The author provides a review of the pharmacokinetics, clinical usage, and anesthetic considerations of the digitalis class of compound—the cardiac glycosides.

The use of digitalis preparations dates to the 1500s. However, it was not until the late 1700s that Withering recognized that such compounds elicited an effect on the heart. By 1790, the cardiac effects of digitalis were labeled as their primary mode of action. Digitalis compounds continue to be popularly employed for therapeutic control of various cardiac ailments.

The term digitalis is used in this article to refer to any steroid that exerts positive electrophysiological effects on the heart.

The most common sources of digitalis and related compounds are the leaves of the Digitalis purpurea, or royal purple foxglove, from which are derived digitoxin, digitalis leaf, and gitalin, and the leaves of the Digitalis lanata, from which are derived digoxin, lanatoside C, and deslanoside. Ouabain is derived from another source, the seeds of the Strophantus gratus.

Chemical structure and properties

All cardiac glycosides contain a steroid nucleus with an unsaturated 5- to 6-membered lactone ring attached at the C-17 position. The double bond (demonstrating unsaturation) of the lactone ring and the steroid nucleus appears to be essential for eliciting cardiac activity.

Note that three deoxyhexoses arise from the number three carbon, and loss of the sugars reduces potency and duration of action. Variations among different glycosides occur in the steroid nucleus and with the substituted sugars. Potent cardioactivity does, however, require the unsaturated lactone ring, the C-14 B-hydroxyl group, and cis-fusion of the C and D rings. The structural formula of digoxin is shown in Figure 1.

Mechanism of action

The most common theory used to discuss the mechanism of action of cardiac glycosides is based on studies demonstrating their effects on intracellular potentials and ion flux. Results have shown that these preparations do not alter production, storage, or liberation of myocardial energy, but do reduce the energy of the sodium pump by inhibiting the activity of the Mg++ and ATP-dependent transport enzyme complex (Na+K+)-ATPase.

It is necessary to review the action of the sodium pump for matters of clarity. The transfer of Na+ and K+ is obligatorily coupled in that neither can proceed without the other. The pump, located within the cell membrane, receives its energy from ATP. The hydrolysis of one ATP provides the energy to pump 3 Na+ ions to the outside of the cell and 2 K+ ions to the inside of...
the cell across concentration gradients, the transport is catalyzed by a specific enzyme: (Na+ + K+) - ATPase, a large lipoprotein. This enzyme, acting as a carrier, has binding sites for Na+ and K+, and thus delivers and releases these ions at opposing sides of the cell membrane. Enzyme activity is dependent on Na+, K+, and Mg++ concentrations.

In 1964, Repke postulated that (Na+ - K+) - ATPase is the receptor for cardiac glycosides, and that their presence blocks the activation of the sodium pump by interfering with the transport of K+ extracellularly. The result, according to Repke, is a net loss of K+ and net gain of Na+ intracellularly. Because the pump requires both Na+ and K+ for proper function, its activity is inhibited. This mechanism is illustrated in Figure 3.

Further evidence exists to support the theory of glycoside-induced sodium pump inactivity. It can be listed as follows:

- A direct relationship exists between the degree of the pump's inhibition and cardiac activity.
- The onset and duration of effects parallel the time of course of inhibition.
- Positive ionic effects are enhanced by an increase in intracellular Na+ and delayed by a decrease in intracellular Na+.
- Other factors, such as acidosis, hyperkalemia, and hypothermia reduce inotropic and inhibitory effects equally.
- Increased extracellular K+ has been shown to slow the uptake of cardiac glycosides by myocardial tissue.

Based on this evidence, it is believed that inhibition of (Na+ + K+) - ATPase, with a concomitant inhibition of sodium pump activity produced by cardiac glycosides, is the basis for the inotropic effects and cardiac activity.
Physiological effects

Cardioactive steroids exert several effects on the myocardium. All properties of the cardiac muscle—contractility, conduction, refractiveness, and automaticity—are altered.6

Contractility. The most significant pharmacodynamic effect exerted by the glycosides is a positive inotropic action on the normal and failing heart. This is the direct result of increased systolic contraction, along with decreased duration of systole. Improvement of myocardial contractility occurs as a result of a stimulated sodium-calcium transport system.

The role of calcium in excitation contraction is very important: calcium binds the troponin-tropomyosin complex, allowing an actin-myosin reaction.

Sodium is linked to calcium in a special transport system whereby sodium efflux is coupled with calcium influx. Inhibition of the sodium pump produces a net gain of sodium intracellularly. Increased intracellular sodium concentrations stimulate the sodium-calcium transport system. Calcium uptake is increased, excitation contraction coupling enhanced, and myocardial contractility increased.8

Conduction. Conduction through the A-V node and Purkinje fibers is depressed by cardiac glycosides. The initial effects are due to vagal stimulation, but with a full digitalizing dose, depression is accomplished by decreasing the rate of rise of action potential and decreasing resting potentials.8 The end result is a prolonged P-R interval.

Refractiveness. Digitalis and related compounds prolong the atrial refractory period, thus decreasing atrial impulses and minimizing the number of depolarization waves reaching the ventricle. An increased refractory period slows conduction in the A-V node and in the His bundle, resulting in a prolonged P-R interval. This prolongation allows for a slowing of ventricular rate and a subsequent increase in circulation. Improved circulation causes a vagal effect, slowing conduction through the His bundle even further.

Automaticity. Automaticity is increased directly due to an increased rate of diastolic depolarization and indirectly by the automatic nervous system.

Clinical uses

There are several digitalis-like preparations on the market today. The choice of preparation depends on the desired onset and duration of action, along with the desired route of administration. Common cardiac glycoside preparations are shown in Table I.9

Congestive heart failure. Digitalis therapy is most widely used to treat congestive heart failure. The positive inotropic action (1) increases cardiac output; (2) decreases the filling pressure of either the failing left or right ventricle or of both ventricles; and (3) increases diuresis.

An explanation of the cardiac effects of the use of glycosides has already been given, but it should be mentioned that the decreased rate of sinus tachycardia in congestive heart failure is accomplished by a diminished sympathetic tone and is not a direct effect of digitalis.9

<table>
<thead>
<tr>
<th>Cardiac glycoside preparations</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Ouabain</td>
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<tr>
<td>Deslanoside</td>
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<tr>
<td>Digoxin</td>
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<tr>
<td>Digitoxin</td>
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<tr>
<td>Digitalis leaf</td>
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As is commonly known, edema is an adverse effect of the failing heart, and the diuresis that results from digitalization is welcomed. Edema is a result of (1) decreased renal blood flow and glomerular filtration rate; (2) increased capillary hydrostatic pressure resulting in decreased extracellular fluid reabsorption; and (3) stimulation of the renin system with secondary aldosteronism.\textsuperscript{1,8}

Augmentation of the force of myocardial contraction overcomes many of these influences. It has also been postulated that glycosides interfere with tubular reabsorption of sodium, thus decreasing net H\textsubscript{2}O formation.

\textit{Atrial fibrillation.} Digitalis and related compounds are extremely useful in the treatment of atrial fibrillation. The rapid ventricular rate commonly associated with this arrhythmia causes a reduction in work capacity that can lead to heart failure. Digitalis is given to patients with atrial fibrillation to restore myocardial efficiency, reduce ventricular rate, and eliminate the pulse deficit.\textsuperscript{1} It accomplishes this by prolonging the refractory period, thereby decreasing atrial impulses and ventricular rate by both vagal and direct mechanisms.

\textit{Atrial flutter.} Atrial flutter is usually accompanied by a 2:1 A-V block.\textsuperscript{9} Glycosides are used to treat atrial flutter in hopes of converting the flutter to fibrillation, increasing the degree of block, or restoring sinus rhythm to normal. Conversion of flutter to fibrillation facilitates management of the ventricular rate. Augmentation of the degree of block protects the heart from sudden changes in ventricular rate.\textsuperscript{1}

\textit{Paroxysmal atrial tachycardia.} Cardiac glycosides are sometimes used in the management of paroxysmal atrial tachycardia. The mechanism of action is probably due to reflex vagal stimulation.

A summary of the physiological effects produced by cardiac glycosides appears in Table II.

**Toxicity**

The incidence of digitalis toxicity reportedly varies from 8-35\%; mortality attributable to cardiac toxicity ranges from 3-21\%.\textsuperscript{10} Given these percentages, it is evident that cardiac toxicity is a major concern with digitalis overdose. Most common arrhythmias associated with overdosage are produced by stimulation of ectopic centers at various levels in the heart and production of A-V block.\textsuperscript{11}

No specific arrhythmia is associated with digitalis toxicity; however, the most frequently appearing include bigeminy, ventricular extrasystoles, and various degrees of heart block. Sinus bradycardia, atrial, ventricular and junctional tachycardia, atrial and ventricular fibrillation, and sinus arrest have also been seen.\textsuperscript{8,11} Mobitz type II block is usually not associated with digitalis toxicity.\textsuperscript{10}

Electrocardiographic changes include depressed S-T segment and inverted T wave. Overdosage can precipitate heart failure or aggravate failure that is already in existence.

Other clinical manifestations include gastrointestinal disturbances such as abdominal pain and diarrhea. Nausea and vomiting occur due to glycoside effects on the chemoreceptor trigger zone.\textsuperscript{1,8} Visual symptoms include photophobia, scotomata, blurred vision, and halos around objects.\textsuperscript{1,2,6} Neurological complaints range from malaise and headache to confusion, delirium, and hallucinations.

Extracardial symptoms such as fatigue, anorexia, and psychic and visual disturbances can be related to digitalis intoxication. Investigation of such symptoms and subsequent adjustment in digitalis therapy can prevent severe cardiac disturbances.\textsuperscript{12}

Several factors have been known to amplify digitalis toxicity. These include:

(1) \textit{Electrolyte imbalance.} Hypokalemia is the most frequent cause of toxicity. Low serum K+ levels often accompany diuretic therapy. The de-

| Table II |
|---|---|
| **Physiological effects produced by cardiac glycosides** | |
| **Response** | **Mechanism** |
| ↑ Cardiac output | ↑ Inotropic effect |
| ↓ Venous pressure | ↑ Inotropic effect |
| ↓ Peripheral vascular resistance | ↓ Tone of peripheral resistant vessels |\textsuperscript{9} |
| ↑ Arterial pressure | Direct peripheral action; central reflex action |
| ↓ Heart rate | ↑ Inotropic effect |
| | ↑ Vagal stimulation |
| | ↑ Conduction |
| | ↑ Refractiveness |
| ↓ O\textsubscript{2} consumption | ↑ Left ventricular end diastolic pressure |
| | ↑ Inotropic effect |
| ↑ Diuresis | ↑ Cardiac output |
| | ↑ Tubular reabsorption of Na+ |
pletion of intracellular potassium and an abnormal ratio between intracellular and extracellular concentrations of potassium are determining factors. Calcium and digitalis have synergistic effects. Thus, hypercalcemia will enhance sensitivity to digitalis. Hypercalcemia should be suspected in surgical patients with metastatic breast or bronchogenic carcinomas, hyperparathyroidism, hyperthyroidism, or Paget's disease of the bone. Hypomagnesemia due to diuretic therapy increases the arrhythmogenic effects of digitalis.

(2) *Thyroid function.* The hypothyroid is sensitive; the hyperthyroid is resistant. The mechanism has not yet been clearly defined.

(3) *Acute hypoxia and chronic obstructive pulmonary disease.*

(4) *Renal function.* The excretion of digitalis is related to creatinine clearance.

(5) *Liver function.* Decreased hepatic blood flow or impaired function increases sensitivity to toxicity.

(6) *Age.* Children appear very tolerant, but the elderly are sensitive to toxicity. Since digitalis is bound to muscle tissue, the dosage should be reduced in elderly persons with their decreased muscle mass.

**Treatment of intoxication**

The key to successful treatment is early recognition that an arrhythmia is related to digitalis intoxication. This can be determined by drawing serum digitalis levels. Serum levels greater than 2.4 ng/ml should be closely monitored.

As stated previously, the type of dysrhythmia presenting varies, and treatment is commensurate with the disturbance. The more common manifestations, including ectopic beats, 1° A-V block or atrial fibrillation with a slow ventricular response, usually require temporary withdrawal of the drug. Any disturbance that impairs cardiac output requires active intervention. Drugs of choice include phenytoin, lidocaine, propranolol, and potassium if hypokalemia is present.

Experimental studies have demonstrated that digitalis-specific antibodies of their Fab fragments (fragment with specific binding properties) reverse pharmacological and toxic effects of cardiac glycosides in vitro and in vivo model studies. Fab fragments have been used successfully to reverse digoxin-induced intractable hyperkalemia and advanced A-V Block. The suggested advantage of using Fab fragments rather than IgG is that Fab fragments offer rapid clearance and reduced variability in the time course of toxicity reversal.

**Anesthetic implications**

The use of cardiac glycosides is widespread in the adult population; thus the effects of anesthetic agents on digitalis tolerance are of considerable interest to the anesthetist.

Inasmuch as the therapeutic index of digitalis is quite low, and digitalis itself is capable of inducing acute and chronic dysrhythmias, knowledge concerning potential anesthetic/digitalis-induced ventricular dysrhythmias is essential.

Inhalation anesthetics protect the heart from ventricular arrhythmias caused by acute digitalis administration, and digitalis also appears to partially desensitize the myocardium to the dysrhythmic effects of catecholamines during inhalation anesthesia. However, most anesthetics, inhalation or intravenous, have an additive effect on glycoside-induced conduction disturbances.

Chung reports that halothane, enflurane, ketamine, droperidol, fentanyl citrate and droperidol (Innovar®), and d-Tubocurarine increase the tolerance of the heart to digitalis-induced arrhythmias while Na thiopental and fentanyl have no effect. There has been no documentation about the effects of isoflurane (Forane®) and digitalis. Succinylcholine-, neostigmine-, and diazepam-induced ventricular arrhythmias have been reported.

No one specific agent is contraindicated, but caution should be exerted when using those agents that have been known to produce dysrhythmias.

Whether or not to withhold digitalis preoperatively is a question that remains in controversy. The anesthetist should strive to maintain normal fluid and electrolyte balance, acid-base balance, circulatory parameters and renal function in an effort to eliminate dysrhythmias caused by disturbances in these modalities and concomitant glycoside therapy.

**REFERENCES**


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