Heart failure in a district general hospital: are target doses of beta-blockers realistic?

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Summary

Background: Carvedilol therapy reduces mortality in patients with chronic heart failure. Multi-centre studies suggest a low first dose failure rate and high levels of tolerability to carvedilol. Little is known, however, concerning the eligibility and tolerance to treatment with carvedilol within a district general hospital setting.

Aim: To evaluate the eligibility and tolerance of patients with heart failure to carvedilol within a district general hospital.

Design: Prospective clinical audit analysis.

Methods: We assessed 100 heart failure patients eligibility to commence carvedilol therapy. In those who satisfied clinical criteria, we evaluated first dose failure rate, target dose achievement, reasons for intolerance, heart rate and blood pressure reduction and resource requirements over a six-month period.

Results: Of 100 patients, 16% had contra-indications to commence carvedilol therapy. In those who satisfied clinical criteria, we evaluated first dose failure rate, target dose achievement, reasons for intolerance, heart rate and blood pressure reduction and resource requirements over a six-month period.

Conclusions: In the general setting, eligible patients appear to display a high first dose failure rate, poor tolerance to higher doses and achievement of a ‘target dose’ of carvedilol. Responses to adrenergic blockade were similar to previously published data, irrespective of the final tolerated dose, suggesting that the concept of achieving a ‘target dose’ may not be clinically useful. Guidelines and treatment protocols for heart failure should reflect not only what is considered gold standard, but also what is practical in general hospitals.

Introduction

Heart failure is common, affecting 1–2% of the general population.1 The management of this condition accounts for 1–2% of healthcare expenditure in the UK, and in other countries in the developed world.2 In recent years, randomized controlled trials have shown that the use of β-blockers in patients with heart failure is associated with significant reductions in morbidity and mortality. They have also shown high levels of tolerability and low first-dose failure rates.3–6 In the UK, it is estimated that...
85% of heart failure patients are eligible for treatment with β-blockers, but the proportion actually taking a β-blocker is approximately 11%. Thus in clinical practice, the uptake of β-blockers by patients with heart failure appears inadequate, despite broad eligibility and confirmed drug efficacy.

Two β-blockers are currently licensed for the treatment of heart failure in the UK: carvedilol and bisoprolol. Carvedilol blocks α₁-, β₁- and β₂-receptors, in contrast to β-blockers such as bisoprolol and metoprolol, which interact primarily with β₁ receptors. The COMET investigators have recently shown that carvedilol has a survival advantage in chronic heart failure compared to metoprolol, which is a selective β₁ receptor antagonist. Bisoprolol, similar in pharmacological action to metoprolol, has been shown to have low tolerability and considerable resource requirement in the general hospital setting. In this report we evaluated the eligibility, tolerability and target dose achievement for carvedilol in patients with heart failure, in a district general hospital setting.

Methods

Study patients

The Hillingdon Hospital was the setting for this study, and is a typical London district general hospital. The catchment population is 275,000, and local general practitioners refer their patients with heart failure to the cardiology unit for evaluation. Patients with an established diagnosis of cardiac failure were recruited consecutively, over a 6-month period, from the cardiology out-patient clinics and the hospital discharge registry. Heart failure was diagnosed by clinical presentation and echocardiography to document the extent of systolic left ventricular dysfunction. Patients with current or past symptoms of angina, prior myocardial infarction or coronary revascularization were assumed to have an ischaemic contribution to the aetiology of their heart failure. Patients then attended the hospital to commence β-blocker therapy, using the drug carvedilol. Patients attended a specialist nurse run outpatient clinic with medically qualified supervision at the point of drug prescription.

Study eligibility

Upon arrival, each patient underwent full clinical examination, including heart rate, blood pressure and examination for features indicative of fluid overload. The NYHA (New York Heart Association) class of heart failure was recorded. A 12-lead resting electrocardiogram was performed. Contra-indications to initiating treatment with carvedilol were: bradycardia (<50 bpm) or high degrees of atrio-ventricular block unprotected by pacemaker implantation; systolic blood pressure <90 mmHg; significant reversible airways disease (requiring regular use of bronchodilator therapy); previous intolerance to β-blockers; and significant non-cardiac frailty (making recurrent hospital attendances for drug titration difficult). Other co-morbid conditions, including peripheral vascular disease, severe chronic obstructive airways disease and cardiac conduction disorders (1st degree and Mobitz type I (Wenkebach) atrio-ventricular block or pacemaker implantation) were not considered absolute contra-indications to initiating carvedilol therapy.

Study protocol

Patients who fulfilled the eligibility criteria received an initial dose of 3.125 twice daily of carvedilol. Pulse and blood pressure recordings were monitored for 1 h. In the absence of any adverse effects, patients were discharged on 3.125 mg twice daily with a follow-up appointment in 14 days. To improve compliance, all patients were advised that they might experience a transient worsening of their symptoms. At each subsequent visit, patients were examined clinically and an electrocardiogram was repeated. The dose of carvedilol was increased successively on a fortnightly basis to 6.25 mg, 12.5 mg and finally a target dose of 25 mg twice daily. This was in accordance with the titration schedule used in the COPERNICUS (Carvedilol prospective randomized cumulative survival) trial. Clinical evaluation was used to assess tolerance at each visit, and a temporary maintenance of dose or dose reduction was permitted, where necessary. Overall follow-up duration was 6 months.

Results

We identified 100 patients, over a 6-month period, who were assessed for initiation of carvedilol therapy. The baseline characteristics are shown in Table 1; 90% were Caucasian, 5% Asian, and 5% were of Afro-Caribbean ethnicity. Mean New York Heart Association class was II and mean left ventricular ejection fraction was 30.1%. A permanent pacemaker had been previously implanted in five patients.

Eligibility

Of the 100 patients, 16 were ineligible due to absolute contra-indications. The main reasons were...
hypotension (4), previous intolerance (4), general non-cardiac frailty (4), severe COPD (3) and resting bradycardia (1). Twenty-two were already taking optimal doses of a $\beta$-blocker (21 bisoprolol, 1 carvedilol) for heart failure and were not included for up-titration. Thus 62 met the eligibility criteria to commence carvedilol therapy. One patient later refused to initiate $\beta$-blocker therapy. (Figure 1) Sixty-one thus commenced the titration schedule with carvedilol. This cohort ($n=61$) had a mean age of 67 years (SE 1.56; age range 32–91 years), mean NYHA class of II and mean left ventricular ejection fraction of 28.9% (SE 1.65). An ischaemic aetiology was a contributing feature in 62.3% ($n=38$) of patients.

**First-dose failure rate and intolerance**

In those patients who commenced carvedilol ($n=61$), 11.5% either failed the initial in-hospital dose of 3.125 mg or were unable to tolerate the subsequent first two weeks maintenance dose of 3.125 mg twice daily. This cohort that failed first the dose titration phase had a mean age 73 years (range 65–82) and a mean left ventricular ejection fraction of 20.0%. The mean NYHA class was III. An ischaemic aetiology was a contributing feature in 57.1% of these patients. (Table 2) Failure in achieving this first titration phase was due to increasing dyspnoea ($n=3$), hypotension ($n=2$), bradycardia ($n=1$) and severe dry eyes ($n=1$). The titration phase achievement by this cohort is shown in Figure 2.

**Haemodynamics and target dose achievement**

The ‘target dose’ of 25 mg carvedilol twice daily was achieved by 6.6%. This cohort had a mean age of 60 years (range 40–68) and a mean left ventricular ejection fraction of 38.8%. The mean NYHA class was III. An ischaemic aetiology was a contributing feature in 75% of patients. (Table 2) Overall, the mean carvedilol dose level for the whole cohort ($n=54$) was 7.81 mg twice daily and the median dose was 6.25 mg twice daily. The mean heart rate and systolic blood pressure reductions from baseline were 15 (SE 1.2) bpm and 17 (SE 1.7) mmHg, respectively (Table 3).

**Resource requirements**

Over a 6-month follow-up period, approximately 155 h of work time were required (of a trained heart failure specialist nurse and doctor) to assess 100 patients with heart failure and treat those eligible for carvedilol therapy. This equates to a mean of 152 min per patient initiated, and relates to whether patients required dose reductions, adjustment to
existing therapy or maintenance of current dose level and therefore subsequent clinic appointments. Medical supervision was necessary to alter concomitant medications and to prescribe at each titration level.

**Table 2** Demographic comparison between first-dose failure and target-dose achievement cohorts

<table>
<thead>
<tr>
<th>Demographic</th>
<th>First-dose failure cohort (n = 7)</th>
<th>Target-dose achievement cohort (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>73</td>
<td>60</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>7/0</td>
<td>3/1</td>
</tr>
<tr>
<td>Mean NYHA class</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>Mean LV ejection fraction (%)</td>
<td>20.0</td>
<td>38.8</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>57.1</td>
<td>75.0</td>
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</table>

LV, left ventricular.

**Figure 2.** Patient achievement by study phase.

**Discussion**

The benefits of β-blocker therapy (carvedilol, bisoprolol and metoprolol) for chronic heart failure have been demonstrated by multiple large randomized...
controlled trials.3–6 Furthermore, carvedilol appears superior, in terms of survival benefit, when compared to selective β1 antagonists such as metoprolol.9 In this study, 16% of patients were considered to have absolute contraindications to the initiation of carvedilol, and 22% were taking a β-blocker as part of their existing therapy. In a previous study we evaluated the use of bisoprolol for heart failure and found that 43% of patients were considered to have absolute contra-indications to initiation, and only 6% were already on a β-blocker. The proportion of patients with frailty and COPD not initiated on bisoprolol were higher than in this study using carvedilol. This may account for the perceived discrepancy between the two studies.10 In this study, we used a broader approach to patient selection, based on an increasing body of evidence for β-blockers for certain heart failure patient subgroups. Recent studies have confirmed the tolerability of carvedilol in heart failure patients with COPD11 and evidence in treating fairly ill patients.12 The improvement in the use of β-blockers between the two studies may be a consequence of this previous study, as well as an increased eligibility of certain patient groups.

Bellotti et al. previously showed that only 4% of heart failure patients were treated with β-blockers by general internists, compared to 41% by cardiologists.13 It is therefore possible that the use of β-blocker therapy in heart failure has marginally improved, outside the context of clinical trials and specialty heart failure services. There have been many postulated historical reasons for poor uptake of β-blocker use. These include physician prejudice and mistrust of a drug class previously contra-indicated for heart failure, and the requirement of adequate resources to up-titrate patients under the supervision of trained personnel. The improvement we have shown at our centre may be due to a change in practice brought about by relatively recent clinical governance, the advent of evidence-based medicine based on multiple large randomized controlled trials and the role of the heart failure nurse.

Multiple large randomized controlled trials using carvedilol have previously reported high tolerability in the short and long term, and relatively high dose achievement. In the US Carvedilol Heart Failure Study Group, 1197 patients were enrolled with chronic heart failure. They found only a 5.6% failure rate of the two-week open-label ‘run in’ period, and the 696 patients titrated on carvedilol achieved mean daily doses of 45 ± 27 mg of carvedilol.3 The Carvedilol prospective randomized cumulative survival study group evaluated 2289 patients with severe heart failure. They found that 65.1% of the 1156 patients started on carvedilol reached the target dose of 25 mg twice daily.6 The Australia/New Zealand carvedilol studies also 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.14 An additional carvedilol study from Australia found that 88% of 808 patients were able to tolerate doses of 12.5 mg or 25 mg twice daily.15

The majority of patients in randomized controlled trials appear to tolerate carvedilol and achieve high doses. However, the run-in design used in some trials can lead to patient selection bias, and younger patient cohorts cannot be automatically used to extrapolate true tolerability in the general population. The patients started on carvedilol in this study were on average 5.4 years older than those evaluated by the COMET investigators.9 The tolerability and indeed feasibility of using carvedilol for heart failure, in the general unselected population, was previously unknown. The first dose failure rate of carvedilol in this study cohort was 11.5%. Only 6.6% of those initiated on carvedilol achieved the ‘target dose’ used in previous multi centre studies. This is substantially less than that expected from the trial data.

The reasons for intolerance reported in our study appear to be a consequence of what, to that individual, represents excessive β-receptor blockade. The mean reductions in heart rate (15 bpm) and systolic blood pressure (17 mmHg) in this study were similar, irrespective of dose used, and correlated well with

<table>
<thead>
<tr>
<th>Carvedilol dose (mg twice daily)</th>
<th>Baseline mean HR (bpm)</th>
<th>Mean HR reduction (bpm)</th>
<th>Baseline mean systolic BP (mmHg)</th>
<th>Mean systolic BP reduction (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.125 (n=18)</td>
<td>83</td>
<td>13</td>
<td>124</td>
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<tr>
<td>6.25 (n=20)</td>
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<td>128</td>
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<td>12.5 (n=12)</td>
<td>83</td>
<td>17</td>
<td>139</td>
<td>22</td>
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<tr>
<td>25 (n=4)</td>
<td>81</td>
<td>14</td>
<td>139</td>
<td>9</td>
</tr>
<tr>
<td>Mean</td>
<td>83</td>
<td>15</td>
<td>129</td>
<td>17</td>
</tr>
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</table>

Table 3 Dose comparison of heart rate (HR) and systolic blood pressure (SBP) reduction
results from the COMET study. This suggests that the concept of achieving a ‘target dose’ may not be useful in the general hospital setting, and the focus should be on individual patient response. Bristow et al., however, have previously shown a dose-dependent beneficial effect on left ventricular ejection fraction, hospitalization and mortality, despite similar effects on haemodynamic parameters. This suggests that final dose of β-blocker is important. Contrary to this, the MERIT HF study concluded that patients receiving a lower dose of metoprolol succinate CR/XL (<100 mg daily, mean 76 mg daily) achieved a similar survival benefit to those on a higher dose (>100 mg daily, mean 192 mg daily). Clearly, clarification is needed over whether low- and high-dose carvedilol provide the same clinical and prognostic improvement needs.

Maggioni et al. assessed beta blockade as treatment for chronic heart failure, enrolling 3091 patients and initiated a β-blocker (carvedilol, bisoprolol or metoprolol) in 32.7%. They reported better tolerability to carvedilol, with a mean dose of 17 mg twice daily (vs. 7.81 mg twice daily in this study). This study was aimed at providing information regarding the effectiveness of these drugs in patients outside of a clinical trial setting. However a large proportion (42.4%) of enrolled patients were not initiated on β-blockers. The predominant reasons for exclusion given were the presence of COPD and age >75 years. With the partial exclusion of these important groups, it is questionable whether this study gives a true representation of the general setting in the UK, and may partly explain the higher doses achieved.

The use of carvedilol in heart failure is a treatment that requires considerable time and enthusiasm. Our patients had to be recruited from out-patient clinics, and time was spent in arranging appointments and in some cases transport for elderly patients. Medical supervision was required to confirm clinical status, and to prescribe and adjust concomitant medications. Additional electrocardiograms, echocardiograms, Holter recordings, lung function tests and biochemistry were subsequently requested. The resource implications are considerable for a condition that has an incidence of 3.9 cases, rising to 16.8 cases per 1000 population per year in patients over the age of 85 years in the UK. Titration of carvedilol (COPERNICUS protocol) is less time-consuming than using bisoprolol (CIBIS-II protocol), due to fewer titration phases and subsequent monitoring requirements. The current prescription of carvedilol is more expensive than bisoprolol in the UK. Carvedilol has been shown to decrease overall expenditure for care in heart failure patients and be cost-effective compared to not using a β-blocker, however it has also been shown that the cost per life year saved was greater when compared to bisoprolol and metoprolol. These economic issues are dynamic, and will change along with variable drug costs.

The use of β-blockers for heart failure is part of ‘gold standard’ therapy, and should be encouraged. Drug tolerability at higher doses may be an issue, especially in the general setting that includes older patients with multiple co-morbidities. Although 88.5% tolerated carvedilol, only a minority (6.6%) achieved the ‘target dose’. Therefore, unlike clinical trials, much lower doses of carvedilol were attained in this study. The final dose of β-blocker appears to be specific to each patient. Reductions in heart rate and systolic blood pressure were similar in our patients, irrespective of the dose achieved. Heart rate reductions at low doses of carvedilol were comparable with that seen in previous studies, suggesting that lower target doses may be acceptable. The COMET trial may have shown that carvedilol is the β-blocker of choice in the treatment of chronic heart failure, but a mortality trial is required to assess the efficacy of low-dose carvedilol. Our study supports the concept that patients have an individual response to the effects of β-blockade, and that this should be the future basis for ‘dose targets’. Guidelines and treatment protocols for heart failure should reflect not only that which is considered ‘gold standard’, but also what is practical and necessary in general hospitals.

References


