EDITORIAL REVIEW

The use of digitalis glycosides in sinus rhythm

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Historical perspective
Throughout the last 200 years the use of digitalis glycosides has constantly revealed the weakness of the contemporary understanding of congestive heart failure; in consequence the reputation of these drugs has either soared or slumped according to physicians’ prejudices. Withering (1785) identified Digitalis purpurea as the diuretic ingredient of the Shropshire woman’s herbal brew and in his study of 160 patients he showed that it could relieve dropsy in most of his cases. Although he knew that the drug ‘influenced the pulse’, the concept of heart failure was not recognized, and the primary cardiac action of the drug was not then known. The indications for its use were ill-defined and with more widespread prescription many patients, with little prospect of improvement, were exposed to serious risk from toxic side-effects. Withering knew of no other agent with comparable properties, and he succeeded where many other failed by adopting a reliable dosage regimen and using an experimental approach in each case. He was conscious of the questions that were to inhibit the sustained use of the drug for over 100 years. How does digitalis work? What identifies patients who will benefit? How can the clinical response be measured? How may the risks of treatment be avoided? All are lively questions even today!

After the rejection of digitalis as a dangerous drug of dubious efficacy at the end of the eighteenth century, and the drug being sidetracked for much of the nineteenth century as a treatment for fevers (Keele, 1966), McKenzie (1911) re-introduced digitalis into cardiovascular therapeutics because its atrioventricular nodal blocking properties slowed the ventricular response in atrial fibrillation. He showed that digitalis was particularly beneficial in patients with mitral stenosis and atrial fibrillation. With Lewis (1942) he developed the concept that heart failure was caused by ‘fatigue’ of the ventricular muscle and they proposed that relief in mitral stenosis resulted from cardiac slowing because this allowed the muscle to rest. This controversial aspect of the history of clinical cardiology has been reviewed by McMichael (1975), who concluded that there was evidence from McKenzie’s own work that a factor independent of heart rate control was contributing to clinical benefit. Nonetheless, McKenzie and Lewis considered atrial fibrillation as the specific indication for digitalis and were convinced that few other cases benefited from it. In North America, some workers attempted to examine systematically the effects of digitalis in patients with a variety of cardiac conditions and rhythms. Comparisons of the action of digitalis in sinus rhythm and in atrial fibrillation were made by Christian (1922), Luten (1924) and Marvin (1927). These authors reported a total of over 130 patients and showed that digitalis was associated with improvement in about half the cases in which it was used. They proposed that patients with sinus rhythm benefited as much as those with atrial fibrillation. Gavey & Parkinson (1939) reviewed the controversy, and from their own work concluded that for patients with non-rheumatic atrial fibrillation or sinus rhythm, there was a similar beneficial result from use of digitalis. Patients with rheumatic atrial fibrillation, who showed the greatest reductions of heart rate, responded best of all.

With the advent of haemodynamic studies in man, the place of digitalis as first choice in the treatment of heart failure became more firmly established. The glycosides were shown to have an inotropic action in animals and in man, both with normal and abnormal hearts (Smith & Haber,
The subcellular and ionic mechanisms for this action were thought by most workers to result from a glycoside-induced inhibition of membrane-bound Na\(^+\) + K\(^+\)-dependent adenosine triphosphatase (ATPase), which resulted in a rise in the intracellular pool of free Ca\(^{2+}\). The mechanism of this rise was not understood, but the effect would be a facilitation of excitation–contraction coupling (Lee & Klaus, 1971). Intravenous usage was certainly associated with reductions of intracardiac diastolic pressures and increases in cardiac output. If the syndrome of heart failure was caused by reduced contractility of the ventricular muscle, and if this abnormality was chronically reversible, there appeared to be every reason why these drugs should work in the long term. The appeal of this approach was that the prolonged systolic time intervals, the diminished velocity of circumferential fibre shortening, the reduced peak rate of change of ventricular pressure (dp/dt) etc. could all be favourably influenced by digitalis glycosides. This inotropic activity, considered to be the key to digitalis action, has reinforced teaching in several medical textbooks that digoxin is indicated in all forms of heart failure irrespective of the cause and whatever the rhythm (Scott, 1973; Beeson & McDermott, 1975; Goodman & Gilman, 1975).

Although some doubts have been expressed about the basis for such practice (Editorial, 1976), the volume of prescriptions for digoxin in the U.K. has continued to rise steadily for the last 5 years, and in this decade the digitalis glycosides have become the fourth most commonly prescribed drug in the United States (Schick & Scheuer, 1974). For all this, there has been little evidence that chronic stimulation of the diseased heart yields clinical improvement that could not be produced by alternative means.

**Role of diuretics**

In Gavey & Parkinson’s (1939) study on digitalis, an examination was made of the response to diuretics in 16 patients with heart failure in sinus rhythm who had been refractory to cardiac glycosides. All had a diuresis, including some in whom oedema was not obvious. It is surprising that the demonstration that for some patients a diuretic was more effective than digitalis did not suggest the need for a comparison of the effects of the two drugs. Diuretics were regarded as little more than adjuvants to therapy because they did not influence ‘myocardial insufficiency’.

Several observations suggested that the haemodynamic abnormalities in patients with heart failure could be improved without directly stimulating cardiac muscle. McMichael & Sharpey-Schafer (1944) showed that mechanical lowering of right atrial pressure in such patients produced changes in central venous pressure and cardiac output similar to those produced by digitalis. These observations were extended when Pugh & Wyndham (1949) provided evidence that the intravenous use of diuretics produced similar results.

Later, Rader, Smith, Berger & Eichna (1964) showed that diuretic therapy for heart failure could be used alone on a chronic basis; clinical improvement occurred in the majority of patients. There were changes in haemodynamic variables, but little correlation between such changes and the magnitude of the clinical response; this appeared to most closely parallel the relief of oedema produced by the diuretic. When these workers then added digoxin, increases in cardiac output were seen in some individuals with sinus rhythm, particularly where there had been no haemodynamic change with the mercurial diuretics, but there was no further diuresis or weight change in this subgroup and it was not possible to identify digoxin ‘responders’ on purely clinical criteria.

Modern diuretics such as frusemide and bumetanide are very potent agents for the relief of salt and water retention. These drugs will relieve oedema and symptoms in the majority of patients; the dose may be readily adjusted to the clinical response and the drugs have higher therapeutic/toxic ratios than does digoxin. It is, however, uncommon to find them being used alone but rather in combination with long-term digoxin therapy.

**Is the long-term usage of digitalis worthwhile?**

**Does the inotropic action of digitalis persist?**

This crucial clinically relevant question does not seem to have been asked until recently. Mahler, Karliner & O’Rourke (1974) could demonstrate a maintained improvement in several aspects of myocardial performance in the conscious dog given intramuscular digoxin for 8 days. Subsequently, Crawford, Karliner & O’Rourke (1976) showed similar changes in normal man over a period of 10–14 days; these effects were small, although significant. Dobbs, Kenyon & Dobbs (1977) demonstrated a maintained shortening of left ventricular ejection time over a period of 1 month in patients with heart disease who were given
Do the biochemical changes accompanying digoxin action persist in the long term?

Grahame-Smith (1978) has studied digoxin binding to the Na\(^+\) + K\(^+\)-dependent ATPase system in the erythrocyte membrane; this system has been used as a model for digoxin action on cardiac muscle (Erdman & Hasse, 1975).

During the initial administration of digoxin to patients in sinus rhythm with heart failure, there appeared to be a fall in the number of receptors on the erythrocyte surface available for binding a \(^{3}H\)digoxin marker, as a result of the occupation of receptor sites by unlabelled digoxin. The associated inhibition of the Na\(^+\) + K\(^+\)-dependent ATPase system in the erythrocyte membrane could be correlated with the observed shortening of time intervals in cardiac systole. However, after treatment for a minimum of 2 months, a reverse trend was found despite the maintenance of therapeutic plasma concentrations. \(^{3}H\)Digoxin binding increased to pretreatment values, and the inhibition of the Na\(^+\) + K\(^+\)-dependent ATPase system was diminished; systolic time intervals lengthened. The erythrocyte apparently became pharmacologically tolerant to digoxin during long-term therapy. If the erythrocyte model is at all relevant to inotropic action then the results suggest that this pharmacological effect on the heart may also diminish with time.

Prevalence of digitalis toxicity with long-term use

Digitalis toxicity has been called “one of the most prevalent adverse drug reactions observed in clinical medicine” (Smith, 1975). It has been found in up to 19% of patients admitted to hospital who are using the drug and there are reports of mortality in similar patients ranging from 7 to 50%. Measurement of digoxin concentrations in the blood does not always detect cardiac toxicity (Ingelfinger & Goldman, 1976).

Does digoxin increase the capacity for exercise in patients with myocardial disease in sinus rhythm?

It has become apparent that congestive heart failure is not simply a state of low cardiac output. It is instead a more complicated syndrome of impaired cardiac function characterized by salt and water retention. The signs and symptoms are predominantly those of intra- and extra-vascular space congestion and any treatment that relieves these features produces improvement in the patient irrespective of the haemodynamic change that ensues. If direct cardiac stimulation by digoxin is not required for relief of the signs and symptoms of heart failure in the majority of cases, if the long-term use of the drug is associated with serious risk...
of toxicity, and if there is doubt about long-term inotropism, then it is important to examine whether the drug provides benefits in the form of improved exercise capacity.

There is remarkably little information available on this point. Bruce, Lind, Franklin, Muir, McDonald, McNichol & Donald (1968) were unable to demonstrate any increase in the maximum dynamic response to exercise in normal subjects given an intravenous dose of digoxin. Selzer & Malmberg (1962) were able to increase the cardiac output response to exercise in some patients with 'latent' heart failure as a result of an intravenous dose of digoxin; unfortunately these authors do not report whether these patients were able to do more exercise as a result.

None of these studies answers the fundamental question about the possibility of a long-sustained benefit resulting from the inotropic action of digoxin in patients with symptomatic congestive cardiac failure. How should this question be resolved and what are the important specifications for a study designed to answer it?

The most important principle is to separate those responses expected with modern diuretics from the benefits obtained from augmenting myocardial contraction. The specific benefit of digoxin as a myocardial stimulant can only be examined after relief of salt and water retention by diuretics.

Patient selection is crucial; those with atrial fibrillation cannot be studied, because not only may much of the benefit from digoxin at rest be due to the induced atrioventricular nodal block, but also this block is lessened on exercise. Furthermore, if the basic physiological action of the glycoside is on cardiac muscle, it would seem sensible to exclude non-myocardial causes of heart failure, such as hypertension and valvular disease.

Haemodynamic variables correlate poorly with clinical condition, and the study design should therefore move away from the traditional evaluation of changes in acute haemodynamics and focus on the measurement of changes in symptoms and exercise capacity. Evidence of relief of dyspnoea and fatigue and the demonstration that the patient can do more work, are of greater importance than detecting improvements in contractility indices or cardiac output. If the subjective responses of the patient can be quantified and shown to be reproducible, they should be subjected to the same statistical analysis as the 'hard' data derived from the exercise test.

Important details of the drug administration should include the use of sufficient diuretic therapy to produce normal or near-normal body fluid volumes. This can be checked by isotope dilution methods, but in all cases attempts should be made to produce a basal 'dry' body weight, with freedom from oedema and evidence of vascular congestion. Adjustments of the digoxin regimen should be made by an experienced independent clinician, for the aim should be to use sufficient dose to ensure maximum physiological activity but avoid toxicity. The patient should be studied both when taking digoxin and also when taking a placebo. The trial should be conducted on a double-blind basis. It is important to eliminate confounding variables such as enforced bed rest or changes in the range of daily activities; such variables may affect symptoms.

In a recent study (McHaffie, Purcell, Mitchell-Heggs & Guz, 1978) some of these conditions were met. Six patients in sinus rhythm had myocardial disease, either past myocardial infarction or cardiomyopathy, causing heart failure. Oral frusemide was used to produce a 'dry' weight and symptoms of breathlessness and fatigue were improved as oedema was eliminated. Three pairs of exercise tests were done during the study period of 3 months and the responses of each patient when using digoxin and diuretics were compared with those when using diuretics alone. Visual analogue scales were employed to measure symptomatic changes at each test. Five patients who completed all tests showed no significant change in symptoms, no difference in work load achieved or any difference in the heart rate, respiratory rate, ventilation or respiratory quotient at each work load whether digoxin was added to or removed from the treatment regimen.

With reference to the criteria of adequacy of a trial suggested above, this study had several limitations. It was not double-blind and the digoxin dosage was not adjusted beyond ensuring that serum digoxin concentrations were within the accepted therapeutic range. There was also no test of maximal exercise capacity. Nevertheless, in this group of patients where salt and water retention could be controlled with diuretics, digoxin did not improve the sense of well-being nor the capacity for exercise. The study showed that diuretics could be used as drugs of first choice for some patients with heart failure in sinus rhythm.

Conclusion

There is ample evidence that digoxin, when used in the short term, stimulates the heart and may relieve...
the symptoms of cardiac failure in patients with normal rhythm. Its role in the treatment of the chronic heart failure syndrome with sinus rhythm remains uncertain. There are genuine doubts that the drug is effective with long-term administration and there is considerable risk of toxicity. A characteristic feature of congestive heart failure is that symptomatic benefit can be obtained by measures that relieve intra- and extra-vascular congestion. Since cardiac stimulation may not be required to achieve this, digoxin may not be essential treatment for such patients. It seems rational to suggest that the achievement of a ‘dry’ weight with diuretics should be the first objective in the treatment of congestive cardiac failure with sinus rhythm. Digoxin could then be administered and withdrawn as required, to ascertain whether the use of this drug further improved the clinical state.

References


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