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Digoxin Use in Modern Medicine

Shan Chen, PharmD Candidate, Troy Khusial, PharmD Candidate, Dipen Patel, PharmD Candidate, Satinder Singh, PharmD Candidate, Tatyana Yakubova, PharmD Candidate, Amy Wang, PharmD, BCPS, MBA, Timothy Nguyen, PharmD, BCPS, CCP, FASCP

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Abstract and Introduction

Abstract

Digoxin, a cardiac glycoside, has inotropic effects in addition to effects on cardiac output. It is used to treat heart failure and atrial fibrillation and has other off-label uses. Digoxin has been shown to reduce hospitalization rates without affecting mortality rates in patients with heart failure. Digoxin is effective for rate control in patients with atrial fibrillation, but its influence on mortality rates is a source of controversy. The use of digoxin is limited because the drug has a narrow therapeutic index and requires close monitoring. Digoxin can cause many adverse events, is involved in multiple drug interactions, and can result in toxicity. Despite its limitations, however, digoxin has a place in therapy.

Introduction

Digoxin is a cardiac glycoside derived from the purple foxglove flower. In 1785, the English chemist, botanist, and physician Sir William Withering published his findings that *Digitalis purpurea* could be used to treat cardiac dropsy (congestive heart failure; CHF).[1] Digoxin has been in use for many years, but was not approved by the FDA for treatment of heart failure (HF) until the late 1990s.[2,3] Another FDA indication for digoxin is atrial fibrillation (AF).[3] Digoxin also has numerous off-label uses, such as in fetal tachycardia, supra-ventricular tachycardia, cor pulmonale, and pulmonary hypertension.[3]

Digoxin acts by inhibiting the sodium-potassium adenosine triphosphatase pump, promoting sodiumcalcium exchange; this results in an upsurge of intracellular calcium, thereby increasing myocardial contractility. Digoxin also has parasympathomimetic properties. By increasing vagal tone in the sinoatrial and atrioventricular (AV) nodes, it slows the heart rate and AV nodal conduction.[4] provides a brief overview of digoxin.

Table 1. Brief Summary of Digoxin

Dosing	Dosage Adjustment	Target Serum Concentration	Bioavailability	Pharmacokinetics
Heart Failure				
LD: not recommended; MD: 0.125–0.2 mg daily	MD: CrCl >120 mL/min—0.25 mg once daily; CrCl 80–120 mL/min—0.25 mg alternating with 0.125 mg once daily; CrCl 30–80 mL/min—0.125 mg once daily; CrCl <30 mL/min—0.125 mg q48h. Patients >70 y should receive 0.125 mg daily or every other day. Reduce by 50% in ESRD	0.5–0.9 ng/mL	Oral: 70%; capsule: 90%; elixir: 80%; IV: 100%	Onset of action: IV—15–30 min; po—30–120 min Peak effect: IV— 1–3 h; po—2–6 h
Atrial Fibrillation				
LD: 0.25 mg po/IV q2h (max 1.5	MD: CrCl >50 mL/min—no adjustment necessary; CrCl 10–50 mL/min—25%-75% of normal daily dosage q36h; CrCl <10			

mg/24 h); MD: 0.125–0.375 mg po/IV daily	mL/min—10%-25% of normal daily dosage q48h. Continuous RRT: 25%-75% of normal daily dosage q36h	0.8–1.2 ng/mL	NA	NA

CrCl: creatinine clearance; ESRD: end-stage renal disease; LD: loading dose; max: maximum; MD: maintenance dose; min: minute; NA: not applicable; RRT: renal replacement therapy.

Source: References 2, 3, 5, 6.

Digoxin has been around for centuries, but its use has been limited by several factors. Because of its narrow therapeutic window, digoxin requires close monitoring. Also, two major drawbacks of digoxin are its adverse effects (AEs) and multiple drug interactions. Despite these limitations, digoxin still plays a role in therapy for HF, AF, and several off-label uses. It is considered adjunctive therapy, rather than first-line therapy, for these indications.[5,6]

According to current guidelines, digoxin may be used as additive therapy with beta-blockers and/or ACE inhibitors/angiotensin receptor blockers (ACEIs/ARBs) in the management of CHF.[5] Digoxin possesses negative chronotropic properties and has been shown to decrease morbidity in patients with AF. It is used mainly as add-on therapy in AF patients whose heart rates are not adequately controlled on beta-blockers alone.[6] Because of its positive inotropic effects, digoxin may have benefits in pulmonary arterial hypertension (PAH), but more studies are needed to assess long-term effects in this patient population.[7]

Digoxin and HF

CHF is a myocardial dysfunction caused by the contractile performance of the heart, ventricular relaxation/filling of the heart, or both. In CHF, contractility is decreased, which in turn reduces cardiac output. Digoxin is effective in patients with CHF because of its positive inotropic properties. Although studies have shown that digoxin reduces hospitalizations and improves symptoms of HF, it has not been proven to decrease mortality.

Digoxin's role in HF has been assessed in numerous trials. One double-blind, controlled trial of digoxin for CHF treatment randomized subjects with cardiac dysfunction to digoxin or placebo for 7 weeks.[8] Placebo subjects deteriorated more quickly than those taking digoxin. Cardiac function, as measured by ejection fraction (EF), was significantly improved in digoxin patients.[8] Many other clinical trials showed that digoxin's positive inotropic effects were useful in the management of CHF.

According to the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline on managing HF, digoxin improves symptoms, quality of life, and exercise tolerance in patients with mild-to-moderate HF, regardless of the underlying rhythm (normal sinus rhythm or AF).[5] Therefore, digoxin may be considered as add-on therapy for patients who have persistent symptoms of HF despite treatment with ACEI/ARBs and/or beta-blockers. Digoxin may also be considered in patients with stage C HF (structural heart disease with prior or current symptoms of HF) or stage D HF (HF symptoms at rest and recurrent hospitalizations despite therapy). HF patients should not take digoxin without an ACEI or beta-blocker. Although digoxin is prescribed for patients with HF and AF, concomitant beta-blocker therapy is usually more effective at controlling ventricular response, particularly during exercise.[5,6]

The initial dosage of digoxin is 0.125 mg to 0.25 mg by mouth daily. The dosage must be adjusted based on renal function and age (). The target serum level of digoxin in HF is 0.5 ng/mL to 0.9 ng/mL.[5]

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LD: 0.25 mg po/IV q2h (max 1.5 mg/24 h); MD: 0.125–0.375 mg po/IV daily	MD: CrCl >50 mL/min—no adjustment necessary; CrCl 10–50 mL/min—25%-75% of normal daily dosage q36h; CrCl <10 mL/min—10%-25% of normal daily dosage q48h. Continuous RRT: 25%-75% of normal daily dosage q36h	0.8–1.2 ng/mL	NA	NA

CrCl: creatinine clearance; ESRD: end-stage renal disease; LD: loading dose; max: maximum; MD: maintenance dose; min: minute; NA: not applicable; RRT: renal replacement therapy.

Source: References 2, 3, 5, 6.

Morbidity and Mortality in HF

Digoxin has been shown effective for decreasing HF symptoms, and its effect on morbidity and mortality has been assessed as well. A randomized, double-blind, placebo-controlled trial was conducted to examine mortality and morbidity in HF patients with a left ventricular EF of ≤0.45 who were receiving digoxin therapy.[9] There were no baseline between-group differences, and follow-up was a mean of 37 months. The primary outcome was mortality; secondary outcomes were a composite of mortality from cardiovascular causes, death from worsening HF, and hospitalization for other causes (digoxin toxicity). In the intent-to-treat analysis, there were 1,181 deaths in the digoxin group and 1,194 deaths in the placebo group (34.8% vs. 35.1%, 95% CI 0.91–1.07, P = 0.8 [nonsignificant]). Fewer digoxin patients than placebo patients were hospitalized (910 and 1,180, respectively; risk ratio 0.72, 95% CI 0.66-0.79, P <.001). Also, the risk associated with the combined outcome of death due to worsening HF or hospitalization was lower in the digoxin group (1,041 vs. 1,291, P <.001). The conclusion was that although digoxin had no effect on overall mortality, it significantly decreased the overall number of hospitalizations attributed to worsening HF.[9]

Digoxin and AF

AF is a common arrhythmia in which irregular electrical impulses are conducted through the heart. These irregular electrical impulses lead to uncoordinated and inefficient heart contractions. As a result, blood pools in the heart, increasing the likelihood of a blood clot, which may lead to serious consequences such as myocardial infarction or stroke. AF can be managed by utilizing either rate or rhythm control agents. Digoxin exhibits its benefit in AF by controlling the heart rate.[6]

One multicenter, randomized, double-blind, crossover trial evaluated the benefit of digoxin versus placebo in 43 patients with paroxysmal AF.[10] Patients were aged ≥18 years and had one or more symptomatic episodes of self-terminating AF per month. The study endpoint was time to occurrence of one or two AF episodes as documented by patient-activated monitors. The median time to two episodes was 13.5 days for placebo and 18.7 days for digoxin (P <.05). The median time to one episode was 3.5 days for placebo, compared with 5.4 days for digoxin (P <.05). Mean ventricular rates during an AF episode were 138 ± 32 beats per minute (bpm) and 125 ± 35 bpm on placebo and digoxin, respectively (P <.01). It was concluded that digoxin reduced the frequency of symptomatic AF episodes and that the effect, although small, may be due to a reduction in ventricular rate rather than an antiarrhythmic action.[10]

A recent retrospective cohort study of 122,465 newly diagnosed AF patients (mean age 72 years) found a higher cumulative mortality rate in those treated with digoxin than in those who were untreated (P <.001).[11] Digoxin treatment was an independent predictor of mortality despite confounders such as age, kidney function, drug adherence, and history of cardiovascular complications.[11] The impact of digoxin on mortality in AF patients needs further investigation.

According to the ACCF/AHA guideline, clinical results with regard to symptoms are similar whether AF is managed by rate control or rhythm control.[6] Although symptom relief is comparable with both methods, rhythm-control therapy confers increased exercise tolerance. Digoxin is one of the medications used to manage heart rate, which is considered controlled when the ventricular response is 60 to 80 bpm at rest and 90 to 115 bpm during moderate exercise. First-line therapies for rate control include diltiazem, verapamil, esmolol, and other beta-blockers.[6] Compared with digoxin, these medications have stronger recommendations and better evidence. Digoxin is not considered first-line therapy, owing to its narrow therapeutic index (which requires monitoring) and numerous drug interactions. Patients at higher risk for digoxin toxicity (i.e., renal impairment, elderly, multiple drug interactions) should be monitored more frequently than healthy, young patients with no comorbidities or concomitant medications.

Digoxin and PAH

PAH is a progressive disease in which restricted blood flow through the pulmonary arteries leads to increased pulmonary vascular resistance and, ultimately, right HF. PAH is defined by an increase in pulmonary arterial pressure of >25 mmHg at rest or 30 mmHg with exercise.[7] Current treatment options for PAH include supportive therapy and concurrent medications including digoxin, diuretics, warfarin, and calcium channel blockers (CCBs).

Pulmonary hypertension is often associated with neurohormonal sympathetic activation, so digoxin may be used because of its sympatholytic properties. Current PAH guidelines briefly mention the use of digoxin for its beneficial effects on cardiac output and on circulating norepinephrine. Hence, the use of digoxin in PAH patients is based on the physician's clinical judgment.[11] The use of digoxin in PAH has not been evaluated extensively, and its mechanism of action is unknown.[12,13] No prospective, randomized trials have been conducted.[13,14]

Warnings and Precautions

Patients with significant sinus or AV block should not be given digoxin without first having a permanent pacemaker implanted. Digoxin should be used with caution with other agents that can depress sinus or AV nodal function (e.g., beta-blockers, nondihydropyridine CCBs). Digoxin also has numerous other drug interactions, which are outlined in . Clinicians should be aware of such interactions and monitor for digoxin toxicity, as well as check levels frequently.[5]

Table 2. Digoxin Drug Interactions

Precipitant	Effect on Digoxin Concentration	Comments
Alprazolam	Increase	Elderly patients are especially likely to have elevated serum digoxin concentrations. Possible mechanism: reduced renal clearance of digoxin. Monitor concentrations and observe patient for digoxin toxicity
Aluminum salts (aluminum hydroxide, magaldrate)	Decrease	Digoxin absorption is decreased. Give digoxin 2 h before administering aluminum salts
Amphotericin B	Increase	Amphotericin B–induced hypokalemia may increase risk of digoxin toxicity
Antiarrhythmics		

(amiodarone, dronedarone, propafenone, quinidine)	Increase	These agents inhibit Pgp, thereby reducing digoxin clearance. Consider reducing digoxin by 30%-50% upon initiating antiarrhythmic
Anticholinergics	Increase	Decrease in GI motility may cause increased digoxin absorption
Antineoplastics (bleomycin, carmustine, cyclophosphamide, cytarabine, doxorubicin, methotrexate, vincristine)	Decrease	Decreased GI absorption of digoxin may lead to decreased digoxin concentrations. Substitute liquid form or liquid-containing digoxin capsules for tablet form
Azole antifungals (itraconazole, ketoconazole)	Increase	Inhibition of digoxin metabolism and clearance responsible for increased digoxin concentrations. Monitoring and possible dosage reductions of digoxin are warranted
Beta-blockers	Increase	Digoxin and beta-blockers slow AV conduction and decrease HR, increasing risk of bradycardia. Carvedilol may elevate digoxin concentrations, increasing risk of toxicity. Monitor digoxin concentrations and HR. Consider 25% dosage reduction in children
Bile-acid sequestrants	Decrease	These agents bind to digoxin, decreasing GI absorption and enterohepatic recycling. Separate administration of sequestrant and digoxin by as much as possible and adjust digoxin dosage as needed
CCBs (diltiazem, nifedipine, verapamil)	Increase	Non-DHP CCBs (e.g., verapamil, diltiazem) in combination may be helpful in controlling AF, but additive effects on AV-node conduction may result in heart block. Diltiazem, nisoldipine, and verapamil may increase digoxin concentrations by inhibiting renal and/or extrarenal digoxin clearance. Monitor serum digoxin concentrations closely and adjust dosage accordingly
Corticosteroids	Increase	Electrolyte disturbances caused by corticosteroids may predispose patient to digitalis-induced arrhythmia. Monitor potassium and magnesium, supplementing if necessary
Loop diuretics (furosemide)	Increase	Diuretics may cause electrolyte disturbances and predispose patient to digitalis-induced arrhythmia. Monitor potassium and magnesium, supplementing if necessary
Macrolide antibiotics (azithromycin, clarithromycin, erythromycin)	Increase	Antibiotics decrease inactivation of digoxin by bacterial metabolism in lower intestine, increasing digoxin's bioavailability. Effect may persist several wk after antibiotic stopped
Metoclopramide	Decrease	Increase in GI motility may cause decreased digoxin absorption
Potassium-sparing diuretics (amiloride, spironolactone)	Increase/decrease	May decrease positive inotropic effects of digoxin, and digoxin serum concentrations may be elevated. Spironolactone interferes with digoxin assay, resulting in falsely elevated concentrations. Monitor patient closely and watch for potentially false digoxin concentrations
Quinine	Increase	Concomitant use causes decreased biliary clearance of digoxin, which increases digoxin serum concentration and risk of toxicity
Rifamycins (rifampin)	Decrease	May increase digoxin clearance, leading to decreased serum digoxin

		concentrations
SSRIs (fluoxetine, paroxetine)	Increase	May displace digoxin from protein binding, resulting in increased serum digoxin concentrations
St. John's wort	Decrease	This Pgp inducer speeds up digoxin metabolism, leading to decreased digoxin concentrations
Sucralfate	Decrease	Concomitant use may result in decreased digoxin concentrations and efficacy. Separate administration by ≥2 h
Sympathomimetics (dopamine, epinephrine)	Increase	Coadministration may cause increased risk of cardiac arrhythmias. Mechanism unknown
Telmisartan	Increase	Coadministration leads to ~50% increase in peak digoxin levels and 20% increase in trough digoxin levels, which may cause toxicity
Tetracyclines	Increase	Tetracycline may alter GI flora, allowing for increased digoxin absorption
Thiazide diuretics (hydrochlorothiazide)	Increase	Diuretic-induced electrolyte disturbances may predispose patients to digoxin toxicity. Monitor potassium and magnesium, supplementing if needed
Thioamines (methimazole, propylthiouracil)	Increase	Hyperthyroid patients who become euthyroid have decreased digoxin clearance, leading to increased serum digoxin concentrations
Thyroid hormone (levothyroxine)	Decrease	Hypothyroid patients who become euthyroid develop increased digoxin clearance, resulting in decreased serum digoxin concentrations
Vasopressin receptor antagonists (conivaptan)	Increase	Conivaptan decreases digoxin clearance; this may increase serum digoxin concentrations, causing toxicity

AF: atrial fibrillation; AV: atrioventricular; CCB: calcium channel blocker; DHP: dihydropyridine; GI: gastrointestinal; HR: heart rate; Pgp: P-glycoprotein; SSRI: selective serotonin reuptake inhibitor.

Source: References 2, 3.

If administered with careful attention to dosage and factors that may alter the drug's metabolism, digoxin is well tolerated by most patients with HF.[15] AEs occur mainly when digoxin is administered in higher dosages, especially in the elderly, and it should be noted that larger dosages have not been found clinically beneficial.[5]

The major AEs of digoxin () include cardiac arrhythmias (ectopic and heart block), gastrointestinal symptoms (nausea, vomiting, anorexia), and neurologic complaints (visual disturbances, disorientation, confusion). Although overt digoxin toxicity occurs when serum levels are >2 ng/mL, toxicity may occur with lower digoxin levels, especially if electrolyte abnormalities such as hypokalemia and hypomagnesemia coexist.[5]

Table 3. Common Signs and Symptoms of Digoxin Toxicity

Noncardiac Adverse Effects	
Anorexia	Cardiac Adverse Effects
Nausea/vomiting	Ventricular arrhythmias

Abdominal pain	Atrioventricular block
Visual disturbances: halos, photophobia, red-green or yellow-green vision	Atrial arrhythmias
Fatigue, weakness	Sinus bradycardia
Confusion, delirium, psychosis	

Source: References 2, 3.

Digoxin Toxicity

Owing to its narrow therapeutic index, digoxin toxicity is quite common. Clinical manifestations of acute digoxin toxicity include arrhythmias, anorexia, confusion, and hyperkalemia.[3] Chronic digoxin toxicity presents similarly, with the addition of halos, green-yellow vision, blindness, lethargy, and fatigue ().[3] Digoxinspecific antibody (DigiFab) is used to treat digoxin poisoning. DigiFab binds to free digoxin, forming a complex that is excreted renally, thereby reducing serum digoxin concentrations.[3]

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Fatigue, weakness	Sinus bradycardia
Confusion, delirium, psychosis	

Source: References 2, 3.

Conclusion

The use of digoxin has been limited because the agent has a narrow therapeutic index and requires close monitoring. Digoxin can lead to many AEs and has multiple drug interactions. Despite its limitations, digoxin still has a place in therapy for HF, AF, and numerous off-label uses. It is considered adjunctive therapy, rather than first-line therapy.

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