HYDRALAZINE AND PRAZOSIN IN THE TREATMENT OF HYPERTENSION

M.J. VANDENBURG, V.L. SHARMAN, PAT WRIGHT, P.J. DREW & J.N. BARNES

The Hypertension Clinic, The London Hospital, London E1 1BB

1 We report the results of an observer blind crossover trial in 31 patients with essential hypertension comparing the hypotensive effect of four doses of prazosin and of hydralazine used as the third step of triple therapy and additional data on the efficacy of low dose combinations of these two drugs.

2 Both drugs had an appreciable antihypertensive effect, 1 mg of prazosin being equivalent to 12.5 mg of hydralazine.

3 Increasing the dose of prazosin from 4 to 8 mg twice daily and hydralazine from 50 to 100 mg twice daily did not consistently reduce blood pressure.

4 The combination of the two drugs at low doses resulted in the blood pressure of more patients being controlled (diastolic blood pressure 90 mm Hg or below) than when either drug was used alone at high dose.

5 The symptoms reported by patients were similar for both drugs. The combination did not lead to an increased reporting frequency.

6 The trial demonstrates one of the problems of a crossover study, namely a treatment/period interaction.

Keywords hydralazine prazosin essential hypertension

Introduction

As evidence increases that morbidity and mortality of hypertensive patients is improved by hypotensive therapy the goal blood pressure of such treatment is being lowered. It is now recommended that hypertensive patients have their therapy increased in a stepwise manner to achieve a goal blood pressure of below 90 mm Hg (Joint National Committee on Detection, Evaluation and Treatment of Hypertensive Patients, 1980).

The recommended first two steps of such therapy are firstly either a β -adrenoceptor blocker or a diuretic alone and then the two in combination. Oral vasodilators are recommended to be added to this therapeutic regime if blood pressure reduction is inadequate (Bannon *et al.*, 1980). There remains a percentage of patients on such triple therapy who require additional treatment. We report the results of an observer blind trial comparing the hypotensive effect of prazosin and hydralazine, used as third drugs in triple therapy, and additional data on the efficacy of combining these two drugs.

Methods

Thirty-six subjects gave their informed consent to participate in the study. In all cases a diagnosis of essential hypertension had been established and despite treatment with once daily slow oxprenolol 320 mg and cyclopenthiiazide 0.5 mg with 16 mmol of potassium, supine diastolic blood pressure had remained above 95 mm Hg on at least two consecutive clinic visits. Drugs were taken at 08.00 and clinic visits took place 6-8 h later. At each visit the same procedure was followed: patients were weighed and then rested for 5 min before their blood pressure was measured using a London School of Hygiene Sphygmomanometer by an observer, unaware of the treatment they were receiving. Two measurements were made lying and a further two after standing for 3 min. Korotkoff phase V diastolic blood pressure was recorded. The average of the two readings in each position was used for the analysis. Pulse rate was measured and symptoms were elicited at each visit by open questioning. The patients were then seen by a trial co-ordinator who prescribed their medication.

Week			-4	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Period			Run-in		Active A								Wash out		Active B								Wash out		Active C								
Treatment	Group 1	Cyclopenthaizide and slow oxprenolol	+ Hydralazine								+ placebo	+ Prazosin								+ placebo	+ combined hydralazine and prazosin												
	Group 2		+ Prazosin									+ Hydralazine																					

Figure 1 Schematic presentation of study design

Trial design (Figure 1)

There were three active treatment periods A, B, and C in the trial, each of 2 months duration, during which vasodilator therapy was given in addition to the diuretic and β -adrenoceptor blocker. Two washout periods separated the active treatment periods when a non-matching placebo was prescribed in place of the vasodilator.

Patients were randomly allocated to one of two groups. Group 1 received hydralazine for active treatment period A and prazosin for period B; Group 2 received the drugs in reverse order. Both groups received combined treatment with hydralazine and prazosin during period C (Figure 1). Patients were seen every 2 weeks throughout the trial, when the dose of medication was altered, so that each patient received each dose of each treatment period, the dose of the drug being increased regardless of the blood pressure obtained (Table 1). There was an additional visit after 1 week of periods A and B if the patient was able to attend the clinic.

Compliance was assessed by return tablet inspection.

Data were analysed using the SPSS package at the University of London Computer Centre Group. Order, treatment, and interaction effects for periods A and B were determined by the method of Hills & Armitage (1979), specific comparisons being made with paired and unpaired Student's *t*-tests. Only specific comparisons were made for the period of combined treatment as it was not randomized with the other two treatments.

Results

Patients

Thirty-six patients entered the trial (21 males, 15 females aged 32–65). Five were withdrawn before completion of the first treatment period. Of these four were unable to attend regularly and one became hypotensive on the first dose of prazosin and was subsequently controlled on his original two drugs. Thus 31 patients are included in the analysis of the data for side-effects and blood pressure control. However eight patients are excluded from the comparative blood pressure analysis because side-effects were severe enough to necessitate withdrawal from one or more of the active treatment periods.

Compliance

The compliance of the 23 patients included in the comparative blood pressure analysis was good, in all cases less than 5% of the tablets being returned. Compliance in other patients was poorer during those periods where side-effects were experienced.

Blood pressure

The results for patients in Group 1 (hydralazine then prazosin) and Group 2 (prazosin then hydralazine) are shown separately in Figures 2 and 3. Blood pressure fell in both groups of patients, 1 mg of prazosin being equivalent to 12.5 mg of hydralazine. Increasing the dose of prazosin from 4 to 8 mg twice daily and

Table 1 Doses prescribed of hydralazine and prazosin during separate use (active treatment A and B) and combined use (active treatment C)

Week of active treatment period	Hydralazine treatment (mg twice daily)	Prazosin treatment (mg twice daily)	Combined treatment	
			Hydralazine (mg twice daily)	Prazosin (mg twice daily)
1	12.5	0.5	25	1
2	12.5	1	25	1
3–4	25	2	25	2
5–6	50	4	50	2
7–8	100	8	50	4

Figure 2 Group 1: Systolic and diastolic blood pressure lying and systolic blood pressure standing 0- - 0 for Group 1 at each clinic visit.

Figure 3 Group 2: Systolic and diastolic blood pressure lying and systolic blood pressure standing 0- - 0 for Group 2 at each clinic visit.

hydralazine from 50 to 100 mg twice daily did not lead to a consistent further reduction in blood pressure because some patients developed an increase in blood pressure during therapy with the final dose of each therapy. Systolic blood pressure showed a postural fall but diastolic did not. There was no evidence of an order effect but analysis revealed a significant treatment order interaction with regard to the first 6 weeks of prazosin therapy. The hypotensive efficacy of prazosin, when determined by change from pre-treatment values (week 10 for Group 1 and week 0 for Group 2), being influenced by whether prazosin therapy was given for active treatment A or B (Table 2). This was related to the blood pressure of Group 1 which did not return to baseline values after the 2 week washout period following cessation of hydralazine therapy (Table 2). The blood pressure of group 2 returned to baseline after cessation of the prazosin period, therefore hydralazine treatment was not associated with a treatment order interaction.

The effect of prazosin and hydralazine in combination on blood pressure was greater than when either drug was used alone (Figure 4) and this resulted in more patients having their blood pressure controlled during the combined treatment period (Table 3). There was no difference in the response to hydralazine of either fast or slow acetylators.

Heart rate and weight

There was no significant change in heart rate or weight during treatment with hydralazine but treatment with prazosin was associated with a decrease in heart rate and an increase in weight. At maximum doses of hydralazine the patients' heart rate was significantly higher and weight significantly lower than at maximum doses of prazosin (Table 4). During combined treatment heart rate did not alter significantly but weight was increased.

Symptoms

Six patients completed each phase of the trial without symptoms. Twenty-five of the 31 patients who entered the trial developed symptoms. Four patients had symptoms on both hydralazine and prazosin preventing completion of the treatment periods of both drugs. Of these only two would continue with combined treatment during which their symptoms returned.

Four other patients had symptoms on prazosin and would not continue with that drug; however they completed the period of hydralazine therapy, and two continued to combined treatment during which the symptoms returned. The other 17 patients experienced mild symptoms during the study but were able to complete the treatment periods.

Table 2 Change (from week 0 for active treatment A and week 10 for active treatment B) in calculated mean arterial pressure (mm Hg) during and 2 weeks following hydralazine and prazosin therapy (active treatment A, first wash out period and active treatment B).

Treatment week	Prazosin				Hydralazine				Placebo First wash out period
	2	4	6	8	2	4	6	8	
Group 1									
Hydralazine then prazosin	-3	-0	-7	-13	-9	-12	-15	-19	-10
Group 2									
Prazosin then hydralazine	-16	-13	-17	-14	-11	-14	-18	-17	-3
Significance of difference between Group 1 and 2	0.01	0.01	0.05	NS	NS	NS	NS	NS	0.05

Table 5 shows the symptoms reported by the patients during the trial. It will be seen that the number and type of symptoms was similar during treatment with hydralazine and prazosin and that combined therapy did not increase the number of reports.

Discussion

Oral vasodilators are recommended for the treatment of hypertension if the combination of β -adrenoceptor blocker and diuretic fails to produce a satisfactory reduction of blood pressure (Anonymous, 1979). Such triple therapy is very effective at lowering blood pressure (Aronow *et al.*, 1978), and both hydralazine

and prazosin have been shown to further decrease the diastolic blood pressure when so used (Marshall *et al.*, 1977; Wilcox & Mitchell, 1977).

In this trial hydralazine and prazosin lowered the blood pressure of patients receiving therapy with a thiazide and a β -adrenoceptor blocker. Prazosin, 1 mg, was equivalent to 12.5 mg of hydralazine, a similar ratio to that reported in the Veterans Administration Study Group Report (1981).

Both drugs were effective at decreasing the blood pressure at very low doses, 12.5 mg of hydralazine and 0.5 mg of prazosin twice a day. Doubling the dose of each drug at the top of its dose response curve, from 100 to 200 mg a day of hydralazine and 8 to 16 mg a day of prazosin, produced no consistent increase in therapeutic effect. Indeed in four patients on

Figure 4 Comparison of calculated mean arterial pressure (mm Hg $\pm$ s.e. mean) at two doses of hydralazine (H) and prazosin (P) used separately and during combined treatment (Com) with half the dose of each drug. (Between treatment P values are shown.)

Table 3 The number of patients in whom lying diastolic blood pressure was controlled below 90 mm Hg at each trial visit during active treatment periods A, B, and C.

<i>The numbers of patients whose diastolic blood pressure was controlled below 90 mm Hg</i>			
Week	Hydralazine	Prazosin	Combined
2	0	1	3
4	1	1	11
6	3	4	14
8	6	5	11

hydralazine and five on prazosin there was a rise in diastolic blood pressure of over 5 mm Hg. There were no important differences between the blood pressure lowering effects of hydralazine and prazosin and their side-effects were similar. These findings disagree with those of Kincaid Smith *et al.* (1976) who reported that prazosin produced better blood pressure control and fewer side-effects than hydralazine.

Neither of the vasodilators used in this study caused an increase in heart rate, probably the result of the co-prescription of a β -adrenoceptor blocker. Indeed heart rate decreased during prazosin treatment.

The findings of the Hypertension Detection and Follow Up Program (1979a, b) have led to the recommendation that diastolic blood pressure of patients with hypertension be reduced to below 90 mm Hg. In our study triple therapy including either prazosin or hydralazine alone proved disappointing with only approximately 25% of patients achieving adequate blood pressure control. These findings are similar to those of the cross sectional survey of Ramsay (1980) who found that only 20% of such patients had a diastolic blood pressure below 96 mm Hg on triple therapy after 6 months treatment. A fourth drug is therefore necessary for the remaining patients. In our trial, the combination of hydralazine and prazosin

Table 5 The reported symptoms of patients during hydralazine, prazosin and combined treatment (one patient may have reported more than one symptom)

(a) Symptoms of patients refusing to continue to combined treatment period		
	Prazosin	Hydralazine
Dizziness	3	3
Nausea	2	2
Headaches	0	1
'Unwell'	1	0
Dry mouth	1	0
Total	7	6

(b) Symptoms reported by patients entering combined treatment period			
	Prazosin	Hydralazine	Combined
Dizziness	6	5	7
Headaches	4	2	2
Tiredness	2	4	0
Nausea	2	0	0
Depression	1	2	0
Dry mouth	2	0	0
Diarrhoea	0	1	0
Breathlessness	0	1	1
Chest pain	0	0	1
Bloated	0	1	0
Irritable	0	1	0
Total	17	17	11

was more effective than either drug alone at reducing and controlling blood pressure (Figure 4 and Table 3). The effect of the two drugs was additive, the combination at low dose producing a greater fall in blood pressure than either hydralazine or prazosin used alone at their maximum dose.

This study shows that the combination of hydralazine and prazosin is as well tolerated as either drug alone and that a greater decrease in blood pressure is

Table 4 Blood pressure, heart rate and weight at the end of treatment with hydralazine, prazosin and the combination (mean $\pm$ s.e. mean)

			<i>Maximum dose of</i>			
Variable			<i>Trial start</i>	<i>Hydralazine</i>	<i>Prazosin</i>	<i>Combined treatment</i>
Blood pressure (mm Hg)	lying	Systolic	177.9 $\pm$ 4.3	153.7 $\pm$ 3.7**	152.6 $\pm$ 4.6**	141.5 $\pm$ 4.1**
		Diastolic	114.4 $\pm$ 2.5	97.6 $\pm$ 2.1**	99.6 $\pm$ 3.2**	90.6 $\pm$ 2.8**
	standing	Systolic	166.9 $\pm$ 4.0	148.1 $\pm$ 3.7**	142.7 $\pm$ 4.5**	132.1 $\pm$ 4.8**
		Diastolic	116.0 $\pm$ 2.4	99.8 $\pm$ 2.5**	101.2 $\pm$ 3.5**	92.4 $\pm$ 3.4
Heart rate (beats min)	lying		72.4 $\pm$ 1.8	72.9 $\pm$ 1.7 [†]	67.5 $\pm$ 1.7**	70.8 $\pm$ 1.7
	standing		75.6 $\pm$ 1.9	76.0 $\pm$ 1.7	73.2 $\pm$ 2.1	74.5 $\pm$ 1.8
Weight (kg)			74.3 $\pm$ 2.4	75.3 $\pm$ 2.4 [†]	76.1 $\pm$ 2.4**	76.4 $\pm$ 2.3**

Significant difference from start of treatment, ** $P < 0.01$

Significant difference between maximum dose hydralazine and prazosin $\div P < 0.05$

achieved using the drugs together. These findings are in agreement with the uncontrolled report of Russell *et al.* (1980).

Crossover trials are often criticized because of the possible introduction of order or carry over effects. No order effects were detected for the first two treatment periods. Within each of these periods, dose and time were indistinguishable variables, as would occur in clinical practice.

The treatment/order interaction for prazosin was unexpected. On known pharmacokinetics a 2 week washout period after hydralazine therapy should have been adequate, although the duration of a drug's therapeutic effect may be in excess of its pharmacokinetic half-life. In the case of hydralazine this may be due to the drug binding to the vessel walls.

The period of combined treatment was not randomized with the other treatment periods because in

clinical practice combined treatment would follow the failure of single vasodilator treatment.

The combination of hydralazine and prazosin may be recommended for patients not controlled by triple therapy. Indeed it would appear beneficial to use the combination of both drugs before the maximum recommended dose of either is reached.

We would like to thank Professor J.M. Ledingham, Professor D. Vere and Dr M. Chaput De Santoing for helpful advice and constructive criticism as well as the statisticians consulted on appropriate analytical methods for such a complex trial, Steve Evans, Jack Grimshaw and Graham Kimber, who in addition to recommending the use of the 'BMDP analysis of variation with repeated measurements' (which did help the understanding of the trial) stated 'this is why statisticians prefer simple parallel study designs'.

Special thanks are due to the many patients who attended the clinic every 2 weeks for 6 months.

References

- ANONYMOUS. (1979). When to use oral vasodilators for hypertension. *Drug and Therapeutics Bulletin*, **17**, No. 15.
- ARONOW, W.S., VAN HERICK, R., GREENFIELD, R., ALIMADADIAN, H., BURWELL, D. & MANN, W. (1978). Effect of timolol plus hydrochlorothiazide plus hydralazine on essential hypertension. *Circulation*, **57**, 1017-1021.
- BANNON, L.T., BEEVERS, D.G. & WRIGHT, N. (1980). ABC of blood pressure reduction, drug treatment. *Br. med. J.*, **281**, 982-984.
- HILLS, M. & ARMITAGE, P. (1979). The two-period cross over trial. *Br. J. clin. Pharmacol.*, **8**, 7-20.
- HYPERTENSION AND DETECTION FOLLOW-UP PROGRAM COOPERATIVE GROUP. (1979a). Five year findings of the Hypertension Detection and Follow-up Program. Reduction in mortality of persons with high blood pressure, including mild hypertension. *J. Am. med. Ass.*, **242**, Suppl. 23, 2562-2571.
- HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP. (1979b). Five years findings of the Hypertension Detection and Follow-up Program. Mortality, race-sex and age. *J. Am. med. Ass.*, **242**, Suppl. 23, 2572-2577.
- JOINT NATIONAL COMMITTEE ON DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE (1980). The 1980 Report of the Joint National Committee on detection evaluation and treatment of high blood pressure. *Arch. int. Med.*, **140**, 1280-1285.
- KINCAID-SMITH, P., HUA, A.S.P., MYERS, J.B., MACDONALD, I. & FANG, P. (1976). Prazosin and hydralazine in the treatment of hypertension. *Clin. Sci. mol. Med.*, **51**, Suppl 13, 617S-619S.
- MARSHALL, A.J., BARRITT, D.W., POCKOCK, J. & HEATON, S.T. (1977). Evaluation of beta blockade, bendrofluazide, and prazosin in severe hypertension. *Lancet*, **i**, 271-274.
- RAMSAY, L.E. (1980). Diuretic and beta-blocker in hypertension—then what? *J. Roy. Coll. Phys. Lond.*, **14**, 249-253.
- RUSSELL, G.I., SWART, S., BING, R.F., THURSTON, H. & SWALES, J.D. (1980). Combined prazosin and hydralazine in resistant hypertension. *Lancet*, **i**, 543.
- VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS (1981). Comparison of prazosin and hydralazine in patients receiving hydrochlorothiazide. A randomized, double-blind clinical trial. *Circulation*, **64**, 772-779.
- WILCOX, R.G. & MITCHELL, J.R.A. (1977). Contribution of atenolol, bendrofluazide, and hydralazine to management of severe hypertension. *Br. med. J.*, **2**, 547-550.

(Received March 3, 1983,
accepted July 7, 1983)