Efficacy and Tolerability of Fosinopril 10mg and Hydrochlorothiazide 12.5mg Combination in Elderly Patients with Mild to Moderate Hypertension
A French Multicentre Study

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Summary

The objective of the study was to evaluate the efficacy and tolerability of the combination of fosinopril 10mg (FOS) and hydrochlorothiazide (HCTZ) 12.5mg versus placebo in the treatment of elderly patients with mild to moderate hypertension. The study included two distinct phases: Phase I was a short-term phase consisting of a 4-week single-blind, placebo lead-in period followed by a randomised, double-blind, parallel group where patients were treated with either a combination tablet of FOS 10mg with HCTZ 12.5mg or placebo given once daily for 8 weeks. A total of 150 patients, ranging from 60 to 91 years of age, were included in this study. Phase II was a long-term extension of phase I and was a 12-month open-label follow-up in which all patients started therapy with FOS 10mg/HCTZ 12.5mg. After 4 weeks of initial therapy, escalation to FOS 20mg/HCTZ 12.5mg was allowed for seated diastolic blood pressure (SeDBP) > 90mm Hg. Clinic visits were scheduled at months 1, 3, 6, 9 and 12. Data from 118 patients were analysed. The mean SeDBP decreased from baseline more in the FOS/HCTZ group (−12.2mm Hg) than in the placebo group (−6.4mm Hg). Similar results were observed for supine diastolic and systolic blood pressure. After 8 weeks of treatment, 58.2% of patients showed normalised (≤90mm Hg) SeDBP with Fos/HCTZ vs 30.3% in the placebo group (p < 0.001). The mean decrease from baseline in SeDBP was −14.3mm Hg and −18.4mm Hg at 1 month and 12 months, respectively, demonstrating efficacy of the lower dose combination (10/12.5mg). The mean seated systolic blood pressure (SeSBP) also decreased from baseline and was −24.5mm Hg and −28.5mm Hg at months 1 and 12, respectively. The results for supine blood pressure corroborated the findings for seated blood pressure. Four patients died either during (2) or shortly after (2) long-term therapy. 5 patients discontinued long-term therapy because of adverse events, 14 patients experienced 16 serious adverse events. Cough was the most common adverse effect reported in 10.4% of patients. No symptomatic orthostatic hypotension was reported.

Fosinopril 10 or 20mg when administered in combination with hydrochlorothiazide 12.5mg once daily for 12 months was found to be an effective anti-hypertensive treatment in elderly patients with mild to moderate hypertension.
Angiotensin converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension because of their effectiveness and acceptable tolerability profile. Fosinoprilat sodium, a phosphinic acid derivative, is an ACE inhibitor that has previously demonstrated its efficacy and tolerability in the once-daily treatment of mild to moderate hypertension.

Fosinopril (FOS) is a prodrug that is completely hydrolysed to the active diacid fosinoprilat, the excretion of which is equally divided between the renal and biliary routes in humans. Pharmacokinetic, efficacy and tolerability profiles are identical in elderly and younger patients. Furthermore, the effects of fosinopril on cerebral haemodynamics are favourable by maintaining cerebral blood flow and potentially broadening the autoregulatory plateau.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic and an antihypertensive agent that affects the renal tubular mechanism of electrolyte reabsorption. Diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6 to 12 hours.

The combination of an ACE inhibitor and a diuretic is commonly used in clinical practice. It is known that the antihypertensive effect may be additive when ACE inhibitors are administered with a diuretic. It has also been demonstrated that when antihypertensive agents with different mechanisms of action are given in combination, the effective dose of each is smaller than the effective dose of the individual drugs given alone. The lower doses minimise potential dose-dependent adverse effects.

The objective of the study was to evaluate the efficacy and tolerability of the fixed combination of fosinopril 10mg and hydrochlorothiazide 12.5mg given as a single tablet once daily in the treatment of elderly patients with mild to moderate hypertension.

Patients and Methods

Patients

Men and women (aged ≥ 60 years) with mild to moderate hypertension (seated diastolic blood pressure 95 to 110mm Hg inclusive) were eligible to enter the study. The qualifying blood pressure was measured 3 times on 2 consecutive visits separated by 1 week during the lead-in period. Patients with significant cardiovascular disease, gastrohepato-intestinal disease or renal disease were excluded. The following therapies were permitted: hypoglycaemic agents, antibiotics, anticonvulsants, paracetamol, aspirin as antiplatelet prophylaxis, and NSAIDs not exceeding 5 consecutive days. Other antihypertensive drugs were not allowed.

The protocol was approved by a regional ethics committee for all sites, and all patients gave their informed consent.

Patients were instructed to take 1 tablet at the same time every morning, except on clinic visit days when the tablet was taken after the visit. The timing was to ensure that the blood pressure determinations were taken 24 ± 3 hours after taking the previous morning’s dose.

At each visit, the blood pressure and pulse were determined in the seated, supine and standing positions. Three recordings of the seated diastolic (SeDBP) and systolic (SeSBP) blood pressure were made and the mean calculated.

Methods

The study consisted of two distinct phases:

Phase I: This was a short-term phase, which included the two following periods:

a) A 4-week, single-blind, placebo lead-in period during which time all patients received a placebo. At the entry visit, patients provided a complete medical history, underwent a physical examination and laboratory analysis. Patients were eligible to enter the double-blind period if the SeDBP was in the specified range as described above;

b) An 8-week, randomised, double-blind treatment period where patients with qualifying SeDBP (95 to 110mm Hg) were assigned either a placebo or a combination of FOS 10mg with HCTZ 12.5mg. Visits were scheduled after 2, 4 and 8 weeks of double-blind treatment.