The original description by Withering of the use of digitalis for "dropsy" was published in 1785. Even allowing for the fact that Withering’s observations were uncontrolled, the dramatic diuresis and relief of dyspnoea with the use of foxglove in patients with “dropsy” left him in little doubt about its efficacy.

Two hundred years later, digoxin was regarded as one of the cornerstones of therapy for heart failure, but controversy persisted about its efficacy, particularly in patients in sinus rhythm. More recently, the advent of neurohormonal antagonists (angiotensin-converting enzyme [ACE] inhibitors, β-blockers and spironolactone) that both produce improvements in survival and reduce symptoms has relegated digoxin down the list of therapeutic options for heart failure. Questions have been raised about the incremental benefit of adding digoxin to these newer agents, and there are concerns about the hazards of using digoxin in patients with heart failure. Two studies in the 1980s reported that digoxin use was associated with increased mortality in survivors of myocardial infarction. In addition, other drugs with positive inotropic properties were found to increase mortality in patients with heart failure.

Atrial fibrillation and flutter are the only arrhythmias for which there is widespread support for the use of digoxin, and the use of digitalis preparations in these conditions predates their recognition as specific arrhythmias. There is no doubt that some of Withering’s original patients had atrial fibrillation. In 1836, Bouillaud described digitalis as the “opium of the heart” in the treatment of a patient with severe mitral stenosis and a rapid irregular pulse which, despite remaining irregular, was slowed dramatically by digitalis. Bouillaud was undoubtedly referring to the ability of digitalis to slow the ventricular rate in atrial fibrillation. Early in the 20th century, James McKenzie and Thomas Lewis firmly established the place of digitalis as the treatment of choice for chronic atrial fibrillation.

Thus, in the early years of the 21st century, digitalis, usually in the form of digoxin, is still widely prescribed to control the ventricular response rate in patients with chronic atrial fibrillation.

How does digoxin work?

Although digoxin has traditionally been considered to be a positive inotropic agent (via inhibition of Na⁺–K⁺-ATPase and secondary activation of the Na⁺–Ca²⁺ membrane exchange pump), there is considerable evidence that its primary benefit is mediated via neurohormonal modulation. Several investigators have reported that digoxin enhances vagotonic responses and inhibits sympathetic activity. Furthermore, these neurohormonal modulatory effects are seen with lower doses of digoxin (< 0.25 mg/day), whereas the positive inotropic actions are seen when doses in excess of 0.25 mg per day are used.

Hypokalaemia and hypomagnesaemia, usually a consequence of diuretic use, lower the threshold for digoxin toxicity. The use of spironolactone or other potassium-sparing diuretics in combination with digoxin is likely to limit this problem. Patients taking digoxin in combination with diuretics (including spironolactone) should have their serum electrolytes and renal function monitored regularly.

Information on the pharmacology of digoxin is provided in Box 1.

Digoxin in heart failure

Randomised controlled trials

The role of digoxin in the management of heart failure was clarified by a number of well-designed randomised placebo-controlled clinical trials in the 1990s (Box 2). The

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1: Pharmacology of digoxin

Action
- Increases vagal tone (central effect), leading to slowed ventricular response in atrial fibrillation.
- Reduces sympathetic tone, especially when this is abnormally high, in heart failure. This is probably mediated partly via vagotonic actions and partly via direct effects.
- Positive inotropic action mediated via direct blockade of Na⁺–K⁺-ATPase on cell membranes. This leads to increased intracellular Na⁺ concentration, which in turn increases intracellular Ca²⁺ concentration via the Na⁺–Ca⁺⁺ exchanger.

Toxicity
- Common (seen in 10%–20% of patients on long-term digoxin therapy).
- Cardiotoxicity is most serious and may manifest as ventricular or supraventricular arrhythmias, including sudden increased prevalence of cardiac death (this was almost exactly balanced in Digitalis Investigation Group trial by reduction in “pump failure” deaths). Also, vagotonic actions can produce bradycardia or supraventricular arrhythmias, including prolonged PR interval and high-grade heart block.
- Non-cardiac toxicity includes nausea, vomiting, diarrhoea, visual effects, including “yellow” vision, and gynaecomastia.

The largest and most important of these was conducted by the Digitalis Investigation Group (DIG),³ which involved 7788 patients with heart failure, all of whom were in sinus rhythm on entry into the trial. The large majority were maintained on therapy with diuretics and ACE inhibitors. β-Blocker use was not reported in the trial, but was probably very low. Trial participants comprised 6800 patients with systolic heart failure (left ventricular ejection fraction, < 45%), and 988 patients with preserved systolic function. The average maintenance dose of digoxin was 0.25 mg daily, and patients were followed up for 3–5 years. Digoxin therapy had no effect on mortality (the primary endpoint of the study), but did reduce the need for hospital admission, mainly because of reduced hospitalisations for worsening heart failure (E2). (See Box 3 for an explanation of levels of evidence). The benefit of digoxin appeared to be greater among patients with more severe heart failure (i.e., those with lower ejection fraction, greater cardiomegaly, and higher NYHA [New York Heart Association] class (E2)). However, the benefit was also observed in those with milder systolic heart failure and in those with preserved systolic function.

The DIG study⁹ did not report the impact of digoxin on symptomatic status and quality of life. However, the benefit of digoxin in reducing hospitalisation for heart failure suggests that digoxin helped to maintain a stable clinical condition. Similar conclusions were drawn from two smaller and shorter studies of digoxin withdrawal in patients with stable heart failure: the PROVED¹⁰ and RADIANCE¹¹ trials. In both studies, withdrawal of digoxin was associated with a decline in exercise capacity, deterioration in left ventricular systolic function, and significantly increased risk of hospitalisation for worsening heart failure (E2).

A recent retrospective analysis of the DIG study reported that digoxin therapy was associated with a significantly increased risk of death in women, but not in men.¹⁴ However, this finding should be interpreted with extreme caution, as the analysis according to sex was not pre-specified and women comprised only a small proportion (up to 22%) of the study population. Thus, this mortality difference could simply be a chance finding. Alternatively, the increased mortality could be explained by a higher rate of digoxin toxicity in women, as digoxin levels at 1 month were significantly higher in women than in men.

β-Blocker use was very low in the randomised controlled clinical trials of digoxin described above. The subsequent demonstration that β-blockers have a marked benefit when given with ACE inhibitors has raised the question of whether β-blockers have rendered digoxin redundant in the management of patients with heart failure. One study tested this hypothesis in 47 patients with heart failure and atrial fibrillation, and found that the average 24-hour heart rate was lower, and the mean left ventricular ejection fraction higher, in patients receiving both carvedilol and digoxin than either drug alone (CAFE study; see Box 2).¹² The authors concluded that patients with atrial fibrillation and heart failure should be treated with the combination of a β-blocker and digoxin.

2: Randomised placebo-controlled trials of digoxin in heart failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Rhythm</th>
<th>Primary endpoint</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIG⁹</td>
<td>7788</td>
<td>Sinus rhythm</td>
<td>Mortality</td>
<td>No effect</td>
<td>28% decrease in hospitalisation for CHF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(secondary endpoint)</td>
</tr>
<tr>
<td>PROVED¹⁰</td>
<td>86</td>
<td>Sinus rhythm</td>
<td>Exercise tolerance Rate of worsening CHF</td>
<td>Greater decline in exercise tolerance and higher rate of worsening CHF in digoxin-withdrawal group</td>
<td>Withdrawal design: diuretics ± digoxin</td>
</tr>
<tr>
<td>RADIANCE¹¹</td>
<td>178</td>
<td>Sinus rhythm</td>
<td>Rate of worsening CHF Exercise tolerance</td>
<td>Higher rate of worsening CHF and greater decline in exercise tolerance in digoxin-withdrawal group</td>
<td>Withdrawal design: diuretics + ACEI ± digoxin</td>
</tr>
<tr>
<td>CAFE¹²</td>
<td>47</td>
<td>Atrial fibrillation (chronic or paroxysmal)</td>
<td>24-Hour heart rate LVEF</td>
<td>Lower mean 24-hour heart rate and higher LVEF with β-blocker + digoxin</td>
<td>Crossover design: diuretics + ACEI ± β-blocker ± digoxin</td>
</tr>
</tbody>
</table>

CHF = Congestive heart failure. LVEF = Left ventricular ejection fraction. ACEI = Angiotensin-converting enzyme inhibitors.
Serum digoxin levels are above 1.0 ng/mL. Toxicity (including death) rises rapidly when the average serum digoxin levels are near the upper end of the accepted therapeutic range.19 A study of 12 patients with chronic atrial fibrillation confirmed that medium-dose diltiazem was comparable, in terms of rate control at rest, to a therapeutic dose of digoxin and superior to digoxin during exercise.20 High-dose diltiazem (360 mg/day) was superior to digoxin, both at rest and during exercise.20

Atrial fibrillation

Very recently, the results of the AFFIRM trial, involving 4060 patients with atrial fibrillation randomly allocated to a “rhythm control” versus a “rate control” strategy, were published.21 This benchmark trial showed no difference in mortality and other important secondary endpoints, including quality of life, between the two strategies. A substudy of 1968 patients from the rate-control arm of AFFIRM found that both β-blockers and calcium-channel blocking agents were effective as first-line agents in about 50%–70% of patients, and that digoxin (which was allowed to be added as a second-line agent) appeared to increase the rate control efficacy of these agents modestly.22

The use of digoxin in paroxysmal atrial fibrillation, either to revert the arrhythmia to sinus rhythm or to suppress further paroxysms, was widespread in the second half of the 20th century and remains a popular strategy. However, contrary to common belief, there is no evidence from controlled trials to suggest that digitalis increases the likelihood of reversion to sinus rhythm in patients with recent onset atrial fibrillation. Indeed, there is no electrophysiolog-
Atrial flutter

Most studies of digoxin in atrial fibrillation or flutter have either enrolled patients with atrial fibrillation only, or have combined patients with atrial fibrillation and atrial flutter. There is certainly no reason to believe that digoxin has any role for either pharmacological cardioversion or prophylaxis for atrial flutter (any more than it does for atrial fibrillation), and common observation supports the widely-held belief that digoxin is less effective at rate control in patients with atrial flutter than it is in those with atrial fibrillation (E4).

In 2003, there is little or no role for digoxin in managing arrhythmias other than atrial fibrillation or flutter. It has been widely used in the past to treat re-entrant supraventricular tachycardia in adults and children, but newer agents have superseded it for treating these arrhythmias. It has occasionally been recommended for use in multifocal atrial tachycardia, and there are occasional observational reports of efficacy for this, but its use for this indication is limited by the fact that these patients commonly have pulmonary hypertension and hypoxia, which renders them more liable to digitalis toxicity. Other agents, such as β-blockers and verapamil, are probably best used in this situation. There is no evidence for efficacy of digoxin in suppressing ventricular arrhythmias and every reason to suspect that the agent should be avoided in this situation. (It is of course occasionally observed that patients treated with digoxin for left ventricular dysfunction show reduced ventricular ectopy concomitant with improvement in their underlying condition.)

Recommendations

Digoxin has a limited but useful role, either alone or in combination with other agents such as β-blockers, diltiazem or verapamil, in achieving satisfactory resting ventricular rate control in patients with chronic atrial fibrillation (E1). In patients who lead a predominantly sedentary lifestyle, particularly the elderly, digoxin alone may be the agent of choice for chronic atrial fibrillation (E4). Certainly, digoxin carries a potential advantage over the other agents in that it is very unlikely to precipitate worsening ventricular function in patients whose ventricular function is either depressed or unknown. Other than this, there is no role for digoxin in pharmacological reversion of atrial fibrillation, and little or no support for the use of digoxin in the management of other arrhythmias.

Important messages for patients are shown in Box 4.

Competing interests

None identified.

References


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Heart failure (HF), also known as congestive heart failure (CHF) and congestive cardiac failure (CCF), is when the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs. Signs and symptoms of heart failure commonly include shortness of breath, excessive tiredness, and leg swelling. The shortness of breath is usually worse with exercise or while lying down, and may wake the person at night. A limited ability to exercise is also a common feature. Chest pain, including Digoxin therapy has no effect on mortality in heart failure. Digoxin may be useful for maintaining clinical stability and exercise capacity in patients with symptomatic heart failure. Digoxin appears to be of most benefit in patients with severe heart failure, cardiomegaly and a third heart sound. Digoxin should be used as a second-line drug after diuretics, angiotensin-converting enzyme inhibitors and β-blockers in patients with congestive heart failure who are in sinus rhythm. Atrial fibrillation and flutter are the only arrhythmias for which there is widespread support for the use of digoxin, and the use of digitalis preparations in these conditions predates their recognition as specific arrhythmias. The toxic effects of digoxin include life-threatening cardiac arrhythmias, particularly ventricular tachycardia and ventricular fibrillation, severe bradycardia (slow heart rate), heart block, loss of appetite, nausea or vomiting, and neurological problems including confusion and visual disturbances. Notably, at least 30 percent of people with toxic digoxin levels experience no symptoms. Not long ago, digoxin was a mainstay of therapy for both heart failure and atrial fibrillation. However, in recent decades newer drugs have been developed that are more effective, and safer to use. Most experts now recommend using digoxin only in individuals in whom this drug is likely to offer some particular and substantial benefit. And when it is used, it must be used cautiously. Was this page helpful?