CARDIAC GLYCOSIDES USES IN HEART

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ABSTRACT
Digitalis is a plant-derived cardiac glycoside commonly used in the treatment of chronic heart failure (CHF), atrial fibrillation, and reentrant supraventricular tachycardia. Direct inhibition of membrane-bound sodium- and potassium-activated adenosine triphosphatase (Na+/K+-ATPase), which leads to an increase in the intracellular concentration of calcium ([Ca²⁺]). Approximately 0.4% of all hospital admissions in the United States are related to digitalis toxicity, while about 1.1% of outpatients on digoxin and 10-18% of people in nursing homes develop this toxicity. The most common precipitating cause of digitalis intoxication is depletion of potassium stores, which occurs often in patients with heart failure as a result of diuretic therapy and secondary hyperaldosteronism. Cardiac toxicity can also occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration due to a reduction in clearance and/or i

INTRODUCTION AND HISTORY
Digitalis is a plant-derived cardiac glycoside commonly used in the treatment of chronic heart failure (CHF), atrial fibrillation, and reentrant supraventricular tachycardia.¹² Digoxin is the only available preparation of digitalis in the United States. Cardiac glycosides are found in certain flowering plants, such as oleander and lily-of-the-valley. Indigenous people in various parts of the world have used many plant extracts containing cardiac glycosides as arrow and ordeal poisons. The ancient Egyptians used squill (Urginea maritima) as a medicine. The Romans employed it as a diuretic, heart tonic, emetic, and rat poison. Digitalis, or foxglove, was mentioned in the year 1250 in the writings of Welsh physicians. Fuchsius described it botanically 300 years later and named it Digitalis purpurea.

William Withering published his classic account of foxglove and some of its medical uses in 1785, remarking upon his experience with digitalis. He recognized many of the signs of digitalis toxicity, noting, "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, slow pulses, even as low as 35 in a minute, cold sweats, convulsions, syncope, death."

During the early 20th century, as a result of the work of Cushny, Mackenzie, Lewis, and others, the drug was gradually recognized as specific for treatment of atrial fibrillation. Only subsequently was the value of digitalis for treatment of CHF established. Cardiac glycosides enhance cardiac contractility and slow conduction through the atrioventricular (AV) junction by increasing vagal tone.³

Cardiac glycoside toxicity has been known to result from ingestion of some plants, including yellow oleander (Thevetia peruviana) and foxglove, and a similar toxidrome has been associated with the use of herbal dietary supplements that contain cardiac glycosides.

Digoxin is among the top 50 prescribed drugs in the United States.⁴ In 2011, the American Association of
Poison Control Centers reported 1601 single exposures to cardiac glycoside drugs. Cardiac glycosides account for 2.6% of toxic plant exposures in the United States. Most of these exposures are in children.

Digoxin-specific fragment antigen-binding (Fab) antibody fragments have contributed significantly to the improved morbidity and mortality of toxic patients since their approval in 1986 by the US Food and Drug Administration (FDA).

**PATHOPHYSIOLOGY**

Digoxin and other cardiac glycosides cause direct vasoconstriction in the arterial and venous system in vascular smooth muscle. The positive inotropic effect of digitalis has the following 2 components.

Direct inhibition of membrane-bound sodium- and potassium-activated adenosine triphosphatase (Na⁺/K⁺-ATPase), which leads to an increase in the intracellular concentration of calcium ([Ca²⁺]i).

Associated increase in a slow inward calcium current (iCa) during the action potential (AP); this calcium current is the result of movement of calcium into the cell, and it contributes to the plateau of the AP.

Digitalis glycosides bind specifically to Na⁺/K⁺-ATPase, inhibit its enzymatic activity, and impair active transport of extruding sodium and transport of potassium into the fibers (3:2 ratio). As a result, intracellular sodium ([Na⁺]i) gradually increases, and a gradual, small decrease in intracellular potassium ([K⁺]i) occurs.

Cardiac fiber calcium [Ca²⁺]i is exchanged for extracellular sodium (3:1 ratio) by a transport system that is driven by the concentration gradient for these ions and the transmembrane potential. Increase in [Na⁺]i is related crucially to the positive inotropic effect of digitalis.

In addition, by a mechanism that is not defined clearly, the increase in [Ca²⁺]i increases the peak magnitude of iCa; this change parallels the positive inotropic action. The change in iCa is a consequence of the increase in [Ca²⁺]i and not of the increase in [Na⁺]i. Thus, more calcium is delivered during the plateau of each AP to activate each contraction.

A fall in intracellular pH accompanies the digoxin-induced increase in [Ca²⁺]i, which leads to activation of a sodium/hydrogen exchange pump. This results in extrusion of hydrogen, an increase in [Na⁺]i, and greater inotropy. The mechanism described assumes that Na⁺/K⁺-ATPase is the pharmacologic receptor for digitalis and that when digitalis binds to these enzymes, it induces a conformational change that decreases active transport of sodium. Digitalis apparently binds to ATPase in a specific and saturable manner, producing a conformational change of the enzyme such that the binding site for digitalis probably is on the external surface of the membrane. Furthermore, the magnitude of the inotropic effect of digitalis is proportional to degree of inhibition of the enzyme.

Digitalis, in therapeutic concentrations, exerts no effect on the contractile proteins or on the interactions between them.

**Electrophysiologic effects**

The electrophysiologic effects of cardiac glycosides include the following:

- Decreased resting potential (RP) or maximal diastolic potential (MDP), which slows the rate of phase-0 depolarization and conduction velocity.
- Decrease in action potential duration (APD), which results in increased responsiveness of fibers to electrical stimuli.
- Enhancement of automaticity, which results from an increase in the rate of phase 4 depolarization and from delayed after-depolarization.

In general, cardiac glycosides slow conduction and increase the refractory period in specialized cardiac conducting tissue by stimulating vagal tone. Digitalis has parasympathetic properties, which include hypersensitization of carotid sinus baroreceptors and stimulation of central vagal nuclei. Digoxin also appears to have variable effects on sympathetic tone, depending on the specific cardiac tissue involved.

**EPIDEMIOLOGY**

Approximately 0.4% of all hospital admissions in the United States are related to digitalis toxicity, while about 1.1% of outpatients on digoxin and 10-18% of people in nursing homes develop this toxicity. According to a large study published in 1990, definite digoxin toxicity occurred in 0.8% of patients with heart failure treated with digoxin.

A study by See et al estimated that 5156 emergency department (ED) visits for digoxin toxicity occurred annually in the United States between 2005 and 2010. The study, which used data from the National Electronic Injury Surveillance System—Cooperative Adverse Drug
Event Surveillance Project, the National Ambulatory Medical Care Survey, and the National Hospital Ambulatory Medical Care Survey, also estimated that 1% of ED visits for adverse drug events in patients aged 40 years or older resulted from digoxin toxicity, with this figure rising to 3.3% for patients aged 85 years or older.

In 2011, the American Association of Poison Control Centers (AAPCC) reported 1,336 single exposures to plant cardiac glycosides and 1,601 single exposures to drug cardiac glycosides.

The AAPCC reported that the number of digitalis exposures was far less than that of calcium channel blocker toxicities (5,140 cases) or beta-blocker toxicities (10,485 cases). However, the mortality rate from digitalis toxicity was far higher, with 27 deaths reported versus 26 deaths from calcium channel antagonists and 9 deaths attributed to beta-blocker toxicity.

In the United States, hospitalizations for digitalis toxicity declined dramatically from 1991 to 2004. This decline has been attributed to a number of factors, including increased awareness of drug interactions, replacement of digoxin with other drugs and procedures (eg, catheter ablation) for the treatment of heart failure and arrhythmias, and the availability of accurate, rapid radioimmunoassays to monitor drug levels.

Internationally, approximately 2.1% of inpatients are taking digoxin. Of all patients admitted to the hospital, 0.3% develop digoxin toxicity.

ETIOLOGY

Clinical digoxin toxicity represents a complex interaction between digoxin and various electrolyte and renal abnormalities. A patient with normal digoxin levels (0.5-2 ng/mL) but renal insufficiency or severe hypokalemia may have more serious cardiotoxicity than a patient with high digoxin levels and no renal or electrolyte disturbances.

Acute overdose or accidental exposure to plants containing cardiac glycosides may cause acute toxicity. Deteriorating renal function, dehydration, electrolyte disturbances, or drug interactions usually precipitate chronic toxicity.

The most common precipitating cause of digitalis intoxication is depletion of potassium stores, which occurs often in patients with heart failure as a result of diuretic therapy and secondary hyperaldosteronism. Dosing errors, especially in infants receiving parenteral digoxin, is a frequent cause of digoxin toxicity and is usually associated with high mortality.

Toxicity may also occur via increased bioavailability. Bioavailability varies depending on the drug formulation. For example, Lanoxin has 25% less bioavailability than Lanoxicaps. Certain antibiotics that suppress intestinal flora may increase absorption of digoxin.

CARDCIAL SYMPTOMS

Cardiac symptoms include the following.

- Palpitations
- Shortness of breath
- Syncope
- Swelling of lower extremities
- Bradycardia
- Hypotension
- Dyspnea

DIAGNOSIS

Studies in patients with possible digitalis toxicity include the following.

- Serum digoxin level
- Electrolytes
- Renal function studies
- ECG

Serum digoxin level

- Therapeutic levels are 0.6-1.3 to 2.6 ng/mL
- Levels associated with toxicity overlap between therapeutic and toxic ranges
- False-negative assay results may occur with acute ingestion of nondigoxin cardiac glycosides (eg, foxglove or oleander)
- Levels determined less than 6-8 hours after an acute ingestion do not necessarily predict toxicity
- The best way to guide therapy is to follow the digoxin level and correlate it with serum potassium concentrations and the patient's clinical and ECG findings.

Electrolytes

- In acute toxicity, hyperkalemia is common
- Chronic toxicity is often accompanied by hypokalemia and hypomagnesemia

Electrocardiography

- Digoxin toxicity may cause almost any dysrhythmia
- Classically, dysrhythmias associated with increased automaticity and decreased AV conduction occur
- Sinus bradycardia and AV conduction blocks are the most common ECG changes in the pediatric population, while ventricular ectopy is more common in adults
- Nonparoxysmal atrial tachycardia with heart block and bidirectional ventricular tachycardia are particularly characteristic of severe digitalis toxicity.

MECHANISM OF ACTION

Digoxin inhibits sodium-potassium ATPase, an enzyme that regulates the quantity of sodium and potassium inside cells. Inhibition of the enzyme leads to an increase in the intracellular concentration of sodium and thus (by
stimulation of sodium–calcium exchange) an increase in the intracellular concentration of calcium. The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system. The autonomic effects include: (1) a vagomimetic action, which is responsible for the effects of digoxin on the sinoatrial and atrioventricular (AV) nodes; and (2) baroreceptor sensitization, which results in increased afferent inhibitory activity and reduced activity of the sympathetic nervous system and renin-angiotensin system for any given increment in mean arterial pressure. The pharmacologic consequences of these direct and indirect effects are: (1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action); (2) a decrease in the degree of 39 activation of the sympathetic nervous system and renin-angiotensin system (neurohormonal deactivating effect); and (3) slowing of the heart rate and decreased conduction velocity through the AV node (vagomimetic effect). The effects of digoxin in heart failure are mediated by its positive inotropic and neurohormonal deactivating effects, whereas the effects of the drug in atrial arrhythmias are related to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system (CNS). This increase in sympathetic activity may be an important factor in digoxin toxicity.\[32,29,30,31\]

**PHARMACOKINETICS**

**Absorption**

Absorption of digoxin from LANOXIN Tablets has been demonstrated to be 60% to 80% complete compared to an identical intravenous dose of digoxin (absolute bioavailability). When LANOXIN Tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced. Comparisons of the Systemic Availability and Equivalent Doses for Oral Preparations of LANOXIN Product Absolute Bioavailability Equivalent Doses (mcg)a Among Dosage Forms LANOXIN Tablets LANOXIN Injection/IV 60 - 80% 100% 62.5 50 125 100 250 200 500 400 a For example, 125-mcg LANOXIN Tablets equivalent to 100-mcg LANOXIN Injection/IV. In some patients, orally administered digoxin is converted to inactive reduction products (e.g., dihydrodigoxin) by colonic bacteria in the gut. Data suggest that 1 in 10 patients treated with digoxin tablets will degrade 40% or more of the ingested dose. As a result, certain antibiotics may increase the absorption of digoxin in such patients. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as 2-fold in some cases.\[32,33,34\]

**Distribution**

Following drug administration, a 6- to 8-hour tissue distribution phase is observed. This is followed by a much more gradual decline in the serum concentration of the drug, which is dependent on the elimination of digoxin from the body. The peak height and slope of the early portion (absorption/distribution phases) of the serum concentration-time curve are dependent upon the route of administration and the absorption characteristics of the formulation. Clinical evidence indicates that the early high serum concentrations do not reflect the concentration of digoxin at its site of action, but that with chronic use, the steady-state post-distribution serum concentrations are in equilibrium with tissue concentrations and correlate with pharmacologic effects. In individual patients, these post-distribution serum concentrations may be useful in evaluating therapeutic and toxic effects (see DOSAGE AND ADMINISTRATION: Serum Digoxin Concentrations). Digoxin is concentrated in tissues and therefore has a large apparent volume of distribution. Digoxin crosses both the blood-brain barrier and the placenta. At delivery, the serum digoxin concentration in the newborn is similar to the serum concentration in the mother. Approximately 25% of digoxin in the plasma is bound to protein. Serum digoxin concentrations are not significantly altered by large changes in fat tissue weight, so that its distribution space correlates best with lean (i.e., ideal) body weight.\[35,36,37\]

**Metabolism**

Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites, which include 3β-digoxigenin, 3-keto-digoxigenin, and their glucuronide and sulfate conjugates, are polar in nature and are postulated to be formed via hydrolysis, oxidation, and conjugation. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system.\[38,39,40\]

**Excretion**

Elimination of digoxin follows first-order kinetics (that is, the quantity of digoxin eliminated at any time is proportional to the total body content). Following intravenous administration to healthy volunteers, 50% to 70% of a digoxin dose is excreted unchanged in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. In healthy volunteers with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. The half-life in anuric patients is prolonged to 3.5 to 5 days. Digoxin is not effectively removed from the body by dialysis, exchange transfusion, or during cardiopulmonary bypass because most of the drug is bound to tissue and does not circulate in the blood.\[41,42,43,44,45\]
**Special Populations**

Race differences in digoxin pharmacokinetics have not been formally studied. Because digoxin is primarily eliminated as unchanged drug via the kidney and because there are no important differences in creatinine clearance among races, pharmacokinetic differences due to race are not expected. The clearance of digoxin can be primarily correlated with renal function as indicated by creatinine clearance. The Cockcroft and Gault formula for estimation of creatinine clearance includes age, body weight, and gender.\(^{(46,47)}\)

**Hemodynamic Effects**

Digoxin produces hemodynamic improvement in patients with heart failure. Short- and long-term therapy with the drug increases cardiac output and lowers pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance. These hemodynamic effects are accompanied by an increase in the left ventricular ejection fraction and a decrease in end-systolic and end-diastolic dimensions.\(^{(48)}\)

**Chronic Heart Failure**

Two 12-week, double-blind, placebo-controlled studies enrolled 178 (RADIANCE trial) and (PROVED trial) patients with NYHA class II or III heart failure previously treated with digoxin, a diuretic, and an ACE inhibitor (RADIANCE only) and randomized them to placebo or treatment with LANOXIN. Both trials demonstrated better preservation of exercise capacity in patients randomized to LANOXIN. Continued treatment with LANOXIN reduced the risk of developing worsening heart failure, as evidenced by heart failure-related hospitalizations and emergency care and the need for concomitant heart failure therapy.

**Heart Failure: Adults: Infants and Children**

In general, divided daily dosing is recommended for infants and young children. In the newborn period, renal clearance of digoxin is diminished and suitable dosage adjustments must be observed. This is especially pronounced in the premature infant. Beyond the immediate newborn period, children generally require proportionally larger doses than adults on the basis of body weight or body surface area. Children over 10 years of age require adult dosages in proportion to their body weight. Some researchers have suggested that infants and young children tolerate slightly higher serum concentrations than do adults. Digitalization may be accomplished by either of two general approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount of digoxin accumulated in the body. If rapid digitalization is considered medically appropriate, it may be achieved by administering a loading dose based upon projected peak digoxin body stores. Maintenance dose can be calculated as a percentage of the loading dose. More gradual digitalization may be obtained by beginning an appropriate maintenance dose, thus allowing digoxin body stores to accumulate slowly. Steady-state serum digoxin concentrations will be achieved in approximately five half-lives of the drug for the individual patient. Depending upon the patient’s renal function, this will take between 1 and 3 weeks.\(^{(49,50,51,52)}\)

**Rapid Digitalization With a Loading Dose:**

Lanoxin Injection Pediatric can be used to achieve rapid digitalization, with conversion to an oral formulation of Lanoxin for maintenance therapy if these trends in favor of a treatment benefit.

**ADVERSE REACTIONS**

In general, the adverse reactions of digoxin are dose-dependent and occur at doses higher than those needed to achieve a therapeutic effect. Hence, adverse reactions are less common when digoxin is used within the recommended dose range or therapeutic serum concentration range and when there is careful attention to concurrent medications and conditions. Because some patients may be particularly susceptible to side effects with digoxin, the dosage of the drug should always be selected carefully and adjusted as the clinical condition of the patient warrants. In the past, when high doses of digoxin were used and little attention was paid to clinical status or concurrent medications, adverse reactions to digoxin were more frequent and severe. Cardiovascular adverse reactions accounted for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions. However, available evidence suggests that the incidence and severity of digoxin toxicity has decreased substantially in recent years. In recent controlled clinical trials, in patients with predominantly mild to moderate heart failure, the incidence of adverse experiences was comparable in patients taking digoxin and in those taking placebo. In a large mortality trial, the incidence of hospitalization for suspected digoxin toxicity was 2% in patients taking Lanoxin compared to 0.9% in patients taking placebo. In this trial, the most common manifestations of digoxin toxicity included gastrointestinal and cardiac disturbances; CNS manifestations were less common.\(^{(53,34,55)}\)

**Adults: Cardiac:** Therapeutic doses of digoxin may cause heart block in patients with pre-existing sinoatrial or AV conduction disorders; heart block can be avoided by adjusting the dose of digoxin. Prophylactic use of a cardiac pacemaker may be considered if the risk of heart block is considered unacceptable. High doses of digoxin may produce a variety of rhythm disturbances, such as first-degree, second-degree (Wenckebach), or third-degree heart block (including asystole); atrial tachycardia with block; AV dissociation; accelerated junctional (nodal) rhythm; unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy); ventricular tachycardia; and ventricular fibrillation. Digoxin produces PR prolongation and ST segment depression which should not by themselves be considered digoxin toxicity. Cardiac toxicity can also
occur at therapeutic doses in patients who have conditions which may alter their sensitivity to digoxin.

**Gastrointestinal:** Digoxin may cause anorexia, nausea, vomiting, and diarrhea. Rarely, the use of digoxin has been associated with abdominal pain, intestinal ischemia, and hemorrhagic necrosis of the intestines. CNS: Digoxin can produce visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy, confusion, and mental disturbances (such as anxiety, depression, delirium, and hallucination).

**Other:** Gynecomastia has been occasionally observed following the prolonged use of digoxin. Thrombocytopenia and maculopapular rash and other skin reactions have been rarely observed.

**DRUG INTERACTIONS**

Potassium-depleting diuretics are a major contributing factor to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and spironolactone raise the serum digoxin concentration due to a reduction in clearance and/or in volume of distribution of the drug, with the implication that digitalis intoxication may result. Erythromycin and clarithromycin (and possibly other macrolide antibiotics) and tetracycline may increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine, certain anticancer drugs, and metoclopramide may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. Rifampin may decrease serum digoxin concentration, especially in patients with renal dysfunction, by increasing the nonrenal clearance of digoxin. There have been inconsistent reports regarding the effects of other drugs [e.g., quinine, penicillamine] on serum digoxin concentration. Thyroid administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias. Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in advanced or complete heart block. Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Digoxin concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting, or discontinuing carvedilol.\[56,57,58,59\]

**CONTRAINDICATIONS**

Digitalis glycosides are contraindicated in patients with ventricular fibrillation or in patients with a known hypersensitivity to digoxin. A hypersensitivity reaction to other digitalis preparations usually constitutes a contraindication to digoxin.

**WARNINGS Sinus Node Disease and AV Block:** Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. The drug may cause severe sinus bradycardia or sinoatrial block in patients with pre-existing sinus node disease and may cause advanced or complete heart block in patients with pre-existing incomplete AV block. In such patients consideration should be given to the insertion of a pacemaker before treatment with digoxin.\[60\]

**PROGNOSIS**

Prognosis in digitalis toxicity worsens with increasing age and associated comorbid conditions. In general, older people have a worse outcome than other adults, who, in turn, have a worse outcome than children. Morbidity and mortality rates increase if the patient has a new dysrhythmia, advanced AV block, or other significant ECG abnormality.

The lethal dose of most glycosides is approximately 5-10 times the minimal effective dose and only about twice the dose that leads to minor toxic manifestations. Morbidity is usually 4.6-10%; however, morbidity is 50% if the digoxin level is greater than 6 ng/mL. The 2014 AAPCC report had follow-up data for 471 of the 1,336 patients exposed to plant cardiac glycosides. Outcomes in these patients were as follows: no clinical effect in 326 patients; minor effects in 113, moderate effects in 26, major in 5, and 1 death. Outcomes in 1,134 of the 1,601 patients with digoxin poisoning were as follows: no clinical effect in 262, minor in 155, moderate in 558, major in 132, and 27 deaths.

**CONCLUSIONS**

Digoxin evidently counteracts the hypertensive effect of ouabain. Hence, the result of the actions of the different endogenous cardioinhibitory steroids seems to be a cooperative effect in handling salt and water homeostasis. Because ouabain and digoxin are both inhibitors of the sodium pump, the hitherto used rationale of digoxin therapy becomes muddled. How can this paradoxical physiological action of ouabain and digoxin be explained on a molecular level? Is there a different tissue distribution of the different cardiac glycosides, a difference in their affinities at the various pump isofoms, differences in the signal transduction pathway are there other receptors for cardiac glycosides besides the sodium pump.

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