

Digoxin in heart failure and cardiac arrhythmias

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THE ORIGINAL DESCRIPTION by Withering of the use of digitalis for “dropsy” was published in 1785.¹ 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,² 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.^{3,4} In addition, other drugs with positive inotropic properties were found to increase mortality in patients with heart failure.⁵

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.¹ 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.⁶ 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.⁶

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 $\text{Na}^+/\text{Ca}^{2+}$ membrane

ABSTRACT

Heart failure

- 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.
- Digoxin should be used as a first-line drug in patients with congestive heart failure who are in atrial fibrillation.

Arrhythmias

- 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.
- In patients who lead a predominantly sedentary lifestyle (perhaps particularly in those who are elderly), digoxin alone may be the agent of choice.

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exchange pump), there is considerable evidence that its primary benefit is mediated via neurohormonal modulation.^{7,8} 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.⁷

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, as 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 Ca⁺⁺ 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 bradyarrhythmias, including prolonged PR interval and high-grade heart block.
- Non-cardiac toxicity includes nausea, vomiting, diarrhoea, visual effects, including “yellow” vision, and gynaecomastia.

largest and most important of these was conducted by the Digitalis Investigation Group (DIG),⁹ 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 (ie, those with lower ejection fraction, greater cardiomeg-

aly, 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

| Trial | Number of patients | Rhythm | Primary endpoint | Outcome | Comments |
|------------------------|--------------------|---|---|--|---|
| DIG ⁹ | 7788 | Sinus rhythm | Mortality | No effect | 28% decrease in hospitalisation for CHF (secondary endpoint) |
| PROVED ¹⁰ | 86 | Sinus rhythm | Exercise tolerance Rate of worsening CHF | Greater decline in exercise tolerance and higher rate of worsening CHF in digoxin-withdrawal group | Withdrawal design: diuretics \pm digoxin |
| RADIANCE ¹¹ | 178 | Sinus rhythm | Rate of worsening CHF Exercise tolerance | Higher rate of worsening CHF and greater decline in exercise tolerance in digoxin-withdrawal group | Withdrawal design: diuretics + ACEI \pm digoxin |
| CAFE ¹² | 47 | Atrial fibrillation (chronic or paroxysmal) | 24-Hour heart rate LVEF | Lower mean 24-hour heart rate and higher LVEF with β -blocker + digoxin | Crossover design: diuretics + ACEI \pm β -blocker \pm digoxin |

CHF = Congestive heart failure. LVEF = Left ventricular ejection fraction. ACEI = Angiotensin-converting enzyme inhibitors.

3: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system¹³ for assessing the level of evidence.

- E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- E3₁ Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- E3₂ Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a parallel control group.
- E3₃ Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- E4 Level IV: Evidence obtained from case series, either post-test, or pre-test and post-test.

What is the optimal dose of digoxin?

The median maintenance dose of digoxin in the DIG Study was 0.25 mg per day — 70% of patients were maintained on this dose. The steady-state serum digoxin level in patients receiving this dose (available in a subset of patients) averaged between 0.8 ng/mL and 0.9 ng/mL (therapeutic range 0.5–2.0 ng/mL). Higher maintenance doses of digoxin (0.375 mg per day) were used in the PROVED¹⁰ and RADIANCE trials,¹¹ but there was no evidence that increasing the dose in the range 0.2–0.39 mg per day resulted in any symptomatic improvement.¹⁵ There are several lines of evidence showing that the risk of digoxin toxicity (including death) rises rapidly when the average daily digoxin dose exceeds 0.25 mg per day or when trough serum digoxin levels are above 1.0 ng/mL.¹⁶

It is particularly important to use lower maintenance doses of digoxin (0.125–0.25 mg/day) in the elderly because of the age-related decline in renal function. This issue is likely to arise frequently in clinical practice, as the elderly constitute the bulk of the population with heart failure. Furthermore, digoxin toxicity may be difficult to recognise in the elderly.¹⁷ Taking concomitant medications that increase serum digoxin concentrations (eg, amiodarone, quinidine, verapamil) may also necessitate a reduction in the maintenance dose. Cautions also apply to the use of a number of herbal preparations and so-called complementary medicines in patients taking digoxin. For example, squill, strophanthus and oleander contain cardiac glycosides and can trigger toxicity, while senna and cascara may augment potassium loss, leading to toxicity, and St John's wort reduces serum digoxin levels by about 25%.

Digoxin in diastolic heart failure

Diastolic heart failure has been increasingly recognised as a clinical entity, particularly in the elderly and in women.¹⁸ There is little information about the use of any drug therapy in diastolic heart failure. However, the DIG study included

a large subgroup of almost 1000 patients with diastolic heart failure.⁹ The benefit of digoxin in this subgroup was similar to that observed in the main trial.

Digoxin is an appropriate drug for controlling the ventricular response rate to atrial fibrillation in association with diastolic heart failure, as the onset of this arrhythmia may cause marked symptomatic deterioration.

Recommendations

Digoxin is indicated for the management of heart failure. Its primary indication is to maintain clinical stability and exercise capacity in patients with symptomatic heart failure (NYHA class II-IV). For patients in sinus rhythm, it should be used as a second-line drug after diuretics, ACE inhibitors and β -blockers (E4). For those in atrial fibrillation, it should be used as a first-line drug (E2). Maintenance doses of digoxin should not exceed 0.25 mg per day, and may need to be lower in women and the elderly.

Important messages for patients are shown in Box 4.

Digoxin for arrhythmia

While there is little doubt that appropriate doses of digoxin (see above) will slow the resting ventricular rate in most patients with chronic atrial fibrillation (E1), it has been known for many years that digoxin is far less successful in controlling exercise-induced or stress-induced tachycardia in atrial fibrillation in many patients, even when plasma drug concentrations 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-

4: Important messages for patients

- Digoxin is a useful drug, but taking the correct dose is critical, and side effects do occur.
- Digoxin should be taken exactly as prescribed, and any possible side effects, such as unexplained nausea, vomiting or visual changes, should be reported at once to your doctor.

ical reason to suppose such an effect. Digoxin shortens the effective refractive period of the atrial myocardium and, if anything, would be expected to make atrial fibrillation more likely to occur and persist.

It is certainly possible that, in patients with concomitant heart failure, the beneficial effects of digitalis on the myocardium may improve haemodynamic variables enough to produce spontaneous reversion to sinus rhythm. However, it must be remembered that spontaneous reversion is quite common in recent onset atrial fibrillation, and that restoration of normal rhythm during treatment with digoxin does not prove cause and effect.

A small, but well designed randomised double-blind placebo-controlled trial in 36 patients with recent onset atrial fibrillation, and without heart failure, who were given either 1.4 mg digoxin orally over 14 hours or placebo capsules, reported reversion to sinus rhythm in eight out of 18 patients taking placebo and nine out of 18 patients taking digoxin.²³ This, of course, was not statistically significant. The mean time to conversion in those patients who returned to sinus rhythm during the observation period was 5.1 hours in the digoxin group compared with 3.3 hours in the placebo group. A number of similar studies have produced very similar results, including a much larger (239 patients), multicentre Swedish study.²⁴ These are referenced in the latest guidelines for the management of atrial fibrillation, published jointly by the American Heart Association, the American College of Cardiology and the European Society of Cardiology (AHA/ACC/ESC).²⁵ These guidelines state very clearly that “digitalis glycosides are generally no more effective than placebo for conversion of recent onset AF [atrial fibrillation] to sinus rhythm. Digoxin may prolong the duration of episodes of paroxysmal AF in some patients” (E1).

What of the widespread practice of using digitalis as prophylactic therapy in patients with paroxysmal atrial fibrillation? There are no comparable randomised placebo-controlled studies of this strategy, but a study of 139 episodes of atrial fibrillation during ambulatory monitoring in 72 patients did not support it.²⁶ Thirty-one of the patients were taking digoxin, and there was no difference between those taking and those not taking digoxin, either in the frequency of attacks or in the ventricular rate during attacks (140/minute v 134/minute). Furthermore, digoxin therapy was associated with a significantly greater number of prolonged attacks of atrial fibrillation (defined as those lasting more than 30 minutes). In keeping with this and other observations, the AHA/ACC/ESC guidelines state that “the evidence available does not support a role for digitalis in suppressing recurrent AF in most patients”.²⁵

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.

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