LETTERS TO THE EDITOR

Digoxin Withdrawal in Patients With Heart Failure

The report by Uretsky et al. (1) is the second of two recent withdrawal studies (1,2) that claim to show some advantage from the use of digoxin in the treatment of patients with heart failure. The two studies add to the large number of earlier studies that have used the withdrawal design (3). The authors are parsimonious in enumerating the limitations of their study.

A withdrawal study addresses the question whether stopping the use of a drug brings about a change in the clinical condition of the patient, not whether the drug should have been prescribed in the first place. Patients are selected from those known to tolerate the drug. Such a subset of patients with heart failure may have unique characteristics.

The major clinical question is whether digoxin has a positive inotropic effect or brings about clinical benefit to selected patients with heart failure but whether the addition of digoxin to optimal treatment with a diuretic agent and angiotensin-converting enzyme inhibitor confers any additional advantage to the patient. If a withdrawal study is undertaken to test this hypothesis, then on withdrawal of the drug those patients randomized to placebo should have their therapy manipulated either by an increase in the diuretic agent, the addition of a combination of diuretic agents or an alteration in the dose of the angiotensin-converting enzyme inhibitor. The two recent studies are at best tests of the efficacy of digoxin (not in dispute under particular circumstances) but are decidedly not a fair test of a therapeutic strategy.

The most serious criticism of withdrawal studies is that interpretation of the results is ambiguous. If, as was observed in this study, there is deterioration in the placebo group on withdrawal of the investigational drug, a possible conclusion would be that the drug has conferred benefit. An alternative conclusion is that the drug was sufficiently efficacious to conceal any clinical deterioration while the drug was being administered but at the same time caused harm. Inotropic drugs can hasten cell death in the presence of myocardial ischemia or in metabolically challenged myocytes. Under such circumstances, cessation of the drug will be followed by deterioration of the patient. The deterioration is a measure of the harm caused by the drug. Thus, the same outcome can be used to argue for efficacy or harm. Withdrawal studies are quite correctly not used to investigate new drugs in heart failure.

The debate on the clinical use of digoxin will continue for many years. The key issue is whether a potentially harmful drug adds benefit to established conventional treatment and whether there are subgroups of patients in whom there is a particular benefit or harm. The outcome of the current mortality study conducted by the National Institutes of Health may provide more convincing evidence for the use of digoxin, namely, to influence long-term mortality rather than to ameliorate symptoms.

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References

Reply

Dr. Poole-Wilson has several concerns about the recently published placebo-controlled digoxin trial (PROVED) (1). He questions the scientific validity of a drug withdrawal design. Such a design was necessitated by the nearly universal use of digoxin in the treatment of heart failure in this country at the time that this study was promulgated. A limitation of this design, not mentioned by Dr. Poole-Wilson, is more on the ethical level, that is, clinical worsening in the group withdrawn from the active therapeutic agent. To safeguard against “excessive” deterioration, the protocol mandated that study coordinators contact patients weekly by telephone to assess clinical status. If in a controlled trial, all measured baseline variables are not significantly different and the only difference during active phase is drug (digoxin) withdrawal in one patient group, then it is completely reasonable to conclude that a worsening in the placebo-treated group is due to withdrawal of the active agent (digoxin) (i.e., digoxin has clinical efficacy). On the basis of the PROVED study, it is an extrapolation to conclude that beginning digoxin therapy in patients with clinical heart failure improves their clinical status, but it is more a “small step” than a “leap” of faith.

Dr. Poole-Wilson questions whether digoxin can improve clinical status in patients taking an angiotensin-converting enzyme inhibitor and diuretic agents. The RADIANCE trial, with identical methodology to PROVED, except that patients were taking an angiotensin-converting enzyme inhibitor by design, showed nearly identical results to the PROVED trial (2).

Whether, in addition to an angiotensin-converting enzyme inhibitor, using digoxin or increasing the dose of a diuretic agent, as Dr. Poole-Wilson suggests, is a more appropriate strategy in the treatment of decompensated heart failure, we would leave to the treating physician. We would remind Dr. Poole-Wilson of the negative effects of diuretic agents, particularly hypokalemia and hypomagnesemia, which may increase the propensity to fatal arrhythmias and also further activation of potentially harmful neurohormonal axes.

Dr. Poole-Wilson states that the PROVED trial cannot answer whether digoxin “should have been prescribed in the first place.” We would remind Dr. Poole-Wilson that digoxin was prescribed in all patients for at least one episode of clinical heart failure secondary to systolic dysfunction. We would venture to say that tolerance to oral digoxin is high and that this “subset” probably represents the vast majority of patients with systolic dysfunction and clinical congestive heart failure.

Finally, Dr. Poole-Wilson muddies the issue of clinical efficacy of a drug and its effect on survival. The PROVED (and RADIANCE) trials