EDITORIAL COMMENT

Whither Withering’s Legacy?

Digoxin’s Role in Our Contemporary Pharmacopoeia for Heart Failure*

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“The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.”

William Withering, 1785 (1)

“In bringing forward a subject so debated as digitalis and its action, the only apology the writer can offer is that for years he has studied effects clinically . . . He has tried to bring to the inquiry a mind free from prejudice on either side, and impressed with the wish to elicit the truth.”

J. Milner Fothergill, 1871 (2)

“The Digoxin Investigation Group trial changes one fundamental aspect of the treatment of heart failure: digoxin’s inability to substantially influence morbidity and mortality eliminates any ethical mandate for its use . . .”

Milton Packer, 1998 (3)

“Digitalis is part of the first-line therapy for patients with clinical heart failure and left ventricular dysfunction.”

Shahbudin H. Rahimtoola, 2005 (4)

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It is unlikely that any other therapeutic tack in medicine has been debated as much, as long, or with as great intensity and enmity as the prescription of digitalis glycosides for the treatment of dropsical heart failure (1–4). The two-century-old debate will likely never completely end because more sophisticated, evidence-based consensus are unlikely to appear. However, we may be closer to the end than ever before, if for no other reason than because we may tire of the debate (3). It is unlikely that a large, properly powered and controlled, morbidity-mortality end point clinical trial will ever again be performed with a digitalis preparation in chronic heart failure. Thus, in this issue of the Journal, Adams et al. (5) offer a statistically elegant re-analysis of the Digitalis Investigation Group (DIG) trial. Two previous DIG trial database analyses by Rathore et al. (6) and a recent re-analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) trial by Domanski et al. (7) help to put some important questions to rest, albeit a fitful one.

Withering had no real insight into the pharmacologic and physiologic effects of foxglove tea. Indeed, he could not link precisely the condition of dropsy to congestive heart failure, or even the heart per se, although he came tantalizingly close. For many years the clinical effects of digoxin, particularly in patients with normal sinus rhythm, were thought to be related to the inhibition of sodium, potassium, and adenosine triphosphatase interaction, which translated into increased cardiac contractility. More recently, it has been suggested that the putative benefits of digoxin relate more to neurohormone modulation, including sensitization of arterial and cardiac baroreceptors, vagolytic-induced decreased sympathetic nervous system tracking, and suppression of renal renin secretion (8,9). Whatever the most important pharmacologic and physiologic actions of digoxin may be, benefits have been suggested in several small, short-term follow-up, clinical trials (8–10) and two larger, but non-morbidity end point “digoxin-withdrawal” studies (11,12). In aggregate, the benefits seem primarily related to improvement in symptoms and exercise or functional capacity.

The beauty of the DIG trial was, unlike smaller studies, its power to address more definitively the question of major morbidity (hospitalizations, in particular) and mortality. The DIG trial, which provided substrate for the analysis by Adams et al. (5), was a 6,800-patient randomized, double-blind, placebo-controlled clinical study of digoxin added to diuretics and angiotensin-converting enzyme inhibitors in patients generally with left ventricular ejection fraction ≤45% (13). A stratification for ejection fraction >45% allowed patients into the trial with symptomatic congestive heart failure and more preserved systolic function. During a three-year follow-up period, there were no statistically significant mortality differences between the treatment and control groups. However, the clinically important end points of hospitalization for worsening heart failure and all-cause hospitalizations were significantly diminished. A systemic review and meta-analysis of several clinical trials also suggested that digoxin reduces hospitalization rates while improving symptoms related to chronic heart failure (14).

Problematic with the DIG trial observations, however, have been retrospective database subset analyses suggesting that digoxin was associated with adverse events. One analysis suggested that digoxin actually reduced deaths related to worsening heart failure while, arguably, increasing events related to problematic arrhythmias (14). These observations led to an underwhelming response from the clinical community (3). Indeed, more contemporary trial data suggest that the use of digoxin has decreased. For example, in the SOLVD “treatment” trial published in 1991 (15), 67% of participants were on digoxin compared with 53% in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) low-ejection study

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published in 2004 (16). Although conducted more than one decade apart, these two studies were very similar in design characteristics. Observations perhaps linked to the DIG trial include the subsequent analysis of the trial dataset, and the overwhelming evidence that other drugs (beta-blockers, in particular) clearly reduced heart failure mortality, although fortunes of this drug have waned.

One DIG trial analysis raised specific concerns about the use of digoxin in women (17). There was a 5.8% difference between men and women with respect to all-cause mortality. More specifically, the mortality rate in women assigned to digoxin was 33.1% versus 28.9% in the placebo group, whereas the rates in men were 35.2% and 36.9%, respectively. A significant interaction analysis existed between men and women (p = 0.034) and, in the multivariable analysis, digoxin seemed to be associated with a higher risk of death in women (hazard ratio 1.23, 95% confidence interval 1.02 to 1.47). This analysis is weakened by several factors, including its post-hoc retrospective subgroup nature and an imbalance in important clinical characteristics between the treatment groups that became apparent during the trial. Indeed, at the one-month follow-up mark, the digoxin concentrations were significantly higher in women than men, and an adjustment was not made for this in the analysis of mortality (18). Higher digoxin levels become exceedingly important. Indeed, overall, “suspected digoxin toxicity” was noted in 11.9% of the digoxin cohort versus 7.9% for placebo, and this difference resulted in 2.0% of the digoxin and 0.9% of the placebo group being hospitalized. As Rahimtoola has pointed out, serum digoxin concentrations were >2.0 ng/ml (clearly a toxic level) in 2% of the digoxin group, and 5% of this cohort had levels in the 1.5- to 2.0-ng/ml range (a range previously thought reasonable but now believed also to be too high) (4,8). When stratified for gender, 2.3% of men versus 3.4% of women had levels at the 1-month point >2.0 ng/ml (17). Indeed, in a later analysis by Rathore et al. (6), this concept was extended, at least for the male DIG trial cohort. This analysis demonstrated an increased mortality rate when digoxin levels were ≥0.9 ng/ml and suggested benefit (at least in men) when levels are in the 0.5- to 0.8-ng/ml range.

Put simply, digoxin “toxicity” seems to be the problem. Indeed, concentrations previously thought reasonable (as much as 2.0 ng/ml) are likely excessive. One must remember that the dosing scheme in the DIG trial would be considered aggressive by some today. The initial dosage of the study drug was determined by a somewhat-complex nomogram based on age, gender, weight, and serum creatinine. The goal was, of course, to achieve “therapeutic” and non-toxic digoxin levels, but what this target should have been was unclear, as now seems the case. In fact, it was not until these post-hoc analyses of the DIG trial database that a radically lower dose and serum concentration of digoxin was felt appropriate. Further support of this “low” dose and serum level concept comes from an analysis (also retrospective) of the combined Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) and Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) database, which suggested that low doses of digoxin producing serum concentrations of 0.9 to 1.2 ng/ml resulted in clinical benefit compared with control patients not receiving the drug (19). As in the DIG trial, even patients with levels <0.9 ng/ml did better than those receiving placebo. Also, a dose-response pattern with increasing serum concentrations of digoxin could not be identified. Today, prescribing low doses of digoxin to achieve lower serum concentrations is the best approach for patients with congestive heart failure.

The admirable analysis done by Adams et al. (5) closes, then, the DIG trial questions initially raised by the Krumholz team in 2002 and then further studied in men in 2003 (6,17). The Adams et al. (5) multivariable analysis focused on patients having serum concentrations of digoxin measured 6 to 30 h after the last dose of study drug at 4 weeks and also demonstrated a significant linear relationship between serum digoxin concentration and mortality in women (p = 0.008) as well as in men (p = 0.002) with no gender interaction (p = 0.766). The compendium of information demonstrates satisfactorily that the issue is not gender but, rather, the dose of digoxin and resulting serum concentrations. Overall, there appears to be morbidity reduction in both men and women taking digoxin when the serum concentrations are 0.5 to 0.9 ng/ml, whereas serum concentrations greater than this appear harmful irrespective of gender. It is, then, comforting to note that in the earlier SOLVD trial, an analysis of the interaction between gender and digoxin treatment on mortality also suggested no difference in survival between men and women based on digoxin use (7).

In the end, whither digoxin? Certainly it seems not the withering of this therapy. The compendium of evidence suggests that, as does the last American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for Chronic Heart Failure, digoxin should still be prescribed for the treatment of heart failure symptoms unless contraindicated. This important strategy ameliorates symptoms and prevents hospitalizations for decompensated heart failure rather than affecting mortality reduction (19–21). These end points are important and compelling. This recommendation from the ACC/AHA is based on multiple clinical trial observations and general agreement that the therapy is useful and effective, earning it a class IA endorsement. In view of the more recent insight gained into the use of digoxin in heart failure, it is hoped that this particular recommendation remains intact as the Guideline is updated. Also important is the fact that the vast majority of contemporary clinical trials in heart failure cohorts add study interventions to baseline therapies usually comprising the digoxin, angiotensin-converting enzyme inhibitor, and beta-blocker troika. As well, we now have reassuring data indicating lower doses and serum concentrations of digoxin are effective and safe. Indeed, doses of digoxin resulting in
serum concentrations <0.9 ng/ml appear the optimal target. Granted, therapy of heart failure remains difficult, and building polypharmacy protocols can be problematic. Nonetheless, digoxin should still be an important and often, but appropriately, prescribed heart failure treatment. Long live Withering’s legacy!

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