Inotropic therapy for heart failure: paradise lost

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Online publish-ahead-of-print 2 September 2009

This editorial refers to ‘Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled parallel group ESSENTIAL trials’, by M. Metra et al. on page 3015

The effort to demonstrate efficacy and safety of an oral phosphodiesterase III (PDE3)-inhibiting inotropic drug in patients with chronic heart failure has been long, arduous, and largely unsuccessful. The persistence of the effort is based on the widely held perception that heart failure is precipitated and sustained by a left ventricular contractile deficit and that PDE3 inhibitors can correct that deficit, improve haemodynamics, hopefully improve symptoms, and perhaps even prolong life. The results of the ESSENTIAL trials, reported by Metra et al., once again threaten this hypothesis.

This class of drug was introduced clinically 25 years ago. Since that time we have learned much about the left ventricular functional and structural contributions to symptoms and progression of heart failure, and have gained insights into the therapeutic potential for vasodilator, nitric oxide-enhancing, neurohormonal-inhibiting, and positive inotropic agents. It should now be possible to design studies of experimental interventions in populations likely to respond and with endpoints likely to be achieved if the intervention is effective.

The investigators took advantage of this prior experience in designing the ESSENTIAL trials to test the therapeutic potential of enoximone properly. They selected patients that remained highly symptomatic with frequent episodes of decompensation despite appropriate background pharmacological therapy. They separated symptomatic endpoints, which were appropriately evaluated early after 6 months of therapy, from longer term mortality and hospitalization data. This distinction accepts the concept that haemodynamic improvement should relieve symptoms but not necessarily alter prognosis, which is more dependent on left ventricular structural improvement. They approached the longer term data as a safety rather than an efficacy assessment, thus recognizing that slowing progression of disease is not a likely benefit of a PDE inhibitor but that the potential for adverse morbidity events must be assessed. They also employed a lower dose of the PDE3 inhibitor, enoximone, in view of the apparent side effects and mortality risk identified in previous trials of larger doses of this and other PDE3 inhibitors. Furthermore, they theorized that background β-blocker therapy not utilized in most prior PDE inhibitor trials might mitigate any adverse effects of the drug.

Despite a robust study population of 1854 patients in 16 countries, no overall benefit of enoximone could be demonstrated. Were their methods adequate to detect a benefit if present? Improved quality of life should have been the most sensitive guide to efficacy, but they utilized a crude global assessment rather than a more rigorously validated quantitative disease-specific instrument. The 6-minute walk test they employed has been widely used to establish effectiveness of therapy, but variable results suggest that it may not be a sensitive guide to modest degrees of clinical improvement. Nonetheless, the absence of benefit on these efficacy endpoints suggests that any possible favourable effect was too small to be detected.

As in most trials of unapproved drugs the authors are reluctant to close the door on further development. They have mined their database to find possible responders to the therapy, I share their interest in seeking possible subgroups who might respond favourably. Heart failure is a heterogeneous syndrome in which mechanisms vary and therapeutic responsiveness is likely to diverge. The mean response in large-scale outcome trials does not necessarily provide insight into individual patient management. It must always be remembered that equality or non-inferiority of outcome between two treatments in a clinical trial does not necessarily imply that the treatments are equal but merely that the net effects are equal. Individual patients may not respond similarly. However, in the absence of a stronger signal for benefit in the overall population, any benefit in a substantial subgroup would necessarily be masked by an adverse effect in another subgroup. It is therefore highly unlikely that the drug will be clinically useful.

Progression of heart failure to morbid and mortal endpoints is largely related to progressive structural alterations in the left ventricle. Drugs that favourably affect prognosis exert a beneficial effect on this remodelling process. Serial echocardiography or magnetic resonance imaging can document this effect. Since the ESSENTIAL trials did not monitor sequential changes in left
ventricular structure, probably because previous studies have not demonstrated a favourable effect with these drugs, it is not possible to assess the influence of enoximone on progression of the ventricular remodelling. The fact that more patients in the enoximone than in the placebo group deteriorated after discontinuing treatment raises the possibility that at least in some patients the disease progression may have been accelerated. A further important safety assessment would have been to monitor morbid events in the two groups after termination of treatment when a disease-accelerating effect of enoximone might become apparent.

The authors would like to cling to the possibility that there still is a place for enoximone in therapy. In commenting &gt;20 years ago on a failed trial with milrinone, an earlier PDE3 inhibitor that was touted as the panacea for heart failure, I characterized the result as ‘Paradise Postponed’ (after John Mortimer 1985).15 Two decades of studies later there has been no documentation of efficacy of this class of drugs. Perhaps it is now time to characterize the status of PDE3 inhibitors for heart failure as ‘Paradise Lost’ (after John Milton, 1667).

Conflict of interest: none declared.

References