Once Daily Felodipine Monotherapy in Mild to Moderate Hypertension

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Abstract

In a single-blind study conducted at our centres, 78 hypertensive patients were enrolled with 58 completing the study according to the protocol. Mean supine and standing blood pressures were significantly reduced after treatment with felodipine, reductions being 27/21 mmHg ($p<0.0001$) and 25/19 mmHg ($p<0.0001$) respectively. Of 46 patients given felodipine 5 mg, 44 (95.7%) achieved target blood pressure defined as a diastolic blood pressure of <90 mmHg, while all 12 patients on felodipine 10 mg did so. The 2 patients who did not achieve target pressure at the final visit did so on previous visits. There were no differences in pre and post-treatment laboratory variables. Treatment was discontinued in 6 patients because of headaches. No adverse events of clinical significance were reported in the 58 patients who completed the study. In conclusion, we found felodipine given once daily to be effective in the treatment of mild to moderate hypertension.

Key words: Hypertension, felodipine, effective.

Introduction

Felodipine, a dihydropyridine calcium antagonist, acts by selective relaxation of vascular smooth muscles, thereby lowering systemic vascular resistance and consequently producing substantial decreases in blood pressure without any detrimental effects on cardiac output[1].

Felodipine is indicated in the management of hypertension. In patients with mild to moderate disease, felodipine monotherapy effectively lowers blood pressure[2]. It is proven to be as effective as atenolol[3,4] and hydrochlorothiazide[5,6] in terms of antihypertensive activity.

As all previous studies were conducted in Caucasian populations[7], we decided to embark on a study to evaluate the efficacy and tolerability of felodipine monotherapy, given once daily, in Malaysian patients with mild to moderate hypertension.

Methods

Entry criteria

Male and female patients, aged between 20 and 70 years, with untreated essential hypertension and with diastolic blood pressure (phase V) greater than 95 mmHg, were recruited into the study. Informed consent was obtained in all cases. Previously treated patients were also considered for recruitment if they met entry criteria, after all previous antihypertensive medication had been withdrawn for at least 2 weeks prior to commencement of the study.

Patients excluded in this study were those who had a myocardial infarction less than 3 months prior to the commencement of the study, female patients of childbearing potential who were not on any contraception and lactating mothers. Patients with clinically significant abnormalities in the pre-drug laboratory screen and those with impaired liver or renal function, unstable diabetes, suspected or confirmed malignancy were also excluded. Additionally, any hypertensive patients with a systolic blood pressure greater than 200 mmHg and/or diastolic pressure greater than 120 mmHg were similarly excluded.

Study design

This was an open, single-blind study where previously untreated patients started with a run-in period of 2 weeks. During this time they received, daily, a matching placebo tablet which was similar to active tablet in physical attributes of size and colour. Patients who were on previous medication had all treatment withdrawn and underwent a wash-out period of at least 2 weeks prior to run-in, during which time they were also administered the placebo. If, at the end of the run-in period, their diastolic pressure was below 95 mmHg, they were no longer eligible for the study and were withdrawn. If the diastolic blood pressure was equal to or greater than 95 mmHg, these patients were confirmed hypertensive and active treatment with felodipine (Plendil-Astra Sweden) 5 mg once daily in the morning was instituted. During active treatment, patients were reviewed every second week. Should their diastolic blood pressure remain at 90 mmHg or lower, patients were maintained at the same dose level. If their diastolic pressure was above 90 mmHg, the dose was stepwise doubled, until a maximum of 20 mg felodipine daily. Total treatment duration was 6 weeks.

Clinical and laboratory assessments

At the initial visit, a general medical history was taken and physical examination conducted. An electrocardiogram was done and a chest X-ray taken, if none had been performed in the previous 6 months. Height and weight were measured together with supine and standing systolic and diastolic blood pressures and pulse rate. At all subsequent visits, blood pressure and heart rate were recorded. The monitoring for adverse events was performed at every visit. A standard laboratory screen was performed pre and post-treatment. For compliance check, patients were asked to return their unused medication at each clinic visit.

Statistical analyses

A Student's paired t-test was used to analyse the treatment effects on blood pressure, heart rate and weight measurements while the Wilcoxon's signed rank test[8] which was most appropriate, was adopted to analyse treatment effects on haematologic and serum chemistry variables, as these were less than normally distributed.

The protocol was approved by the Ethics Committees of both the centres involved.

Results

Seventy-eight patients (Males:58, Females:20) were entered into the study (see Table I) of which 58 patients (Males:43, Females:15) completed the study according to the protocol. The remaining 20 patients were excluded from evaluation for various reasons listed in Table I.

Table I
Patients included in efficacy evaluation

No of patients entered		78
No of patients excluded from evaluation		20
No of patients completed		58
Reasons for exclusion		
(a)	Not meeting inclusion criteria	
	DB<95 mmHg at end of run-in	11
	TIA* at end of run-in	1
(b)	Withdrawals	
	Non-compliance due to ADE†	4
	Drug discontinued due to ADE	2
	Protocol violation	1
	Late for visit	1
	Grand total	**20**

*TIA — transient ischaemic attack, †ADE — adverse drug event.

Mean age of all patients was 47.4 years (range:25-68; n=78), mean weight 70.4±11.0 kg and the racial breakdown gave 38 Chinese, 12 Indian and 28 Malay patients. Laboratory analysis gave the following mean values: haemoglobin 15.5±18 g/dl, serum creatine 89.0±22.7 µmol/L, alkaline phosphatase 59.1±18.3 IU/L and ALAT 37.2±21.3 IU/L. Of the 58 patients valid for analysis, most (96%) were on some previous antihypertensive therapy. Monotherapy was observed in 23 patients while double combinations were seen in 26 and triple combinations in 7 patients. Only 2 patients were previously untreated. The common antihypertensive agents used in these patients were beta-blockers, diuretics and vasodilators (see Table II).

The corresponding supine and standing blood pressure and heart rates at the various study periods of entry, at end of run-in and upon completion of treatment with felodipine in the 58 patients are as outlined in Table III. Patients at the end of the run-in had initial mean diastolic pressures of 102.1 mmHg, giving a mean reduction of 20.6 mmHg. Correspondingly, systolic pressure reduction was at a mean of 27.1 mmHg. These were both statistically significant ($p<0.0001$).

Heart rate significantly ($p<0.0001$) increased during the treatment period.

Similar effects were seen with standing blood pressure and heart rate.

Responders to treatment were defined as patients in whom supine diastolic blood pressure was equal to or lower than 90 mmHg (i.e., DBP<90 mmHg). In this context, 44 of 46 patients (95.7%) who were on felodipine 5 mg at end of treatment were responders while all 12 on felodipine 10 mg responded to treatment with good blood pressure control. The 2 patients on felodipine 5 mg who failed to achieve target blood pressure of 90 mmHg or less at the final visit, had, nevertheless, supine diastolic pressure of 86 and 83 mmHg respectively at the previous visit such that the dose of felodipine was not increased.

Table II
Previous antihypertensive history

	No of patients
Amiloride HCI & hydrochlorothiazide	5
Atenolol	7
Bendrofluazide	1
Captopril	1
Chlorothiazide	1
Doxazosin	2
Enalapril	2
Frusemide	1
Hydralazine	2
Hydrochlorothiazide	21
Methyldopa	7
Metoprolol	25
Nifedipine	4
Prazosin	25
Propranolol	28
Verapamil	1

Table III
Mean blood pressure and heart rate during the study period

	At entry (n=77)	At end of run-in	On completion (n=58)	Difference (mean±s.d.)
Supine				
Systolic mmHg	142.3	153.5	126.4	27.1±15.3
Diastolic mmHg	94.1	102.1	81.5	20.6±8.2
Heart rate	68.6	77.4	84.3	-6.9±10.6
(beats/min)	(42^100)	(56^112)	(60^134)	
Standing				
Systolic mmHg	141.6	152.3	127.7	24.7±15.7
Diastolic mmHg	96.3	105.3	86.2	19.1±8.9
Heart rate	72.2	83.3	90.4	-7.0±11.64
(beats/min)	(46^100)	(62^115)	(67^136)	

Laboratory screen for standard variables pre and post-treatment showed no statistical difference in any of the laboratory values.

Patient compliance, assessed by tablet counts of unused medication returned by patients at subsequent clinic visits, was good.

In the evaluation for tolerability of treatment, all events reported before and after are presented in Table IV. There were greater incidences of headaches and dizziness while on treatment than prior to it. In the early phase of the study, 6 patients were withdrawn as a result of headaches.

Table IV
Adverse events reported during the study (n=66)

	No of reports*	
	Run-In	Treatment
Abdominal fullness	0	1
Ankle oedema	0	1
Body ache	1	0
Breathlessness	0	1
Chest pains	0	1
Cramps	1	0
Dizziness	0	3
Drowsiness	0	1
Drunken state	0	1
Early gouty arthritis	0	1
Facial swelling	1	0
Fast breathing on exertion	0	1
Feeling hot	1	1
Flushing	0	2
General itchiness	0	1
Giddiness	1	0
Hand tremors	1	0
Hard stools	0	1
Headaches	9	24
Headache, muscle ache	1	0
Headache, with nausea	0	1
Headache with sore throat	1	0
Heavy head	2	2
Impotence	0	1
Insomnia	0	1
Light head	0	1
Micturition	1	0
Nervousness, left index finger shaking	1	0
No appetite	0	1
Palpitations	2	3
Rashes	0	1
Sore throat/myalgia	1	0
Tiredness	1	2

* Includes more than 1 report per patient at each visit.

Discussion

In the conduct of the study at our centres, patients who were recruited were mainly those in whom hypertension had been clearly established and who were also already on antihypertensive drug treatment.

New, untreated patients were few because both centres are referral centres and do not routinely see 'walk-in' patients as such.

Although most of these patients were already on antihypertensive treatment, with close to 40% of them being on monotherapy and 57% on two or more drug combinations, blood pressure control was not optimal, as mean supine diastolic pressure at entry was 94.1 mmHg. At the end of the placebo-treated run-in period, mean supine diastolic pressure was at 102.1 mmHg. Heart rates similarly increased from a mean 72.2 to 83.3 beats per minutes, an effect which might be partly contributed by beta-blocker withdrawal.

All patients (n=58) given the initial dose of felodipine 5 mg once daily responded to treatment with an overall lowering of supine diastolic blood pressure, but only 44 patients achieved and maintained target diastolic blood pressure of or below 90 mmHg during the entire treatment period.

Two patients who were on felodipine 5 mg once daily had controlled diastolic blood pressure (86 mmHg and 83 mmHg) at week 4 of active treatment until the last visit when they registered diastolic blood pressures of 97 mmHg and 94 mmHg respectively. Although by definition these 2 patients were classified non-responders at the felodipine 5 mg dose level, we believe that their blood pressures might have further responded to an increased dose of felodipine 10 mg daily.

The remaining 12 patients who had required an increase of their daily dose of felodipine to 10 mg achieved excellent diastolic blood pressure control for the remaining 4 weeks of the treatment period. Response rate in this group was 100%.

Table III shows the mean diastolic pressure for the whole group of patients at completion of the study to be 81.5 mmHg (supine) and 86.2 mmHg (standing). This is a significant improvement on their end of run-in diastolic pressures of 102.1 mmHg and 105.3 mmHg respectively. There was no orthostatic hypertension observed during therapy and this is a therapeutic advantage. A significant increase in pulse rate during treatment was noted. This was expected and was attributed to compensatory reflex tachycardia consequent to peripheral vasodilation induced by felodipine. From the earlier studies reported, tachycardia following felodipine administration could be easily overcome by the concomitant administration of a beta-blocker.

To determine tolerability of felodipine treatment, all patients (n=66) were asked a non-specific, non-leading question before and after treatment whereupon patients' spontaneous reports were recorded. As Table IV shows, patients on treatment tended more often to complain about the incidence of headaches which is again, not unexpected, due to the mode of action of the drug. However, most patients have reported it as being mild and transient in nature, mirroring reports from studies performed previously. There were, nevertheless, 6 patients who had such severe headaches that treatment had to be discontinued. There were 3 reports of dizziness (in 2 patients) and 2 of flushing (also in 2 patients) but only 1 patient with dizziness and tiredness for 21 days since initiation of therapy refused to continue with the study. A common adverse event of calcium channel blockers, which is the development of peripheral oedema, was not observed in any of our patients. This could be linked to the fact that felodipine also has natriuretic properties[1], thereby contributing to diuresis.

Notwithstanding the above, it is also relevant to note that adverse event reporting during the run-in period is a one-off case whereas during the treatment period, patients report on 3 different occasions and therefore, the frequency of adverse events during treatment is accordingly reflected.

Treatment with felodipine did not have any adverse effect on the laboratory variables.

In conclusion, we found felodipine monotherapy to be an effective treatment regimen in mild to moderate hypertension among Malaysian adults. Its convenient daily dosing, relative absence of disturbing adverse events and therapeutic efficacy should prove beneficial for the many patients who are not optimally controlled on their existing therapy. For the few patients who do not tolerate the drug at all, alternative regimes will have to be identified.

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