A QUESTIONNAIRE STUDY OF \( \beta \)-ADRENERGIC BLOCKADE IN DILATED CARDIOMYOPATHY IN JAPAN

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A questionnaire study on the effect of \( \beta \)-blockade in dilated cardiomyopathy was performed. In 89 cases obtained from 24 institutions, either metoprolol (72 patients, \( 41.4 \pm 29.3 \) mg/day, 14.1 \pm 13.2 months, mean \pm SD), propranolol (5 patients, \( 23.8 \pm 24.3 \) mg/day, 25.0 \pm 25.3 months), carteolol (4 patients, \( 7.5 \pm 2.9 \) mg/day, 9.0 \pm 2.8 months) or another \( \beta \)-blockers (8 patients) was administered. Nine patients died during the follow-up period. Overall effectiveness as evaluated by the attending physicians showed improvement in 51 patients (57.3\%), no change in 26 patients (29.2\%), deterioration in 11 patients (12.4\%) or was indeterminate in one patient. New York Heart Association (NYHA) functional class improved significantly from 2.6 to 2.3 (\( p < 0.01 \)). Heart rate decreased from 83.1 to 70.1 (\( p < 0.01 \)). Cardiothoracic ratio decreased from 55.5\% to 53.9\% (\( p < 0.01 \)). Left ventricular ejection fraction of the left ventricle measured by echocardiogram increased from 29.8\% to 37.8\% (\( p < 0.01 \)). Exercise tolerance during a treadmill test and ventricular arrhythmias in Holter electrocardiograms improved significantly. There was no change in blood pressure. When the patients in different functional classes were compared, the patients of NYHA class III improved more frequently than those of NYHA class II (69\% vs 53\% \( p < 0.01 \)). Improvement of left ventricular end-diastolic dimension and left ventricular ejection fraction was more prominent in patients of class III than in those of class II. NYHA functional class and cardiothoracic ratio were significantly improved only in class III. NYHA functional class began to improve at 2 weeks, but ejection fraction increased significantly after 3 months. It is concluded that \( \beta \)-adrenergic blockade has a beneficial effect in most patients with dilated cardiomyopathy.

\( \beta \)-ADRENERGIC blocking agents have historically been contraindicated in patients with advanced congestive heart failure. The activated sympathetic drive supporting the failing heart and circulation is compensa-

tory, and interruption by \( \beta \)-blockade could result in pump failure and possibly death. Indeed, case reports have demonstrated the complications of standard dosages of \( \beta \)-blockers when given to chronic congestive heart failure patients. Recent investigations have questioned the role of activated sympathetic activity in congestive heart failure.

Key words:
- Dilated cardiomyopathy
- \( \beta \)-adrenergic blockade
- Adrenergic receptor
- Heart failure

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TABLE I DOSE AND DURATION OF β-BLOCKER TREATMENT

<table>
<thead>
<tr>
<th>β-blocker</th>
<th>n</th>
<th>Initial Dose (mg/day)</th>
<th>Maintenance (mg/day)</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol:</td>
<td>72</td>
<td>12.2±11.9</td>
<td>41.4±29.3</td>
<td>14.1±13.2</td>
</tr>
<tr>
<td>Propranolol:</td>
<td>5</td>
<td>15.0±8.7</td>
<td>23.8±24.3</td>
<td>25.0±25.3</td>
</tr>
<tr>
<td>Carvedilol:</td>
<td>4</td>
<td>0.5</td>
<td>7.5±2.9</td>
<td>9.0±2.8</td>
</tr>
<tr>
<td>Pindolol:</td>
<td>3</td>
<td>1.9±1.5</td>
<td>2.6±0.3</td>
<td>8.0±6.2</td>
</tr>
<tr>
<td>Arotinolol:</td>
<td>2</td>
<td>15.0</td>
<td>15.0</td>
<td>7.5±4.9</td>
</tr>
<tr>
<td>Atenolol:</td>
<td>1</td>
<td>25.0</td>
<td>25.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Acebutolol:</td>
<td>1</td>
<td>unknown</td>
<td>200.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Xamoterol:</td>
<td>1</td>
<td>200.0</td>
<td>200.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

NYHA (n=86)

I  3  12
II 32  45
III 45  24
IV 6  5

before  after

Fig. 1. New York Heart Association (NYHA) functional classification in patients with dilated cardiomyopathy before and after treatment with β-blockade. NYHA functional class improved significantly.

Suggest that additional controlled observations are needed before such treatment can be generally accepted and recommended. To investigate the use of β-blockade for the treatment of dilated cardiomyopathy in Japan, we carried out a questionnaire study.

METHODS

As a collaborative research project of the committees for Idiopathic Cardiomyopathy, Ministry of Health and Welfare and Japanese Circulation Society, we sent questionnaires to 126 institutions in Japan which had a division of cardiology in 1989, and questionnaires were returned from 24 institutions. The questionnaire included age and sex of the patients, diagnostic criteria, a therapeutic protocol of administration of β-blocker, concomitant medications and assessment of parameters such as clinical history, physical examination, electrocardiography, chest X-ray, echocardiography,

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TABLE II OVERALL EFFECTIVENESS AND NYHA FUNCTIONAL CLASS

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved (%)</td>
<td>3 (33%)</td>
<td>17 (53%)</td>
<td>31 (69%)*</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Unchanged (%)</td>
<td>2 (67%)</td>
<td>13 (41%)</td>
<td>7 (15%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Deteriorated (%)</td>
<td>0</td>
<td>2 (6%)</td>
<td>7 (15%)</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

*p<0.01 vs class II by χ² analysis

Holter electrocardiography and exercise tolerance test. The effect of β-blockers was evaluated at 2 weeks, 4 weeks, 3 months, 6 months and 12 months of the treatment. Eighty-nine cases with dilated cardiomyopathy were evaluated. Sixty-seven were male and 22 female. The age of the patients was 51.2±14.3 years (range 13—75). Exclusion criteria included active myocarditis and a known secondary cause of heart disease.
such as coronary artery disease, restrictive or hypertrophic disease, alcoholism, or endocrine or autoimmune disease. Asthma or chronic obstructive pulmonary disease, which are contraindications to β-blockade, were also exclusion criteria. Metoprolol was given to 72 patients (dose 41.4±29.3 mg/day, mean ± SD, duration 14.1±13.2 months), propranolol to 5 patients (23.8±24.3 mg/day, 25.0±25.3 months), carteolol to 4 patients (7.5±2.9 mg/day, 9.0±2.8 months), pindolol to 3 patients (2.6±0.3 mg/day, 8.0±6.2 months), atenolol to 2 patients (15 mg/day, 7.5 months), acebutolol to 1 patient (200 mg/day, 58 months), atenolol to 1 (25 mg/day, 28 months), and xamotolol to 1 (200 mg/day, 0.7 months) (Table I). In most of the institutions, the β-blocker dose was initially low then increased gradually. Permissible concomitant medications during the study included diuretics, digitalis glycosides, antiarrhythmic drugs, and anticoagulants. Serial functional assessment included clinical history, physical examination, electrocardiography, chest X-ray, echocardiography, Holter electrocardiography and exercise tolerance test (Bruce’s protocol). Ejection fraction was calculated by means of the Teicholz formula. Abnormality in Holter electrocardiograms was classified by Lown’s grade. Relationship between duration of the treatment and the effect was classified. Differences between baseline and treatment variables were compared with Student’s t tests, Wilcoxon signed-rank test or χ² analysis. Values are expressed as mean ± SD.

RESULTS

Nine patients died during the follow-up period. Overall effectiveness evaluated by attending physicians showed improvement in 51 patients (57.3%), no change in 26 patients (29.2%), deterioration in 11 patients (12.4%) or was indeterminate in 1 patient. NYHA functional class improved in 32 of 86 patients (37%), was unchanged in 50 patients (58%) and deteriorated in 4 patients (5%). Mean value of NYHA class improved significantly from 2.6±0.7 to 2.3±0.6 (p<0.01, Fig. 1). Heart rate decreased from 83.1±13.8 to 70.1±11.3 (p<0.01). Cardiac output ratio decreased from 55.5±7.4%
to 53.9\pm 7.2\% \ (p<0.01, \ Fig.2). Left ventricular end-diastolic dimension by echocardiogram decreased from 66.3\pm 8.9 \text{ mm} to 62.0\pm 9.3 \text{ mm} \ (p<0.01, \ Fig.3). Ejection fraction of the left ventricle by echocardiogram increased from 29.8\pm 10.1\% \ to 37.8\pm 14.7\% \ (p<0.01, \ Fig.4). Exercise tolerance in treadmill test improved significantly from 8.1\pm 3.5 \text{ to} 10.3\pm 3.3 \ (p<0.05, \ Fig.5). There was a significant decrease in Lown’s grade in ventricular arrhythmia by Holter electrocardiograms from 3.8\pm 1.2 to
3.3 ± 1.5 (p<0.01, Fig. 6). There was no change in blood pressure, or left atrial dimension. When the patients in different functional classes were compared, the patients of NYHA class III improved more frequently than those of NYHA class II (69% vs 53% p<0.01) (Table II). Table III shows the relationship between NYHA functional class and clinical variables. Improvement of left ventricular end-diastolic dimension and left ventricular ejection fraction was more prominent in patients of class III than in those of class II. NYHA functional class and cardiothoracic ratio were significantly improved only in class III. NYHA functional class began to improve 2 weeks after treatment from 2.6±0.7 to 2.4±0.7 (p<0.01) and improved further as the treatment was continued (2.0±0.7 at the 6th month, 2.2±0.6 at the 12th month) (Fig. 7). However, ejection fraction improved more slowly than NYHA functional class and significant improvement was seen 3 months after the treatment from 30.2±9.5 to 35.6±12.2 (p<0.01) and improved further as the treatment continued (39.0±11.1 at the 12th month) (Fig. 8).

DISCUSSION

To investigate the use of β-adrenergic blocking agents for the treatment of dilated cardiomyopathy in Japan, we conducted a study by questionnaire in 1987 as a collaborative research effort of the committees for Idiopathic Cardiomyopathy, the Ministry of Health and Welfare and the Japanese Circulation Society. Although the protocol or the dose was not the same in each institution, the overall results showed that β-blocker treatment in these 33 patients with dilated cardiomyopathy improved NYHA functional class, left ventricular function and exercise tolerance in our preliminary study11

In the present study, more patients were evaluated from a larger number of institutions. Duration of treatment was longer and initial dose was low in most of the institutions. Most of the institutions used metoprolol, but other β-blockers were also used. Overall effectiveness showed improvement in more than half of the patients and the frequency of deterioration was relatively low. NYHA functional class, cardiothoracic ratio, left ventricular end-diastolic dimension, left ventricular ejection fraction and exercise tolerance were improved significantly after treatment. In addition, ventricular arrhythmias in Holter electrocardiograms showed a significant decrease in this study. It is interesting that the more prominent effects of β-blockers were seen in patients of NYHA class III than in those of class II. It is also interesting that the NYHA functional class began to improve at 2 weeks, but the ejection fraction did not improve until later. However, clinical variables continued to improve for 6 to 12 months after beginning treatment. This study confirmed that the effect of β-blockers appeared gradually and long term treatment was necessary to obtain full improvement.

Waagstein and his colleagues in Göteborg, Sweden, first described the potential benefits and safety of β-blockade in heart failure in 1975! Seven patients with advanced, unexplained heart failure were selected because of tachycardia at rest. Six patients were given practolol (cardioselective β-blocker with intrinsic sympathomimetic activity, ISA) and one patient, alprenolol (nonselective β-blocker with ISA), for a mean duration of treatment of 5.4 months. All showed improvements in noninvasive measurements of ventricular function. This initial report was extended by the same group in 24 patients? The survival rates in the group treated with β-blocker were 83%, 66%, and 52% at 1, 2, and 3 years, respectively, whereas the control group had survival rates of 46%, 19%, and 10%, respectively. Contrary to the positive results of the Göteborg group, 2 double-blind, randomized trials of β-blockade showed no improvement. Ikram and Fitzpatrick studied acebutolol, a cardioselective β-blocker with ISA, in 17 patients with dilated cardiomyopathy treated for 1 month! No significant improvement in ventricular function, exercise performance, or functional class was noted in the 15 patients who finished the trial. However, this trial was of short duration (1 month). More recently, Waagstein and his co-workers studied the effect of withdrawal and readministration of metoprolol in 33 patients with dilated cardiomyopathy!2 Twenty-four patients with improved NYHA functional

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class were subjected to withdrawal of metoprolol. Eight patients did not deteriorate during a 12-month period. Sixteen patients deteriorated, and 4 patients died. In twelve patients, metoprolol was introduced and they subsequently improved. Heilbrunn and coworkers reported that metoprolol therapy for 6 months was associated with an increase in myocardial $\beta$-receptor density, significant improvement in resting hemodynamic output, and improved contractile response to catecholamine stimulation. They concluded that a restoration of $\beta$-adrenergic sensitivity was associated with metoprolol therapy, possibly related to the observed up-regulation of $\beta$-adrenergic receptors.\textsuperscript{13}

Gilbert et al. studied bucindolol, a nonselective $\beta$-blocker with direct-acting or nonspecific vasodilator properties, in 24 patients with dilated cardiomyopathy in a double-blind randomized fashion.\textsuperscript{14} Twenty-two patients finished the protocol of 3-month duration with a significant improvement in left ventricular ejection fraction and cardiac index and a decrease in the pulmonary artery wedge pressure and heart rate in the bucindolol-treated group. Central venous plasma norepinephrine levels were significantly decreased after active drug treatment, which may indirectly reflect the improvement in ventricular function. Recently, long-term bucindolol therapy was studied. Seventeen of 20 patients entering long-term therapy (from an initial group of 24 patients studied short-term) were continuing therapy at the end of evaluation. In these patients, bucindolol therapy was associated with maintained or improved functional class and with increases over baseline in mean ejection fraction. Ejection fraction, previously noted to be significantly improved at 3 months, was further augmented during long-term therapy, and last evaluated at a mean of 16 months. Bucindolol maintained maximal exercise performance.\textsuperscript{15} Another nonselective $\beta$-adrenergic blocking agent, labetalol has been studied in patients with dilated cardiomyopathy. Labetalol, a combined $\alpha$- and $\beta$-blocking agent, was administered to 12 patients for 8 weeks in a randomized, crossover, double-blind design. Labetalol improves symptomatology, exercise capacity, and exercise hemodynamics and reduces systemic vascular resistance in patients with dilated cardiomyopathy.\textsuperscript{16}

Most previous studies on the effect of $\beta$-blockers in dilated cardiomyopathy used a $\beta_1$-selective agent, metoprolol, and data about the effects of $\beta$-adrenergic blockers with intrinsic sympathomimetic activity have been limited.\textsuperscript{2-8,17} Recently, we studied the effects of carteolol, a nonselective adrenergic receptor blocker with ISA, and compared them with those of metoprolol in our murine model of dilated cardiomyopathy.\textsuperscript{18} After 3 months of treatment heart weight to body weight ratio and histopathological scores were significantly lower in mice given carteolol than in the control group. Furthermore, left ventricular cavity dimension, left ventricular wall thickness, and myocardial fiber diameter of the left ventricle were significantly reduced in mice given carteolol compared with the control group. Metoprolol did not cause any significant changes compared with the control group. This study suggests that carteolol prevents the development of myocardial lesions similar to those in dilated cardiomyopathy.\textsuperscript{18} Although metoprolol at 30 mg/kg/day is nearly equivalent to carteolol at 1-10 mg/kg/day, the different effects may have been due to the doses administered or to the characteristics of carteolol such as ISA and nonselectivity. Carteolol has a vasodilator action that is mediated in part by $\beta$-adrenoceptor stimulation, and ISA may favor the upregulation of $\beta$-adrenergic receptors in the failing heart.\textsuperscript{19} Furthermore, because immunologic mechanisms may participate in the control of $\beta$-adrenergic receptors\textsuperscript{20} and because the release of immunoregulatory cells from the spleen is thought to be controlled by a $\beta_2$-and not a $\beta_1$-receptor,\textsuperscript{21} $\beta$-nonselectivity may be favorable for immunoregulation. In our clinical study, heart rate did not change after treatment with carteolol (unpublished observation) although metoprolol decreased heart rate. Therefore, carteolol may be superior to metoprolol in patients with lower heart rate.

Further studies with larger numbers of subjects are necessary to confirm the benefits of $\beta$-blockade to major morbidity and mortality and to assess whether potential benefits are restricted to patients with dilated cardiomyopathy or can also be extended to...
patients with heart failure due to ischemic heart disease and other causes. Whether the beneficial effects noted for metoprolol and other β-blockers are qualitatively or quantitatively distinct is not addressed by these studies and must be determined by future comparative trials. A large, multicenter, randomized, double-blind investigation organized by the Göteborg group, Metoprolol in Dilated Cardiomyopathy, was initiated in 1986 and is ongoing. The results of this trial will clarify the effect of metoprolol treatment on symptomatic and objective parameters of cardiac performance, the effect on arrhythmias and sudden death, and effect on survival rate. Furthermore, future comparative trials must be performed to investigate what kind of β-blocker is most effective or to determine which patients should receive β-blocker.

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7. CURRIE PJ, KELLY MJ, MCKENZIE A, HAR-