REVIEW

Pharmacological Treatments of Congestive Heart Failure: A Look at Yesterday, Today and Tomorrow

Tai Akera

Department of Pharmacology and Toxicology, Michigan State University, MI, USA

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Abstract

Digitalis glycosides have been used for more than 200 years to treat chronic congestive heart failure although they often fail to provide adequate support in a patient with a severely depressed heart at the dose that does not cause toxicity. Improvement of this class of drugs is not feasible because both the therapeutic and toxic actions are caused by the same mechanism, i.e., inhibition of the sarcolemmal sodium pump. Despite the initial optimism with "newer" positive inotropic drugs, they are not free from toxicity which is caused by Ca$^{2+}$ overload or from their tendency to inhibit relaxation. Moreover, these drugs fail to reduce risk factors in patients with advanced heart failure. Mortality of these patients is reduced by vasodilator therapy combined with digitalis and a diuretic. This therapy reduces preload and afterload, and hence workload, in addition to increasing the force of myocardial contraction, and minimizes deficiencies of failing heart. In this regard, importance of nonpharmacologic therapies for reduction of cardiac workload should also be emphasized. All these treatments, however, are palliative. We know very little about the basic changes that lead to heart failure, and treatments to prevent those changes are presently unavailable.

Introduction

Congestive heart failure, or chronic circulatory insufficiency, occurs when the heart muscle cannot develop sufficient pumping force to deliver an adequate blood supply to
various organs. Because the underlying deficiency is a reduction in myocardial contractility, it would appear logical to treat the condition with cardiac positive inotropic agents. Underlying pathological conditions may vary, but clinical symptoms are similar. These include fatigue, reduced exercise tolerance, shortness of breath, edema of lower extremities and finally pulmonary edema. It was these types of edema, William Withering\textsuperscript{1} found some 200 years ago, that could be successfully remedied by the leaves of foxglove (digitalis). He also noted that the drug retards the pulse "to an alarming degree without any preceding effect.” Effects of digitalis on the heart muscle had been suggested by many: in 1938 Cattell and Gold\textsuperscript{2} unequivocally demonstrated that the primary site of the beneficial action of digitalis was the cardiac muscle. Following the purification of the digitalis glycosides, digoxin and digitoxin became the mainstay of therapy for congestive heart failure.\textsuperscript{3}

During congestive heart failure, several mechanisms are triggered in an attempt to compensate for the inability of the heart to pump adequate amounts of blood. First, end-diastolic volume increases. This increase in “preload” causes the heart muscle to contract with a greater force, as indicated by the Frank-Starling’s law, at the expense of a decreased energetic efficiency. In addition, the intravascular blood volume, and therefore preload, may also be increased by activation of the renin-angiotensin-aldosterone axis. Sympathetic tone also increases, forcing the heart to work harder to eject enough blood, again at the expense of decreased energetic efficiency. The cardiac glycoside restores myocardial contractility and reverses all these symptoms if the underlying pathological changes are not too extensive.

The glycosides, however, are by no means "ideal" drugs. They have inherent and notorious tendency to produce toxicity. When a patient is given about 70 percent above the “optimal” dose of digitalis, severe toxicity may result. Thus, the glycoside, with a calculated therapeutic index (the ratio between toxic and therapeutic doses) of approximately 1.7, is among the most toxic drugs in current use. Intoxication due to overdose of digitalis is a frequent, serious and potentially fatal complication of its therapeutic use.

**Attempts to improve digitalis glycosides**

The adverse reaction to the digitalis glycoside includes symptoms of central origin such as anorexia, nausea, vomiting, weakness and yellow vision. The major toxicity of digitalis, however, is characterized by various types of cardiac arrhythmias. The treatment of congestive heart failure is frequently initiated by the concurrent use of digitalis and diuretics. Such combined therapy is dramatically effective. Edema, typical of congestive heart failure, normally disappears within a week, and the general condition of the patient improves. At this time, however, the plasma potassium concentration is lowered because of the combined action of digitalis and diuretics. Digitalis produces
stronger actions when the plasma potassium concentration is low. Therefore, a toxic reaction to digitalis may develop unless the dosage of digitalis is reduced.

The major problem with digitalis is its low therapeutic index. Therefore, enormous efforts have been made to improve the therapeutic index of digitalis by modifying its chemical structure. From time to time, new derivatives claiming to have better therapeutic indices have been reported; however, a good separation of therapeutic and toxic actions has not been achieved. Moreover, many claims for "safer" drugs (for example, the aminosugar glycoside4) are contradicted by others.5

Because several hundreds of compounds have already been tested yielding disappointing results, one may ask if it is possible to separate the therapeutic and toxic actions of the glycoside. This question was originally posed by Cattell and Golda6 in 1941. Their tentative conclusion based on several compounds available at that time was that these two actions of the glycoside are not separable by chemical modification of the cardiac glycosides. A definite answer does not come from synthesizing compounds and testing their therapeutic indices because there is always a possibility that the "next" compound may show a separation of the therapeutic and toxic actions. Chemical modifications have been successful for many other classes of drugs. A definite answer to the above question, however, has come from studies into the mechanisms of the therapeutic and toxic actions of the cardiac glycosides.

**Mechanism of actions of digitalis glycosides**

The primary mechanism responsible for the positive inotropic action of the cardiac glycosides is the inhibition of the cardiac sarcolemmal sodium pump.7 A 20 to 40% inhibition of the pump causes a 10 to 20% increase in the intracellular Na+ concentration observed during the diastolic phase.8 During this phase, the Na+/Ca2+ exchange mechanism in the sarcolemma normally mediates Na+ influx coupled with Ca2+ efflux.9 Therefore, an elevation of the intracellular Na+ is likely to reduce the amount of Ca2+ to be extruded by the exchange mechanism. This may cause an extra amount of Ca2+ to be taken up by the sarcoplasmic reticulum. If this sequence of events occur, it will increase the amount of Ca2+ to be released from the sarcoplasmic reticulum triggered by membrane excitation, and thereby increases the force of myocardial contraction.

The above hypothesis is supported by findings (1) that digitalis preferentially increases developed tension that is dependent on Ca2+ released from the sarcoplasmic reticulum over that which is dependent on transmembrane Ca2+ influx10 and (2) that digitalis increases cellular Ca2+ during the diastolic phase instead of increasing Ca2+ influx during membrane excitation.11,12 Digitalis does increase intracellular Ca2+ transients; however, this is the result of the increased Ca2+ loading of, and Ca2+ release from, the sarcoplasmic reticulum.

The mechanisms for the toxic actions of the cardiac glycosides are more complex
involving both direct actions on the heart muscle and indirect actions on the autonomic system. Ventricular tachyarrhythmias are the most prominent toxic effect of the cardiac glycoside resulting from its direct action. A popular hypothesis is that a toxic concentration of the cardiac glycoside causes a 60-80% inhibition of the sodium pump, modifies Na⁺/Ca²⁺ exchange, increases the diastolic Ca²⁺ concentration in the cytoplasm, causes Ca²⁺ overload of the sarcoplasmic reticulum (see above) and causes an oscillatory release of Ca²⁺ from the intracellular stores and transient inward currents which in turn cause oscillatory afterpotentials. Oscillatory afterpotentials that originate in the cardiac Purkinje fibers are obviously the cause of ventricular arrhythmias.

Indirect actions of digitalis on the autonomic nervous system are the primary cause of digitalis-induced atrio-ventricular (AV) block which is another cause of arrhythmias. In addition, neural effects of digitalis modify the sensitivity of the heart to the direct arrhythmogenic actions. Neural effects of the cardiac glycosides, including changes in the sensitivity of the baroreceptors, are most likely to result from Na⁺,K⁺-ATPase inhibition of nervous tissue. Therefore, it may be concluded that the receptors that mediate both the therapeutic and toxic actions of the cardiac glycoside are the sodium pump. Moreover, these two actions of the glycoside share several common steps that follow sodium pump inhibition.

This is the reason why we cannot completely separate the therapeutic and toxic actions of the glycoside by modifying its chemical structure. Such modifications either increase or decrease the affinity of the drug for the receptor site but cannot alter only one of the two actions. A partial improvement may be possible because a part of the toxicity results from neural effects. It should be pointed out, however, that the surgical elimination of sympathetic influences to the heart increases the dose of digoxin needed to cause arrhythmias but reduces its lethal dose. Similarly, an increase in toxic dose accompanied with a decrease in lethal dose was observed with an aminosugar derivative of digitoxigenin which appears to block sympathetic input to the heart in addition to inhibiting the sodium pump.

**Newer positive inotropic agents**

During the last decade, efforts by pharmaceutical companies have yielded a number of newer positive inotropic agents that have an entirely different mechanism of action. An “ideal” positive inotropic drug that is useful in the treatment of chronic heart failure should be orally active, efficacious in the failing and hypertrophied heart, and free from tolerance development. It should have a high therapeutic index and a negative chronotropic effect. Moreover, it should promote relaxation of heart muscle, and should cause neither vasoconstriction nor an increase in oxygen consumption. The prototype “newer positive inotropic” drug, amrinone, has been claimed to increase developed
tension in patients resistant to digitalis treatment. Although it has many of the favorable characteristics described above, it does have a positive chronotropic effect and increases oxygen consumption in isolated heart muscle preparations. More importantly, amrinone has many adverse effects such as gastrointestinal intolerance (anorexia, abdominal pain, diarrhea), headache, fever, liver function abnormalities, reduced platelet survival, thrombocytopenia, ventricular arrhythmias and cardiac ischemia. Apparently, many of these side effects are caused by mechanisms unrelated to the positive inotropic effect, and therefore chemical modification of amrinone resulted in the synthesis of milrinone, a potent positive inotropic drug which does not have many of the above undesirable effects.

Most of the "newer" positive inotropic agents can be classified as selective inhibitors of type F-III phosphodiesterase. These agents increase myocardial contractility with a minimal positive chronotropic effect and therefore do not share common characteristics with classical phosphodiesterase inhibitors such as methylxanthines. Drugs that are undergoing clinical trials include imidazole derivatives fenoximone, piroximone and CI-914. The bipyridine derivatives amrinone and milrinone appear to fall into this category; however, developers of these compounds insist that phosphodiesterase inhibition accounts for only a part of the positive inotropic action of amrinone or milrinone. A quinolone derivative, OPC-8212, has a potent positive inotropic effect in isolated canine heart muscle preparations. Despite claims that this drug has a pharmacological profile different from the above newer positive inotropic agents, it too has been shown to inhibit cardiac phosphodiesterase. Again, it is unknown if a part or all of the positive inotropic effect of OPC-8212 is due to phosphodiesterase inhibition.

Why is there a reluctance in admitting that the newer positive inotropic agents act by inhibiting phosphodiesterase? This is because catecholamines and the classical type I phosphodiesterase inhibitors have many undesirable effects such as positive chronotropic effects, reduced energetic efficiency and potential for arrhythmogenicity. All these effects are presumably related to an increase in cyclic AMP concentrations. It seems, however, that the increase in tissue cyclic AMP caused by adenylyl cyclase activation of glucagon, histamine or forskolin also results in different pharmacological profiles when compared to those caused by catecholamines or methylxanthines. Chronotropic effects of phosphodiesterase inhibitors may or may not be observed depending upon the distribution of the sensitive phosphodiesterase and whether cyclic GMP concentration is simultaneously altered.

An advantage of phosphodiesterase inhibitors may be their ability to cause vasodilation. The relative contributions of increased contractility and vasodilation to the beneficial effect of amrinone are controversial. This issue has been probably complicated by the wish of some that the newer positive inotropic drug works indeed via the positive inotropic effect instead of vasodilation. Vasodilation will reduce afterload and preload,
and therefore reduces the work load of the failing heart. A combination of the inotropic and vasodilating actions may indeed be highly desirable (see below).

These agents improve energetic efficiency resulting from hemodynamic improvements; i.e., a decrease in end-diastolic volume and a reduction in impedance of peripheral circulation. Moreover, amrinone has been shown to shorten the duration of Ca$^{2+}$ transients, a result anticipated from cyclic AMP-induced stimulation of the Ca$^{2+}$-pump in the sarcoplasmic reticulum. This may indicate a reduced tendency for cellular Ca$^{2+}$ overload. If the myocardial force of contraction is enhanced by augmenting Ca$^{2+}$ transients, then a rapid removal of Ca$^{2+}$ after the transient may be the only way to reduce the tendency for Ca$^{2+}$ overload. Alternatively, however, enhanced Ca$^{2+}$ uptake into the sarcoplasmic reticulum may promote cellular Ca$^{2+}$ overload, as suggested from the studies on digitalis that Ca$^{2+}$ overload of this intracellular organelle is the cause of digitalis toxicity. In fact, amrinone has been shown to augment the arrhythmogenic action of digitalis and some of the new phosphodiesterase inhibitors also cause arrhythmias in high concentrations.

An experimental drug, BAY k 8644, has an entirely different mechanism of action. This drug augments Ca$^{2+}$ influx through the slow channels during membrane excitation, and produces a strong positive inotropic effect. Because Ca$^{2+}$ influx is increased only during the early phase of intracellular Ca$^{2+}$ transients, it has less tendency for Ca$^{2+}$ overload compared with the cardiac glycoside. Bay k 8644, however, is developed from dihydropyridine Ca$^{2+}$ antagonists that have high affinity for Ca$^{2+}$ channels in vascular smooth muscle, and causes a strong vasoconstriction. Therefore, this drug cannot be used for the treatment of chronic heart failure.

**Alternative therapy**

When failing heart muscle cannot develop a force sufficient to meet demand, positive inotropic drugs may be used to increase myocardial contractility. Alternatively, the demand, or the afterload and perhaps preload, may be reduced such that the force of failing heart becomes sufficient to provide the necessary cardiac output. Therefore, nonpharmacologic therapies such as reducing physical activity, instituting emotional rest and restricting salt and water intake are important. Pharmacological reduction of cardiac workload can be achieved by lowering the blood pressure, dilating blood vessels and reducing circulating blood volume. A combination of various antihypertensive drugs and diuretics may be used for this purpose. The therapy is apparently successful. Moreover, vasodilator therapy with a combination of hydralazine (300 mg per day) and isosorbide dinitrate (160 mg per day) has been shown to reduce mortality of patients with chronic congestive heart failure receiving digoxin and a diuretic.

It should be noted that the treatment with digitalis or the newer positive inotropic drugs does not reduce the mortality of patients. In fact, chronic therapy with digoxin
or amrinone has been suspected of accelerating the progression of myocardial failure.\textsuperscript{27,28} One problem with the inotropic drugs is that they represent palliative forms of therapy. The inotropic drugs force the failing heart to work harder without correcting the underlying pathophysiological changes that are responsible for the failure of the myocardium. In this regard, vasodilator therapy, although also a symptomatic treatment, offers the advantage of reducing the work load of the failing heart, and this appears to contribute to the risk reduction.

Apparently, the best therapeutic regimen available today is vasodilator therapy combined with the cardiac glycoside and a diuretic. Therefore, it is necessary to understand the basis for rational therapy with the cardiac glycosides in order to take full advantage of the combination therapy.

\textbf{Rational use of digitalis glycosides}

The Na\textsuperscript{+},K\textsuperscript{+}-ATPase inhibition by the cardiac glycoside undoubtedly increases myocardial contractility; however, the role of digitalis therapy in the management of patients with heart failure who remain in sinus rhythm has been controversial. This is because full inotropic effects to support moderately or severely depressed heart may not be obtained in patients owing to the low therapeutic indices of the cardiac glycosides.

Serum concentrations of digoxin and digitoxin associated with the appearance of serious toxicity are 2 ng/ml and 20 ng/ml, respectively. With a calculated therapeutic index of approximately 1.7, at least 50\% of the above concentration is required to obtain the positive inotropic effect. Therefore, it is necessary to maintain the serum glycoside concentration within a narrow range during chronic treatment. This task is complicated by variations in the pharmacokinetics of the cardiac glycosides.

The absorption of digoxin following oral administration varies from 45 to 85\% depending upon the individual and the type of preparation used. Differences in bioavailability of digoxin tablets has been a problem, but is anticipated to be reduced in the future. Absorption is nearly complete with digitoxin, which has a higher lipid solubility compared to digoxin. Differences in the rate and extent of absorption, and also differences in renal clearance should be considered when digoxin is used, and differences in hepatic function, and ensuing variations in the rate of metabolism should be considered for digitoxin.

Development of radioimmunoassay methods for digoxin and digitoxin now provide a means for circumventing pharmacokinetic problems. By re-adjusting the dosage schedule using the feedback from plasma glycoside concentrations, it is possible to achieve a predetermined concentration (target concentration strategy). This approach, however, does not solve the problem that a given serum concentration of the glycoside may cause either a therapeutic or toxic effect. Therefore, it is important to know the nature and extent of changes in digitalis sensitivity of the myocardium under various
A moderate sodium pump inhibition produces positive inotropic effects whereas an inhibition exceeding the reserve capacity of the pump causes toxicity. Therefore, the degree of sodium pump inhibition required to elicit toxicity is determined by the reserve capacity of the pump. A reduction in the number or turnover rate of functioning sodium pump units, an increase in Na⁺ load to the pump and a decrease in extracellular K⁺ reduce the reserve capacity and reduce the tolerance of heart to toxic actions of the glycoside. Moreover, an increase in intracellular Na⁺ or a decrease in extracellular K⁺ concentration stimulates glycoside binding to the receptor, the sarcolemmal Na⁺,K⁺-ATPase. The glycoside binds to the receptor site when this enzyme is in the Na⁺-induced form. The fraction of the enzyme in this form is small, and is increased by a reduction of extracellular K⁺ or an elevation of intracellular Na⁺. Therefore, hypokalemia, tachycardia, electrical cardioversion, hypoxemia and hypothyroidism reduce tolerance of the patient to the digitalis glycosides and may provoke digitalis intoxication. In addition, hypercalcemia or magnesium depletion enhances digitalis toxicity by promoting cellular Ca²⁺ overload. An increase in circulating catecholamine concentrations or an enhanced sympathetic discharge also reduces tolerance of the heart to digitalis-induced arrhythmias.

In an animal model of senescent Fischer 344 rats, the rate of Na⁺ influx is increased and the number of sodium pump sites is decreased, thereby reducing the tolerance of the heart to digitalis-induced toxicity. We do not know if the same condition occurs in man; however, old age has been identified as one condition which reduces the tolerance of the patient to the digitalis glycosides. It should be noted that the inotropic effect of the glycoside is augmented only by an enhanced glycoside binding to its receptor site whereas the toxic effect is augmented by an enhanced glycoside binding and also by a reduced reserve capacity of the sodium pump. Therefore, under the above conditions, a sufficient positive inotropic effect may not be obtained by the cardiac glycoside before the onset of arrhythmias, and therefore it may be wiser to use one of the "newer" positive inotropic agents. In acute myocardial infarction, the digitalis sensitivity of the unaffected area, at which the positive inotropic effect is expressed, is unchanged whereas that of the ischemic and border areas is increased. Therefore, the use of a glycoside cannot be recommended.

It appears, therefore, that digitalis should not be the drug of choice under the conditions in which the tolerance of the patient to the glycoside is reduced because the therapeutic index of the glycoside is generally lowered and the necessary level of stimulation of the heart may not be obtained. Some of the conditions, such as hypokalemia, can be corrected relatively easily, and the glycoside can be used. The number of the sodium pump sites in the myocardium is reduced in hypothyroidism. This condition can be treated by triiodothyronine; however, the induction of the sodium
pump and restoration of normal digitalis sensitivity may take several days. If the patient
is not in a situation where digitalis tolerance is lowered, then the target concentration
strategy can be used successfully to ensure adequate dosage regimens.

The future

We can safely predict that pharmaceutical companies will continue their search
for positive inotropic drugs with greater safety, efficacy and potency. It should be
noted, however, that the positive inotropic agents, either digitalis glycosides or the
newer drugs, provide only a symptomatic treatment of congestive heart failure. In
this regard, these drugs are not significantly different from other palliative therapies
such as diuretics and vasodilators. Obviously, a more logical treatment should be the
correction of the underlying pathophysiological changes which cause the heart to fail.

Many biochemical changes have been known to occur in the failing heart.\(^\text{32}\) These
include changes in intracellular \(\text{Ca}^{2+}\) distribution, dysfunction of the subcellular organ-
elles, changes in membrane structure and alterations in relative abundance of isoenzymes
of myosin, creatine kinase and \(\text{Na}^+,\text{K}^+\)-ATPase. It should be pointed out that most of
these changes have been observed in animal models of chronic heart failure; and that
changes in the relative abundance of isoenzymes, for example, may be irrelevant in
human heart failure because one or the other genes for these enzymes may not be
expressed in man. More importantly, however, we know very little about the initial
and critical events that cause the heart to fail. Some of the observed biochemical
changes probably represent adaptation and are beneficial. It seems, therefore, essential
to identify those changes that are desirable and those which contribute to the process
that causes the heart to fail, and to find a means of modifying the latter process.

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