Why inotropes continue to disappoint in heart failure

Despite their low therapeutic index, cardiac glycosides have been used for centuries for the treatment of heart failure. In the past two decades pharmaceutical companies have developed several new orally active drugs, which like the glycosides have positive inotropic activity in vitro. It was hoped that they would replace the glycosides and be administered long-term to patients with heart failure but with a lower incidence of adverse effects. Unfortunately the development of these drugs was based on a series of unproven assumptions: that glycosides have an advantageous effect in patients with heart failure, that the benefit is due to the cardiotonic action that can be demonstrated in vitro, and that other drugs with positive inotropic effects in vitro will therefore be beneficial in vivo.

Far from assuming that positive inotropic effects are beneficial there should be concern that if glycosides (and other cardiotonic drugs) have genuine inotropic effects in vivo this might worsen prognosis by increasing myocardial oxygen consumption, unless there is a concomitant improvement in mechanical efficiency.

Glycosides slow atrioventricular conduction and control the ventricular response in patients with atrial fibrillation. This improves ventricular filling and cardiac output and allows the heart to operate at a more mechanically efficient rate. Even in sinus rhythm, glycosides slow the heart rate—at least in part by neurally mediated mechanisms. There is little evidence that other effects of glycosides improve the symptoms of patients with heart failure. There is certainly no evidence that glycosides reduce mortality, though the results of a continuing study of digoxin in patients in sinus rhythm should be available soon.

Because there is as yet no proven benefit from the inotropic effects of glycosides, the search for a replacement cardiotonic magic bullet for the treatment of heart failure may have been ill-founded. Further, the positive inotropic effects of the newer cardiotonic agents are inversely related to the severity and duration of heart failure, as indeed are the effects of calcium, the final mediator of electromechanical coupling. Other effects of these drugs, such as vasodilatation, become relatively more important, but the arguments about how much of the acute haemodynamic change seen is due to vasodilatation and how much is the result of increased contractility are of academic interest. What concerns patients is whether they improve symptoms and survival.

Some drugs (for example, amrinone and prenalol) were withdrawn early in their development because their adverse effects exceeded those of the glycosides which it was hoped they would replace. The effects of the remaining drugs on symptoms and exercise capacity are not clear cut but do not suggest an important benefit. The answer to the question about survival is clear. The partial β-adrenergic agonist, xamoterol, and the phosphodiesterase inhibitor, milrinone, shortens survival. The results of the United Kingdom clinical trial of oral enoximone has not been published but the study has been terminated prematurely by the independent ethics committee because of excess deaths in those given enoximone compared with the placebo group. A smaller multicentre trial of enoximone had shown an adverse effect on survival. Phosphodiesterase inhibitors and β adrenergic agonists increase cyclic AMP and it has been argued that this property may be responsible for reduced survival. This has led to the claim that cardiotonic agents which do not increase cyclic AMP may have a less detrimental effect. This is unproven.

Meanwhile clinical trials have demonstrated that some vasodilators and, to a greater extent, ACE inhibitors which unload the failing myocardium improve both symptoms and survival. It may be relevant that ACE inhibitors have negative inotropic effects. Despite evidence that, when administered in the manner for which they were developed, milrinone and enoximone reduce survival they are still licensed for use. Both may be given on a short-term basis by intravenous infusion which seems illogical because they were developed specifically because their pharmacokinetics favoured long-term oral administration. In the setting of acute heart failure in a patient with previously good myocardial function they may have a greater inotropic effect than in patients with chronic heart failure but their long half-lives mean that rapid titration of dose which may be necessary in such patients is impossible. There is certainly no proven advantage over cheaper drugs for circulatory support and no evidence that they improve outcome.
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