Effect of flosequinan on exercise capacity and cardiac function in patients with chronic mild heart failure: A double-blind placebo-controlled study

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Summary. Although beneficial effects of a new vasodilating agent, flosequinan, have been demonstrated in patients with severe heart failure, its efficacy has not been studied in patients with a less severe form of chronic heart failure. In this study, the effects of 4 weeks' administration of flosequinan, 50 mg daily, and placebo on exercise capacity, cardiac function, and symptoms of heart failure were investigated in 24 patients with chronic mild heart failure (New York Heart Association functional class, mainly class II) in a double-blind clinical trial. When the parameter changes during the treatment period of the flosequinan and placebo groups were compared, no significant difference was found in any of the measurements except for left ventricular fractional shortening determined from M-mode echocardiograms; it was increased by 2.9 ± 1.3% in the flosequinan group whereas it was decreased by 1.3 ± 0.9% in the placebo group (P < 0.05 vs flosequinan treatment). However, when compared to baseline values, flosequinan significantly increased exercise time in the symptom-limited maximal exercise test (704 ± 103 to 763 ± 107 s, P < 0.05) and the oxygen uptake at the anaerobic threshold (13.8 ± 1.3 to 16.7 ± 1.4 ml/min/kg, P < 0.05), and improved symptoms assessed with a new heart failure severity classification (a median value of 2.0 to 1.5, P < 0.05). These improvements were not observed in the placebo group. Serious adverse effects were not observed in either group. These results suggest that flosequinan is useful for the treatment of chronic mild heart failure as well as severe heart failure.

Key words: Flosequinan—Heart failure—Exercise capacity—Cardiac function

Introduction

Vasodilating agents are widely used in the treatment of chronic heart failure. However, their effects on exercise tolerance are diverse, largely depending on the characteristics of the individual agents. Previous studies have shown that some vasodilators improve exercise capacity only after several months of administration, although they immediately improve the hemodynamics [1–3]. This time delay in improvement of exercise capacity may be attributed to the time lag for recovery of myocardial function through the unloading effect of vasodilators.

Flosequinan (7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone) is a novel vasodilator which dilates both arteries and veins [4]. In single dose and short-term administration, flosequinan has been reported to improve resting hemodynamics in patients with chronic heart failure [5–7]. This drug has been also reported to increase the exercise time, peak oxygen uptake and anaerobic threshold with short-term administration in patients with severe heart failure [8–10]. Thus the drug appears to be promising as a vasodilator which can promptly improve exercise capacity. However, the effect on exercise capacity has not been studied in patients with less severe forms of heart failure. Moreover, the effects of flosequinan on cardiac function have not been extensively studied, and it is thus not clear whether improved exercise capacity is secondary to recovery of cardiac function, or whether this is due to mechanisms other than the improvement of cardiac function.

In the present study we investigated the effects of 4 weeks’ administration of flosequinan on exercise
capacity, cardiac function, and symptoms in patients with mild heart failure due to left ventricular dysfunction.

Methods

Patients

The criteria for patient selection were (1) underlying myocardial disease or regurgitant valvular disease (aortic or mitral regurgitation), (2) cardiothoracic ratio (CTR) of greater than 55% or left ventricular fractional shortening determined by M-mode echocardiography of less than 25%, and (3) a stable New York Heart Association (NYHA) functional class of I-III for at least 2 months. Twenty-four patients who fulfilled the criteria were entered in the study from February 1989 to April 1991. There were 16 males and 8 females, ranging in age from 37 to 76 years (mean, 58 years). The underlying disease was dilated cardiomyopathy in 16 patients, old myocardial infarction in 2, aortic regurgitation in 2, and mitral regurgitation in 4. Twenty-two patients were classified as NYHA functional class II, and the remaining two patients were class I and III. Thus, most patients had mild heart failure. The CTR ranged from 43% to 79% (mean, 55%), and fractional shortening ranged from 8.3% to 47.1% (mean, 19.5%). Seventeen patients had sinus rhythm and seven had atrial fibrillation. Twenty-two patients had been treated with digitalis and/or diuretics. These drugs for standard treatment were continued throughout the study without changes in dose or regimen. In two patients who had been on other vasodilators or inotropic agents, the study was commenced 4 weeks after withdrawal of these agents.

Prior to entering the study, patients received an explanation of the test compound, and written or oral informed consent was obtained from all patients.

Protocol

During the run-in period of 2–4 weeks, the patient’s condition was confirmed to be stable by a doctor’s interview, and exercise tests were repeated 2–4 times at intervals of 1 week or more to familiarize the patients with the exercise protocols. On the last day of the run-in period, chest X-rays, echocardiographic examination, and hematological and biochemical examinations were performed.

In the treatment period, either flosequinan or placebo was randomly administered orally once a day in the morning for 4 weeks. Double-blind sequential analysis according to the method of Armitage [11] was employed in this study. In the sequential analysis, pairs of two patients were entered in order, and a patient from each pair was randomly assigned to flosequinan therapy and the other to placebo. At the end of the treatment, symptoms, physical findings, exercise capacity, and laboratory data were obtained.

Exercise test

A ramp exercise test was conducted on a sitting bicycle ergometer in 20 patients. In one center, the test was done on a treadmill in 20 patients as the bicycle exercise was not routinely performed in this center. Two of these four patients were assigned to the flosequinan group, and the other two patients to the placebo group. The bicycle exercise test was conducted with 1-minute unloading pedaling, followed by an initial loading and subsequent 15-W incremental loading every 1 or 2 min. The initial loading was selected according to the severity of heart failure to avoid exercise duration of more than 10 min. The treadmill exercise was performed according to Bruce’s protocol [12] modified to increase the workload every 2 min. Exercise was terminated at the onset of either severe dyspnea or fatigue. The initial load and the rate of ramp loading of individuals were kept constant throughout the trial. Gas exchange data were collected continuously during exercise using a breath-by-breath respirometer system (Minato Co., model RM-200 or RM-300, Tokyo, Japan). Volume calibration was performed with a 21-calibration syringe, and calibration of oxygen and carbon dioxide analyzers was performed with mixed gases of known concentrations (14.93% oxygen, 5% carbon dioxide, and 80.07% nitrogen). Oxygen uptake, carbon dioxide output, and minute ventilation were obtained as the mean value of every 30 s. As indicators of exercise capacity, exercise time, oxygen uptake at the end of exercise (VO₂symp) and oxygen uptake at the anaerobic threshold (VO₂AT) were assessed. The anaerobic threshold was defined as the time point at which the ratio of minute ventilation to oxygen uptake begins to increase rapidly [13]. Heart rate and blood pressure were measured at rest and every minute during exercise.

Echocardiograms

Resting M-mode echocardiograms were recorded at the tip of the mitral valve under the guide of two-dimensional imaging. The left ventricular end-diastolic dimension and end-systolic dimension were measured in a standard fashion [14] as the mean value of three consecutive cardiac cycles in patients with sinus rhythm and five consecutive cycles in patients with atrial fibrillation. Fractional shortening was calculated by the following equation: (end-diastolic dimension − end-systolic dimension)/end-diastolic dimension.

Subjective symptoms

The principal physicians questioned the patients for subjective symptoms and evaluated the severity of heart failure.

Table 1. Heart failure severity classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Classification</th>
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<tbody>
<tr>
<td>0</td>
<td>Heart failure is absent: breathlessness does not occur while ascending stairs at normal speed, and daily normal activities do not produce any symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Heart failure is suggested: rest is not required, although breathlessness occurs while ascending stairs at normal speed</td>
</tr>
<tr>
<td>2</td>
<td>Heart failure is mild: rest is required while ascending stairs at normal speed, and daily normal activities produce edema in the legs in the evening</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure is moderate: unable to walk even on the level for very long because of breathlessness. Dyspnea occurs at rest, and edema appears in the legs in the evening</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure is severe: dyspnea occurs while walking on the level, when urinating and defecating, and even at rest. Edema is definitely present in the legs</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure is very severe: unable to walk or stand up. Severe dyspnea occurs at rest (orthopnea, nocturnal dyspnea, and so on). Severe edema with hydrothorax and ascites is present in the legs</td>
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