Selections from Current Literature

Digoxin in chronic heart failure

William E Cayley Jr


Introduction

*Digitalis purpurea* (foxglove) has been used for centuries. It was among the herbal remedies used in ancient Rome, and in the 16th century it was used in Ireland, Germany and England for ‘dropsy’ and other medical conditions. In 1785, William Withering reported on his study of digitalis extract used in 163 hospitalized patients, concluding that its beneficial action was due to effects on the power and motion of the heart. Pure digitoxin was first isolated from foxglove in 1875, and digoxin, the glycoside used today, was first isolated in 1957.1 Evidence to guide optimal management of heart failure continues to evolve, however, and the role of digitalis in heart failure has been called “the oldest continuing controversy in the history of medicine.”2 The articles in this selection provide food for thought on the place of digoxin in modern evidence-based management of heart failure.


This summary of the most recent guidelines on heart failure3 introduces a new staging system and makes stage-specific evidence-based management recommendations. Under the new ACC/AHA stages of heart failure, stage A describes patients at high risk of heart failure but without symptoms, stage B describes patients with structural abnormalities of the heart but no heart failure symptoms, stage C describes patients with an abnormal heart and symptomatic heart failure, and stage D describes patients with end-stage disease. The guidelines report multiple trials demonstrating the benefit of blood pressure control, and some specifically supporting angiotensin-converting enzyme inhibitors (ACEIs), in stage A heart failure. For stage B heart failure, some trials support ACEIs and β-blockers for left ventricular dysfunction (LVSD), though multiple trials support ACEIs and β-blockers for stage B patients with prior myocardial infarction and for all stage C patients. Use of digoxin for symptom control in stage C is also supported by multiple trials, as is the use of diuretics. For stage D, there is some evidence reported to support using all interventions applicable to stages A, B and C, plus close attention to fluid status and consideration of specialty referral.

Comment

Updating recommendations for heart failure in light of new evidence, this guideline recommends using digoxin in heart failure primarily for symptom relief. However, while the volume of material reviewed for the full updated guideline3 is impressive, a close review of the references indicates much of the information on digoxin is somewhat dated; of the 21 references cited in the section on digoxin, 14 are from 1990 or before (most from the 1970s), and only four are from 1996 or later. The largest trial reported is from the Digitalis Investigation Group4 (see below), and there appears to be scant documentation of research into using digitalis along with other currently recommended interventions such as ACEIs, β-blockers or spironolactone.


This trial randomized 6800 patients with clinical heart failure and confirmed systolic dysfunction (ejection fraction of 45% or less on echocardiography, angiography or nuclear scanning) to digoxin or placebo in addition to ‘background therapy’ with ACEIs and diuretics. Digoxin dosing was determined by algorithm, with a median starting dose of 0.25 mg daily, and patients were followed for ~3 years. Digoxin did not reduce all-cause mortality (35% in both groups) or cardiovascular mortality (30% in both groups), but did provide a statistically significant reduction in the number of patients hospitalized for heart failure, from 35% in the placebo group to 27% in the treatment group.

Comment

One of the largest trials to date, the Digitalis Investigation Group (DIG) study, indicated the relative benefits of...
ACEIs, already known to reduce heart failure mortality, and digoxin. While there seemed to be no evidence that digoxin therapy increased or decreased mortality, the absolute risk reduction of 7% in patients hospitalized means that one heart failure admission could be prevented by treating 14 patients with digoxin for 3 years. This seems to have been the most important piece of evidence behind the ACC/AHA recommendations to use digoxin for management of heart failure symptoms, but subsequent re-examination of data from this study has raised some additional questions that will be addressed below.


This Cochrane Review combined findings from the DIG study and 10 smaller studies to assess the impact of digitalis on patients with heart failure and sinus rhythm. Most of the patients in the 11 reviewed studies had NYHA class I–III heart failure, an average ejection fraction of 25–30%, and were being treated with diuretics and ACEIs. Meta-analysis of the eight studies addressing mortality found that digitalis did not decrease mortality rates, while meta-analysis of the four studies addressing hospitalizations found a statistically significant reduction in hospital admissions. Though the DIG study did not address clinical outcomes, meta-analysis of the 10 smaller studies found a statistically significant 77% relative reduction in risk of clinical deterioration at 3 months with digitalis therapy.

Comment
Three points relative to the use of digitalis for heart failure in patients in sinus rhythm emerge from this review. First, it demonstrates that the DIG study is essentially the only large randomized controlled trial of digitalis in heart failure in recent years—the other 10 studies in the review corroborated findings from the DIG study, but had far fewer patients. Secondly, it provides evidence that while digitalis in heart failure can improve morbidity by reducing hospitalizations and rates of clinical deterioration, it does not appear to improve mortality. Third, given the populations in the studies reviewed, it demonstrates that most of the evidence to date on using digitalis in heart failure applies to a fairly well defined population of patients with established LVSD, symptomatic heart failure and concurrent treatment with ACEIs and diuretics. The place of digitalis in combination with spironolactone or β-blockers is not adequately addressed by the studies included in this review.


This study sought to determine whether a lower or higher serum digoxin concentration (SDC) is more clinically beneficial by re-analysing data from two major studies on the effect of digoxin withdrawal. The PROVED trial evaluated digoxin withdrawal in clinically stable heart failure patients on treatment with diuretics and digoxin, and the RADIANCE trial evaluated withdrawal of digoxin from clinically stable heart failure patients on treatment with ACEIs, diuretics and digoxin. Together, the two trials had randomized 266 patients, with predominantly NYHA class II heart failure and average ejection fractions of 24–29%. Each trial had an initial 8 week stabilization phase and a 12 week study phase, and patients continuing digoxin were classified into three groups by SDC (SDC <0.9 ng/ml, SDC 0.9–1.2 ng/ml and SDC >1.2 ng/ml). Multiple regression and categorical analyses found that patients withdrawn from digoxin had higher rates of treatment failure, had shorter duration of treadmill exercise time and had declines in left ventricular ejection fraction (LVEF) compared with patients continued on digoxin. Comparisons between the groups of patients who continued digoxin therapy found no significant differences in clinical end-points or change in LVEF between the low, medium or high SDC groups.

Comment
While this analysis did not document any specific benefits to low, medium or high SDCs, the short durations of the PROVED and RADIANCE studies make it impossible to draw any conclusions about the relative long-term benefits of different SDCs. Further, the relatively low numbers in each SDC group (there were only 32, 44 and 51 patients in the low, medium and high SDC groups, respectively) suggest that the two studies together had inadequate patient numbers to detect any meaningful difference in outcomes between the groups. Though the patients continued on digoxin did better on all end-points than those who had digoxin stopped, this really only demonstrates that patients benefiting from digoxin do worse over 12 weeks if it is stopped, not that the general population of heart failure patients will necessarily benefit from digoxin.


This study-within-a-study reports on the effect of digoxin on quality of life and functional status in a subgroup of 569 patients out of the total group of 7788 patients in the DIG study. Health-related quality of life (HQoL) was measured with a questionnaire using items drawn from several instruments previously validated in heart failure patients, and functional status was assessed using a 6 min walk test. Patients, 298 on digoxin and 291 on placebo, were evaluated at baseline, 4 months and 12 months. Compared with the rest of the DIG participants, patients in this substudy had slightly higher LVEF, slightly less use of ACEIs (88 versus 94%) and nitrates (38 versus 43%), and a shorter duration of heart failure (10 versus 18 months),...
but were comparable on all other characteristics evaluated. At the 12 month assessment, each group did show a few improvements on individual parts of the HQoL questionnaire, and the digoxin group showed a small but statistically significant improvement from baseline on the 6 min walk, but there were no statistically significant differences between the digoxin or placebo groups on any variable at either 4 or 12 months.

**Comment**

While the PROVED\(^5\) and RADIANCE\(^6\) trials documented better clinical status over a relatively short 12 week study period for patients with LVSD who continued digoxin compared with those who stopped treatment, this study sought to provide more solid evidence on the morbidity benefits of digoxin by evaluating HQoL indicators in patients in the much longer and larger DIG study.\(^4\) A broader range of patients with LVSD, both on and off digoxin, were randomized, and follow-up was at 12 months rather than 12 weeks. The absence of any difference in HQoL measures between the two groups raises further questions as to the importance of digoxin for symptom control in patients with LVSD.


In another report on information from the DIG study,\(^4\) this paper examines associations between SDCs and clinical outcomes using public data from the original DIG database. The 1171 men randomized to digoxin with valid SDCs obtained 1 month into the study were divided into three groups according to the 1 month SDC (0.5–0.8, 0.9–1.1 and \(\geq 1.2\) ng/ml) and their rates of death and hospitalization were compared with the 2611 men randomized to placebo who were alive at 1 month into the study. There were statistically significant trends towards older age, lower body mass index (BMI) values, higher serum creatinine (SCr) values, and more frequent use of nitrates and diuretics in the patients with higher 1 month SDCs, but on all other baseline characteristics all four patient groups were essentially the same. During an average of 4 years follow-up, there was no difference found between the placebo group and the total group of patients on digoxin in rates of all-cause mortality (36%) or all-cause hospitalization (67%). When patients were grouped by 1 month SDC, however, rates of all-cause mortality and all-cause hospitalization were statistically significantly lower in the group with an SDC of 0.5–0.8 ng/ml (30 and 62%) and were statistically significantly higher in the group with an SDC of \(\geq 1.2\) ng/ml (48 and 70%), while the rates for the group with an SDC of 0.9–1.1 ng/ml (39 and 72%) were not significantly different from the placebo group.

**Comment**

While the original DIG trial\(^4\) suggested that digoxin reduced hospitalizations but not mortality for patients with heart failure, this retrospective review finds lower rates of hospitalization and death for those with initial SDCs in the lower range, while patients in the middle SDC range had no benefit and those in the high range actually were harmed. However, since this was a retrospective study, some questions remain: (i) since patients with higher SDCs appear to have been older with poorer renal function and perhaps sicker, perhaps the increase in mortality was due to other conditions and not due the higher SDC; and (ii) while SDC at 1 month predicted mortality and hospitalization rates, does this really tell us which SDC is the best target for long-term treatment?


This study examined whether using digoxin for heart failure treatment increases the risk of primary cardiac arrest (PCA) for patients with impaired renal function. Review of records from an HMO over a 15 year period identified 935 patients with heart failure (573 case patients who had a PCA and 362 clinically similar control patients who did not have a PCA) who were then grouped by their last serum creatinine (SCr) value. Among patients not treated with digoxin, those with SCr of 1.2–1.4 mg/dl and those with SCr of 1.5–3.5 mg/dl had no increased risk of PCA compared with those with normal renal function (SCr \(\leq 1.1\) mg/dl). For the patients treated with digoxin, those with SCr \(\leq 1.1\) had no increase in PCA risk, but those with SCr 1.2–1.4 had a statistically non-significant increase in the odds ratio (OR) of PCA (1.6) and those with SCr 1.5–3.5 had a statistically significant increase in the OR of PCA (\(>2.5\)). These relationships persisted despite multiple adjustments for other factors that might be associated with risk of PCA (such as serum potassium level, use of other drugs for heart failure and other measures of disease severity and co-morbidity).

**Comment**

While the retrospective review of the DIG trial\(^7\) (above) found increased mortality with increasing SDCs, this retrospective case–control study suggests that using digoxin in the setting of impaired renal function can also lead to bad outcomes. While the DIG review did not attempt to adjust for the fact that the patients with higher SDC also tended to have higher SCr levels (leaving open the possibility that impaired renal function was the true root cause of increased mortality), this study did adjust for a number of other plausible confounders, yet found that the increased risk of PCA associated with digoxin use and elevated SCr persisted. While not a prospective randomized trial, this information raises a caution regarding the treatment of heart failure in patients with abnormal renal function.
Summary

While the recent ACC/AHA guidelines report evidence to recommend digoxin for relief of heart failure symptoms, this information comes mainly from the large DIG trial which only documented a reduction in hospitalizations with digoxin therapy. Though some of the smaller trials included in the Cochrane review suggested that digoxin leads to lower rates of clinical deterioration, and the retrospective analysis by Adams et al. found withdrawal of digoxin led to clinical deterioration at 12 weeks, data from the HQoL substudy of the DIG trial found that digoxin provided no benefit over placebo in quality of life after 12 months of therapy. However, there is evidence suggesting a definite benefit (reduced rates of hospitalization and mortality) with lower SDCs (0.5–0.8 ng/ml) and a definite risk with higher SDCs (0.9–1.1 ng/ml), and suggesting increased risk of cardiac arrest if digoxin is used for patients with impaired renal function (SCr 1.5–3.5 mg/dl). Nevertheless, it is important to remember that much of this information is from retrospective reviews of previous studies, and that while most of the patients in these studies did have ejection fractions below 45%, for the most part their other medications were limited to ACEIs and diuretics, with few patients on β-blockers or spironolactone. Thus, for patients with heart failure, depressed ejection fractions and on treatment with ACEIs and diuretics, we have good prospective evidence that digoxin reduces hospitalizations, and fair retrospective evidence that lower SDCs may reduce mortality while higher SDCs may increase mortality, and we have fair retrospective evidence that digoxin used for patients with abnormal renal function may increase the risk of cardiac arrest. With other recent evidence advocating for β-blockers and spironolactone in the treatment of heart failure, however, it is hard to know without further trials what the added benefit (or potential harm?) would be of digoxin therapy in combination with these medications. The use of digoxin may well be the oldest continuing controversy in the history of medicine, but the answers we have at this point only raise further questions to feed that continuing controversy.

References