Diuretic and β-Blocker in Hypertension—Then What?

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Thiazide diuretics and β-adrenergic blockers are widely accepted as the drugs of choice in hypertension. However, this combination fails to control the blood pressure in 20 per cent of compliant patients with mild hypertension[1], and failure is more common in moderate and severe hypertension. In this situation it is usual to add a third drug, in the so-called stepped treatment approach[2]. The possible choice of third drug is wide and includes vasodilators (hydralazine, prazosin), centrally acting sympatholytic drugs (methyldopa, clonidine, reserpine) and post-ganglionic adrenergic blockers (bethanidine, guanethidine, debrisoquine). When prescribed with diuretics and β-blockers there is evidence that hydralazine[1,3-5], prazosin[6-8] and methyldopa[9,10] have an additional hypotensive effect.

Since the study of Zacest et al., in 1972[3], many reviews have recommended a vasodilator as the drug of third choice[11-19] although no comparative studies with the other classes of drug available have been published[18]. The only comparative study of 'third drugs' has been a small short-term comparison of two vasodilators, hydralazine and prazosin, which favoured prazosin[20]. Comparative studies of third drugs will have a major impact on the standard treatment of moderate and severe hypertension[18], but they pose difficult questions in the planning stage; for example, what drugs should be compared, what type of study design should be used, and how many patients will be needed? While preparing a protocol for such a study, the use of third drugs in the Glasgow Blood Pressure Clinic was surveyed retrospectively, in the hope of answering some of these questions.

Methods

In 1969, hypertension clinics in four teaching hospitals amalgamated to form the Glasgow Blood Pressure Clinic. Data for all patients are recorded in standard format, edited centrally, and stored in a computer[21]. For each clinic visit the computer produces a printed record that is filed centrally to form a case record for each patient. Information on blood pressure and treatment is virtually complete, but recording of adverse effects is less complete and may be biased. There is no uniform policy of treatment or follow-up but it is uncommon for patients taking antihypertensive drugs to be discharged. All patients taking a diuretic plus a β-blocker who had a third antihypertensive drug added were identified by a manual search of the records in June 1978. There were 110 patients treated at three hospitals by 32 doctors. The data were analysed by chi-square, with Yates' correction when appropriate, and Student's t test for unpaired samples.

Results

Pattern of Prescribing

A third drug was added on 119 occasions in 110 patients. Inclusion of those who had a third drug added on two occasions did not influence the results, and the data are presented as if for 119 separate patients. Hydralazine was prescribed most commonly (44 per cent), followed by methyldopa (26 per cent), prazosin (18 per cent), clonidine (8 per cent) and bethanidine (5 per cent). The prescribing pattern varied greatly between the three hospitals (Table 1) with hydralazine, methyldopa and clonidine each emerging as the drug of choice in one hospital. The difference in use between hospitals was significant for each of these drugs (p<0.001), and only prazosin was used reasonably uniformly in each hospital. The drugs were prescribed mainly in 1975-1977. The frequency of prescribing of individual drugs was constant in these three years with the notable exception of prazosin. This drug contributed 34 per cent of the prescriptions in 1975, was not used in 1976, and contributed 18 per cent in 1977. As described elsewhere[22]
these fluctuations were related to the warning about first dose reactions from the Committee on Safety of Medicines, and to subsequent publications suggesting a safer starting regime.

**Patient Characteristics**

The outcome of treatment could not be assessed in 24 patients; 21 were treated for less than four months at the time of study, 2 were discharged from the clinic, and in one patient the third drug was stopped by another doctor who thought it was unnecessary. Of the remaining 95 patients, 49 were men, the mean age was 50 years, and the mean blood pressure immediately before adding the third drug was 188/118 mmHg recumbent and 181/118 mmHg standing—91 of the patients were taking propranolol or oxprenolol (mean dose 618 mg), 2 atenolol, and 2 pindolol; 47 were taking bendrofluazide (mean dose 7.2 mg), 32 were taking cyclopentiazide (mean dose 0.42 mg), and 16 took various other diuretics.

**Comparability of Groups**

Patients given different third drugs did not differ in age, weight, blood pressure, frequency of secondary hypertension, β-blocker, dose of β-blocker, or duration of attendance at the clinic (Table 2). They did differ in hospital attended and also in sex. Hydralazine was prescribed significantly more often to men (x² = 15.1, p<0.01) due to the pattern in hospital A, where 90 per cent of men but only 44 per cent of women received this drug (x² = 11.6, p<0.001). The groups also differed in the diuretic used, with an excess of cyclopentiazide treatment in those given hydralazine (x² = 10.8, p<0.02).

**Outcome of Treatment**

**Early failure** was deemed to have occurred if, within four months of starting treatment, the third drug was stopped, a fourth drug was added, or the patient was admitted to hospital to control the blood pressure. Twenty-five per cent of all patients had early failure (Table 3), 17 per cent because of adverse effects, and 8 per cent because of insufficient hypotensive response. Early failure was most frequent with prazosin (8/15 patients) and the difference from all other drugs approached significance (x² = 7.6, p<0.1). When compared directly to hydralazine the failure rate was significantly higher with prazosin (x² = 4.2, p<0.05). Failure of prazosin was not usually due to first-dose reactions, as reported elsewhere[22]. Factors related to early failure were sought for each drug. Women were more likely to stop hydralazine because of early adverse effects (5/12 women versus 1/29 men; x² = 7.1, p<0.01) and this did not appear to be a function of body weight or age. Patients with early failure of prazosin were older than those who continued on the drug (62±SD 4.4 years versus 41±13.6 years, p<0.02).

**Results at 6 months.** Data from the visit nearest to 6 months after starting the third drug, within the range 4-10 months, were examined (see Table 3). Of the initial

| Table 2. Characteristics of hypertensive patients prescribed different third drugs. Mean (and standard deviation). |
|---------------------------------------------------------------|
| **Hydralazine** | **Methyldopa** | **Prazosin** | **Clonidine** | **Bethanidine** |
| (n = 43) | (n = 24) | (n = 15) | (n = 9) | (n = 4) |
| Men (%)* | 72 | 42 | 20 | 33 | 50 |
| Age (years) | 50 (9) | 49 (12) | 50 (14) | 53 (8) | 55 (10) |
| Weight (kg) | 71 (14) | 73 (10) | 72 (15) | 69 (13) | 74 (2) |
| Duration at clinic (months) | 21 | 22 | 27 | 15 | 54 |
| Secondary hypertension (%) | 16 | 17 | 15 | 0 | 0 |
| Supine BP (mmHg): systolic | 187 (12) | 191 (30) | 190 (26) | 179 (34) | 187 (30) |
| diastolic | 118 (12) | 117 (14) | 116 (13) | 121 (11) | 117 (16) |
| Dose propranolol/oxprenolol (mg/day) | 657 | 605 | 691 | 502 | 320 |
| Bendrofluazide (%) | 37 | 58 | 55 | 67 | 75 |
| Cyclopentiazide (%)** | 53 | 21 | 33 | 11 | 0 |
| * x² = 15.1, p<0.01, due to excess of males receiving hydralazine. |
| **x² = 10.8, p<0.02, due to excess of cyclopentiazide in patients receiving hydralazine. |

| Table 3. Outcome of treatment at 6 months (range 4-10 months). |
|---------------------------------------------------------------|
| **Hydralazine** | **Methyldopa** | **Prazosin** | **Clonidine** | **Bethanidine** | **Total (%)** |
| (n = 43) | (n = 24) | (n = 15) | (n = 9) | (n = 4) | |
| No. of patients | 43 | 24 | 15 | 9 | 4 | 95 |
| Early failure | 9 | 5 | 8 | 2 | 0 | 24 (25%) |
| Diastolic >106 mmHg | 12 | 9 | 3 | 3 | 3 | 30 (32%) |
| Diastolic 96-105 mmHg | 9 | 6 | 1 | 3 | 0 | 19 (20%) |
| Diastolic <96 mmHg | 13 | 4 | 5 | 1 | 1 | 22 (23%) |
| Adverse effects present | 7 | 8 | 4 | 1 | 2 | 22 (23%) |
| Duration treatment (months)* | 6.3 | 6.0 | 5.6 | 6.9 | 5.5 |  |
| Daily dose (mg)* | 101 | 954 | 10.0 | 0.54 | 42.5 |  |
| *Excluding early failures. |
Table 4. Mean (and SD) fall in blood pressure (mmHg) at 6 months (range 4-10 months).

|                | Hydralazine (n = 34) | Methyldopa (n = 19) | Prazosin (n = 7) | Clonidine (n = 7) | Bethanidine (n = 4) |
|----------------|----------------------|---------------------|-----------------|-----------------|-------------------|
| **Recumbent:** |                      |                     |                 |                 |                   |
| systolic       | 19 (27)              | 19 (32)             | 14 (23)         | 16 (44)         | 5 (42)            |
| diastolic      | 13 (14)              | 9 (17)              | 7 (16)          | 16 (20)         | 5 (15)            |
| **Standing:**  |                      |                     |                 |                 |                   |
| systolic       | 18 (22)              | 28 (31)             | 14 (25)         | 19 (44)         | 4 (33)            |
| diastolic      | 17 (16)              | 13 (18)             | 9 (13)          | 14 (22)         | 7 (5)             |

Table 5. Outcome at 6 months (range 4-10 months) in patients treated with a vasodilator (hydralazine, prazosin) or a sympathetic blocker (methyldopa, clonidine, bethanidine).

| Diastolic BP (mmHg) | Early failure | >106 | 96-105 | <96 | Adverse effects |
|---------------------|---------------|------|--------|-----|----------------|
| Vasodilator (58)    | 17 (29%)      | 15   | 10     | 16  | 11 (19%)       |
| Sympathetic blocker (37) | 7 (19%) | 15   | 9      | 6   | 11 (30%)       |

95 patients, 57 per cent had either stopped the third drug or had a recumbent diastolic blood pressure higher than 105 mmHg; 43 per cent had diastolic pressures of 105 mmHg or lower, and 23 per cent had diastolic pressures of 95 mmHg or lower. Defining success as continued treatment and a recumbent diastolic pressure below 96 mmHg, the drugs did not differ significantly, with the success rate varying between 11 per cent for clonidine and 30 per cent for hydralazine. These figures are based on small numbers. The mean changes in blood pressure over 6 months are shown in Table 4. The drugs differed little, although a postural fall in blood pressure was evident only with methyldopa. There was no significant difference between the drugs in the frequency of adverse effects recorded at the 6 month visit (see Table 5). The doses of diuretic and ß-blocker did not change over the 6 month period.

**Vasodilators versus Sympathetic Blockers.** The outcome of treatment in 58 patients given a vasodilator (hydralazine or prazosin) and 37 patients given central or post-ganglionic sympathetic blockers is summarised in Table 5. The differences in early failure rate, blood pressure control and adverse effects at 6 months did not approach significance (all p<0.1). Patients treated with a vasodilator had a somewhat better chance of good blood pressure control (diastolic <96 mmHg) and freedom from adverse effects.

**Discussion**

Short-term controlled studies cannot answer many important therapeutic questions satisfactorily[23,24] and the case for more realistic evaluation of antihypertensive drugs has been made recently[25]. Using standard data recording it proved possible to examine the results of routine treatment in a large clinic, but this also has several shortcomings. The treatments were not allocated in a random manner, and differences between the groups, for example in the hospital attended or in sex, may have biased the outcome. Blood pressure measurements were not blind, and single readings rather than replicates were used. Over a six-month period blood pressure is expected to rise slightly through progression of the hypertension, and to fall more markedly due to placebo effect and to the phenomenon known as regression to the mean[25]. In this survey these flaws would weaken, but not bias, the comparison between drugs, but the figures in Table 4 probably over-estimate the hypotensive action of all the drugs. The number of patients in each group was small, and failure to separate the drugs statistically certainly does not preclude important differences between them. For these reasons, many of the findings in this survey should be regarded as hypotheses to be tested in further study. However, firm conclusions can be drawn from the pattern of prescribing, and from the overall outcome of treatment.

Centrally acting sympathetic drugs, and not vasodilators, were considered the third drugs of choice in two hospitals, and in the third hospital, where hydralazine was clearly favoured, less than half the women were treated with this drug. Concern about sexual dysfunction in men taking centrally acting drugs presumably explains the sex difference in prescribing. The vasodilators did not prove clearly superior to the sympathetic blocking drugs in any respect (Table 5), and it should be noted that the number of patients in the overall comparison exceeded considerably the number generally included in controlled comparative trials. Relative freedom from adverse effects has been considered an important advantage of the vasodilators[18]. Objective methods of recording adverse effects are not used in the clinic, and the expected difference may not have emerged for this reason. However, such is the reputation of the sympathetic blocking drugs for producing adverse effects that any bias present would be expected to favour the vasodilators. The recommendation of vasodilators[11-19] without the benefit of comparative studies[18] is presumably based on clinical experience. Experience in this clinic does not support any clear preference, and comparative studies are obviously needed.
The results for the individual drugs underline the importance of conducting studies in large and representative populations of patients; for example, early failure with prazosin was more common in older patients, and the results of any study restricted to younger hypertensives might be biased in favour of this drug. Again, hydralazine was prescribed mainly for men, yet was stopped because of adverse effects significantly more often in women. The general trend in favour of hydralazine seen in Table 3 (less frequent early failure, better hypertensive response, fewer adverse effects) may be due entirely to this sex difference. The only large published experience with hydralazine as a third drug[1] was in many respects a model study, but the patients were all men. It is conceivable from the present survey that the third drug of choice could be a vasodilator for men, and a centrally acting sympatholytic drug for women.

Overall, the results of triple therapy were disappointing in this clinic, with the third drug failing within four months in a quarter of the patients. Reduction of the diastolic pressure below 105 mmHg affords substantial protection against vascular complications in more severe hypertension[26], but even this modest aim was achieved at six months in less than half the patients. It has been suggested that triple therapy including a vasodilator will normalise the blood pressure in 90 per cent of hypertensive patients[14]. This depends on the definition of hypertension used, and also disguises the fact that patients who are not controlled by two drugs (diuretic and β-blocker) do not fare very well when a third drug is added. This seems true even in mild hypertension. In a large study of patients with diastolic blood pressure between 90 and 114 mmHg[1], diuretic plus β-blocker treatment failed in 19 per cent of patients, and inclusion of hydralazine reduced the failure rate to 8 per cent. It seems that hydralazine will fail to normalise the blood pressure in approximately 40 per cent of patients with mild hypertension who need a third drug. The present findings contrast with the successful results with the same drugs in short-term studies in more severe hypertension[3,5,8]. It could be argued that the third drugs were not used aggressively enough, as the mean doses (see Table 3) were well below the maximum recommended doses. Alternatively, the problem may not be poor drug potency but failure in other aspects of management. Attention to recognised causes of apparent treatment resistance such as drug interactions, compensatory expansion of the extracellular fluid volume or irregular tablet taking[27-29], might have improved the results. Poor compliance with treatment was often suspected, and the use of methods for monitoring compliance in routine practice deserves consideration. Management of noncompliant patients remains difficult even when they can be identified[28], but addition of a third drug that will not be taken does not seem a logical solution.

In summary, the management of hypertensive patients who do not respond to a diuretic/β-blocker regime poses considerable problems. There is no unanimity on the third drug of choice, no single drug appears clearly superior to the others, and vasodilators were not clearly superior to sympathetic blocking drugs. Controlled comparative studies are needed and will have a major impact on standard treatment. The pattern of prescribing suggests that hydralazine, methyldopa and prazosin might be compared, although other drugs such as clonidine deserve consideration. Short-term crossover studies in a small number of patients will not provide definitive answers. Parallel group studies over a period of months will be needed, and the population studied should include patients of both sexes and a wide age range, allowing examination of responses according to these, and other, variables. Use of standardised replicate blood pressure measurements would increase the power of the study compared to this survey, but the sample size needed might still be numbered in hundreds. The available third drugs may prove equally potent in lowering blood pressure, and objective methods of recording and weighting adverse effects would then be crucial. Suitably designed self-administered questionnaires[30] might be useful in this respect. Some measure of compliance with treatment would be needed. Studies that will provide definitive results may require considerable organisation and finance, but there should be no shortage of suitable patients.

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Continued from page 253

deposited similar sets in the Royal Society, the British Museum, the Society of Antiquaries, and the Académie Royale des Sciences in Paris. Another set in the Linnean Society has pasted in an etched print of a finch on which is written 'Edward's first tryal at Etching, A.D. 1759.' In 1769 his health began to fail, and so he sold all remaining copies of his works and everything appertain-

ing thereto to James Robson of New Bond Street. Edwards died in 1778 and was buried in the churchyard at West Ham where a memorial stone commemorated his association with the College and records that 'his Natural History of Birds will remain a lasting monument of his knowledge and ingenuity'.

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