SCIENTIFIC LETTER

Obstacles to the initiation of β blockers for heart failure in a specialised clinic within a district general hospital

M Mahmoudi, S McDonagh, PA Poole-Wilson, S W Dubrey

Heart 2003;89:442-444

β Adrenergic receptor blockers (β blockers) are indicated for patients with mild to moderate heart failure (New York Heart Association (NYHA) class II and III) of ischaemic or non-ischaemic aetiology.¹ The evidence for their use in stable patients equals or surpasses that for the angiotensin converting enzyme (ACE) inhibitors.

In the UK, estimates suggest that 85% of heart failure patients are eligible for treatment with β blockers. Studies show that the proportion actually taking a β blocker for definite heart failure is around 11%. What remains unclear, outside of clinical trials, is the applicability of β blocker use in the general population with stable heart failure. We report our experience from a district general hospital on the feasibility of routine prescription of β blockers as add-on treatment for stable heart failure.

METHODS

Patients with an established diagnosis of cardiac failure were recruited consecutively, over a nine month period, from the cardiology outpatient clinics. Patients attended a specialist nurse run outpatient clinic with medical supervision at the point of drug prescription.

Contraindications to initiating treatment with β blockers included bradycardia (<50 beats/min) or high degrees of atrioventricular block unprotected by pacemaker implantation, blood pressure of < 90 mm Hg systolic, significant reversible airways disease (requiring regular use of bronchodilator treatment), and a previous intolerance of β blockers. If these conditions were satisfied then 1.25 mg of bisoprolol was administered. Pulse and blood pressure recordings were monitored for four hours. Patients were advised that they

might experience a transient worsening of their symptoms. At each subsequent visit, the dose of bisoprolol was increased successively to 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg and 10 mg, according to tolerance and as used in CIBIS II (cardiac insufficiency bisoprolol study II).²

RESULTS

We recruited 100 consecutive patients (68 male) with stable cardiac failure (mean age 69 years, range 38-88 years). Mean duration of heart failure was 34 months; 17% were in NYHA class I cardiac failure, 49% in class II, 25% in class III, and 9% in class IV. At screening 89 patients were taking an ACE inhibitor, 30 were on spironolactone, 22 on nitrates, and four patients on an angiotensin II antagonist. Permanent pacemakers had been previously implanted in four patients. Atrial fibrillation was present in 34 patients. Digoxin was prescribed in 40 patients, either for rate control or as part of their anti-failure treatment. A total of five patients were on β blockers for reasons other than heart failure. These treatments were not changed.

Of the 100 patients screened, 43 (43%) were ineligible to commence bisoprolol. The two main reasons for this were chronic obstructive airways disease or asthma in a combined total of nine patients and general frailty in eight patients. The remaining reasons for ineligibility are shown in fig 1 and includes six patients who refused further treatment.

Of the remaining 57 patients, six were already on a β blocker for heart failure; in all six cases this was bisoprolol. Thus, 51 patients were identified, not already on bisoprolol, who were eligible to commence the titration schedule with bisoprolol. This 57 patient cohort had mean values for age of

Figure 1 Reasons for ineligibility of 43 patients to start treatment with bisoprolol. Patients in the category of unsuitable were decided by the patients' hospital consultant. The category "Other" included patients with poor comprehension or compliance, and in one patient trifascicular block on the ECG. COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

Figure 2 A summary of the dose titration algorithm for the outpatient prescription of bisoprolol showing the number of patients reaching each particular stage of recruitment, eligibility, and tolerance of bisoprolol treatment.

66 years, duration of heart failure of 30 months, NYHA class of 2.1, and left ventricular ejection fraction of 36%. An ischaemic aetiology was contributory in 44% (25/57) of these patients.

In those patients who commenced bisoprolol ($n = 51$), a total of 12 patients (23%) failed either the initial in-hospital dose of 1.25 mg of bisoprolol ($n = 9$ patients) or were unable to tolerate the subsequent first week's daily maintenance dose of 1.25 mg of bisoprolol ($n = 3$ patients) (fig 2). No patient was in NYHA class IV and only two were in class III heart failure. The mean value for NYHA class was 1.8. Failure in achieving this first titration phase was caused by increasing dyspnoea in four patients, severe fatigue in three patients, bradycardia in three patients, hypotension in one patient, and impotence in one patient.

There were 45 patients either on bisoprolol at the start of screening or being titrated through the CIBIS II protocol. Patients reaching each particular level are illustrated in fig 2. The mean dose of bisoprolol achieved was 5.42 mg daily. The four main reasons for failure to achieve a maximum dose titration were bradycardia in 16 (34%), hypotension in 14 (30%), fatigue in eight (17%), and dyspnoea in three (6%) patients. Of the four patients with permanent pacemakers, two were unable to tolerate the initial dose and the remaining two tolerated a dose of 5 mg of bisoprolol.

The target dose of 10 mg of bisoprolol daily was achieved by nine patients. These patients had a mean left ventricular ejection fraction of 38%. One patient was NYHA class IV and four were class III. The mean value for NYHA class was 2.4. Patients who achieved a 10 mg dose of bisoprolol did not differ from

those patients who failed to reach even stage I of the schedule, in age, duration of heart failure, NYHA class or left ventricular ejection fraction. There was a non-significant trend towards a higher dose of bisoprolol being tolerated in patients with a higher NYHA class.

The assessment was of an initial 100 patients and subsequent titration of therapy in 57. This required between 504–603 hours of work time (63–76 eight hour days) by a trained heart failure nurse. The range of hours is related to whether patients had to be “dropped back” to a lower dose and reassessed, or were accepting of a dose as being “their” target maximum.

DISCUSSION

The benefits of β blocker therapy in the treatment of heart failure are universally accepted. A retrospective analysis of CIBIS II concluded that these agents should be used regardless “of age, NYHA class, presence of diabetes, renal impairment, or concomitant therapy with digitalis, amiodarone or aldosterone antagonist”.³ Despite these recommendations we have shown that only 6% of those seen in an outpatient population were taking a β blocker as part of their treatment for heart failure. This is similar to that recently reported in a French study in which only 5% of patients were on β blockers.⁴

In general, outside of a clinical trial or a specialty heart failure clinic, the use of β blocker treatment in heart failure remains poor. The reasons are threefold. In part, it rejects a historic prejudice on the behalf of physicians. It may also be caused by a lack of necessary facilities to initiate and supervise this form of treatment. Thirdly, a proportion of patients will not tolerate the use of β blockers either alone or after their addition to existing treatments. In clinical trials most patients (85–90%) have been able to tolerate β blockade in the short and long term, but in the general population the tolerability remains unknown. We have shown that, in an outpatient population with stable heart failure, just over half (57%) are eligible to be tried on β blocker treatment. Only nine of our original 100 patients screened, representing 15.8% (9/57) of those actually commenced on β blockers, were able to achieve the target dose used in the CIBIS II trial.²

Most patients with heart failure are already on diuretics and/or ACE inhibitors, and many patients have pathological conditions which preclude them from β blocker treatment. In addition, the use of amiodarone and digoxin are now widespread in this type of patient and both of these treatments require careful consideration when used with a β blocker. For these reasons, targets for β blocker dosages should be regarded as individual to a particular patient and cannot be rigidly dictated. The majority of our patients (67%, 31/45) were “suited” to doses of bisoprolol of 5 mg or less per day. In the MERIT HF (metoprolol CR/XL randomized intervention trial in heart failure) and CIBIS II studies, where tolerability to β blockade was not a prerequisite to recruitment, 64% achieved the target dose of 200 mg of metoprolol per day and 57% the target dose of 10 mg of bisoprolol, respectively. In the earlier CIBIS study only 51% of patients reached the lower target dose of 5 mg of bisoprolol daily. In the MDC (metoprolol in dilated cardiomyopathy) trial, 96% of patients tolerated the test dose of metoprolol. Subsequent tolerability of β blocker treatment with low dose metoprolol is simply reported as good with no quantification. Both the US and the Australia/New Zealand carvedilol studies had a “run in” design which selected out patients who had experienced adverse effects from the drug and who were not then recruited into the main body of the trial. Tolerability cannot be assessed with such a study design.

The reasons we report for intolerance are predominantly a consequence of what, to that individual, represents excessive β receptor blockade. We found no association between NYHA class of heart failure or the age of patients who were intolerant of therapy with bisoprolol. Krum and colleagues found

that NYHA class was a marker of intolerance, with 22% in class IV intolerant compared to 3%, 9%, and 13% for NYHA classes I–III, respectively.³ In the COPERNICUS (carvedilol prospective randomised cumulative survival) study, remarkably high tolerability for carvedilol was reported, in which 73% of patients were titrated up to the target dose of 25 mg twice daily. Moreover, this was a study notable for including patients with particularly severe heart failure, in whom left ventricular ejection fractions were less than 25%.

We have also shown that the use of β blockers in heart failure is a treatment that requires considerable time and enthusiasm. The resource implications are large for a condition that has been shown to have an incidence in the UK of between 1.3–2.9%, rising to 8% in patients over the age of 65 years.

The use of β blockers, although beneficial, is certainly not applicable in every patient with heart failure. Less than half (45%, 45/100) of the patients with stable heart failure in this survey were able to tolerate titration of β blockers as part of their treatment. The dose of β blockade, while not established, appears to be something that is specific for every individual patient. Some comfort with this concept can be obtained from a recent analysis of the MERIT HF experience which concluded that patients receiving a lower dose of metoprolol achieved a similar survival benefit to those on a higher dose.⁶

Authors' affiliations

M Mahmoudi, S McDonagh, S W Dubrey, Department of Cardiology, Hillingdon Hospital, Uxbridge, Middlesex, UK
PA Poole-Wilson, National Heart & Lung Institute, Faculty of Medicine, Imperial College, London, UK

Correspondence to: Dr SW Dubrey, Hillingdon Hospital, Pield Heath Road, Uxbridge, Middlesex UB8 3N; simon.dubrey@thh.nhs.uk

Accepted 2 October 2002

REFERENCES

- 1 Lechat P, Packer M, Chalon S, *et al*. Clinical effects of beta adrenergic blockade in chronic heart failure. A meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;**98**:1184–91.
- 2 CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
- 3 Erdmann E, Lechat P, Verkenne P, *et al*. Results from post-hoc analysis of the CIBIS II trial: effect of bisoprolol in high risk patient groups with chronic heart failure. *Eur J Heart Failure* 2001;**3**:469–79.
- 4 Zannad F, Briancon S, Juilliere Y, *et al*, and the EPICAL Investigators. Incidence, clinical and etiologic features and outcomes of advanced chronic heart failure. The EPICAL study. *J Am Coll Cardiol* 1999;**33**:734–42.
- 5 Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. *Heart* 2000;**84**:615–19.
- 6 Wickstrand JCM, Hjalmarson A, Waagstein F, *et al*. Achieved metoprolol CR/XL dose and clinical outcomes, analysis of the experience in MERIT HF. *Circulation* 2001;**104**:II:753.

IMAGES IN CARDIOLOGY

Three dimensional images with ECG gated multislice computed tomography revealed stenosis of the descending aorta in 2 month old baby

A 14 day old male infant diagnosed with aortic interruption syndrome underwent aortic arch repair surgery. On his 70th day of life, he did not take sufficient milk and showed tachypnoea with cyanosis. There was a pronounced difference in blood pressures between the upper and lower limbs. Angiography showed that the descending aorta had severe stenotic segment at the origin of left subclavian artery. To clarify the relation between the aorta and surrounding tissue, enhanced multislice computed tomography (CT) (Aquilion, Toshiba, Tokyo) was performed using the following protocol: 1 mm slice thickness, helical pitch 1.5, and 6 ml of

Iomeprol 300 as the intravenous contrast material. CT scanning was performed with retrospective ECG gated reconstruction. After the acquisition, we extracted volume data from end systole and end diastole, and three dimensional images were reconstructed by volume rendering. In the left superior posterior views, the stenotic lesion was observed in the proximal portion of the descending aorta in both cardiac phases and there was no compression by surrounding tissue, including the pulmonary artery (PA). It was easy to determine the spatial relation between the PA and the descending aorta. The stenotic site was more clearly observed at end systole than at end diastole. These images clearly indicate that the stenosis was not the result of compression by other vessels or organs. Thus, after this examination, percutaneous transluminal angioplasty was performed with good results.

N Funabashi
T Honda
M Terai

nobusada@ma.kcom.ne.jp