocytopenic Purpura (ITP), Hemophilia A and B, and von Willebrand's disease, may result in either extensive petechiae or ecchymosis, but laboratory evaluation can distinguish these disorders from inflicted bruises. Other disorders associated with vascular inflammation, such as Henoch Schonlein Purpura, result in purpuric, palpable lesions of the lower extremities and torso, the pattern of which also can be helpful in distinguishing it from inflicted injury.

Burns. Inflicted burns are a significant cause of morbidity and mortality. Inflicted burns account for 25% of all hospital admissions for children with burns.[9] Inflicted burns can be due to scald injury, in which a hot liquid is thrown at a child or a child forcibly is immersed in hot liquid, or due to contact injury, in which a hot implement forcibly is held against the child's skin.

Pathophysiology. The depth and extent of a burn depends on the temperature of the implement or liquid that contacts the skin, as well as the duration of this contact. Burns can be characterized by the depth to which they penetrate the epidermis, dermis, subcutaneous tissue, muscle, and bone. A superficial thickness burn is characterized by thermal injury to the epidermis. This appears as a "sunburn," with erythema of the skin and minimal pain and tenderness to palpation. A partial-thickness burn can be characterized by the depth of the dermis that is penetrated by the thermal injury. A superficial partial-thickness burn is characterized by injury to the upper half of the dermis and typically forms blisters that have underlying pink skin with brisk capillary refill. In contrast, deep partial-thickness burns penetrate into the lower half of the dermis, and the skin underlying the blisters is paler and drier due to more extensive capillary damage. Partial-thickness burns may heal with or without scarring.[10] Full-thickness burns result from thermal injury that results in destruction of both the epidermis and dermis.

Duration of exposure and temperature has been determined to predict the likelihood of a full-thickness burn due to hot water. Young children typically tolerate bath water that is less than 101°F.[7] Hot tub temperatures can vary between 104-108°F, while water that is 110°F most often is painful to an adult.[7] Water that is 120°F will cause full-thickness burns in approximately 10 minutes, while water that is 150°F will cause full-thickness burns within two seconds.[11,12] Similar formulations for duration of exposure and temperature have not been determined for hot objects.

History. There are several aspects of the history as to how the burn occurred that are helpful in distinguishing accidental from inflicted burns. Accidental burns have a clear history of contact with a hot object or liquid. Accidental burns usually are seen in children whose behavior can place them within reach of such objects. Children who can sit well and reach easily can pull containers of hot liquid toward and onto them, especially while seated on a caregiver's lap. Toddlers can reach up to pull such containers of hot liquid from the table, stove, or microwave down onto themselves. Older children who have the dexterity to play with and ignite matches or lighters may cause contact burns on the hands and face and, more seriously, may ignite clothes or furniture.

Historical hallmarks of inflicted burns include those with no explained mechanism or those purported to have been inflicted

by a young child who cannot provide such a history. Victims of inflicted burns tend to lack the behavioral and motor skills that place them within reach of hot objects or liquids. When such children encounter hot objects or liquids, they will try to remove themselves from contact with such by pulling or turning away, or attempting to climb out of a tub or sink filled with hot liquid. The caregive may provide a history that the child performed a task of which the child is not capable, such as a very young infant manipulating a lighter or turning on a hot water faucet.

Physical Examination. Children with accidental scald burns from hot liquids most often have burns that are on the anterior plane of the body and have concentric radiation of the depth of the burn.[9] For example, a child who reaches up and pulls a hot liquid down onto himself may have burns of the face, chest, and arm. The point of contact of the hot liquid on the body will have the deepest burn. As the hot liquid travels down the body, it cools, leaving burns that are not as deep.[9] The demarcation between normal and burned skin tends to be irregular, depending on the path that the hot liquid travels down the body. Accidental scald burns also can be caused by hot foods, which tend to be more viscous and adherent, prolonging the time of contact with the skin and occasionally causing deeper burns than water at a similar temperature. Clothing does not protect against the degree of burn injury, as hot liquids can soak into the fabric, prolonging contact with the skin.

Scald burns suggestive of inflicted injury include those with clear demarcation lines, especially around the hands and feet, ("stocking-glove"), (*see Figure 2*) as well as those that involve protected areas of the body, such as the genitalia.[7,9,13] A pattern of burn injury that is pathognomic for inflicted injury is one that involves the genitalia and lower extremities. This occurs when a child forcibly is restrained or dunked into a bathtub of hot water. As children are lowered into the water, they reflexively flex their hips and knees, protecting the creases in the groin and popliteal fossa. The resultant burn, therefore, involves the anterior and, to a lesser extent, posterior aspects of the lower extremities and the lower half of the torso. If the buttocks are pressed against the floor of the sink or tub, the area around the gluteal cleft may be spared, resulting in a doughnut pattern of burn.[7,13] Similarly, if the soles of the feet are pressed against the floor of the sink or tub, they may be spared as well. If the child struggles, the watermark level (the highest level to which the water immerses the body) may be irregular and wavy on the lower abdomen.[7] If any part of the child's body rigidly is restrained in the hot water, the watermark level will be rather straight.[7] Children who accidentally enter a tub of hot water typically will not sit down in the water, and alternately may stand on one leg or the other until removed from the hot water. The resulting burns may involve the lower extremities only, with splash burns scattered elsewhere on the body.

Accidental contact burns tend to be on the anterior plane of the body and often are solitary. When school-age children experiment with matches or cigarette lighters, there tends to be a single burn on the palmar aspect of the thumb or index finger. When children reach out or up to touch an iron, there may be burns on the palms. If the child reaches up to pull the iron down and the iron falls onto the child, there may be burns on the face, hand, arm, or foot, depending on the trajectory of the iron as it fell. Contact burns on the posterior portions or well-protected areas of the body, such as the genitalia, neck, or axillae, are suggestive of inflicted contact burns.

Medical Conditions that May Be Confused with Abusive Burns. There are a few medical conditions that may be mistaken for abusive burns. Dermatological conditions that cause the formation of bullae, or blisters, include bullous impetigo and epidermolysis bullosa. In bullous impetigo, which most often is caused by *Staphylcoccus aureus* or *Streptococcus pyogenes*, bullae that are several millimeters in diameter can form. These bullae may appear in crops and coalesce together. When these bullae rupture, the base may appear as an erythematous, glistening macule that may be mistaken for partial-thickness burns due to cigarettes, which tend to have a smaller diameter. The yellow crust that may appear on top of ruptured impetiginous lesions is easy to remove with water, while that of a partial-thickness burn due to a cigarette is much more adherent.[13] In addition, the center of a cigarette burn most often will be deeper than the periphery. Epidermolysis bullosa is a rare, inherited condition in which large bullae can form either spontaneously or over areas of friction. Again, when these bullae rupture, they appear similar to partial-thickness burns. Both impetigo and epidermolysis bullosa are not painful, in contrast to partial-thickness burns. Some forms of candidal and ammoniacal diaper dermatitis may appear as a partial-thickness burn, but can be characterized by diffuse, nontender erythema of the skin surrounding the area of skin sloughing.[13]

Fractures

Fractures are common injuries in children who have been physically abused. A 1991 study found that of 39 young children with humeral and femoral fractures, 23% were inflicted.[14] A subsequent study by these same investigators of 253 fractures in children younger than 3 years of age demonstrated that 24% were due to abuse.[15] While there are some fracture patterns that are pathognomic for inflicted injury, such as posterior rib fractures (*see Figure 3*), there can be overlap among fracture patterns in both inflicted and accidental injuries.

History. A child who sustains a fracture most often has a change in demeanor. A child may cry, become irritable and difficult to console, and have limited use of the affected extremity. Caregivers may note that handling the infant or child in a particular way caused the child to cry or become irritable. Such a change in behavior helps to localize the time at which the fracture most likely occurred. Children who do not roll, pull to stand, cruise, or walk are least likely to sustain fractures in general because their motor activity typically would not place them in a situation at risk for fracture. Lack of witnesses, no provided mechanism of injury, or a mechanism of injury that suggests a developmental level more advanced than that which is expected are all historical factors that should raise concern of inflicted injury.

Physical and Radiological Examination. The fracture pattern may provide clues as to the mechanism of injury. Spiral fractures typically occur from twisting mechanisms. Such fractures of the long bones in children who are not ambulatory strongly should raise the possibility of inflicted injury. In some cases, these frac-

tures may occur as the caregiver grasped the child's extremity during a fall, and a consistent history of such should make one less suspicious of an abusive injury. In toddlers and younger children who are ambulatory, accidental spiral fractures of the femur may occur as a child is running, then trips and twists the lower extremity while falling.[14] Spiral humeral fractures in young, non-ambulating children historically have been considered to be abusive.[14] There have been, however, recent case reports to suggest that such fractures sometimes may be accidental. For example, a case of a witnessed humeral fracture, which incidentally was videotaped, has been reported in an infant who rolled from the prone to supine position, entrapping the upper extremity in the process.[16] In addition, linear skull fractures may be seen in short, vertical, household falls from beds, chairs, and changing tables onto firm surfaces, and when children tumble down flights of stairs.[17,18]

However, there are some fracture patterns that are highly suggestive for child abuse. Posterior rib fractures, such as those close to the rib neck and head, are due to levering of the posterior rib neck over the transverse spinous process as the rib cage is squeezed vigorously.[19] This fractures the inner cortex of the posterior rib neck and the postero-lateral arc of the rib. When the thorax undergoes severe anterior and posterior compression, the fracture line may extend to the anterior rib's articulation with the sternum. In addition, sternal fractures may be due to direct blows, and without a history of such trauma, are highly specific for inflicted injury.[19] Metaphysial corner fractures, also known as "bucket handle" fractures, occur due to axial traction on a child's limbs. As the ligamentous attachments are weaker than the ligaments themselves, the metaphysis may be sheared, leaving the periosteum intact. Such a fracture appears as a "bucket handle" and also is considered to be pathognomic for abuse.[20] These fractures most often are seen at the distal regions of the long bones, such as the femur, tibia, and humerus. Multiple fractures in different stages of healing are highly suggestive of repetitive trauma and, therefore, child abuse, but also should prompt one to consider other causes of bony fragility that have a propensity for fractures. However, when multiple, healing fractures are seen with other unexplained injuries, it becomes more likely that these injuries are due to child abuse.

Dating Skeletal Trauma. Fractures undergo a predictable pattern of healing. When fractures occur, there is attendant swelling due to hemorrhage and inflammation in the surrounding tissues. While symptoms of soft-tissue hemorrhage and inflammation may resolve in several days, it can be present on plain radiographs up to 10 days after the fracture occurred. Subperiosteal new bone formation can be apparent on plain radiographs as early as 4-7 days after injury, followed by loss of definition of the fracture line within 10-21 days after injury. The peak of soft callus formation most often is apparent radiographically within 10-21 days after the injury. Hard callus most often is seen within 14-42 days after injury, with complete remodeling evident at three months to one year after the injury.[21]

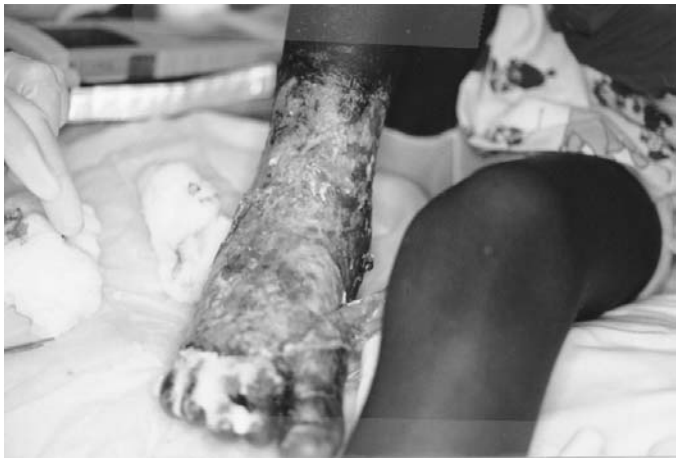
Diagnostic Imaging. Occult skeletal trauma most often is seen in children younger than 2 years of age, and in this age group, a skeletal radiographic survey will have the greatest yield of detecting such trauma. A skeletal radiographic survey should not be confused with a baby-gram or body-gram. These previously utilized surveys employed a one- or two-exposure study that captured the child's entire skeleton and are inadequate to assess for occult fractures, such as metaphysial corner fractures or posterior rib fractures.

It may be useful to repeat the skeletal survey several weeks after the initial study, as some fractures can be detected only when healing. One study found that a second skeletal survey demonstrated additional injuries in 14/23 (61%) young children evaluated for suspected abuse.[22] Many of these additional injuries included metaphysial and rib fractures.

Medical Conditions with Propensity to Fractures. There are several acquired and congenital medical conditions that may lead to bony changes or fractures that could be confused with abusive fractures.[23] One such condition is osteogenesis imperfecta, a rare, inherited condition that results in bony fragility and propensity for fractures with routine handling or minor trauma. Children with such medical conditions may present with radiographic findings of multiple fractures in different stages of healing. The hallmark of this disorder is a genetic mutation resulting in the abnormal synthesis of type 1 collagen. Most cases are inherited in an autosomal dominant fashion, though cases due to spontaneous mutation also may occur.[7]

Nutritional rickets can lead to bony lesions that may be confused with metaphysial fractures. A recent study demonstrated that such infants are African-American, breast-fed, between 5 and 25 months of age, and did not receive supplemental vitamin D.[24] All of the infants in this sample had radiological findings of widening of the growth plate; fraying, cupping, and irregularity of the metaphysis; and osteopenia. In addition, all patients were hypophosphatemic as well.

Figure 2. Full-thickness Burns



Full-thickness burns of the foot in an 8-year-old who was forced to stand in hot water for 10 minutes. Note the clear demarcation between burned and normal skin.

Abusive Head Trauma

While trauma is the most common cause of death in childhood, abusive head trauma is the most common cause of trau-

matic death in infancy. In 1946, pediatrician Robert Salinger characterized the original "battered babies."[25] He described an infant nurse who confessed to killing three infants and injuring many more in her care. She would become angry and frustrated about an infant's crying and would grab the infant about the chest or the upper extremities and shake him violently until the infant ceased to cry. Autopsies on two of these infants revealed diffuse subdural hemorrhage over both cerebral hemispheres.

Pathophysiology. The biomechanical forces necessary to cause this spectrum of injuries have been understood only recently. In 1972, Caffey described the "Whiplash Shaken Infant Syndrome," which suggested that the pathogenesis of injuries such as subdural hemorrhage and retinal hemorrhage to rotational deceleration forces of the head.[26] Such forces cause the dura to slide along the surface of the brain, rupturing the vessels in the subdural space. Similarly, the vitreous humor slides along the surface of the retina, disrupting the vessels that course between the layers of the retina, resulting in diffuse retinal hemorrhage.[27]

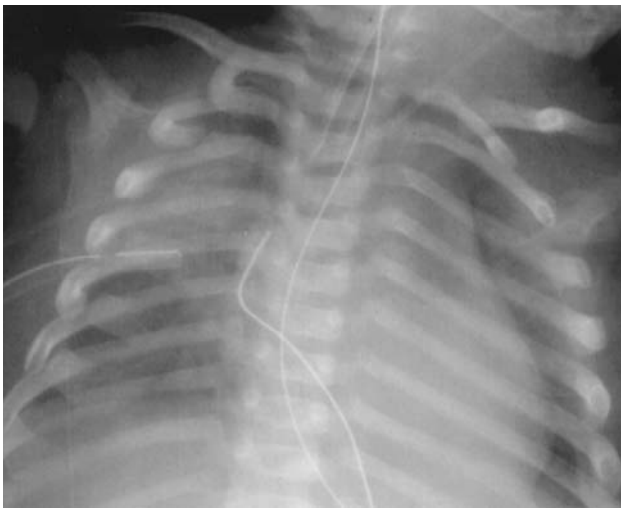
There has been some disagreement as to whether shaking alone or shaking and impact is necessary to cause this spectrum of injuries. In a 1987 study, researchers constructed a biomechanical infant model and demonstrated that the forces necessary to cause concussion and subdural hemorrhage were generated only when this infant model was shaken and impacted on a fixed, hard surface.[28] Such evidence of impact injury to the head may not be apparent on initial examination, and may be recognized only when the scalp is shaved or the galea exposed at surgery.[29] Other investigators have suggested that vigorous, violent shaking alone generates the force necessary to cause these injuries.

History. Caregivers who inflict these injuries sometimes are unaware that they have injured the child. However, a competent observer to such injuries inherently would realize that the caregiver's actions would be injurious to the child. Infants and children often are shaken due to a caregiver's unrealistic expectations of the infant or child or as a disproportionate response to increasing levels of frustration. In some instances, it may be difficult to determine if the caregiver's intent was to inflict harm or simply to stop the infant or child from crying. Recent studies have demonstrated that perpetrators who injure children in this manner are most likely to be, in descending order, fathers, male paramours, female babysitters, and mothers.[30]

The histories provided by caregivers may be vague, such as, "I found him like this when he awoke from a nap." There may be suggestion to a remote, poorly defined event, such as, "He may have fallen off the couch yesterday." There is much literature to support the concept that household falls or falls down stairs rarely result in life-threatening brain injury except if a space-occupying lesion, such as an epidural or large intracranial hemorrhage, is present.[18,31,32]

Children with abusive head trauma can have a wide spectrum of symptoms and signs. Children with milder injuries may have only irritability, vomiting, poor feeding, or sleepiness. These are symptoms that overlap with a myriad of common pediatric illnesses and, thus, these children might not be recognized to have sustained an inflicted head injury. Children with severe injuries often present with more ominous symptoms and signs, such as apnea, unresponsiveness, seizures, or cardiopulmonary arrest. The highest incidence of such injury is in children younger than 6 months of age, due to their proportionally larger head, weak neck muscles, and poor head control, though varying degrees of injury can be seen in children up to 2 years of age.[29] Older but physically smaller children with developmental delays also can suffer from these injuries.

Figure 3. Acute Rib Fractures



Acute rib fractures of the right posterior and anteriolateral 2nd-6th and left 2nd-5th posterior ribs in a 3-month-old infant, who also sustained a right pneumothorax requiring tube thoracostomy, and a left pulmonary contusion.

Physical Examination. On physical examination, there may not be obvious signs of trauma to the head, neck, or chest. Scalp contusions may be seen only when the head is shaved or when the scalp is exposed during craniotomy.[29] The extent of brain injury largely determines the signs and symptoms a child may have. There may be focal neurological signs, such as hypertonicity or flaccidity, gaze palsies, or unequal pupils. The child may be irritable or unresponsive to pain. Focal or generalized seizures may be apparent. Cardiopulmonary arrest may be due to significant brain injury, either from direct deceleration injury to the brain stem and upper cervical cord or due to subsequent hypoxia and ischemia from cerebral edema.[29]

Retinal hemorrhages are present in 60-95% of patients with abusive head trauma.[27,29] They sometimes may be appreciated on direct ophthalmoscopy without mydriatics, but often the true extent of such may be appreciated only with dilated, indirect ophthalmoscopy. Typically, retinal hemorrhages seen in those children with abusive head trauma are multiple and often extend to the periphery.[27,29] They can occur in multiple layers of the retina, most often in the nerve fiber and ganglion cell layers, and appear to be flame-shaped. Intraretinal and preretinal hemorrhages are more often dot-, blot-, or boat-shaped hemorrhages.[27,29] Retinal hemorrhages may be either unilateral or bilateral. Retinoschesis, internal splitting of the retina, macular folding,

and vitreous hemorrhage are other retinal abnormalities often associated with abusive head trauma.[27,29]

On occasion, retinal hemorrhage may be seen in head injuries associated with accidental mechanisms. A recent case series documented three cases of accidental falls and found that retinal hemorrhages were present on the same side as the subdural hemorrhage.[33] However, the retinal hemorrhages noted in this case series were isolated to the posterior pole of the retina, did not cover a significant surface area of the retina, did not extend to the periphery, and were not accompanied by retinal folds or detachment.

Cardiopulmonary resuscitation typically does not cause retinal hemorrhages. Odom and colleagues performed dilated indirect ophthalmoscopy on hospitalized children who underwent at least one minute of closed chest compressions during cardiopulmonary resuscitation. Of the 43 patients studied, only one patient had retinal hemorrhages, which were few in number. This patient also had evidence of activated coagulation at the time of the ophthalmoscopic examination.[34] Retinal hemorrhage may be seen in up to 30% of infants shortly after birth, but typically resolve after 6 weeks of age.[35,36]

Radiographic Evaluation. Computed tomographic (CT) scanning is the most rapid, reliable tool in the diagnosis of abusive head trauma. Acute subdural and subarachnoid hemorrhage, the most common brain injuries seen in children with abusive head trauma, can be appreciated readily on CT by experienced clinicians. Typically, a subdural hemorrhage can be thin and extensive, but occasionally may be large enough to cause mass effect.[37] There is a high propensity for subdural hemorrhage to involve the interhemispheric fissure, but it also can involve the convexities, and can be unilateral or bilateral.[28,37] Subarachnoid hemorrhages are usually multifocal and can be seen most often along the falx or the tentorium.[38] Skull fractures, as well, can be detected by CT scan, suggesting impact of the head onto a fixed, hard surface. Skull fractures most often are linear, but can be stellate or diastastic as well.

Children with more severe deceleration injury to the brain may have evidence of diffuse cerebral edema and diffuse axonal injury. This may appear as a reversal of the differentiation between the gray and white matter, also known as the reversal sign.[39] The gray matter therefore will appear less dense than the deeper gray matter structures of the basal ganglia and brain stem, as well as the white matter. Diffuse axonal injury arises from shearing injuries to the structures along the gray-white matter interface. Acute, punctate hemorrhage may be present along the gray-white matter junction of the gyri , the corpus callosum, or the basal ganglia.[39]

Magnetic resonance imaging (MRI) may be useful to detect small extra-axial fluid collections not appreciated on CT scans, diffuse axonal injury, and to narrow the window of time in which the injury occurred.[39] MRI can be difficult to obtain in children requiring mechanical ventilation and inotropic support, and should be considered as an adjunct to CT scans.

Other hallmarks of shaking injury include posterior and anterolateral rib fractures and metaphyseal fractures. When children present acutely with brain injury due to shaking, these injuries may not be detected readily on plain radiographs at the time of initial presentation to the ED. At the time of the acute injury, such fractures may not have overlying tenderness, edema, or crepitus, and there may not be loss of function of the involved extremity. Such fractures may be detected only with skeletal scintigraphy, which can be difficult to obtain in children who have significant brain injury that requires mechanical ventilation and inotropic support. Plain radiography obtained within 10 days of initial presentation may be the only modality to demonstrate these fractures in this sicker group of patients with abusive head trauma.[39] When these fractures are present with the previously described CNS and retinal findings, this constellation of injuries is pathognomic for abusive head trauma.

Outcome. Long-term outcome of survivors of abusive head trauma tends to be poor, and is dependent on the severity of symptoms on initial presentation.[40-42] Children who present with apnea, seizures, and coma are more likely to have long-term neurologic sequelae such as developmental delay, seizures, and static encephalopathy. The overall mortality from such injuries can be as high as 25%.[40]

Closed Head Trauma that May Be Confused with Abusive Head Trauma. Some children who have contact injuries to the head, either from short vertical falls or blows to the head, may sustain epidural hemorrhage, subdural hemorrhage, or cerebral contusion. When there is a contact injury to the head, the point of impact causes the inner table of the skull to bend inward, putting it under compression, which may injure blood vessels within the epidural or subdural space, as well as the parenchyma of the brain itself.[43] These focal injuries may be accompanied by a skull fracture as well. At the same time of this inbending of the skull, there also is simultaneous outbending of the skull around the site of impact.[43] This puts the outer table of the skull under tension, and a skull fracture may result, either proximate to or remote from the site of impact. As the skulls of infants are somewhat more elastic, the tension on the outer table of the skull as it bends outward from an impact site may not always result in a fracture.[43] These children typically do not present with significant alterations in mental status, unless the EDH or SDH is large enough to cause mass effect and focal cerebral edema.[43] In contrast to children who have head injury due to shaking, the outcome of children with subdural hemorrhage due to impact injury typically is good, as most often the hemorrhage is not extensive and spontaneously resolves within 48 hours after injury, with little neurological sequelae.[44]

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Physician CME Questions

Please read the text, answer the following questions, check your answers against the key, and then review the materials again regarding any questions answered incorrectly. ***To receive credit for this activity, you must return the enclosed CME evaluation by fax to 1-800-850-1232.***

1. Which of the following fractures in a 12-month-old child is most suggestive of child abuse?
   A. Clavicle fracture
   B. Linear skull fracture
   C. Tibia fracture
   D. Bilateral anterolateral rib fractures

2. Which of the following most often is seen in children with abusive head trauma?
   A. Epidural hemorrhage
   B. Subdural hemorrhage
   C. Cerebral contusion
   D. Hydrocephalus

3. Which of the following individuals is mandated to report child abuse?
   A. Biological parent
   B. Girlfriend/boyfriend of a parent
   C. School crossing guard
   D. School teacher

4. Which is the most useful modality to detect injuries due to abusive head trauma?
   A. Plain radiography
   B. Ultrasound
   C. MRI
   D. CT scan

CME Answer Key: 1. D; 2. B; 3. D; 4. D

In Future Issues:

Ethics: ED Professionalism