HAZARDS OF ANTIHYPERTENSIVE THERAPY

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Hypertension is a very common disorder in man, carrying with it, in the more severe case, a significant mortality.[1] During the past decade a vast number of new drugs have been marketed for its treatment, with widely varying degrees of therapeutic usefulness.

Two major problems have emerged, namely whom to treat and how. It is difficult to know, in certain circumstances, when a blood-pressure recording becomes pathological,[2] while, unfortunately, all drugs so far introduced into medical practice for the treatment of hypertension have proved to have unwanted side-effects.

In this article, the possible hazards that may be encountered in treating hypertensive patients with drugs are reviewed; only drugs in current use will be considered.

(A) SIDE-EFFECTS COMMON TO SEVERAL DRUGS

After the administration of certain drugs (e.g. ganglion-blocking agents, bretylium and guanethidine) the tone of the musculature of peripheral blood vessels is decreased. Consequently, on assuming the erect posture, pooling of blood occurs in the affected vessels. This leads in turn to a fall in venous return and to a fall in blood pressure[3] (postural hypotension), which may manifest itself variously[4] as dizziness, syncope, blurring of vision, transient hemiparesis, weakness, fatigue, lassitude, pain in the neck, aggravation of intermittent claudication, appearance or aggravation of angina pectoris,[5] or impairment of renal function.

The occurrence of hypotension is particularly hazardous in patients with cerebrovascular disease, ischaemic heart disease, or renal dysfunction, whether they be overt or latent, because the fall in filtration pressure to the organ concerned not only interferes with its function, but also may gravely prejudice its survival.[3]

(B) SIDE-EFFECTS OF INDIVIDUAL DRUGS

1. Diuretics (Benzothiadiazine Group)

The greatest hazard arising from the prolonged use of these diuretics is the production of hypokalaemia. The following two factors, resulting from the action of the drug on the renal tubule, facilitate urinary loss of potassium:

(*a*) Adequate amounts of sodium ions are usually present in the distal tubular fluid for ion exchange to occur, and

(*b*) The production of hydrogen ions for ion exchange in the renal tubular cells is blocked by inhibition of carbonic anhydrase.[6]

The presence of any of the following symptoms should make one suspect the presence of hypokalaemia; bitter taste, thirst, gastro-intestinal symptoms, weakness, malaise. The chief dangers of potassium depletion are muscular paralysis,[7] increased danger of digitalis toxicity,[8] precipitation of hepatic coma in cirrhotic subjects (suggested by tremors, confusion, somnolence),[9] while long-continued depletion has been shown to result in renal[10] and myocardial[11] damage.

Occasional patients manifest gastro-intestinal intolerance (cramps, nausea, vomiting, diarrhoea).[8]

Some patients show a rise in serum uric acid while on therapy. In those with a hereditary gouty predisposition, overt gout has been precipitated.[12,13] This is attributed to inhibition of renal tubular secretion of uric acid. Impaired glucose tolerance with the appearance of frank diabetes has also been reported.[14]

Rarer complications have included thrombocytopenia,[8] agranulocytosis,[15] aplastic anaemia, photosensitivity,[16] renal colic with haematuria and uric-acid crystalluria,[17] skin rashes,[8] yellow vision,[18] and acute pancreatitis.[19]

2. Drugs Acting on Afferent Nerve Endings (Veratrum Alkaloids)

These preparations are all very liable to cause nausea and vomiting from an action on the nodose ganglion of the vagus.[20] Doses that produce a useful fall in blood pressure usually also stimulate vomiting. They may also produce blurred vision, weakness, mental confusion, choking, salivation, diarrhoea, warmth, excessive perspiration, and a burning sensation behind the sternum.[21,22]

3. Drugs Acting as Autonomic Ganglion Blocking Agents

All these drugs have an intense blocking action at the preganglionic synapse in sympathetic and parasympathetic ganglia.[23] The parasympathetic blockade may lead to many distressing symptoms, namely:[4,24]

(*a*) Visual: paralysis of accommodation with blurring of near vision, raised intraocular tension.

(*b*) Gastro-intestinal: dry mouth, nausea, constipation and, most serious of all, paralytic ileus.

(*c*) Genito-urinary: difficulty with starting micturition, urinary retention, impotence.

These drugs are able to cross the placenta and cases of foetal paralytic ileus occur.[25]

Individual drugs can also give rise to characteristic side-effects:

(*a*) Hexamethonium bromide, when used for a long period, occasionally gave rise to bromism or to pulmonary changes (cough, dyspnoea).[26]

(*b*) Mecamylamine crosses the blood-brain barrier. Toxic effects on the brain[27] (tremor, slurred speech, increased muscle tone, brisk reflexes, with or without psychiatric features such as confusion, delirium and hallucinations) may occur.

4. Drugs Acting on the Central Nervous System

(*a*) *Rauwolfia alkaloids*

The most serious side-effect is agitated mental depression, the first symptom of which may be early-morning insomnia.[28,29] There is a suicidal risk as well. The appearance of depression is related to the duration of treatment, the dosage employed, and the patient's previous personality.

Patients may also complain of nightmares and decreased libido, while epilepsy may become more frequent in those prone to the condition. A parkinsonian-like syndrome also occurs.[30] All the above neuropsychiatric complications may be related to the depletion of catechol amines and of 5-hydroxytryptamine (5HT), which occurs in the brain in patients taking these compounds.[31]

The central parasympathetic effects[23] of rauwolfia alkaloids result in blurring of vision, ptosis, salivation, nasal stuffiness, and reactivation of peptic ulcers.

Diarrhoea is common and may be the result of the central parasympathetic effect or of released 5HT on the bowel wall.[31]

Weight may be gained not only from an increased appetite but also from the accumulation of oedema fluid. Cardiac failure may supervene.

'Reserpine' interferes with the autonomic nervous system in two ways: (a) It inhibits the action of reflex mechanisms contributing to the stability of the vascular system, and (b) it decreases the amounts of circulating catechol amines. Consequently bradycardia and prolonged hypotension have followed surgical anaesthesia. General anaesthetics potentiate this effect.[32,33]

(*b*) *Hydralazine*

It has been proposed[34] that the toxic effects of this drug can be divided into 3 subdivisions as follows:

(*i*) Hypersensitivity type: A number of complications occur which bear a striking resemblance to the collagen group of diseases. The commonest complication in this group by far, and the one that has restricted the use of the drug more than any other, is what has been called 'the hydralazine syndrome'. The first phase ('rheumatoid-arthritis phase') may be preceded by a peculiar chest pain. Following this come chills and migrating arthralgia and myalgia. Should the drug be continued a true symmetrical arthritis of small joints of the hands develops. If the drug is still continued, then a condition resembling disseminated lupus erythematosus follows. Some cases go into remission if the drug is discontinued at this stage but even after 7 years' activity the condition was still present in some cases.[35] Rarer complications in this group include giant urticaria, polyarteritis nodosa,[36] pancytopenia,[37] and fatal hypotension after a small oral dose.[38]

(*ii*) Polyneuritis type: These cases may have been due to a conditioned pyridoxine deficiency.[34]

(*iii*) Acute cardiovascular type: These may be the result of the release of histamine-like substances secondary to the inhibition of histaminase; or due to a central depressant effect of the drug.[34] Headache is a very common symptom,[39,40] while tachycardia, palpitations, retrosternal distress, angina,[5] oedema, nasal stuffiness, dyspnoea, nervousness, anxiety, malaise, tingling, and paraesthesiae, may all occur.

5. Drugs acting on the Postganglionic Sympathetic Nerve Fibres or their Terminations

(*a*) *Bretylium tosylate*

Sudden unpredictable falls in blood pressure, as a result of irregular absorption of the drug from the bowel or when its

excretion is impaired in renal disease,[41] make the use of bretylium dangerous. It may also lead to hypotension occurring during exercise. This has been ascribed to the fact that during exercise pooling of blood occurs because autonomic reflexes are inhibited as the result of the drug's action on the post-ganglionic nerve fibres.[42]

Another common complaint with bretylium has been one of pain in the region of the parotid salivary glands, brought on by eating or by sucking sweets. The cause is as yet uncertain.

As sympathetic fibres are blocked, parasympathetic effects predominate,[41] namely (i) gastro-intestinal (salivation, diarrhoea), (ii) visual (blurring of vision, bilateral Horner's syndrome,[43] peculiar sensations about the eyes[44]), (iii) cardio-vascular (bradycardia, nasal congestion and stuffiness) and (iv) genito-urinary (failure of ejaculation, polyuria[41]). Intolerance to bretylium may also occur (nausea and indigestion).[41]

Muscle weakness and fatigue have sometimes been prominent symptoms.[41,45] This has been attributed variously to hypotension, neuromuscular block, and myopathic changes.[46]

Dyspnoea, chest pain and oedema may occur and it has been suggested that increased pulmonary vascular resistance during exercise may be the cause.[45,47]

Tremor, confusion and insomnia[45] are uncommon with bretylium, and so are skin rashes.[48]

(*b*) *Guanethidine*[49,50]

Hypotension occurs, but is less common than with bretylium since its absorption from the bowel is more regular, more complete, and more predictable.

Parotid pain is probably less common than with bretylium.

Guanethidine crosses the blood-brain barrier to a greater extent than bretylium, hence tremor and depression are commoner.

The following side-effects that occur when bretylium is used may also be noted with guanethidine; parasympathetic effects, muscle weakness, myalgia, intolerance, fluid retention, and oedema.

6. Drugs Modifying the Formation or Destruction of Catechol Amines and of 5-Hydroxytryptamine (5HT)

(*a*) *Rauwolfia alkaloids* (see above).

(*b*) *Monoamine-oxidase inhibitors*

The use of these drugs in hypertension is still largely experimental. Their most serious side-effects include toxic hepatitis, optic neuritis and toxic amblyopia, while excessive stimulation of the psyche, muscle twitching, dryness of the mouth, constipation, diaphoresis, dyspnoea, oedema, anaemia, vertigo, and impotence, have all been reported.[51]

(*c*) *Methyldopa*

No symptoms attributable to parasympathetic blockade occur.[52]

The drug may produce drowsiness,[52] sedation, severe depression,[53] nightmares,[54] disturbance of sleep rhythm, and mood changes.[55] Dry mouth, tiredness, fatigue, indigestion, lassitude,[52] nasal stuffiness, failure of ejaculation, and diarrhoea, have all occurred now and then. Some of these effects may be due to decreased formation of dopamine, noradrenaline, adrenaline and 5HT at various sites in the body, e.g. the brain.

More serious toxic effects of the drug have been drug fever, liver damage,[56] oedema with sodium retention[57] which may go on to heart failure, and toxic effects on the bone marrow.[53,58]

DISCUSSION

No attempt has been made in the above review to indicate the frequency of side-effects in percentages. These have been found to vary widely from one report to another while, with newer drugs, time may reveal that some side-effects are more important and more frequent than is at present believed. Throughout, however, the most important side-effect has usually been dealt with and stressed.

The following suggestions have been formulated in an attempt to assist in the reduction of the incidence of side-effects in patients undergoing treatment for hypertension:

1. The careful selection of patients.

2. The avoidance of drugs which

(*a*) have been found to produce major side-effects when a therapeutic dose is given (e.g. veratrum alkaloids, hydralazine, certain ganglionblocking agents);

(*b*) are still being investigated (e.g. monoamine-oxidase inhibitors); and

(*c*) are unreliable and unpredictable in their absorption and effects (e.g. bretylium tosylate).

3. The use, whenever possible, of drugs that potentiate each other, thus allowing smaller doses of each to be used (e.g. thiazide diuretics, reserpine, guanethidine, ganglion-blocking agents, methyldopa).

4. The avoidance of ready-made combinations of drugs, since the dose of each individual drug cannot be regulated to suit the patient.

5. Regular follow-up of patients and a careful watch for early signs of toxicity (e.g. reserpine).

6. The prevention of complications (e.g. potassium supplements for all patients on diuretics).

7. The symptomatic treatment of side-effects when they occur and cannot be avoided.

Finally, before using any drug, it is probably wise to answer the following questions (as suggested by D. R. Laurence[59]):

(*a*) Should the patient be treated at all?

(*b*) What do I hope to change in the patient?

(*c*) Can the drug that I propose using produce the desired change?

(*d*) What other effects will the drug have, and will these be harmful to the patient or not?

SUMMARY

The difficulty of selecting patients with hypertension for treatment is referred to.

The side-effects of drugs in current use in the treatment of hypertension are reviewed.

Some measures are suggested to reduce the incidence of side-effects during therapy.

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