HYDRALLAZINE OR PHENTOLAMINE AS ADJUNCTS TO β -ADRENOCEPTOR BLOCKADE/THIAZIDE THERAPY IN HYPERTENSION

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- 1 Ten patients not maximally controlled on an oxprenolol/cyclopenthiiazide regimen for moderately severe hypertension were treated in a double blind crossover trial with either hydrallazine (75-150 mg/day) or phentolamine (60-120 mg/day) or placebo in addition to their other therapy.
- 2 Additional phentolamine therapy did not lower blood pressure significantly when compared with placebo.
- 3 Additional hydrallazine (75-150 mg/day) produced an approximate 10 mm, Hg fall in diastolic blood pressure, but no significant fall in systolic blood pressure.
- 4 Pulse rates did not alter with the addition of hydrallazine or phentolamine.
- 5 In patients who fail to attain optimal blood pressure response to β -adrenoceptor blocking drugs it is suggested that the addition of hydrallazine is a useful measure.

Introduction

In the last 5-10 years β -adrenergic receptor blocking drugs have gained a useful role in the treatment of hypertension. Their possible protective role (Wilhelmsson, Vedin, Wilhelmsen, Tibblin & Werko, 1974; Lambert, 1974; A Multicentre International Study, 1975) in prevention of ischaemic heart disease is an additional attraction.

Used singly or, more effectively, in combination with thiazide diuretics, β -adrenoceptor blockers have been shown to reduce blood pressure in the majority of patients. However, there is a small proportion of patients who do not respond maximally even with large doses of β -adrenoceptor blockers.

Oxprenolol hydrochloride, a non-selective β -adrenergic blocking agent with intrinsic sympathomimetic activity, in combination with diuretic therapy has been reported to lower blood pressure to acceptable levels in 65% (Geisling & Regoli, 1973) to 88% (Forrest, 1973) of patients. It is also our experience that with oxprenolol-diuretic regimen, in a small proportion of patients diastolic blood pressure fails to fall below levels which we have arbitrarily set at 100 mm.Hg.

Majid, Meeran, Benaim, Sharma & Taylor (1974) and Taylor (1974) have recently reported in open studies that the β -adrenergic receptor blocking drug, phentolamine, when taken orally in combination with oxprenolol and thiazide, resulted in significant lowering of blood pressure without postural effects or exercise-induced hypo-

tension. A hypotensive response to oral phentolamine alone (Galloway, Webster & Petrie, 1974) or in combination with β -adrenoceptor blockers (Johnson, Labrooy & Munro-Faure, 1974), however, has not been confirmed.

Hydrallazine, a peripheral vasodilator, has been shown to be a useful agent in combination with a β -adrenoceptor blocker-diuretic regimen (Aenishanslin, Pestalozzi-Kerpel, Duback, Imhof & Turri, 1972; Zacest, Gilmore & Koch-Weser, 1972).

We decided to compare the effects of phentolamine with hydrallazine in a double-blind within patient crossover trial against placebo in those patients with diastolic blood pressures in the range 100-130 mm Hg currently attending our out-patient clinic.

Methods

Ten out-patients (Table 1) who were taking at least 480 mg/day oxprenolol together with cyclopenthiiazide K (two tablets daily) for not less than 8 weeks and who had persisting diastolic pressures of 100 mm Hg or above were selected for additional therapy with either phentolamine or hydrallazine. Informed consent was obtained for the study and each patient was randomly allocated according to sex and age to treatment with

Table 1 Clinical data before addition of hydralazine or phentolamine

Patient	Age (years)	Sex	Diagnosis	Hypertensive encephalopathy	Fundoscopy	Serum creatinine ($\mu\text{mol/l}$)	Cardiomegaly X-ray	Cardiomegaly ECG	Dose oxprenolol (mg)	Duration oxprenolol (months)
1	42	M	Essential	-	I	78	+	L VH	1280	4
2	58	M	Essential	+	IV	378	+	L VH	480	3
3	57	F	Unilateral CPN	-	II	89	-	L VH + strain	480	5
4	46	M	Essential	-	II	111	-	Antero lateral ischaemia	800	4
5	46	F	Essential	-	I	78	-	-	800	18
6	44	M	Essential	-	II	89	-	Infero lateral ischaemia	1280	6
7	46	M	Radiation nephritis	-	I	116	+	L VH	800	7
8	48	M	Angina Essential Angina Previous myocardial infarct	-	II	102	+	Old MI	1120	9
9	34	F	CPN	-	II	590	-	-	960	3
10	50	M	Essential	-	I	86	-	-	640	5

Essential = idiopathic hypertension; CPN = chronic pyelonephritis; L VH left ventricular hypertrophy; MI myocardial infarct

placebo, hydralazine (25 mg three times daily) or phentolamine (20 mg three times daily) for 2 weeks (Figure 1). At the end of this period the dosage of hydralazine, or phentolamine, was doubled for a further 2 weeks. Thereafter placebo was administered for a 1 week 'wash out' period and patients were reallocated to a different treatment regime for 4 weeks, again followed by 1 week 'wash out' and subsequent reallocation for 4 weeks on the final treatment regime.

All blood pressures were recorded at the same time of day (a.m.) by the same specially trained clinic assistant, using the London School of Hygiene and Tropical Medicine sphygmomanometer.

All patients were supervised at weekly intervals when blood pressure was measured after 3 min supine rest, after 1 min standing and also standing after 2 min exercise using a modified Master Two-Step Test apparatus.

Two blood pressure readings in each position were measured, and the lower one recorded. Pulse rates were recorded after supine rest and after exercise at the time of blood pressure recordings.

Diastolic blood pressure was taken at the disappearance of the arterial sounds (Korotkoff V). At the end of each treatment period a self-administered questionnaire, on the lines suggested by Bulpitt & Dollery (1973) was completed for elucidation of side effects, and a 24 h creatinine clearance measured, in addition to ECG, chest X-ray, biochemistry, haematology and anti-nuclear factor estimations.

A weekly supply of tablets was dispensed, and at the end of each week a count of remaining tablets was made.

Statistical evaluations were made using Student's *t*-test.

Results

Blood pressure recordings prior to and during the trial are shown in Table 2.

Mean $\pm$ s.d. blood pressures (mm Hg) for the whole group prior to the addition of therapy were as follows: supine $173.9 \pm 22.4/118.3 \pm 18.18$, erect $167.6 \pm 22.8/119.4 \pm 19.34$, post exercise $166.9 \pm 21.9/110.6 \pm 18.0$. The pre-treatment systolic blood pressures and the pre-treatment supine diastolic pressure were significantly higher than the respective recordings in the first 2 weeks of placebo treatment: supine $156.7 \pm 26.7/107.2 \pm 16.9$, erect $149.3 \pm 24.2/110.9 \pm 18.9$, post-exercise $152.8 \pm 11.9/104 \pm 10.6$ mm Hg, ($P < 0.05$); as a result comparisons of hydralazine and phentolamine were made only against respective recordings in placebo periods.

Figure 1 Trial design.

The mean $\pm$ s.d. blood pressure recordings in treatment weeks 1 and 2, and in weeks 3 and 4, are shown in Figures 2 and 3 respectively.

Systolic pressures during additional treatment with hydrallazine or phentolamine were not significantly different from placebo whether supine, erect or after exercise in weeks 1 and 2 or weeks 3 and 4 of therapy ($P > 0.05$).

Diastolic blood pressures, however, were significantly lower than placebo during additional treatment with hydrallazine (75 mg/day) in the erect (100.1 ± 17.4 mm Hg) and post-exercise (95.1 ± 16.3 mm Hg) positions in weeks 1 and 2 ($P < 0.05$). Additional therapy with phentolamine did not alter blood pressure significantly ($P > 0.05$).

Pulse rates during β -adrenoceptor blockers and thiazide therapy only were 76.7 ± 9.7 beats/min, supine, and 83.8 ± 13.3 beats/min, post-exercise. No significant alteration in pulse rates in weeks 3 and 4 of therapy occurred with additional placebo (72.9 ± 9.4 beats/min, supine, and 87.0 ± 13.4 beats/min, post-exercise) and phentolamine (72.1 ± 8 beats/min, supine, and 81.8 ± 12.6 beats/min, post-exercise) and hydrallazine (76.7 ± 10.4 beats/min, supine, and 89.6 ± 15.8 beats/min, post-exercise) ($P > 0.05$).

All patients appeared to fully comply with tablet taking since at the end of each treatment period the number of tablets ingested agreed with the number prescribed, in every patient.

Mean $\pm$ s.d. creatinine clearance (70.2 ± 44.28 ml min⁻¹ 1.73 m⁻²) for the whole group of patients did not significantly differ from placebo during treatment with either hydrallazine or phentolamine.

No changes in biochemical, haematological or antinuclear factor status occurred with treatment. ECG and chest X-ray remained unchanged.

The only side effects attributable to treatment were that one patient reported mild diarrhoea

during additional phentolamine treatment, and one patient had transient headache after introduction of hydrallazine.

Discussion

Pickering (1974) has stressed that the risk of developing cardio-vascular complications is greater the higher the blood pressure. The effect of therapy on this risk has been examined in the Veterans Administration studies, where sub-optimal control or partial reduction of blood pressure, reduces the frequency of cerebral complications (Taguchi & Freis, 1974), while a far greater reduction of complications ensues when blood pressure is maximally controlled (Veterans Administration Study, 1967). It would thus appear that there is a need for maximal reduction in blood pressure in the hypertensive patient.

We have demonstrated that under trial conditions the addition of low dosage hydrallazine is effective in reducing diastolic blood pressure by about 10 mm Hg when compared with placebo, in a group of patients already under β -adrenoceptor blockade and diuretic therapy. This confirms the results of other studies where hydrallazine has been found to be a useful addition to beta blocker-diuretic therapy in hypertension (Aenishanslin *et al.*, 1972; Zacest *et al.*, 1972). The dosage of hydrallazine chosen in this study (25 mg three times daily) is unlikely to lead to the lupus erythematosus syndrome, since there is little correlation with this syndrome in patients receiving less than 300 mg/day (Alarcon-Segovia, Wakim, Worthington, 1967). Theoretically also the combination of β -adrenoceptor blocking drugs and vasodilators can increase the effect on blood pressure and minimise the prescription of vasodilators alone in increased dosage.

Table 2 Mean $\pm$ s.d. blood pressure (mm Hg) during the trial ($n = 10$)

Treatment		Weeks 1 and 2			Weeks 3 and 4		
		Supine (mm Hg)	Erect (mm Hg)	Post-exercise (mm Hg)	Supine (mm Hg)	Erect (mm Hg)	Post-exercise (mm Hg)
β -adrenoceptor blocking drug + thiazide	S	173.9 $\pm$ 22.4	167.6 $\pm$ 22.8	166.9 $\pm$ 21.9	—	—	—
	D	118.3 $\pm$ 18.2	119.4 $\pm$ 19.3	110.6 $\pm$ 18.0	—	—	—
Additional placebo	S	156.7 $\pm$ 26.7	149.3 $\pm$ 24.2	152.8 $\pm$ 11.9	155.4 $\pm$ 33.0	146.7 $\pm$ 34.9	147.6 $\pm$ 13.2
	D	107.2 $\pm$ 16.9	110.9 $\pm$ 18.91	104.0 $\pm$ 10.6	105.7 $\pm$ 18.1	106.1 $\pm$ 17.2	99.5 $\pm$ 18.3
Additional hydralazine	S	151.9 $\pm$ 30.2	145.2 $\pm$ 32.5	150.1 $\pm$ 22.6	146.3 $\pm$ 28.4	144.0 $\pm$ 28.3	149.0 $\pm$ 18.3
	D	99.4 $\pm$ 18.8	100.1 $\pm$ 17.4	95.1 $\pm$ 16.3	95.8 $\pm$ 18.2	100.3 $\pm$ 17.1	92.9 $\pm$ 20.5
Additional phentolamine	S	164.0 $\pm$ 66.1	147.1 $\pm$ 19.4	155.9 $\pm$ 17.7	153.4 $\pm$ 23.1	148.2 $\pm$ 27.2	151.3 $\pm$ 23.8
	D	104.6 $\pm$ 13.9	106.7 $\pm$ 11.1	100.8 $\pm$ 13.6	101.9 $\pm$ 16.0	105.3 $\pm$ 15.0	97.8 $\pm$ 14.9

S systolic blood pressure; D diastolic blood pressure

Figure 2 Blood pressure response to placebo (□), hydralazine (75 mg/day, ■) or phentolamine (60 mg/day, ▨), weeks 1 and 2. * significantly lower than placebo, $P < 0.05$. **Figure 3** Blood pressure response to placebo (□), hydralazine (150 mg/day, ■) or phentolamine (120 mg/day, ▨), weeks 3 and 4. * significantly lower than placebo, $P < 0.05$.

Aenishanslin *et al.* (1972) have reported that oxprenolol counteracts the rise in heart rate caused by vasodilatation with hydralazine. Our findings confirm that the addition of hydralazine to patients treated with oxprenolol does not result in a rise in heart rate, while the blood pressure lowering effect is maintained.

We cannot fully explain why a significant further reduction in diastolic blood pressure was not obtained with doubling the dosage of hydralazine from 75 mg/day to 150 mg/day. However, no attempt was made to measure the acetylator status or plasma concentrations of hydralazine in our patients. It has been shown that, when given similar doses of hydralazine, slow acetylators and patients with impaired renal excretion of hydralazine have a greater blood pressure reduction than fast acetylators or those with normal renal function (Zacest & Koch-Weser, 1972).

In contrast to the findings of Majid *et al.* (1974) and Taylor (1974), we were unable to demonstrate any hypotensive effect of combined phentolamine and β -adrenoceptor blocker therapy and this confirms the experience of others (Johnson *et al.*, 1974). The maximal cardiovascular response to phentolamine occurs between 1 and 2 h after ingestion (Frei, Imhof & Dubach, 1974) and blood pressures were recorded within this time period throughout the study and it would seem that the lack of response cannot be explained wholly on the basis of missing peak action of the drug. From this study we have, however, experience of one patient who did respond to greatly increased dosage (420 mg/day) and frequency of phentolamine administration in combination with β -adrenoceptor blockade.

In conclusion, it would seem that in patients not maximally controlled with a β -adrenoceptor blocker-diuretic regimen, the addition of small doses of hydralazine is a useful therapeutic measure.

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