EDITORIAL COMMENT

Low-Dose Digoxin in Patients With Heart Failure: Less Toxic and At Least as Effective?*

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Chronic heart failure (CHF) is an increasingly large medical and epidemiological problem, associated with a high morbidity and mortality. Until recently, angiotensin-converting enzyme inhibitors, in combination with diuretics, were the cornerstone in the treatment of CHF. In many patients, digoxin was also part of the standard treatment, and it was assumed that digoxin would be of additional (long-term) benefit in these patients. Results of the Digitalis Investigation Group (DIG) trial, however, have shown that, although digoxin caused a 6% reduction in overall hospitalizations, it did not affect mortality (1). This somewhat disappointing result would “conclude the debate on digitalis,” as Dr. Packer commented in his accompanying editorial (2). He pointed out that digoxin’s inability to substantially reduce morbidity and mortality would eliminate a mandate for its use, as the list of other drugs that—in contrast to digoxin—had shown such an effect would increase. Obviously, the latter particularly applies to beta-blockers, which in recent years have been proven to cause a significant and clinically relevant reduction in both morbidity and mortality. Because of these favorable findings, beta-blockers are rapidly becoming part of the standard treatment of CHF, and in recent guidelines a prominent role for these drugs is reserved in all classes of CHF (3). As a result, the relative importance of digoxin will probably further diminish, although data showing a decline in its use are not yet available. Assuming that the place of digoxin in patients with CHF and atrial fibrillation is (still) unquestioned (3), uncertainty remains regarding the place of digoxin in the treatment of patients with CHF and sinus rhythm.

The study by Adams et al. (4) in this issue of the Journal provides important new information on this subject. These investigators have re-analyzed data from two digoxin withdrawal studies: the Prospective Randomized Study Of Ventricular function and Efficacy of Digoxin (PROVED) (5) and the Randomized Assessment of Digoxin and Inhibitors of ANgiotensin-Converting Enzyme (RADIANCE) (6). Their primary objective was to investigate the relation between serum digoxin concentrations (SDCs) in the two trials and the end points of clinical efficacy, in particular the rate of worsening CHF, change in left ventricular ejection fraction (LVEF), and change in treadmill time.

For this purpose, patients were divided at randomization into four groups: one group consisted of those who discontinued digoxin (placebo group), and the three other groups were patients who were divided according to their SDC at randomization. The latter three groups had the following characteristics: lowest tertile (<33 percentile, ≤0.9 ng/ml, mean 0.78 ± 0.02 ng/ml); middle tertile (33 to 66 percentile, 0.9 to 1.2 ng/ml, mean 1.09 ± 0.01 ng/ml); and highest tertile (>66 percentile, >1.2 ng/ml, mean 1.52 ± 0.03 ng/ml). The principal finding of the Adams et al. (4) study was that, whereas patients in all three digoxin groups generally fared better than those on placebo, multiple regression analysis showed there was no relationship between randomization SDC and any of the study end points. In other words, there was no difference among the three “digoxin groups” during the study. Importantly, patients in the low SDC category performed significantly better (p < 0.05) on all clinical end points compared to those in whom digoxin was discontinued: they were less likely to experience worsening CHF, and both their LVEF and treadmill exercise times were significantly higher.

This result is important and deserves attention as it may have clinical implications. It is unlikely that many new data on digoxin will become available in the next few years, and many CHF patients around the world are still using the drug. The present data must therefore be examined carefully, and some limitations to the Adams et al. (4) study must be discussed. The major limitation of their study is obviously the way the data were collected: the two original studies had a withdrawal design; also, for the present analysis, patients were not randomly assigned to the three SDC groups. The limitations of the withdrawal design are well known, but also the three groups were divided by SDC, and not by different doses of digoxin. Indeed, Table 2 in the Adams study shows that there was no difference in digoxin doses among groups. This means that, with the same dose, different SDCs were reached, which may suggest that in the “high” SDC group, the drug accumulated as a result of a clearance problem, in particular renal dysfunction. Although many clinical variables were included in the investigators’ multivariate analysis, renal function was not among them (see also their Table 1), and given the fact that this parameter has been shown to be one of the most powerful predictors of prognosis in CHF (7), and also in the DIG database (8), the difference in SDC may have been (partly) a reflection of differences in renal function. One might thus speculate that a possible benefit of the higher dose could have been offset by the more impaired renal function (and more advanced CHF).

Another problem with the design is that after eligibility...
was confirmed, patients were uptitrated before randomization to doses that corresponded to SDCs of 0.9 to 2.0 ng/ml. In the highest tertile this led to a SDC of 1.52 ± 0.08 ng/ml at the beginning of the study, but it had dropped to 1.25 ± 0.08 ng/ml at the end of the study, which was not so different anymore from the SDC at the end of the study in the “middle” tertile (1.14 ± 0.09 ng/ml). In other words, if a true difference in clinical effect would be present among the three SDC groups, such a small difference in the actually measured SDC during the study would make it less likely that a clinical difference would surface.

The other main limitation of the Adams et al. study is the small sample size together with the short follow-up; particularly, if the digoxin group is broken up in three groups, only small groups of (40 to 50) patients remain. This leads to few clinical events, and one wonders whether the 6% dropout during the 12-week study in the “low” SDC group would have led to a significant difference between this group and the “middle” (9%) and “high” tertile (12%) SDC groups had the number of patients been higher or the follow-up longer.

The main finding of the Adams et al. report is that patients with low SDCs perform at least as well as those with higher SDCs. In two earlier and fairly large trials with milrinone (9) and pimobendan (10), higher SDC levels were associated with increased mortality, particularly when SDCs were >1.0 ng/ml; however, in both trials positive inotropic drugs were examined, and the untoward effects of digoxin may have been increased in this setting.

The data of the DIG study could also be very important in this respect, as it is also referred to in the present study (4). In the main publication this is not discussed (1), but in a letter to the editor this was pointed out (11) to which the authors responded that “there was no relation between digoxin levels and clinical efficacy . . . , but that [this analysis] is potentially confounded . . . [by other variables]” (12). Interestingly, in a review paper discussing the DIG trial, Gheorghiade and Pitt (13) state that “in the DIG trial there was an association between serum concentration and mortality” and they continue that “this finding was observed even at serum concentrations within the so-called therapeutic range” (13). Given this confusion, and the clinical relevance of the problem, I strongly believe that a proper multivariate analysis (including also renal function and concomitant drug use) should be conducted to assess the relation between clinical outcome and SDCs in the 1,485 patients in the DIG trial in whom they were measured.

In the DIG trial, the mean one-month SDC for all digoxin patients was 0.86 ng/ml (1). When related to specific dose, SDC values for 0.125 mg (17.5% of the population), 0.25 mg (70.3%), 0.375 mg (10.8%), and 0.50 mg (1.0%) were 0.76 ng/ml, 0.89 ng/ml, 0.88 ng/ml, and 0.88 ng/ml, respectively. At one month, 88.3% of all patients had SDCs within the “therapeutic range” of 0.5 to 2.0 ng/ml, and only 2% had SDC levels >2.0 ng/ml. However, 20% of patients had SDC levels of 1.0 to 1.5 ng/ml, and 5% of patients had SDCs of 1.5 to 2.0 ng/ml (Dr. Richard Gorlin, oral presentation at the 45th American College of Cardiology Sessions, Orlando, Florida, March 1996). One may thus conclude that the dosing regimen worked well for the prespecified margins that were assumed optimal at the time the DIG trial was designed (1990). However, since then, data have emerged, including those reported in the present study (4), and in others discussed above, that SDC levels above 1.0 ng/ml are not leading to additional benefit, and in fact may be harmful, and should thus be avoided. In light of this finding, 27% of all patients may have had too high SDCs, which may have significantly and negatively affected the outcome.

Increasing evidence shows a dissociation between the neurohormonal effects of digoxin that are achieved at low SDCs and the hemodynamic (positive inotropic) effects that mainly emerge at higher SDC levels (13–16). Because the neurohormonal effects of digoxin are generally assumed to be beneficial, and the positive inotropic effect should probably be minimalized if evident at all, this would also be a mechanistic explanation of why relatively lower doses of the drug should be preferred.

The only way to truly investigate whether lower doses of digoxin are better than higher doses is to conduct a prospective, randomized, placebo-controlled study with sufficient power. Such a mortality study should also stratify for beta-blocker use at baseline; because these agents are now used on a large scale, they may significantly affect outcome in CHF, and they may possibly enhance the effect of digoxin (13).

With regard to the design of such a study, a placebo-controlled trial would probably be feasible nowadays, and the high- versus low-digoxin groups should be divided by SDC rather than by dose. The DIG study has made clear that an algorithm is able to guide SDCs, and also SDC levels remain rather stable over time (1). Conversely, it has also been made clear that even with low doses of digoxin, SDC levels >1.0 ng/ml are often reached. This may well be related to the presence of renal dysfunction in such a CHF population. In the DIG trial, serum creatinine concentrations ≥1.7 mg/dl were found in only 5% of patients <50 years old, but this increased to 30% of patients ≥80 years old (8). The target dose in such a trial should probably be 0.5 to 1.0 ng/ml, although sufficient data about the minimum required dose are scarce. In the DIG study, 12% of patients had SDCs <0.5 ng/ml (Dr. Richard Gorlin, ACC 1996), and it would be useful to examine this subgroup of patients.

What should be the next step in the research regarding digoxin in CHF, and do we need further investigation into this issue? Given the fact that vast numbers of patients are still taking the drug, and that many questions still remain, the answer to this, in my opinion, must be positive. The first thing that could be done relatively easy would be to examine more thoroughly the dose (SDC) issue in the DIG trial. To obtain a convincing answer, I believe a second mortality
study is required. Whether such a trial will ever be conducted is doubtful, however. Investigators are generally less inclined to further analyze results of clinical trials with a negative or neutral outcome such as DIG, and of course this reluctance applies even more to designing a second trial in the same field as the first (negative) trial (17).

In addition, digoxin is an inexpensive drug, and a large mortality study is a very expensive and uncertain project. For this reason, it is not very likely that a pharmaceutical company will embark on such a project. The only way to conduct such a study would probably be through “non-pharmaceutical” grants, derived from local or national health foundations, or large organizations such as the National Institutes of Health. In a world where cost-benefit considerations play an increasingly important role, health policymakers should seriously consider such an option.

In conclusion, despite limitations, the present data provide further support for the suggestion that low SDC levels might be superior to higher SDC levels in patients with CHF. I hope these data will provide a new stimulus to investigate the potential place of this drug in CHF. This can be accomplished by several lines of research, of which further analysis of the DIG database would seem useful. To obtain true and convincing answers, however, I believe a second digoxin mortality trial in CHF, targeted at lower SDC levels (0.5 to 1.0 ng/ml), must be seriously considered.

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