Efficacy and tolerability of moexipril and nitrendipine in postmenopausal women with hypertension

Abstract  Objective: The aim of this study was to compare the efficacy and tolerability of the new angiotensin-converting enzyme (ACE) inhibitor moexipril and the calcium antagonist nitrendipine in postmenopausal women with mild to moderate hypertension.

Methods: After a 4-week placebo run-in period, 93 postmenopausal women (age range 44–70 years) with primary hypertension were randomized to receive moexipril 15 mg once daily or nitrendipine 20 mg once daily for 8 weeks. The mean sitting systolic (SSBP) and sitting diastolic blood pressures (SDBP) at baseline were 161.3/103.0 mmHg in the moexipril group, and 162.2/102.3 mmHg in the nitrendipine group.

Results: After the 8 weeks of treatment, the SSBP/SDBP reductions were 21.2/15.2 mmHg in the moexipril group and 18.2/13.6 mmHg in the nitrendipine group. Blood pressure responses were adequate in 82.2% of the moexipril-treated patients and in 80.9% in the nitrendipine-treated group.

Adverse events were more frequent with nitrendipine than with moexipril. The most common adverse events in the nitrendipine group were headache (23.4%), flushing (21.3%) and ankle oedema (14.9%). In the moexipril group the most common adverse event was cough (8.9%).

Conclusion: The results of the study suggest that moexipril and nitrendipine are equieffective in the given dosages. In the patient population of postmenopausal women, the ACE inhibitor moexipril appears to have an advantage over the calcium antagonist nitrendipine with regard to tolerability.

Key words  Moexipril · Menopause · Hypertension

Introduction

Cardiovascular disease (CVD) is the leading cause of death in both men and women, and yet it was considered to be mainly a male problem until the mid-1980s. Postmenopausal women develop CVD at the same rate as men, albeit approximately 6–10 years later [1]. It is generally assumed that women lose their cardiovascular advantage after the menopause, although there are contradictory findings and statistics do not confirm a definite relationship between the menopause per se and increases in blood pressure and cholesterol with age [2–4].

Hypertension is the most prevalent cardiovascular risk factor and is a major determinant of the development of cardio-renal failure and cerebrovascular disease [5–9]. Whereas premenopausal women have been found to be haemodynamically younger than men of the same age [10] and high blood pressure is more frequent in younger men, the reverse is true in women after middle age [11]. In the United States at least 50% of 43 million hypertensive people are female [12]. However, data from prospective, placebo- or active-controlled studies exclusively performed in hypertensive, postmenopausal women are scarce.
Therefore, the objective of the present study was to compare the efficacy and the tolerability of the new angiotensin-converting enzyme (ACE) inhibitor moexipril and the long-acting dehydropyridine calcium antagonist nitrindipine in the treatment of postmenopausal women with mild to moderate hypertension. Moexipril is a prodrug, which is hydrolysed by the liver to its active metabolite moexiprilat [13]. Nitrindipine was chosen as a comparator, since this drug was the first long-acting calcium antagonist to be investigated in a placebo-controlled prospective outcome trial in elderly hypertensive patients [14].

Subjects and methods

The efficacy and tolerability/safety of moexipril and nitrindipine were assessed in a 12-week comparative, multicentre, double-blind, parallel group trial in 92 postmenopausal women with mild to moderate essential hypertension. The study was conducted in eight out-patient clinics and comprised a 4-week single blind placebo run-in period during which patient eligibility was determined, followed by 8 weeks of double-blind treatment. The protocol was approved by the local area health board ethics committees and was conducted in accordance with the Declaration of Helsinki. All patients gave their written informed consent prior to the study, which complied with the current laws of the country in which it was performed (Italy).

Postmenopausal status was confirmed by suppressed estradiol and stimulated follicle stimulating hormone (FSH) levels. Its aetiology was either natural (n = 68) or artificial (bilateral oophorectomy or radiation of the pelvis and ovaries; n = 24). Aged between 44 and 70 years, the subjects were judged to have essential hypertension on the basis of a thorough medical history, physical examination and laboratory evaluation. Newly diagnosed hypertensive patients or patients willing to withdraw from their current anti-hypertensive therapy were considered for study entry. Subjects were excluded on evidence of severe renal impairment (creatinine clearance <30 ml min\(^{-1}\)), unstable angina pectoris, recent myocardial infarction, congestive heart failure, history of allergy to ACE inhibitors or calcium antagonists and/or other active, serious or chronic disease. Prior to study entry patients were informed of the most common adverse reactions associated with the drugs.

Design

After the 4-week placebo run-in period, eligible patients were randomized to receive moexipril 15 mg or nitrindipine 20 mg once daily. Since nitrindipine was only available in the form of capsules and moexipril as tablets a double dummy technique had to be used to guarantee the double-blind character of the study. An adequate response was defined as either a decrease in sitting diastolic blood pressure (SDBP) to less than 90 mmHg or a drop of ≥10 mmHg compared with SDBP at baseline.

Methods

Throughout the treatment phase visits took place at weeks 4 and 0 (placebo run-in), and weeks 1, 4 and 8 (active treatment). Blood pressure, vital signs, concomitant medications and adverse events were assessed at all visits. At weeks 0 and 8 laboratory evaluations and electrocardiogram (ECG) were performed.

Blood pressure measurements

The primary endpoint of the study was the change from baseline in trough SDBP. The response rates, defined as the percentage of patients at endpoint with a diastolic blood pressure of less than 90 mmHg or with a reduction in diastolic blood pressure of 10 mmHg or more, were also assessed. All blood pressure measurements were performed in triplicate with a standard cuff sphygmomanometer and were taken on the patient’s right arm with a minimum of 1 min between the measurements. The recorded blood pressure was the average of the three readings.

Systolic blood pressure was determined when the initial tapping sounds were heard for two consecutive beats (corresponding to phase I), and the diastolic blood pressure was determined when Korotkoff’s sounds disappeared, corresponding to phase V. Standing blood pressure was determined immediately after standing up from the sitting position and repeated 2 min later while the patient was still upright. The assessment of blood pressure occurred for all visits at similar times in the day, preferably in the morning 24 (3) h after the previous day’s dose and before the next drug intake.

Laboratory methods

Standard laboratory evaluations including blood chemistry, haematology and urinalysis were done at baseline (week 0), at week 4 and during the last visit at week 8. A central laboratory was used for all sites.

Adverse event assessment

Occurrence of adverse events was a safety variable and served as the secondary objective of the study. An adverse event was defined as any adverse, noxious or pathological change from pre-existing conditions occurring during the clinical trial, whether or not it was considered to be drug-related. Adverse experiences were volunteered by the patient or observed by the investigator. Pre- versus post-treatment results of physical examination, ECG and laboratory tests were also included in the safety evaluation. The adverse events were assessed at each visit by questioning in a general way and were graded by the investigator as serious or non-serious, mild, moderate or severe. Their relationship to the medication was characterized as none, likely, possible, probable or highly probable [15].

Statistical analysis

According to the objectives of the study and the assumptions of the sample size made in the protocol, moexipril versus nitrindipine treatment was tested at a 5% significance level using a classical null hypothesis. This hypothesis was tested by analysis of covariance (ANCOVA) with factors “treatment”, “centre” and their interaction “treatment*centre”, and baseline diastolic blood pressure as covariate. The primary efficacy parameter was the reduction in SDBP. Sitting systolic blood pressure (SSBP) was considered to provide confirmatory evidence. Response rates were analysed by the Cochran-Mantel Haenszel test for general association. The primary analyses were performed on an intention to treat basis, as were the assessments of adverse events. All adverse events were tabulated using standard adverse experience dictionary codes. Comparison between treatment groups for each category of adverse events were performed using Fisher’s exact test (two-sided) for the number of patients who reported at least one adverse event, and each adverse event with an incidence of >5% in either treatment group. All tests were two-sided and P-values < 0.05 were considered to be significant.

Results

The first patient entered the study at the first centre on 3 October 1994. The last visit of the last patient at the last centre took place on 30 October 1995. During the 10 months of recruitment 96 patients entered the screening/