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CHAPTER **129**

Cardiac Glycoside Poisoning

Cardiac glycosides (CGs) are naturally occurring substances whose medicinal benefits have been recognized for more than 200 years [1]. Digoxin is the major CG used for medicinal purposes today. It is most widely used in the treatment of congestive heart failure and acute atrial fibrillation associated with a rapid ventricular response rate [2]. Although digoxin is responsible for most cases of CG poisoning, exposure to plant (i.e., dogbane, foxglove, lily of the valley, oleander, red squill, and Siberian ginseng) and animal (i.e., *Bufo* toad species) sources and topical aphrodisiacs can also result in serious toxicity [3–6].

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PHARMACOLOGY

Digoxin exerts a positive inotropic effect, thereby enhancing the force of myocardial contraction. Direct effects of digoxin include prolongation of the effective refractory period in the atria and the atrioventricular (AV) node, which diminishes the conduction velocity through those regions. CGs are readily absorbed through the gastrointestinal tract; digoxin has up to 80% bioavailability [7,8]. Digoxin is primarily eliminated by renal excretion and has a volume of distribution (V_d) of 5.1 to 7.4 L per kg [9]. The half-life of digoxin is 36 to 48 hours [2,8]. Changes in protein status do not appreciably affect digoxin pharmacokinetics because only 25% of the drug is bound to serum proteins. The generally accepted therapeutic serum concentration range for digoxin is 0.8 to 2.0 ng per mL for inotropic support in patients with left ventricular dysfunction. Higher concentrations (1.5 to 2.0 ng per mL) may be needed for ventricular rate control in patients with atrial dysrhythmias. Digoxin is primarily eliminated by the kidneys. In patients with renal dysfunction, digoxin clearance is reduced.

Antacid gels (not tablets) and cholestyramine impair absorption and decrease the bioavailability of digoxin [10]. The use of herbal supplements such as guar gum, St. John's wort, and wheat bran have been found to decrease plasma digoxin concentrations [11]. Whereas, concurrent medication use with amiodarone, diltiazem, erythromycin, indomethacin, omeprazole, quinidine, quinine, tetracycline, verapamil, and warfarin can increase serum digoxin concentrations [10,12]. Renal digoxin clearance is reduced by concomitant medication use such as amiloride, nifedipine, spironolactone, and triamterene [10].

Toxicity results from an exaggeration of therapeutic effects [7]. Cardiac glycosides bind to and inactivate the sodium-potassium–adenosine triphosphatase pump (Na^+-K^+-ATPase) on cardiac cell membranes [7,13]. This pump maintains the electrochemical membrane potential, vital to conduction tissues, by concentrating Na^+ extracellularly and K^+ intracellularly. When Na^+-K^+-ATPase is inhibited, the Na^+-calcium exchanger removes accumulated intracellular sodium in exchange for calcium [7]. This exchange increases sarcoplasmic calcium and is the mechanism responsible for the positive inotropic effect of digitalis [7]. Intracellular calcium overload causes delayed afterdepolarizations and gives rise to triggered dysrhythmias [7]. Increased vagal tone and direct AV depression may produce conduction disturbances. The decreased refractory period of the myocardium increases automaticity [7,13,14].

CLINICAL PRESENTATION

Differences between the presentations of patients with CG poisoning due to a single acute ingestion and those with chronic toxicity resulting from excessive therapeutic doses are illustrated in Table 129-1. Diagnosing chronic CG toxicity is more difficult because the presentation may mimic more common illnesses, such as influenza or gastroenteritis. Patients with chronic CG toxicity may present with constitutional, gastrointestinal, psychiatric, or visual complaints that may not be recognized as signs of digitalis toxicity [15,16]. Symptoms most commonly reported include fatigue, weakness, nausea, anorexia, and dizziness [15–19]. Neuropsychiatric signs and symptoms include headache, weakness, vertigo, syncope, seizures, memory loss, confusion, disorientation, delirium, depression, and hallucinations [17,20–25]. The most frequently reported visual disturbances are cloudy or blurred vision, loss of vision, and yellow-green halos or everything appearing "washed in yellow" (xanthopsia) [16,19,24,26].

Table 129-1

Cardiac manifestations of CG toxicity are common and potentially life threatening. An extremely wide variety of dysrhythmias have been reported [14,15,18,19,21,27–31]. Dysrhythmias frequently associated with CG toxicity include premature ventricular contractions, paroxysmal atrial tachycardia or atrial fibrillation with a conduction block, junctional tachycardia, sinus bradycardia, AV nodal blocks, ventricular tachycardia, and ventricular fibrillation [13–15,18,19,21,29–31]. Atrial tachycardia (enhanced automaticity) with variable AV block (impaired conduction), atrial fibrillation with an accelerated or slow junctional rhythm (regularization of atrial fibrillation), and fascicular tachycardia are highly suggestive of CG toxicity [32,33]. Bidirectional ventricular tachycardia, a narrow-complex tachycardia with right bundle-branch morphology, is highly specific for digitalis toxicity [30,34,35]. A helpful classification of digitalis-induced dysrhythmias is shown in Table 129-2 [14].

Table 129-2

True end-organ digoxin sensitivity is seen with myocardial disease, myocardial ischemia, and metabolic or electrolyte

TABLE 129-1. Characteristics of Acute and Chronic Digitalis Toxicity

Clinical Finding	*Acute Toxicity*	*Chronic Toxicity*
Gastrointestinal toxicity	Nausea, vomiting	Nausea, vomiting
Central nervous system toxicity	Headache, weakness, dizziness, confusion, and coma	Confusion, coma
Cardiac toxicity	Bradydysrhythmias, supraventricular dysrhythmias with AV block; ventricular dysrhythmias are uncommon	Virtually any dysrhythmia (ventricular or supraventricular dysrhythmias with or without AV block); ventricular dysrhythmias are common
Serum potassium	Elevated but may be normal (high levels correlated with toxicity)	Low or normal (hypokalemia secondary to concomitant diuretic use)
Serum digoxin level	Markedly elevated	May be within "therapeutic" range or minimally elevated

AV, atrioventricular.
Adapted and combined from references 15,17,20,29,63.

disturbances [35,36]. Hypokalemia, hypomagnesemia, and hypercalcemia predispose to toxicity [2,13,36–39]. The elderly are at increased risk [1,36,39,40]. Renal dysfunction, hepatic disease, hypothyroidism, chronic obstructive pulmonary disease, and drug interactions alter sensitivity to CGs [1,13,35].

DIAGNOSTIC EVALUATION

Essential laboratory tests include serum digoxin levels, electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, and electrocardiogram. Additional laboratory tests should be obtained as clinically indicated. Serum digoxin levels should be interpreted in the overall clinical context and not relied on as the sole indicator of toxicity [7,41]. Serum digoxin levels can assist in the diagnosis of CG poisoning [42] but often are unreliable indicators of toxicity [33]. A therapeutic level does not exclude poisoning, as predisposing factors can cause an individual to become poisoned despite a level within the therapeutic range. Conversely, levels above the therapeutic range do not always cause toxicity [43].

TABLE 129-2. Digitalis-Induced Dysrhythmias

- Ectopic rhythms (reentry or enhanced automaticity or both)
  - Atrial tachycardia with block
  - Atrial fibrillation
  - Atrial flutter
  - Nonparoxysmal junctional tachycardia
  - Premature ventricular contractions
  - Ventricular tachycardia
  - Ventricular flutter and fibrillation
  - "Bidirectional" ventricular tachycardia
  - Parasystolic ventricular tachycardia
- Depression of pacemakers
  - SA arrest
- Depression of conduction
  - SA block
  - AV block
  - Exit block
- Ectopic rhythms with depression of conduction
- AV dissociation (suppression of dominant pacemaker with escape pacemaker or inappropriate acceleration of lower pacemaker)
- "Triggered" automaticity
  - Accelerated junctional impulses after premature ectopic impulses
  - Ventricular dysrhythmias triggered by supraventricular dysrhythmias
  - Junctional tachycardia triggered by ventricular tachycardia

AV, atrioventricular; SA, sinoatrial.

High serum digoxin levels after an acute ingestion are not always indicative of toxicity [44,45]. Digoxin follows a two-compartment model of distribution, with relatively rapid absorption into the plasma compartment and then slow redistribution into the tissue compartment [2,21,43,45]. Serum digoxin levels most reliably correlate with toxicity when obtained after distribution is complete, which occurs 6 hours or more after oral or intravenous digoxin administration [2,43].

Naturally occurring digitalis glycosides from plants and animals can cross-react with the digoxin assay. The degree of cross-reactivity is unknown, and no good correlation has been established between serum levels of these glycosides and toxicity [3–5,46]. A false-positive digoxin assay, usually less than 3 ng per mL, may occur in patients not receiving digoxin therapy because of endogenous digoxinlike immunoreactive factors. These factors may be present in neonates and patients with renal insufficiency, liver disease, and pregnancy [47–50].

Acute poisoning may result in markedly elevated serum K^+ levels [51]. A 37% incidence of hyperkalemia has been noted in patients with severe acute poisoning [52]. Hyperkalemia may be a better indicator of end-organ toxicity than the serum digoxin level in the acutely poisoned patient [45,53,54]. In contrast, hypokalemia and hypomagnesemia are commonly seen in the chronically intoxicated patient, presumably as a result of concomitant diuretic use.

MANAGEMENT

The management of CG poisoning includes supportive care, prevention of further drug absorption, antidotal therapy, and safe disposition. Meticulous attention to supportive care and a search for easily correctable conditions, such as hypoxia, hypoventilation, hypovolemia, hypoglycemia, and electrolyte disturbances, are top priorities. All patients should have vascular access established and continuous cardiac monitoring. Patients

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with clinical toxicity or elevated serum digoxin levels should be admitted to the intensive care unit.

Prevention of further drug absorption should be addressed after life support measures have been initiated. Activated charcoal effectively binds digoxin, and multiple doses of activated charcoal enhance intestinal digoxin elimination after oral and intravenous digoxin administration [55,56]. Gastric lavage has little if any benefit in the management of digoxin toxicity.

Conventional treatment of bradydysrhythmias includes the use of atropine, isoproterenol, and cardiac pacing. Although atropine sulfate has been used with variable success in patients with digitalis toxicity exhibiting AV block [21,57,58], isoproterenol may increase ventricular ectopy and cardiac tissue may be unresponsive to electrical pacing, the fibrillation threshold may be lowered, and the pacing wire itself may induce ventricular fibrillation [15,59,60]. Digoxin-specific antibody fragments (Fab) are now considered first-line therapy in patients with symptomatic bradycardia [61].

Digoxin-specific antibody Fab is also the treatment of choice for life-threatening ventricular dysrhythmias. If this therapy is not immediately available, phenytoin and lidocaine, which depress increased ventricular automaticity without slowing AV nodal conduction, should be the initial therapy [1,15,33,62]. Bretylium has been reported to be effective [63], and amiodarone was successful in two cases refractory to other antidysrhythmics [64,65]. Intravenous magnesium, 2 to 4 g (10 to 20 mL of a 20% solution) over 1 minute, may also be useful [66–68]. Quinidine and procainamide are contraindicated in digitalis toxicity because they depress AV nodal conduction and may worsen cardiac toxicity [1]. Electrical cardioversion of the digitalis-toxic patient should be performed with extreme caution and considered a last resort. A low energy setting (e.g., 10 to 25 W per second) should be used and preparations made to treat potential ventricular fibrillation [1,4,15,47].

Hyperkalemia is common in patients with acute digoxin poisoning, and empiric administration of supplemental potassium should be avoided [45,69]. This increase in serum potassium level reflects a change in potassium distribution and not an increase in total body potassium stores. Significant hyperkalemia due to acute overdose is another indication for digoxin-specific antibody Fab. If digoxin-specific antibody Fab are not immediately available and the patient has hyperkalemia with associated electrocardiogram changes, intravenous glucose and insulin, sodium bicarbonate, continuous inhaled β agonists such as albuterol (if there is no tachydysrhythmia or ectopy), and sodium polystyrene sulfonate should be administered. Intravenous calcium should be avoided because additional calcium may enhance cardiac toxicity [18,70]. Hemodialysis may be of benefit in a CG-poisoned patient with renal failure and hyperkalemia.

Supplemental potassium may be beneficial in chronic digitalis toxicity when diuretic-induced hypokalemia is a factor. Potassium should be administered cautiously, as renal dysfunction may be the cause of digitalis toxicity. Hypomagnesemia is common in patients with chronic CG toxicity, and supplemental magnesium is recommended for such patients [66,71].

Digoxin-specific antibody Fab are antibody fragments produced by enzymatic cleavage of sheep immunoglobulin (IgG) antibodies to digoxin. Affinity chromatography is used to further isolate these fragments. The advantages of Fab over IgG include a larger V_d with increased tissue penetration, decreased immunogenicity, and increased renal excretion [52,72–74].

Digoxin-specific antibody Fab therapy is indicated for patients with dysrhythmias that threaten or result in hemodynamic compromise and patients with serum potassium greater than 5.0 to 5.5 mEq per L after acute CG overdose [32,52,53,75]. Chronically poisoned patients who are asymptomatic can often be managed with discontinuation of digoxin and close observation. The threshold for treatment with digoxin-specific antibody Fab should be lower in those patients with signs of cardiac toxicity or who have predisposing conditions such as chronic pulmonary disease, hypokalemia, hypothyroidism, renal dysfunction, or underlying cardiac disease [16]. Animal studies and case reports suggest digoxin-specific antibody Fab may be an effective treatment for patients poisoned by plant or animal sources of CG [3,5,6,76].

Digoxin-specific antibody Fab can reverse digitalis-induced dysrhythmias, conduction disturbances, myocardial depression, and hyperkalemia [52,75,77–81]. In a multicenter study, 90% of patients with digoxin or digitoxin toxicity had a complete or partial response to digoxin-specific antibody Fab therapy [52]. Complete resolution of toxicity occurred in 80% of the patients, and partial response occurred in 10%. The time to initial response from end of digoxin-specific antibody Fab infusion was within 1 hour (mean 19 minutes), and the time to complete response was 0.5 to 6.0 hours (mean 1.5 hours) [52,78]. Treatment failures have been attributed to inadequate or delayed dosing, moribund clinical state before digoxin-specific antibody Fab therapy, pacemaker-induced dysrhythmias, and incorrect diagnosis of digitalis toxicity [27,52,81].

Digoxin-specific antibody Fab dosage (number of vials) calculations 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 [78]. A 40-mg dose of digoxin-specific antibody Fab (one vial) binds 0.6 mg of digoxin. The number of vials required can be calculated by dividing the total body burden by 0.6. The body burden can be estimated from the milligram amount of an acute ingestion or by multiplying the serum digoxin level (ng per mL) by the volume of distribution of digoxin (= 5.6 L per kg times the body weight in kg) and dividing by 1,000.

A median dose of 200 mg (five vials; range, 120 to 480 mg) was required to treat effectively 150 seriously digitalis-toxic patients with a mean serum digoxin level of 8.0 ng per mL [52]. A severely toxic patient in whom the quantity ingested acutely is unknown should be given 5 to 10 vials at a time and the clinical response 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 1 to 2 vials of digoxin-specific antibody 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.

The dose of digoxin-specific antibody Fab needed to treat nondigoxin CG poisoning is unknown but likely to be greater than that necessary for digoxin poisoning. Starting with 5 to 10 vials and repeating this dose as necessary is a reasonable approach.

Free digoxin levels are decreased to zero within 1 minute of digoxin-specific antibody Fab therapy, but total serum digoxin levels are markedly increased (Fig. 129-1) [52,72,78,82,83]. Because most assay methods measure total (bound and free)

Fig.129-1

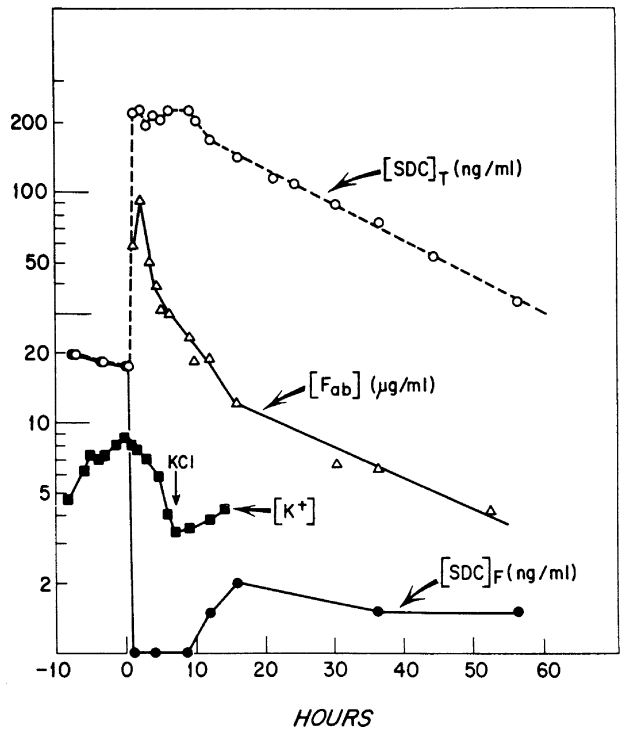

FIGURE 129-1. Time course of serum potassium concentration in mEq per L, $[K^+]$ (*squares*); total serum digoxin concentration, $[SDC]_T$ (*open circles*); free serum digoxin concentration, $[SDC]_F$ (*closed circles*); and serum concentration of sheep digoxin-specific Fab fragments, [Fab] (*triangles*). The scale on the vertical axis is logarithmic. On the horizontal axis, 0 denotes the time at which administration of digoxin-specific Fab fragments was started. [Reprinted from Smith TW, Haber E, Yeatman L, et al: Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 294:797, 1976, with permission. Copyright © 2006 Massachusetts Medical Society. All rights reserved.]

digoxin, very high digoxin levels are seen after digoxin-specific antibody Fab treatment, but they have no correlation with toxicity [47,79,84]. Serum levels may be unreliable for several days after digoxin-specific antibody Fab therapy [82]. The digoxin-Fab complex is excreted in the urine and has a half-life of 16 to 20 hours [73,80,83]. In patients with renal failure, elimination of the digoxin-Fab complex is prolonged and free digoxin levels gradually increase over 2 to 4 days after digoxin-specific antibody Fab administration [40,83,85,86]. In one report of 28 patients with renal impairment given digoxin-specific antibody Fab, only one patient had recurrent toxicity, which occurred 10 days after digoxin-specific antibody Fab treatment and persisted for 10 days [40]. Monitoring of free digoxin concentrations may be beneficial for titrating effect in those patients reliant on the inotropic action of digoxin, detecting rebound toxicity in patients with renal impairment, assessing the need for further treatment with digoxin-specific antibody Fab, or in guiding the reinstitution of digoxin therapy [84]. Hemodialysis has not been reported to enhance digoxin-Fab complex elimination [83,84].

Digoxin-specific antibody Fab therapy has been associated with mild adverse drug events such as rash, flushing, and facial swelling [27,52,81,87]. Neither acute anaphylaxis nor serum sickness has been described, however [52,81,88]. Before digoxin-specific antibody Fab administration, an asthma and allergy history should be obtained. Intradermal skin testing should be considered in high-risk patients. If a patient with a positive skin test is dying, however, the risk-benefit ratio obviously favors treatment [81]. A precipitous drop in the serum potassium, recurrence of supraventricular tachydysrhythmias previously controlled by digoxin, and development of cardiogenic shock in a patient dependent on digoxin for inotropic support have all been associated with digoxin-specific antibody Fab therapy [52,81,89]. Recurrent toxicity has been observed in 3% of patients [81]. In most, it was attributed to inadequate initial dose of digoxin-specific antibody Fab dosing and reversed with a repeat dose [81].

Patients who receive digoxin-specific antibody Fab require continued monitoring in an intensive care unit for at least 24 hours. Those with elevated drug levels resulting from chronic therapy who are hemodynamically stable can be observed on a telemetry unit. Discontinuing the use of digoxin or decreasing the dose, modifying predisposing factors, and closely monitoring subsequent therapy are necessary to avert further toxic episodes. Patients with suicidal ingestions should have a psychiatric evaluation before discharge.

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