Bisoprolol in chronic heart failure

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The evidence for the use of beta-blockers in heart failure is substantial. Latest recommendations and guidelines suggest that most heart failure patients should be on a drug regimen of an angiotensin-converting enzyme inhibitor, diuretic and a beta-blocker. However, despite the evidence from trials, the majority of patient are not yet treated appropriately, with only 5% receiving a beta-blocker.

Bisoprolol (Cardicor®, Merck Pharmaceuticals, West Drayton, Middlesex) is a highly selective beta-1 adrenoreceptor blocker (Bethge et al, 1991; Wellstein et al, 1987) which has been shown to confer major benefits in the treatment of chronic heart failure (CHF) resulting from left ventricular systolic dysfunction. This overturns the conventional wisdom that beta-blockers are contraindicated in CHF owing to their acute negative inotropic effect. There is now convincing evidence that beta-blockers are of benefit in CHF. Alongside angiotensin-converting enzyme (ACE) inhibitors they are now first-line therapy in stable CHF patients. This review summarizes the clinical trial findings on bisoprolol, its characteristics and indications, and guidance on its use and the management of CHF.

CHRONIC HEART FAILURE

CHF is a major public health problem, disabling, often severely, about 2% of the adult population and 8% of over 75 year olds (Hobbs, 1999). Despite the use of various classes of drug, about half of all patients with cardiac insufficiency die within 5 years of diagnosis. Furthermore, over the next 20–40 years, as people live longer and the ability to keep myocardial infarction (MI) survivors alive increases, the problems CHF poses — its profound effect on patient's quality of life and the economic burden it places on every western health-care system — seem certain to increase.

Over the past decade, ACE inhibitors have become the evidence-based mainstay of CHF management. There is now powerful evidence from clinical trials (Packer et al, 1996; Merit Study Group, 1999; CIBIS II Investigators and Committees, 1999) to indicate that all patients with symptomatic CHF and low left ventricular ejection fraction (LVEF) who can tolerate beta-blocking therapy should receive it.

The concept of introducing beta-blockers in the treatment of CHF at first seems contradictory. If the problem of CHF were a weak and failing pumping mechanism, using a drug that decreases the contractility of the myocardium would seem to be contraindicated. However, that is not a correct understanding of the aetiology.

The use of beta-blockers in CHF stems from a changed focus which views its neurohormonal, not just its haemodynamic, aspects. The increased sympathetic nervous system activity found in CHF has detrimental long-term effects: higher plasma noradrenaline (norepinephrine) concentrations are associated with worse survival. Results have shown that blocking the overstimulated sympathetic nervous system is useful, and beta-blockers prevent the adverse consequences of increased sympathetic stimulation.

CIBIS-II

The first randomized, double-blind, placebo-controlled trial of a beta-blocker (bisoprolol) in CHF with sufficient power to address all-cause mortality as a primary end-point was the second Cardiac Insufficiency Bisoprolol Study (CIBIS II Investigators and Committees, 1999). Secondary end-points were cardiovascular mortality, hospital admissions, cardiovascular mortality plus cardiovascular hospitalizations, and permanent treatment withdrawal.

An earlier trial, CIBIS-I (CIBIS Investigators and Committees, 1994), involving 641 patients, had shown a 20% reduction in 2-year mortality compared with placebo but did not

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reach statistical significance. However, a subgroup analysis showed a 53% mortality reduction in patients with idiopathic dilated cardiomyopathy.

CIBIS-II had been intended to last for 46 months but was stopped after only 28 months when the second interim analysis revealed a highly significant mortality trend favouring bisoprolol.

The trial recruited 2647 ambulatory, mostly male patients, at 200 centres in 18 European countries. They were aged 18–80 years (mean 61.8 years) and were New York Heart Association (NYHA) class III (n=2202, 83%) or IV (n=445, 17%) with stable symptomatic systolic CHF (LVEF <35%) on existing standard therapy with diuretics and ACE inhibitors.

Patients were randomized to receive bisoprolol or placebo in addition to their standard antianginal therapy. A starting dose of bisoprolol 1.25 mg/day was titrated to 2.5 mg/day by week 2 and slowly (as required with beta-blockers) up to 10 mg/day over 4–6 months. Thus the most common bisoprolol dose during the maintenance phase was 10 mg/day, which was reached in 546 patients; 152 reached 7.5 mg/day and 176 reached 5.0 mg/day.

Some 4000 patient years with a mean follow-up of 1.3 years were completed before the trial was stopped. There were 156 (11.8%) and 228 deaths (17.3%) (P<0.0001) in the bisoprolol and placebo groups respectively, representing a relative reduction of 32%.

Sudden death (strictly defined as a death within 1 hour without previous worsening of heart failure and death which was witnessed) showed a 42% relative reduction over a wide range of sub-groups (P=0.0011), together with a trend, not statistically significant, in reduction in pump failure. There were no significant differences in deaths from MI, other cardiovascular deaths or non-cardiovascular deaths. Bisoprolol was well tolerated, with 15% permanent treatment withdrawals, the same as with placebo.

There were 440 (33%) and 513 (39%) all-cause hospital admissions in the bisoprolol and placebo arms respectively, showing a 15% reduction in admissions for any cause and a significant 36% relative reduction in hospital admissions for CHF in patients receiving bisoprolol. A significant improvement of the functional status according to NYHA classification was shown.

During the initiation and titration of bisoprolol, there were hospital admissions as a result of bradycardia (0.53%), hypotension (0.23%) and acute decompensation (4.97%), but these were not more frequent than with placebo (0%, 0.3% and 6.74%). A significant trend of more admissions for hypotension among placebo patients might reflect a positive effect of beta-blockade on ventricular function.

There were 20 fatal and disabling strokes in the bisoprolol group compared with 15 in those receiving placebo.

Discussing these findings, the investigators (CIBIS II Investigators and Committees, 1999) observed that beta-blockade with bisoprolol, assessed by hospital admissions, had benefits not only for all-cause mortality in CHF patients, but also for morbidity, especially for worsening heart failure. As there was no run-in period, the trial patients were not selected for tolerance of bisoprolol. Benefit occurred irrespective of the cause of heart failure or NYHA class of severity, the greatest effect being in patients with ischaemic heart disease who were NYHA class III at baseline.

It is now thought that overactivation of neurohormonal systems are the primary cause of many of the manifestations of heart failure, rather than mechanical problems. The excessive activation of the sympathetic nervous system in heart failure maintains cardiac output at the expense of a chronic increase in cardiac workload. Eventually this will lead to an exacerbation of cardiac failure. Beta-blockers block the overstimulated sympathetic nervous system, reducing heart rate, catecholamine myocardial toxicity and renin release, whereas ACE inhibitors inhibit the excessive activation of the renin–angiotensin system.

COST EFFECTIVENESS

CIBIS-II was the only CHF trial to carry out a prospective health economic analysis (Malek, 1999; McMurray, 1999). This showed that the overall cost of care of patients with CHF was 5–10% lower with bisoprolol than with usual therapy, even allowing for the extra costs related to the drug initiation and titration

CHARACTERISTICS OF BISOPROLOL

Pharmacodynamic properties

Bisoprolol has been used for the treatment of hypertension and angina for the past decade in the UK and is now the first selective beta-blocker to be licensed for the treatment of heart failure. It is a highly beta-l-selective adrenoreceptor blocking agent (Bethge et al, 1991; Wellstein et al, 1987), lacking intrinsic stimulating activity. Because it shows only low affinity to the beta-2 receptors concerned with metabolic

regulation, it is not generally expected to influence the airway resistance and beta-2 mediated metabolic effects. Its beta-l selectivity extends beyond the therapeutic range. Bisoprolol is lipid-neutral and it does not disturb carbohydrate metabolism.

In acute administration in patients with coronary heart disease without CHF, bisoprolol reduces the heart rate and stroke volume, and thus the cardiac output and oxygen consumption. In chronic administration, the initially elevated peripheral resistance decreases.

Pharmacokinetic properties

Bisoprolol is well absorbed and has a bioavailability of about 90% after oral administration. Its plasma protein binding is about 30% and the distribution volume is 3.5 litres/kg. Total clearance is about 15 litres/hour. The 10–12 hour half-life in plasma gives a 24-hour effect after once-daily dosing.

Bisoprolol is excreted from the body by two routes, with half being metabolized by the liver to inactive metabolites which are then excreted by the kidneys, and half excreted by the kidneys in an unmetabolized form. Because elimination takes place in the kidneys and liver to the same extent, patients with impaired liver function or renal insufficiency do not generally need dosage adjustment. The pharmacokinetics in patients with stable CHF and with impaired liver or renal function have not been studied. The kinetics of bisoprolol are linear and independent of age.

In patients with CHF NYHA class III, bisoprolol plasma levels are higher and the half life is longer than in healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half life is 17±5 hours.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blockers, bisoprolol caused maternal toxicity (lower food intake and body weight) and embryo/fetal toxicity (higher incidence of resorptions, reduced birth weight, retarded physical development) at high doses, but was not teratogenic.

TREATMENT

The aims of treatment are to improve quality of life and overall wellbeing, and to prolong life. The major influences on quality of life of CHF patients are dyspnoea and fatigue, which can be reduced by alleviating oedema and fluid retention. This involves recognizing patients who are volume-overloaded and low cardiac output. As hospital admissions are the main cause of the high costs of heart failure therapy, keeping patients out of hospital by improving their well-being is a primary goal of treatment.

The findings of CIBIS-II support those of the US Carvedilol Programme (Packer et al, 1996) and the Metoprolol CR XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF; Merit Study Group, 1999). Both of these, like CIBIS-II, were stopped early because beta-blockade substantially reduced death and hospitalization. Together they show conclusively that beta-blockers can now be regarded as part of the standard, evidence-based therapeutic regimen for most patients with stable chronic NYHA class II or III CHF. These patients will tolerate the careful addition of bisoprolol to full conventional therapy, including ACE inhibitors (or other vasodilator in cases of intolerance to ACE inhibitors), diuretics and cardiac glycosides.

In addition to all the usual precautions (bradycardia) and contraindications (such as asthma), it is essential to note that the use of beta-blockade is restricted to carefully selected stable patients, with a heart rate >55 beats per minute and systolic blood pressure >90 mmHg.

Bisoprolol in CHF must be initiated at far lower doses than in hypertension, angina or after MI. Treatment should be introduced with caution, using a very low initial dose (1.25 mg/day). Patients should be observed for 4 hours and, if the therapy is tolerated, gradual dose up-titration over at least 12 weeks after initiation can be undertaken, with monitoring for adverse effects (especially worsening CHF) before and after each dose titration. In practice, this means seeing patients every 2–4 weeks during this period. To aid this titration, bisoprolol is available in 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg dosage strengths.

Bisoprolol therapy is inadvisable in unstable patients and might even be hazardous, because they might be more dependent on the sympathetic nervous system for cardiovascular support. That is why the clinical trials enrolled only stable, ambulatory patients.

Ideally, patients should be ambulatory, out of hospital, and on stable medication for at least 4 weeks. They should not have been hospitalized with heart failure in the previous 2 months.

Expectations from treatment

Bisoprolol confers long-term prognostic benefit (fewer deaths, less hospitalization) and neither doctor nor patient should expect the instant symptom improvement seen with ACE inhibitors. Indeed, not all patients will tolerate beta-blockade and some may feel a bit worse at first.

Dealing with problems

Some patients with CHF given bisoprolol may feel less well, become more breathless or develop ankle oedema. Unless the patient is in crisis (dyspnoeic at rest, orthopnoeic or hypoperfused), bisoprolol should not be stopped. The dose can be reduced, and not raised again until the signs and symptoms of deterioration have been resolved for at least a month. Increasing the dose of diuretic will usually achieve symptomatic improvement, while reducing or withdrawing any concomitant medications of no intrinsic value in CHF, such as nitrates or calcium antagonists, will usually resolve any hypotensive problem.

Early setbacks are usually temporary and the treating physician should endeavour to titrate the beta-blocker dose upwards very gradually to the 10 mg/day maintenance therapy that most patients were able to tolerate in CIBIS-II.

The main potential problem in long-term maintenance therapy is, again, worsening CHF. The approach is the same as during initiation and upwards titration: we should adjust other therapies rather than stop bisoprolol, although it will, of course, need to be temporarily discontinued if a patient is shocked, otherwise hypoperfused or severely breathless.

MANAGEMENT

It is recommended that, when considering bisoprolol, the treating physician should be experienced in the management of CHF. Although treatment initiation is most likely to occur in the hospital setting, most eligible patients are in the community and subsequent dose titration may in future be managed in primary care.

To assist the best management of the condition, particularly the need for careful dose regulation, detailed guidelines for general practitioners are currently being finalized.

Nurses may also be able to play a key role in the administration of bisoprolol to patients with CHF and a training programme is being developed.

CONCLUSIONS

Despite advances in the treatment of CHF, notably improved survival with ACE inhibitors, even 'mild' CHF results in considerable morbidity and mortality. There is now ample and convincing evidence that the use of a beta-blocker such as bisoprolol can do much to redress this situation.

Beta-blockade appears to work chiefly by blocking the overstimulated sympathetic nervous system. It may also protect the heart against the direct toxic effects of high levels of circulating catecholamines, and reduce the energy expenditure of the heart. In the treatment of CHF, beta-blockers must be very carefully titrated. **HM**

Conflict of interest: Dr Davis has sat on an advisory board for Merck Pharmaceuticals on the instigation of beta-blockers in heart failure.

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KEY POINTS

- Bisoprolol (Cardicor®, Merck Pharmaceuticals, West Drayton, Middlesex) is currently the only selective beta-blocker licensed for the treatment of stable chronic heart failure (CHF).
- The use of beta-blockers in CHF stems from a changed focus which views its neurohormonal, not just its haemodynamic, aspects.
- There is now powerful evidence from clinical trials to indicate that all patients with symptomatic CHF and low left ventricular ejection fraction who can tolerate beta-blocking therapy should receive it.
- CHF is a major public health problem, affecting 2% of adults, about half of whom die within 5 years of diagnosis. The problems it poses seem certain to increase, and treatment to prolong life and improve its quality is vital, especially if this takes place in the community rather hospital.
- Bisoprolol treatment should be introduced with caution, using a very low dose, with patients closely monitored. If the therapy is tolerated, gradual dose titration upwards over at least 12 weeks after initiation can be undertaken, again with close monitoring for adverse effects. If necessary, dosing can be interrupted or reduced.