Efficacy of carvedilol on complex ventricular arrhythmias in dilated cardiomyopathy: double-blind, randomized, placebo-controlled study

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Aims The aim of the present study was to investigate whether the addition of carvedilol to conventional therapy in dilated cardiomyopathy patients is associated with further benefits in the treatment of complex non-sustained ventricular arrhythmias (Lown class III, IV or V).

Methods and Results We recruited 168 patients with ischaemic or idiopathic dilated cardiomyopathy, with complex ventricular arrhythmias. Patients able to tolerate low doses of carvedilol were randomized to treatment with carvedilol or placebo for 6 months. Carvedilol treatment improved ventricular function and reduced the incidence of arrhythmic episodes. Notably, by the end of the first month of treatment, the antiarrhythmic efficacy of the drug was significantly greater in patients with ischaemic than in those with idiopathic dilated cardiomyopathy, an effect that could probably be attributed to the anti-ischaemic properties of carvedilol. After 3 months, at a time when ejection fraction was significantly improved in all treated patients, the antiarrhythmic efficacy of carvedilol was similar in the two study groups.

Conclusions Carvedilol antiarrhythmic efficacy was paralleled by the improvement in ejection fraction, independent of the aetiology of heart failure. The possibility of adding to an already ‘optimized’ conventional therapy a drug able to reduce the incidence of complex non-sustained ventricular arrhythmias is a therapeutic option that should be considered in the treatment of these patients.

Key Words: Dilated cardiomyopathy, heart failure, carvedilol, complex non-sustained ventricular arrhythmias.

Introduction

Heart failure is associated with a high incidence of ventricular arrhythmias[1]. Symptomatic and/or sustained ventricular and supraventricular arrhythmias should always be treated. Although current diagnostic and therapeutic protocols are widely accepted[2-5], the prognostic significance and particularly the management of non-sustained or asymptomatic arrhythmias in patients with heart failure remain controversial[6-9]. However, in everyday clinical practice considerable attention is given to ventricular arrhythmias, perhaps because they may be regarded as an easy target attempting to prevent sudden death[7-9].

The aim of our study was to investigate whether the administration of a third-generation beta-blocker such as carvedilol may confer further benefits in the treatment of complex ventricular arrhythmias, as evidenced by Holter monitoring, in patients with congestive heart failure and low ejection fraction already receiving ‘optimized’ conventional therapy. This potential antiarrhythmic effect of carvedilol may be additive to its already recognized clinical and haemodynamic efficacy.

Methods

From May 1996 to September 1998 we recruited 168 patients (127 men and 41 women, mean age 54 ± 9 years) with ischaemic (n=109) or idiopathic (n=59) dilated cardiomyopathy, presenting complex ventricular arrhythmias (Lown class III, IV or V) at 48-h Holter monitoring. All patients had been symptomatic for heart failure (NYHA functional class II, III and IV) for at least one year, with an ejection fraction to the echocardiography lower than 0.35. To be included in the study, patients had to be clinically stable, with no
change in their usual medications in the last two weeks, and should not have required intravenous inotropic drug therapy or have experienced weight changes for at least 48 h prior to the enrollment. Exclusion criteria were: uncorrected valvular heart disease, active myocarditis, obstructive and restrictive cardiomyopathy, acute myocardial infarction, stroke, unstable angina, coronary angioplasty or aortocoronary bypass surgery in the three previous months, sick sinus syndrome, first degree atioventricular block with a PQ interval >0.24 s, second or third degree atioventricular block (unless controlled by a pacemaker), systolic blood pressure >160 or <85 mmHg, diastolic blood pressure >100 mmHg, heart rate <65 beats min⁻¹, clinically relevant endocrine, renal or hepatic disease, drug or alcohol abuse, therapy with calcium antagonists, α/β adrenergic agonists or antagonists, chronic obstructive lung disease or documented episodes of sustained ventricular tachycardia (>30 s, >120 beats min⁻¹).

All patients were on digitalis and diuretics; 140 (83%) were also receiving ACE (angiotensin-converting enzyme) inhibitors, and 43 (26%) patients were taking nitrates (40 mg twice daily).

To assess the therapeutic efficacy of carvedilol on the incidence of arrhythmic episodes and on ventricular function, all patients underwent baseline 48-h Holter monitoring and transthoracic M-mode, twodimensional and Doppler echocardiography. Two-lead (D₂ and V₃) Holter monitoring (CardioData Inc., Marlborough, MA, U.S.A.) was performed for 48 h, with the patients recording in a diary the activities performed during the daytime and any relevant symptom. From these recordings mean heart rate, total premature ventricular contractions per hour, repetitive premature ventricular contractions per hour and episodes of non-sustained ventricular tachycardia were calculated over a 24-h period. An ACUSON 128 Cardiovascular system (ACUSON Computed Sonography, Mountain View, CA, U.S.A.) with a 2.25 MHz phased array sector scanner was used for echocardiograms. Echocardiographic ejection fraction assessment was performed by a single operator, not aware of the subject’s identity.

Patients of both groups (idiopathic and ischaemic dilated cardiomyopathy) were enrolled in a parallel, double-blind, placebo-controlled, randomized treatment protocol. During a preliminary ‘run-in’ phase, all patients received carvedilol (6-25 mg twice daily) for two weeks, in order to determine before the randomization which patients were unable to tolerate low doses of carvedilol. The study drug was temporarily reduced to 3-125 mg twice daily in patients with bradycardia (heart rate <50 beats min⁻¹) or arterial hypotension (blood pressure <90/60 mmHg), with a further attempt to increase the carvedilol dose during the following week. Patients able to tolerate the initial dose were then randomly assigned to receive placebo or carvedilol (1:1 randomization) in double-blind fashion, while maintaining their heart failure treatment. During this phase 12.5 mg of carvedilol was administered twice daily for another two weeks, and then the amount of carvedilol increased to the final dose of 25 mg twice daily. The dose was increased to 50 mg twice daily in patients weighing >85 kg, if tolerated. The same protocol was followed for patients randomized to placebo treatment, which was administered in tablets similar to the study drug. At the end of the up-titration phase, carvedilol or placebo were maintained for 6 months (maintenance phase). Concomitant therapy with digitalis, diuretics, ACE inhibitors and nitrates was maintained, although the dosage could be adjusted according to the clinical conditions of the patient or to the appearance of side-effects possibly related to these drugs. One, three and 6 months after the beginning of the maintenance phase, echocardiography and 48-h Holter monitoring were repeated, in order to re-evaluate ejection fraction and to assess the incidence of ventricular arrhythmias.

Baseline comparisons between groups (ischaemic and idiopathic cardiomyopathy) and treatments (placebo or carvedilol) were performed by analysis of variance for continuous variables and contingency tables for categorical variables. The results following drug therapy were compared using analysis of variance. Within each group, data obtained before and after treatment were compared by applying Student’s t-test for paired data. A value of P<0.05 was considered statistically significant for all test results. All data were reported as means ± SD (standard deviation).

Results

Of the 168 patients enrolled in the study, 13 (7.7%) did not complete the first ‘run-in’ phase either because of adverse reactions or administrative reasons. Adverse reactions included dizziness, worsening of heart failure, bronchospasm and postural hypotension. In the following double-blind treatment phase, the remaining 155 patients (101 with post-ischaemic dilated cardiomyopathy and 54 with idiopathic dilated cardiomyopathy) were randomly assigned to carvedilol (51 and 27, respectively) or placebo (50 and 27, respectively). Baseline clinical characteristics were comparable in ischaemic and idiopathic dilated cardiomyopathy patients randomized to placebo or carvedilol (Table 1).

During the double-blind phase 20 patients (12.9%) failed to complete the study: seven (9.0%) in the carvedilol-treated group and 13 (16.9%) in the placebo group. The reasons for being excluded from the study are shown in Table 2. Carvedilol efficacy was evaluated in the remaining 135 patients who completed the 6-month trial.

Results are reported in Table 3. Carvedilol antiarrhythmic efficacy was already evident after 1 month of treatment in both ischaemic and idiopathic dilated cardiomyopathy patients, with significant reductions in the total premature ventricular contractions per hour, the repetitive premature ventricular contractions per hour and the non-sustained ventricular tachycardia.
Notably, all these antiarrhythmic effects were significantly more evident in ischaemic patients than in idiopathic dilated cardiomyopathy patients. In contrast, no significant reduction in ventricular arrhythmias was observed in the placebo-treated groups. Ejection fraction did not change in either the placebo-treated or the carvedilol-treated groups.

At 3 months carvedilol-treated patients experienced a further reduction in the total premature ventricular contractions per hour, the repetitive premature ventricular contractions per hour and non-sustained ventricular tachycardia, with no significant difference in the reduction of arrhythmic episodes between the ischaemic and idiopathic groups. In contrast, no change in the number of arrhythmic episodes was observed in the placebo-treated groups. Ejection fraction improved in the carvedilol-treated patients, but not in the placebo-treated groups.

No further difference in either ventricular arrhythmias or ejection fraction was observed at the 6-month follow-up visit. One month of carvedilol treatment significantly reduced heart rate, with no further change recorded afterwards. In contrast, no change in heart rate was observed in the placebo-treated patients over the 6 months of the study. The adverse effects observed during the up-titration and maintenance phases in the carvedilol- and the placebo-treated groups are reported in Table 4. These adverse effects led to the exclusion of patients from the study only in few cases.

**Table 1 Baseline characteristics of patients at randomization**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ischaemic patients (n=101)</th>
<th>Idiopathic patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carvedilol (n=51)</td>
<td>Placebo (n=50)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.6 ± 8.0</td>
<td>54.1 ± 7.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>38/13</td>
<td>39/11</td>
</tr>
<tr>
<td>NYHA class II/III/IV</td>
<td>21/28/2</td>
<td>23/26/1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>22.3 ± 5.3</td>
<td>23.1 ± 5.7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119.2 ± 20.4</td>
<td>122.1 ± 21.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>70.3 ± 10.7</td>
<td>71.2 ± 9.8</td>
</tr>
<tr>
<td>HR (beats.min⁻¹)</td>
<td>85.3 ± 7.9</td>
<td>86.1 ± 9.0</td>
</tr>
<tr>
<td>PVCt</td>
<td>388.5 ± 62.3</td>
<td>378.2 ± 57.1</td>
</tr>
<tr>
<td>NSVT</td>
<td>7.5 ± 3.2</td>
<td>7.1 ± 3.5</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>41.1 ± 17.6</td>
<td>41.6 ± 11.9</td>
</tr>
<tr>
<td>Heart failure duration (years)</td>
<td>4.2 ± 0.8</td>
<td>4.4 ± 0.7</td>
</tr>
</tbody>
</table>

Concomitant therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=77)</td>
<td>(n=78)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>89%</td>
<td>86%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

LVEF=left ventricular ejection fraction; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; PVCt=premature ventricular contractions (total per hour); PVCr=premature ventricular contractions (repetitive per hour); NSVT=non-sustained ventricular tachycardia (number of episodes per 24 h).

**Table 2 Reasons for failure to complete the study**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Placebo patients (n=77)</th>
<th>Carvedilol patients (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>2 (2.6)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5 (5.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0.0)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (5.2)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Violation of protocol</td>
<td>2 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>13 (16.9)</td>
<td>7 (9.0)</td>
</tr>
</tbody>
</table>

Percentages indicated in parenthesis.

Discussion

The clinical manifestations of heart failure include a high incidence of complex ventricular arrhythmias. Frequent premature ventricular beats are present in 80% of these patients, and the incidence of non-sustained ventricular tachycardia is >40%/[^11][^10]. Several possible causes of this elevated proarrhythmic tendency have been described in the literature[^11]. The presence of complex ventricular arrhythmias, and in particular of non-sustained ventricular tachycardia, is associated with the degree of left ventricular dysfunction, patients with low ejection fraction presenting a higher incidence of ventricular tachyarrhythmias[^12][^14]. Moreover, in these patients a significant correlation has been reported between the presence of complex ventricular arrhythmias and the risk of sudden death[^7][^19].

The choice of antiarrhythmic therapy is controversial and it is not supported by large-scale trials, which established a clear proarrhythmic effect of some antiarrhythmic drugs[^16][^17] and a deleterious hemodynamic effect of other compounds due to their negative...
Heart rate Baseline 86.4 ± 9.3 84.7 ± 8.2
1 Month 87.7 ± 9.8 86.9 ± 7.5* 83.7 ± 5.4 70.0 ± 6.0*
3 Months 88.3 ± 8.2 68.0 ± 5.3* 84.8 ± 3.5 68.7 ± 3.8*
6 Months 87.7 ± 8.5 67.1 ± 5.0* 85.6 ± 2.9 67.4 ± 3.7*
PVCt Baseline 374.7 ± 56.0 391.0 ± 63.1
1 Month 345.6 ± 56.0 135.8 ± 43.9** 356.6 ± 87.4 201.5 ± 84.9*
3 Months 339.3 ± 91.5 95.3 ± 38.4** 360.1 ± 90.8 97.8 ± 33.1**
6 Months 345.3 ± 95.1 90.2 ± 35.4** 362.7 ± 91.0 95.2 ± 30.3**
PVCr Baseline 6.3 ± 4.0 6.2 ± 3.0 7.8 ± 3.4 6.8 ± 3.3
1 Month 6.5 ± 3.6 1.8 ± 1.3† 7.1 ± 3.5 3.0 ± 2.1*
3 Months 6.0 ± 2.2 1.0 ± 0.6† 7.1 ± 3.8 1.1 ± 0.8***
6 Months 5.6 ± 2.2 0.9 ± 0.7† 7.4 ± 3.9 0.9 ± 0.7**
NSVT Baseline 12.8 ± 7.4 13.5 ± 7.9 14.8 ± 9.4 13.6 ± 8.3
1 Month 12.1 ± 5.9 3.4 ± 3.0† 13.2 ± 8.6 5.9 ± 3.7*
3 Months 11.5 ± 6.8 1.3 ± 1.2† 12.8 ± 8.7 1.3 ± 1.5**
6 Months 11.3 ± 6.2 1.1 ± 1.0† 13.3 ± 9.1 1.5 ± 2.2***
LVEF Baseline 23.5 ± 6.0 21.9 ± 5.4 21.2 ± 5.8 22.2 ± 3.9
1 Month 22.8 ± 6.2 22.5 ± 4.7 20.6 ± 4.4 23.4 ± 3.2
3 Months 23.3 ± 5.1 28.1 ± 5.1* 20.7 ± 4.8 28.9 ± 3.7*
6 Months 22.5 ± 5.1 29.2 ± 3.6* 20.2 ± 3.9 29.5 ± 3.0*

PVCt = premature ventricular contractions (total per hour); PVCr = premature ventricular contractions (repetitive per hour); NSVT = non-sustained ventricular tachycardia (number of episodes per 24 h); LVEF = left ventricular ejection fraction.
*P<0.05 compared with baseline.
†P<0.05 compared with idiopathic patients treated with carvedilol.
‡P<0.05 compared with visit at 1 month.

In the idiopatic dilated cardiomyopathy patients, the only reasonable target in the attempt to reduce antiarrhythmic efficacy was higher in the ischemic than in the idiopathic dilated cardiomyopathy patients. Besides...
the known effects of carvedilol on the action potential, on the reduction of cardiomyocyte automaticity and on potassium shift\cite{32-34}, this difference may be ascribed to its anti-ischaemic properties\cite{35}.

From the 3rd month, the increased antiarrhythmic efficacy of carvedilol was paralleled by a concomitant improvement of the ejection fraction, independently of heart failure aetiology. This observation was indirectly confirmed by the data at 6 months, at a time when no further change in either ejection fraction or the antiarrhythmic efficacy was observed with respect to the 3-month control. It therefore appears clear that the antiarrhythmic effects of carvedilol cannot be dissociated from the concomitant improvement in left ventricular function and the consequent improvement in haemodynamics. All the placebo-controlled trials\cite{28,29,36-42} that evaluated the effects of beta-blockers in heart failure patients reported an improvement in ejection fraction after 2 to 3 months of treatment, an effect which was quantitatively more pronounced when compared with ACE inhibitor therapy (5–10% with carvedilol and 2–3% with ACE inhibitors, respectively)\cite{43}.

We are not aware of studies that assessed the effects of carvedilol on complex ventricular arrhythmias in patients with heart failure in relation to ejection fraction changes. Should our results be confirmed by larger trials, we will have a supplementary treatment option with obvious practical benefits.

Our results confirm data obtained in other studies on different antiarrhythmic agents, in which the improvement in the ejection fraction was a critical parameter in the assessment of the antiarrhythmic efficacy of a drug\cite{12,44,45}. Undoubtedly, the effects of chronic carvedilol administration tend to reset the haemodynamic imbalance which is present in heart failure patients by contributing to improved cardiac performance, thereby reducing the incidence of complex arrhythmias, which may be viewed as an expression of myocardial dysfunction.

Overall, carvedilol was optimally tolerated by our patients. If we consider that the ‘run-in’ phase represents a pre-selection (with only 13 patients out of 168 who were ineligible for the double-blind phase), the side-effects reported by patients treated with carvedilol were minimal and easily managed by adjusting the concomitant therapy. Only seven patients randomized to carvedilol treatment failed to complete the double-blind phase of the study (Table 2).

It has to be underscored that carvedilol treatment reduced the occurrence of non-sustained ventricular tachycardia episodes, whose presence at Holter monitoring in congestive heart failure patients has been considered an independent risk factor for sudden death, independent of heart failure aetiology\cite{46,47}, and requires drug treatment. Recently this issue has been investigated by two important studies on amiodarone. The GESICA study showed that low-dose amiodarone may reduce both sudden death and overall mortality in patients with congestive heart failure, although in the subgroups with evidence of non-sustained ventricular tachycardia amiodarone did not modify the risk of sudden death related to this arrhythmia\cite{49}. In another study (Congestive Heart Failure-Survival of Antiarrhythmic Therapy), which enrolled a larger number of patients with ischaemic cardiomyopathy and used a higher dosage of amiodarone than the GESICA study, amiodarone was not effective on mortality, although it reduced the incidence of non-sustained ventricular tachycardia, an effect already evident after two weeks of treatment\cite{51}. These two studies confirm the negative prognostic implication of non-sustained ventricular tachycardia in heart failure patients and the impossibility of reducing the risk of arrhythmia-related mortality, even when drug therapy appears to suppress arrhythmias. Moreover, with amiodarone serious side-effects still represent the main limitation to its use in chronic treatment.

It is therefore evident that the main effective therapy of complex ventricular arrhythmias in patients with heart failure is represented by the treatment of heart failure. The possibility of administering a drug which, when added to ‘optimized’ conventional therapy, is able to improve the haemodynamic profile and to reduce the incidence of arrhythmias, including non-sustained ventricular tachycardia, while causing few side-effects, is a therapeutic option to consider in the treatment of these patients. The limited sample size of our study and the duration of follow-up, at present limited to 6 months, does not allow us to report data on mortality related to arrhythmic events. Should our results after one year of treatment confirm the positive trend in controlling the incidence of arrhythmias in these patients, we may well have a better indication for the added advantage carvedilol could offer in the management of this syndrome which carries such an adverse prognosis.

References


