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Hypotensive Drugs

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Abstract
Based on a Dissertation read before the Royal Medical Society on Friday, 23rd October 1959.
The arterial blood pressure is controlled by the autonomic nervous system. Information about the level of the arterial pressure is obtained by the stretch receptors of the aortic arch and the carotid sinus. An increase in pressure is registered as an increase in sensory discharge frequency and vice-versa. The sensory impulses reach the medulla by the carotid sinus nerves, the cardia-aortic nerves and the vagi. The central nervous mechanisms are such that changes in the arterial pressure evoke compensatory changes in the dynamics of the circulation. A fall in carotid sinus pressure, for example, evokes peripheral arteriolar constriction. an increase in venous tone and an increase in heart rate. Generalised arteriolar constriction increases total peripheral resistance. An increase in venous tone tends to increase the venous tilling pressure and the stroke volume of the heart. The combined increase in stroke volume and heart rate produces a rise in cardiac output, which, together with the increase in peripheral resistance, restores the original arterial pressure

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HYPOTENSIVE DRUGS

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The arterial blood pressure is controlled by the autonomic nervous system. Information about the level of the arterial pressure is obtained by the stretch receptors of the aortic arch and the carotid sinus. An increase in pressure is registered as an increase in sensory discharge frequency and vice-versa. The sensory impulses reach the medulla by the carotid sinus nerves, the cardio-aortic nerves and the vagi. The central nervous mechanisms are such that changes in the arterial pressure evoke compensatory changes in the dynamics of the circulation. A fall in carotid sinus pressure, for example, evokes peripheral arteriolar constriction, an increase in venous tone and an increase in heart rate. Generalised arteriolar constriction increases total peripheral resistance. An increase in venous tone tends to increase the venous filling pressure and the stroke volume of the heart. The combined increase in stroke volume and heart rate produces a rise in cardiac output, which, together with the increase in peripheral resistance, restores the original arterial pressure.

The circulatory adjustments which regulate arterial blood pressure require a normally functioning sympathetic nervous system; peripheral arteriolar constriction is brought about by the release of noradrenaline from sympathetic nerve endings or by the release of adrenaline from the adrenal medulla; the same mechanisms are also responsible for the increase in venomotor tone and in part for the increase in heart rate.

The patient with early essential hypertension has compensatory reflex mechanisms which function in the normal way. The difference between him and the normal man is in the actual level of arterial blood pressure. The "setting" of these mechanisms has become altered so that the pressure level which they maintain is above the normal range. Immediately the pressure is lowered to a physiological level the homeostatic mechanisms act to restore the hypertensive state. Sustained lowering of the arterial pressure can, however, be obtained by the use of drugs which prevent the normal functioning of the homeostatic reflexes. The anatomical pathways for these reflexes can be interrupted at many points:—

1. Carotid sinus and aortic arch.
2. Central nervous system.
3. Sympathetic ganglia.
4. Sympathetic post-ganglionic nerves.
5. Peripheral adrenergic receptors.

1. Drugs Acting on the Carotid Sinus and Aortic Arch

Plants of the genus Veratrum contain alkaloids with characteristic properties. Selective extraction yields the mixture of alkaloids known as Veriloid and further purification gives the pure crystalline alkaloids protoveratrine A and B.

The intravenous injection of protoveratrine is followed by a rapid fall in blood pressure. This is accompanied by bradycardia and persists for one to three hours.

The veratrum alkaloids can be given orally and they have been used in the treatment of moderate hypertension and in pre-eclampsia. They suffer from several disadvantages, however. The duration of the effect is short and there is a low therapeutic ratio. The dose which lowers blood pressure is only slightly less than the dose which produces vomiting.

The veratrum alkaloids produce a fall in blood pressure by actions on sensory receptors in the heart, lungs and carotid sinus. Probably the pressure receptors are sensitised so that a given sensory discharge frequency is produced by a lower arterial pressure. If this is the case, the veratrum alkaloids can be described as "re-setting" the pressure regulating mechanisms so that they control the blood pressure at a lower level. Theoretically a drug which acts in this way is the ideal hypotensive agent; the pressure regulating mechanisms are not abolished, they are re-adjusted to a physiological level. It is unfortunate that the veratrum alkaloids have such a short action and are so liable to produce undesirable side effects.

2. Drugs which act on the Central Nervous System

The normal functioning of those parts of the central nervous system which regulate the circulation is modified by a large number of drugs.

Normal sleep is associated with a fall in arterial blood pressure. This occurs in both normal and hypertensive people and when the sleep is drug-induced. To this extent the hypnotics are hypotensive agents.

The acute rises in arterial pressure associated with emotion or excitement are prevented or reduced by the sedatives and tranquillisers.

During surgical anaesthesia the blood pressure is lowered; the total peripheral resistance is reduced by a direct effect on the arterioles and by a remote effect on the vasomotor centre. The force of myocardial systole is also reduced. Certain general anaesthetics, notably halothane, appear to block transmission in the autonomic ganglia. Slight increases in the concentration of halothane inhaled are often associated with abrupt falls in arterial blood pressure.

The administration of a medium-acting barbiturate, for example sodium amytal, to a hypertensive patient often produces a marked fall in arterial blood pressure.

3. Drugs which act on Sympathetic Ganglia

Special interest is attached to this synapse because it is a point on the vasoconstrictor pathway which is vulnerable to specific blockade.

Although ganglionic transmission is a continuous process, for convenience of description it may be divided into several stages:

1. Saltatory conduction in the pre-ganglionic nerve fibre.
2. Non-saltatory conduction in the non-myelinated terminal fibrils.
3. Release of acetyl choline at the boutons terminaux.
4. The crossing of the "synaptic gap" by acetyl choline.
5. The adsorption of acetyl choline at the receptor sites on the post-synaptic membrane.
6. Depolarisation of the membrane and the initiation of a propagated action potential.

Transmission may be blocked at each stage by the use of suitable

pharmacological agents. Stages 5 and 6 are interrupted by nicotine, the tetra-alkylammonium compounds, the methonium salts, mecamylamine and pempidine. Special interest is attached to this group because it includes the most specific ganglion blocking agents.

Langley in his classical studies on the anatomy and physiology of the autonomic nervous system, made extensive use of nicotine. He was able to demonstrate the presence of peripheral synapses which were selectively blocked by nicotine. Low doses of nicotine stimulate sympathetic ganglia and provoke the release of adrenaline from the adrenal medulla. The drug has important actions on a large number of other sites and is not suitable for clinical ganglion blockade.

Burn and Dale in 1914 showed that tetraethylammonium bromide closely resembled nicotine. The tetraethylammonium ion was shown to block ganglion transmission without preliminary stimulation. However, the latter suffered from several disadvantages; it had to be given by injection and the hypotensive effect was short. In addition the drug produced neuromuscular blockade. Nevertheless tetraethylammonium bromide was used in the emergency treatment of acute left ventricular failure secondary to hypertension and as a diagnostic tool to predict the response to sympathectomy.

Barlow and Ing in Oxford, and Paton and Zaimis in London developed the methonium compounds, which consist of two quaternary ammonium groupings linked by a polymethylene chain. The pharmacological properties are determined by the length of this chain. The members of the series with 5 or 6 methylene groups are very active as ganglion blocking drugs, but do not prevent neuromuscular transmission.

The penta- and hexa-methylene compounds, pentamethonium, and hexamethonium, were tested on hypertensive patients. They were very effective hypotensive agents but absorption from the alimentary tract was poor and unpredictable. The drugs were given parenterally and hypertensive patients were taught self-administration.

A large number of structural analogues was prepared. Among these was pentolinium (Ansolysen) which is closely related to pentamethonium but better absorbed. In many cases it was possible to obtain adequate control of blood pressure with oral pentolinium. However quaternary ammonium salts as a group are absorbed slowly and to an incomplete extent. Further progress was not made until the advent of the "amine" ganglion blocking drugs, mecamylamine (Inversine) and pempidine, which are absorbed rapidly and almost completely after oral ingestion.

Following absorption there are important differences in behaviour between the quaternary ammonium and the amine ganglion blocking drugs. Hexamethonium is confined to the extracellular fluid compartment and does not penetrate the blood-brain barrier. It is excreted by glomerular filtration and not reabsorbed by the renal tubules. The restricted distribution, the absence of binding to tissue protein and the rapid excretion combine to produce rapid removal of the drug. For this reason the degree of ganglion blockade produced by hexamethonium fluctuates relatively rapidly.

The secondary amine mecamylamine is distributed throughout the body fluids. It is bound to the tissue proteins and tubular reabsorption in the kidney reduces the rate of excretion. Thus the degree of ganglion blockade produced by mecamylamine is more uniform than with hexamethonium. Mecamylamine penetrates the blood-brain barrier and some patients develop tremors.

The difference between hexamethonium and mecamylamine are due to the differences in the state of the nitrogen atoms in the two molecules. The heavily charged quaternary ammonium cation is not able to penetrate cell

membranes. The substituted amines are readily absorbed by cells as the free bases.

It is not possible to state which is the better of the two drugs mecamylamine and pempidine at present. A clinical trial of these two drugs is being conducted in the Royal Infirmary, Edinburgh, using a "double blind" technique.

The Cardiovascular Effects of Ganglion Blockade

Ganglion blockade produces only a slight fall in the supine blood pressure of the normal subject. The fall is greater, however, in the hypertensive patient. This is probably due to the fall in total peripheral resistance which results from the interruption of the sympathetic vasoconstrictor pathway. A much greater fall in both diastolic and systolic pressures is obtained when the patient stands erect. This is due to haemodynamic changes which can no longer be corrected.

With the assumption of the erect posture the hydrostatic pressure distending the veins of the abdomen and lower limbs is increased. In the absence of compensatory venoconstriction these veins dilate and accommodate a larger proportion of the total venous blood. The volume which remains in the great veins near the heart is therefore decreased. This is accompanied by a fall in venous filling pressure and in cardiac output. Reduced cardiac output and reduced peripheral resistance together produce a fall in arterial blood pressure. Normally this would evoke the compensatory reflex mechanisms described earlier, but ganglion blockade prevents this.

When the degree of ganglion blockade is excessive the pressure may fall from hypertensive to hypotensive levels. This is commonly associated with symptoms of cerebral ischaemia, dizziness, "light-headedness" and fainting. Many physicians encourage their patients to take enough drug to produce symptoms of postural hypotension once or twice during the day. They are also advised to take advantage of the postural effect by sleeping with the head of the bed raised.

The effects of ganglion blockade on peripheral blood flow vary from one tissue or organ to another:

1. Skin. The sympathetic adrenergic innervation of skin vessels is constrictor. Ganglion blockade is usually associated with an increase in blood flow to the foot and to the hand. This is due largely to increased skin flow.
2. Voluntary muscle. The sympathetic innervation of the arteries and arterioles of skeletal muscle is largely dilator. Forearm flow, which is chiefly muscle flow, is usually unchanged by ganglion blockade.
3. Brain. The blood flow to the brain is under autonomous control; it remains almost constant in spite of wide variations in arterial blood pressure. In the healthy young adult cerebral ischaemia is only produced by severe postural hypotension, but the aged hypertensive is quite different. Hypertensive arteriolar sclerosis offers a high, relatively fixed resistance to blood flow. Ganglion blockade reduces arterial pressure and predisposes to thrombosis, ischaemia and infarction.
4. Myocardium. Reduction in the aortic diastolic pressure has a two-fold effect. The coronary blood flow may be reduced but so also is the work demanded from the myocardium. The effect on coronary ischaemia depends on which predominates.
5. Kidney. The renal blood flow is never increased by ganglion

blockade. There is evidence that the reduction in renal blood flow produced by the fall in arterial pressure is temporary; adaptation may restore normal blood flow after a few hours.

Carefully controlled treatment by ganglion blockade with regular attendance at hypertensive clinics can be very successful. Some patients enjoy adequate control with the minimum of side effects. Others experience all the side effects at dose levels which are not adequate to control hypertension. The majority have one or two side effects.

It may require a great deal of encouragement to convince a patient with severe hypertension but minimal symptoms that the treatment is worthwhile; he feels better without treatment.

Almost all patients receiving ganglion blocking drugs are constipated, but most procure regular motions with Senokot or Petrolagar. A few develop an "all-or-none" bowel action. Without laxatives they are completely constipated yet the smallest effective dose of a mild purgative produces diarrhoea. Apart from the inconvenience involved, this hampers treatment; when constipated, more of the hypotensive drug is absorbed; when loose, part is lost in the motions. Smooth control of the arterial pressure becomes very difficult.

Urine retention is an important side action in older men with benign prostatic hypertrophy. Secondary hypertensive disease in brain, myocardium or kidney may prevent surgical relief of the obstruction, whilst the danger of acute retention prevents treatment by ganglion blockade.

Ganglion blockade may retard the progression of hypertensive renal disease but renal function is seldom improved. The reduction of renal blood flow has an adverse effect on impaired renal function. Further nitrogen retention may occur and renal failure can develop. Patients with a blood urea nitrogen level over 60 mg. per 100 ml. usually deteriorate on ganglion blocking drugs.

Other common side effects of ganglion blockade are blurred vision, dry mouth, reduced appetite and impotence. They seldom prevent continued therapy. The majority of the side effects are due to the interruption of transmission through parasympathetic ganglia. This prevents the normal functioning of the ciliary body, the salivary glands, the peristaltic reflex, the gastric and intestinal mucosae, the innervation of the bladder and the reflexes involved in erection and ejaculation.

Attempts to produce specific sympathetic ganglion block have not been successful in spite of the anatomical and physiological differences between sympathetic and parasympathetic ganglia. There are, however, drugs which act specifically on post-ganglionic sympathetic nerves.

4. Drugs which act on Sympathetic Post-Ganglionic Nerves

(*a*) RESERPINE.

Plants of the genus Rauwolfia have been used for centuries in Africa and India chiefly in the treatment of insanity. Only in this century, however, have the Rauwolfia alkaloids become recognised as hypotensive agents.

Three preparations from Rauwolfia are available; Raudixin is a powdered preparation of the whole root; Rauwiloid is a partially purified mixture of alkaloids; and reserpine is a pure crystalline alkaloid, the most important of the Rauwolfia group.

Reserpine produces changes in behaviour; a treated animal lies quietly in its cage showing the minimum of spontaneous activity. It is inattentive and lacks concentration. Left alone it merely sleeps. Comparable doses

produce a similar effect in man. This sedation is different from that produced by the barbiturates.

The cardiovascular effects of reserpine are bradycardia and a fall in arterial blood pressure. Other effects are increased gastro-intestinal motility, constriction of the pupil, relaxation of the nictitating membrane and loss of the pilo-erection response to cold. These effects develop very slowly, even after intravenous injection of the drug. Careful observation of animals soon after injection has revealed transient hyperglycaemia, pilo-erection, elevation of the arterial blood pressure and contraction of the denervated nictitating membrane.

The mode of action of reserpine has been elucidated recently. In 1955 Brodie and his co-workers showed that reserpine liberates 5-OH tryptamine from brain and other tissues. Other pharmacologically active amines occur in brain, notably noradrenaline and adrenaline. Methods for their extraction, purification and assay have been developed by M. Vogt. They have a very similar distribution to 5-OH tryptamine, being found in the hypothalamus, mid-brain and medulla. Recently it has been shown that these compounds are also liberated by reserpine.

Sympathomimetic amines are also stored in adrenergic nerves and in the adrenal medulla. Following reserpine the concentration of these compounds is reduced. In the cat, for example, reserpine reduces the noradrenaline in the superior cervical ganglion from about 4.5 microgrammes per gramme to 1.5 or less. When the concentration falls below 1.0 microgramme per gramme, peripheral transmission fails. Impulses pass through the ganglion but they fail to excite the effector structure. Apparently the quantity of noradrenaline released from the nerve terminals is reduced to an ineffective level.

Reserpine appears to allow the sympathomimetic amines to leak out from cells into the plasma. A transient rise in the plasma adrenaline concentration after reserpine has been demonstrated in rabbits. This probably accounts for the transient hyperglycaemia, hypertension, pilo-erection and contraction of the denervated nictitating membrane.

The repeated administration of therapeutic doses of reserpine to man is probably adequate to deplete the noradrenaline and adrenaline content of the sympathetic tissues; this has not yet been proved, however. Probably the hypotensive effect of reserpine is due to this.

Reserpine is widely used in the treatment of hypertension. Some cases respond well to reserpine alone. The hypotensive action is moderate and they do not develop postural hypotension. Reserpine potentiates the blood pressure lowering effects of the ganglion blocking drugs without enhancing the undesirable side effects.

The therapeutic ratio for reserpine is very much higher than for the veratrum alkaloids; nevertheless it has several side actions. Nasal congestion, diarrhoea and dreams are the most common. The sedative effects are advantageous in over-active hypertensive patients. Some, however, experience severe depression. This is the most serious disadvantage of reserpine and often limits the use of the drug. A derivative with hypotensive effects but no central depression would be valuable.

(*b*) BRETYLIUM TOSYLATE (DARENTHIN).

In 1957 Exley described a choline xylyl ether called T.M.10; this compound is parasympathomimetic but has highly characteristic effects in addition. When a dose of 5-15 milligrammes per kilo is given intravenously to a cat peripheral sympathetic transmission is prevented. Impulses pass through the sympathetic ganglion and along the post-ganglionic sympathetic

nerve but the innervated organ is not excited. For example, stimulation of the cervical sympathetic chain no longer elicits a contraction of the nictitating membrane. Stimulation of the sympathetic nerves to the heart does not increase the heart rate, nor does stimulation of the sympathetic nerves to the salivary glands produce salivation. Each of these structures responds normally to adrenaline and noradrenaline however. The block in transmission appears to be at the adrenergic nerve ending.

The properties of T.M.10 excited great interest and many structural analogues were prepared. The aim was to obtain a compound with the sympathetic blocking properties of T.M.10 but without the parasympathomimetic effects. This aim has been realised in bretylium.

Bretylium tosylate (Darenthin) is a simpler molecule than T.M.10. The anion is p-toluene sulphonate but this is not necessary for pharmacological activity.

Bretylium produces a specific sympathetic blockade; it lacks the parasympathomimetic effects of T.M.10. Low doses which prevent the effects of sympathetic nerve stimulation do not prevent conduction along the nerve. They appear to stop the release of noradrenaline from the nerve ending. Large doses given over a long period do not deplete the noradrenaline stores, so that a reserpine-like action seems unlikely.

Bretylium does not antagonise adrenaline or noradrenaline. On the contrary the treated animal becomes more sensitive to the sympathomimetic amines. The drug does not prevent the release of adrenaline from the adrenal medulla. It seems likely therefore that the influence of the adrenal on arterial blood pressure will be increased in patients treated with Bretylium.

Bretylium is a quaternary ammonium ion and is not well absorbed from the alimentary tract. This is a disadvantage but it does not prevent oral administration. Following absorption the drug is selectively accumulated by adrenergic nerves. Carbon 14 labelled bretylium is found at these sites but not in the central nervous system. Urinary excretion is rapid and none of the drug can be detected in the urine after 24 hours.

The cardiovascular effects of bretylium are similar to those of ganglion blockade. In healthy young adults there is little change in supine blood pressure but the erect blood pressure is reduced. In hypertensive patients the supine pressures are lowered to a moderate extent but a much larger drop occurs when the patients stand erect. Postural hypotension occurs with large doses, especially after a heavy meal. Following oral ingestion the effects appear in about an hour. The maximum effect is seen after about three hours.

Bretylium is undergoing clinical trial in many parts of the country. Suitable patients are those who have severe hypertension and would otherwise be subjected to ganglion blockade. Tolerance develops to bretylium as it does to the ganglion blocking drugs but the undesirable side effects of the latter are not produced. Patients on bretylium do not complain of constipation, dry mouth, blurred vision and loss of appetite. Early experience suggests that bretylium will have the same effects as ganglion blocking drugs on impaired renal function.

The development of a specific sympathetic blocking agent represents a major advance in the drug treatment of severe hypertension. Bretylium also provides the experimental pharmacologist with an exciting new tool.

5. Drugs which act on Adrenergic Receptors

Several peripheral antagonists of adrenaline and noradrenaline are known. They prevent access to adrenergic receptors. Some of them, like the ergot

alkaloids and tolazoline have additional actions which make them unsuitable for clinical use. Others, for example phentolamine (Rogitine), have an established place in the diagnosis of phaeochromocytoma. All the specific adrenaline antagonists are much more effective against adrenaline or noradrenaline circulating in the blood than against noradrenaline released at nerve endings. They are ineffective in the treatment of essential hypertension.

6. Other Drugs

In addition to the hypotensive agents described above, there are others which do not fit into the classification used. Hydralazine (Apresoline) is occasionally used in the treatment of patients with hypertension and impaired renal function. This drug is unique amongst the hypertensives in that it increases renal blood flow. However, the serious toxic effects of the drug restrict its use.

Chlorothiazide (Saluric) is a potent oral diuretic. Where hypertension is associated with fluid retention as in pre-eclampsia, patients often respond to this drug with a copious diuresis and a fall in arterial blood pressure. Chlorothiazide has also been shown to potentiate the effects of the hypotensive drugs. The dose of a ganglion blocking drug required for a given depression of the arterial blood pressure may be reduced by half. The mode of potentiation is not clear.

The peripheral vasodilator drugs, for example glycerol trinitrate and amyl nitrite, reduce peripheral resistance and lower blood pressure. The effect is variable and transient however, and a reflex tachycardia is produced. They are not suitable for the sustained lowering of blood pressure in hypertensive patients.

Summary

1. The arterial blood pressure in the patient with early essential hypertension is regulated by the carotid sinus reflexes. Many of the drugs which lower arterial blood pressure interfere with the reflex mechanism.
2. Several drugs which lower arterial pressure by actions on the sensory and central parts of the reflex pathway are described. The cardiovascular effects of ganglion blocking agents are outlined; attention is drawn to the desirability of specific sympathetic blockade.
3. Recent work on reserpine is described and the need for a similar drug without depressive effects is emphasised. The recently introduced specific sympathetic blocking agents are of great theoretical and practical interest. Several other hypotensive agents are given brief mention.

FURTHER READING

The following list is intended as a guide to review articles and publications of a similar nature. These contain full references to original literature:—

Hypotensive Drugs

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