Management of Hypertension

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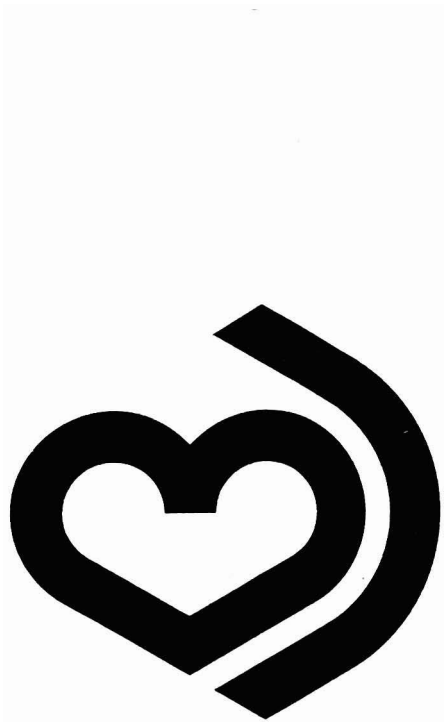


SECTION 1

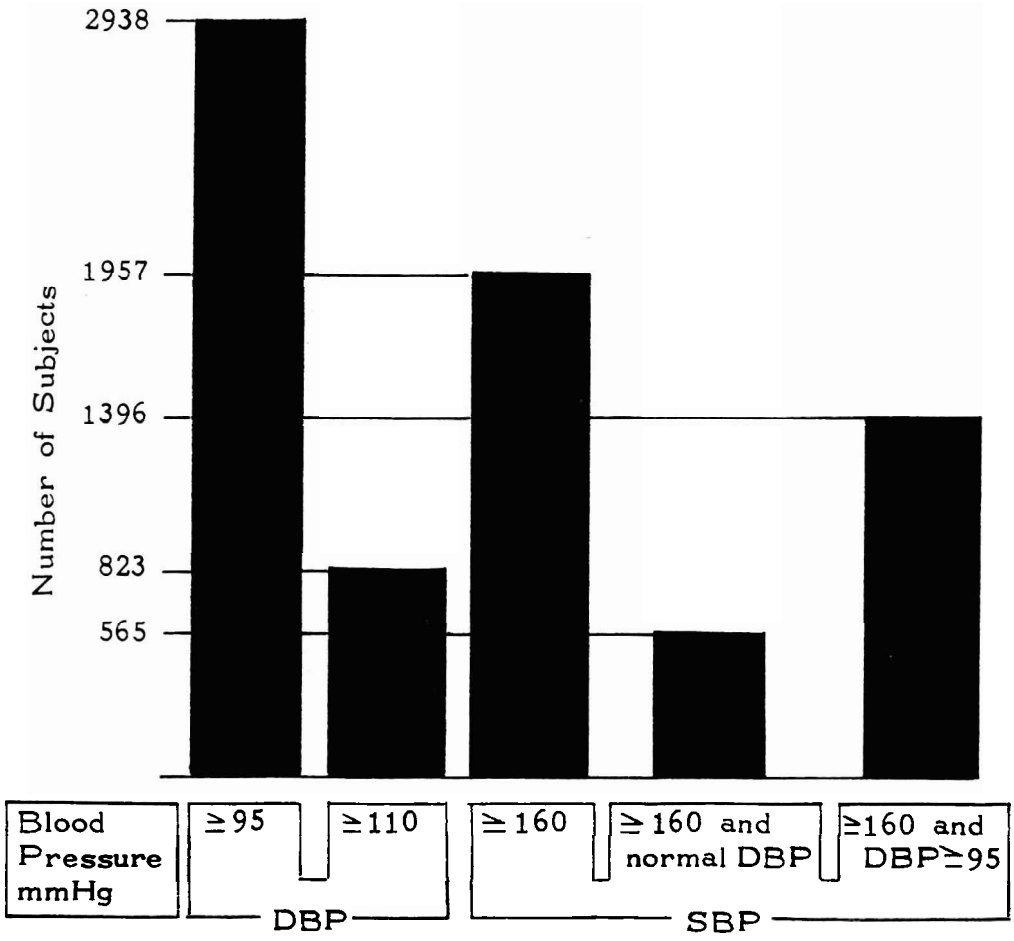
HYPERTENSION IN THE COMMUNITY

Introduction

The frequency of hypertension in Ireland is somewhere between 5 per cent and 20 per cent of the adult population, depending on how we define hypertension. In the Irish Heart Foundation study of 15,171 men aged 25-74, 19.3 per cent had diastolic pressures of 95 mmHg and over and more than a fourth of these had a diastolic blood pressure of 110 mmHg or more (Table 1).

Table 1 PERCENTAGES OF 15,171 SUBJECTS WITH ELEVATED BLOOD PRESSURE

SBP = SYSTOLIC BP mm Hg
DBP = DIASTOLIC BP mm Hg



The true frequency of hypertension is probably about 10 per cent of the population if we consider only young and middle-aged adults.

Elevated blood pressure is asymptomatic and uncomplicated in the early stages. It does however increase the risk of certain diseases, notably coronary heart disease and stroke. In Ireland, as in many western countries, coronary heart disease is the commonest cause of death. Cerebrovascular disease also accounts for a high proportion of deaths and a heavy toll in morbidity. Together coronary heart disease and stroke cause 50 per cent of all deaths in this country. Renal failure and heart failure also add to the list of serious hypertensive complications.

Hidden Hypertensives

Because hypertension is frequently asymptomatic, many hypertensive subjects remain undetected. More than 60 per cent of hypertensive subjects in the Irish Heart Foundation study had no previous history of the condition. Studies from other western countries report a somewhat similar prevalence of undetected or hidden hypertension.

Risk Factors

It is clear that in Ireland there are large numbers of adult men and women with undetected hypertension who are at high risk from developing complications, one of the most important of which is coronary heart disease. However, elevated blood pressure constitutes only a part of the total coronary risk profile. It is now well established that coronary heart disease is multifactorial in origin. Apart from elevated blood pressure, other important risk factors for cardiovascular disease are cigarette smoking and high blood lipid levels. Physical inactivity and reduced glucose tolerance may also be of importance but are probably of less significance than smoking and hyperlipidaemia.

Elevated blood pressure itself increases the risk of developing coronary heart disease fourfold. However, the hypertensive subject who also smokes cigarettes and has elevated blood lipids has a risk of coronary attack up to thirty times greater than those free from these characteristics. These facts are of practical importance when we note the frequency with which hypertensive subjects exhibit other coronary risk factors. The relevance of this to the management of the hypertensive patient is obvious. Table 2 shows the frequency with which other coronary risk factors occur in combination with elevated blood pressure amongst Irishmen.

Benefits of Treatment

On the basis of evidence from carefully controlled trials, we know that antihypertensive drug treatment is effective in reducing the frequency of stroke, heart failure and kidney failure in patients under 60 years with moderate to severe hypertension. Recent evidence suggests that treating hypertension also reduces the frequency of coronary attack.

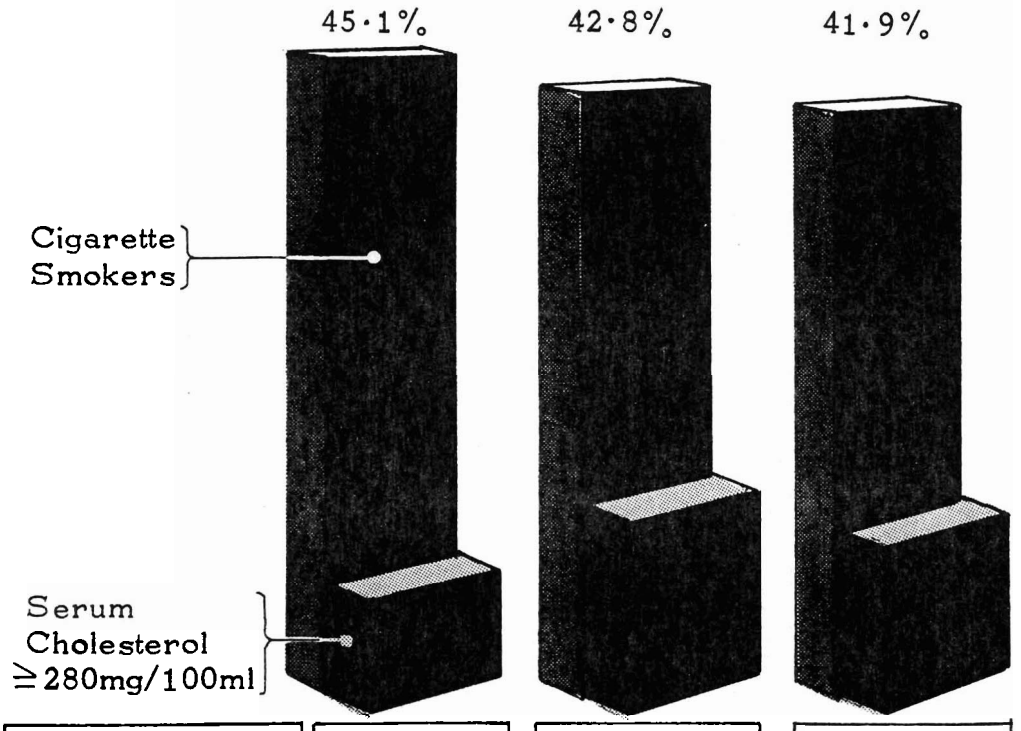
The effectiveness of antihypertensive treatment in preventing stroke in the over-60 age group is uncertain, although there is some evidence that treatment may continue to be effective in older people. Nor do we know the value of treating mild hypertension.

From the point of view of community health and preventive medicine, the group most likely to benefit from antihypertensive drug treatment includes the moderate to severe hypertensives who are less than 60 years. The financial burden of detecting and managing a large number of men and women with mild hypertension or who are over 60 years would be considerable, and the results might be less impressive than in those under 60 years or with a diastolic pressure of 105 mmHg or greater.

There is no evidence that treatment with antihypertensive drugs will prevent recurrence of stroke in patients with clinical cerebrovascular disease, although a recent report would suggest that the recurrence of a coronary attack may be reduced by treating hypertensive patients with myocardial infarction or angina of effort.

There is no agreement yet about the level of blood pressure which merits treatment, but patients with moderate to severe hypertension should receive treatment. Unfortunately population studies in Western communities indicate that only a

Table 2 FREQUENCY OF ELEVATED SERUM CHOLESTEROL AND CIGARETTE SMOKING IN DIFFERENT BLOOD PRESSURE CATEGORIES



DBP (mmHg)	<95	95 - 109	≥110
Subjects (15171)	12233	2115	823

minority of detected hypertensives are on adequate treatment. Wilber and Barrow, in studying a population sample in Baldwin County in the United States, found that only 30 per cent of known hypertensives were on treatment and of these only one half were under good control. More than half of all the hypertensive patients had lost contact with their doctors within three months of detection. In another study only 11 per cent of patients treated for hypertension in 1961 were still on treatment 5 years later. We found the same results during the course of our screening programme in the Irish Heart Foundation.

These rather depressing findings serve to emphasise the need for better professional and public education. A major problem is to ensure long-term patient compliance, particularly in relation to drug therapy. Close and continued communication between doctor and a well-informed patient is essential if treatment is to be satisfactory and adequate. Also, side-effects of drugs must be tolerable and must be explained if good adherence is to be expected. There is no doubt that a major factor preventing effective community control of hypertension is poor patient compliance. We can expect compliance to remain poor unless physicians communicate more effectively with their patients, and follow them up throughout treatment. In the clinical management of hypertension the physician is in effect practising preventive medicine. In dealing with asymptomatic patients over the long-term, the strategy in many respects differs from the usual clinical approach and the somewhat easier task of dealing with symptomatic disease.

Community Control Programme

There are good reasons for establishing a community control programme for hypertension. The high frequency of undetected cases, the relative ease of detection, the favourable influence of treatment, and the introduction of newer drugs which are easier to administer, and which have fewer side-effects are factors which favour such a programme. Since April, 1976 the Irish Heart Foundation has been promoting a hypertension control programme which is now operating in all Health Board areas. This programme includes screening centres from which hypertensive subjects are referred to the general practitioner. An important part of this programme is an evaluation of patient compliance.

The prevention of coronary heart disease, stroke and vascular disease would dramatically improve life-expectancy for our middle-aged population. The practising physician can make a significant contribution to improving community health by the detection and successful management of his hypertensive patients. The prevention of coronary heart disease and stroke will to a large extent be a reflection of the family doctor's care and dedication in this new and exciting field of preventive medicine.

SECTION II

THE EVALUATION OF HYPERTENSION

Initial Measurement

The examining doctor has a unique opportunity to detect previoulsy undiagnosed hypertension - over ninety per cent of the population attend their family doctor at least once in five years. Members of the public are encouraged to have their blood pressure checked once every two years, and the family doctor should endeavour to measure the blood pressure in all patients who have not attended within the previous two years. Ideally every patient attending should have the blood pressure checked.

Hypertension can be diagnosed only by recording the blood pressure with a sphygmomanometer. A sphygmomanometer should be maintained in good working order. Mercury manometers are preferred to the aneroid type, because these are more reliable. The pressure cuff of the sphygmomanometer should measure a standard 12 x 30 cms. In the case of a cuff held in place by a "tail", the latter should be long enough to support the entire bag.

The subject should be seated and relaxed with the arm bared and free from restricting clothing. Korotkoff actually described five phases associated with changing auscultatory phenomena in the measurement of blood pressure. We need only concern ourselves with the first phase, (the appearance of sounds on releasing the cuff pressure denoting the systolic blood pressure), the fourth phase (muffling of sounds), and the fifth phase (disappearance of sound). The fourth and fifth phases may be simultaneous but there can be a difference as much as 10 mmHg, a factor which could have considerable implications, not only in the assessment of treatment, but also in the diagnosis and prognosis of hypertension for employment and insurance purposes. There is disagreement as to whether the fourth or fifth phase is a more accurate measurement of diastolic pressure - the so-called "diastolic dilemma". Until this controversial matter has been decided - and opinion will probably favour acceptance of the fifth phase (as in the United States and many European countries) - it is recommended that we record the fifth phase only. In patients without a fifth phase, where the sound continues to a very low level or to zero, it is best to accept the fourth phase.

The Significance of Measurement

A casual blood pressure reading serves only as a possible indicator of hypertension, and it is well to remember that physiological stimuli, such as exertion and anxiety, may temporarily elevate the blood pressure. A patient once labelled "hypertensive" by a doctor may carry this tag for life. For the young patient particularly this may have serious implications for future employment, insurance, mortgage and pension rights, to say nothing of the prognostic implications and the inconvenience of lifelong management. Bearing these facts in mind it is well to take time over the diagnosis of this disease. The average of two or three measurements should be taken at each visit, and blood pressure measurements should be obtained on at least two separate occasions before treatment is prescribed, unless the initial diastolic blood pressure is greater than 120 mmHg.

Elevation of the systolic pressure does appear to be associated with increased cardiovascular risk, but the benefits of treatment of isolated high systolic pressure are doubtful. A systolic blood pressure which is disproportionately high, particularly in the young patient, is an indication for further evaluation.

Bearing these facts in mind and taking the fifth phase (disappearance of sound) as the diastolic pressure, the following recommendations can be made:

DBP (mmHg)	Recommendations	Drug Treatment
120 o greate	Immediate evaluation	May be urgent
105 –	Confirm in one week	Probably indicated
95 –	Check in one month	Possibly indicated
90 –	Check in 2 - 3 months	Unlikely

History

The history should seek any symptoms relevant to the cardiovascular system, such as angina or breathlessness. A history of weakness, muscle cramps and polyuria might suggest hyperaldosteronism, whereas headaches, palpitation and excessive sweating, particularly if paroxysmal and associated with elevation of the blood pressure suggests phaeochromocytoma. A previous history of blood pressure and the patient's tolerance of, and adherence to, treatment should be noted. Other risk factors, such as cigarette smoking, oral contraceptives and other hormones, a high salt intake and a family history of high blood pressure or cardiovascular disease should be assessed.

Examination

Elevation of the blood pressure is only one sign in a patient with cardio-vascular disease. The clinical examination should be directed towards detecting other manifestations of cardiovascular illness which may be even more important than the level of the blood pressure.

The presence of left ventricular hypertrophy, accentuation of the second sound in the aortic area, and cardiac failure suggest long-standing and significant hypertension.

Examination of the optic fundi may show arterio-venous nipping, arterial narrowing and irregularity, haemorrhage, exudates or papilloedema, all signs of significant hypertension.

On examination of the abdomen the presence of renal bruits may indicate renal artery stenosis. Large kidneys may denote polycystic disease, and coarctation of the aorta should be excluded by checking that the femoral and radial pulses are synchronous.

Examination of the patient with hypertension is not complete without a routine urinalysis to detect the presence of blood or protein possibly indicating renal disease, or glucose indicating diabetes mellitus. Height and weight should be recorded.

Investigations

It is now generally accepted that the majority of patients with hypertension do not need detailed investigation and the following are sufficient in most cases:

Urinalysis and, if abnormal, urine microscopy
Serum Creatinine and/or Blood Urea
Serum Potassium
Serum Cholesterol
Electrocardiogram

More detailed investigation may be indicated in patients under the age of forty, those with evidence of target organ damage, patients with a sudden onset of severe hypertension, and those with severe hypertension who fail to respond to therapy. Patients with hypokalaemia should also be investigated. If on the completion of the clinical assessment and investigation there remains suspicion of a possible cause for the hypertension, the patient should be referred for detailed evaluation.

Conclusions

To avoid misdiagnosis, considerable care should be taken in the measurement of blood pressure. Evidence of hypertensive disease of the heart, retinal vessels, kidneys and vascular tree should be carefully sought. The detection of other cardiovascular risk factors is as important as the blood pressure measurement. Detailed investigation is only necessary in a minority of patients with hypertension.

The Object of Management

The word management has been carefully chosen for the heading of this section. All patients with sustained diastolic pressures in excess of 90 mmHg will require management, probably for the rest of their lives, although they may never need drug therapy. Patients with sustained diastolic pressures above 105 mmHg will also require management for the rest of their lives but for many in this group drug therapy will be part of management.

The general measures outlined below are common to the management of all patients with hypertension regardless of the severity, whereas drug treatment will be reserved for those failing to respond to these general measures.

The object of management is to achieve and maintain a diastolic blood pressure of 90 mmHg or less with as few adverse symptoms as possible. This can be achieved in over 80 per cent of patients but the doctor may have to see the patient frequently to adjust or modify therapy, especially in patients with persistently high blood pressure.

Explanation and Reassurance

The patient with hypertension has an illness that may require life long attention, a fact that must be fully explained to the patient who should be also told that hypertension is one of the major risk factors in the aetiology of cardiovascular disease, especially stroke, and to a lesser degree coronary artery disease, peripheral vascular disease and renal disease. It should be emphasised that the disease is usually asymptomatic, that there is no cure for hypertension, but that we can offer to control elevated blood pressure provided the patient adheres to the management and treatment regimen for the remainder of his or her life. One of the major problems in the management of hypertension is convincing the patient to adhere to treatment. Somewhere between one-third and one-half of patients on treatment for hypertension fail to take prescribed medication. Failure to adhere to a prescribed regimen is partly due to inadequate information about the illness, and particularly failure to appreciate the need for life-long surveillance. Too often the patient accepts the diagnosis, and takes medication for the time prescribed in the false belief that the problem has thereby been solved.

Having explained the nature and consequences of hypertension, it is not unreasonable to reassure the patient that, provided he or she co-operates, the onset of premature cardiovascular disease can be averted, and a normal life expectation restored.

The patient should be told the level of blood pressure, the name of the drug prescribed, and in particular its potential side-effects. It should be pointed out that if one drug is not suitable, another of equal efficacy can be substituted, and that in nearly every patient effective treatment can be provided.

General Measures

1. Smoking

The role of smoking in the aetiology of cardiovascular disease cannot be overstressed. It must be emphasised to the patient that we are already dealing with one serious risk factor, namely hypertension, and that the addition of smoking greatly augments the total risk to which the patient is exposed. Patients with hypertension must be firmly advised to stop smoking cigarettes altogether, and if possible, to stop all forms of smoking because of the well established propensity of the cigarette smoker to inhale the pipe or cigar when he changes to these alternative forms of smoking. If the patient will not cease cigarette smoking he should be encouraged to reduce tobacco intake to an absolute minimum, and to use tipped cigarettes with a low tar and low nicotine content.

2. Dietary Modifications

(I) Calorie reduction: Obesity of itself may not be a very potent risk factor for cardiovascular disease, bui weight reduction may lower blood pressure quite substantially. Furthermore, the patient who is overweight is generally in a poor state of health and physical fitness, and he should be instructed to reduce his total calorie intake in order to maintain ideal body weight.

(II) Salt reduction: In some countries much importance is attached to salt reduction in the management of hypertension. There may not be a place for strict reduction, but some patients do consume excessive amounts of salt and may benefit by being more prudent in their intake. A simple means of restricting salt intake is to refrain from adding salt to food and to avoid very salty food.

(III) Fat and Cholesterol Reduction: There is no conclusive evidence as yet that reduction of saturated fat and cholesterol in the diet will postpone the onset of cardiovascular disease, but as our intake of these substances, notably in dairy produce, is often too high, it is reasonable to recall the association of hyperlipidaemia and atherosclerosis, and to suggest prudence in

3. Exercise

The sedentary existence so common in our society has not been proven as a causative factor in cardiovascular disease, but regular physical exercise is associated with a sense of physical and psychological well-being. With a properly prescribed, enjoyable and regular exercise programme, patients will be better motivated to follow advice about treatment and lifestyle modification. There is certainly no harm in encouraging patients to take exercise in keeping with their age, inclinations and circumstances.

4. Interaction of Stress and Personality

Much attention has been devoted to personality and the complex effects of stress on the individual, particularly in relation to susceptibility to cardiovascular disease. It is extremely difficult to prove cause and effect. On the practical side it is difficult to modify personality, but patients can be encouraged to avoid stressful situations, and to take relaxation in a form to suit their needs, whether this be through meditation (transcendental or otherwise), an afternoon nap, massage, exercise or drugs. In general we do not recommend the use of tranquillisers, certainly over the longterm, but selected patients may be helped initially by the judicious use of a suitable tranquilliser under strict supervision.

5. Drug Treatment

Patients with diastolic pressures greater than 120 mmHg usually need urgent drug treatment, but those with milder elevation of blood pressure, i.e. the majority, may respond to the general measures outlined above, and many patients will not need additional drug treatment.

The drugs available for the treatment of hypertension are considered in detail in the next section. Beta-blockers are now accepted by most experts as the drugs of first choice because they are effective whilst being reasonably free of side-effects, and may be administered in once -daily dosage, thus improving patient adherence. Furthermore, they may be used to treat concomitant disorders, such as anxiety, angina pectoris and arrhythmias. Disadvantages are that the dose must be adjusted to the individual patient, and care must be taken in using beta-blockers in patients with a history of asthma or bronchitis. In these patients cardioselective preparations are safer, but still need to be given cautiously. The high cost of these drugs is a major problem which must be balanced against efficacy and reasonable freedom from side-effects.

The choice of drugs for the treatment of hypertension will be influenced bv the doctor's experience, by his knowledge of the medical literature, by the patient's response and tolerance, and by cost. One drug will not suit all patients, but all uncomplicated cases of essential hypertension will respond to some conventional drug regimen.

The following regimens are selected on the basis of the author's preferences, and the general trends in the treatment of hypertension in most European countries and the United States. Either regimen can be modified and many doctors may prefer to start all patients on a diuretic, later adding a beta-blocker, or methyldopa, or an adrenergic neurone-blocking drug as required.

Regimen 1

Until recently thiazide diuretics were the first line of drug treatment in hypertension. However, these drugs are not without their side effects - hyperuricaemia, diabetes mellitus and hypokalaemia. Futhermore, being effective in only mild hypertension, additional treatment is usually necessary, thus decreasing the chances of patient compliance. Because of these problems many doctors prefer to start treatment with a beta-blocker alone.

Most beta-blockers can be administered once daily for the treatment of hypertension (this is not necessarily so in the treatment of angina pectoris and arrhythmias). The starting dosage is usually modest, for example atenolol 100 mgm daily, and this can be then increased at weekly intervals until satisfactory cont·ol of blood pressure is achieved. If, after achieving effective beta-blockade as judged by a fall in the resting pulse rate to below 55 per minute, the blood pressure is not adequately controlled (diastolic below 90 mmHg), a thiazide diuretic such as bendrofluazide 2.5 mg daily is added. It is common practice to give a combined prepartaion of a thiazide and a potassium supplement, although there is evidence that in the hypertensive patient who is not in heart failure this may be unnecessary.

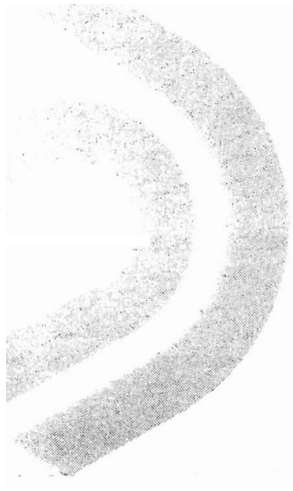
If hypertension remains uncontrolled with a beta-blocker and a diuretic, a vasodilator may be added. Vasodilators alone will produce a fall in blood pressure, but this is rapidly counteracted by sympathetic outflow which will reverse this trend. However, if prior beta-blockade has been achieved, this compensatory sympathetic excess is attenuated and the hypotensive effect of the vasodilators is uninhibited. Hydrallizine is one of the vasodilators most commonly used, but drug-induced systemic lupus erythematosis may occur: this is unlikey if the dose does not exceed 200 mgm daily.

Regimen II

In this regimen we include the "older" drugs as well as some new compounds. It is customary to commence treatment with a thiazide diuretic, and if satisfactory control of blood pressure is not achieved, methyldopa, clonidine, prazosin, or an adrenergic neurone-blocker, such as guanethidine, may be added. The side-effects of these drugs are considered in the next section. It should be emphasised that with methyldopa lethargy and drowsiness may be quite incapacitating, and the patient may fail to attribute the symptoms to the drug. In particular we should be alert to the propensity of older people to side-effects such as depression and fatigue on methyldopa, beta-blockers and other preparations.

6. Follow-Up

Should the hospital, the general practitioner or both, follow-up patients with hypertension? There should be no doubt about the fact that all patients with hypertension must be seen regularly by a doctor, or by nursing staff under the supervision of a doctor. This is necessary, firstly to encourage the patient to adhere to the management regimen, secondly to ensure that adequate control of blood pressure is maintained, thirdly to detect side-effects which might prevent the patient taking prescribed therapy or cause the patient serious morbidity, and, finally, to anticipate the onset of cardiovascular complications and to institute appropriate therapy. The ideal arrangement would seem to be for the patient to attend the hospital clinic once or twice yearly, and to attend his own doctor monthly initially, and quarterly once blood pressure control has been achieved.



SECTION IV

THE CLINICAL PHARMACOLOGY OF DRUGS USED IN THE MANAGEMENT OF HYPERTENSION

Introduction

In this section we provide the background information necessary for the rational use of the various agents in the management of patients with essential hypertension.

The classification used is very arbitrary but follows the usual convention. Thus, while we speak of diuretics and beta-adrenergic blocking drugs, we really don't know their precise mechanism of antihypertensive action. However, this is the best working classification presently available. Because of the similarity of drugs within groups, there is frequently little to choose between various members. Thus efficacy, time, course of action and unwanted effects may vary only slightly. While costs must not become an overriding influence, it is obvious that in many cases the only discernable difference between drugs is indeed one of cost and within the same group of drugs it is easy to highlight this fact. However, when trying to decide the relative merits of different groups e.g. diuretics as against beta-adrenergic blocking drugs, the equation becomes more complex and cost may recede in importance.

The drug list provided at the end of each section is not intended to be exhaustive, but collectively they probably account for all but a small percentage of drugs used in the treatment of hypertension. In ascribing values to starting and maximum doses we have necessarily been arbitrary. Many clinicians and indeed the respective pharmaceutical companies might disagree with the values we have given. However, it is our intention that these figures and the extrapolated monthly wholesale costs should act merely as a rough guide to dose and cost.

DIURETICS

Diuretics have been the mainstay of antihypertensive therapy for the past 15 years. Even though the position of this group is in the process of reassessment, diuretics still have an important role in the antihypertensive armamentarium.

Mechanism of Antihypertensive Action

It is not clear how diuretics exert their antihypertensive effect in established essential hypertension. In many cases the diuretic action leads to a decrease in plasma volume. However, in the stable clinical situation the diuretic efficacy is not readily related to the antihypertensive effect. It has been postulated that a second mechanism of action is to decrease sensitivity of arterioles to the vasoconstrictor action of catecholamines. This effect is loosely defined as "vasodilatory".

Classification

Most diuretics currently used in the management of hypertension fall into one of three groups:

A) **Thiazides:** The thiazides exert their diuretic action by preventing sodium reabsorption in the distal tubule proximal to the site of sodium/potassium exchange. The diuretic effect is gradual in onset and variable in duration from 8 - 24 hours. They may cause hypokalaemia, impaired glucose tolerance, and hyperuricaemia.

B) **Loop Diuretics:** These are so called because thy exert the diuretic effect by inhibiting sodium reabsorption in the ascending limb of the loop of Henle. They are highly effective diuretics, their onset of action is abrupt and the duration is shorter than that of the thiazides. They have similar metabolic side-effects to the thiazides.

C) **Potassium Sparing Diuretics:** These act at the site of sodium/potassium exchange. Spironolactone competes with aldosterone and thus decreases exchange and thereby conserves potassium. Amiloride and triamterene do not compete with aldosterone but the end-result is similar in that exchange is impaired.

Which Diuretic in Hypertension?

There are in all 32 diuretic preparations listed in MIMS. Many of these are combinations of potassium with a potassium-losing diuretic while others are combinations of potassium-losing and potassium-sparing diuretics. In the vast majority of patients with essential hypertension, a thiazide alone is the diuretic of first choice. Loop diuretics are if anything less effective antihypertensive agents. In addition they are more expensive (see Table 3). While there is a good case to be made for potassium-sparing diuretics when hypokalaemia is the problem, these drugs do not have any substantial advantage over thiazides in uncomplicated hypertension. All three members of this group are much more expensive than thiazides.

Which Thiazide?

We feel there is little evidence to indicate important differences in efficacy, duration of antihypertensive action or unwanted effects with these drugs and therefore the deciding factor becomes one of cost. The five cheapest (methychlorthiazide, bendrofluazide, hydrochlorthiazide, cyclopenthiazide and hydroflumethiazide) vary in price from 50p -75p per month (wholesale price).

Potassium Depletion

All diuretics which inhibit sodium reabsorption from the renal tubule proximal to the site of sodium or potassium exchange in the distal tubule may cause potassium depletion. In essential hypertension less than 5 per cent of patients develop potassium depletion on thiazide diuretics, and therefore many experts feel that potassium supplements or the use of potassium sparing diuretics is not necessary on a routine basis. Suggestive symptoms of potassium depletion include lethargy, tiredness and muscle weakness. Plasma potassium of less than 3 mmol/L is valuable confirmatory evidence and in addition there may be ECG changes.

(i) Diet

Some patients, particularly the elderly, have an inadequate potassium intake because their diets are deficient in meat and fresh fruit. Appropriate dietary advice should therefore be given. In addition, sodium intake is an important determinant of potassium loss and modest restriction of sodium in the diet will help to minimise the problem of hypokalaemia.

(ii) Potassium Supplements and Potassium Sparing Diuretics

In the event of potassium depletion either potassium supplements or potassium sparing diuretics may be employed. Only under very well supervised circumstances in hospital should potassium and potassium sparing diuretics be used simultaneously as dangerous hyperkalaemia may rapidly ensue. Fixed dose combinations of diuretic and potassium do not contain enough potassium to replenish losses once potassium depletion has occurrred, and it is then necessary to supplement the dietary potassium intake.

Slow K contains 8.0 meq/tablet of potassium and doses as high as 48 meq/day (6 tablets) may be required. While these preparations are not free of ulcerogenic potential, they are considerably safer than enteric-coated potassium chloride. An alternative vehicle for potassium is as an effervescent drink which is rather foul tasting, but is drinkable. Potassium-sparing diuretics such as amiloride, spironolactone and triamterene conserve potassium in amounts sufficient to replenish stocks but this takes some weeks usually.

Table 3 DIURETICS: Preparations, dose and cost

GROUP	DRUG NAME		Tablet size, mg.	Average daily dose, mg.	Average cost month £
	Trade	Approved			
THIAZIDE	*Centyl	Bendrofluazide	2.5, 5.0	5.0	0.75
AND	Enduron	Methychlorothiazide	5.0	5.0	0.72
RELATED	*Esidrex	Hydrochlorothiazide	25, 50	50	1.58
	*Hydosaluric	Hydrochlorothiazide	25, 50	50	0.73
	*Hygroton	Chlorthalidone	50, 100	50	0.95
	*Navidrex	Cyclopenthiazide	0.5	0.5	0.50
	Nephril	Polythiazide	1.0	1.0	0.93
	Saluric	Chlorothiazide	500	1,000	1.00
	Zaroxolyn	Metolazone	2.5, 5.0, 10.0	5.0	1.50
POTASSIUM					
SPARING ≠	Midamor	Amiloride	5.0	10	2.30
	Dytac	Triamterene	50	150	4.96
	Aldactone	Spironolactone	25, 100	200	1.71
"LOOP"	*Burinex	Bumetanide	1.0	1.0	1.22
	Edecrin	Ethacrynic Acid	50	50	0.90
	*Lasix	Frusemide	40	40	1.53

Wholesale price based on starting and maximum daily doses. The retail price is on average 50 per cent greater.

**Available in fixed dose ratio combinations with potassium. The potassium content varies from 6.7 to 10.0 meq. The majority contain approximately 8.0 meq/tablet. Many of the potassium containing preparations are at lower diuretic strength than for diuretic alone, e.g. Centyl K tablets contain bendrofluazide 2.5 mg plus 7.7 meq of potassium and Navidrex K tablets contain 0.25 mg of cyclopenthiazide plus 8.0 meq of potassium.*

≠All potassium-sparing diuretics are available in fixed dose ratio combinations with a thiazide.

Other Metabolic Effects

Thiazides and the loop diuretics are diabetogenic when used on a prolonged basis. Patients with impaired glucose tolerance exhibit further deterioration of glucose tolerance. The risk of worsening of glucose tolerance is related to the duration of diuretic therapy.

Thiazides and loop diuretics also decrease uric acid clearance by the kidney so that an increase in blood uric acid is not uncommon in patients taking these agents on a long-term basis. In many cases, the increase is marginal but in some patients the hyperuricaemia is clinically significant and clinical gout may occur; the responsible diuretics should then be stopped.

BETA-ADRENERGIC BLOCKING DRUGS

Mechanism of Action

Beta-adrenergic blocking drugs probably exert their antihypertensive effect at a number of different sites–

1. Central nervous system
2. Plasma renin-lowering effect
3. Decrease in cardiac output.

Some drugs in this group, notably propranolol and/or metabolites, gain access to the brain in significant amounts and act by decreasing sympathetic outflow. The renin-lowering effect seems to be particularly important in the group of essential hypertensive patients who have elevated plasma renin activity. These patients are usually younger adults. A decrease in cardiac output is seen after initiating beta-blocker therapy but this is usually accompained by an increase in arteriolar tone so that initially no fall in blood pressure occurs. However, after some weeks arteriolar tone diminishes and the antihypertensive effect becomes apparent.

Classification of Beta-Adrenergic Blocking Drugs

These drugs may be classified (Table 4) by the presence or absence of:

a. Cardioselectivity
b. Direct cardiac depressant effect
c. Intrinsic sympathomimetic activity
d. Alpha-blocking activity

a. **Cardioselectivity**

Selectivity in this context is a relative term, and as such is of considerable importance. Some drugs e.g. atenolol and metoprolol, have much greater blocking potential for $beta_1$(cardiac) receptors than for $beta_2$(noncardiac) receptors. The non-cardiac beta receptors include those in the bronchial smooth muscle and arterioles. Thus, we would expect conventional clinical doses of a cardioselective drug to have much less effect on the bronchi and arterioles than would propranolol which is non-selective. On theoretical grounds it may be more rational to use selective blockers in hypertension on the basis that stress-induced increase in blood pressure is less with this drug. However, this idea has not gained widespread acceptance at present.

While one must be very wary in using beta-adrenergic blocking drugs (be they selective or not) in asthmatics, clearly the cardioselective agents are safer. Similarly, in patients who have peripheral vascular disease, the cardioselective drugs are preferable.

In summary, therefore, selective drugs are preferable to non-selective drugs when $beta_2$blocking activity is contraindicated e.g. in bronchial asthma and peripheral vascular disease.

b. **Direct cardiac depressant effects**

The terms 'direct depressant effect'and 'quinidine-like effect' and 'local anaesthetic effect' are used to describe actions of these drugs on the heart which are not related to the beta-blocking action. These terms are not synonymous but they tend to go together. From the point of view of left ventricular function such as cardiac output, the presence or absence of direct depressant effects is probably of no clinical significance, as they are seen only under laboratory conditions when very large doses are used, and this property need not influence our choice of drugs.

c. **Intrinsic sympathomimetic activity**

Some drugs e.g. acebutolol, can under certain circumstances be shown to possess sympathomimetic activity. In clinical practice, this possibly means less efficacy, but it is argued that drugs with this property are safer than those without intrinsic sympathomimetic activity. In terms of antihypertensive effect it is unlikely that the presence or absence of this property is important.

d. **Alpha-adrenergic blocking activity**

Noradrenaline exerts its hypertensive effect by stimulation of alpha receptors in arterioles. This vasoconstrictor action can be blocked by using alpha adrenergic blocking drugs. A number of such drugs are available but for a variety of reasons have proven unsuitable for antihypertensive therapy. The manufacture of a drug - labetolol - which has both alpha and beta-blocking activity, is theoretically a very exciting development. The alpha-blocking action causes arteriolar dilation and thereby cause a decrease in resistance and a fall in blood pressure. The beta-adrenergic blocking activity antagonises the reflex increase in cardiac output and heart rate consequent on the vasodilatation and thereby augments the hypotensive effect. In addition, the long term effects of the drug acting as a beta-blocking agent should contribute to blood pressure lowering. This is a new drug and more studies and clinical experience must accrue before we can assess its proper place in anti-hypertensive treatment.

Unwanted Effects

All beta-adrenergic blocking drugs may precipitate heart failure, but this probably never occurs in patients with normal hearts; it is more likely to occur in patients who have been in congestive heart failure previously, and may arise after one or two doses. Thus, tentative initial dosing and prior digitalization is advisable in those considered to be at risk, or else use an alternative antihypertensive drug.

Bradycardia may occur and in some cases will limit the clinical efficacy of beta-blockers. One should not increase the dose when the resting heart rate falls below 50 beats per minute.

Bronchospasm and peripheral circulatory problems occur due to blockade of beta-adrenergic receptors in bronchial smooth muscle and in arterioles. As indicated above, these problems can be minimised but not necessarily abolished by using cardioselective agents. If beta-adrenergic blockers must be used in asthma, it is wise to have a beta$_2$ stimulant such as salbutamol (Ventolin) or terbutaline (Bricanyl) to hand.

A number of central nervous system side-effects have been noted with the beta-adrenergic blocking agents. These include sleep disturbance, nightmares, drowsiness, lethargy and depression. These effects initially alerted investigators to the possibility of a central nervous system site of the antihypertensive effect of propranolol. It is thought that drugs such as propranolol, which penetrate the blood brain barrier easily, are more common offenders. However, there are no clear comparative data which indicates that one drug in this group is more likely to cause unwanted central nervous system side-effects that any other.

Which beta-adrenergic blocker to use

In making the choice of a beta-adrenergic blocking agent the following considerations are important:

1. Will the drug be effective throughout 24 hours?
2. Are the additional pharmacological properties of the agent important?
3. Which is safest?
4. Which is least expensive?

Because it seems that the fewer tablets the patient has to take and the fewer occasions on which he has to do so, the more likely it is that he will adhere to treatment it is important to keep tablet taking to a minimum. It is very likely that all beta-adrenergic blocking agents currently available can provide adequate blood pressure control throughout 24 hours if taken on a twice per day basis. Indeed, it may be that once blood pressure control is established, any of these drugs could be given as a single daily dose to maintain blood pressure at the appropriate level. Thus, drugs such as propranolol which have quite short plasma half-lives have an antihypertensive duration of action sufficient to control blood pressure throughout a 12 and possibly a 24-hour period.

The importance of added properties has been discussed above. The use of a cardioselective agent is particularly desirable in patients with bronchospasm or arterial disease, and in those who develop peripheral circulatory problems when given a non-selective drug. The combination of alpha and beta-receptor blockers in one drug holds promise for the future, but the unwanted effect of postural hypotension could be a potentially limiting factor.

There is probably no significant difference in safety between one beta-blocker and another apart from that conferred by cardioselectivity. A possible danger with all beta-blockers is the oculo-cutaneous syndrome, which occurred with practolol, but there is no evidence that any of the beta-blockers currently in long-term use have this serious side effect.

Table 4

Pharmacological properties of some currently available β – adrenergic blocking drugs.

Cardioselective	Non-Cardioselective
Atenolol	Propranolol
Metoprolol	Sotalol
Acebutolol (ISA)	Timolol
	Oxprenolol (ISA)
	Pindolol (ISA)
	Labetolol (Alpha)

ISA – Intrinsic Sympathomimetic Activity

Alpha – Alpha Blocking Activity.

Table 5

Beta Adrenergic Blocking Drugs: Preparations, Dose and Cost.

Drug Name		Tablet	Daily dose, mg.		Approximate
Proprietary	**Approved**	Strength, mg.	Starting	Max.	Cost/Month
Betaloc	Metoprolol	50, 100	100	400	£2.52 – £ 9.36
Betim	Timolol	10	10	60	£1.85 – £ 9.25
Blocadren	Timolol	10	10	60	£1.85 – £ 9.25
Inderal	Propranolol	40, 80, 160	80	480	£2.48 – £10.08
Lopresor	Metoprolol	50, 100	100	400	£2.52 – £ 9.36
Sectral	Acebutolol	200	400	1,200	£4.44 – £13.32
Sotacor	Sotalol	80	160	640	£3.59 – £14.36
Tenormin	Atenolol	100	100	300	£6.92 – £20.76
Trandate	Labetolol	20, 100	300	2,400	£7.02 – £37.31
Trasicor	Oxprenolol	40, 80, 160	160	640	£5.04 – £18.15
Slow Trasicor	Oxprenolol	160	160	480	£6.98 – £20.92

Wholeasle price – based on starting and maximum daily doses.

The retail price is on average 50% greater.

ADRENERGIC NEURON BLOCKING DRUGS

There are three drugs belonging to this group which are available for clinical use and these are listed in Table 6. Guanethidine has been in use in the treatment of hypertension for nearly 20 years and prior to the widespread use of beta-blockers and the advent of other new antihypertensive agents, was very widely used. Bethanidine and debrisoquine were subsequently introduced and have some advantages and disadvantages when compared with guanethidine.

Mechanism of action

Adrenergic neuron-blocking drugs act by preventing the release of noradrenaline from sympathetic nerve endings. This results in a decrease in sympathetic control of arterioles which is most marked when sympathetic activity is called on to maintain blood pressure as when standing or on exertion.

Unwanted effects

The most common side-effect is postural hypotension. In fact, if there is not a significant difference between supine and standing blood pressure it is quite likely that either the patient is not reponding or he is failing to take medication. The paralysis of sympathetic control is most dramatically seen on exertion when blood pressure may fall to frighteningly low values with accompanying dizziness, unsteadiness or loss of consciousness – "effort syncope". Patients should be warned in advance of the possibility of postural hypotension and effort syncope. They should be advised to get out of bed gradually as dizziness is very common at this time of day. Sudden exertion, such as running to catch a bus, should be avoided. Male sexual dysfunction is quite common, the main problem being failure of ejaculation. Impotence rarely occurs.

As with many effective antihypertensive agents, fluid retention may occur and it is usually recommended that diuretics should be used in combination with any member of this group. Occasionally severe diarrhoea may occur and may necessitate reduction or cessatio of treatment; this is less common with bethanidine and dibrisoquine.

Dose

Dose adjustment with these drugs is often difficult, particularly in severe hypertension, because there is a wide rang of individual responsiveness necessitating step-wise increases in dose which may be very time-consuming. In addition these drugs have relatively steep dose-response curves with the result that once an effecti dose has been achieved, relatively small further increases may produce a marked fa in blood pressure.

These drugs should be avoided in patients with cerebrovascular disease as these cases obviously should not be subjected to the postural hypotension.

There is probably little to choose between the three drugs in this group. Guanethidine has the advantage that its long duration of action permits once per day dosage and bethanidine has the advantage of apparently producing less gastrointestinal upsets. Also the short duration of action with bethanidine and debrisoquine perhaps gives more flexibility in dosage, but this advantage is somewhat offset by the necessity for more frequent doses. The relative costs of these drugs are given in Table 6. It is apparent that, at the arbitrary maximum values given, debrisoquine is significantly less expensive than the other two.

Table 6

Adrenergic Neuron Blocking Drugs – Preparation, Dose and Cost.

Drug Names		Tablet	Daily Dose, mg.		Approximate
Approved	**Proprietary**	Strength, mg.	Starting	Maximum	cost/month
Guanethidine	Ismelin	10, 25	20	100	£1.60 – £7.09
Bethanidine	Esbatal	10, 50	20	100	£1.44 – £6.58
Debrisoquine	Declinax	10, 20	20	60	£1.54 – £3.36

Wholesale price – based on starting and maximum daily doses.

The retail price is on average 50% greater.

METHYLDOPA

Methyldopa has been widely used in the treatment of hypertension since 1962.

Mechanisms of action

When initially introduced, it was thought that methyldopa exerted its antihypertensive effect by acting as a false neurotransmitter. Certainly some methyldopa is converted to methylnoradrenaline, and this substance has less activity as a neurotransmitter than does noradrenaline itself. A second possible mechanism of action is that methyldopa exerts its effect by inhibiting the formation of noradrenaline. The third and most likely mechanism of action is that methyldopa acts by suppressing sympathetic outflow from the brain.

Place in the treatment of hypertension

Until recently methyldopa was considered by many to be first line antihypertensive drug, and it vied with thiazide diuretics as the drug of first choice when initiating therapy. With the ascendency of the beta-adrenergic blocking drugs, methyldopa has gradually lost its favoured status. However, there are undoubtedly many patients with mild or moderate hypertension who are adequately controlled on this drug.

Unwanted effects

Postural hypotension occurs but not as commonly as with the adrenergic neurone blockers.

Drowsiness, lethargy, depression and sedation are common side effects which stem from its depressant effect on the central nervous system. A rare but important unwanted effect of methyldopa is that it may cause haemolytic anaemia in approximately one per cent of patients. More frequent is the occurrence of a positive Coombs test in about ten per cent of patients. The occurrence of haemolysis or a positive Coombs test warrants discontinuation of the drug.

Methyldopa may also cause jaundice. In some patients it causes a flu-like syndrome which is associated with hepatitis, occuring shortly after starting treatment.

Trade Name	Approved Name	Tablet Strength mg.	Daily Dose mg. Start	Max.	Cost/month
Aldomet	Methyldopa	125 250 500	500	2.000	£2.76 to £10.8

RESERPINE AND RAUWOLFIA

Several alkaloids, including reserpine have been isolated from the root of *Rauwolfia serpentina.* These possess a variety of pharmacological effects but from the antihypertensive viewpoint only reserpine and the whole root preparation are of interest. These agents have marked activity on the central nervous system and on the autonomic nervous system.

They are effective antihypertensive agents and in addition have the advantage of a very long duration of action. However, they can cause a large number of troublesome side effects - sedation, extrapyramidal problems (rare), abdominal cramps, diarrhoea, facial flushing, nasal congestion and nightmares.

As part of its central nervous system depressant effect they may cause psychological depression. In 5 - 10 per cent of patients this may be very severe indeed. In addition, it may aggravate existing depression. More subtle degrees of mental slowing, lethargy and drowsiness probably occur in a large number of patients.

It has recently been suggested that long term reserpine therapy is associated with carcinoma of the breast. This, however, has not been confirmed in a number of subsequent careful studies.

Reserpine is still used fairly extensively in the treatment of hypertension and undoubtedly is effective and trouble free in many patients. However, it is particularly important to keep in mind the central nervous system and depressant effects of the drug, and in no circumstances should it be prescribed for patients who are depressed or those who have a history of depression.

Table 7

Reserpine/Rauwolfia: Preparation, dose and cost

Trade Name	Approved Name	Tablet Strength, mg.	Daily Dose, mg. Starting	Maximum	Cost /Month
*Raudixin	Rauwolfia serpentine Whole Root	50	50	300	£0.38 – £2.29
Rauwiloid	Rauwolfia serpentine Alkaloid Hydrochloride	2.0	2.0	4.0	£0.55 – £1.10
Serpasil	Reserpine	0.1, 0.25	0.25	1.0	£0.34 – £1.34

Wholesale price – based on starting and maximum daily doses. The retail price is on average 50% greater.

**Rautrax is a combination of Rauwolfia serpentine whole root (50 mg), a thiazide – hydroflumethiazole (50 mg) and potassium chloride.*

CLONIDINE

Clonidine has been available for approximately five years. It is the prototype of antihypertensive agents which act at a central site. It blocks alpha receptors in the brain and thus decreases sympathetic outflow. It is moderately effective and exerts its maximum antihypertensive effect at very low doses (compared to other antihypertensive agents).

Its central site of action is reflected in its spectrum of side effects which include drowsiness, sedation and dry mouth.

It is probably unique among antihypertensive agents in that stopping it can result in alarming rebound hypertension. This is accompanied by many of the symptoms and findings of increase in sympathetic activity – increase in heart rate, apprehension and raised plasma renin activity. Blood pressure may rise to levels in excess of those found prior to starting therapy. Patients must be informed of this possibility and warned that sudden cessation of dosing is extremely risky. This rebound may be worsened by concomitant treatment with propranolol and perhaps other beta-adrenergic blocking drugs.

Table 8

Clonidine: Preparation, dose and cost.

Trade Name	Approved Name	Tablet Strength, mg.	Daily Dose, mg. Starting	Maximum	Cost/month
Catapres	Clonidine	0.1, 0.3	0.1	1.2	£1.57 – £14.69

Wholesale price – based on starting and maximum daily doses.

The retail price is on average 50% greater.

VASODILATORS

Definition and mechanism of action

Vasodilator antihypertensive agents act directly on the resistance blood vessels - the arterioles. They do not interact with alpha or beta-receptors in the arterioles but seem to have a non-specific effect on calcium. By combining with calcium they reduce the tone of arterioles and therefore decrease peripheral resistance and blood pressure. With the exception of prazosin they do not have any important additional haemodynamic actions.

The efficacy of hydrallazine as a blood pressure lowering agent is limited by the compensatory baroreflex action which a fall in blood pressure activates. The resultant increase in sympathetic tone causes an increase in venous return, stroke volume and heart rate and thereby leads to an increase in cardiac output. The increase in cardiac output tends to increase blood pressure and thus to offset the original hypotensive action of the vasodilator. In addition, hydrallazine increases plasma renin activity and aldosterone causing sodium retention. This drug is therefore relatively ineffective alone. It is possible however to attenuate this reflex action by also administering drugs which antagonise sympathetic actions for example, reserpine, methyldopa, adrenergic neuron-blocking drugs and beta-adrenergic blocking drugs. The most popular and best method is to combine hydrallazine with a beta-blocking drug. The haemodynamic end-result of combined vasodilator and beta-blockade is a fall in peripheral resistance with an unchanged cardiac output.

The beta-adrenergic blocking drugs not only increase the antihypertensive effect of a vasodilator but also minimise the side-effects that occur with these drugs. Thus, unpleasant effects such as palpitation associated with the tachycardia and angina pectoris which is frequently noted by patients with ischaemic heart disease, occur rarely if the beta-blocker is used in addition. Prazosin is unusual in that,even though it acts by decreasing peripheral resistance, it does not produce significant reflex increase insympathetic tone. This is thought to occur because it has some activity on sympathetic neurons whereby noradrenaline release is inhibited. There is some debate whether prazosin acts as a direct vasodilator or whether in fact some of its antihypertensive effect is mediated by sympathetic blockade.

Hydrallazine

Hydrallazine has been in use since the 1950's and while it fell into disrepute in Europe it has always been rather popular in the U.S. When given alone it has limited efficacy and tends to cause palpitation and angina pectoris. In addition, it may cause a systemic lupus erythematosis-like syndrome. The occurence of this syndrome is dose related and is extremely rare if doses in excess of 200 mg per day are avoided. The syndrome is reversible in most cases. Fortunately, combination of hydrallazine with a beta-blocker permits use of relatively safe doses of hydrallazine.

The usual starting dose is 25 mg twice per day. Patients frequently complain of headaches but this usually resolves. Hydrallazine should not be used alone in the treatment of hypertension in view of its limited efficacy and side-effects.

Prazosin

Prazosin has been recently introduced but has been quite extensively studied in Europe and Australia. Initial dosage should be cautious as there have been many reports of patients becoming extremely hypotensive on exposure to an initial dose. This "first dose hypotension" is apparently dose-related, and if small doses, for example 0.5 - 1.0 mg, are used the problem is unlikely to occur. In the absence of adequate blood pressure control, the dose can be quite rapidly increased to 2 mg three times a day, and so on to a maximum of 20 mg a day.

Table 9

Vasodilators:
Preparations, dose and cost.

Trade Name	Approved Name	Tablets, mg.	Dosing		Cost/Month
			Starting	Maximum	
Apresoline	Hydrallazine	25, 50	50	200	£0.89 – £ 3.46
Hypovase	Prazosin	1, 2, 5.	*6	20 ≠	£4.38 – £12.97
Sinetens	Prazosin	2, 5.	*6	20	£3.81 – £12.69

Wholesale price – based on starting and maximum daily doses.

The retail price is on average 50% greater.

**Initially a 0.5 mg dose should be used, after three such doses the daily dose can be raised to 3 or 6 mg.*

≠*Starting dose based on 6 mg per day.*

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