Lisinopril in the Treatment of Congestive Heart Failure in Elderly Patients: Comparison versus Captopril

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Summary. The present study was performed in order to compare the efficacy, safety, and tolerability of lisinopril, a long-acting angiotensin-converting enzyme (ACE) inhibitor, with captopril, the shorter acting ACE inhibitor available, in the treatment of elderly patients (mean age 70 ± 0.5 years) with congestive heart failure (mean left ventricular ejection fraction 33.5 ± 1%). The study was organized according to a double-blind, parallel-group, randomized multicenter protocol. After a 14-day placebo run-in period, patients were randomized to receive either lisinopril 5 mg orally once per day or captopril 12.5 mg orally once per day. The dose of the study drug could be doubled at 2-week intervals for 6 weeks. The maximal dose was lisinopril 20 mg once per day or captopril 25 mg twice per day. The addition of either captopril or lisinopril to a regimen of diuretics caused a significant increase in exercise tolerance assessed by bicycle ergometry after 12 weeks of treatment (530 ± 21 seconds vs. 431 ± 13 seconds, p < 0.01; 555 ± 19 seconds vs. 463 ± 12 seconds, p < 0.01, respectively). Both drugs significantly increased left ventricular ejection fraction and stroke volume, were equally effective in improving NYHA class, and were well tolerated, with no differences detectable between treatments. The results of this study indicate that lisinopril 5–20 mg once daily is at least as effective and well tolerated as captopril 12.5–50 mg daily in the treatment of elderly patients with congestive heart failure.

Key Words. ACE inhibitors, exercise tolerance, ejection fraction, therapy

Although the efficacy of angiotensin-converting enzyme (ACE) inhibitors in the treatment of congestive heart failure is well established [1–4], questions remain concerning the safety and tolerability of long-acting as compared with short-acting ACE inhibitors. In particular, several studies [5,6] have demonstrated in adult patients with congestive heart failure that short and long-acting ACE inhibitors were comparable with respect to safety profiles. However, Packer and co-workers [7] reported that when large, fixed doses of ACE inhibitors are used in the treatment of patients with chronic heart failure, long-acting agents may produce prolonged hypotensive effects that may compromise renal and cerebral function, thus reducing the tolerability of the treatment as compared with short-acting agents. Furthermore, O’Neill et al. [8] observed a high incidence of putative adverse reactions in elderly patients with heart failure treated with enalapril, which induces prolonged serum ACE inhibition. On the contrary, only few adverse drug reactions were reported during captopril treatment for heart failure in old age [9,10]. On the other hand, long-acting ACE inhibitors allow a reduction in dosing and an increase in therapeutic efficacy [5].

Since elderly people show the highest incidence of heart failure, it seems reasonable to assume that the number of these patients will increase dramatically in the future [11]. We, thus, planned the present study to compare the efficacy, safety, and tolerability of lisinopril, a long-acting ACE inhibitor, with those of captopril, a shorter acting ACE inhibitor, in the treatment of the elderly patients with congestive heart failure in NYHA functional class II and III.

Methods

Study population

Male or female elderly patients ranging in age from 65 to 80 years, with clinical signs and symptoms of congestive heart failure (NYHA functional class II or III) and...
echocardiographic evidence of a left ventricular ejection fraction < 45%, were considered eligible for entry into the study. All patients were in sinus rhythm, on stable doses of diuretics, and capable, at two baseline exercise tests performed before randomization, to exercise for 3–12 minutes on a bicycle ergometer, with the exercise duration limited by dyspnea or fatigue, or both.

Exclusion criteria included: myocardial infarction or cardiac surgery (including percutaneous transluminal coronary angioplasty) within the last 3 months, stable or unstable angina, cerebrovascular accident within the previous 6 months, intermittent claudication, right heart failure, severe pulmonary disease limiting exercise performance, atrial fibrillation, arrhythmias that required therapy other than amiodarone, patients with fixed heart-rate pacemakers, hemodynamically significant aortic or mitral valve stenosis or regurgitation; and clinically relevant renal, hepatic, endocrine, or hematological disorders. Also excluded were patients with systolic arterial blood pressure >90 mmHg or >160 mmHg, patients with a history of ACE-inhibitor intolerance, patients with hyperkalemia or hypokalemia, patients receiving other investigational therapy, and alcohol abusers.

At the beginning of the study, treatment with potassium-sparing agents, digitalis glycosides, calcium-channel blockers, β-blockers, vasodilators (such as hydralazine and prazosin), and all antihypertensive medications, if present, were withdrawn. The cardiovascular drugs allowed were loop diuretics, long-acting nitrates, and anticoagulants.

All patients were informed of the aims, methods, possible benefits, and hazards of the study. Written, informed consent for participation in the study was obtained. This study was conducted in accordance with the Declaration of Helsinki, and local ethics committee approval was obtained.

Study design
This study was organized according to a double-blind, parallel-group, randomized, multicenter protocol. The study incorporated a run-in period of 14 days, during which the dose of diuretics was optimized according to the patients’ symptoms, and all therapies not allowed were withdrawn. Subsequently, patients were randomized to either lisinopril or captopril for 12 weeks. During the run-in period, placebo tablets were administered to the patients in a single-blind fashion. At the end of the run-in period, patients were assigned to one of the treatment groups using a computer-generated random scheme.

The initial dose of the double-blind treatment was given as a single oral dose of either 2.5 mg lisinopril or 6.25 mg captopril. To achieve double-blind treatment during the active treatment period, a double-dummy technique was employed. On each day patients who received lisinopril also took the appropriate number of placebo tablets, matching captopril and vice versa. In the case of patients randomized to lisinopril, after monitoring the effect of the initial dose (one-half tablet of lisinopril = 2.5 mg), 1 tablet po (5 mg) was taken per day. An increase in dose to 10 mg/daily po was made after 2 weeks if the following conditions were met: standing systolic blood pressure >90 mmHg, no symptoms of hypotension (syncope, faintness, orthostatic dizziness), and the need for an additional therapeutic effect in the opinion of the investigator. A further increase of the dose of the study medication (20 mg/daily po) could be made after a further 2-week period according to the above-mentioned criteria. The dose of lisinopril could be reduced at any visit in case of symptomatic hypotension or any other adverse event that, in the opinion of the physician, could be related to the drug.

One tablet (12.5 mg po) was given once daily to the patients who received captopril after monitoring the effect of the initial dose (one-half tablet of captopril = 6.25 mg). An increase in the dose of the study medication to 12.5 mg po twice daily was made after 2 weeks of treatment if the above-mentioned criteria of safety and the need for further therapeutic effect were met. The dose of captopril was increased to a maximum of 25 mg po twice daily (if after a further 2-week treatment the criteria for increasing the dosage were satisfied). We did not increase the daily number of doses because it has been reported that multiple daily doses of captopril may be unnecessary in elderly patients with heart failure [10]. As specified for lisinopril-treated patients, the dosage of captopril could also be reduced by the physician. Thus, by the end of the first 6 weeks after randomization, the dose titration was completed and both study groups remained on an optimal ACE-inhibitor dosage until the end of the study.

Clinical assessment
A physical examination and symptom review of each patient were performed at the time of the recruitment and were repeated at each visit until the end of 12 weeks of randomized treatment. An exercise test was performed using an electromagnetically braked bicycle ergometer. Exercise began with a workload of 20 W maintained for 3 minutes, followed by a 20-W increase in the workload every 3 minutes (ramp protocol) until a symptom-limited endpoint was reached. The endpoint of exercise for all patients was dyspnea, leg fatigue, or maximal blood pressure or heart rate values. Cuff blood pressure was also measured during exercise at the end of each step using a mercury sphygmomanometer; the 12-lead ECG was recorded continuously during exercise. All tests were performed in the fasting state at the same time in the morning, and medications were delayed on the day of the exercise test until all measurements were completed. All patients underwent a bicycle exercise test on two separate occasions during the placebo run-in phase before entering into the randomized treatment phase of the study. The first exercise test was aimed at familiarizing the patient the