

CLINICAL PRACTICE

Digitalis reappraised: Still here today, but gone tomorrow?

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Digoxin is one of the oldest of drugs acting on the heart and still one of the most frequently used. While in atrial fibrillation digoxin continues to have a valid role in the control of ventricular rate when added to beta-blockers and calcium antagonists, digoxin for heart failure is no longer a supportable option in view of the negative recent meta-analysis.

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In 1673, William Harvey wrote that 'the heart is to be regarded as the primary cause of life'.^[1] In 1705, Thomas Sydenham, an English physician, linked dropsy to difficulty in breathing,^[2] marking the beginnings of the concept of heart failure (HF) for which digitalis, described by Withering in 1801, was the first natural remedy to be used.^[3] Withering was most impressed with its diuretic effects, but he also observed that 'digitalis had power over the motion of the heart to a degree, yet unobserved in any other medicine'. Despite this auspicious history, the use of digoxin is now in serious question as shown by the most recent largest and longest study, from Quebec, in which digoxin use over 14 years was associated with a 14% greater risk of all-cause mortality in patients aged ≥ 65 years with atrial fibrillation (AF) regardless of concomitant HF.^[4] The present article, and other reports since digoxin therapy was last reviewed in the *SAMJ* in 2011,^[5] forcefully bring to our attention that the decision to treat with digoxin potentially exposes the patient to serious risks such as drug toxicity and even death,^[4] as also shown in a recent study on American veterans.^[6]

Swings in digitalis use

Digitalis has gone through several phases. Historically it has been long regarded as essential first-line therapy for HF, together with the diuretics. As data on ineffectiveness or tolerance came in, its use declined, especially in the UK. Thereafter use declined again for several reasons, the first of which was that there were no recent studies to eliminate major doubts regarding the ideal dose and blood levels.^[4-6] Even in the large Digitalis Investigation Group (DIG) trial in 1997, when HF therapy was relatively primitive and did not have the benefit of beta-blockade and angiotensin-converting enzyme inhibitors, there were only limited benefits.^[7] Thereafter, positive haemodynamic data in several small studies and the major withdrawal studies re-established the reputation of digoxin, but that was 21 years ago.^[8] Currently the declining use relates in part to the increasing realisation that digoxin is a very complex drug with a very narrow therapeutic-toxic window and numerous drug interactions (see Tables 6-6 and 6-7 in Teerlink *et al.*^[9]).

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.

Digoxin kinetics, toxicity and contraindications

Digoxin is rapidly absorbed into the circulation where it is unbound to plasma proteins, with a therapeutic level of 0.65 - 1.3 nmol/L, which is about half of the previous toxic level as shown in Fig. 6-12 in Teerlink *et al.*^[9] Also of note is the role of the plasma potassium level in the expression of digoxin toxicity, whereby low potassium levels sensitise the heart to the prevailing digoxin level. The blood half-life is about 36 hours. About 70% is excreted unchanged in the urine after tubular excretion, with the remainder undergoing non-renal clearance by the liver and in the stools.^[9]

In brief, toxicity and major contraindications are as follows:

- Digitalis toxicity is the major complication, 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 which are not widely available.
- Hypertrophic obstructive cardiomyopathy
- Some cases of Wolff-Parkinson-White syndrome
- Atrioventricular nodal heart block if significant.

Recent studies

There are four recent studies, of which the largest and the most recent in clinical practice, in Quebec, showed that digoxin use over 14 years was associated with a 14% greater risk of all-cause mortality in patients aged ≥ 65 years with AF, regardless of concomitant HF.^[10] This study reached the public arena via the *New York Times*, which reported on 8 August 2014 that 'the investigators followed more than 100,000 people with newly diagnosed AF and found that those prescribed digoxin were more likely to die over the next several years than those who received other treatments'.^[11] Further population studies may never be undertaken owing to lack of funding and lack of urgency.

The three other recent reports are of note.^[12-14] In the first, the authors identified adults with incident systolic HF between 2006 and 2008 within the Kaiser Permanente Northern California group who had no prior digoxin use.^[12] The important result was that digoxin use, during a median 2.5 years of follow-up in 2 891 patients with incident systolic HF, was independently associated with an increased risk of death (hazard ratio 1.72; 95% confidence interval 1.25 - 2.36), although there was no difference in HF hospitalisation.

The researchers had controlled for medical history, laboratory results, medications, HF disease severity, and the propensity for digoxin use in their patient population.

Digoxin to control ventricular rate in HF

Even those authorities who still hold that there a place for digoxin in HF therapy^[15] admit that the place of digoxin in AF is insecure and will probably diminish further in the future, because of the drug's inability to reduce heart rate during exercise on the one hand, and the outcome of studies such as the defective negative study of Whitbeck *et al.*^[13] on the other.

Regarding the other major use of digoxin to control the heart rate in HF, in a recent single-centre study on 1 269 unselected consecutive patients with both AF and HF, therapy with a beta-blocker alone or with a beta-blocker plus digoxin was associated with a similar decrease of just over 40% in risk of death ($p=0.005$).^[16] Of further note, digoxin given alone was associated with a worse survival probability, similar to that of patients without any rate control treatment.

Conclusions

There are very few arguments left in favour of the use of digitalis in the control of heart rate in AF. After the negative mortality data from one large recent study of digitalis in HF, enthusiasm for its further testing in HF has diminished further. Ideally an even larger, multicentre, prospective randomised controlled trial could add new conclusive data. Such a trial is, however, very unlikely to be done in view of the low likelihood of digoxin's finding a prominent place in the current increasingly sophisticated therapy of HF.^[9] In the

absence of such a trial, it would be safe to predict that digoxin for the indication of HF would not be passed by regulatory agencies on the basis of present data.

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