Title
Digitalis toxicity: a fading but crucial complication to recognize.

Journal
The American journal of medicine, 125(4)

ISSN
1555-7162

Authors
Yang, Eric H
Shah, Sonia
Criley, John M

Publication Date
2012-04-01

Peer reviewed

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Digitalis Toxicity: A Fading but Crucial Complication to Recognize

Eric H. Yang, MD,[a] Sonia Shah, MD,[b] John M. Criley, MD[b]

[a]Division of Cardiology, Department of Medicine, University of California at Los Angeles; [b]Division of Cardiology, Department of Medicine, Harbor-UCLA Medical Center, Torrance, Calif.

ABSTRACT

Digoxin usage has decreased in the treatment of congestive heart failure and atrial fibrillation as a result of its inferiority to beta-adrenergic inhibitors and agents that interfere with the deleterious effects of the activated renin-angiotensin-aldosterone system. As a result of reduction of usage and dosage, glycoside toxicity has become an uncommon occurrence but may be overlooked when it does occur. Older age, female sex, low lean body mass, and renal insufficiency contribute to higher serum levels and enhanced risk for toxicity. Arrhythmias suggesting digoxin toxicity led to its recognition in the case presented here.
 • The American Journal of Medicine (2012) 125, 337-343

KEYWORDS: Arrhythmia; Digitalis; Digoxin; Heart failure; Toxicity

Cardiac glycosides have been used for the treatment of congestive heart failure for over 2 centuries, and in the treatment of arrhythmias for over 100 years, and were for many years a leading agent responsible for iatrogenic morbidity and mortality. The development of more effective cardiac drugs in the last half of the 20th century has led to diminished utilization, but not abandonment of glycosides. The incidence of toxicity has subsequently decreased, as has the level of suspicion of more recently trained physicians.

CASE PRESENTATION

A 73-year-old African-American male with multiple medical problems was admitted for recurrent episodes of syncope associated with coughing, and increasing weakness and dyspnea on exertion at 10 feet. He denied any history of palpitations, chest pain, or paroxysmal nocturnal dyspnea.

The patient's comorbidities included obesity, hypertension, diabetes mellitus, and dyslipidemia. He also had a history of chronic renal insufficiency with an admission creatinine of 3.78 mg/dL, or glomerular filtration rate of 16.8 mL/min/1.73 m^2; the serum level ranged from 2.7 to 4.1 mg/dL for the past 2 years before admission. He was diagnosed with nonischemic cardiomyopathy by cardiac catheterization a decade prior, with normal coronary arteriography and a left ventricular ejection fraction of 10%-15% on ventriculography. A transthoracic echocardiogram a year before admission demonstrated an improved left ventricular ejection fraction of 50% on medical therapy. He had no known allergies, and denied any tobacco, alcohol, or illicit drug use.

His outpatient regimen had consisted of digoxin 0.125 mg daily, carvedilol 25 mg twice a day, diltiazem extended-release 120 mg daily, simvastatin 20 mg daily, furosemide 40 mg twice a day, valsartan 160 mg daily, spironolactone 25 mg daily, amlodipine 10 mg twice a day, calcium acetate 667 mg with meals, isosorbide dinitrate 10 mg 3 times daily, hydralazine 10 mg 3 times daily, and subcutaneous insulin. He had been taking this regimen consistently for approximately 2 years.

An electrocardiogram on admission demonstrated sinus rhythm, first-degree atrioventricular block with a PR interval of 236 ms, and a left bundle branch block pattern with a QRS width of 176 ms, which had been present on previous electrocardiograms. A corrected QT interval was increased at 529 ms. Premature ventricular complexes also were noted (**Figure 1**).

Funding: None.

Conflict of Interest: None.

Authorship: All authors had a significant role in writing the manuscript.

Requests for reprints should be addressed to Eric H. Yang, MD, Division of Cardiology, Department of Medicine, University of California at Los Angeles, 100 UCLA Medical Plaza, Suite 630, Los Angeles, CA 90095.

E-mail address: Datsunian@gmail.com.

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2011.09.019

The patient subsequently developed altered mental status, associated with hypercarbic hypoxemic respiratory failure that required endotracheal intubation. A repeat transthoracic echocardiogram performed on hospital day #3 showed a depressed left ventricular ejection fraction of 25%-30%, with global left ventricular hypokinesis, but no significant valvar disease. His clinical state was further complicated by worsening renal failure, necessitating hemodialysis on hospital day #18. He also required emergent tracheotomy due to traumatic self-extubation, causing vocal cord paralysis and tracheal trauma.

During this time, digoxin was administered along with his congestive heart failure medications. The patient had a prolonged hospital course due to renal failure and respiratory issues, including pneumonia. On hospital day #32, 2 hours after receiving his daily digoxin dose, the patient was noted to be nonresponsive, and bradycardia was noted on the telemetry monitor. An electrocardiogram revealed complete atrioventricular heart block with a sinus rhythm of 90 beats per minute, and a fascicular escape rhythm of 50 beats per minute with multiple premature ventricular complexes (**Figure 2**). A repeat electrocardiogram 10 minutes later demonstrated resolution of complete atrioventricular block with return of the left bundle branch block pattern and a prolonged PR interval of 276 ms. When seen by the cardiology consultation service, the patient was resting comfortably and denied any nausea, vomiting, vision changes, seeing green or yellow, chest pain, or palpitations. On examination the patient was afebrile, with a heart rate of 83 beats per minute, blood pressure of 115/59 mm Hg, respiratory rate of 20 breaths per minute, and oxygen saturation of 100% on tracheostomy collar. His jugular venous pressure was estimated at 10 cm H_20. Auscultation revealed regular rhythm with no murmurs, rubs, or gallops. He had decreased breath sounds in his posterior lung bases. No peripheral edema was present.

Serum potassium was 3.9 mmol/L, bicarbonate 24 mmol/L, and a digoxin level was 1.6 ng/mL, previously obtained approximately 30 hours before the patient's presentation of heart block. Digoxin levels were obtained 2 hours before the daily administration of digoxin.

Because of a high clinical suspicion for digoxin toxicity, digoxin and atrioventricular nodal blocking agents (carvedilol and diltiazem) were discontinued.

Approximately 3 hours after the return of sinus rhythm, the patient developed bradycardia, became unresponsive,

CLINICAL SIGNIFICANCE

- Digoxin toxicity, although an infrequent occurrence, may be present in older patients (women more than men) with renal insufficiency or other drugs that interfere with glycoside pharmacokinetics.
- Arrhythmias caused by digitalis glycosides include blockage of sinoatrial and atrioventricular conduction and enhanced automaticity of atrial, junctional, and ventricular cells.
- Anti-digoxin antibody administration is indicated for patients with refractory, life-threatening arrhythmias and hemodynamic instability.

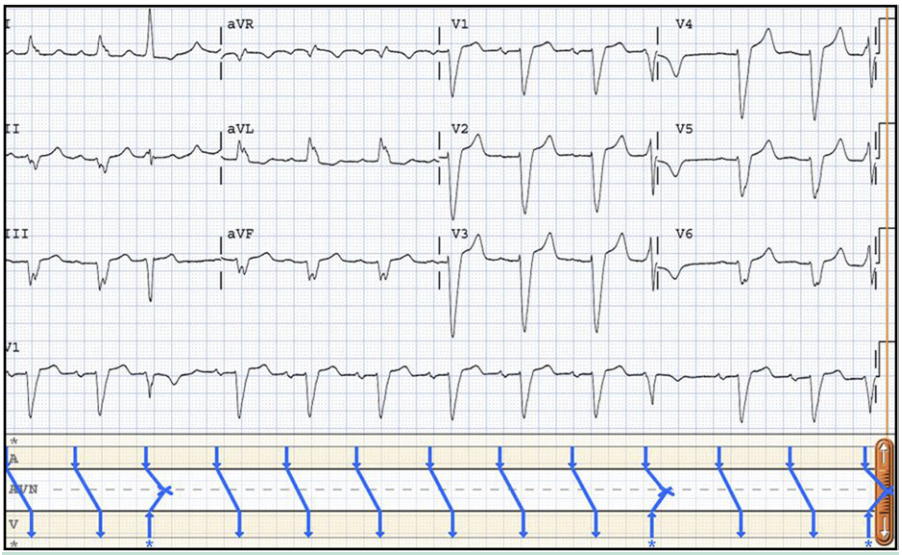

Figure 1 Electrocardiogram on admission. Sinus rhythm rate 73 beats per minute, with 3 ventricular premature complexes (*), first-degree atrioventricular block (PR interval of 236 ms), and left bundle branch block. Ladder indicates delayed atrioventricular conduction and premature ventricular complexes (*upward arrows) followed by compensatory pauses.

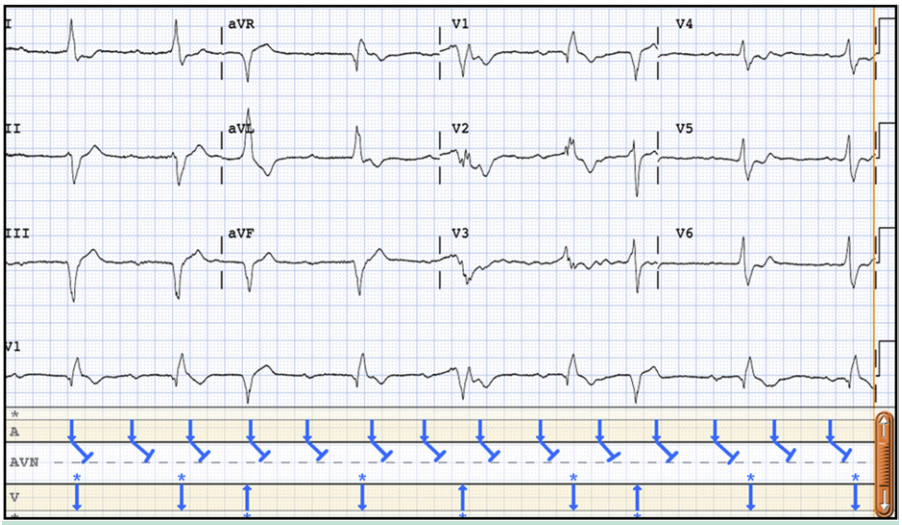

Figure 2 Complete heart block. Sinus rhythm, rate 87 beats per minute, ventricular rate 50 beats per minute, with 3 premature ventricular complexes (PVCs). The prevalent QRS complexes exhibit a superior axis and are positive in lead V1, suggesting an escape focus in the left posterior fascicle (downward arrows). The PVCs (upward arrows) reset the fascicular pacemaker.

and progressed to pulseless electrical activity. Precordial chest compressions were initiated while epinephrine and atropine were administered. Ventricular fibrillation ensued, which required 3 200-joules countershocks to convert to a hemodynamically stable wide complex tachycardia (**Figure 3**). Intravenous amiodarone and sodium bicarbonate were administered, but the patient was noted to develop third-degree atrioventricular block with sinus rhythm of 64 beats per minute, and an escape rhythm suggestive of an origin from the left posterior fascicle with a rate of 47 beats per minute. Because of mounting suspicion of digoxin toxicity, confirmed by a 4.3-ng/mL serum digoxin level, 7 vials of 38-mg digoxin-specific antibody fragments were administered as an intravenous bolus. A temporary transvenous pacemaker electrode was placed in the right ventricle.

The patient gradually regained atrioventricular node conduction with first-degree atrioventricular block (PR interval of 350 ms) with left bundle branch block (**Figure 4**), which he maintained throughout the remainder of his hospitalization. The right ventricular pacemaker electrode was removed 2 days later. The patient remained neurologically intact, with no further cardiac events and

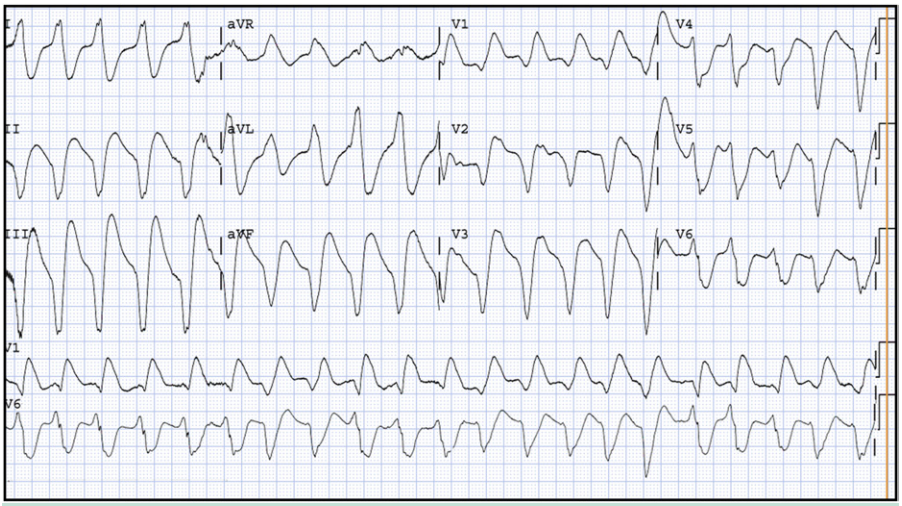

Figure 3 Rhythm after successful countershock and return of spontaneous circulation. There is a wide complex irregular tachycardia, rate 124 beats per minute. Atrial activity is not evident. The varying QRS morphology suggests a polymorphic ventricular tachycardia.

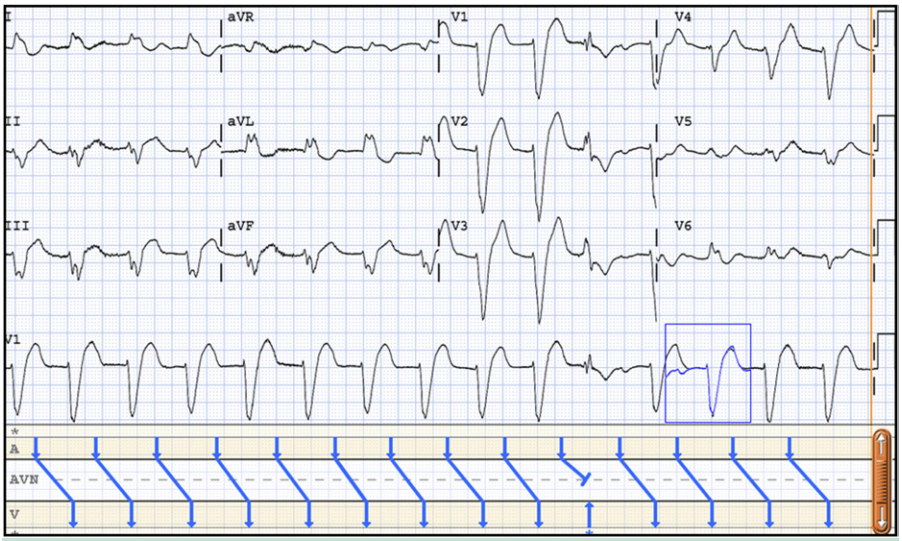

Figure 4 Rhythm after resolution of polymorphic ventricular tachycardia. A regular wide complex rhythm is seen with a rate of 90 beats per minute. Initially, the rhythm appears to be an accelerated ventricular rhythm, but a premature ventricular complex allows a sinus beat to manifest showing the underlying rhythm to be sinus, with a PR interval of approximately 350 ms. Superimposition of the visible P and QRS morphology on another QRS complex (blue box) shows the concealment of the P wave in the downsloping of the T wave. The prolonged PR interval and the presence of premature ventricular complexes are consistent with digoxin toxicity.

was eventually discharged to a ventilator management facility.

DISCUSSION

Digitalis glycosides have been used extensively for over 200 years, since British physician and botanist William Withering first reported on the foxglove's medical properties in treating ascites, anasarca, and dropsy.[1] Over the past several decades, digitalis administration has evolved from an antiquated practice of titrating doses until toxic manifestations arose, to a lower dosing regimen guided by serum levels. Digoxin continues to play a role in treatment of chronic systolic/diastolic heart failure and atrial fibrillation. However, due to several landmark studies showing physiologic and symptomatic improvement[2-5] but no demonstrable impact on overall survival in heart failure,[2] other agents shown to have significant morbidity and mortality benefits, including beta-blockers, angiotensin-converting enzyme-I inhibitors, and aldosterone antagonists, have been preferentially employed. Estimates of digoxin usage in heart failure in the past decade have decreased from approximately 80% to <30%, with only 8% of patients being started on digoxin with symptoms of heart failure before discharge.[6,7]

By current guidelines, digoxin is indicated for the treatment of Stage C heart failure (structural heart disease with prior/current symptoms of heart failure). It currently holds a Class IIa indication for pharmacologic treatment for patients with current or prior symptoms of heart failure and reduced left ventricular ejection fraction to decrease hospitalizations for heart failure.[8] Digoxin holds a Class I indication for intravenous and oral use to control the heart rate in patients with atrial fibrillation and heart failure. It also holds a Class IIa indication to be used in conjunction with either a beta-blocker or nondihydropyridine calcium channel antagonist to control the heart rate at rest and during exercise in atrial fibrillation.[9]

Derived from *Digitalis lanata*, a species of the foxglove plant, digoxin is an inhibitor of the intrinsic membrane protein sodium-potassium adenosine triphosphate-ase pump, resulting in elevated intracellular sodium concentration, a reduction in cytoplasmic potassium, and a resultant increase in calcium available to the contractile elements thought to be responsible for a modest increase in myocardial contractility.

At therapeutic levels, digitalis decreases automaticity and increases the cellular membrane potential. However, with toxic concentrations, arrhythmias originate from increased cell excitability secondary to a decreased resting cellular membrane potential. Increased automaticity can result from afterdepolarizations and aftercontractions due to spontaneous cycles of Ca^{2+} release and reuptake.[10] In addition, digitalis has significant neurohormonal effects in heart failure; it exerts sympatholytic activity by inhibiting efferent sympathetic nerve activity, resulting in lower concentrations of epinephrine and renin.[11-13] It also normalizes the blunted baroreflex response that is responsible for excessive sympathetic nerve activation and downregulation of cardiac β-receptors.[11,14]

The bioavailability of digoxin is approximately 66%, with a plasma half-life ranging from 20-50 hours. It has a large volume of distribution of approximately 6 L/kg, with plasma protein binding around 20%. In patients with normal renal function, steady-state plateau concentrations usually take 7-10 days (length of 4-5 half-lives). The drug is extensively distributed into fat, making dialysis ineffective in digitalis toxicity. In patients with end-stage renal disease, the half life can be as long as 4-6 days.[15,16]

Concomitant metabolic disorders or medications also can increase digoxin concentrations. Hypokalemia, hypomagnesemia, and hypercalcemia—which can be induced by diuretic use—can exacerbate digoxin toxicity at lower serum levels by promoting sodium pump inhibition. In addition, multiple drug interactions can occur with digoxin use that can reduce its clearance in the renal system.[7,9,10] Interacting drugs that are used in a variety of cardiac disease states, including amiodarone, verapamil, quinidine, macrolides, itraconazole, and cyclosporine, have been demonstrated in in vitro studies to inhibit P-glycoprotein transport in renal tubular cells.[17-21] P-glycoprotein is a 170-kDa membrane efflux transport protein that is located in the liver, pancreas, kidney, colon, and jejunum. Its theoretical mechanism involves active transport of digoxin into the urine, which leads to decreased clearance in the presence of glycoprotein inhibitors. If such drugs must be used, close monitoring and digoxin dosing should be reduced to avoid toxicity.

Both cardiac and extra-cardiac symptoms of digoxin toxicity have been extensively described over the history of digoxin use. The more prominent features of extra-cardiac manifestations have involved visual disturbances, including hazy or blurring vision, flashing lights, halos, and green or yellow patterns. Anorexia and nausea, vomiting, and other nonspecific gastrointestinal symptoms can occur in 30%-70% of patients with suspected digoxin toxicity.[16]

Multiple arrhythmias have been documented due to the complex pharmacologic effects of digitalis toxicity, with ventricular extrasystoles being a common manifestation.[22,23] A mechanistic classification of arrhythmias related to digitalis toxicity was devised by Fisch and Knoebel in 1985[23] (**Table**). The most common arrhythmic manifestation of digoxin toxicity are premature ventricular complexes, which can present multifocally or as ventricular bigeminy.[24] Arrhythmias such as junctional tachycardia, junctional escape rhythm, parasystole, and bidirectional ventricular tachycardia are more likely due to automatic foci triggered by digoxin. On the other hand, atrial flutter, atrial fibrillation, premature ventricular complexes, and ventricular tachycardia/flutter/fibrillation are most likely caused by a reentry mechanism (ie, macroreentry circuit conduction, slow-fast pathway interactions). Bidirectional ventricular tachycardia, a pathognomonic arrhythmia of digoxin toxicity, is characterized by alternating QRS complexes of fascicular origin at regular intervals through the left bundle branch fibers.[25] Finally, sinus arrest and sinoatrial exit block also have been reported.

Table Classification by Fisch and Knoebel[23] of Arrhythmias That Can Be Induced by Digitalis Toxicity, Categorized by Mechanism

Ectopic rhythms due to reentry or enhanced automaticity, or both
Atrial tachycardia with block
Atrial fibrillation
Atrial flutter
Nonparoxysmal junctional tachycardia
VPCs
Ventricular tachycardia
Ventricular flutter and fibrillation
Bidirectional ventricular tachycardia
Parasystolic ventricular tachycardia
Ectopic rhythms from multiple sites of specialized conducting tissue
Depression of pacemaker
Sinoatrial arrest
Depression of conduction
Sinoatrial block
AV block
Exit block
Ectopic rhythms with simultaneous depression of conduction
Atrial tachycardia with high degree AV block
AV dissociation due to suppression of dominant pacemaker with escape of subsidiary pacemaker or acceleration of a lower pacemaker, or dissociation with AV junctional rhythm
Triggered automaticity
Accelerated junctional impulses after premature ectopic impulses
Ventricular arrhythmias "triggered" by supraventricular tachycardia
Junctional tachycardia "triggered" by ventricular tachycardia

AV = atrioventricular; VPC = ventricular premature complex.

Digitalis is thought to have multifactorial effects on the atrioventricular node, by prolonging its effective refractory period and through partial vagal and antiadrenergic influence.[24] In many situations, both ectopy and depression of pacemakers and conduction, respectively, can overlap. This can cause inhibition at one level while triggering accelerated or escape pacemaker rhythms at another level. Digoxin has minimal effect on conduction velocity in the atrium, ventricle, His bundle, or bundle branches; thus, left bundle branch block, right bundle branch block, or intraventricular conduction delay patterns are rarely due to digoxin toxicity.[23]

The recommended target level of serum digoxin concentration of <1.0 ng/m is based on post hoc analyses of the Digitalis Investigation Group (DIG) study, which found that digoxin at a serum concentration of 0.5-0.9 ng/mL was associated with less mortality and rehospitalization in systolic and diastolic heart failure patients.[26] It is important to note that the serum digoxin concentration should be measured at least 6 hours after the last dose of digoxin in order to avoid overestimation of serum digoxin concentrations, because the drug will be in its distributive phase from the blood to extravascular tissues.[16] Of note, drugs such as

aldosterone, potassium canrenoate, and herbal medications such as Chan Su, Siberian ginseng, Asian ginseng, ashwagandha, and danshen have been documented to falsely elevate serum digoxin levels.[27]

Excluding toxicity due to intentional overdose from suicidal gestures, multiple studies have looked for risk factors that predispose patients towards developing digitalis toxicity. A subgroup post hoc study of the DIG study that digoxin was associated with a significantly higher risk of death among women (adjusted hazard ratio of 1.23) compared with placebo.[28] In a retrospective study of the DIG trial of the relationship of serum digoxin concentration and outcomes with women in heart failure, a level of 0.5-0.9 ng/mL had a beneficial effect of digoxin on morbidity and no excess in mortality. However, women with serum digoxin concentrations of ≥1.2 had a hazard ratio for death of 1.33 (95% confidence interval, 1.001-1.76, $P = .049$).[29]

Elderly patients, or those with chronic renal insufficiency or end-stage renal disease, also are at increased risk, as previously discussed. An observational surveillance study of patients who received treatment with Digoxin Immune Fab therapy noted that more than 60% of the patients studied were men or women above the age of 70 years, with two thirds of these patients having moderate to severe impaired renal function.[30] A retrospective cohort of hemodialysis patients on digoxin showed that digoxin use was associated with a 28% increased risk for death. Increasing serum digoxin concentrations were significantly associated with mortality, especially in patients with predialysis serum potassium levels of <4.3 mEq/L.[31]

The development of digoxin antibody Fab fragments has been shown to be highly effective in treating life-threatening signs of digoxin toxicity,[30,32] especially in the presence of refractory, life-threatening arrhythmias, hemodynamic instability, and hyperkalemia. The volume of distribution of antidigoxin Fab is 0.4 L/kg, with a half-life of about 12-20 hours in patients with normal renal function. It is indicated for digoxin toxicity presenting with life-threatening arrhythmias or hyperkalemia. The amount of antidigoxin Fab needed in acute ingestion of digoxin can be determined by 2 methods:[16]

$$\text{Dose (no. of vials)} = \text{Total amount ingested (mg)}/0.5^{*}$$

*mg of digoxin bound per vial of Fab

The second equation uses the serum digoxin concentration in determining the dose:

$$\text{Dose (no. of vials)} = \frac{\text{serum digoxin concentration } (\mu g/L) \times \text{weight (kg)}}{100}$$

After administration, serum digoxin concentration levels cannot be used for accurate assessment due to the rapid extraction of digoxin from tissues into plasma. The resultant high concentrations detected are from the Fab-digoxin complex. Because of the quick reversal of the physiologic effects of digoxin, hypokalemia, exacerbation of heart failure, and rapid ventricular response from previously controlled atrial fibrillation can occur. Hickey et al[30] also reported that the risk of rebound digoxin toxicity was 6-fold higher if less than half of the calculated full neutralizing dose was administered.[30]

The occurrence of digitalis toxicity has substantially decreased over the past several decades, which is attributed to decreasing usage, decreased dose administration, and improved serum level monitoring. In a prospective study in 1971, up to 23% of admitted patients on digoxin were thought to have toxic manifestations; 41% of these patients died.[33] The DIG trial, undertaken in the early 1990s, reported digoxin toxicity in 11.9% of patients receiving digoxin, but also 7.9% of those receiving placebo by clinical suspicion; by factoring in the placebo rate as a false-positive rate, the "corrected" actual incidence of digoxin toxicity would be approximately 4%. More recently, an analysis of a group of academic medical centers in the US in 1996 showed an incidence of digoxin toxicity in 0.07% of all hospital admissions.[34]

A suggested approach for administration and monitoring of digoxin in heart failure is to achieve a serum digoxin concentration of 0.7-1.1 ng/mL. In patients with normal renal function (creatinine clearance ≥90), oral digoxin at 0.25 mg daily can be started with a serum concentration check after 5 days (the serum digoxin concentration should be checked at least 6 hours after the last oral dose). With a creatinine clearance of 60-89, daily oral digoxin 0.125 mg should be started with a serum digoxin concentration check at 5 days. Patients with a lower creatinine clearance of 30-59 should be started on digoxin 0.125 mg every other day, with a serum digoxin concentration check at 4 days. A creatinine clearance of <30 should warrant extreme caution of digoxin use.[35] Intravenous administration of digoxin is rarely indicated and should never be used solely for heart failure treatment. Intravenous "loading" of digoxin can be considered for ventricular rate control in atrial fibrillation in the absence of an accessory pathway,[9] but caution is warranted in the setting of a decreased glomerular filtration rate. Repeated measurements of serum digoxin concentration are not necessary unless the patient's renal function changes, an interacting drug is started or discontinued, or if there are significant weight changes.

Although digoxin toxicity has significantly decreased over the past several decades due to decreased usage, serum monitoring, improved dose-determination methods and drug interaction education and awareness, it is still a life-threatening condition that patients with the aforementioned risk factors can develop. Thus, careful monitoring of digoxin administration, as well as recognition of digitalis-toxic arrhythmias and clinical manifestations, can lead to effective treatment and decreases in morbidity and mortality.

References

1. Withering W. *An Account of the Foxglove and Some of its Medical Uses: with Practical Remarks on Dropsy and Other Diseases.* London: CGJ and J Robinson, London; 1785.
2. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336: 525-533.
3. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22(4):955-962.
4. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients whith chronic heart failure with angiotensin-converting-enzyme inhibitors. *N Engl J Med*. 1993;329(1):1-7.
5. Khand AU, Rankin AC, Martin W, et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol*. 2003;42:1944-1951.
6. Gheorghiade M, Braunwald E. Reconsidering the role for digoxin in the management of acute heart failure syndromes. *JAMA*. 2009; 302(19):2146-2147.
7. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation*. 2006;113:2556-2564.
8. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;119:e391-e479.
9. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011;57:e101-e198.
10. Hauptman PJ, Kelly RA. Digitalis. *Circulation*. 1999;99:1265-1270.
11. Gheorghiade M, Ferguson D. Digoxin: a neurohormonal modulator in heart failure? *Circulation*. 1991;84:2181-2186.
12. Newton GE, Tong JH, Schofield AM, et al. Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. *J Am Coll Cardiol*. 1996;28(1):155-161.
13. Krum H, Bigger JT, Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol*. 1995;25(2):289-294.
14. Rahimtoola SH, Tak T. The use of digitalis in heart failure. *Curr Probl Cardiol*. 1996;21(12):781-853.
15. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev*. 2004;23(3):135-143.
16. Bauman JL, DiDomenico RJ, Galanter WL. Mechanisms, manifestations, and management of digoxin toxicity in the modern era. *Am J Cardiovasc Drugs*. 2006;6(2):77-86.
17. Tanigawara Y, Okamura N, Hirai M, et al. Transport of digoxin by human P-glycoprotein expressed in a porcine kidney epithelial cell line (LLC-PK_1). *J Pharmacol Exp Ther*. 1992;263(2):840-845.
18. Okamura N, Hirai M, Tanigawara Y, et al. Digoxin-cyclosporin A interaction: modulation of the multidrug transporter P-glycoprotein in the kidney. *J Pharmacol Exp Ther*. 1993;266(3):1614-1619.
19. Hori R, Okamura N, Aiba T, Tanigawara Y. Role of P-glycoprotein in renal tubular secretion of digoxin in the isolated perfused rat kidney. *J Pharmacol Exp Ther*. 1993;266(3):1620-1625.
20. Wakasugi H, Yano I, Ito T, et al. Effect of clarithromycin on renal excretion of digoxin: interaction with P-glycoprotein. *Clin Pharmacol Ther*. 1998;64:123-128.
21. Verschraagen M, Koks CH, Schellens JH, Beijen JH. P-glycoprotein system as a determinant of drug interactions: the case of digoxin-verapamil. *Pharmacol Res*. 1999;40(4):301-306.
22. Ma G, Brady WJ, Pollack M, Chan TC. Electrocardiographic manifestations: digitalis toxicity. *J Emerg Med*. 2001;20:145-152.
23. Fisch C, Knoebel SB. Digitalis cardiotoxicity. *J Am Coll Cardiol*. 1985;5:91A-98A.
24. Irons GV, Orgain ES. Digitalis-Induced dysrhythmias and their management. *Prog Cardiovasc Dis*. 1966:8;539-569.
25. Morris SN, Zipes DP. His bundle electrocardiography during bidirectional tachycardia. *Circulation*. 1973;458:32-36.
26. Ahmed A, Rich M, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J*. 2006;27(2):178-186.
27. Dasgupta A. Therapeutic drug monitoring of digoxin: impact of endogenous and exogenous digoxin-like immunoreactive substances. *Toxicol Rev*. 2006;25:273-281.
28. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002;347:1403-1411.
29. Adams KF, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol*. 2005;46:497-504.
30. Hickey AR, Wenger TL, Carpenter VP, et al. Digoxin immune Fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol*. 1991;17:590-598.
31. Chan KE, Lazarus JM, Hakim RM. Digoxin associates with mortality in ESRD. *J Am Soc Nephrol*. 2010;21:1550-1559.
32. Antman EM, Weger TL, Butler VP Jr, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: final report of a multicenter study. *Circulation*. 1990; 81:1744-1752.
33. Beller GA, Smith TW, Abelmann WH, et al. Digitalis intoxication: a prospective clinical study with serum level correlations. *N Engl J Med*. 1971;284:989-997.
34. Gandhi AJ, Vlasses PH, Morton DJ, Bauman JL. Economic impact of digoxin toxicity. *Pharmaeconomics*. 1997;12:175-181.
35. Rahimtoola SH. Digitalis therapy for patients in clinical heart failure. *Circulation*. 2004;109:2942-2946.