Digitalis, Yesterday and Today, But Not Forever

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Editorial

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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 purges[2] that gave 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 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, digoxin use in HF is now in serious question as shown in a placebo-controlled trial in severely ill patients given modern antifailure therapy[4] and as supported by the accompanying article.[5] With this background, the current status of digoxin therapy needs overview,

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Mechanisms of Action

Digoxin has complex modes of action. It remains the only drug for chronic HF that inhibits the sodium pump, which indirectly promotes calcium influx by sodium–calcium exchange, thereby giving rise to the well-known inotropic effect, yet at the same time setting the stage for calcium-mediated toxicity. Inhibition of the Na/Ca exchanger of itself is not powerful enough to achieve therapeutic or toxic intracellular levels of calcium.[6] A newly described mechanism is that digoxin further acts at nanomolar concentrations by inhibition of a novel gene channel, the cardiac potassium channel human ether-a-go-go–related channel, thereby promoting inotropic effects and arrhythmias.[6] Thus, cardiac glycosides are able to delay cardiac repolarization at nanomolar concentrations via human ether-a-go-go–related channel trafficking inhibition.

Phases of Digoxin Use for HF With Sinus Rhythm

Historically, digitalis or digoxin use in HF has gone through several phases. Digitalis was initially regarded as essential first-line therapy for HF, together with the diuretics,[3] and then data on ineffectiveness or tolerance came in and its use declined, especially in the United Kingdom. Thereafter, positive data in the 2 major withdrawal studies and 1 large well-designed study reestablished the applicability of digoxin.[7–9] Now, new trials have cast serious doubt on the benefit of digoxin added to contemporary antifailure therapy, with digoxin even having a negative effect on mortality.[4,5]

Current use of digoxin is now declining for several reasons. First, there are major doubts on the ideal dose and blood levels.[5] Second, even in the large Digitalis Investigation Group (DIG) trial at a time when HF therapy was relatively primitive by current standards[9] and did not have the benefit of β-blockade and angiotensin-converting enzyme inhibitors,[4,9] there were only limited benefits without decreased mortality.[9] Third, the narrow therapeutic-toxic window and numerous drug interactions (see Tables 6-6 and 6-7 in ref. 10) have cast further doubt. Fourth, and based on several retrospective analyses of the DIG trial,[11,12] digoxin came to be accepted as an add-on in otherwise optimally treated chronic HF. For example, digoxin at low serum digoxin concentrations significantly reduced mortality and hospitalizations in patients with ambulatory chronic systolic and diastolic HF.[12]

Assessment of Digoxin in Current Guidelines

In the current European Society of Cardiology guidelines on HF,[13] digoxin has several recommendations to some extent differing from each other. Most positively, it is recommended as a second-line drug added to β-blockade to control the ventricular with a rating of class 1, level B (Table; Figure 3). More realistically, digoxin for HF also falls into the group of less-certain benefits where it is classified as class IIb, level B, with the wording: digoxin could be considered to reduce risk of hospitalization in patients with sinus rhythm and ejection fraction ≤45% or in patients who cannot tolerate β-blockers or ivabradine when the latter is used as an alternative if the heart rate is ≥70 bpm. The guidelines advised that patients should also receive an angiotensin-converting enzyme/angiotensin receptor blocker and a mineralocorticoid receptor antagonist. An additional recommendation was that digoxin could also be considered to reduce risk of hospitalization if the ejection fraction were ≤45% plus persisting symptoms, despite therapy by a β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and a mineralocorticoid receptor antagonist. This overall assessment of digoxin was largely based on the data in the 1997 study[9] and on expert opinion.

The current American (American College of Cardiology Foundation/American Heart Association) guidelines state that digoxin can be beneficial in patients with HF with reduced ejection fraction unless contraindicated to decrease hospitalizations for HF.[14] The rating was class IIa with level of evidence, B. Six references cited in historical order, covering the years 1977 to 1993, will now be reviewed. The earliest

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of 3 cited small early trials comparing digoxin with placebo in 46 patients with prior acute HF found an increased forced expiratory volume, whereas in 9 previously untreated patients digoxin shortened left ventricular ejection time as evidence of the inotropic effect.[15] In a second small trial with a randomized, double-blind, crossover protocol in 25 outpatients without atrial fibrillation, the severity of HF was reduced by digoxin in 14 patients but not in the other 11.[16] In the third small trial, 20 patients with congestive HF were given 7 weeks of digoxin titrated to a serum level of 1.54 to 2.56 nmol/L (too high by present standards)[10] that gave small improvements in dyspnea, walking test score, in clinical assessment of HF, and in ejection fraction.[17]

The next cited trial was longer for >12 weeks and on 230 patients in sinus rhythm with moderately severe HF.[18] Digoxin decreased HF from 47% to 15%. However, a discordant note was struck in another study in which digoxin was compared with captopril therapy for HF.[19] Captopril improved exercise time and New York Heart Association class (41% versus 22%), but digoxin did not.[19]

These led to the well-designed study of the Digitalis Investigation Group,[9,11] in which patients with a left ventricular ejection fraction of <0.45 were randomly assigned to digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and angiotensin-converting enzyme inhibitors (median dose of digoxin, 0.25 mg/d). Digoxin did not reduce overall mortality but reduced the rate of hospitalization both overall and for worsening HF. This was the most important study of those reviewed in the American Heart Association guidelines. Besides the inevitable inherent pharmacokinetic problems of measuring blood and not tissue levels of digoxin, the trial was limited by the antifailure therapy of that time, which did not include β-blockers and spironolactone/eplerenone, and thus only poorly and indirectly applicable to the modern therapy of HF.

Of further note, none of these early trials asked the simple question: what would happen if digoxin were added to diuretic and angiotensin-converting enzyme inhibitor therapy? Yet it is the addition of digoxin to more advanced antifailure therapy that is being recommended in the current European and American guidelines.

Relevant to the combination of digoxin and modern antifailure therapy is the observational study on 5010 patients enrolled in the Valsartan Heart Failure Trial (Val-HeFT). Baseline digoxin use increased all-cause mortality (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.95–1.57) and HF hospitalizations (HR, 1.41; 95% CI, 1.12–1.78) even after baseline differences were controlled in a multivariable analysis using propensity scores.[20] Correctly, the authors plead for future assessment of data from larger prospective HF registries.

Pharmacokinetic Problems of the DIG Study

The Digitalis Investigation Group published their study 16 years ago, when as already emphasized contemporary optimal medical therapy for HF was not available. The study had other defects as well. There was no strict randomization and dose control because 44% of the patients were already on digoxin, and these were randomly assigned to receive either placebo or the same dose of digoxin without any initial washout period. In the remaining 56%, the calculation of the dose by the pharmacokinetic method of Jelliffe and Brooker[21] could only give the expected plasma concentration. However, as Jelliffe[22] recently emphasized, these calculations could not take into account that digoxin has ≥2-compartment behavior, whereas its pharmacological and clinical effects do not correlate with serum digoxin concentrations[11] but with those in the peripheral nonserum compartment. Thus, the dose–effect of digoxin is not settled, with the present estimated therapeutic serum level range being decisively different from the previous higher range (see Figures 6–12 in ref. 10).

Only 1 Randomized Modern Study

That takes us to the only strictly randomized study in the modern HF therapy era, a long jump from the prior Digitalis study in 1977. Added digoxin was randomized to severely ill patients awaiting transplantation for advanced HF.[4] Almost all patients were treated by β-blockers and angiotensin-II modulation. The HR of increased risk of death in the digoxin-treated group was increased seriously (HR, 2.28; 95% CI, 1.51–3.43; $P<0.001$). However, these patients were not remotely typical of ambient patients with HF.

What Does the Current Study Add?

Thus, with this overall highly unsatisfactory data basis on which to judge the supposed benefits of digoxin given to patients with HF in the modern era, the present study is of considerable importance.[5]

The authors support the point of view that recent clinical guidelines, such as those of the European Society of Cardiology or American Heart Association, are based on limited much older trial data. They therefore evaluated the effectiveness and safety of digoxin in a contemporary cohort of patients with incident systolic HF. The authors adopted a new user design[23] that begins by identifying all of the patients in a defined population (in terms of both people and time) who have started a new course of treatment with the study medication. Study follow-up for end points begins at precisely the same time as initiation of therapy. The study is further restricted to patients with a minimum period of nonuse before initiation. This report includes all patients in the study population meeting these criteria.

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. They used multivariable-extended Cox regression to examine the association between new digoxin use and risks of death and HF hospitalization, controlling for medical history, laboratory results, medications, HF disease severity, and the propensity for digoxin use.

They found that among 2891 newly diagnosed patients with systolic HF, 529 (18%) received digoxin. During a median 2.5 years of follow-up, incident digoxin use was associated with significantly higher rates of death (14.2 versus 11.3 per 100 person-years) and HF hospitalization (28.2 versus 24.4 per 100 person-years). In multivariable analysis, incident digoxin use was associated with higher mortality (hazard ratio, 1.72; 95% CI, 1.25–2.36) but no difference in the risk

of HF hospitalization (hazard ratio, 1.05; 95% CI, 0.82–1.34). Their conclusion was that digoxin use in patients with incident systolic HF was independently associated with a higher risk of death but no difference in HF hospitalization.

This conclusion is the opposite of what the earlier studies favoring digoxin use in the bygone era of imperfect therapy for HF had found, with the new conclusion that therapy for HF that includes β-blockade and full angiotensin-II modulation dispenses with the need for taking the risks of adding digoxin therapy. The data at our disposal, taking into account the current study, allow us to seriously question the advice on digoxin given by both the current and influential guidelines, European and American.[13,14]

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Disclosures

None.

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