CARDIOVASCULAR MEDICINE

β Blockers in older persons with heart failure: tolerability and impact on quality of life

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Objective: To determine tolerability and symptom changes associated with the introduction of bisoprolol treatment in older patients with heart failure.

Design: Prospective observational cohort study.

Setting: Geriatric medicine outpatient department of a university hospital.

Patients: 51 patients (mean age 78 years, range 70-89 years) with stable symptomatic heart failure caused by left ventricular systolic dysfunction.

Interventions: Bisoprolol tablets, 1.25-10.0 mg.

Main outcome measures: Tolerability; changes in symptoms and exercise tolerance.

Results: 69% of patients tolerated bisoprolol. Mean tolerated dose was 7.6 mg. There was no change in symptoms or exercise capacity in those who tolerated bisoprolol. Perceived health status and symptoms of anxiety and depression improved during the titration period.

Conclusions: The rate of withdrawal from bisoprolol treatment in older patients with congestive heart failure was twice that previously reported in younger patients. The mean tolerated dose was similar to that found in trials reporting clinical efficacy. There was no evidence of a negative impact on symptoms or exercise capacity in patients who tolerated bisoprolol.

There is accumulating evidence that the addition of a β blocker to standard treatment with angiotensin converting enzyme (ACE) inhibitors and diuretics in patients with congestive heart failure improves morbidity and mortality.¹⁻³ However, older people were underrepresented in these β blocker trials. In the two landmark clinical trials showing the efficacy of β blockers in congestive heart failure (CIBIS-II and MERIT-HF), the mean age of the participants was under 63 years.^{1,2} People over 80 years of age were excluded. In contrast, the mean incident age for congestive heart failure is 76 years, and the prevalence rises steeply with increasing age.⁴⁻⁷ Hence the populations studied in these trials were significantly younger than those treated in routine clinic practice.

CIBIS-II and MERIT-HF had low treatment failure rates of 15% and 10%, respectively. However, older persons were excluded from those studies, so the incidence of treatment failure and side effects in old people remains unclear. As co-morbidity and polypharmacy tend to be more common with increasing age, one could postulate a greater treatment failure rate. For older patients the treatment goal of symptom control may be as important as increased life expectancy. However, the impact of β blockers on symptoms in older patients with congestive heart failure is unknown so we have an inadequate basis for extrapolating the results of the β blocker clinical trials to older people.

Our aim in this study was to determine the tolerability of the β blocker bisoprolol in older patients with stable congestive heart failure. We also wished to determine any changes in symptoms, exercise tolerance, and perceived health status at the end of the bisoprolol titration period.

METHODS

This was an observational study in which all participants were given open label bisoprolol tablets.

Participants

Eligible patients were aged over 70 years and had a diagnosis of congestive heart failure. Over a six month period, consecu-

tive patients who fulfilled the entry criteria for the study were recruited from a hospital outpatient clinic. At the time of recruitment into the trial all had congestive heart failure with one or more of the following symptoms: dyspnoea on exertion; orthopnoea; paroxysmal nocturnal dyspnoea; oedema; fatigue. The symptoms corresponded to class II or III of the New York Heart Association (NYHA) classification. All patients underwent transthoracic echocardiography before starting treatment. The ejection fraction was measured by modified Simpsons' rule⁸ with the patient in the left lateral decubitus position. Patients with an ejection fraction under 40% were considered for inclusion in the study. Permission to undertake the study was granted by Sunderland local research ethics committee, and written informed consent was obtained from each participant before entry into the study.

A six week period of clinical stability was required before enrolment, defined as no increase in NYHA classification. In the case of patients with recent myocardial infarction or unstable angina this was extended to three months. Cardiovascular treatment was unchanged in the two weeks before bisoprolol was started. Current treatment with a diuretic and an ACE inhibitor, or with an angiotensin II receptor antagonist in patients intolerant of ACE inhibitors, was mandatory; the use of digoxin, spironolactone, or amiodarone was optional.

Exclusion criteria

Exclusion criteria were as follows:

- a history of myocardial infarction or unstable angina pectoris in the previous three months
- percutaneous transluminal coronary angioplasty or coronary artery bypass graft in the previous six months

Abbreviations: ACE, angiotensin converting enzyme; CIBIS-II, cardiac insufficiency bisoprolol study II; CMSS, co-morbidity symptom scale; GHQ, general health questionnaire; HAD, hospital anxiety and depression scale; MERIT-HF, metoprolol CR/XL randomised intervention trial in congestive heart failure; NYHA, New York Heart Association

- atrioventricular block greater than first degree without a permanent pacemaker
- resting heart rate of less than 60 beats/min
- resting systolic blood pressure of less than 100 mm Hg
- renal failure (serum creatinine > 200 μ mol/l)
- severe peripheral vascular disease (defined as rest pain, a claudication distance of less than 25 m, or patients awaiting peripheral angioplasty or lower limb revascularisation)
- reversible obstructive lung disease
- pre-existing or planned treatment with β blockers
- cognitive impairment (as defined by a Forstein mini-mental state examination score <24°).

Bisoprolol test dose

Following informed consent, eligible patients were given a test dose of bisoprolol. On the day of the test dose they were asked to omit their regular diuretic and ACE inhibitor and attend day hospital where an oral dose of 1.25 mg bisoprolol was given at 10.00 am. The patient remained rested in a seated position for the test dose and the subsequent monitoring period of four hours. Blood pressure, heart rate, and symptoms were recorded at half hourly intervals for four hours. If patients developed symptoms associated with hypotension during this monitoring period they were withdrawn from the study. For the purpose of the study, first dose hypotension was defined as a fall in systolic blood pressure of 20 mm Hg or more, or to a systolic blood pressure of less than 100 mm Hg, with or without associated symptoms.

Titration period

Patients were started on bisoprolol 1.25 mg daily and the drug was increased successively to 2.5 mg, 3.75 mg, and 5.0 mg at weekly intervals, and then at monthly intervals to 7.5 mg and 10 mg according to tolerance. Patients were reviewed at weekly intervals for three weeks and monthly thereafter. The patients had a final visit two weeks after the maximum tolerated dose was established. In patients with worsening heart failure, the baseline heart failure treatments were increased before bisoprolol was decreased. In those who could not tolerate the 10 mg dose the reason was recorded. Reasons for withdrawal of bisoprolol were also recorded.

Measurement of perceived health status, co-morbidity, and exercise ability

Congestive heart failure symptoms were assessed using the Guyatt congestive heart failure scale—a disease specific scale suitable for measuring heart failure symptoms in clinical trials in congestive heart failure¹⁰—which has been validated for use in older persons.¹¹ Perceived health status was evaluated using the general health questionnaire (GHQ),¹² and anxiety and depression using the hospital anxiety and depression scale (HAD).¹³ The co-morbidity symptom scale (CMSS) was used to determine the patient rated index of overall symptomatic comorbidity.¹⁴ Exercise capacity was measured by the six minute walking test,¹⁵ using a method validated for older subjects with congestive heart failure.¹¹

All assessment scales were administered and exercise capacity determined before the bisoprolol test dose. Patients who tolerated bisoprolol had repeat scale assessments and six minute walking tests two weeks after they were established on the maximum tolerated dose.

Statistical analysis

Data were recorded on standard proformas and analysis performed using SPSS version 10. Ninety five per cent confidence intervals for tolerability were calculated. Six minute walking distance and scores for Guyatt, GHQ, HAD, and CMSS were compared by Wilcoxon signed ranks test within group analysis.

Table 1 Drug treatment, pulse rate, and blood pressure at entry to the study (n = 51)

Variable	
Mean pulse rate (beats/min)	78
Mean systolic blood pressure (mm Hg)	135
Mean diastolic blood pressure (mm Hg)	74
Number on diuretics	51
Mean dose of frusemide (mg) (range)	61 (40–160)
Number taking ACE inhibitor	51
Mean dose of lisinopril (mg)	12.6
Mean dose of enalapril (mg)	13.5
Number taking spironolactone	7
Number taking digoxin	20
Number taking amiodarone	2

ACE, angiotensin converting enzyme inhibitor.

RESULTS

Sixty six patients were approached but 11 declined consent. Four who agreed to take part were subsequently found to have evidence of obstructive pulmonary disease with significant airways reversibility and hence were excluded, so the final number of participants was 51. Their mean age was 78 years (range 70–89 years). Twenty eight (55%) were male and 23 female. Baseline variables including pulse, blood pressure, and drug treatment on entry are given in table 1. Patients tolerating bisoprolol were followed for a mean of 13 weeks (range 3–17 weeks).

Test dose

Mean systolic and diastolic blood pressures during the test dose observation period are shown in fig 1. In seven patients (14%), systolic blood pressure remained unchanged following the bisoprolol test dose, remaining greater than 100 mm Hg throughout the four hour observation period and not altering by more than 20 mm Hg from baseline. Forty four patients (86%) had significant first dose hypotension. In 28 patients (55%), systolic blood pressure fell to below 100 mm Hg following the first dose of bisoprolol. A further 16 patients (31%) had a systolic blood pressure fall of greater than 20 mm Hg from baseline, but the pressure remained above 100 mm Hg throughout the observation period. Four patients developed symptoms, all when systolic blood pressure was less than 100 mm Hg and all complaining of dizziness. Symptoms resolved by the end of the observation period. These four patients were withdrawn from the study.

Figure 1 Changes in mean systolic and diastolic blood pressure during the test dose observation period.

Table 2 Reasons for withdrawal of bisoprolol (n = 16)

Reason for withdrawal	n
Symptomatic hypotension with first dose	4
Hypotension	3
Fatigue	3
GI disturbance	2
Worsening CHF	1
Bronchospasm	1
Rash	1
Insomnia	1
Total	16

CHF, congestive heart failure; GI, gastrointestinal.

Table 3 Reasons for intolerance of 10 mg dose of bisoprolol (n = 14)

Reason for intolerance of higher dose	n
Hypotension	7
Bradycardia	1
Fatigue	5
GI disturbance	1

Bisoprolol tolerability

Thirty five patients (69%) tolerated bisoprolol throughout the titration period (95% confidence interval (CI) 54% to 81%). The reasons for treatment withdrawal are shown in table 2. Mean tolerated dose was 7.6 mg (range 1.25–10 mg). Twenty one patients tolerated 10 mg, four tolerated 7.5 mg, one tolerated 5 mg, and nine tolerated less than 5 mg. Reasons for not tolerating the maximum dose are given in table 3. Ten of the 35 patients tolerating bisoprolol required an increase in the dose of either diuretic or ACE inhibitor or both during the titration period.

Changes in symptom scales and exercise ability

All patients completed the assessment scales at entry. All 35 patients who tolerated bisoprolol completed repeat assessment scales; 29 of 35 patients who tolerated bisoprolol were able to complete two walking tests. Six were unable to perform a walking test owing to poor mobility.

Following completion of bisoprolol titration there was no significant change in disease specific symptoms for congestive heart failure or exercise capacity. Significant improvements in the scores for GHQ and HAD were noted between baseline and the end of the study. No changes in symptomatic co-morbidity (CMSS) were noted (table 4).

DISCUSSION

This was an uncontrolled observational cohort study. In view of the weight of evidence for the use of β blockers in younger patients with congestive heart failure we thought it was inappropriate to include a placebo arm in our study. We felt the patients recruited into our trial were representative of those seen in routine clinical practice. They were a consecutive cohort recruited from a hospital outpatient clinic, with a mean age of 78 years. Many had high levels of co-morbidity as measured by the co-morbidity symptom scale.

We found that older individuals had approximately twice the rate of withdrawal when started on bisoprolol compared with the trial population in CIBIS-II. Reasons for withdrawal were diverse and consistent with either worsening congestive heart failure or recognised side effects of β blocker treatment. However, when our patients tolerated bisoprolol, the maximum tolerated dose was very similar to that seen in CIBIS-II.

Table 4 Comparison of Guyatt CHF, HAD, and CMS scales, GHQ, and six minute walk before and after bisoprolol treatment

	Pre-bisoprolol	Post-bisoprolol	p Value*
Number of participants	35	35	
Guyatt	70.2 (18.8)	70.8 (13.0)	>0.05
HAD	8.1 (5.8)	7.0 (5.7)	0.02
GHQ	18.0 (9.8)	14.9 (8.6)	0.03
CMSS	8.9 (5.4)	8.3 (5.4)	>0.05
Number of participants	29	29	
Six minute walk (m)	247 (103)	281 (99)	>0.05

Values are mean (SD).

*Wilcoxon signed rank test.

CMSS, co-morbidity symptom scale; GHQ, general health questionnaire; Guyatt, Guyatt congestive heart failure scale; HAD, hospital anxiety and depression scale.

Sixty per cent of patients who tolerated the drug reached maximum dose, compared with 50% in CIBIS-II; furthermore, 66% tolerated 5 mg or more, compared with 79% in CIBIS-II.

From these observations we conclude that the rate of withdrawal from bisoprolol is higher in older people. However, when bisoprolol is tolerated, doses comparable to those achieved in the clinical trials can be achieved. The use of bisoprolol may then confer the same morbidity benefits as that seen in the CIBIS-II trial, but in the absence of data from randomised controlled trials in older persons with congestive heart failure this cannot be confirmed.

We found a high incidence of first dose hypotension. While this was severe and symptomatic in only a minority, we would suggest that at present it is preferable to initiate β blocker treatment in older people with congestive heart failure in a closely monitored environment. Patients who experienced asymptomatic first dose hypotension were able to tolerate subsequent upward dose titration. Thus the occurrence of asymptomatic first dose hypotension should not preclude older patients with congestive heart failure from starting regular β blocker treatment.

There was no evidence from our study that symptoms of congestive heart failure or of co-morbid illnesses, general health perception, feelings of anxiety and depression, or exercise capacity were adversely affected during the bisoprolol titration period. In fact, scores for the GHQ and HAD were significantly better, suggesting improvements in perceived health status and reduction in anxiety and depression during this period. However, as there was no placebo arm in our study we cannot directly attribute these improvements to β blocker treatment. It is important to recognise that the initiation and titration of β blockers in this group of older patients with congestive heart failure was time consuming and labour intensive, requiring frequent titration visits. It is possible that this frequent contact with health care professionals was responsible for the symptom improvement observed in our study.

Conclusions

Older patients with stable congestive heart failure were twice as likely to be intolerant of bisoprolol as a large, younger trial population. However, older patients who do tolerate bisoprolol can achieve therapeutic doses with no overall negative impact on the symptoms of congestive heart failure or on their exercise ability. There was an improvement in general health perception and symptoms of anxiety and depression during the titration period. β Blockers should be considered in older patients with symptomatic congestive heart failure once they have been stabilised on an ACE inhibitor and a diuretic.

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Conflict of interest: JB has spoken at a research meeting sponsored by Merck Pharmaceuticals. JB, AS, JO'C, and CSG have been secondary investigators in clinical trials sponsored by MSD.

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IMAGES IN CARDIOLOGY

Coronary occlusion caused by embolisation from a mass in the sinus of Valsalva

A 55 year old woman presented with acute chest pain of four hours' duration. Her medical history revealed she suffered from chronic depression, which was treated with a monoamine oxidase inhibitor. She also smoked cigarettes. On admission, the patient was normotensive (systolic blood pressure 125 mm Hg), had no signs of congestive heart failure, and had normal peripheral pulse. No murmurs were heard on auscultation. The ECG showed a regular sinus rhythm of 85/min and signs of an acute anterolateral infarction. The patient was transferred immediately to the catheterisation laboratory where aspirin, heparin, and glyceryl trinitrate were administered intravenously and emergency coronary angiography was performed. In the left coronary artery, the left anterior descending branch was proximally occluded. Also the posterolateral branch of the ramus circumflexus was occluded (upper panel, centre). The right coronary artery appeared to be normal. In the sinus of Valsalva a round structure was seen, indicative of embolisation of the left coronary artery (lower panel, centre). Subsequently, primary angioplasty of the left anterior descending coronary artery was performed, but blood flow could not be restored. Transoesophageal echocardiography revealed an echodense structure 0.5 x 1 cm, located in the left coronary sinus of Valsalva, just proximal to the ostium of the left coronary artery (upper and lower panels, right). The aortic root itself showed no abnormalities. Suspecting that a thrombus in the sinus of Valsalva with embolisation was the cause of the coronary occlusion, thrombolysis was

administered intravenously. However, no signs of reperfusion were seen. The following day the patient's haemodynamics deteriorated and, despite maximal cardiac and respiratory support, she died. No permission for necropsy was given.

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