EFFICACY AND ADVERSE EFFECTS OF DOXAZOSIN IN THE TREATMENT OF HYPERTENSION

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ABSTRACT

Doxazosin, a selective alpha 1 adrenoceptor antagonist recently approved for use in Malaysia, was assessed in six patients attending an outpatient hypertensive clinic. All patients had essential hypertension and their blood pressure was not under optimum control with the current medication regimen; lack of optimum control being considered as a sitting diastolic pressure of above 95 mmHg. Patients' baseline values for blood pressure, heart rate, anthropometric parameters together with haematological, biochemical and electrocardiographic parameters were established. Following this doxazosin was added at 1 mg daily and the dose titrated every two weeks until optimum control was obtained. Patients were followed upto 12 weeks of treatment and all parameters were measured again at the end of this period. All patients responded favourably and blood pressure was controlled, ie sitting diastolic pressure below 90 mmHg, with doxazosin 1-4mg daily. The systolic pressure fell from a mean of 164 mmHg to 141 mmHg (14%) and diastolic pressure from a mean of 99 mmHg to 86 mmHg (13%). None of the patients had any adverse effects attributable to doxazosin. Heart rate, body weight, haematological and biochemical parameters and electocardiograms did not show any significant change with doxazosin. The above findings suggest that doxazosin is an effective and well tolerated antihypertensive drug. However the significance of the findings is uncertain because of the limited numbers of patients who could be admitted to the study during the alloted time.

KEY WORDS : Hypertension, Doxazosin

INTRODUCTION

Effective blood pressure control significantly reduces morbidity and mortality in hypertensive patients(1). This benefit is due to reduction in the incidence of accelerated hypertension and hypertensive complications such as cerebrovascular disease,cardiac failure and renal failure (1) and has been shown for patients whose diastolic blood pressure, prior to therapy, was over 90 mmHg(2,3).

Different drugs used in the treatment of hypertension have different adverse effects and varying metabolic consequences in addition to affecting the complications of hypertension differently(4).Thus there is no single drug ideally suitable for the whole range of hypertensive patients. Rather, the best drug needs to be identified according to the needs of the patient, taking into account any metabolic derangements and complications that may exist.The recommended first choice antihypertensive drugs have evolved with many changes during the past two decades.Vasodilator alpha blockers (eg. doxazosin) currently occupy the slot of first choice drugs, together with angiotensin converting enzyme inhibitors and calcium channel blockers(4).

Doxazosin is a newer alpha 1 adrenoceptor antagonist. This group of drugs selectively block post synaptic alpha 1 adrenoceptors, resulting in decreased contraction of smooth muscle cells. This effect causes arteriolar dilatation and also venodilatation. The arteriolar dilatation is the major contributor to the antihypertensive effect of doxazosin.

Doxazosin was recently approved for use as an antihypertensive in Malaysia and no data is available regarding its use in hypertension in this country.

METHODS

Six hypertensive patients - five female and one male - were included in the trial during the allotted time period.

Patient selection - Patients diagnosed as having essential hypertension, whose blood pressure was not adequately controlled with their current therapy were included in the trial. For the purposes of the trial, inadequate control of hypertension was taken as a sitting diastolic pressure of 95 mmHg or above. Those with a sitting diastolic pressure of above 115 mmHg were considered to have severe hypertension and were excluded.Patients whose current medication included an alpha blocking drug were also excluded. Written consent was obtained from the patients included in the trial and they were allowed to continue the medication they were currently receiving. Other exclusion criteria were documented hypertension related acute illness in the three months prior to screening.

Trial design - The study period for each patient consisted of a two-week baseline period, an eight-week treatment titration period and a four-week maintenence period. Patients were seen at weekly intervals during the baseline period and at two week intervals thereafter. Patients who demonstrated a sustained diastolic hypertension of 95 - 115 mmHg during the baseline period proceeded to the treatment phase.

Treatment commenced with the addition of doxazosin 1mg daily to the patient's current medication regimen. The dose of doxazosin was adjusted by doubling the dose at two week intervals until diastolic blood pressure was below 95 mmHg, or a maximum dose of 8mg daily was administered.Once the optimum dose of doxazosin was achieved, patients continued with that optimum dose until the end of the trial.

Blood pressure was recorded after the patient had been sitting at rest for at least 5 minutes. Two measurements were taken at two minute intervals and the mean of the two readings was considered to be the true blood pressure. Heart rate was also recorded on two occasions at an interval of two minutes and the mean calculated.Diastolic blood pressure was measured at disappearance of Korotokoff's sounds

Height and weight were recorded at the screening visit and weight monitored at each visit.

Some haematological and biochemical parameters and electrocardiography were performed at the commencement of treatment and at the end of the trial. The parameters measured were haemoglobin, haematocrit, total white cell count, platelet count,total bilirubin, total serum protein and serum albumin, serum aspartate transaminase, serum alanine transaminase, serum alkaline phosphatase, serum sodium and potassium,blood urea, serum creatinine, fasting blood glucose, fasting serum total cholesterol and triglycerides.

Baseline values of blood pressure, heart rate, body weight and haematological and biochemical parameters were compared with the end-of-trial values and analysed statistically by means of paired 't' tests.

RESULTS

Six patients were admitted to the study and all six completed the period of therapy with doxazosin.

Their ages ranged from 35 years to 64 years with a mean of 53,2 years. The mean weight at start of therapy was 59.4 kg and the mean height 152cm. duration of hypertension in these patients ranged from 5 years 20 years with a mean of 12.5 years (Table 1).

	Range	Mean ±S.D.
AGE(years)	35 - 64	53.2 ±11.0
BASELINE WEIGHT(Kg)	46 -70.5	59.4 ± 10.3
HEIGHT (cm)	148 -162	152 ± 5.2
DURATION OF HYPERTENSION (years)	5 - 20	12.5 ± 5.4

Table 1 - Age, weight on starting therapy, height and duration of hypertension of subjects

Four out of the six patients were on one other antihypertensive drug and two were on two other antihypertensives. The two latter patients were also receiving lipid lowering agents and one of them aspirin (Table 2). Table 3 lists the concomitant drugs taken by the patients.

Number of other concomitant antihypertensive drugs	Number of patients
1	4
2	2

Table 2 - Number of concomitant antihypertensive medication

Concomitant drugs	Number of patients
Enalapril	3
Quinapril	1
Indapamide	1
Nifedipine	1
Metoprolol	1
Atenolol	1
Cholestyramine	1
Gemfibrozil	1
Aspirin	1

Table 3 - List of concomitant medication

All patients who entered the study completed the period of drug therapy and none of them showed any adverse effects (Table 4).

	Total	Percentage
Completed trial	6	100%
Adverse effects	Nil	0%

Table 4 - Completion rate and rate of adverse effects

At the end of the titration period of drug therapy, four patients were on 1mg doxazosin daily,one on 2mg daily and the other on 4mg daily (Table 5).

Daily dose of doxazosin	Number of patients	Percentage
1mg	4	66.6%
2mg	1	16.7%
4mg	1	16.7%

Table 5 - Dose of doxazosin at the end of trial

The mean systolic and diastolic blood pressures at 2nd week of baseline (at the commencement of doxazosin therapy) were 164 mmHg and 99 mmHg respectively. The mean values at the end of the study were 141 mmHg for systolic and 86 mmHg for diastolic. There was a significant difference between the blood pressures both systolic and diastolic, with the values at end of trial being lower ($P < 0.05$ for systolic pressure and $p < 0.001$ for diastolic) Figure 1 shows the pattern of change, for the duration of the study.

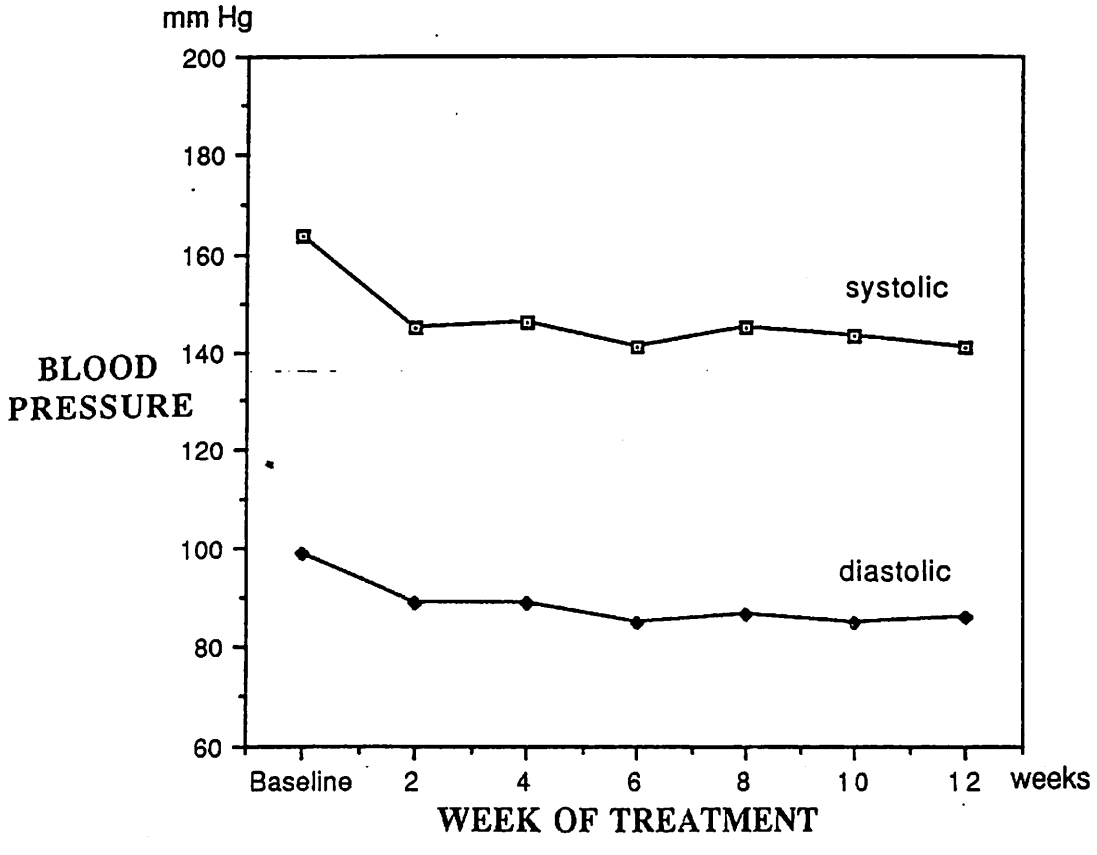

Fig 1 - Effect of doxazosin on blood pressure (sitting)

The mean heart rate at baseline was 82/min which was not significantly different from the mean value of 75/min at the end of the study (Fig 2).

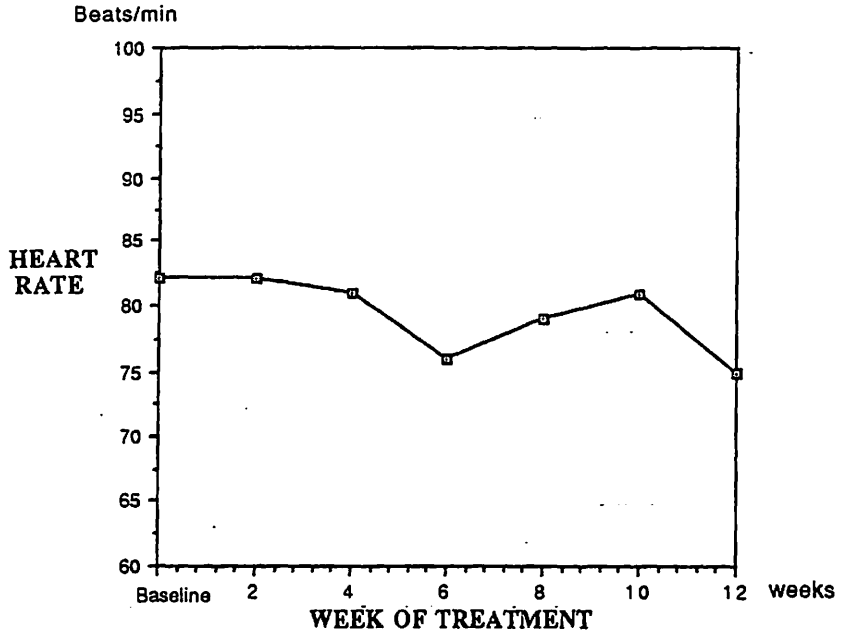

Fig 2. Effect of doxazosin on heart rate

The mean baseline weight was 59.4kg. The weight tended to increase marginally during the period of doxazosin therapy. However, at no time during the study was the weight significantly higher than at baseline (Fig 3).

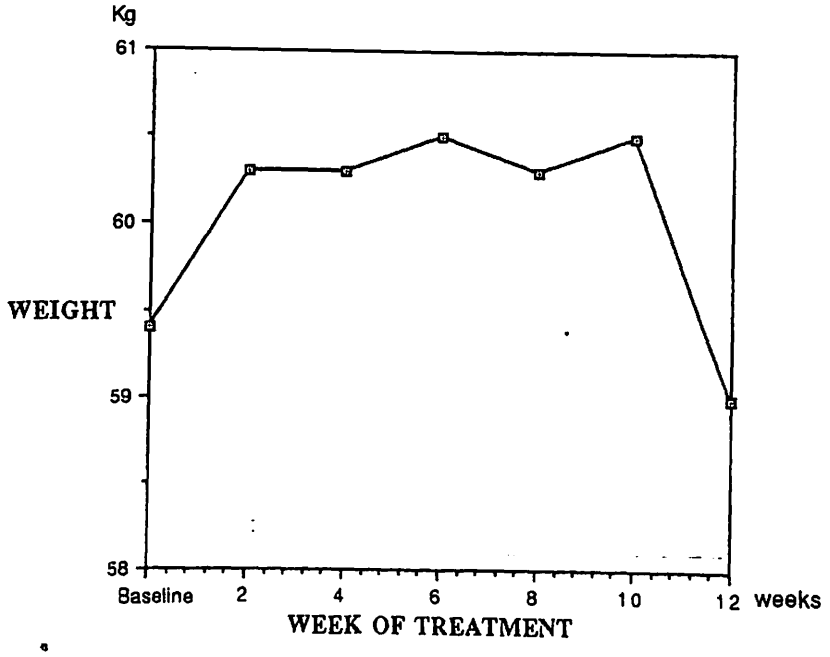

Fig 3- Effect of doxazosin on weight

The comparison of haematological and biochemical parameters at baseline and end of study is shown in Table 6. In none of the parameters was there a significant change after doxazosin therapy.

PARAMETER	BASELINE	END-OF-TRIAL
Haemoglobin (g/dl)	12.9	12.2
Haematocrit (%)	40.1	37.3
Total white cells (1,000/mm^3)	6.9	6.4
Platelet count (1,000/mm^3)	255.2	269.8
Serum bilirubin (micromol/L)	10.3	9.8
Serum total protein (g/L)	76.0	74.5
Serum albumin (g/L)	42.5	42.3
Aspartate transaminase (IU/L)	28.1	21.8
Alanine transaminase (IU/L)	34.5	23.7
Alkaline phosphatase (IU/L)	73.8	69.0
Blood urea (mmol/L)	4.7	5.4
Seum creatinine (micromol/L)	97.0	99.5
Serum urate (micromol/L)	395.0	388.8
Serum sodium (mmol/L)	141.3	141.3
Serum potassium (mmol/L)	3.7	3.9
Fasting blood glucose (mmol/L)	5.3	4.8
Fasting total cholesterol (mmol/L)	6.3	6.7
Fasting serum triglycerides (mmol/L)	2.2	1.4

Table 6 - Haematological and biochemical parameters at baseline and at end of study.

One of the six patients had electrocardiographic evidence of left ventricular hypertrophy while the other had normal electrocardiograms. None of the patients showed a change in the ECG findings at the end of the study.

DISCUSSION

Several studies carried out in the western countries have demonstrated the efficay of doxazosin in the treatment of mild to moderate hypertension (5,6,7). It has been compared with many other first choice antihypertensive drugs with regard to its blood pressure lowering effect and also the effect on various biochemical parameters. Such antihypertensive drugs include beta adrenoceptor blockers(8,9,10),angiotensin converting enzyme inhibitors (11) and calcium channel blockers (12). Doxazosin has also been used together with the above drugs in the treatment of hypertension with good effects.

The aim of this study was to assess the antihypertensive efficacy and tolerance of doxazosin in mild to moderate hypertension in the Malaysian population.The study also sought to assess the suitability of doxazosin as one component of a multiple drug regimen in hypertension.

In patients who had been diagnosed as having essential hypertension and who were on a drug regimen which did not successfully control the blood pressure, addition of doxazosin to the regimen effectively lowered the blood pressure to satisfactory levels. For the purposes of this study, a sitting diastolic pressure of less than 90 mm Hg was considered to be satisfactory. Most patients responded to the addition of doxazosin in a low dose - 1-2mg daily. This is in comparison to the recommended maximum daily dose of 16mg. Only one patient needed a relatively higher dose of 4mg daily for effective blood pressure control. This demonstrates that doxazosin not only is an effective antihypertensive but also is an ideal drug to be used in a multiple drug regimen becuase it does not seem to loose its own efficacy or lower that of the other drugs when used in combination with them.

None of the patients suffered any adverse effects with the addition of doxazosin. The heart rate and the body wieght were not adversely affected. In fact the heart rate showed a gradual decrease with dixazosin although it was not statistically significant.The absence of a rise in heart rate is a desired property of any vasodilator antihypertensive drug.

All biochemical and haematological parameters remained stable. This is in keeping with the results of many previous studies done with doxazosin. There was no significant change in serum cholesterol and triglycerides although some previous studies have shown a beneficial effect on blood lipids(5,6). There was, however, a downward trend in serum triglycerides.
The one patient with electrocardiographic evidence of left ventricular hypertrophy did not show any signs of regression of hypertrophy over the duration of the study. This is to be expected as the duration of the study was too short to observe any possible reversal of structural changes in the heart.

In conclusion doxazosin is seen to be an effective drug in mild to moderate hypertension. It is well tolerated and can be used together with the other commonly used first line antihypertensive drugs without loss of efficacy of any of the drugs involved. This study failed to demonstrate the lipid lowering effect of doxazosin shown in previous studies. Doxazosin does not seem to adversely affect any haematological or biochemical parameter.

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