mittant 2:1 heart block. Isolated ventricular ectopic beats were observed in four patients (three in group 1), any symptomatic bradycardia occurred in three patients (all in group 2). No fatalities occurred during the study, although one patient extended the site of infarction (as gauged by progressive electrocardiographic changes) and died 48 h after completion of the study. No change in haematology, urea, electrolytes or blood sugar was seen following tocainide.

Nausea and vomiting occurred in six out of eleven patients (three in each group), two of whom had not received morphine. The onset of three coincided in all six patients with the times of maximal plasma concentration. Side effects previously reported to occur frequently, such as tremor and hot and cold sensations or paraesthesia, occurred in only two patients and were mild. The six patients who experienced nausea and vomiting received cyclizine with no benefit; the three patients who developed bradycardia received atropine. Other medication was morphine (six patients) and oral diazepam (all patients).

Therapeutic levels of tocainide are uncertain. Winkle *et al.* (1976) found a 70% reduction in chronic ventricular premature contractions in 11 out of 15 patients with serum levels above 6.0 µg/ml. Woosley *et al.* (1977) showed the minimum effective plasma concentration for suppression of more than 75% of ventricular ectopic beats in 8 out of 12 patients to be between 3.5 and 7 µg/ml. In our study a level of 6 µg/ml was obtained within 15 min and persisted for 8 h in group 2, although levels in group 1 fell slightly below this value around 2 h. Since the initial peak was approximately twice the therapeutic level (and is in good agreement with values obtained previously by

Harrison *et al.*, 1978), the time of infusion and amount delivered could be reasonably halved.

Danillo (1979) suggested that side effects do not correlate well with plasma concentration, but previous studies (Harrison *et al.*, 1978; Woosley *et al.*, 1977) show a good association as was seen in our study. The strong relationship of unwanted side effects to plasma concentration provides an additional argument for a decrease in the initial dosage given.

Nausea and vomiting have not been prominent side effects previously noted. It is well known that myocardial infarction can produce vomiting, especially if opiate analgesia is used, but it is noted that two patients who had profound nausea and vomiting did not have opiate medication and appeared clinically stable before the tocainide was given. Predictably those patients who vomited had lower plasma levels, and this may limit the usefulness of oral tocainide in this acute state.

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P.P. SUTTON

*Department of Pharmacology and Therapeutics,
Ninewells Hospital, Dundee*

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Present address:

Royal Free Hospital School of Medicine, Pond Street,
Hampstead, London NW3 2QG.

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DOUBLE-BLIND CROSS-OVER COMPARISON OF HYDRALAZINE AND PRAZOSIN IN HYPERTENSIVE SUBJECTS ON A β -ADRENOCEPTOR BLOCKING AGENT (ATENOLOL)

Vasodilator therapy has found increasing use in the treatment of hypertension usually in patients in whom inadequate blood pressure control has been

achieved using either a β -adrenoceptor blocking agent or a combination of β -adrenoceptor blocking agent and thiazide diuretic (Gilmore, Weil &

Chidsey, 1970; Zacest, Gilmore & Koch-Weser, 1972; Winchester, Ward, McKillop & Kennedy, 1976). Hydralazine and prazosin are the two vasodilators used almost exclusively. They have different pharmacological properties and modes of action yet, although used almost interchangeably, there have been no direct comparisons made between them when used chronically. However it is a common clinical finding that while both are powerful anti-hypertensive agents, some patients respond to one while failing to do so to the other. We have, therefore, compared these two agents since their use clinically is now widespread.

Twenty-five patients were admitted to the trial and five dropped out for reasons unrelated to their drug treatment. Each subject made ten visits in all to the clinic.

All patients except one were already on treatment and except for this one individual all had already been attending the hypertension clinic for at least 1 year (and in most cases for much longer). Previous treatment in the majority included a β -adrenoceptor blocking agent but not hydralazine or prazosin.

Blood pressures were taken after 5 min in the supine position and then after 1 min standing erect. A standard mercury sphygmomanometer was used for these measurements. The first two visits were a run in period on existing therapy. Blood pressures and heart rates were determined and if on both occasions either systolic blood pressure exceeded 160 mm Hg or diastolic exceeded 100 mm Hg they proceeded to the trial proper (Phase V diastolic pressure was used).

After the run in period they were randomized in a double-blind manner to either the hydralazine or the prazosin groups. Their previous therapy was then stopped and they were started on atenolol 100 mg daily together with placebo prazosin and placebo hydralazine. At the end of 3 weeks one agent became active using identical tablets to the placebo. Each patient attended at 3 week intervals and the dose increased if the criteria used for entry into the trial were still exceeded, i.e., at least one systolic pressure reading greater than 160 mm Hg or one diastolic level greater than 100 mm Hg. After three such visits the

subjects reverted to atenolol and placebos for 3 weeks and then the process was repeated with the other agent active. Eleven patients received active prazosin in the first stage and nine hydralazine. There were eleven males and nine females and the average age was 50 ± 8.5 years (mean $\pm$ s.d.). Hydralazine was increased from 75 mg to 150 mg to 225 mg as necessary according to the blood pressure control achieved, and prazosin from 3 mg to 6 mg to 9 mg all in divided doses. The doses of the two drugs were thought to be equivalent (Hua, Myers & Kincaid-Smith, 1978). Statistical analysis was carried out using paired and unpaired Student's *t*-tests.

The results are shown in Table 1. When compared to atenolol alone neither vasodilator significantly reduced the supine systolic blood pressure and hydralazine had no effect on diastolic supine blood pressure either although trends towards such reductions were present. Prazosin, when added, did reduce supine diastolic blood pressure compared to that with atenolol alone ($P < 0.05$). However when the values for supine diastolic pressure on either atenolol and hydralazine and atenolol and prazosin were compared directly no significant difference emerged between them although the mean value on prazosin was lower than that seen with hydralazine. Both vasodilators, as might be expected, were more powerful in reducing erect blood pressure and significant reductions in systolic and diastolic pressures were achieved by both agents when compared to atenolol alone (all $P < 0.01$). Atenolol itself significantly lowered erect and supine blood pressures compared to the run in period values ($P < 0.05$).

Seven patients required 1 mg three times daily, eight 2 mg three times daily and one 3 mg three times daily of prazosin to achieve blood pressure of less than 160/100 mm Hg both erect and supine. Four subjects failed to achieve this target. Similarly seven patients required 25 mg three times daily, five 50 mg three times daily and one 75 mg three times daily of hydralazine to lower blood pressure below 160/100 mm Hg. Seven patients on hydralazine failed to achieve this level of blood pressure. In no patient, however, did the combinations of atenolol and either

Table 1 Mean $\pm$ s.d. blood pressure (mm Hg) during the study

	Supine BP		Erect BP	
	Systolic	Diastolic	Systolic	Diastolic
Run-in period	179 $\pm$ 25	111 $\pm$ 11	168 $\pm$ 28	112 $\pm$ 12
First atenolol period	164 $\pm$ 23	102 $\pm$ 11	162 $\pm$ 24	104 $\pm$ 10
Second atenolol period	160 $\pm$ 37	98 $\pm$ 19	157 $\pm$ 37	103 $\pm$ 17
First hydralazine period	151 $\pm$ 30	95 $\pm$ 15	147 $\pm$ 25	96 $\pm$ 14
Second hydralazine period	154 $\pm$ 26	94 $\pm$ 14	149 $\pm$ 30	97 $\pm$ 13
Third hydralazine period	149 $\pm$ 20	96 $\pm$ 11	139 $\pm$ 22	93 $\pm$ 13
First prazosin period	154 $\pm$ 28	95 $\pm$ 15	149 $\pm$ 27	97 $\pm$ 15
Second prazosin period	155 $\pm$ 30	93 $\pm$ 11	152 $\pm$ 33	94 $\pm$ 12
Third prazosin period	151 $\pm$ 29	92 $\pm$ 12	140 $\pm$ 28	94 $\pm$ 13

vasodilator fail to achieve some reduction in run in blood pressure.

Atenolol significantly reduced the heart rate when introduced ($P < 0.01$). The addition of neither hydralazine nor prazosin had any further effect on heart rate, in particular, in the presence of atenolol neither agent caused tachycardia.

There was little to choose between the combinations of atenolol and hydralazine and atenolol and prazosin in this study. Prazosin did reduce supine diastolic blood pressure significantly whereas hydralazine did not when compared to atenolol alone. At the time of commencement of this trial (2 years ago) the dosage of the two drugs as chosen were considered to be equivalent although since that time larger doses of prazosin (up to 25 mg or more daily) have been widely used.

No attempt was made to determine the acetylcholinesterase status of our subjects (Zacest & Koch-Weser, 1972). This is of importance when considering the efficacy of hydralazine but we decided to omit it because it is a test not widely available and not likely to be carried out by the average practitioner when prescribing the drug. We have not included a diuretic in our protocol, as would be more usual with triple combination

therapy (i.e. β -adrenoceptor blocker + diuretic + vasodilator). We did this because it seemed to us that an increasing number of patients are being treated with β -adrenoceptor blockers and vasodilators alone. However this may mitigate against hydralazine which has possibly a greater tendency to cause sodium and water retention than does prazosin.

We conclude that under the conditions of this study both prazosin and hydralazine when combined with atenolol reduce erect systolic and diastolic blood pressures when compared to atenolol alone. In the supine position blood pressures were again lower but the only reduction to achieve statistical significance was the diastolic pressure in those treated with prazosin.

JOHN VANN JONES

Cardiac Department, John Radcliffe Hospital, Oxford OX3 9DU

JANICE M. STEINER

Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE

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