Digitalis Toxicity

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Abstract: **Digitalis toxicity is a frequently encountered clinical problem. Drug interactions leading to digitalis toxicity are very common. Within this group, the interaction of digitalis and verapamil is increasingly recognized as an important cause of digitalis toxicity. The use of digoxin-binding antibodies represents a significant advance in the treatment of this problem and can be lifesaving in the setting of massive overdose. A case report of digitalis toxicity and a review of this problem and its treatment are presented. (J Am Bd Fam Pract 1989; 2:49-54.)**

Digitalis preparations are frequently prescribed, and a significant number of patients, especially the elderly, take them regularly. Because of the ubiquitous use of this drug and the increased frequency of digitalis toxicity, the rapid diagnosis of digitalis toxicity is essential. Results from measuring digitalis blood levels can help the physician provide optimal care to patients. Where digitalis levels are not available, the physician must depend on the signs, symptoms, and typical EKG and laboratory findings of digitalis intoxication to confirm the diagnosis.

Several factors contribute to digitalis toxicity. Among these, drug interactions (especially verapamil-digoxin) are common. While mortality from digitalis toxicity is still high, an important advance in its treatment has been made with the clinical use of digitalis-binding antibodies. The purpose of this paper is to present a brief case report of digitalis toxicity and to review the problem and treatment of digitalis toxicity. Special emphasis on the verapamil-digoxin interaction and the clinical use of digitalis-binding antibodies is made.

Case Report

A white middle-aged man came to the emergency department in the early morning with complaints of chest pain, vomiting, and diarrhea. His only medications were digoxin 0.25 mg daily and verapamil 80 mg three times daily. He was tachypneic, markedly bradycardic (heart rate was 36 beats per minute), and hypotensive (blood pressure was 96/60 mmHg). In addition, he was somnolent but arousable and had miotic pupils. The physical examination was otherwise unremarkable.

A 12-lead electrocardiogram showed atrial fibrillation with a high-grade delay in AV conduction. The Q-T interval was markedly shortened. The ventricular rate was 31, and there were long asystolic intervals in V4–V6. There was sagging of the S-T segments in leads II, III, and aVF and upward sloping S-T segments in aVR. There were peaked T waves in V2 and V3, suggestive of hyperkalemia (Figure 1).

Other pertinent laboratory findings were: serum potassium, 6.1 mEq/L (6.1 mmol/L); BUN, 18 mg/dL (3.0 mmol/L); and creatinine, 1.1 mg/dL (97μmol/L). Cardiac enzymes were normal. Serum calcium level was 9.4 mg/dL (2.3 mmol/L). Urine and serum drug screens were negative for narcotics. A serum digoxin level of 30.80 ng/mL (39.44 nmol/L) was reported and confirmed.

The patient received doses of atropine, 0.5 mg intravenously, to increase the heart rate adequately to maintain a blood pressure, 100 mmHg systolic. After the digoxin level was reported, the patient was given phenytoin, 600 mg intravenously for approximately 45 minutes.

Arrangements were made to transport the patient to a referral hospital for treatment with digitalis-binding antibodies. At the referral center, while awaiting a repeat digoxin level in order to calculate the correct dose of digitalis-binding antibodies, the patient developed a refractory ventricular tachycardia, which degenerated to ventricular fibrillation. He could not be resuscitated and died approximately 10 hours after initial presentation.

Digitalis

Digitalis is most frequently prescribed for its positive inotropic effect in patients with congestive

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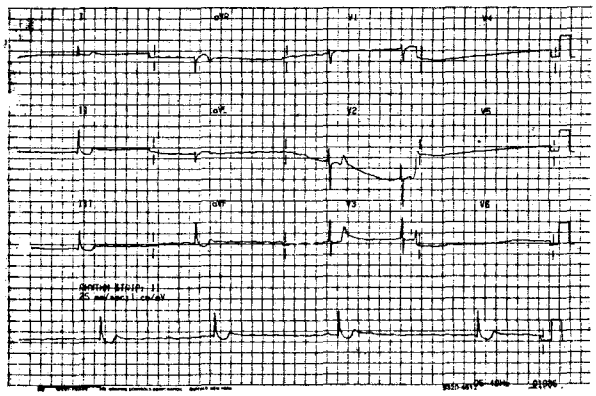

Figure 1. Electrocardiogram showing atrial fibrillation with high-grade AV conduction delay and long asystolic interval in the lateral chest leads. Note the sagging S-T segments in leads II, III and aVF consistent with digitalis effect. The Q-T interval is shortened. Note also tall peaked T waves in V2 and V3, suggestive of hyperkalemia.

heart failure and for slowing the ventricular rate in patients with atrial fibrillation or flutter. The most frequently used cardiac glycosides are digoxin and (less commonly) digitoxin. Digitoxin is primarily metabolized by the liver and has a much longer half life (approximately 7 days) than does digoxin (approximately 1.5 days), which is primarily excreted by the kidney. Both drugs are excreted in the bile, and enterohepatic recirculation plays a role in their metabolism.[1] Because digitalis toxicity represents an exaggeration of its pharmacologic actions, a review of these actions is in order.

Most of the pharmacologic action of digitalis occurs through its effect on the cell-membrane-bound sodium-potassium ATPase pump. Through inhibition of this system, there is an intracellular loss of the potassium ions and an intracellular gain of sodium and, subsequently, calcium ions through the sodium-calcium exchange mechanism. In cardiac muscle, increased intracellular calcium improves actin and myosin interaction. This leads to the increased velocity of muscle shortening and increased velocity of developed tension, which is the positive inotropic effect of digitalis.[2] The rapid influx of sodium ions into myocardial cells increases phase 4 depolarization and increases myocardial automaticity, which may lead to the appearance of latent pacemakers in the myocardium and the conducting system. Sodium influx is also responsible for lowering the resting membrane potential, leading to increased excitability of myocardial tissue.[1,3]

Digitalis also has clinically important effects on heart rate and impulse conduction in the heart. The slowing of the heart rate is due primarily to increased vagal tone, which decreases the rate of sinoatrial node depolarization. Digitalis increases the refractory period in the atrioventricular (AV) node and ventricular conducting system. At the same time, the refractory period of the myocardium is decreased, leading to improved impulse conduction. Digitalis also decreases conduction velocity through a direct effect on the AV node.[1,3]

Digitalis Toxicity

Digitalis toxicity is an extremely common and potentially lethal problem that often is not recognized.[3,4] Mortality rates as high as 50 percent at serum digoxin levels of 6.0 ng/mL (7.68 nmol/L) and above have been reported.[4] The liability to digitalis toxicity is primarily due to the narrow margin between therapeutic and toxic levels of the drug.[1,4]

The signs and symptoms most frequently associated with digitalis toxicity are perhaps best described by Withering in 1785, who wrote of this drug:

> The foxglove when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometime inability to retain it; slow pulse, even as slow as 35 beats in a minute, cold sweats, convulsions, syncope, death.[5]

The majority of these signs and symptoms are due to the effect of digitalis directly on the central nervous system.[1]

By virtue of its action on the sodium-potassium ATPase pump, digitalis use leads to hyperkalemia, which can be significant with high serum digoxin levels.[3,4]

The mechanisms involved in the expression of digitalis toxicity are outlined by Goodman.[3] There are: (1) depression of conduction, (2) alteration of impulse formation and increased heterogeneity of refractory periods, (3) other cardiac factors such as cardiac ischemia or inflammation, and (4) noncardiac factors that accentuate the signs of toxicity.[3]

Depression of conduction and alteration of impulse function are directly responsible for the

Table 1. *Dysrythmias Seen with Digitalis Toxicity.*

Sinoatrial block
Sinus bradycardia
Second-degree AV block (usually Type I)
Complete AV block
Premature depolorizations arising outside the cardiac conducting system
Supraventricular tachycardia with AV block
Atrial fibrillation with a regular ventricular response

dysrhythmias seen with digitalis toxicity. While almost any dysrhythmia may be seen, some of the more commonly encountered are listed in Table 1. When any degree of atrioventricular block is seen in combination with excitant dysrhythmias (i.e., atrial tachycardia with AV block), digitalis toxicity is likely.[3]

Digitalis uptake by abnormal or diseased cardiac tissue is different from uptake by normal tissue, leading to variation in cellular recovery times. In patients with cardiac disease, rhythm disturbances may occur at therapeutic serum digoxin levels. Resolution of these dysrhythmias after withdrawal of the drug is strong evidence for drug toxicity.

There are a number of other factors that lead to digitalis toxicity. The elderly are predisposed as are patients with underlying heart disease, renal disease, conditions associated with hypoxemia and hypothyroidism, and electrolyte abnormalities, including hypernatremia, hypokalemia, hypercalcemia, and hypomagnesemia.[1,3,6]

Drug interactions contribute significantly to the production of toxic levels of digoxin. The hypokalemia associated with diuretic administration not only sensitizes the heart to digitalis effects but also may result in elevated serum digoxin concentration.[7] It is well recognized that concurrent administration of quinidine predictably results in increased serum digoxin levels, and the digoxin dose should be reduced by 50 percent whenever quinidine is administered concurrently.[7] The association of increased serum digitalis levels in patients receiving verapamil concurrently is emerging as a very clinically important interaction.[8,9] This interaction may now be encountered clinically as frequently as the above-mentioned digitalis-quinidine interaction. Drugs that commonly interact with digitalis to increase digitalis levels or to potentiate the effect of digitalis are listed in Table 2.

The mechanism of increased serum digoxin levels in patients taking both verapamil and digoxin is decreased renal and nonrenal clearance of digitalis. The renal effect is primarily through decreased active tubular secretion of digitalis.[7,8] In the presence of renal disease, this effect is accentuated. With concomitant verapamil administration, the increase in serum digoxin may be 70–100 percent above pretreatment levels.[7]

Because both drugs slow conduction through the AV node, pronounced suppression of AV nodal conduction could be expected in some patients using these drugs in combination.[9] We recently prescribed digitalis for an elderly diabetic woman with atrial fibrillation and a rapid ventricular response. When verapamil was given for hypertension, she developed complete heart block, necessitating placement of a temporary pacemaker.

On the other hand, verapamil seems to suppress certain digoxin-induced dysrhythmias so that the cardiac conduction manifestations of digitalis toxicity may not be expressed.[7]

These actions mandate the reduction in digoxin dose even in patients with therapeutic levels or desired effect at subtherapeutic levels when verapamil is begun.[7] Generally, the dose of digoxin should be halved and the patient monitored frequently both clinically and with digoxin levels to decrease the possibility of digitalis intoxication.

With digitalis toxicity, cardiac rhythm disturbances are not infrequently fatal. In high doses, however, digitalis may be directly lethal. The membrane-bound sodium-potassium ATPase system in all body tissues ceases to function, and resting membrane potentials are reduced. With the myocardial cells unable to act as pacemakers, the result is asystole and, ultimately, complete loss of cardiac electrical activity.[10]

Table 2. *Medications Interacting with Digitalis to Increase Serum Digitalis Levels.*[7]

Quinidine
Amiodarone
Verapamil
Diltiazam
Spironolactone
Triamterene
Diuretic-induced hypokalemia
Tetracycline, Erythomycin

Treatment of Digitalis Toxicity

The diagnosis of digitalis toxicity should be considered for patients taking digitalis who become acutely ill, especially those with predisposing factors. Treatment should be considered from two perspectives: (1) efforts to lower the digitalis level, and (2) efforts to treat its direct pharmacologic effects.

In treating the pharmacologic effects of digitalis, a life-threatening complication is marked hyperkalemia. A result of the inhibition of the sodium-potassium ATPase pump in all tissues, profound hyperkalemia usually occurs only in the setting of renal disease or massive overdose. Hyperkalemia seen with digitalis intoxication *usually* does not require specific therapy; however, when marked hyperkalemia develops, serum potassium should be carefully lowered with insulin and glucose or ion exchange resins. Mild hyperkalemia lessens the effect of some of the dysrhythmias seen with digitalis toxicity. Hypokalemia, which tends to accentuate these dysrhythmias, *must* be avoided. The use of intravenous calcium, with hyperkalemia in the setting of digitalis toxicity, is contraindicated because of elevated intracellular calcium concentrations. After the diagnosis of acute digitalis intoxication, serial determinations of the serum potassium levels should be obtained.

Phenytoin and lidocaine are useful in suppressing the increased ventricular automaticity without suppressing conduction through the AV node in the digitalis toxic patient. Phenytoin is particularly useful because it does not decrease the inotropic effects of digitalis and does suppress some supraventricular dysrhythmias.

Phenytoin should be given intravenously at a rate of 50 mg to 100 mg every 5 minutes with close blood-pressure monitoring until the dysrhythmia is controlled, phenytoin toxicity occurs, or a maximum of 600 mg to 1000 mg is given.[3] Lidocaine is given as a 1 mg per kg intravenous bolus followed by an infusion of up to 4 mg per minute.[11]

A temporary transvenous pacemaker may be used to abolish ventricular tachyarrhythmias by overdrive suppression. It should be used with great caution, however, because of the increased myocardial excitability and decreased fibrillatory threshold. For the same reason, electric cardioversion of dysrhythmias other than ventricular fibrillation should be used only as a last resort. If cardioversion is attempted, low-energy levels should be employed.[3]

In patients with severe bradyarrhythmias, atropine 0.5 mg should be administered intravenously to block the vagotonic effects of digitalis.[3]

While treating the specific problems related to digitalis toxicity outlined above, prevention of further intestinal absorption of the drug is accomplished by emesis or lavage and by the administration of activated charcoal and a cathartic. Charcoal is most effective when given early after ingestion; however, repeated charcoal administration of 1 gram per kilogram body weight every 2 to 4 hours is beneficial because of the enterohepatic recirculation of digitalis.[3]

Similarly, steroid-binding resins such as cholestyramine can prevent further absorption from the gastrointestinal tract and reduce serum half-life by interrupting enterohepatic circulation. The usefulness of cholestyramine has been most impressive in treating digitoxin toxicity, but it would also be useful to consider in digoxin toxicity.[12]

Digoxin Antibody Fragments

The most promising treatment for massive digitalis overdose is the use of digitalis-specific antibodies. In patients with massive overdose, conventional therapy is ineffective, and survival is unusual. Antibodies of high affinity and specificity for digoxin have been used in the laboratory to determine serum digoxin concentrations for many years. In the early 1970s, these antibodies were first considered for intravenous treatment of digitalis toxicity. The use of *whole* digoxin-specific antibodies was believed to be limited by several potential problems. To avoid these problems, digoxin-specific antibody *fragments* (Fab) were developed.[13,14]

Digoxin immune Fab (Digibind™) has been found to be highly effective in rapidly reversing life-threatening digoxin and digitoxin intoxication in a number of patients.[13,15] The mechanism of action of these antibody fragments has been well described. Circulating digoxin is rapidly bound by the Fab fragments, resulting in a concentration gradient favoring movement of digoxin from receptor sites in the heart into the circulation. Thus, there is a rapid reduction in *free* serum digoxin concentrations and an initial increase in *total* (bound and unbound) serum digoxin due to drug release from receptors in the heart and other tissues. After digoxin is bound by the circulating antibody fragments, it is pharmacologically inactive. This complex is then excreted by the kid-

ney.[13-15] It is important that a digoxin level be determined before administration of the digoxin antibody fragments. A standard serum digoxin concentration after the antibody is given will not give an accurate assessment of free (active) digoxin but will measure bound (inactive) digoxin as well.[15]

In a recent multicenter study of 63 patients with severe digitalis toxicity, 53 of 56 patients included in the final analysis were safely and effectively treated with Digibind™. They generally responded within 30 minutes of administration. This 95 percent response rate was achieved in patients with life-threatening cardiac rhythm disturbances, hyperkalemia, or both, many of whom had failed to respond to conventional measures. There were no obvious allergic or systemic reactions. There was no evidence of renal deterioration, nor was there a significant difference in the response of patients with or without preexisting renal impairment.[16]

The therapeutic effects of digitalis are also reversed with the use of digitalis antibody fragments. Reappearance of a rapid ventricular response to atrial fibrillation or heart failure may occur. Similarly, a rapid fall in serum potassium concentration occurs as a consequence of reversing the effects of digitalis. Potassium concentrations should be monitored closely during therapy with Fab fragments to avoid hypokalemia.[16,17]

To determine the appropriate dose, two simple calculations are necessary. The body load (BL) of digoxin is the serum digoxin concentration (digoxin) in nanograms per milliliter multiplied by the patient's weight (wt) in kilograms and the volume of distribution of digoxin in the body (5.6 in liters per kilogram) divided by 1000.

$$BL(mg) = (digoxin \times wt \times 5.6)/1000$$

Each 4 mL vial contains 40 mg of purified digoxin antibody fragments, which will bind approximately 0.6 mg of the body load of digoxin. Thus, one can calculate the total number of vials required by dividing the total body load of digoxin in mg by 0.6 mg/vial.

$$Vials = BL(mg)/0.6(mg)$$

In clinical trials, an average of 10 vials was used. If the digoxin level is unknown, the manufacturer recommends 20 vials be given. The cost of digoxin immune Fab fragments to a hospital is approximately $175 per vial.[17]

Summary

A case report of lethal digitalis poisoning has been presented, which has highlighted the interaction between verapamil and digoxin. Because both of the drugs are used commonly now, increased frequency of concurrent use and increased frequency of the production of digitalis toxicity by this interaction is anticipated. Some cases of toxicity may be prevented by prophylactically lowering the digitalis dose when verapamil is added and by closely monitoring for toxicity.

Digitalis-binding antibody fragments offer a major advance in our ability to deal with a significant clinical problem. As this therapy becomes available outside of major medical centers, physicians prescribing digitalis preparation should become knowledgeable in the use of the digitalis-binding antibody fragments. The appropriate role of this therapy currently is in the setting of massive, life-threatening digitalis overdose. As more clinical experience is gained, this role may be redefined. Familiarity with the use of digitalis-binding antibodies will enhance our ability to deal with this common problem.

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ANNOUNCEMENT

The International Center for Family Medicine (ICFM) will hold its regional meeting in Puerto Rico on March 28–April 2, 1989. The Director General, Dr. Julio Ceitlin, tells us that this meeting will be co-hosted by the Puerto Rico Chapter of the American Academy of Family Physicians and will be of interest to all family physicians. He also tells us that members of the ICFM will get a discounted registration fee ($150 for ICFM members and $250 for nonmembers).

The venue is most attractive and at a decent time of the year at the San Juan Hotel in San Juan, Puerto Rico. Those physicians interested either in joining the ICFM or attending the regional meeting, please get in touch with the Secretary, Nicholas J. Pisacano, M.D., 2228 Young Drive, Lexington, Kentucky 40505.