Factors in the choice of antihypertensive therapy

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Introduction

Even more difficult than choosing the appropriate drug to treat the hypertensive patient is the decision whether to treat him or not. This decision, which is usually based on the level of the blood pressure and consideration of epidemiological risk factors, is not the main thrust of this paper. Let it be sufficient to make three statements about it. First that the decision to treat the hypertensive patient with drugs is too often taken too lightly. Second that based on the evidence of the Medical Research Council Mild Hypertension Trial (1985) we may be treating unnecessarily too many hypertensive patients—especially females. Third, based on the evidence of the European Working Party of Hypertension in the Elderly (Amery *et al.*, 1985), we may be denying the benefits of therapy to many elderly hypertensive patients.

There are numerous drugs available to treat patients with hypertension and these may be used alone or in combination (Table 1). Broadly, the choice of agent can either be empirical or based on a consideration of the pathophysiology of the patient. The initial question must be does it matter which drug is chosen?

For patients with severe hypertension the choice of agent is perhaps not critical (Dollery, 1985). Provided the height of the blood pressure is overwhelmingly the most important determinant of the patient's prognosis and the benefit conferred by treatment is related directly to the magnitude of blood pressure reduction, the choice of agent is largely immaterial i.e. any agent which lowers blood pressure will be effective. Clearly possible adverse reactions must be taken into account, but in malignant hypertension for example the first priority is reduction of blood pressure. The same assumptions cannot be made in patients with mild hypertension.

This paper will describe four approaches which have been used to select the appropriate drug for hypertensive patients—biochemical profiling, demographic profiling, benefit profiling and finally a clinical consideration of the individual patient. Further, the paper will largely address

Table 1 Available antihypertensive drugs

Diuretics
β-adrenoceptor blocking drugs
Slow calcium channel antagonists
Angiotensin converting enzyme inhibitors
Vasodilators
α-adrenoceptor blocking drugs
α- and β-adrenoceptor blocking drugs
Centrally acting drugs
[Ganglion blockers and adrenergic neurone blockers are considered obsolete]

itself to choices within the four most widely used drug groups—diuretics, β-adrenoceptor blocking agents, slow calcium channel antagonists (calcium antagonists) and angiotensin converting enzyme inhibitors (ACE inhibitors).

Biochemical profiling

Arterial blood pressure is regulated by many factors both haemodynamic and biochemical, many of which can be measured. However the cost and inconvenience of doing so is considerable, and the benefits resulting from measurement would have to be high for such practices to be widely used. Further, for such assessments to be at all clinically reliable they would have to be carried out on at more than one time point.

(a) Renin

Laragh (1973) introduced the concept of the vasoconstrictor-volume analysis for understanding and treating hypertension. According to this hypothesis, patients with hypertension can be categorised according to plasma renin activity (PRA) and those with the higher levels of PRA respond better to β-adrenoceptor blockers (Buhler *et al.*, 1972; Hollifield *et al.*, 1976) than those with lower levels of PRA who respond better to diuretics (Adlin *et al.*, 1972). This view has not been generally accepted. 'PRA has

shown itself to be a quite inappropriate and unfaithful index in the choice between β -adrenoceptor blockers and diuretics as first step agents' (Zanchetti, 1985). The introduction of ACE inhibitors revived the argument as to the usefulness of PRA as a marker for their relative effectiveness (Case *et al.*, 1977); much of the clinical work on this has been done by MacGregor and is described elsewhere in this volume (MacGregor, 1987). Again it must be said that the effectiveness of ACE inhibitors is much greater than would be predicted from measurements of PRA—for example anephric patients have been shown to respond very satisfactorily to ACE inhibitors (Man in't Veld *et al.*, 1980). The antihypertensive effect of calcium antagonists has been shown to relate inversely with PRA (Buhler *et al.*, 1982) but the more important correlation may be with age, as discussed below.

(b) *Catecholamines*

Plasma noradrenaline and adrenaline are raised in some patients with essential hypertension. Further, during exercise, tilting, modulation of baroreceptor function by lower body suction or by means of a neck pressure chamber, catecholamines may rise or fall (Grassi *et al.*, 1985). This, however, does not necessarily help in selecting those patients whose increased sympathetic activity differentiates them from other groups of hypertensive patients, and which might form the basis for drug selection. It has been further suggested (Wallin *et al.*, 1981) that a change in plasma noradrenaline is a better indicator of altered sympathetic activity directed to muscle bound vessels than of vessels more directly involved in blood pressure control. Thus plasma catecholamines seem unlikely to form the basis of choice of antihypertensive drugs on a theoretical basis, let alone a practical one since their quantitation poses many problems.

(c) *Membrane markers*

Zanchetti (1985) has raised the possibility that the known abnormalities in ion transport across blood cell membranes in patients with hypertension may form the basis of choice of antihypertensive drugs. These changes, however, are not yet the basis of safe markers of hypertension, let alone of further value. Costa *et al.* (1985) have shown that a correlation exists between intralymphocytic $\text{Na}^+ : \text{K}^+$ ratio and diastolic blood pressure before and during therapy with captopril and hydrochlorothiazide; but it demands great extrapolation to conceive of this becoming a useful step in selecting antihypertensive drugs.

Demographic profiling

This has currently greater credence as a guide to the choice of antihypertensive therapy than biochemical measurements, although, paradoxically at least some of the theoretical basis underlying demographic profiling may be biochemical.

(a) *Race*

It has been shown both in Africa (Seedat & Reddy, 1971) and USA (VA Cooperative Study, 1982) that black patients respond better to thiazide diuretics than to β -adrenoceptor blockers. Further, there is evidence from a variety of sources that white populations respond better to ACE inhibitors than do black populations. This may be based on the Laragh theory discussed above, and it has clear therapeutic implications. One of the interests of this work is to discover what happens to blood pressure response to various drugs in an immigrant population. The answer to this may depend in part on how that population maintains its original culture, and eating habits.

(b) *Age*

Buhler and his colleagues (1982) have shown clearly that the elderly respond better to verapamil, the calcium channel antagonist, than do the young. Whether this again is based on lower PRA levels in the elderly is open to discussion, but Buhler has gone on to suggest that in broad terms, the elderly respond better to diuretics and calcium channel antagonists whereas the young respond better to β -adrenoceptor blockers and ACE inhibitors.

(c) *Cigarette smoking*

One of the clear conclusions from the MRC Mild Hypertension Trial (1985) was that cigarette smokers, both male and female showed a smaller fall in blood pressure when given propranolol than did non smokers, whereas no such difference was shown with thiazides. Now cigarette smoking is known to increase the clearance of propranolol (Dawson & Vestal, 1981), and thus it is possible that this difference in response has a pharmacokinetic basis. There are, however, other possible explanations because cigarette smoking causes many other biochemical and haemodynamic changes. It will be of interest to see if a similar difference in response between smokers and non-smokers occurs with non-metabolised β -adrenoceptor blockers such as sotalol and atenolol.

Benefit profiling

Dollery (1985) introduced the concept of benefit analysis. His starting assumption was that there is no such thing as optimal treatment for a patient aged 50 years with a blood pressure of 160/100 but there are both risk factors and drug contraindications to be taken into account. He has used, in formulating this theory, recent trials of the treatment of mild hypertension. Thus for a thiazide diuretic, positive indications include age, black race, the presence of congestive heart failure, while negative indications include diabetes mellitus, gout, ischaemic heart disease and obesity (the last two are open to considerable debate). For a β -adrenoceptor blocker, positive indications include ischaemic heart disease (again open to debate) while negative indicators include asthma, and peripheral vascular disease.

Considerations of the individual patient

This type of assessment brings us back to a consideration of the individual patient, and the possibility of using the patient's own response as the basis for either continuing therapy or changing it (Hansson, 1985). For a patient, the benefit conferred by any form of therapy must be balanced by consideration of the adverse effects. In terms of hypertension and its treatment, the efficacy of the agent used will primarily be based on its ability to cause a sustained fall in blood pressure. Allied to this there should be a reversal of any end organ damage, or a failure of that damage to progress. If neither of these

criteria apply, and patient compliance is reasonably well ascertained, the agent should be changed.

Any adverse reactions suffered by the patient must be noted and classified as major or minor. Obviously there is little point in improving a patient's life span if he is miserable and incapacitated because of the measures taken to treat him. Therein lies part of the skill of the physician. This has been encapsulated in the term 'quality of life', a rather nebulous, all embracing term which is widely used and is discussed elsewhere in this symposium. Finally, the cost of the medication must be taken into account.

Conclusions

Several methods have been proposed to aid the choice of antihypertensive agents. Biochemical profiling has so far proved disappointing both theoretically and practically. Part of the problem may lie in our current inability to measure biochemical factors at several time points, using cheap, reproducible and rapid methodology. Demographic profiling shows more promise and this may merely be a reflection of biochemical differences in population groups; so far positive results have been shown with respect to age, colour and cigarette smoking. Variants of these two methods are benefit profiling and assessment of the individual patient response. This is an extremely active area in hypertension research and as further biochemical and population studies are conducted, new hypotheses will be proposed and therapy modified accordingly.

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