Drug Treatment of Disease

DRUGS IN THE TREATMENT OF HYPERTENSION*

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There are now many drugs which effectively lower blood-pressure, but the management of the patient with hypertension remains difficult. This is not only because there is, as yet, no agent that will lower blood-pressure predictably and without side-effects, but also because the success of treatment is so often limited by co-existing vascular or renal disease.

Many patients with hypertension do not require drug treatment, and drugs should never be regarded as more than a part of the therapeutic regime. General management remains important, and simple measures such as reduction of weight and the avoidance of excessive mental and physical strain contribute to the well-being of the patient and the reduction of blood pressure. A routine incorporating adequate rest and sleep, with amylobarbitone sodium, 3 gr. (200 mg.) at night, is often helpful. Rigid salt restriction is no longer practised, but the avoidance of table salt and salty foods potentiates the effect of the ganglion-blocking drugs and helps in the control of cardiac failure.

The use of antihypertensive drugs calls for considerable co-operation from the patient. Sympathetic handling by a physician in whom the patient has confidence will make it easier to overcome the difficulties and disappointments associated with this form of treatment. It is desirable for the patient to have some understanding of the disease and of the drugs that he is receiving so that he may recognize hypotensive symptoms and side-effects and take appropriate action. At the same time, the doctor must ensure that the patient has no excessive fears about his blood-pressure and does not worry about the exact level—which is better left untold.

Rauwolfia

The alkaloids derived from the root of *Rauwolfia serpentina* have a moderate hypotensive effect. To some extent this may be due to a tranquillizing action, but there is also a more direct central hypotensive effect. When used alone the rauwolfia alkaloids lower the diastolic pressure by 10 to 20 mm. Hg in some, but not all, patients. They have a more striking effect when used with the ganglion-blocking drugs, which they potentiate. The full fall in pressure may not occur for two to three weeks.

The side-effects are usually minor and include nasal stuffiness, flushing of the skin, diarrhoea, and headache. Muscular pains and rigidity are sometimes complained of, and lactation has developed in some patients. Retention of sodium occurs and may interfere with regimes designed to produce loss of weight. The most serious side-effect is depression. Though not common, it can be severe and in some patients has led to suicide.

There are many preparations available, and various claims have been made that certain of them are free

from the more serious side-effects. These claims have not, as yet, been fully substantiated. The preparations in common use are reserpine, "raudixin," and "rauwiloid." Reserpine ("serpasil"), a single alkaloid, is given in doses of 0.1 to 0.5 mg. thrice daily. Raudixin, the refined whole root, is administered in 50-mg. tablets, 3 to 8 a day. Rauwiloid, a mixture of alkaloids, is given in doses of 2-4 mg. thrice daily. The use of tablets combining the rauwolfia drugs with other hypotensive agents is unwise. They do not permit the necessary flexibility in treatment, they often contain ineffective amounts of the various constituents, and they prevent assessment of the relative merits of the component drugs.

Chlorothiazide Derivatives

Chlorothiazide and related drugs are chiefly used for their diuretic effect, but they also have a slight hypotensive action. They have a strong potentiating effect when used with ganglion-blocking and adrenergic-blocking agents. The mode of action seems to be through a reduction of plasma volume which accompanies depletion of sodium. The most important side-effects of chlorothiazide therapy are those associated with depletion of potassium, but a few patients complain of nausea and vomiting. Though there are some pharmacological differences between the various derivatives of chlorothiazide available, from the practical point of view there is little to choose between them except on the basis of cost and the size of the tablets.

Chlorothiazide ("saluric") is given in doses of 250 mg.-500 mg. three times a day, hydrochlorothiazide ("esidrex" or "hydrosaluric") 25-50 mg. thrice daily, and hydroflumethiazide ("hydrenox" and "nalex") 25-50 mg. thrice daily. When the chlorothiazide drugs are given every day, as they have to be for treatment of hypertension, it is always advisable to give a supplement of potassium—e.g., 1 g. of potassium chloride thrice daily. When treating patients with ganglion-blocking or adrenergic-blocking drugs, it is dangerous to give chlorothiazide intermittently—for example, two or three days in the week—as this results in large swings in blood-pressure from day to day.

Veratrum Alkaloids and Hydrallazine

The veratrum alkaloids, alkavervir ("veriloid") and protoveratrine ("puroverine," "provell maleate"), cannot be advocated because the effective dose is so close to the toxic dose that vomiting is usually provoked. Hydrallazine ("apresoline") retains a limited place in treatment because of its unique action in lowering blood-pressure and at the same time increasing cardiac output and flow of blood to the kidneys. Unfortunately, side-effects are common and severe. They include headache, flushing, nausea, fever, rashes, and joint pains, and thus disseminated lupus erythematosus may be simulated. Its use is now reserved for those patients in whom the renal function is severely impaired, and it is usually given together with another hypotensive drug. Treatment is

*An article on the "Pharmacology of Hypotensive Drugs," by Dr. M. Harington, appeared earlier in this series (March 5, p. 717).

started with a dose of 25 mg. thrice daily, which may be increased until a total of 300 mg. is being given in the day.

Ganglion-blocking Drugs

These block the ganglia of both sympathetic and parasympathetic systems. The reduction in blood-pressure is only slight when the patient is lying down but becomes considerable in effective doses when the patient is erect. This postural effect is due to the abolition of the vasoconstriction which normally occurs on standing, and to the pooling of blood.

Side-effects from this group of drugs are frequent and are largely due to the parasympathetic blockade. Constipation is almost invariable, and paralytic ileus may occur. The patient must be informed of the importance of regular bowel action and advised on the use of laxatives. Other unpleasant symptoms from this form of treatment include blurring of vision, dryness of the mouth, diarrhoea, difficulty in micturition, and impotence. Neostigmine 7.5 mg. and pilocarpine 3 mg. thrice daily are both of some value in combating these symptoms. Physostigmine drops ($\frac{1}{2}\%$) help to relieve the blurring of vision, but new spectacles may be necessary. When hypotensive symptoms occur, the patient should lie down and they will usually pass off quickly.

The most frequently used members of this group of drugs are pentolinium, mecamlamine, and pempidine.

Pentolinium ("ansolysen," tablets of 10, 40, and 200 mg.) is a quaternary ammonium compound and resembles hexamethonium. Only a small percentage is absorbed, and the degree of absorption is variable. As a result the control of the blood-pressure may be erratic. Treatment should be started with 20 mg. thrice daily, each dose being taken at least one hour before a meal. The dose may be increased every two or three days. Eventually a total daily dose of about 600 mg. is usually required.

Mecamlamine ("inversine," tablets of 2.5 mg. and 10 mg.) is a secondary amine, and has the advantage of being regularly and completely absorbed. It has a prolonged action, which can be a disadvantage when there are side-effects. It has a distinctive side-effect in producing neurological signs—particularly tremor—but this is uncommon. It is usually wise to begin with 2.5 mg. twice daily (e.g., at 7 a.m. and 5 p.m.) and then gradually increase the dose until the drug is being taken four times a day. The eventual dose is commonly between 40 and 80 mg. a day.

Pempidine ("perolysen," "tenormal," tablets of 1, 5, and 10 mg.) is a tertiary amine and closely resembles mecamlamine except that its action is not as prolonged, and, it is claimed, it does not give rise to neurological signs. Treatment may be started with 2.5 mg. twice daily and gradually increased until it is being taken four times a day.

When starting therapy with the ganglion-blocking drugs, frequent recordings of the blood-pressure are necessary, and for this reason treatment is best begun in hospital. In assessing the drugs the patient's blood-pressure should be recorded first in the recumbent position and immediately afterwards when he stands erect. The aim should be to maintain the diastolic pressure below 100 mm. Hg in the erect position. Minor dizziness may have to be tolerated if the blood-pressure is to be satisfactorily controlled, but faintness calls for a reduction in dosage. When troublesome side-effects are

occurring without an adequate fall in pressure, rauwolfia or chlorothiazide should be added and the dose temporarily halved, and then gradually increased to the necessary level. Tolerance develops to all these drugs, and the doses may have to be increased for some weeks or even months after treatment has started.

Though treatment with the ganglion-blocking drugs may be complex and unpleasant, it has been possible to achieve satisfactory control of blood-pressure in many patients without producing undue discomfort. In such cases there is no indication to change to the more recently introduced adrenergic-blocking drugs.

Adrenergic-blocking Drugs

The recent introduction of drugs that will selectively block the peripheral sympathetic nervous system has been a major development in pharmacology but of still unproved value in therapeutics. These drugs do not affect the ganglia, and no paralysis of the parasympathetic system occurs. The hypotension which they produce is largely orthostatic, and the fall in pressure is even greater on exercise. Hypotensive symptoms are common and may be severe, particularly on exertion. Strenuous effort should therefore be avoided.

Side-effects occur occasionally and are relatively slight. They include nasal stuffiness, parotid pain at meal-times, muscular weakness, exertional dyspnoea, diarrhoea, and impotence. The diarrhoea can usually be relieved by propantheline ("pro-banthine") 15 mg. thrice daily. There is good evidence that hypertensive patients with nitrogen retention are more readily precipitated into uraemia by these drugs than by the other hypotensive agents. For this reason some physicians have already abandoned their use.

The two drugs of this group in current use are bretylium tosylate and guanethidine.

Bretylium tosylate ("darenthin," 200-mg. tablets) is absorbed irregularly, and large swings of pressure may occur. The effect starts in about 1–2 hours and lasts from 4–8 hours. It is customary to begin treatment with 100 mg. thrice daily, each dose being taken after a meal. Some patients develop hypotension with as little as 50 mg. Initially, several recordings of the blood-pressure each day are desirable. 100 mg. may be added to each dose until an adequate response has been obtained.

Guanethidine ("ismelin," tablets of 10 and 25 mg.) differs from bretylium in that its hypotensive action lasts for two to four days with a transitory peak of effect at about four hours. This means that doses are additive from one day to another, and the full effect of a particular daily dosage will not be appreciated for about three days. Because of this prolonged action, smoother control of blood-pressure is obtained, but when hypotensive symptoms develop they take a long time to abate. Treatment should be started with 10 mg. once daily, and the dose increased not more frequently than every four days by 10 mg. at a time. Most patients require from 30 mg. to 60 mg. daily, which is best given in divided doses.

Tolerance develops with both bretylium and guanethidine, and a gradual increase of dosage may be necessary for several months. This has proved a serious disadvantage with bretylium, because the number of tablets required may become excessive and because treatment may suddenly become ineffective. As with the ganglion-blocking drugs, rauwolfia and chlorothiazide

potentiate their action. If these drugs are to be added to the adrenergic-blocking drugs, the dose of the latter should first be halved and then gradually increased.

Indications for Drug Therapy and the Choice of Drug

A large number of patients with high blood-pressure need no antihypertensive drug. Systolic hypertension alone can be ignored—except as evidence of vascular sclerosis—and diastolic hypertension must be persistently raised above 100 mm. Hg before drug treatment has to be considered. Remediable conditions such as phaeochromocytoma, coarctation of the aorta, and unilateral renal disease must be looked for and treated.

The severity of the hypertension must be assessed, with particular attention given to the state of the heart, brain, ocular fundi, and kidneys, before treatment can be planned. Middle-aged women and the elderly often tolerate high levels of pressure for years without mishap, and if there is no evidence of secondary cardiac or renal damage, and if the retinal examination reveals no exudates, haemorrhages, or papilloedema, energetic drug treatment need not be given. Younger patients with labile hypertension and no evidence of vascular deterioration usually require no more than small doses of phenobarbitone.

At the other end of the scale are those patients in whom the lowering of the blood-pressure is of the greatest importance. If there are retinal signs of papilloedema, soft exudates, or haemorrhages, or left ventricular hypertrophy with failure associated with a diastolic pressure of 120 mm. Hg or more, then vigorous treatment is imperative. Provided that renal function is not severely impaired and there has been no recent myocardial infarction, guanethidine is probably the drug of choice, though it yet remains to be proved that its long-term use in the severest grades of hypertension (malignant hypertension) is as beneficial as mecamlamine. When cardiac failure is present, the addition of chlorothiazide with potassium supplements will serve the double purpose of providing a diuretic and potentiating the hypotensive effect. In those without evidence of coronary, cerebral, or renal vascular disease, the diastolic pressure should be reduced to about 90 mm. Hg when the patient is standing. In the older patient and those in whom there are other signs of vascular disease, a fall to 100 to 110 mm. Hg is safer and may be adequate.

In a less serious state but still requiring control of blood-pressure are those patients in whom the hypertension has led to left ventricular enlargement, as shown on physical examination or electrocardiographically, renal damage, as shown by albuminuria or a rise in the blood urea, or episodes of cerebral thrombosis or haemorrhage, or is undoubtedly progressing. In some of these cases rauwolfia or chlorothiazide alone may be sufficient, but in many the more powerful adrenergic-blocking or ganglion-blocking drugs are necessary.

Hypotensive drugs must be used cautiously when there are signs of coronary or cerebral vascular disease or evidence of renal failure. Lowering of the blood-pressure can lead to coronary and cerebral thrombosis and to uraemia, yet the persistence of high blood-pressure increases the dangers of cardiac and renal failure and of cerebral haemorrhage. There is no solution to this dilemma, but the wisest course of action is to lower the blood-pressure cautiously, with special care

being taken to avoid hypotensive episodes. Rauwolfia or chlorothiazide should be employed in the first place, but, if these prove inadequate, treatment should be started with guanethidine or, perhaps, mecamlamine. No attempt should be made to achieve normotensive levels, and one must be satisfied with a diastolic pressure of 100–110 mm. Hg.

There remains a group of patients in whom the blood-pressure is persistently raised but who show little or no evidence of harmful effects from it. Some physicians feel that high blood-pressure on its own should not be treated and that one should await the signs of hypertensive disease before subjecting patients to the hazards of the antihypertensive drugs. On the other hand, there is no doubt that many patients in the younger age groups with isolated hypertension will eventually develop irreversible changes in their blood vessels and kidneys as a result of the raised diastolic pressure. If the blood-pressure can be brought down safely and without discomfort, then it seems right to do so, but, as yet, no drugs can be relied upon to do this in every patient. It is worth trying rauwolfia or chlorothiazide initially, and, if they fail, then guanethidine or mecamlamine. If it is impossible to achieve a satisfactory fall in pressure without side-effects or hypotensive symptoms, then it is probably best to abandon drug treatment for the time being.

Conclusion

In spite of the frequency of side-effects and of hypotensive symptoms, satisfactory control of the blood-pressure can be achieved in most hypertensive patients. In the milder cases, rauwolfia and chlorothiazide are the drugs of choice. In the more severely affected patients guanethidine or mecamlamine should be tried. One or other will usually produce an adequate fall in pressure with few undesirable effects. With the careful use of the drugs described, the prognosis of patients with hypertension is improved and their symptoms are usually relieved.

AMENDMENTS TO BRITISH NATIONAL FORMULARY, 1960

Hydrocortisone and Neomycin Ear-drops

The formula was, at the time of publication, identical with that of two proprietary preparations. One, Hydromycin Ear-drops, which was supplied in packs containing 3 ml., has recently been replaced by Hydromycin D Ear-drops containing prednisolone instead of hydrocortisone acetate. The other preparation, Neo-Cortef Ear-drops, is supplied in 5 ml. packs. The two editions are, therefore, amended as follows:

Standard Edition

Page 74. Aurist. Hydrocort. et Neomyc.

Amend the quantity to be dispensed unless otherwise directed from 3 ml. to 5 ml.

Additions

Page 7. Amend Hydromycin Ear-drops to Neo-Cortef Ear-drops.

Proprietary Preparations

Page 214. Delete reference to Hydromycin Ear-drops.

Alternative Edition

Page 174. Hydrocortisone and Neomycin Ear-drops.

Amend 3 ml. to 5 ml.

Additions

Page 8. Delete Hydromycin Ear-drops.

Proprietary Preparations

Page 240. Delete reference to Hydromycin Ear-drops.

Corrections

Standard Edition

Page 9. Amendments to Composition.

Add Elix. Chloral. pro Inf.

Page 84. Crem. Calam.

Amend Water, 465 gr. (approximate percentage 49); to Water to 960 gr.

(approximate percentage to 100).

Page 148. Tab. Acetazolam.

Add B.P. to English title.

Page 221. Amend Sinachar to Sinaxar.

Page 220, 228. Amend Raspenyl to Respenyl.