Bisoprolol

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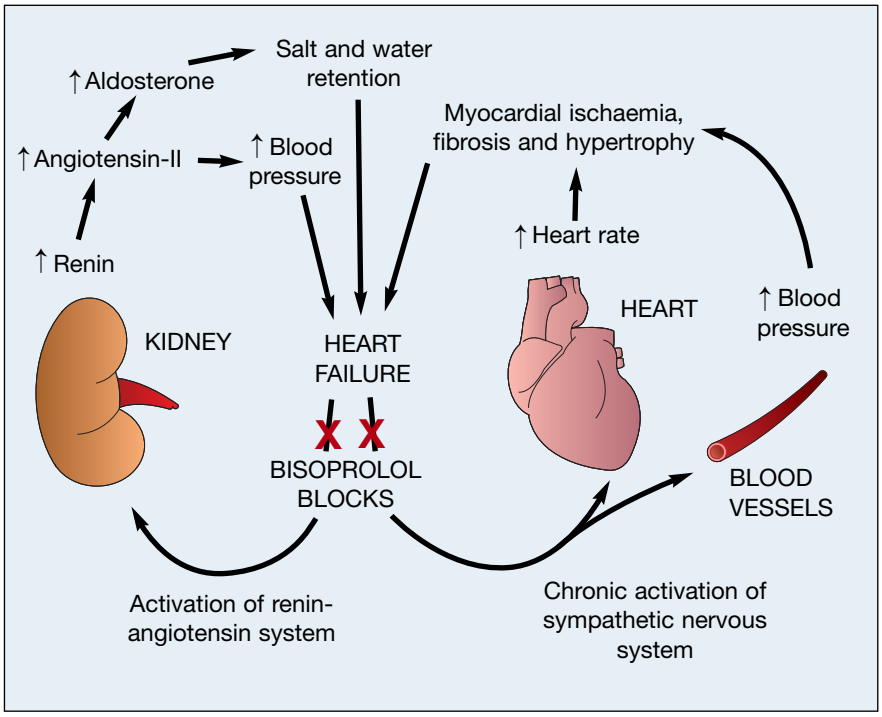
Introduction

Beta-blockers have been used in the treatment of cardiovascular disease for 50 years. Bisoprolol has been available for approximately 15 years. It has four main indications for use: chronic heart failure, ischaemic heart disease, hypertension and tachyarrhythmias. The use of beta-blockers in heart failure is now established, overcoming the previously held belief that they should be avoided in this clinical setting because of negative inotropic effects. The selective beta-1 adrenoceptor action of bisoprolol favours its use in the treatment of patients with heart failure. Although beta-blockers are licensed for the management of hypertension, concerns over adverse metabolic effects have discouraged first-line use for this indication in patients with or without diabetes, unless they have other indications, i.e. heart failure, ischaemic heart disease or tachyarrhythmias.

Pharmacology

Figure 1 outlines the pharmacological action of bisoprolol. It is a highly selective beta-1 adrenoceptor antagonist. Activation of beta-1 receptors increases heart rate and blood pressure, and therefore myocardial oxygen consumption. The pathophysiology of heart failure includes the chronic activation of the sympathetic nervous system, worsening ventricular function by myocardial ischaemia, fibrosis and hypertrophy. Noradrenaline is also thought to be directly toxic to the myocardium. Activation of the renin-angiotensin system also contributes to the pathophysiology of heart failure through the effect of salt and water retention.

Figure 1. Pharmacological action of bisoprolol in heart failure



Bisoprolol blocks beta-1 receptor activation, resulting in reduced myocardial oxygen demand, and also blocks the activation of the renin-angiotensin system. These combined effects, and the fact that it reduces the frequency of atrial and ventricular tachyarrhythmias in this group at increased risk, give it the properties that have allowed it to be shown to have efficacy in patients with chronic heart failure.

The half-life of bisoprolol is approximately 11 hours in healthy populations. However, in patients with heart failure the half-life increases to approximately 17 hours. The relatively long half-life allows once-daily dosing. Fifty percent of it is excreted unchanged in the kidneys and the other 50% is metabolised by the liver.

Trials of safety and efficacy

The two main trials looking at the use of bisoprolol in heart failure are CIBIS (the Cardiac Insufficiency Bisoprolol Study) and CIBIS II.[1,2] Both were multicentre, randomised double-blind, placebo-controlled trials with the latter having more patient numbers (CIBIS, n=641; and CIBIS II, n=2647). In both trials, patients had stable heart failure (NYHA [New York Heart Association] class III or IV) with the majority of patients having heart failure as a result of ischaemic heart disease. They were randomised to receive placebo or bisoprolol (starting at 1.25mg a day, titrated to 5mg in CIBIS and 10mg in CIBIS II). Patients in both studies continued to receive standard treatment, which was usually a diuretic and

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ACE inhibitor. Both studies were powered for the primary endpoint of all-cause mortality. In CIBIS, the secondary endpoint was bisoprolol tolerability. The secondary endpoints in CIBIS II were all-cause hospital admissions, cardiovascular mortality, the combined endpoint of cardiovascular mortality or cardiovascular hospital admissions, and permanent premature treatment withdrawals. The mean follow-up period in CIBIS was 1.9 years and 1.3 years in CIBIS II.

All-cause mortality was lower for bisoprolol in CIBIS but did not achieve statistical significance (16.6% *vs* 20.9%, relative risk 0.80, CI 0.56–1.15). This is likely to be due to lack of statistical power and the low doses of bisoprolol. CIBIS II showed a significantly lower mortality for bisoprolol (11.8% *vs* 17.3%, hazard ratio 0.66, CI 0.54–0.81). CIBIS II also showed a reduced mortality with bisoprolol regardless of the aetiology of the heart failure.

In both studies, there was no significant difference in terms of percentage of treatment withdrawals. Although the total number of adverse events reported in CIBIS II was almost equal for both groups (1328 for bisoprolol compared with 1321 for placebo), some types of events occurred more frequently with bisoprolol – including dizziness, bradycardia, hypotension and fatigue.

Specific evidence for use in diabetes

As an established risk factor for ischaemic heart disease a higher proportion of diabetes patients go on to develop chronic heart failure as a consequence. There has been no trial specifically designed to test the efficacy of bisoprolol for heart failure in patients with diabetes. However, a retrospective subgroup analysis of the CIBIS II data identified 302 patients with type 2 diabetes, 155 (12%) in the placebo group and 157 (12%) in the bisoprolol group.[3] There was a non-significant mortality benefit for bisoprolol *vs* placebo (relative risk 0.81, CI 0.51–1.28).

In another study primarily looking at data for the use of metoprolol in patients with diabetes and heart failure, the investigators report pooled data from CIBIS II, MERIT-HF (a randomised trial looking at metoprolol in heart failure), and COPERNICUS (a randomised trial of carvedilol in heart failure).[4] They showed similar survival benefits for diabetes patients using beta-blockers compared to non-diabetes patients (25% CI 4–40% *vs* 36% CI 27–44%).

Discussion

Bisoprolol is a long-acting beta-blocker used for a number of cardiovascular indications. Its beta-1 selectivity gives it a pharmacological advantage for use in the treatment of stable chronic heart failure. There is good evidence for the use of bisoprolol across a range of doses for heart failure independent of aetiology. Patients with diabetes are at a higher risk of developing chronic heart failure; while no specific trials have been done looking at the use of bisoprolol in patients with diabetes, the *post-hoc* subgroup analysis of the CIBIS II data suggests the likelihood of benefit although the numbers involved were too small to show any statistically significant difference between those on treatment groups. Patients with diabetes and chronic heart failure should be treated in the standard way with diuretics and ACE inhibitors or angiotensin-II receptor blockers. Once stable on these treatments, attempts should be made to introduce a beta-blocker starting at a low dose and titrating up the dose as tolerated given the likelihood of prognostic benefit. Bisoprolol is an appropriate choice of beta-blocker for this indication.

In recent times, evidence showing an increased incidence of new onset diabetes in beta-blocker users has led to discouragement from using them as first-line treatment in hypertensive patients without diabetes. Due to adverse metabolic effects this advice applies to patients with diabetes as well, as per recent National Institute for Health and Clinical Excellence (NICE) guidelines. However, in the high proportion of diabetes patients who suffer from ischaemic heart disease and/or cardiac failure the benefits of beta-blockers are so significant that they are still highly recommended in this context. This point is also emphasised in the recent NICE guidelines. There is some evidence suggesting that third generation beta-blockers may have superior metabolic effects to their predecessors, but NICE felt it was too inconclusive to make specific recommendations concerning this.

Key points

- Bisoprolol is a once-daily beta-1 receptor blocker which improves mortality in heart failure
- Although the trials were not powered to show efficacy in subjects with diabetes, there is no evidence that bisoprolol, or other beta-blockers, does not give the same benefit in people with diabetes
- Patients with diabetes and heart failure should be considered for treatment with beta-blockers and bisoprolol is licensed for this indication

Conflict of interest statement

Dr Smith and Dr McKay have no conflicts of interest to declare. Dr Fisher has received speaker's fees from Merck.

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