Beta-blockade in the management of chronic heart failure

Another step in the conceptual evolution of a neurohormonal model of the disease

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Although heart failure has been viewed primarily as a haemodynamic disorder, the development of pharmacologic agents that address the haemodynamic derangements has not proved to be a successful approach to its management. Consequently, attention in recent years has shifted to the development of neurohormonal antagonists in the hope that prolonged interference with the renin-angiotensin system and the sympathetic nervous system would have favourable effects on the natural history of heart failure. Both converting-enzyme inhibitors and beta-adrenergic blockers have been shown to produce long-term haemodynamic and clinical benefits in patients with left ventricular systolic dysfunction in controlled clinical trials. For both classes of drugs, the improvement evolves gradually over several months, although initiation of therapy may be accompanied by undesirable (but usually transient) haemodynamic effects. This pattern of response contrasts sharply with the response pattern seen with direct-acting vasodilators that stimulate neurohormonal systems (e.g. flosequinan). Initiation of treatment with flosequinan produces immediate clinical benefits due to the haemodynamic actions of the drug, but this improvement may disappear within weeks as a result of neurohormonal activation, which also may contribute to the increased risk of death seen during long-term administration of the drug. Recognition of the prognostic importance of neurohormonal activation has led to the hope that long-term treatment with beta-blockers might reduce mortality in heart failure, in a manner similar to that seen with converting-enzyme inhibitors. Large-scale, long-term studies are being planned to evaluate this possibility.

Key Words: Heart failure, neurohormones, beta-blockade, clinical trials.

Introduction

Because heart failure has been traditionally regarded as a haemodynamic disorder, treatment strategies for heart failure have largely been based on haemodynamic principles. Consequently, physicians have been advised to administer drugs to patients with heart failure that produce haemodynamic benefits, and to avoid treatment with drugs that can adversely affect haemodynamic measurements. This approach has resulted in the development and evaluation of several hundred difference positive inotropic and peripheral vasodilator drugs for heart failure. At the same time, physicians have viewed beta-blockers as being contra-indicated in this disorder.

Unfortunately, this haemodynamic model has not been a useful guide to the management of patients with heart failure. Positive inotropic drugs can increase cardiac output and ejection fraction, but the long-term administration of these drugs is not accompanied by clinical benefits and may increase the risk of death. Peripheral vasodilator agents can ameliorate loading conditions in the failing heart, but the long-term administration of many vasodilators fails to improve symptoms and may be associated with an enhanced mortality rate. These clinical results have cast considerable doubts about the validity of the haemodynamic model of heart failure. Such doubts have led to a re-evaluation of drugs (e.g. beta-blockers) that have long been regarded — at least according to the haemodynamic model of the disease — as being contra-indicated in these patients.

The renewed interest in the use of beta-adrenergic blockers for heart failure emerges at a time
when physicians have shifted their attention from the haemodynamic model to a new model — the neurohormonal model of heart failure. According to this model, neurohormonal activation is the critical event in the disease and contributes importantly to its progression. Consequently, studies of the effects of drugs on neurohormonal systems should be an important part of the evaluation of a new agent, since the ability of some drugs to activate neurohormonal systems may contribute to the disappointing results that have been reported with positive inotropic agents or peripheral vasodilators. More importantly, the neurohormonal abnormalities of heart failure could emerge as specific therapeutic targets. This concept has led to the widespread interest in the development of neurohormonal antagonists for heart failure, specifically the angiotensin converting-enzyme inhibitors (which block the renin angiotensin system) and the beta-adrenergic blockers (which block the adverse effects of the sympathetic nervous system).

Clinical results with beta-blockers for heart failure

In contrast to nearly all other agents that have been used to treat chronic heart failure, beta-blocking drugs do not produce immediate haemodynamic benefits. In fact, cardiovascular function may deteriorate shortly after initiation of beta-blockade in a fashion similar to the decline seen after the administration of other drugs that interfere with the positive inotropic actions of the sympathetic nervous system. Long-term therapy with beta-blockers, however, appears to improve cardiac performance, symptoms and exercise tolerance — possibly by neutralizing the deleterious effects of prolonged adrenergic activation. The initial encouraging (but uncontrolled) reports using alpenrolol, practolol, metoprolol and propranolol have recently been confirmed in double-blind, placebo-controlled trials using metoprolol (50 mg twice daily), bisoprolol (5 mg once daily), bucindolol (100 mg twice daily) and carvedilol (25 mg twice daily).

Metoprolol and bisoprolol are beta-1 selective beta-blockers, but carvedilol and bucindolol have additional pharmacologic properties that may contribute to their haemodynamic and clinical benefits. Unlike other beta-blockers, carvedilol and bucindolol exert vasodilator effects which could enhance their efficacy and reduce the risks of worsening heart failure during initiation of therapy. In controlled studies, systemic vascular resistance decreased in patients treated with carvedilol and bucindolol, and dizziness was an important side-effect of treatment as it is with other vasodilators. However, the importance of vasodilatation in mediating the efficacy of carvedilol and bucindolol remains uncertain, since metoprolol (which has no direct vasodilating action) may also decrease systemic vascular resistance, presumably due to the withdrawal of vasoconstrictor influences as heart failure improves. Yet, in addition to its vasodilating effects, carvedilol exerts anti-oxidant actions and reduces the proliferation of vascular smooth muscle. These additional neurohormonal properties may be particularly useful in heart failure since this disease is characterized both by heightened formation of oxygen free radicals in the failing heart as well as peripheral vascular remodelling.

The contrasting effects of beta-blockers on haemodynamic and neurohormonal mechanisms may explain the unique time course of action of these drugs in patients with heart failure. In our experience the initiation of therapy with a beta-blocker may be accompanied by clinical deterioration in 10–20% of patients, although this short-term deterioration is often responsive to changes in background therapy. This early risk appears primarily to be related to the haemodynamic actions of these drugs, largely as a result of interference with the positive inotropic actions of endogenous catecholamines. However, if treatment with the beta-blocker can be maintained through the first 4 weeks of therapy, this short-term haemodynamic risk appears to dissipate, and the patient commonly begins to show clinical improvement after 2–4 months of therapy. Present evidence suggests that this delayed benefit may relate to the neurohormonal effects of the beta-blockers, since this pattern of early risk and delayed benefit is also characteristic of other neurohormonal antagonists (e.g. converting-enzyme inhibitors). Yet, this is opposite to the response pattern seen with direct-acting vasodilators that stimulate neurohormonal systems (e.g. flosequinan). Initiation of treatment with flosequinan produces immediate clinical improvement due to the haemodynamic action of these drugs, but these benefits may disappear within weeks as a result of neurohormonal activation, which also may contribute to the increased risk of death seen with this drug during long-term administration.

Future developments of beta-blockers in heart failure

Recognition of the prognostic importance of neurohormonal activation has led to the hope that long-term treatment with beta-blockers may reduce mortality in heart failure, in a manner similar to that seen with converting-enzyme inhibitors. Early studies with beta-blockers in post-infarction patients suggested that long-term treatment could reduce the risk of death; this effect was particularly apparent in patients with clinical evidence of heart failure at the time of enrolment in the study. These intriguing results, however, were attributed to an anti-ischaemic or anti-arrhythmic action of the beta-blockers rather than to a beneficial effect on the natural history of heart failure.

However, recent observations from long-term studies of beta-blockers in patients with heart failure and normal coronary arteries (i.e. dilated cardiomyopathy) have raised the possibility that beta-blockers may improve survival by retarding the rate of progression of the underlying disease. In the Metoprolol in
Dilated Cardiomyopathy (MDC) trial[23], long-term treatment with metoprolol reduced the risk of worsening heart failure, as reflected by a decrease in the rate of hospitalization for heart failure and a decrease in the rate of clinical deterioration requiring listing of the patient for cardiac transplantation. In the Cardiac Insufficiency Bisoprolol Study (CIBIS)[12], long-term treatment with bisoprolol also reduced the risk of hospitalization for worsening heart failure and produced a nonsignificant 21% decrease in the risk of death. Yet, in the subgroup of patients with normal coronary arteries (e.g. dilated cardiomyopathy), bisoprolol therapy was associated with a significant decrease in mortality rate. In a single centre study carried out in New York City[14], treatment with carvedilol for 3-4 months was associated with a significant decrease in the combined risk of worsening heart failure, life-threatening ventricular arrhythmia and death. These findings suggest that beta-blockade may reduce the risk of progression as well as mortality in patients with heart failure regardless of the underlying cause. This possibility argues strongly against the concept that the benefits of beta-blockers in these patients are related solely to an anti-ischaemic effect or anti-arrhythmic effect of these drugs.

Two large-scale trials are being planned to evaluate in a definitive fashion the effects of beta-blocking agents on the survival of patients with chronic heart failure. One trial — which will be carried out in North America — will evaluate the effects of bucindolol on mortality, and the other — which will be carried out in Europe, Australia and New Zealand — will evaluate the effects of carvedilol on survival. The results of these studies should be available in the next 3 to 4 years.

If these studies confirm the encouraging results that have emerged in earlier reports, they will provide a strong support for the hypothesis that neurohormonal factors — and not merely haemodynamic stresses — contribute importantly to the progression of chronic heart failure.

References

[8] Mann DL, Kent RL, Parsons B, Cooper G. Adrenergic effects of the beta-adrenoceptor antagonist metoprolol in patients with normal coronary arteries (e.g. dilated cardiomyopathy), bisoprolol therapy was associated with a significant decrease in mortality rate. In a single centre study carried out in New York City[14], treatment with carvedilol for 3-4 months was associated with a significant decrease in the combined risk of worsening heart failure, life-threatening ventricular arrhythmia and death. These findings suggest that beta-blockade may reduce the risk of progression as well as mortality in patients with heart failure regardless of the underlying cause. This possibility argues strongly against the concept that the benefits of beta-blockers in these patients are related solely to an anti-ischaemic effect or anti-arrhythmic effect of these drugs.

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