A NEW LOOK AT THE TREATMENT OF SEVERE HYPERTENSION

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SUMMARY

1. Although it is now easy to treat most patients with hypertension without producing troublesome side effects, a few patients remain refractory to conventional methods of treatment. These patients will progress to die of renal failure unless the blood pressure is controlled.

2. Thiazides potentiate the effect of other hypotensive agents and this potentiation is probably independent of their diuretic action. Diazoxide actually produces salt and water retention at the same time as marked decrease in the blood pressure. Spironolactone in a dose of 400 mg daily produced a highly significant reduction in blood pressure in an unselected group of patients with severe refractory hypertension.

3. β-Adrenergic blocking agents either alone or in combination with other drugs may be useful in the control of severe hypertension. An increasing effect on the blood pressure was demonstrated with doses between 1 and 2 g per day.

4. A new drug, prazosin hydrochloride, with properties somewhat similar to hydralazine but with few side effects promises to be useful in the control of severe refractory hypertension particularly in combination with β-adrenergic blocking drugs.

Key words: hypertension, thiazides, diazoxide, spironolactone, β-blockers, prazosin.

The effectiveness of hypotensive drugs was first clearly established in the most severe form of hypertension, namely malignant hypertension (Smirk, 1957; Harington, Kincaid-Smith & McMichael, 1959). Marked benefit resulted from only Rauwolfia alkaloids and poorly absorbed ganglion-blocking drugs (Smirk, 1957; Harington et al., 1959). It is disappointing that in spite of the large numbers of more effective hypotensive agents which have become available since 1959 there has been little further improvement in the survival of patients with severe and malignant hypertension (Breckenridge, Dollery & Parry, 1970).

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TABLE 1. Cause of renal failure in patients admitted to dialysis-transplantation at Royal Melbourne Hospital, 1963–72: 144 cadaveric renal transplants, pathological diagnosis known in 130 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>76</td>
<td>56.3</td>
</tr>
<tr>
<td>Atrophic pyelonephritis</td>
<td>25</td>
<td>18.5</td>
</tr>
<tr>
<td>Polycystic and medullary cystic</td>
<td>15</td>
<td>11.1</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Other (specified)</td>
<td>11</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>130</td>
<td></td>
</tr>
</tbody>
</table>

Uraemia is still the major cause of death in severe hypertension although uraemic deaths have decreased proportionally far more than cerebral or cardiovascular deaths. In our experience, however, patients rarely present with terminal renal failure due to malignant essential hypertension, thus only two of 130 patients admitted to our dialysis and transplantation programme since 1963 have had this diagnosis (Table 1). Over the same period no patient with

![Diagram](image_url)

**Fig. 1.** The course in a patient admitted with malignant hypertension, papilloedema and a diastolic blood pressure of 190 mmHg. Control of the blood pressure led to an initial deterioration of renal function, the serum creatinine rising from 4.6 to 9.2 mg/100 g over the first month. Thereafter renal function gradually improved in spite of rather unsatisfactory control of the lying BP (see Fig. 4).
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essential hypertension progressed to terminal renal failure. Most uraemic deaths in both treated and untreated patients occur in the first few months (Harington et al., 1959; Kincaid-Smith, McMichael & Murphy, 1958) and progression to terminal renal failure may be very rapid in patients with impaired renal function unless the blood pressure is adequately controlled. In such patients deterioration in renal function is usual during control of the blood pressure but should only be temporary in patients with essential hypertension (Fig. 1). After an initial deterioration renal function may steadily improve even with suboptimal control of the blood pressure (Fig. 1).

However, the drastic procedure of bilateral nephrectomy has been reported as a means of controlling hypertension in patients who were not in terminal renal failure (Mahony, Storey, Gibson, Stokes, Sheil & Stewart, 1972). Although we agree with Pohl & Thurston (1972) that these nine patients with essential hypertension in whom bilateral nephrectomy was performed (Mahony et al., 1972) had not had a thorough trial of hypotensive therapy, such patients are commonly admitted to units whose expertise lies in the field of dialysis rather than in control of the blood pressure. It is therefore very important that every attempt should be made to improve on and simplify present methods of treating refractory hypertension so that these can be widely applied by physicians other than those primarily concerned with the treatment of hypertension. This paper is aimed particularly at the treatment of severe refractory hypertension and recent methods of controlling severe hypertension which are not widely used are outlined.

MATERIAL AND METHODS

Details of doses and methods are given in the sections dealing with different hypotensive agents. The patients studied were in-patients or out-patients of the Royal Melbourne Hospital. Of the out-patients who presented with severe hypertension between 1959 and 1972 350 attend the hypertension clinic at this hospital. Sodium intake is not restricted in patients with hypertension unless they are on dialysis. With a free sodium intake potassium supplements are rarely required although almost all patients are treated with thiazides.

Benzothiadiazide derivatives

With the exception of diazoxide, drugs in this group are not usually potent hypotensive agents in their own right. It is, however, necessary to emphasize once more the ability of thiazides to potentiate the hypotensive effect of other drugs. Although it was widely recognized 15 years ago that the simple addition of a thiazide may very rapidly convert a patient with refractory hypertension into one in whom the blood pressure is easily controlled, thiazides are still not universally tried in the treatment of severe refractory hypertension (Mahony et al., 1972). No simple explanation will fit all the situations in which thiazides potentiate the action of other hypotensive agents (Conway & Lauwers, 1960; Tobian, 1967).

Diazoxide (3-methyl-7-chloro-1,2,4-benzothiazide) provides the most outstanding example of a complete divorce between the effect on the blood pressure and that on salt and water excretion. Troublesome oedema and sodium retention may accompany a dramatic fall in the blood pressure during treatment with diazoxide. The hypotensive action of other benzothiadiazides also fails to correlate with their diuretic and natriuretic effects (McQueen & Morrison, 1960; Grieble & Johnston, 1962). The hypotensive effect of thiazides persists after restoration of the plasma volume and total body sodium to near normal levels in spite of an increase in
cardiac output (Conway & Palmero, 1963) and even complete restoration of the plasma volume does not return the blood pressure to its initial value (Grieble & Johnston, 1962; Winer, 1961; Varnauskas, Cramer, Malmerona & Werko, 1961). Thus although thiazides probably reduce the tone of the pre-capillary arteriole (Tobian, 1967; Goodman & Gilman, 1970; Lancet, 1972) the mechanism that determines this change is not clearly understood.

From the clinical point of view it may be very important in patients with refractory hypertension to recognize that the hypotensive effects of thiazides are not dependent on their diuretic action. There is a tendency to withhold thiazides in patients with impaired renal function, e.g. none of the nine patients recently subjected to bilateral nephrectomy for uncontrolled hypertension had apparently been treated with any thiazide other than an occasional injection of parenteral diazoxide (Mahony et al., 1972). In patients with impaired renal function resistant to the diuretic effect of thiazides the potentiation of the hypotensive effect of other agents by...
the addition of thiazides may nonetheless convert a severe resistant form of hypertension into one which is easily controlled (Fig. 2).

The immediate fall in blood pressure in animals produced by a large injection of hydrochlorothiazide is associated with an inhibition of the vasopressor response to stimulation of adrenergic vasomotor fibres similar to that seen with bretylb tosylate and guanethidine (Preziosi, de Schaepdryver, Marmo & Miele, 1961).

The immediate effects of an intra-arterial injection of thiazides in animals and the importance of a large rapid 'bolus' injection when using diazoxide (Mathew & Kincaid-Smith, 1971) caused us to study recently the effect of a rapid 'bolus' type injection of 0.5–1.0 g of chlorothiazide in a group of hypertensive patients. In one of eleven patients studied in this way the immediate effect was almost as impressive as that of diazoxide (Fig. 3). Although there was no response in five patients who were taking oral thiazides six patients who had not previously received thiazides showed a mean fall of 24% in their systolic blood pressure and 12% in the diastolic blood pressure in the first 10 min after this rapid injection (P<0.01).

The effects of intravenous diazoxide are well recognized. One of the disadvantages of this method of treatment is the need in some patients to repeat intravenous injections at frequent intervals. Oral diazoxide re-introduced by Pohl & Thurston (1971) represents a major step forward in the treatment of severe refractory hypertension. We have had the same impressive results as Pohl & Thurston (1971) in lowering the blood pressure in patients refractory to control by other methods (Fig. 4) and have not as yet encountered problems related to hyperglycaemia (de Broe, Mussche, Ringoir & Bosteels, 1972) using concomitant oral hypoglycaemic agents.
Spironolactone

A double-blind controlled cross-over comparison of spironolactone (dose: 100 mg four times a day) and placebo was carried out in patients selected from our hypertension clinic purely on the basis of refractory hypertension. These patients had standing diastolic pressures of 115 mmHg or higher on three successive visits to the clinic in spite of maximum tolerable doses of other drugs.

Fig. 5 illustrates a highly significant effect of spironolactone compared with placebo. Spironolactone produced marked lowering of the systolic and diastolic blood pressure both standing and lying. The relatively minor weight loss which accompanied this fall in blood pressure in some patients makes it unlikely that the effect is related to natriuresis or diuresis particularly as the blood pressure rises when frusemide is substituted for spironolactone. Since
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**FIG. 5.** Highly significant decrease in the standing and lying systolic and diastolic blood pressures produced when spironolactone (400 mg/day) (Sp.) was substituted for placebo (Pl.) in a double-blind controlled cross-over study.

**FIG. 6.** The dose-response curve of the lying diastolic blood pressure to increasing doses of propranolol in three patients with severe refractory hypertension. (Diastolic BP > 140 mmHg.)
FIG. 7. Comparison of the effect of placebo and MK 950, a new β-adrenergic blocking drug, in a group of patients whose initial diastolic blood pressure was over 110 mmHg. The dose of MK950 was 5-15 mg/day.

FIG. 8. Response over the first 4 weeks of treatment with prazosin hydrochloride, a new peripheral vasodilator, which can produce a very significant fall in supine systolic and diastolic blood pressure when used on its own. Doses were increased where necessary from 1-5 to 15 mg/day.
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This trial was conducted we have used spironolactone in this high dose in a large number of patients with severe hypertension. Hyperkalaemia was only observed in patients with impaired renal function and could usually be controlled by low potassium diet. Gynaecomastia developed in only one patient.

β-Adrenergic blocking agents

The hypotensive effects of β-adrenergic blocking agents has been well demonstrated (Pritchard & Gilliam, 1969; Zacharias & Cowen, 1970). One important advantage of this group of drugs in the treatment of severe refractory hypertension is that they have less effect on sexual function than many other drugs and this has been the major cause of default of male patients from our hypertension clinic (M. C. Laver, unpublished work). Another major benefit achieved by the use of β-adrenergic blocking drugs has been better control of the lying blood pressure particularly diastolic blood pressure (Fig. 6).

We found an increasing response with increasing doses of propranolol up to 1–2 g/day (Fig. 6). We have not, however, found a similar increasing hypotensive effect by using prindilol.
With increasing doses of the latter drug headache, tachycardia and an actual rise in blood pressure has been observed. Both these points are being subjected to more careful analysis and double-blind comparison of prindilol and propranolol which we are conducting at present. Various \( \beta \)-adrenergic blocking agents are effective when given on their own as shown in Fig. 7 which compares the response to a new \( \beta \)-adrenergic blocking agent (MK 950) with that of placebo in eight patients with diastolic blood pressures over 110 mmHg before treatment.

![Graph](image)

**FIG. 10.** After a period of 8 months of documented severe refractory hypertension which did not respond to a combination of propranolol (360 mg/day), methylldopa (2 g/day) and chlorothiazide (1 g/day) the addition of prazosin hydrochloride (7.5 mg/day) produced a sharp fall in systolic and diastolic blood pressure both standing and lying.

In severe refractory hypertension \( \beta \)-adrenergic blocking agents should always be combined with thiazides. They may also be very effectively combined with hydralazine (Zacest, Gilmore & Koch-Weser, 1972). We have also found that the combination of large doses of propranolol with a new peripheral vasodilator prazosin hydrochloride may be very useful in the control of refractory hypertension.

**Prazosin hydrochloride**

Peripheral vasodilators such as hydralazine have been rather limited in their use in the
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Treatment of hypertension because of the frequency of short-term side effects such as headache, nausea and vomiting and tachycardia and because of the possibility of the more serious long-term side effects of a lupus erythematosus-like illness.

We have recently studied the effects of prazosin hydrochloride a new hypotensive agent with peripheral vasodilator properties somewhat similar to those of hydralazine. In twenty-eight patients this new drug has proved effective and has had surprisingly few side effects. It appears to have the additional advantage of being effective without thiazides and thus is a suitable choice in patients with gout or diabetes.

Fig. 8 shows the response in the first month in a group of patients with moderately severe hypertension treated with prazosin alone. In all patients the blood pressure fell, the effect on the lying diastolic blood pressure being highly significant. In some patients with severe hypertension resistant to other medication prazosin hydrochloride on its own may be very effective (Fig. 9).

The blood pressure may fall sharply when prazosin hydrochloride is added to other medication including large doses of propranolol in patients with severe refractory hypertension (Fig. 10).

These preliminary findings suggest that prazosin hydrochloride may be an important new hypotensive agent. It is effective on its own in moderately severe hypertension and may be very effective in severe hypertension in combination with large doses of propranolol.

Clonidine

This drug has been available for several years and may be very useful in controlling severe refractory hypertension. However, the combination of clonidine in large doses (900 \( \mu \)g/day) with propranolol in large doses (over 1 g/day) has in five patients with impaired renal function been associated with severe mental confusion and coma. Similar effects have been described with clonidine alone in patients with advanced cerebrovascular disease but our patients had no other evidence of cerebrovascular disease and the state was reversible. This syndrome has only been observed with the combined use of large doses of propranolol and clonidine and withdrawal of clonidine has been more effective than withdrawal of propranolol in achieving rapid recovery (P. Kincaid-Smith, P. Fang & M. C. Laver, unpublished work).

DISCUSSION

In spite of the large number of hypotensive agents available in 1972 adequate control of the blood pressure in a patient with severe refractory hypertension often requires considerable time and expertise in adjustment of drug combinations and doses before a satisfactory result is obtained. Side effects have been a serious limiting factor and the final regime must be acceptable both to the physician in terms of blood pressure control and to the patient who will discontinue treatment if side effects are troublesome.

Thiazides, so valuable because of their relative lack of side effects and their considerable ability to potentiate the hypotensive effects of other drugs, are always worth a trial in severe refractory hypertension even if renal function is impaired. Benzothiadiazides include diazoxide, one of the most powerful preparations available for the treatment of severe refractory hypertension. The diabetogenic side effects of long-term diazoxide treatment although potentially serious are far more acceptable in difficult cases than such drastic procedures as bilateral
nephrectomy and permanent dialysis (Mahony et al., 1972). Pohl & Thurston (1971) re-introduced oral diazoxide in combination with a hypoglycaemic agent and it promises to be a most significant advance in the treatment of severe refractory hypertension. The divorce between the diuretic and the hypotensive effects of benzothiadiazides and other diuretic agents so obvious in the case of diazoxide has been further illustrated by controlled studies demonstrating that the stronger diuretic substance frusemide is less effective in controlling the blood pressure than hydrochlorothiazide (Anderson, Godfrey, Hill, Munro-Faure & Sheldon, 1971). Spironolactone (400 mg daily) has proved a most effective drug in the control of an unselected group of patients with severe refractory hypertension and here again our observations suggest that the hypotensive effect is not due to loss of sodium and water. Although the hypotensive effect of spironolactone is well recognized in hyperaldosteronism (Brown, Davies, Ferriss, Fraser, Haywood, Lever & Robertson, 1972) it is unlikely that our unselected group of patients all had hyperaldosteronism although aldosterone estimations were not carried out.

β-Adrenergic blocking agents in large doses, with or without a drug which causes peripheral vasodilation, have further advanced the treatment of severe hypertension. An increasing response to propranolol may be seen with doses in excess of 1·5 g.

The peripheral vasodilator prazosin hydrochloride, on which we have done preliminary studies, seems to be far more acceptable than the somewhat similar agent hydralazine and has produced only minor side effects. It is an effective hypotensive agent either on its own or combined with other drugs. In severe hypertension a combination of prazosin hydrochloride and large doses of β-adrenergic agents has proved very effective.

Although few would accept bilateral nephrectomy as a method of controlling the blood pressure, new effective drugs are still needed for the control of severe refractory hypertension. New hypotensive agents will only be widely used if they are acceptable to the patient and can be administered with ease.

REFERENCES

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