The treatment of hypertension

JOHN CHALMERS

Department of Medicine, Flinders Medical Centre, Adelaide, South Australia, Australia

- 1 A 'retrospective' of the development of the drug treatment of hypertension is presented from the early days of ganglion blockers to the present time together with a review of the evidence of benefit from treatment.
- 2 Current issues and debates are summarised including shortfalls in the control of hypertension in populations, difficulties surrounding the measurement of blood pressure, disagreement on the levels of blood pressure to treat, the goal blood pressures to aim at, issues surrounding lifestyle measures such as the low salt diet and low intensity exercise, and treatment with diuretics and with calcium antagonists.
- 3 A 'perspective' is presented on some avenues for progress in the years ahead. These will include the identification of genetic markers to determine the hypertensive individuals with the greatest risk of death and of cardiovascular complications.

Keywords measurement of blood pressure threshold for treatment goals of treatment lifestyle measures drug therapy calcium antagonists diuretics combination therapy target organ damage morbidity and mortality

Introduction

The first patient I saw in the wards as a medical student in 1959, was a 37-year-old man with two children, who presented with headaches, blurred vision and haematuria, was found to have malignant hypertension and treated with the then state of the art drug, pentolinium tartrate (or: 'Ansolysen'). The debates we absorbed as medical students in the next 3 years were about what harm and good could result from treating patients of various ages, with different levels of blood pressure, and with or without associated conditions or complications, such as cerebrovascular disease, angina, and renal failure.

Almost four decades later, we have made huge strides(?) but the same debates still rage! What good and what harm can we do by treating patients of various ages, with different levels of blood pressure, with various drugs, and with a range of associated conditions or complications? The change is that the argument is about ages over 85 rather than over 60 or 65 years, about levels of systolic pressure as well as diastolic pressure, about diastolic pressures under 90 or 100 mmHg rather than under 110 or 120 mmHg, and about the risks and benefits associated with individual groups of antihypertensive drugs. The other change is that while we all knew how to measure blood pressure, surely the key to the whole field, advances in technology

with automatic and semi automatic devices, with ambulatory and home measurements, have reduced us to new debates about how to measure blood pressure, and whether we really know what it is we are measuring.

Retrospective

Malignant hypertension

It is fitting to note in this festschrift for Colin Dollery that the first evidence of benefit from the treatment of hypertension, was published in 1959 by Harrington, Kincaid-Smith & McMichael [1] from the Hammer-smith Hospital, confirming that treatment with ganglion blockers was remarkably effective in prolonging life and preventing early death. Over the next few years many antihypertensive drugs were introduced including the diuretics, the rauwolfia alkaloids (principally reserpine), the adrenergic neuron blockers (first bretylium and then guanethidine), the vasodilators such as hydralazine and in the mid-sixties, methyldopa. The ganglion blockers were relegated to parenteral use for very severe hypertension, along with intramuscular reserpine. Medical wards in hospitals were full of hypertensive patients with orders such 'Measure BP 4 hourly: Call

Correspondence: Professor John Chalmers, Department of Medicine, Flinders Medical Centre, Adelaide, South Australia 5042, Australia

RMO (or SHO) if Diastolic BP > 120 mmHg and give Ansolysen 2.5–5 mg s.c. or Serpasil 1–2 mg i.m. if instructed'. The ambulatory patient was usually treated with one of the potent agents such as guanethidine or methyldopa, often in combination with a diuretic, which was used as an 'adjunct', to enhance the efficacy of the potent drugs. All of these drugs were given in elephantine doses often as high as 3 g of methyldopa or 1 g of chlorothiazide daily.

Severe and moderate hypertension

The treatment of severe non-malignant hypertension with diastolic blood pressure between 115 and 129 mmHg was validated by Freis' landmark 'VA Study' [2] which demonstrated clear reductions in stroke and in mortality, but not in myocardial infarction. Side effects were the rule and distressing, but tolerable given the predictability of an unhappy ending in the untreated patient. A few years later, Freis published the second 'VA Study', this time in milder hypertension with diastolic pressure between 90 and 114 mmHg [3]. The 'VA' studies were double-blind, placebo controlled and used a standardized initial regimen combining hydrochlorothiazide, reserpine and hydralazine. These studies clearly demonstrated reductions in stroke in the upper end of the blood pressure range, but there were too few deaths and too few coronary events to provide reliable estimates of the benefits of mild-moderate hypertension, especially in the lower part of the blood pressure range studied.

Mild and moderate hypertension—'step therapy'

By the early seventies β -adrenoceptor blockers were accepted as a new major class of antihypertensive drugs, and a consensus emerged for 'step therapy' in which treatment was initiated with a diuretic, and if necessary a β -adrenoceptor blocker was added as the second step, and then a vasodilator (usually hydralazine) as the third step. Thus the next generation of major prospective longitudinal studies on the effects of treating hypertension, generally used a treatment regimen based on combination therapy, usually including a diuretic and/or a β -adrenoceptor blocker, with a bewildering array of additional drugs from among those available. Throughout the sixties and seventies the Hammersmith Hypertension Clinic, led by Colin Dollery published substantive papers laying out the clinical pharmacology, efficacy and safety of antihypertensive drugs such as guanethidine, methyldopa, clonidine, propranolol and the diuretics [4–10].

A dozen major randomised drug trials of antihypertensive therapy including the Hypertension Detection and Follow-up Program (HDFP) [11], the Australian National Blood Pressure Study [12] and The Medical Research Council (MRC) Study [13] were published progressively from 1979 and during the eighties and their collective results were analysed in the meta-analysis

published by Collins *et al.* in 1990 [14]. This report confirmed the reductions in stroke of around 42% predicted by the major observational epidemiological studies [15] but also confirmed the relative lack of success in reducing the incidence of heart attack, first noted by Freis [2, 3], with a reduction of 14% in myocardial infarction, compared with the predictions of 25% [15].

New drugs and monotherapy

The disappointing reduction in myocardial infarction led to much soul searching and considerable suspicion that some of the drugs used had exerted adverse effects which partly counteracted the benefits obtained by lowering the blood pressure. The diuretics, with their well documented metabolic side effects were prime suspects. The publication of these large trials coincided with the development and marketing of three major classes of new antihypertensive drugs, the new generation α -adrenoceptor blockers, the angiotensin converting enzyme (ACE) inhibitors, and the calcium antagonists. Inevitably, the old 'step therapy' regime became too complicated, diuretics were used much less, and the new age of 'monotherapy' was born, in which new and potent drugs could be expected to control hypertension single handed(!) with improved compliance and without the complexity of combination regimes.

Hypertension in the elderly and systolic hypertension

Three studies in elderly subjects were published in the nineties—the SHEP [16], STOP [17] and MRC Study in Older Adults [18]. These studies, based on treatment with diuretics and β -adrenoceptor blockers provided convincing evidence of benefit from the treatment of both systolic hypertension [16] and classical hypertension [17, 18] in elderly subjects, they rehabilitated the diuretics, and they strengthened the case for benefit in relation to coronary artery disease. A meta-analysis of 17 unconfounded, randomised studies, including these three studies in the elderly found a 16% reduction in the incidence of myocardial infarction [19], around two-thirds of the predicted 25% benefit [15].

Lifestyle measures

Throughout this period a consensus gradually grew that lifestyle measures (or non-pharmacological treatment) should be used in all subjects with hypertension, either as a foundation for drugs to build on, or in very mild cases as the only treatment [20–24]. On the other hand there is continuing debate about the hypotensive efficacy of individual lifestyle measures such as exercise and salt restriction, and about the risks and benefits of small amounts of alcohol consumption. There is still no randomized prospective clinical trial evidence that

lifestyle measures reduce cardiovascular morbidity and mortality in hypertensive subjects.

Some current issues

Control of hypertension in populations

The old rule of halves, which I first heard from Colin Dollery, had it that only half the people with hypertension were aware they had hypertension, only half of those were on treatment, and only half of those in turn, had their hypertension well controlled—12% of the population at risk. The most recent major survey in the United States, 'NHANES III' published in 1995 [25] indicates substantial improvement, with 53% on treatment and 24% well controlled—twice as good as the previous reports. However this survey highlights two major problems. The first is that even the improved situation falls woefully short of the ideal, that hypertension should be well controlled in all affected subjects: the short term goal set in the USA is to increase the proportion well controlled to 50% by the year 2000 [25]. The situation in many other countries is much worse than in the USA. The second problem is the economic one. All governments are concerned to contain health costs and in particular the cost of pharmaceuticals—witness their anxiety at the cost of 'the new agents' such as ACE inhibitors and calcium antagonists. A major improvement in the control of hypertension, with better detection and more effective treatment of high blood pressure could cause a huge increase in the national drug bill!

Classification of hypertension

It has been the practice, based on the 1978 WHO Expert Committee Report [26] to use the term 'stage' to indicate the absence, presence and severity of complications, with classification into Stages I, II and III. The level of blood pressure has been classified using the terms 'mild', 'moderate' and 'severe'. However the most recent American recommendations [21] depart from this practice and classify hypertension into four 'stages', ('mild', 'moderate', 'severe' and 'very severe') according to the level of blood pressure. It is my opinion that the practising doctor is best served by retention of the WHO style terminology, with updated blood pressure levels for mild (including borderline), moderate,

and severe hypertension, as shown in Table 1, which is based on the 1993 WHO-ISH recommendations [20].

Measurement of blood pressure

It is ironic that there should be increasing confusion on how to measure the blood pressure, given the quantitative nature of the condition. Available methods include the standard mercury sphygmomanometer, automatic and semi-automatic devices, ambulatory devices and a host of devices designed for home blood pressure measurement. Current controversies include:

- The detection and interpretation of 'white coat hypertension', particularly its prognostic significance [20, 21].
- The place of ambulatory blood pressure monitoring in the routine clinical care of the ordinary hypertensive patient [20–24].
- The relationship between clinic blood pressure, home blood pressure and ambulatory blood pressure readings [27].
- The blood pressure estimate that provides the best prognostic predictor.

If the superiority of ambulatory monitoring for predicting target organ damage such as left ventricular hypertrophy is confirmed [28], it seems likely that ambulatory blood pressure monitoring will eventually find a place in the initial assessment of the hypertensive patient, repeated when intercurrent events occur, with reliance on clinic and/or home blood pressure measurements for routine monitoring in between. One of the key issues will be whether a general relationship can be determined between ambulatory, home, and clinic readings or whether this relationship has to be established in the individual patient.

At what level should high blood pressure be treated?

There is now wide agreement that the decision to lower a raised blood pressure should be taken in the context of a thorough assessment of the 'total' or 'global' cardiovascular risk [20–24]. This means that the threshold for treatment is higher in patients without other risk factors, and progressively lower in subjects with increasing number and severity of risk factors such as a raised cholesterol, left ventricular hypertrophy or diabetes mellitus. Unfortunately there is still considerable diversity on the particular levels of systolic or diastolic blood pressure at which various authorities

Table 1 Classification of hypertension by blood pressure level

	<i>Systolic blood pressure (mmHg)</i>		<i>Diastolic blood pressure (mmHg)</i>	
Normotension	< 140	and	< 90	
Mild hypertension	140–180	and/or	90–105	
Sub group: Borderline	140–160	and/or	90–95	
Moderate and severe hypertension	≥ 180	and/or	≥ 105	
Isolated systolic hypertension	≥ 140	and	< 90	
Sub group: Borderline	140–160	and	< 90	

Table 2 Threshold blood pressure (BP) values for initiation of treatment

	WHO-ISH ¹	JNC(V) ²	CANADA ³	NZ ⁴
<i>Diastolic BP</i>				
Treat all ⁵	95	90	90	100
Treat some ⁶	90	–	–	90
<i>Systolic BP</i>				
Treat all	160	140	150	160
Treat some	140	–	–	140

¹Data from references 20. ²Data from references 21. ³Data from reference 23. ⁴Data from references 24. ⁵'Treat all' indicates levels of blood pressure at which treatment is recommended even if there are no additional risk factors ⁶'Treat some' indicates levels of blood pressure at which treatment is only recommended as the total cardiovascular risk is increased by the presence of additional risk factors.

recommend initiation of treatment, in the presence or absence of other risk factors (Table 2) [20–24]. Some national authorities have attempted to specify in great detail the blood pressure levels that should be treated, according to gender, age, and the cumulative presence of other risk factors [24]. One contentious issue is the influence that increasing age should exert on the threshold for treatment.

What should the goal blood pressure be?

The debate surrounding the 'J-Curve' has simmered down while awaiting the results of the Hypertension Optimal Treatment (HOT) study [29]. Current opinion has swung against the concept of a treatment induced J-Curve for diastolic pressures between 80 and 90 mmHg for a number of reasons-

- A similar phenomenon has been observed in the placebo arm of randomized clinical trials [30];
  - The relationship between cardiovascular events and diastolic blood pressure in large scale observational studies appears to remain linear for diastolic pressures well below 80 mmHg [15];
  - Lowering an already low pressure in the trials for the secondary prevention of myocardial infarction is associated with a decreased risk of recurrent infarction; and
  - Lowering the very low diastolic pressures in the SHEP Study produced benefit rather than harm [16].
- Indeed there is considerable evidence such as that from the Glasgow Blood Pressure Clinic that failure to lower raised blood pressure levels to the normotensive range may contribute to the disappointing reduction of myocardial infarction and other cardiovascular events [31].

Considerable doubt also remains regarding the target blood pressure levels in elderly subjects. There is widespread agreement that greater caution is warranted in elderly subjects, with a target pressure around 140–90 mmHg, whereas a lower pressure may be set as the goal for younger patients, with levels of

120–130 mmHg systolic and 80 mmHg diastolic advised by the WHO-ISH Committee [20].

Diuretics

The debate surrounding the thiazide diuretics, muted after the publication of the SHEP, STOP and MRC Studies in Elderly Subjects [16–18] has been re-kindled by the publication of two case-control studies indicating an increase in the relative risk of sudden cardiac death and cardiac arrest in hypertensive patients treated with non-potassium sparing diuretics [32, 33]. Both reports suffer from the weaknesses inherent in case control studies, which are not randomised and have great potential for bias in the selection of drug treatment according to clinical indication and severity. The two studies reach similar conclusions that the relative risk of sudden cardiac death is greater in patients receiving standard thiazide-like diuretics than in those on a regimen that included a potassium sparing diuretic [32, 33]. However, one of the main findings was that progressive lowering of the dose of the non-potassium sparing diuretic, from around 100 mg to 25 mg hydrochlorothiazide (or its equivalent) reduced the risk of sudden death in much the same way. The question of whether a non-potassium sparing diuretic should always be accompanied by a potassium sparing one in the hypertensive patient without heart failure, can only be resolved by a major prospective randomised clinical trial. Meanwhile it is essential to use the lowest possible doses of diuretics, in the range used in the SHEP, STOP and MRC Studies in the Elderly [16–18], or even lower!

Calcium antagonists

The safety of calcium antagonists was challenged during 1995, on the basis of two case control studies [34, 35] and an extension of previous meta-analyses in patients with coronary artery disease [36]. The debate has raged ever since, with one camp calling for constraints in the use of calcium antagonists in patients with hypertension and the other pointing at the flaws in the use of case control studies and highlighting the fact that most of the evidence in patients with coronary artery syndromes was obtained with the old and superseded short acting preparation of nifedipine (10 mg capsules). Many editorials and statements have been written and much heat exchanged [37–44]. The main salient points are these:

- Case control studies of the sort conducted [34, 35] are notoriously subject to distortion arising out of bias in the selection of appropriate drugs according to clinical indication and severity. The result from such studies can generate hypotheses, they cannot prove them.
- The meta-analysis in coronary heart disease [36] is limited to the short acting capsule form of nifedipine which is no longer used in the chronic treatment of essential hypertension. It cannot be established with certainty, nor refuted with confidence, that these results are applicable to other dihydropyridine calcium

antagonists, or to other classes of calcium antagonists. There is some evidence that longer acting calcium antagonists will not be subject to the same limitations [37, 38, 40, 44].

- The editorial by Buring, Glynn & Hennekens [40] puts it well—'A hypothesis formulated but not yet tested'. The question is, what to do while awaiting the results of the large scale clinical trials that will resolve the issue? It is my view that the JAMA editorial got it right again—the important message from these studies is for health care researchers, not for practising doctors or patients. The value of the longer acting calcium antagonists for the treatment of the patient with hypertension, particularly the more severe or complicated patient, is far too great to relegate the whole class of drugs to secondary status without undeniable evidence.
- The saga highlights critical defects in decision-making by leading investigators, national research agencies and major pharmaceutical companies that should have initiated major prospective trials using the newer agents in hypertensive subjects some 10 years ago, not now that the horse has bolted.

Choice of drugs for initiation of treatment

Since the publication of the various national and international guidelines and recommendations in 1993 [20–24] there has been an ongoing debate whether drug treatment should be initiated with any of the groups of first line drugs [20] or with diuretics and β -adrenoceptor blockers [21, 23]. Proponents of the latter base their case on the lack of evidence from long term studies for reduction in morbidity and mortality in hypertensive subjects treated with the new agents [21, 23]. Those who favour a more flexible approach base their case on the fact that the major trials have established the importance of lowering blood pressure *per se* rather than the value of particular groups of drugs, and on the need to provide the practising doctor with a wide range of choices to treat patients with very different characteristics [20]. Since the publication of those guidelines there has been increasing evidence of the safety and efficacy of ACE Inhibitors in reducing morbidity and mortality in patients with related cardiovascular disorders such as myocardial infarction and heart failure. On the other hand the case reports on calcium antagonists in hypertension have thrown doubts on their efficacy in reducing morbidity or mortality [34, 35] as discussed above. This debate continues and highlights the need for prospective randomised studies using the new drug groups.

Lifestyle measures

The arguments over the use of salt restriction to lower blood pressure in hypertensive patients have not gone away. Interestingly, the JNC(V) recommendations [21] took a very positive view and recommended a low sodium diet on a routine basis. However on the other

side of the Atlantic there are continuing doubts on the efficacy and the safety of sodium restriction as a routine element of regimens for the treatment of patients with hypertension. Direct measurements of sympathetic activity in both normotensive and hypertensive subjects, have revealed that a low sodium diet increases sympathetic nerve activity [45], ensuring the debate will continue for some time to come.

Another element of the non-pharmacological approach has come under a cloud—the use of regular exercise, even though this holds a central place in the policies recommended for non drug treatment. The current recommendations in many guidelines include the use of low intensity exercise, such as a brisk 30 min walk five times a week or a 20 min jog 3 times a week [46]. And yet, as pointed out in a recent editorial there is diversity in the results of short-term studies, little evidence that regular exercise lowers the blood pressure in the longer term, and quite a few gaps and contradictions in the evidence that exercise reduces cardiovascular morbidity and mortality [47]. Much of the difficulty hangs on the different effects of exercise in those who have long performed physical exercise and those who have previously been sedentary, and on the lack of evidence from prospective controlled trials that regular physical exercise is effective in the primary prevention of coronary artery disease [47].

Perspective

Genetic predictors

One of the main limitations to obtaining greater benefits from the treatment of hypertension lies in the difficulty predicting the individual patients at greatest risk and hence with the most to gain. The emphasis on the assessment of total cardiovascular risk has emerged as one approach to the better targetting of therapy to the higher risk patient. However, the major advances in the next few years must come from pinpointing the 'at-risk' patient, and even from delineating the particular risks to which the patient is most susceptible, be it the development of left ventricular failure, of cerebral atherosclerosis, of end stage renal impairment or of heart attack or stroke. This will progressively become possible as current research in clinical genetics bears fruit and we will undoubtedly see the day when individuals with one or more risk factors, or with a family history of hypertension or of associated cardiovascular disorders, are put through a genetic screen to help pick who to treat, and what therapeutic strategy to use to maximise preventive efficacy.

Large scale prospective trials

The present imbroglio with calcium antagonists has highlighted the sad lack of foresight that has left us without answers to very predictable questions. It is essential that investigators, research agencies and

pharmaceutical companies work together to address some of the current issues identified above, as well as new issues as they arise. One of the difficulties will lie in the enormous cost of major prospective trials comparing the effects of new and established treatments for hypertension in reducing morbidity and mortality. When one major study can cost US\$50–100 million, and when the budget of the National Health Research Agency in a small country like Australia is only around US\$100 million each year, the magnitude of the task is readily appreciated. It is desirable that industry not be the sole source of funds and that Governments, that have the ultimate responsibility for footing the National Health Bill, should accept some of the costs of mounting the large scale studies needed to shape national drug prescribing policies. One approach is being pioneered by the Second Australian National Blood Pressure Study (ANBP2; 48). This study, which will compare a diuretic based regime with an ACE inhibitor based regime in 6000 elderly patients over a period of 5 years, will be conducted in general practice in Australia and will be funded jointly by industry and by Government. Merck Sharp & Dohme will provide around US\$10 million for the organisation of the study, salaries of study staff and data management, while the Australian Government will foot the bill for the cost of the drugs and of the visits to general practitioners over the period of 5–7 years by the 6000 patients in the study. The argument accepted by Government was that it would normally be paying for the costs of these visits and of the pharmaceuticals if the patients were not in the trial, and that it had a long term interest to generate the data that would be forthcoming.

Two of the important questions do not involve the use of drugs and are therefore unlikely to be supported by the pharmaceutical industry alone. One is the efficacy of the various lifestyle measures such as sodium restriction and exercise in reducing cardiovascular morbidity and mortality in hypertensive subjects. The other is the prognostic value of ambulatory blood pressure readings in predicting subjects at risk of stroke and heart attack. This will require incorporation of ambulatory blood pressure monitoring side by side with clinic blood pressure measurements in a large number of the major prospective trials of treatment. Once again pharmaceutical companies may be reluctant to fund the additional costs of answering this question, and investigators might have to seek support from Research Agencies for the additional expenses involved.

Partnerships and coalitions of many different kinds will be necessary if we are to have the data we need, when we need it.

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