Prazosin and hydrallazine in the treatment of hypertension

PRISCILLA KINCAID-SMITH, A. S. P. HUA, J. B. MYERS, ILEENE MACDONALD AND P. FANG
Department of Nephrology and University Department of Medicine, The Royal Melbourne Hospital, Victoria, Australia

Summary
1. Two vasodilators, prazosin and hydrallazine, have been compared in three double-blind cross-over studies designed to test their effect when used in combination with a β-adrenoceptor-blocking agent and a thiazide.
2. Single doses of 3 mg of prazosin or 75 mg of hydrallazine were administered to patients whose blood pressures remained uncontrolled on a thiazide and a β-adrenoceptor-blocking agent. Both agents produced significant falls in systolic and diastolic blood pressure apparent at 1 h. The effects of prazosin persisted for 6-7 h and those of hydrallazine for 4-6 h. Tachycardia was more marked and more prolonged after hydrallazine and continued after the blood pressure had risen to base-line levels or above.
3. In 6 week and 12 week double-blind cross-over studies, mean falls in blood pressure were similar with prazosin and hydrallazine. Similar falls in the supine diastolic blood pressure were achieved with 1 mg of prazosin and 20 mg of hydrallazine, but for a given fall in supine diastolic blood pressure, prazosin produced a significantly lower standing diastolic blood pressure.
4. Severe side effects were more pronounced after hydrallazine, which necessitated withdrawal of seven patients, whereas only one patient on prazosin withdrew from the trial because of side effects.

Key words: hydrallazine, hypertension, vasodilators.

Introduction
Theoretically, therapeutic agents which cause peripheral vasodilatation should have an advantage over other hypotensive agents because they reverse the peripheral component of the haemodynamic abnormalities of hypertension.

The clinical value of vasodilators such as prazosin and hydrallazine lies mainly in combination with β-adrenoceptor-blocking agents and thiazide diuretics (Kincaid-Smith, Macdonald, Hua, Laver & Fang, 1975). Hydrallazine was virtually discarded from clinical use as a single agent because of side effects and its recent revival is due to its successful combination with β-adrenoceptor-blocking agents (Zacest, Gilmore & Koch-Weser, 1972). Three double-blind studies of the effects of prazosin and hydrallazine used in combination with thiazides and β-adrenoceptor-blocking agents are reported.

Methods
Three separate studies were carried out.

Twelve-weeks cross-over study
Twenty-two patients with hypertension were started on treatment with 40 mg of propranolol thrice daily and 0.5 g of chlorothiazide twice daily and followed for 2 weeks. In only eight of the twenty-two patients did the diastolic blood pressure remain above 100 mmHg on propranolol and chlorothiazide. These were allocated at random to a double-blind phase in which treatment with identical capsules containing 1 mg of prazosin or 25 mg of hydrallazine was given. Patients were followed for two 12 week periods in a cross-over study receiving either prazosin...
or hydralazine in a dose sufficient to lower the diastolic blood pressure below 95 mmHg.

**Six-weeks cross-over study**

Because of the small numbers qualifying for admission to the double-blind cross-over phase in the above study the trial design was altered. Twenty-four patients on either prazosin or hydralazine in combination with other hypotensive agents were observed for a 3 week control period. They were then allocated at random to a double-blind phase of treatment with identical capsules containing either 1 mg of prazosin or 25 mg of hydralazine. The dose was adjusted to achieve optimum control over two 6 week periods in a cross-over study. During each phase the patients completed a questionnaire about side effects.

**Single-dose cross-over study**

The duration of action of a single dose of prazosin and hydralazine on the blood pressure and heart rate was assessed in sixteen patients not adequately controlled by a combination of a thiazide and a \( \beta \)-adrenoceptor-blocking agent. Patients were observed over an 8 h period commencing at 08.00 hours after a single dose of 3 mg of prazosin or 75 mg of hydralazine in identical capsules. The study was double-blind and the order of administration of prazosin and hydralazine was randomized. The patients were out-patients and were ambulant in the hospital environment during the study. Each patient received identical capsules of prazosin on one occasion and hydralazine on the other.

A London School of Hygiene Sphygmomanometer with a standard cuff was used in all studies.

**Results**

**Twelve-weeks cross-over study**

There was a significant reduction in lying and standing blood pressure readings during administration of identical capsules of both hydralazine and prazosin.

With prazosin the mean fall in systolic blood pressure was \( 14.7 \pm 4.8 \text{ (SEM)} \) mmHg lying and \( 24.2 \pm 5.7 \) mmHg standing and with hydralazine the systolic blood pressure fell by \( 20.7 \pm 2.2 \) mmHg lying and \( 23.3 \pm 3.8 \) mmHg standing.

The diastolic blood pressure fell by \( 15.8 \pm 2.8 \) mmHg lying and \( 13.1 \pm 2.6 \) mmHg standing during the 12 weeks on prazosin, whereas it fell by \( 16.2 \pm 1.3 \) mmHg lying and \( 15.9 \pm 1.26 \) mmHg standing during hydralazine administration.

The criterion of control in this study was the blood pressure, thus the dose of identical capsules varied. Five patients required one capsule (1 mg of prazosin or 25 mg of hydralazine) three times a day. One patient required two capsules (2 mg of prazosin or 50 mg of hydralazine) three times a day and one patient required 1 capsule of hydralazine, but 3 capsules of prazosin three times a day before the blood pressure was 'controlled', that is before the diastolic blood pressure was consistently below 95 mmHg.

**Six-weeks cross-over study**

Of the twenty-four patients sixteen completed the study; eight were withdrawn because of side effects. Seven were unable to tolerate side effects while on hydralazine, but side effects necessitated withdrawal of only one patient on prazosin.

Both agents achieved control of the blood pressure, but for a given degree of control of the supine diastolic blood pressure prazosin produced a greater fall in standing diastolic blood pressure. The 'dose equivalence' between hydralazine and prazosin in this study, that is, the dose required to achieve a given fall in supine diastolic blood pressure, was 1 mg of prazosin: 20 mg of hydralazine.

**Single-dose cross-over study**

There was a prompt reduction in the systolic and diastolic blood pressure, both lying and standing, after oral administration of 3 mg of prazosin or 75 mg of hydralazine in sixteen patients already receiving a \( \beta \)-adrenoceptor-blocking agent and a thiazide.

Significant falls were apparent 1 h after administration of either agent and persisted for 4–6 h after hydralazine and 6–7 h after prazosin.

Table 1 shows details of the blood pressures at the different time-intervals in this study.

Significant lowering of the blood pressure was more prolonged after prazosin, whereas tachycardia was more prolonged after hydralazine. The tachycardia persisted for up to 8 h after hydralazine, whereas the significant hypotensive effect did not persist for longer than 6 h.
Vasodilators in hypertension

**Table 1. Changes in blood pressure and pulse rate after single doses of prazosin or hydrallazine in sixteen patients**

Mean results ± SEM are shown. Significance: *P = 0.05 or less; **P = 0.005 or less.

<table>
<thead>
<tr>
<th>Blood pressure (% change)</th>
<th>Supine</th>
<th>Erect</th>
<th>Heart rate (% change)</th>
<th>Supine</th>
<th>Erect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
</tr>
<tr>
<td>Prazosin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-10.6 ± 1.5**</td>
<td>-6.6 ± 1.4**</td>
<td>-13.9 ± 2.2**</td>
<td>-13.3 ± 2.0**</td>
<td>1.7 ± 3.0</td>
</tr>
<tr>
<td>2</td>
<td>-13.7 ± 3.5**</td>
<td>-10.9 ± 2.3**</td>
<td>-16.7 ± 4.3*</td>
<td>-17.9 ± 3.4**</td>
<td>-1.6 ± 3.0</td>
</tr>
<tr>
<td>4</td>
<td>-9.3 ± 2.0**</td>
<td>-10.7 ± 1.9**</td>
<td>-19.4 ± 3.7**</td>
<td>-17.7 ± 3.1**</td>
<td>3.7 ± 3.5</td>
</tr>
<tr>
<td>6</td>
<td>-10.5 ± 2.6**</td>
<td>-9.7 ± 2.3*</td>
<td>-11.5 ± 2.8*</td>
<td>-17.2 ± 1.7**</td>
<td>-0.1 ± 3.1</td>
</tr>
<tr>
<td>8</td>
<td>-0.04 ± 2.7</td>
<td>0.4 ± 2.3</td>
<td>0 ± 4.5</td>
<td>-4.3 ± 3.7</td>
<td>-2.8 ± 2.8</td>
</tr>
<tr>
<td>Hydrallazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-3.6 ± 2.8</td>
<td>-8.2 ± 2.8*</td>
<td>-4.8 ± 2.1*</td>
<td>-11.8 ± 2.3**</td>
<td>3.8 ± 3.9</td>
</tr>
<tr>
<td>2</td>
<td>-7.9 ± 2.1*</td>
<td>-8.2 ± 2.1*</td>
<td>-7.0 ± 1.8*</td>
<td>-12.7 ± 2.9**</td>
<td>6.1 ± 3.3</td>
</tr>
<tr>
<td>4</td>
<td>-6.4 ± 1.5**</td>
<td>-13.9 ± 2.1**</td>
<td>-7.4 ± 2.4*</td>
<td>-14.8 ± 2.6**</td>
<td>14.2 ± 4.4*</td>
</tr>
<tr>
<td>6</td>
<td>-2.11 ± 2.7</td>
<td>-4.3 ± 1.8*</td>
<td>-6.2 ± 3.1</td>
<td>-13.3 ± 3.0**</td>
<td>7.7 ± 3.6</td>
</tr>
<tr>
<td>8</td>
<td>4.1 ± 1.7*</td>
<td>-1.2 ± 2.8</td>
<td>-0.7 ± 2.7</td>
<td>-5.8 ± 3.3</td>
<td>5.3 ± 4.2</td>
</tr>
</tbody>
</table>

**Discussion**

Substances which lower blood pressure by causing dilatation of peripheral arterioles have undoubted value in the treatment of hypertension.

Prazosin and hydrallazine are likely to make a major clinical contribution in combination with a thiazide and a β-adrenoceptor-blocking agent. In this context both agents are effective and produce further significant falls in blood pressure over a 6 or 12 week period and for periods of 4-7 h after a single dose.

In these single-dose studies 3 mg of prazosin appeared to have some advantages over 75 mg of hydrallazine. Prazosin produced a greater and more prolonged fall in the blood pressure and thus was accompanied by less-prolonged tachycardia than hydrallazine. After hydrallazine, the tachycardia persisted after the effect on the blood pressure had disappeared. Indeed, 8 h after a dose of hydrallazine the blood pressure rose to a level significantly above the base line and significantly above the level recorded after prazosin.

Within the design of the studies reported prazosin was tolerated better than hydrallazine, the latter causing intolerable side effects in more patients.

**References**
