Treating Severe Hypertension

J. D. SWALES, MD, FRCP

Professor of Medicine, Department of Medicine, Clinical Sciences Building, Leicester Royal Infirmary, Leicester

There is of course no absolute category in which one can place the severely hypertensive patient any more than there is a sharp dividing line between individuals who are hypertensive and those who are not. In the aftermath of the celebrated Platt-Pickering controversy of the 1960s we now know that blood pressure levels in unselected populations, as long as these populations are large enough, are distributed as a smooth unimodal curve, although these curves are skewed. As a result of the pattern of referral of patients in the UK, specialist clinics see a highly selected population of patients with the highest blood pressure levels. Thus, the major reason for referral of patients to the Hypertension Clinic in Leicester is difficulty in controlling blood pressure. This is as it should be since the number of individuals who can be helped by antihypertensive treatment far exceeds the capacity of any hospital clinic. Essentially therefore the primary treatment of hypertension has to be carried on outside hospitals while hospital clinics deal with a small proportion of special problems.

Severe Hypertension

Severely hypertensive patients therefore comprise the upper ‘tail’ of the blood pressure distribution and constitute only a tiny minority of patients at significant risk from elevated blood pressure. Although their number is small their risk is correspondingly high since morbidity and mortality are directly related to blood pressure level. For the same reason the incidence of hypertensive organ damage is also high. This of course includes malignant hypertension. The potential rewards of treatment are therefore greater although there are additional problems associated with too rapid a fall in blood pressure in patients with hypertensive vascular disease.

The Search for Secondary Hypertension

It is usually necessary to employ combination therapy of more than one drug in treating severe hypertension. Some of the agents used are relatively new and some of the more potent drugs are fairly toxic. Non-pharmacological treatment obviously has great advantages in this clinical context. Most forms of non-pharmacological treatment (of which diet is the most important) only have a fairly modest effect on blood pressure and so are very unlikely to prove adequate alone. However, if a primary cause of hypertension can be removed this would clearly be of particular value in this group. Thus it is certainly worth excluding contraceptive pills as a contributory cause. Other potential causes such as phaeochromocytoma and primary aldosteronism are rare even in this group of patients and it is probably not justified to go beyond the simple biochemical screening tests for these conditions. The incidence of renal and renovascular hypertension is more debatable. Incidence rates as high as 20 or 30 per cent have been quoted for renovascular hypertension amongst patients referred to specialist hypertension units. It should be borne in mind however that these are highly selected referrals and in many cases patients are referred to units specialising in hypertension with a diagnosis of renovascular disease already made. By contrast, where such patients are excluded the incidence is probably less than 1 per cent even amongst patients referred to hospital [1-3]. When our Hypertension Clinic in Leicester was first set up in 1974 we pursued a policy of fairly intensive investigation and rapid sequence intravenous pyelography was performed on all hypertensive patients in whom operative treatment would be carried out if a cause were found (i.e. excluding the very elderly or those with incidental disease). When this practice was reviewed in 1976[4] we found that nine patients had undergone operation for renal hypertension, i.e. revascularisation of the kidney or unilateral nephrectomy. Over the same period a total of 500 patients had been referred for investigation and treatment of hypertension. However, this does not yield a valid incidence rate in the population of patients who were seen since all nine patients had been referred to us by other physicians or other hospitals with a diagnosis of renal hypertension already made. The de novo diagnosis of hypertension due to unilateral renal disease was not made in any of our patients. Reports of a high incidence of renovascular hypertension should therefore be viewed with considerable suspicion. The key question should always be asked: from what population do these patients originate?

It has been argued that surgically correctable renal and renovascular hypertension is particularly common amongst patients who are severely hypertensive. If so, this might constitute good grounds for more intensive investigation of such patients. Thus Davis et al.[5] reported renovascular hypertension in 31 per cent of 123 adult patients with Grade III or Grade IV retinopathy. No less than 43 per cent of 56 white patients who underwent arteriography in this group had radiological evidence of renovascular hypertension. The presence of renal artery
stenosis does not of course indicate that the lesion was causing high blood pressure amongst these patients as the outcome of surgical treatment was not reported. We examined the prevalence of renal artery stenosis as demonstrated by pyelography (and, if necessary, subsequent arteriography) in patients with accelerated or malignant hypertension seen on the unit over the first six years of its existence. There was no evidence that renal artery stenosis was substantially more common amongst patients with advanced retinopathy (Table 1). It is possible of course that had arteriography been carried out on all the patients (rather than on the ones in whom pyelography showed renal artery stenosis) the prevalence might have been increased but since arteriography is usually performed only where pyelography is abnormal the outcome as far as patient management is concerned is not affected.

Stepped Care Regimen

The most commonly adopted approach to hypertension now is a stepped care regimen or some variant of it. Initial treatment consists of either a diuretic (thiazide compound or potassium retaining diuretic) or a beta adrenocceptor blocker: these are used alone or if necessary in combination. If control is still inadequate a third line drug such as hydralazine or prazosin is added. The combination of diuretic, beta-blocker and vasodilator (triple therapy) controls the majority of severely hypertensive patients. This combination has in recent years tended to replace combinations using either methyldopa or postganglionic adrenergic blockers such as debrisoquine or bethanidine. More recently two groups of agents have been used as replacement for the vasodilator component of triple therapy: these are converting enzyme inhibitors[6] and calcium antagonists[7,8]. The full place of these classes of drug in long-term treatment of hypertension still has to be assessed but already their availability has reduced still further the minority of patients who have unacceptable adverse effects from potent antihypertensive drugs.

Refractory Hypertension

I would like to consider in greater detail the drug treatment of patients whose blood pressure is resistant to conventional triple therapy of diuretic, beta-blocker and vasodilator. Criteria for defining elusive control differ with different clinicians. We regard control as inadequate if diastolic blood pressures of 100 mm Hg or more are regularly observed in the out-patient clinic. In patients over 65 these criteria are relaxed slightly and a cut-off point of 105 mm Hg diastolic blood pressure is taken.

'Refractory' hypertension is a common hospital problem. When we recently analysed our experience over eight years in the Hypertension Clinic[9] 126 of 957 patients referred for management of high blood pressure were regarded as having refractory hypertension.

When confronted with a patient with refractory hypertension the first consideration is whether the patient is actually taking his or her medication. This is usually assumed in discussions of refractory hypertension but obviously this assumption is not always justified. The pharmacological effect of treatment (such as bradycardia with some beta adrenoceptor blockers) may indicate that the patient is at least taking some of his medication on the days on which he attends the clinic. Where severe hypertension persists in spite of the administration of potent drugs the risks of continuing hypertension are sufficiently great for the patient to be admitted to hospital and for medication to be supervised. Even so it is possible for some poorly complying patients to slip through the net although it is fairly unusual for the patient who has been well educated in the risks of hypertension and is prepared to spend a significant period of time in hospital to reject medication either overtly or covertly.

Because patients with refractory hypertension tend to have the highest blood pressure levels of all, accelerated or malignant hypertension is particularly common in this group. For instance 40 of the 126 patients referred to above had either Grade III or Grade IV retinopathy and 69 had evidence of significant renal damage with plasma creatinine values in excess of 120 µmol/litre.

Outcome of Treatment

These patients are at very high risk of myocardial infarction, cerebrovascular accident and renal failure. Although it is obviously unethical to make a comparison with a matched untreated control group it is clear from our experience that treatment of refractory hypertension considerably improves life expectancy. Of particular interest is the pattern of morbidity and mortality (Table 2).

---

**Table 1.** Radiological changes in group of patients with severe hypertension compared with an untreated group of hypertensive patients without retinopathy investigated at the same time. In each case a minority of patients did not have an IVP.

|                      | Control | Severe (Grade III or IV) |
|----------------------|---------|--------------------------|
| Number               | 118     | 62                       |
| Normal IVP           | 60      | 30                       |
| Minor abnormalities  |         |                          |
| (bifid ureter,       | 27      | 22                       |
| hydronephrosis)      |         |                          |
| Renal artery stenosis| 3       | 4                        |

**Table 2.** Outcome of treating 126 patients with refractory hypertension over an 8-year period.

| Outcome                          | Count |
|----------------------------------|-------|
| Total deaths                     | 14    |
| Renal failure                    | 2     |
| Ischaemic heart disease          | 10    |
| Cerebrovascular accident         | 1*    |
| Other                            | 1     |
| Chronic dialysis                 | 5†    |
| Non-fatal myocardial infarction  | 5     |
| Non-fatal cerebrovascular accident| 1    |
| *1 patient died after discontinuing minoxidil treatment |
| †1 patient died of myocardial infarction on dialysis |
Cerebrovascular accidents were particularly uncommon. On the other hand myocardial infarction was a common cause of morbidity and death. Renal failure lay intermediate between the two extremes. End-stage renal disease resulting in either death or transfer to a chronic dialysis programme was in general only encountered in patients with intrinsic renal disease or in those who had already sustained substantial hypertensive renal damage by the time treatment was started. This pattern of mortality exactly mirrors that observed by Breckenridge et al. [10] who also studied patients attending a hypertension clinic, although patients reported in that study covered the complete spectrum of hypertension. The persistence of cardiac deaths as opposed to deaths from cerebrovascular disease has also been fairly consistently observed in large-scale studies of the effects of treating hypertension.

Effectiveness of treatment in preventing cerebrovascular or ischaemic heart disease can only be fairly crudely assessed by the incidence of cardiovascular or cerebrovascular events. In the vast majority of hypertensive patients who have only mild or moderately elevated blood pressure renal function assessed by plasma creatinine or urea is normal, so serial measurements are of limited value. In patients with refractory hypertension however renal impairment is very common and the effect of treatment can be monitored quite usefully.

**Fourth Line Drugs**

These are drugs which are only used when triple therapy has failed. Oral diazoxide and minoxidil are still only used in this situation. Captopril was initially used as a fourth line agent although it is now being used increasingly as an alternative third line agent.

Most of our patients with refractory hypertension have been successfully controlled with either oral diazoxide or minoxidil. These are arteriolar vasodilator which are considerably more potent than hydralazine. Like hydralazine they are preferably combined with a beta-blocker to prevent a reflex increase in sympathetic activity. Both drugs cause sodium retention and hirsutism although the former can be controlled if necessary with large doses of loop diuretics. Oedema is a particular problem in the presence of advanced renal failure and doses of up to 1g frusemide daily, alone or in combination with mesuride (up to 50 mg t.d.s.) are then required. Diazoxide also gives rise to a very high incidence of drug-induced diabetes which may require control with large doses of oral hypoglycaemic agents. In addition nausea and vomiting during the early weeks of therapy are very common and extrapyramidal effects are frequently seen. In spite of these formidable difficulties it was possible to maintain a substantial number of patients on oral diazoxide with excellent results [11]. With the advent of newer agents and in particular minoxidil the need for oral diazoxide has now almost completely disappeared. Twenty-five patients, almost all attending the Hypertension Clinic in its first years, have been treated with oral diazoxide which successfully controlled blood pressure in all but three; in two of these failure was due to refusal by the patient to persevere with treatment.

The majority of patients with refractory hypertension have been treated with minoxidil (2.5 mg twice daily with regular adjustments to a maximum of 60 mg a day). Good blood pressure control was obtained in all but three of 70 patients; one of these with advanced renal failure went on to undergo bilateral nephrectomy with subsequent control of his blood pressure, whilst the other two patients were changed to oral diazoxide. In addition two patients had to be taken off minoxidil because of adverse effects (skin rash, recurrent ventricular arrhythmias).

Changes in renal function are particularly instructive in this group because of its size and duration of follow-up [12]. Renal function was normal in just under half (44 per cent) and remained so even in patients followed for more than four years (Table 3). Patients with renal impairment fell into two groups. A minority had clinical, and usually biopsy, evidence of intrinsic renal disease. In these, treatment had little effect on renal function although death and transfer to chronic dialysis limited the follow-up period (Table 3). In the other patients there was no evidence of intrinsic renal disease and in these a significant improvement in renal function could be observed. Similar findings have been reported in patients

| Time (months) | 0      | 3      | 12     | 24     | 36     | 48     |
|---------------|--------|--------|--------|--------|--------|--------|
| Group 1       |        |        |        |        |        |        |
| Normal renal function | 95 ± 3.5 | 100 ± 5.2 | 98 ± 5.2 | 95 ± 5.5 | 101 ± 5.3 | 105 ± 7.7 |
| (31)           | (31)   | (27)   | (21)   | (17)   | (12)   |        |
| Group 2       |        |        |        |        |        |        |
| Impaired renal function | 214 ± 23.3 | 214 ± 23.2 | 201 ± 24.3 | 203 ± 31.3 | 177 ± 16.9 | 192 ± 39.3 |
| Initial       | —      | —      | —      | —      | —      | —      |
| Final         | (28)   | (28)   | (21)   | (16)   | (12)   | (5)    |
| Group 3       |        |        |        |        |        |        |
| Primary renal disease | 400 ± 76.0 | 400 ± 76.0 | 325 ± 58.6 | 278 ± 20.7 | 278 ± 20.7 | 370 ± 30.7 |
| Initial       | —      | —      | —      | —      | —      | —      |
| Final         | (7)    | (7)    | (5)    | (2)    | (2)    | (1)    |

*P<0.05 compared with initial value
treated with oral diazoxide[13]. The improvement in
renal function depends on two factors. In the immediate
phase of treatment a fall in blood pressure may have a
beneficial effect upon cardiac function and so lead to a
rise in renal blood flow. Second, and probably much
more important, control of blood pressure relieves hyper-
tensive vascular damage to the renal vessels. The immedi-
ate effect of blood pressure control may be detrimental in
patients without cardiac failure. Thus the fall in renal
perfusion pressure and renal blood flow can result in a
temporary decline in renal function by the end of the first
week of control (Fig. 1). This is not of course an

discontinuing treatment since the effect is
relatively short-lived. This has its counterpart in the
effects of over-enthusiastic treatment on cerebral blood
flow; thus there are several reports of brain infarction
resulting from intravenous antihypertensive medica-
tion[14]. In this case the cerebral perfusion pressure falls
below the autoregulatory range for the cerebral vessels
and cerebral perfusion is impaired.

The converting enzyme inhibitor captopril is usually
very well tolerated by patients as it causes neither nausea,
fluid retention nor hirsuties. It has occasionally given rise
to proteinuria and bone marrow depression, usually in
patients with renal failure on high doses of the drug.
Unfortunately in our hands it has been much less effective
as a fourth line drug than earlier reports suggested[15-
17]. We have attempted to control blood pressure in 32
patients with refractory hypertension, using captopril
together with a diuretic (bendroflumethazine 5 mg a day or
frusemide up to 1 g daily). Blood pressure control was
unsatisfactory in 15 of these patients; 10 of these were
transferred to minoxidil treatment, one was left on capto-
pril with a small dose of minoxidil added, one required
treatment with diazoxide; two patients had primary
aldosteronism and were treated with potassium retaining
diuretics. One patient whose treatment was changed
to minoxidil at the time of transfer had developed a severe
pemphigoid skin rash apparently due to captopril. Be-

cause of this high proportion of treatment failures we have
not attempted to assess long-term effects of captopril
treatment upon renal function. There have however been
several reports of an acute deterioration in renal function
associated with captopril treatment. Whilst this could be
due to a hypersensitivity reaction it is also possibly due to a
more specific effect of converting enzyme inhibition.
Angiotensin II is believed to play a role in the autoregula-
tion of renal glomerular filtration rate, i.e. in the main-
tenance of a constant filtration rate in the face of changes
in renal perfusion pressure by adjusting efferent arteriolar
tone. It is possible that preventing formation of angioten-
sin II with converting enzyme inhibitors prevents this
autoregulatory response to blood pressure control. In
most patients this risk appears to be theoretical although
it may be of importance in patients with bilateral renal
artery stenosis or in patients with a renal artery stenosis
and a single functioning kidney[18,19]. It seems likely
that converting enzyme inhibitors such as captopril will
prove of most value in treating less severe degrees of
blood pressure, not associated with significant renal
failure.

Other combinations

In some patients it is possible to avoid the use of minoxidil
or diazoxide by combining more conventional therapy.
One effective manoeuvre is to add a small dose of
prazosin to the existing triple regime of diuretic, beta-
blocker and hydralazine[20]. Such ‘quadruple therapy’
brings many patients into the ‘acceptable control’ group
and it is not associated with any increase in adverse effects
if the dose of prazosin is maintained at a fairly low level
(0.5 mg t.d.s. rising if necessary to a maximum of 5 mg
t.d.s.). The regimen has the disadvantage of being a fairly
complicated one although it is well tolerated and fairly
effective. We have used it particularly where our conven-
tional triple regimen had produced blood pressure levels
which fell only slightly short of the acceptable and in
whom radical revision of treatment was best avoided.
Sixteen patients were effectively controlled in this
way[20].

Captopril may be combined with a vasodilator such as
hydralazine, nifedipine or minoxidil. This may be a
particularly effective combination as all these agents
stimulate the secretion of renin which may tend to
counteract their antihypertensive action. Captopril there-
fore blocks a compensatory response which may limit the
blood pressure lowering action. These combinations are
undoubtedly very effective but in some cases there is a
real risk of a profound hypotensive response and they
should only be attempted after the patient has been
admitted to hospital and with most careful blood pressure
monitoring.

Conclusions

Given adequate compliance by the patient and persever-
ance by the clinician there are now very few patients
whose blood pressure cannot be controlled with the range
of antihypertensive drugs now at our disposal. The
comparative rarity of the condition means that even the most effective treatment of severe refractory hypertension is not going to alter public health statistics. However, the near certainty that we are beneficially affecting the natural history of the disease makes this one of the most rewarding clinical conditions to treat.

This article is based on a paper read at the College Regional Conference in Leicester in September 1983.

References
1. Bech, K. and Hilden, T. (1975) Acta Medica Scandinavica, 197, 65.
2. Dollery, C. T., Beilin, L. J., Bulpitt, C. J. et al. (1977) British Heart Journal, 39, 181.
3. Wilhelmsen, L. and Berglund, G. (1977) American Heart Journal, 94, 543.
4. Swales, J. D. (1976) Lancet, 2, 930.
5. Davis, B. A., Crook, J. E., Vestal, R. E. et al. (1979) New England Journal of Medicine, 301, 1273.
6. Atkinson, A. B. and Robertson, J. I. S. (1979) Lancet, 2, 836.
7. Murphy, M. B., Scriven, A. J. I. and Dollery, C. T. (1983) Hypertension, 5, II, 118.
8. Kendall, M. J. and Dean, S. (1983) Postgraduate Medical Journal, 59, Suppl. 2, 119.
9. Swales, J. D., Bing, R. F., Heagerty, A. M. et al. (1982) Lancet, 1, 894.
10. Breckenridge, A., Dollery, C. T. and Parry, E. H. O. (1970) Quarterly Journal of Medicine, 39, 411.
11. Pohl, J. E. F. and Thurston, H. (1971) British Medical Journal, 4, 142.
12. Taverner, D., Bing, R. F., Heagerty, A. M. et al. (1983) Quarterly Journal of Medicine, 52, 280.
13. Pohl, J. E. F., Thurston, H., Swales, J. D. (1974) Quarterly Journal of Medicine, 43, 569.
14. Ledingham, J. G. G. and Rajagopalan, B. (1979) Quarterly Journal of Medicine, 48, 25.
15. White, N. J., Rajagopalan, B., Yahaya, H. et al. (1980) Lancet, 1, 108.
16. Atkinson, A. B., Brown, J. J., Lever, A. F. et al. (1980) Lancet, 2, 105.
17. Case, D. B., Atlas, S. A., Sullivan, P. A. et al. (1981) Circulation, 64, 765.
18. Curtis, J. J., Luke, R. G., Wkelchel, J. D. et al. (1983) New England Journal of Medicine, 308, 377.
19. Hricik, D. E., Browning, P. J., Kopelman, R. et al. (1983) New England Journal of Medicine, 308, 373.
20. Heagerty, A. M., Russell, G. I., Bing, R. F. et al. (1982) British Journal of Clinical Pharmacology, 13, 539.

Royal Letters

There is a certain splendour in the official style of Charles II, witness his letter to the College in 1680. 'Trusty and well beloved we greet you well. Whereas we have found fit for the ability loyalty and good affection of Dr Timothy Clarke to make choice of him to succeed Dr Quartermaine to the place of second physician to Our Royal Person ... May be by you received and admitted to the enjoyment of the like place, rights, privileges and pre-eminence of what kind soever as the said Dr Quartermaine in his life time did or ought to have held and enjoyed in your College. In which we doubt not of your compliance and so bid you farewell.' The College knew what to do. 'Which orders we willingly obeyed' and made Dr Clarke an Elect. Both Quartermaine and Clarke were Oxford men and early Fellows of the Royal Society. Quartermaine spent much time with the fleet; he was a guest of Pepys on board ship in May, 1660. Clarke seems to have no record apart from his royal appointment.

The royal style was again evident when the College was prosecuting Gerard Van Mulen for unlicensed practice. The king wrote: 'We have received good testimony that he hath practised only in curing the gout and that very successfully.' He goes on to state that he had 'taken him into our protection for his eminent skill in the two particulars above mentioned.' He then called upon the College to 'desist from all further prosecution. And so not doubting your compliance therein, we bid you farewell.' The College knew what to do about this letter; there was no compliance to the royal command. Its reply was firm but polite: 'We humbly beseech your Majesty to leave this matter wholly to the due course and determination of your Majesty’s laws.'