Digoxin toxicity

Pharmacokinetics

Digoxin is bound to plasma proteins (primarily albumin). Because polarity also influences protein binding, digoxin is bound to a lesser degree than digitoxin (25 percent versus 97 percent). Agents that are highly protein bound may displace digitoxin from serum proteins and increase free (i.e., active) drug levels.

Digoxin is widely distributed in body tissues. The highest concentrations are found in muscle. Myocardial concentrations are about 30 times higher than serum levels. Peak serum concentrations occur within minutes of an intravenous dose and 1–2 hours after an oral dose. The final Vd is very large for digoxin (5–7.3 L/kg in adults), rendering hemodialysis relatively ineffective in removing these glycosides. Volumes of distribution are higher in infants and neonates and lower in the elderly (owing to decreased muscle mass), those with renal failure and hypothyroidism, and those taking a variety of drugs.

DGs (digitalis) are eliminated by hepatic metabolism as well as by urinary excretion of unchanged drug. The more polar digoxin is predominantly (60–80 percent) eliminated by urinary excretion, whereas digitoxin is predominantly eliminated by hepatic metabolism. About 8 percent of digitoxin is metabolized to digoxin. Elimination follows first-order kinetics. The elimination half-life of digoxin is about 36 hours. Inactive products of hepatic metabolism (i.e., glucuronide and sulfate conjugates) are excreted in the bile and urine. Enterohepatic recirculation appears to be responsible for the long half-life of digitoxin.

The half-life of digoxin is increased in those with impaired renal or hepatic function.

Pharmacodynamics

A variety of factors may affect dose-response and concentration-effect relationships. Those that increase the effect of DGs may result in clinical toxicity occurring at therapeutic doses and drug levels. Hypokalemia and hypomagnesemia are the most common and readily correctable causes of such toxicity. Not only does hypokalemia potentiate the electrophysiological

effects of DGs, it increases their tissue binding and decreases their renal tubular excretion. Magnesium is important because it blocks calcium channels and modulates sympathetic activity. Hypoxia has a variable effect: by blocking impulse formation, it may decrease tachydysrhythmias owing to increased automaticity; by impairing conduction, it may increase bradydysrhythmias and re-entrant tachydysrhythmias.

Pharmacodynamic Interactions Involving Digitalis Glycosides

Underlying Mechanism	Causes
Increased DG Effect	
Disease/conditions	Advanced myocardial disease
	Acid-base disturbances
	Active myocardial ischemia
	Chronic obstructive pulmonary disease
	Extremes of age
	Hypothyroidism
Hypercalcemia	Calcium salts
Hypokalemia	Amphotericin B
	β-Adrenergic agonists
	Corticosteroids
	Glucagon/glucose/insulin
	Laxatives
	Loop diuretics
	Thiazide diuretics
Hypomagnesemia	Diuretics
Decreased DG Effect	
Hyperkalemia	Captopril
	Potassium salts
	Potassium-sparing diuretics
Hypocalcemia	Hyperphosphatemia

Underlying Mechanism	Causes
	Hypoparathyroidism
Variable Effect	
Decreased sympathetic tone	β-Adrenergic receptor antagonists
	Bretylium
	Guanethidine
	Halothane
	Methyldopa
	Reserpine
Increased sympathetic tone	β-Adrenergic receptor agonist bronchodilators
	Reserpine
	Succinylcholine
	Sympathomimetics
	Theophylline
Decreased vagal tone	Anticholinergic agents
Increased vagal tone	Cholinergic agents
Impaired excitability	Hypoxemia

Pathophysiology

In patients with heart failure, therapeutic doses of DGs increase the force and velocity of myocardial contraction (i.e., contractility), primarily by increasing the availability of cytosolic calcium ions (Ca^{2+}) to the contractile proteins actin and myosin in the sarcoplasmic reticulum. This increased calcium availability enhances excitation-contraction coupling during systole through the normal sarcolemmal exchange of $Ca^{2+}$for sodium ions (Na^{+}) and the ability of DGs to bind to and reversibly inhibit sodium, potassium adenosine triphosphatase (Na^{+}, K^{+}-ATPase). Na^{+}, K^{+}-ATPase is the sarcolemmal enzyme that maintains the resting membrane potential by actively transporting Na^{+} out of cardiac muscle cells in exchange for K^{+}. Inhibition of this enzyme results in increased intracellular Na^{+}, enhanced membrane cycling of Na^{+} and Ca^{2+}, and increased intracellular Ca^{2+} available for uptake and release by the sarcoplasmic reticulum. Increased

intracellular Ca^{2+} may also trigger spontaneous calcium influx and release, resulting in transient late depolarization (afterdepolarization) and enhanced automaticity.

DGs also act on vascular smooth muscle and on the nervous system. In patients with heart failure, vasodilation results from increased vagal activity (via cholinergic inhibition of norepinephrine release at adrenergic-smooth muscle junctions) and decreased sympathetic nervous system tone (via inhibition of sympathetic outflow from the CNS and by enhancing baroreceptor sensitivity). Decreased after load and improved cardiac function are the beneficial results.

In toxic amounts or with rapid administration, DGs may cause vasoconstriction as a result of increased intracellular Ca^{2+} and stimulation of vasomotor centers. Adverse GI effects also appear to be centrally mediated. CNS toxicity is probably due to inactivation of Na^{+}, K^{+}-ATPase, resulting in altered ionic transfer across excitable neuronal membranes with consequent membrane irritability and instability. Adverse GI and CNS effects can occur at therapeutic as well as toxic doses. Gynecomastia, which may occur during chronic therapy, may be due to a direct estrogenic effect or to altered estrogen metabolism secondary to coexistent heart failure.

The electrophysiological effects of DGs are due to their indirect action on the autonomic nervous system as well as their direct actions on cardiac muscle, pacemaker, and conduction cells. At therapeutic doses, DGs decrease automaticity and conduction velocity through the AV node primarily as a consequence of their indirect sympatholytic and vagotonic effects. Vagotonic effects result from cholinergic activation of K^{+} currents and inhibition of Ca^{2+} currents and include membrane hyperpolarization, decreased atrial action potential (AP) duration, and prolongation of the effective refractory period (ERP) of the AV node.

Direct effects include reduction of the AP duration, prolongation of the ERP, and reduction (of the negativity) of the resting membrane potential of the AV node (resulting in decreased amplitude and decreased rate of rise of the AP). These actions are probably due to inhibition of Na^{+}, K^{+}-ATPase with subsequent changes in Na^{+}, K^{+}, and Ca^{2+} concentrations and currents. Shortening of the AP duration is usually accompanied by an increase in the slope of phase 4 (spontaneous diastolic) depolarization and enhanced automaticity of the sinoatrial (SA) node, effects that are directly related to

the intracellular Ca^{2+} concentration and inversely related to the intracellular K^+ concentration.

In contrast, at toxic doses, DGs directly depress SA node automatically and conduction at the AV node. They also increase sympathetic activity and intracellular Ca^{2+}, resulting in an increase in automaticity and afterdepolarizations. Increased automaticity and afterdepolarizations which reach the AP propagation threshold may result in triggered tachydysrhythmias. Because effects on automaticity and conduction in muscle, nodal, and conducting cells are nonuniform, they also promote the development of re-entrant tachydysrhythmias. Following acute DG overdose, inhibition of NA^+, K^+-ATPase may result in increased extracellular K^+ (i.e., hyperkalemia).

Manifestations of Digitalis Glycoside Toxicity

Central Nervous System
Level of consciousness: confusion, lethargy, delirium, coma, convulsions
Psychiatric: depression, emotional lability, unusual dreams, hallucinations (visual), psychosis
Other: dizziness, fatigue, headache, malaise, weakness, paresthesias, vertigo, aphasia, facial neuralgia
Gastrointestinal
Anorexia, weight loss, nausea, abdominal pain, vomiting, diarrhea
Cardiovascular System
Nonspecific: Diaphoresis, lightheadedness, pallor, palpitations, shortness of breath, syncope
Bradydysrhythmias: First-degree AV block; sinus bradycardia; sinus arrest or exit block :asystole
Tachydysrhythmias: ventricular premature beats, atrial premature beats; ventricular fibrillation; fascicular tachycardia
Both: atrial fibrillation or flutter with a slow ventricular rate or third-degree AV block
Uncommon: increased congestive heart failure, mesenteric ischemia
Miscellaneous

Gynecomastia (chronic use); hyperkalemia (acute overdose), allergic reactions (rare)

Acute Versus Chronic Toxicity

Acute and chronic poisoning differs in a number of respects. Patients with acute (oral) overdose are typically asymptomatic on presentation. They may develop extracardiac symptoms within an hour or two of ingestion, but cardiac effects do not usually develop until 6 or more hours after ingestion. In contrast, with chronic poisoning extracardiac effects typically have been present for days or weeks, and patients often present with signs and symptoms of dysrhythmias as well as extracardiac toxicity. Life-threatening dysrhythmias usually occur within 24 hours of acute digoxin overdose and within 5 days of acute digitoxin overdose but can occur at any time during chronic therapy.

Bradydysrhythmias are typically seen after acute overdose whereas tachydysrhythmias are more common in chronic poisoning. Because acute poisoning most often occurs in children and young adults, whereas chronic poisoning usually occurs in older patients, it is unclear whether this finding relates to the acuity of poisoning or to the presence or absence of underlying cardiac disease.

The serum potassium may be high in patients with acute poisoning but is normal or low in those with chronic poisoning (depending on the concomitant use of diuretics). In the setting of acute overdose, the degree of hyperkalemia reflects the effect of DGs on target enzymes and may correlate with clinical toxicity more accurately than drug levels. Serum drug levels (SDLs) are usually markedly elevated in acute poisoning but minimally elevated or even therapeutic in chronic poisoning. The half-life of digoxin may be shortened following acute overdose but appears to be unchanged in chronic poisoning.

LABORATORY STUDIES

The evaluation of symptomatic patients should include a 12-lead ECG, serum calcium and magnesium levels as well as routine electrolytes, BUN and serum creatinine levels, oxygen saturation, and an SDL. Arterial blood gases and a chest radiograph should be obtained in those with dysrhythmias, hypoxia, or hypotension.

Serum Digoxin Level

The SDL ideally should be obtained at least 6 hours after the most recent dose in patients with chronic drug exposure. It should be measured immediately in unstable patients, if chronic non pharmaceutical DG poisoning is suspected, and 1 to 2 hours after acute DG ingestion because the result can be used to exclude or confirm the exposure. Serial SDLs may be useful in assessing the adequacy of GI decontamination and enhanced elimination therapy and in determining the duration of monitoring.

Management

General Measures

The management of DG poisoning includes supportive care, prevention of further DG absorption, enhancement of DG elimination, and in severe cases, the use of the specific antidote digoxin Fab antibodies as always, supportive care is the highest priority. Supportive measures include the establishment of intravenous access, continuous cardiac monitoring, and correction of acid-base and electrolyte abnormalities (including calcium and magnesium) and oxygenation and ventilatory compromise, as well as standard advanced cardiac life support (ACLS) therapies. Unless otherwise noted, standard doses and contraindications should be assumed for the drugs discussed.

Management of Digitalis Glycoside Poisoning

General Measures
Supportive care: ACLS drugs for dysrhythmias (see below); Correction of acid-base, electrolyte, calcium, magnesium, oxygenation and ventilatory abnormalities
Bradydysrhythmias : atropine, electrical pacing, phenytoin; other drugs are of doubtful benefit
Ventricular tachydysrhythmias : electrical cardioversion/defibrillation for unstable or pulseless dysrhythmias; lidocaine, magnesium sulfate, bretylium, phenytoin, procainamide
Supraventricular tachydysrhythmias: esmolol, diltiazem; procainamide and electrical cardioversion for dysrhythmias
Prevention of DG absorption: oral activated charcoal (0.5–1 g/kg); gastric

aspiration or lavage and syrup of ipecac may increase vagal tone and precipitate bradydysrhythmias
Enhancement of DG elimination: repeated doses of activated charcoal (0.5 g/kg every 2 to 4 hr); repetitive doses of cholestipol and cholestyramine less effective and less well tolerated; hemodialysis, hemofiltration, and hemoperfusion are relatively ineffective
Specific Therapy with Digoxin-Specific Fab
Indications: dysrhythmias associated with hypotension or organ ischemia which are not immediately responsive to conventional drugs, which recur despite such therapy, or require electrical cardioversion/defibrillation or pacing; hyperkalemia (serum $K^+ \geq 5.5$ meq/L) in acute poisoning
Calculated dosage(number of 38-mg vials of Digibind):
Acute overdose(based on amount ingested)
2 × dose of oral digoxin elixir or tablets (in mg) × 0.8
2 × dose of oral digitoxin, liquid-filled digoxin capsules, or intravenous digoxin (in mg)
Chronic overdose(based on serum drug level)
2 × serum digoxin level (ng/mL) × 5.6 × body weight (kg)/1000
1.7 × serum digitoxin level (ng/mL) × 0.56 × body weight (kg)/1000
Empirical dose(number of 38-mg vials of Digibind)
Acute DG overdose: 5–15 vials
Chronic DG overdose: 1–4 vials

Supplemental Potassium and Magnesium

These electrolytes may be beneficial in patients with chronic DG poisoning who have deficits of these ions as a result of diuretic use. They should be given cautiously if renal failure is the underlying cause of toxicity. Hyperkalemia following acute overdose may be treated with digoxin Fab antibodies, glucose and insulin, sodium bicarbonate, and the exchange resin sodium polystyrene sulfonate. Calcium is contraindicated due to its potential to exacerbate dysrhythmias. The effects of glucose and insulin and sodium bicarbonate are transient, whereas those of resin and antidotal therapy are not. Because the serum potassium level reflects the severity of acute poisoning as well as the success of antidotal therapy, and hyperkalemia in

this setting is a result rather than a cause of poisoning and may not itself be harmful, the necessity and wisdom of correcting it with measures other than antidotal therapy are not clear.