Drug Treatment of Disease

PHARMACOLOGY OF HYPOTENSIVE DRUGS

BY

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The hypotensive drugs most widely used in current practice fall into five groups according to the site and mode of their main pharmacological actions—namely, the veratrum alkaloids, hydrallazine, the rauwolfia alkaloids, adrenergic blocking drugs, and ganglion-blocking agents. These groups will now be discussed separately. The most suitable regime of treatment for a particular patient, however, may well be a combination of drugs from two or more different groups, and, in addition, chlorothiazide has been shown to have a powerful potentiating effect on certain other hypotensive agents.

Veratrum Alkaloids

These substances are of some historical interest, since preparations of veratrum were used a century ago in the treatment of eclampsia. Many different alkaloids (e.g., protoveratrine, veratridine) and alkaloidal mixtures (e.g., "veriloid") are available, but the effects of each are broadly similar in the sort of doses used clinically. The drugs may be given intravenously if a rapid effect on the blood-pressure is desired, but are more usually given orally, by which route they are reasonably well absorbed.

The veratrum alkaloids act by eliciting the Bezold reflex. The sensory receptors for this reflex lie in the myocardium, and the afferent pathway is by way of the vagus nerves to the brain-stem; its effects include hypotension and slowing of the pulse, and there is also at the same time peripheral vasodilatation. Some experimental evidence exists for a direct action of the drugs on the central nervous system, but it is not certain how far this may play a part in man. Postural cardiovascular reflexes are not blocked by veratrum alkaloids, and postural hypotension is not a feature of their use.

The principal drawback to the clinical effectiveness of the veratrum alkaloids is their tendency to cause nausea and vomiting. The emetic dose is very close to the hypotensive dose, and this relationship holds for all preparations so far tested. Other unpleasant effects in some cases include paraesthesiae in the lips, tongue, and extremities, a feeling of constriction in the throat, or an epigastric or substernal burning sensation. These side-effects may be more prominent after oral administration than when the drugs are given intravenously. They appear to be less severe in patients with toxaemia of pregnancy, who often tolerate veratrum alkaloids well.

Hydrallazine

The chief interest in hydrallazine (1-hydrazinophthalazine) has centred round the ability of this drug under certain circumstances to increase the amount of blood flowing through the kidney at the same time as lowering the blood-pressure. This contrasts with the effect of other hypotensive agents, most of which, and particularly the ganglion-blocking drugs, tend to produce a diminution in renal blood-flow, especially in those patients in whom renal vascular narrowing is already severe.

The mode of action of hydrallazine is complex: it probably acts mainly on centres in the brain stem, but there is also evidence for a direct action on the peripheral vessels as well as a sympatholytic effect. The reduction in blood-pressure after hydrallazine tends to affect the diastolic proportionately more than the systolic pressure. The drug produces a tachycardia, which may be considerable, and an increase in output of the heart. Vasodilatation occurs both in viscera and in the extremities, and an increased blood-flow to the internal organs reflects the raised cardiac output. These effects are particularly seen after intravenous injection of the drug. Hydrallazine is also effective when given orally; with repeated administration by this route some tolerance occurs, and increasing doses may be necessary to maintain a hypotensive action.

Though there is no doubt that hydrallazine is capable of reducing the blood-pressure, its use as a single therapeutic agent is severely limited by the frequency of unpleasant side-effects which occur when an effective hypotensive dose is given. The commonest of these are headache, nausea and vomiting, palpitation, nasal stuffiness, and flushing of the skin. Anginal pain may be precipitated in subjects with coronary artery disease. A febrile reaction with rash may occur, and sometimes after prolonged administration a syndrome develops which has features in common with rheumatoid arthritis or disseminated lupus erythematosus and in which L.E. cells may be found in the blood.

Rauwolfia Alkaloids

Reserpine may be taken as an example of the group of rauwolfia alkaloids, since the actions of individual alkaloids and mixtures in this group are similar, and the majority of pharmacological studies have been carried out with this compound. The tranquillizing effect of reserpine is well-known, and this alone by relieving stress and anxiety may help to lower the blood pressure, but the drug also has a mild but definite hypotensive action in its own right, which becomes evident if the dose given is sufficiently large.

The main site of action of reserpine is a central one, probably on centres in the region of the hypothalamus. A feature of the drug is the long latent period before the onset of its action—namely, one hour or more even after an intravenous dose. The effect is prolonged and also wears off slowly. The drug's exact mode of action is uncertain; it is known to have the property of depleting tissues of 5-hydroxytryptamine (brain, platelets, intestine) and of noradrenaline (artery walls,

brain, adrenal medulla), though the relationship of this effect to its hypotensive action is not clear.

The reduction in blood-pressure which follows reserpine is accompanied by a bradycardia. Apart from this action, and its tranquillizing properties, the drug has many other pharmacological effects which may be of importance in individual cases. Intestinal motility is increased, which may lead to diarrhoea, though this effect may be useful in combating the constipation produced by ganglion-blocking drugs. Flushing of the skin, nasal congestion, and headache are not uncommon. There is an increase in the acidity of gastric secretion. More serious are the effects on the central nervous system which may be seen with larger doses of reserpine; these include mental depression, severe enough on occasion to lead to suicide, and a Parkinsonian syndrome of muscular rigidity and tremor. Other effects which occur in occasional cases are oedema due to sodium retention, and sometimes gynaecomastia and even lactation.

Reserpine potentiates the action of other hypotensive agents, particularly the ganglion-blocking drugs. Its most useful place in the treatment of hypertension would appear to be as part of a combined regime, in which only small doses of reserpine are given and the risk of serious side-effects is minimized.

Adrenergic Blocking Drugs

Of this group of drugs perhaps phenoxybenzamine has received most attention as a hypotensive agent. Phenoxybenzamine belongs to a series of compounds, the β-haloalkylamines, which are effective in blocking stimulation of the sympathetic nerves, but are even more active in blocking the effects of circulating adrenaline and noradrenaline. For this reason it may be used as a diagnostic or therapeutic agent in patients with phaeochromocytoma, though the shorter-acting phentolamine is usually preferred for this purpose.

Phenoxybenzamine may be given intravenously, and is also active when administered by mouth. Its chief pharmacological effect is to cause peripheral vasodilatation, well marked in the skin, which has led to the use of the drug in peripheral vascular disease. In sufficient doses it may also cause some reduction in blood-pressure, particularly in the erect position, since the normal postural vasomotor reflexes are blocked. This effect, however, is inconstant, and phenoxybenzamine has proved disappointing as a hypotensive agent, at any rate when used singly. It is possible that there may be a place for the drug in combination with other, more effective hypotensive drugs, but this suggestion awaits proof.

The recently introduced compound bretylium may also be mentioned under this head. This drug has an unusual action, in that it selectively blocks the peripheral sympathetic nervous system, apparently by accumulating on the adrenergic nerves, without inhibiting the effects of circulating or injected noradrenaline or adrenaline. Indeed, after administration of bretylium, injected noradrenaline has a greater pressor effect than before. It is too early to assess this drug fully, but it is clear that bretylium is effective in reducing the blood-pressure in many hypertensive patients, postural hypotension being particularly marked with its use. Side-effects reported are few, mainly excessive dizziness on standing and nasal stuffiness. A possible disadvantage is that the oral dose is several times greater than the effective parenteral dose, and absorption of the drug from the alimentary tract may be irregular.

Ganglion-blocking Drugs

The ganglion-blocking drugs include the most powerful and rapidly acting hypotensive agents known, and for this reason form the cornerstone of therapy in severe hypertension. They fall chemically and pharmacologically into two groups, the quaternary ammonium compounds, which are poorly absorbed from the gastro-intestinal tract and confined to the extracellular fluids of the body, and the freely absorbed and diffusible secondary and tertiary amines.

Quaternary Ammonium Compounds

The simplest of these, tetraethylammonium, has been known for many years, but as this compound has to be given by injection, and as its duration of action is only a matter of minutes, it is of little value in therapeutic practice. The discovery of pentamethonium and hexamethonium introduced for the first time ganglion-blocking agents with a duration of action long enough to be useful in treatment, and these drugs may be regarded as the prototypes of a long series of quaternary compounds which have been developed subsequently.

All these compounds are poorly absorbed, to the extent of only 5 to 10% of the dose, from the alimentary tract. Absorption is also irregular, depending on the relation of the dose to meals and the presence or absence of constipation, and for this reason these drugs are more safely given by injection. Those compounds which were developed later, such as pentolinium and chlorisondamine, appear to be absorbed somewhat more regularly when given by mouth than hexamethonium, but the oral dose is still considerably larger than the parenteral dose, and the possibility of irregular and excessive absorption is always present. An advantage of the latter drugs is that they have a slightly longer duration of action than hexamethonium, allowing less frequent dosage. All the compounds in this group are excreted entirely in the urine, so that they should be used with caution and in low dosage in the presence of renal failure.

The reduction in blood-pressure produced by the ganglion-blocking agents is most marked in the erect position, due to the blocking of postural vascular reflexes and pooling of blood in the lower parts of the body. This effect is increased when there is vasodilatation, such as after a meal, in hot weather, or when the patient is feverish; it is also augmented by sodium depletion or reduction in blood volume, or following sympathectomy.

All ganglion-blocking drugs so far tested clinically block the ganglia of the sympathetic and parasympathetic systems impartially. The many side-effects due to unwanted blockade of autonomic ganglia are familiar: constipation and abdominal distension are perhaps the most troublesome, but diarrhoea may also occur; blurring of near vision due to paralysis of accommodation, dryness of the mouth, difficulty in micturition, and impotence are all frequently seen. Toxic effects other than those due to ganglionic blockade have not been reported with the quaternary compounds.

Secondary and Tertiary Amines

With the discovery of mecamylamine, a non-quaternary ganglion-blocking agent was made available for the first time. This compound is a secondary amine, and the more recently introduced pempidine, which has many similarities, is a tertiary amine. Both mecamylamine and pempidine have the great advantage that they are fully and regularly absorbed when given by mouth and are therefore more convenient to use in clinical practice. Both drugs are largely excreted in the urine, and their rate of excretion is influenced by urinary *p*H, being greater in an acid and less in an alkaline urine. The chief disadvantage of mecamylamine is that it is very long-acting, so that the dose can only be built up gradually, and if untoward side-effects occur they tend to be prolonged as the drug is slowly excreted. Pempidine is excreted more rapidly, and this makes for easier control of dosage; correspondingly its shorter duration of action (5–6 hours after an oral dose) means that pempidine needs to be administered at more frequent intervals than mecamylamine.

Mecamylamine and pempidine are freely diffusible across cell membranes, and in fact are more concentrated inside the cell than outside the plasma or extracellular fluid. Their exact mode of action is likely to be different from that of the quaternary ganglion-blocking compounds, but their effect is similar, and symptoms from parasympathetic blockade are equally, if not more, frequent with these two drugs. In addition, mecamylamine may sometimes produce alarming symptoms of toxicity to the central nervous system—tremor, confusion, and delirium—though usually only when given in large doses and in the presence of some degree of renal failure.

Chlorothiazide

This drug, in addition to its diuretic action, has a powerful potentiating effect in the hypotensive action of various drugs, in particular the ganglion-blocking agents. In the case of the quaternary ganglion-blocking compounds (such as hexamethonium and pentolinium), this effect of chlorothiazide appears to be principally related to the reduction in volume of the plasma which accompanies the sodium depletion produced by the drug, since the increased sensitivity to the ganglion-blocking agents may be abolished by restoration of the lost plasma volume with sodium-free dextran. It is likely that this also applies to the potentiation by chlorothiazide of the secondary and tertiary amines mecamylamine and pempidine, though the different chemical behaviour of these latter compounds suggests the possibility that other additional factors may play a part.

Chlorothiazide has no direct hypotensive action *per se*, and intravenous administration of the drug is without effect on the blood-pressure. After repeated dosage, however, some hypertensive subjects may develop postural hypotension, and this is particularly noticeable in patients who have undergone sympathectomy. This effect also appears to result from the diminution in plasma volume brought about by chlorothiazide.

Conclusion

There is thus available a wide range of hypotensive agents, many of them active at different points in the circle of reflexes which helps to maintain the established state of hypertension. With our present knowledge, the most satisfactory therapeutic effect in a particular case can be obtained by trial and error, using drugs from the several different groups, either singly or more often in combination.

SHOES FOR CHILDREN

A SURVEY OF RETAIL SHOE-SHOPS IN THE BOROUGH OF EALING

BY

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Doctors and health workers can readily describe suitable designs of children's shoes which promote the growth of healthy feet, but are these shoes in fact to be obtained in the shops? Parents tell of the difficulty experienced in finding shoes of correct style and size, but how true is this? and to what extent can the blame be with the manufacturers for not making such shoes, or with the retailers for not stocking them? If the retailers have them, do they stock a sufficient range of sizes and fittings? How often do the retailers stock other girls' shoes of inferior design as, for example, the fashionable casual style? Again, if well-designed shoes are stocked in the shoe-shops, is it the fitting by the assistants that is at fault? Can it be that the poorly designed shoes are cheaper than the well-fitting ones?

To try to find the answer to some of these questions, an inquiry, by means of a questionary, was made in the Borough of Ealing during the period January–June, 1958. Ealing has long been concerned about the damage done to children's feet by ill-fitting shoes, and has produced much valuable and original research in the past 10 years. Surveys carried out by Dr. D. A. Craigmile in Ealing revealed the incidence and variety of foot defects in children, many of which are known to cause foot pain in adults. The Ealing Contributory Shoe Scheme clearly showed that many of these acquired foot defects can be cured or improved by well-fitting shoes alone. At the present time in this area a foot health nurse visits the schools, inspects the children's feet, and records her findings. Children with early foot defects and in need of advice are asked to attend the foot clinics at which the particular problem can be discussed with the parents. Ealing can thus be regarded as having a high standard of foot care.

In this inquiry the visits to the shoe-shops were carried out by the foot health nurse and myself only, in order to keep the personal error as small as possible. The questionary was completed in each case by one of us in the shop at the time of the interview with the manager, who was on the whole most interested and helpful. Occasionally the manager thought he should first seek permission to answer the questions from his employer, in which case the questionary was left with him for completion and was subsequently collected or returned by post.

A list of footwear retailers in the Ealing area was obtained from the Public Health Inspectors Department. Out of 49 shops selling shoes, 39 sold children's shoes. Of these 39 shops 3 were multiple stores—for example, Woolworths. Some of these 39 shops were branch shops