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Clinical equivalence of two tablet formulations of felodipine

A placebo-controlled study of 24-hour blood pressure control and tolerability

Received: 16 December 1994 / Accepted in revised form: 22 May 1995

Abstract Objective: This study was performed to assess whether a new formulation of felodipine extended release (FER) tablets with a 9 mm diameter is similar to the presently used 11 mm diameter FER formulation with respect to antihypertensive effect and tolerability in patients with essential hypertension. A randomised, double-blind, placebo controlled, three-way cross-over study design was used.

Patients: Twenty-four patients with a supine diastolic blood pressure (DBP) of 95-115 mmHg after a 4-week placebo run-in period were given FER 5 mg 9 mm tablets, FER 5 mg 11 mm tablets and placebo in randomised order. The tablets were given once daily and each double-blind treatment period lasted for two weeks.

Methods: Twenty-four hour ambulatory blood pressure monitoring was performed at the end of each treatment period. The primary effect variable was mean DBP over 24 hours. Nineteen patients had 24-hour blood pressure data valid for analysis using an analysis of variance with patient, treatment, period and carry-over as factors.

Results: Both formulations of FER 5 mg tablets significantly reduced the mean 24-hour DBP compared to placebo. The 9 and 11 mm tablets resulted in, on average, 4.7 and 3.4 mmHg lower mean 24-hour DBP than placebo. There was, however, no significant difference between the two different FER formulations. Both FER formulations were well tolerated and similar to placebo in this respect.

Conclusion: Both FER 5 mg tablet formulations (9 and 11 mm diameter), given once daily, were clinically equivalent with respect to antihypertensive effect and tolerability in patients with mild to moderate essential hypertension.

Key words Felodipine, Hypertension; extended release formulation, tolerability

Different pharmaceutical formulations of a drug often have different pharmacokinetic and pharmacodynamic properties. Also minor changes in drug formulation, such as changing the size of a tablet, may influence these characteristics. It is therefore important to ensure that a new formulation can demonstrate bioequivalence and/or clinical equivalence before it is substituted for the existing formulation.

Felodipine (Plendil®, Astra) is a dihydropyridine calcium antagonist with high vascular selectivity, i.e. therapeutic doses cause precapillary vasodilatation and reduction of vascular resistance, but have no direct cardiac effects [1]. Felodipine is an effective and well tolerated antihypertensive drug [2, 3]. Given in an extended release (ER) tablet formulation felodipine 2.5-10 mg once daily results in a smooth blood pressure reduction lasting for at least 24 h [4].

The first felodipine ER formulation available was a circular tablet with a diameter of 11 mm. A new, smaller tablet formulation with a 9 mm diameter has now been developed. The volume of this new tablet is approximately 50% of the old. In addition to being more easily ingested, the 9 mm tablet has the advantage of requiring less organic solvent during production, thereby reducing the environmental impact of the manufacturing process. A steady state study in 18 healthy male volunteers, comparing 9 mm tablets of felodipine to 11 mm tablets, could not conclusively demonstrate bioequivalence [Bergstrand R., 1990, unpublished data]. Although the different formulations had similar bioequivalence judged from the area under the felodipine plasma concentration versus time curve (AUC24),

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they did not quite fulfill bioequivalence requirements for peak \((C_{\text{max}})\) and trough \((C_{\text{min}})\) plasma concentrations. The \(C_{\text{max}}\) was lower and the \(C_{\text{min}}\) higher for the 9 mm than for the 11 mm tablets.

The main objective of the present study was to evaluate and compare the antihypertensive effects of the 9 and 11 mm felodipine ER 5 mg tablets, administered once daily, in patients with mild to moderate essential hypertension. The mean 24-hour diastolic blood pressure (DBP) obtained from 24-hour ambulatory blood pressure monitoring (ABPM) was the primary effect variable. The tolerability of each regimen was also to be assessed.

**Patients and methods**

**Study design**

This was a randomised, double-blind, placebo controlled, three-way cross-over study. After a 4-week placebo run-in period, patients were allocated to receive felodipine 5 mg 9 mm tablets, felodipine 5 mg 11 mm tablets and placebo in randomised order. Each double-blind treatment period lasted for two weeks with no "wash-out" in between. The blinding was accomplished using a double-dummy technique. The randomisation was performed according to a balanced block design, with a block size of six.

**Patients**

Men and women, aged 18–80 years, with essential hypertension and a supine DBP of 95–115 mmHg after withdrawal of any previous antihypertensive medication and placebo treatment for 4 weeks, were eligible for randomisation. Women of child bearing potential were excluded as were patients with supine SBP exceeding 220 mmHg during the run-in period. Other exclusion criteria were: unstable angina pectoris; onset of angina, myocardial infarction or unstable angina pectoris; onset of angina, myocardial infarction or venous thromboembolism. The main reasons for exclusion were: conditions likely to result in poor compliance; concomitant diseases which could interfere with the patient's well being or assessment; conditions likely to result in poor compliance to the study protocol.

It was calculated that 24 patients would be needed to detect a true difference in DBP of 5 mmHg or more with a power of 80%.

**Methods**

Clinic supine and standing systolic blood pressure (SBP) and DBP (phase V) were measured before study drug administration on the morning of each visit, using a standard mercury sphygmomanometer. The blood pressure measurements were taken in triplicate after the patient had been supine for five minutes and standing for 2 min. Pulse rate was assessed over a 30 s period immediately after the blood pressure measurements.

At the end of each double-blind treatment period, before having taken the morning dose of their study medication, patients had an ambulatory blood pressure monitor (Accutracker II) attached to the nondominant arm. The morning dose was then administered by the investigator and the patient returned to the clinic 24 h later, again without having taken the morning dose. During this 24 h monitoring period, SBP, DBP and pulse rate were recorded every 30 min during the day and hourly overnight (22.00–06.00 h).

Venous blood samples (5 ml) were taken 24 h after dose administration at the end of each double-blind period for the assessment of felodipine plasma concentration. The plasma samples were kept frozen (−20 °C) until analysis using a gas chromatographic method [6].

Tolerability was assessed at each visit as adverse events reported spontaneously or after open questioning ("Have you had any health problems since the last visit?") or from observation by the physician. An adverse event was defined as any unfavourable, unintended event (e.g. signs and symptoms) temporally associated with administration of the study drug, whether or not considered to be drug related.

**Data analysis**

The 24-hour ABPM data were divided into 3-hour intervals, beginning at time of intake of study medication. The means of the valid data for each 3-hour interval were calculated and used in the calculation of mean SBP, DBP and pulse rate for the 24-hour, day-time and night-time periods. The daytime period was defined as 0–12 h after study drug intake and the night-time period as 12–24 h post dose. Mean 24 h data were calculated for 19 of the 22 patients (in one patient ABPM was only performed in one period and in two patients there were several 3 h intervals with no valid data). Descriptive statistics on blood pressure and pulse rate for 3-h intervals include only data from the 15 patients who had at least two valid measurements per 3-h interval during the day and at least one valid measurement per interval during the overnight period. All decisions on exclusions of patients from the analysis due to invalid data were made before the treatment code was broken. Clinic blood pressure and pulse rate data were available for all the 22 patients who completed the study. Mean values for clinic blood pressure and pulse rate were calculated from the averages of the second and third readings.

To describe the trough/peak effect ratio for felodipine the protocol defined the trough effect as the difference in blood pressure between the felodipine and placebo periods in the time interval 21–24 h after dose administration. The peak effect was defined as the corresponding difference in the interval 3–6 hours post dose, since peak felodipine plasma concentrations and effects can be expected in this time interval [7].

**Statistical analysis**

The mean 24-hour blood pressure and pulse rate (ABPM), the clinic blood pressure and pulse rate, and the felodipine plasma concentration at the end of each 2-week double-blind period were compared using an analysis of variance with patient, treatment, period and carry-over as factors. Efficacy results are presented as mean differences between treatments, together with the 95% confidence intervals (CI) and the \(p\)-values for these differences, adjusted for differences in group sizes due to drop-outs. A \(p\)-value < 0.05 was considered statistically significant. For 3-hour intervals, as well as daytime and night-time periods, only descriptive statistics have been used.

**Ethics**

The study was approved by the Ethics Review Committee at each centre. It was performed in accordance with the principles of the Declaration of Helsinki and the Australian NH&MRC Statement on Human Experimentation and conducted according to the Australian Guidelines for Good Clinical Research Practice. Prior to entry, witnessed informed consent was obtained from all patients after they had received full verbal and written information about the study.

**Results**

After completing the run-in period, a total of 24 patients (12 at each centre) were randomised. Two