GUANETHIDINE IN THE TREATMENT OF HYPERTENSION

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In the last decade great advances have been made in the treatment of hypertension, so that it is now possible in most cases, by the use of drugs, singly or in combination, to reduce raised blood pressure to normal or near normal levels during the 24-hour day. The benefit to be derived from treatment is often great, especially in cases of malignant hypertension, and this is particularly so when treatment is started before there is extensive vascular damage (Harington, Kincaid-Smith and McMichael, 1959). In less severe degrees of hypertension, there is symptomatic relief, heart failure is usually relieved, and improvement often occurs in the electrocardiogram (Dustan, Schneckloth, Corcoran and Page, 1959). Unfortunately, when there is much impairment of renal function lowering of the blood pressure may result in progressive renal failure and a further rise of blood urea, and these cases are, therefore, not usually suitable for treatment.

Until recently, the most effective hypotensive drugs blocked transmission of impulses at autonomic ganglia and postural blood pressure control due to paresis of the sympathetic nervous system was often obtained only at the cost of serious side effects due to simultaneous blockage of the parasympathetic ganglia. Great interest was shown, therefore, in new compounds which gave good postural control of the blood pressure by blocking only the sympathetic nervous system without parasympathetic inhibition, first bretylium tosylate (Darenthin) (Boura, Green, McCoubrey, Lawrence, Moulton and Rosenheim, 1959) and later guanethidine (Ismelin) (Maxwell, Mull and Plummer, 1959).

Guanethidine sulphate was synthesized in 1959. It is thought to lower blood pressure by interfering with the metabolism of chemical transmitter substances in post-ganglionic sympathetic nerve fibres only. There are, therefore, no side effects from parasympathetic blockage such as blurred vision, dryness of mouth, constipation and bladder atony, as commonly occur with ganglionic blockage therapy. Its hypotensive action is predominantly postural but not exclusively so, and some fall in blood pressure in addition to the postural effect may be seen. Most patients taking the drug become more hypotensive during exercise and this is especially likely in the early morning when the postural fall is greatest (Dollery, Emslie-Smith and Milne, 1960).

Guanethidine is a cumulative drug, its action being prolonged for at least three days after a single oral dose. In the presence of impaired renal function and after long periods of treatment with high doses, excretion is further delayed (Dollery and others, 1960), and because the effective dose varies, and some patients are sensitive to small doses, great care must be taken in finding the correct dose for each patient. The drug is supplied as tablets containing 10 mg. (white) and 25 mg. (pink). Cost of treatment averages 3d. to 1s. 6d. daily at basic N.H.S. prices.

Benzthiazide diuretics, and, to a lesser extent, Rauwolfia alkaloids, potentiate the action of guanethidine, so that the addition of a benzthiazide diuretic often reduces the amount of guanethidine necessary to obtain a satisfactory fall in blood pressure (Blanshard and Essigman, 1961).

The commonest side-effect is diarrhoea, but muscle aching and weakness, fluid retention, mental depression and failure of ejaculation may also occur. Side effects occur more frequently when large doses of the drug are given. Nasal stuffiness and parotid pain which were frequent with bretylium tosylate occur very rarely with guanethidine. Moreover, there is no significant development of drug tolerance, which is a great advantage over bretylium.

When pheochromocytoma is present or suspected, guanethidine is contraindicated because it may increase the pressor response to adrenaline and noradrenaline secreted by the tumour, and dangerously high blood pressure may result. Recent coronary or cerebral thrombosis is also a contraindication to immediate treatment, but treatment may be started cautiously six weeks later when special care must be taken to avoid episodes of hypotension. Where angina of less
than one year's duration is present, hypotensive therapy may be combined with anticoagulants.

We report here our experience of the use of guanethidine (Ismelin, Ciba) in the treatment of 20 patients with severe hypertension and evidence of hypertensive disease as shown by symptoms and signs of cardiac, renal or retinal disease.

Subjects

Twenty patients (16 women and four men) have been treated for periods up to 20 months; the mean duration of treatment being 11.7 months. Their average age was 49 years (range 18 to 65 years). The patients were admitted to hospital from the outpatient department or directly as an emergency. In hospital, in addition to a detailed history and clinical examination, daily blood pressure readings were taken after a period of bed rest to determine the basal blood pressure level. All patients had routine chest X-ray examination, electrocardiography, ophthalmoscopic inspection, urinanalysis including microscopy and culture, estimation of blood urea and intravenous pyelography. A phentolamine test and examination for urinary catecholamines were undertaken to exclude pheochromocytoma in all cases. The presenting symptoms were headache (15), dyspnea (6), blurring of vision (2) and dizziness (2). In addition, three had hypertensive cardiac failure, 16 had evidence of left ventricular hypertrophy and strain on electrocardiography, and in 10 there was cardiac enlargement clinically. Three had Grade IV and four Grade III retinopathy, five had a raised blood urea (greater than 50 mg. %) and eight had persistent proteinuria presumably due to renal damage.

Before starting treatment a persistent elevation of diastolic pressure was demonstrated (Table 1) by daily blood pressure readings under basal conditions. Eighteen were considered to be suffering from essential hypertension and in two the hypertension was thought to be secondary to chronic pyelonephritis.

The initial dose of guanethidine was 10 mg. daily for four days, and subsequent increments of not more than 10 mg. daily were made at four-day intervals until the standing diastolic pressure was 100 mm. Hg. or less. When a satisfactory fall in blood pressure had been obtained without side effects, the patients were seen at monthly intervals in the outpatient department. The average dose of guanethidine necessary to obtain a satisfactory reduction in blood pressure was 50 mg. (range 10 to 100 mg.). If the patient complained of diarrhoea (more than three stools a day) the dose of guanethidine was reduced by 10 mg. per day and a tablet of a benzthiadiazine diuretic with potassium chloride given in addition. Four patients were given hydrochlorothiazide but more recently six have been given cyclopentiazide containing 600 mg. potassium chloride (Navidrex K, Ciba) instead because it is longer-acting and cheaper. If diarrhoea still persisted, a small dose of pempidine, 2.5 mg. t.d.s., was given as well. Because the incidence of toxic effects increases appreciably with doses of guanethidine over 60 mg. daily, a benzthiadiazine diuretic containing potassium chloride was given routinely even in the absence of side effects if a satisfactory fall in blood pressure had not been obtained with 60 mg. guanethidine. If diarrhoea developed as the dose of guanethidine was increased further, pempidine or propantheline was given in addition.

Patients may be stabilized as outpatients, but, as a few are particularly sensitive to guanethidine, the daily dosage should in these circumstances be increased by not more than 10 mg. at weekly intervals until the stabilization dose is reached, when they may be seen at monthly intervals as before.

Results

Using this regimen it was possible to obtain a satisfactory fall in blood pressure without side effects in all the cases (Table 2). Diuretic was added to guanethidine in seven because more than 60 mg. of guanethidine was required to obtain a satisfactory fall in standing diastolic pressure and in three because of diarrhoea with a dose of guanethidine of less than 60 mg. per day.

Symptoms were relieved in all cases. Hypertensive cardiac failure cleared in all three patients, electrocardiographic evidence of left ventricular hypertrophy and strain was abolished in six and improved in 10, serious retinopathy healed in all seven and proteinuria persisted in one patient only. At least six months' treatment at stabilized dosage was usually necessary before clear objective improvement occurred. Blood urea levels showed little change although in one case the blood urea rose transiently at the beginning of treatment.

<table>
<thead>
<tr>
<th>Diastolic Blood Pressure</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>mm. Hg.</td>
<td></td>
</tr>
<tr>
<td>120/129</td>
<td>2</td>
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<tr>
<td>130/139</td>
<td>10</td>
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<tr>
<td>140/149</td>
<td>5</td>
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<tr>
<td>150/159</td>
<td>3</td>
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Details of Treatment

All the patients were treated in hospital until a satisfactory reduction of blood pressure was obtained.
Side Effects

Diarrhoea, worse in the morning and associated with urgency, occurred in four patients. In three the dose of guanethidine was less than 60 mg. a day but the diarrhoea did not persist in two when the dose was reduced by 10 mg. and cyclopentothiazide added, although one required pempidine as well. One patient having 80 mg. guanethidine and a diuretic developed diarrhoea which was controlled by a small dose of propantheline. Three patients complained of muscle aching and easy fatigue but these symptoms were transient and did not persist when the stabilization dose had been reached. Severe postural hypotension was not troublesome, and, although six patients complained of a feeling of light-headedness on rising from bed in the morning, lasting five minutes or less, this tended to wear off as treatment continued. None of the patients complained of depression. No evidence of drug tolerance was found, and once the correct dose had been arrived at it did not have to be changed.

Discussion

We have found guanethidine to be an effective drug for lowering elevated blood pressure when given as a single morning dose. It is well tolerated and although diarrhoea is a fairly frequent side effect this can usually be readily controlled without an increase in blood pressure readings by reducing the dose of guanethidine by 10 mg. and adding a benzthiadiazine diuretic. If the dose of guanethidine required for blood pressure control is greater than 60 mg. daily, a benzthiadiazine diuretic should be given in addition as the amount of guanethidine required, and, therefore, the incidence of side effects is thereby reduced, and it seems likely that diarrhoea would have been a greater problem had we not adopted this policy. There is complete freedom from side effects due to parasympathetic paresis which often made treatment with ganglionic blockade agents difficult, and in contrast to the earlier sympathetic-blocking agent, bretylum tosylate, drug tolerance has not been a problem. The drug has a slow effect and some weeks are often necessary to obtain satisfactory control of the blood pressure. It is not, therefore, suitable for control of acute hypertensive crises such as acute left ventricular failure with pulmonary oedema or encephalopathy and for these cases parenteral pempidine is to be preferred. That careful treatment with hypotensive agents is worth while is shown by this series, because, in addition to relief of symptoms and fall in blood pressure to normal or near-normal levels, such serious manifestations as left ventricular strain, retinopathy and proteinuria were reduced or abolished in the great majority of the patients treated.

Summary

Guanethidine lowered blood pressure satisfactorily in 20 hypertensive patients and subjective and objective benefit resulted. A combination of guanethidine and a benzthiadiazine diuretic reduces the amount of guanethidine necessary to control the elevated blood pressure, and this combination enables side effects of the drug to be controlled. If more than 60 mg. of guanethidine are necessary for satisfactory control of blood pressure, we recommend that a benzthiadiazine diuretic should always be given simultaneously.

REFERENCES

Dustan, H. P., Schnickloth, R. E., Corcoran, A. C., and Page, I. H. (1958): The Effectiveness of Long-Term Treatment of Malignant Hypertension, Circulation, 18, 644.
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