

Dilated cardiomyopathy and potentially deadly digoxin

Dilated cardiomyopathy (DCM) is a relatively common condition in sub-Saharan Africa, accounting for a substantial portion of patients admitted for heart failure. In the Heart of Soweto study it was the most common cardiovascular disease.¹ Two important contributions to our understanding of this puzzling condition appear in this issue.

The first paper² examines the genetic background of 'idiopathic cardiomyopathy'. Just over 25% of the patients had familial disease, with an autosomal dominant background in 72% of those, recessive inheritance in 17% and X-linked recessive inheritance in 10%. The clear message that emerges is the importance of making sure that otherwise unexplained cardiomyopathy is not familial and genetic in origin. The authors also state that the same holds for peripartum cardiomyopathy.

The second article³ analyses the clinical differences between the familial and non-familial types of DCM. The patients with idiopathic cardiomyopathy were apparently more ill with more symptoms, larger hearts and a trend to lower ejection fractions. However, death rates at the end of the median follow-up period were the same, at about 40%. The use of digoxin emerged as a significant predictor of mortality in the idiopathic but not in the familial group. Digoxin levels are not reported, and nor are plasma potassium levels, which are powerful modulators of the levels at which digoxin becomes toxic (Fig. 1).

The 1997 DIG trial is often quoted in support of the use of digoxin.⁴ However, those were ancient days in terms of the progress of heart failure therapy, well before widespread evidence-based use of the major mortality-reducing agents, namely beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, and long before interventions such as cardiac resynchronisation.⁵ The current approach to drug therapy for chronic heart failure is set out in Table I.

Heart failure with sinus rhythm – swings in digoxin use

Digitalis has gone through four phases.⁵ Historically it was regarded as essential first-line therapy for heart failure, together with the diuretics. Secondly, data on ineffectiveness or tolerance came in and use declined, especially in the UK. Thirdly, positive haemodynamic data in several small studies and the two major withdrawal studies then re-established the place of digoxin.

Currently use is declining again for several reasons. Firstly, there are major disagreements about the ideal dose and blood levels.⁵ Secondly, even in the large DIG trial, when heart failure therapy was relatively primitive and did not have the benefit of beta-blockade and ACE inhibitors, there were only limited benefits.⁴ Thirdly, the very

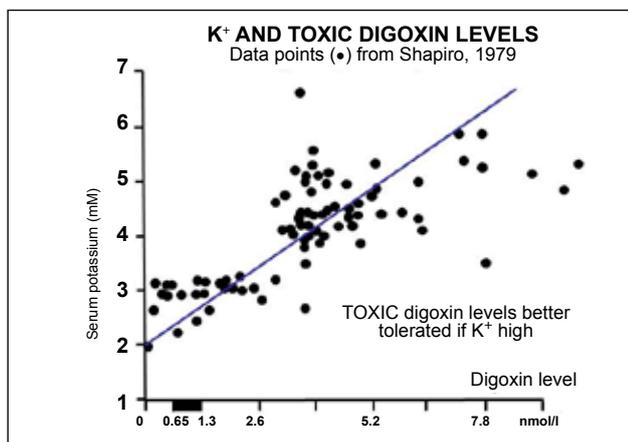


Fig. 1. The relationship between toxic digoxin levels and concurrent blood potassium levels (modified from Fig. 6-10 in Opie and Gersch,⁶ p. 189).

Table I. Chronic heart failure: Drugs that reduce mortality, improve symptoms, or might harm

Reduce mortality – must try to use

1. ACE inhibitors or ARBs
2. Beta-blockers
3. Spironolactone or eplerenone (first check potassium, creatinine)
4. Isosorbide-hydralazine (well tested in African-Americans)

Improve symptoms – use according to clinical judgement

1. Diuretics
2. Nitrates
3. Iron for anaemia
4. Metabolically active agents (if available: trimetazidine, perhexiline)

May be harmful – use cautiously only after due consideration

1. Inotropes and inotropic dilators
2. Anti-arrhythmics, except beta-blockers and amiodarone
3. Calcium channel blockers
4. Digoxin, after checking levels of potassium and creatinine, only in low doses aiming at blood levels of 0.65 - 1.3 nmol/l (0.5 - 1.0 ng/ml). High-dose digoxin, with blood levels of 1.3 - 2.6 nmol/l (1.0 - 2.0 ng/ml), was previously acceptable but no longer is

Modified from Table 6-3 in Opie and Gersch.⁶
ACE = angiotensin-converting enzyme; ARBs = angiotensin-receptor blockers.

narrow therapeutic-toxic window and numerous drug interactions (see Tables 6-6 and 6-7 in Faucier *et al.*⁵) have cast further doubt.

Fourthly, and most tellingly, digoxin is not even considered safe as a last measure in patients with advanced heart failure referred for transplant evaluation.⁶ Patients received full contemporary therapy, almost all being treated by ACE inhibitors/ARBs and beta-blockers, with aldosterone blockers in 46% and devices in 71%. Patients were carefully matched for severity of disease with a control group not given digoxin, yet for the primary outcome of time to death, urgent transplantation or insertion of a device, the use of digoxin was associated with increased hazard, the ratio being 2.28 (95% confidence interval 1.51 - 3.43, $p < 0.001$).

These many problems have relegated digoxin to an optional extra in the management of heart failure, given if at all in lower doses than previously, with the aim of achieving symptomatic rather than mortality benefit.

Heart failure and atrial fibrillation

In the second report in this issue,³ 20 - 25% of patients had atrial fibrillation. How does that affect policy? Increased mortality persists.⁷ In a single-centre study on 1 269 unselected consecutive patients with both atrial fibrillation and heart failure, therapy with a beta-blocker alone or a beta-blocker plus digoxin was associated with a similar decrease of just over 40% in the risk of death ($p = 0.005$). Digoxin alone was associated with worse survival, similar to that of patients without any rate control treatment. There appears to be only one very small study ($N = 14$) focusing on beta-blockade added to digoxin in the treatment of atrial fibrillation in idiopathic cardiomyopathy.⁸ Carvedilol added to digoxin improved left ventricular function. Nonetheless, overall there is no clear place for digoxin in the therapy of heart failure and atrial fibrillation, and the only major study suggests that this drug increased mortality.⁷

Doses and blood levels of digoxin

These are reviewed elsewhere.⁶ Overall, the problem is that no well-designed current studies have prospectively linked the digoxin dose to

both blood levels and clinical outcome. There is now general agreement that the therapeutic-toxic window of digoxin is narrow. Previously, the ideal blood level was pragmatically regarded as 1 - 2 ng/ml (1.3 - 2.6 nmol/l). Currently, lower doses and lower blood levels are strongly supported. Of note, low doses (0.125 mg daily) with a low blood level (mean 0.8 ng/ml) provide as much haemodynamic benefit as previously 'standard doses' (0.25 mg daily, mean blood level 1.5 ng/ml), all this without impairing the autonomic effect as measured by heart rate variability. Digoxin withdrawal studies show that such low doses are as good as the higher doses in maintaining left ventricular function.

Persuasive data come from a retrospective analysis of the large DIG trial on 3 782 heart failure patients followed up for 3 years.⁹ All-cause mortality was modestly decreased, albeit by only 6%, in the tertile with digoxin levels in the previously 'low' range 0.6 - 1.0 nmol/l. This reduction in deaths is more impressive in the propensity-matched re-analysis of the trial,¹⁰ which nonetheless could not get around the basic problem that this trial was done in days gone by, before treatment of heart failure required beta-blockers and ACE inhibitors.

The next higher tertile of digoxin levels in the DIG trial (1.2 - 1.4 nmol/l) had no effect on mortality, whereas the tertile with the previously accepted higher levels (1.6 nmol/l or more) was associated with a mortality increase of 12%.⁹

The practical message – a turnaround level

Digoxin therefore has bidirectional effects on mortality, with the 'turnaround' level being about 1.3 nmol/l,¹⁰ giving a practical therapeutic range of 0.65 - 1.3 nmol/l (Fig. 1) and certainly no higher. Although this conclusion is based on imperfect data and is strictly speaking only hypothesis generating,¹¹ we are unlikely to obtain more decisive data in the near future. To achieve the previous 'therapeutic' but now potentially toxic levels of 1.3 - 2.6 nmol/l, various nomograms have been designed to calculate the dose, taking into account lean body mass and renal function. Clearly these calculations will give too high a dose according to present standards. Note that all these depend on a normal plasma potassium level (Fig. 1).

Digoxin cautions before use

Serum potassium and blood digoxin levels should be measured. However, potassium and creatinine levels are not reported in the accompanying study.³

- **Hypokalaemia** predisposes to toxicity, and potassium must always be checked simultaneously with the digoxin level (Fig. 1).
- **Renal failure.** Digoxin is excreted by the kidneys, so the plasma creatinine must be checked before use. A high circulating level means that caution is necessary and that digoxin, if used at all, should be at an even lower dose.

Digoxin contraindications

Contraindications to digoxin are many and serious.⁵

- The risk of **digitalis toxicity** is the major contraindication, pending a full history of digitalis dosage, blood tests for renal failure, and measurement of serum digoxin and potassium. Digoxin has a blood half-life of 36 hours, so toxicity is not readily reversed and requires digoxin antibodies, not widely available.
- **Hypertrophic obstructive cardiomyopathy** (hypertrophic sub-aortic stenosis, asymmetrical septal hypertrophy) is a contraindication (unless there is atrial fibrillation and severe myocardial failure), because the inotropic effect can worsen outflow obstruction.
- In some cases of **Wolff-Parkinson-White syndrome** with atrial fibrillation, digitalisation may accelerate anterograde conduction over the bypass tract to precipitate ventricular tachycardia or ventricular fibrillation.

- **Atrioventricular (AV) nodal heart block when significant.** Intermittent complete heart block or second-degree AV block or sick sinus syndrome may be worsened by digitalis, especially if there is a history of Stokes-Adams attacks or when conduction is likely to be unstable, as in recent acute myocardial infarction with heart failure or acute myocarditis.
- **Heart failure with preserved ejection fraction (diastolic dysfunction),** seen most notably with concentric ventricular hypertrophy as in hypertension or aortic stenosis, and associated with the paradox of a normal or high ejection fraction, does not respond to digitalis.
- **Fear of breast cancer.** The digoxin molecule has similarities to the oestrogen receptor. Hence digoxin may bind to this receptor with the theoretical risk of increased breast cancer. This fear is confirmed in two large recent Danish studies making use of Danish population databases,^{12,13} both of which show an increased risk of breast cancer with digoxin use in women.

Conclusion

Before using digoxin, be fully convinced that this potentially lethal drug is essential. Why use digoxin for heart failure? Why use a drug with a narrow band of truly safe and effective blood levels? Why use a drug that has no positive hard outcome data in the modern era? Note that blood levels that were previously acceptable are now regarded as toxic. Also note that the patient on digoxin needs their potassium and creatinine levels to be monitored. Finally, it is safe to say that digoxin is a drug that would never be passed by the Food and Drug Administration if it was submitted for registration today. Put simply, digoxin is a dangerous drug, its use perhaps being excusable in earlier years when little was known about its dangers and we did not yet have today's effective therapy for heart failure. The new prospective trials that would have been crucial have not been carried out. It is no wonder that increased mortality was associated with digoxin use in the second of the two studies in this issue of the *SAMJ*.

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