A CLINICAL TRIAL OF GUANETHIDINE IN HYPERTENSION

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Guanethidine (Ismelin, Ciba Su- 5864) belongs to a new series of compounds synthesized in recent years by Mull *et al.*[1] in the Ciba Research Laboratories, Summit, New Jersey.

The hypotensive action of this drug was first described by Maxwell *et al.*;[2] and preliminary clinical reports by Page and Dustan,[3] and Frohlich and Freis[4] appeared in the USA in July and August 1959 respectively. The first British experience with the drug was published by Leishman *et al.*,[5] in December 1959. As these, and the few other clinical reports which have appeared, were generally favourable (Richardson and Wyso,[6] Jaquerod and Spuhler[7]) it was decided to conduct a clinical trial on African and European hypertensive patients in Central Africa.

CHEMISTRY AND PHARMACOLOGY

The clinical name of guanethidine is 2 - (octahydro - 1 - azocinyl) - ethyl - guandidine sulphate, and its structural formula is shown in Fig. 1.

Guanethidine is not chemically related to bretylium, but, generally speaking, has a similar action in that it appears to effect a specific blockade of the sympathetic nervous pathways without a corresponding blocking of the parasympathetic system, such as occurs with ganglion-blocking drugs like pentolinium and pempidine.[5]

Maxwell *et al.*,[8] showed that guanethidine profoundly lowered the arterial pressure of unanaesthetized neurogenic (amphetamine induced) and renal hypertensive dogs. It had a slight hypotensive action in the normotensive unanaesthetized and anaesthetized dog. It was likewise a potent antagonist of the pressor responses elicited by (*a*) bilateral occlusion of the carotid arteries, and (*b*) injection of high doses of amphetamine.

Within a period of 6 - 12 hours after its intravenous injection, the nictitating membranes and the arterial system

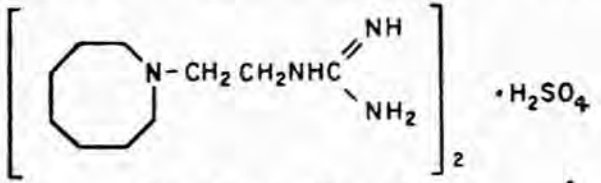

Fig. 1.—Structure of guanethidine. 1

become unresponsive to stimulation of efferent sympathetic fibres. During the same period the nictitating membranes and the arterial system are strongly responsive to injected noradrenaline. These effects last from 4 days to 3 weeks. Zaimis[9] produced evidence that adrenaline may be concerned in the 'recovery' process of a cell after activation. Then the changes produced by guanethidine, bretylium and certain other drugs on the 'recovery' mechanism could be explained as due to a 'displacement' of adrenaline from its points of attachment.

From the clinical aspect, the prolonged action of a single dose of the drug offers the advantage of infrequent dosage and smooth control of hypertension, without the daily oscillations in pressure found in other anti-hypertensive drugs. Unlike the ganglion-blocking drugs it does not produce parasympathetic side-effects such as dry mouth, constipation, and ileus; in fact, owing to the unopposed action of the parasympathetic, diarrhoea may be an annoying but not serious side-effect. It is readily controlled with propantheline bromide.[7]

METHOD, CLINICAL MATERIAL, AND RESULTS

At the start of the investigation all patients were admitted to hospital for full clinical assessment and to allow the effect of previous hypotensive drugs to wear off. As experience with the drug increased, a number were treated entirely as out-patients. All blood-pressure readings were taken first with the patient supine and, when the condition of the patient allowed it, after standing for 2 minutes. This latter precaution is important, because it was found that the full postural hypotensive effect of the drug was not evinced until that period of time had elapsed. In-patients had their blood-pressure readings taken twice daily, out-patients initially every 2 or 3 days, and later, when stabilized, at intervals as long as 4 weeks. When it seemed to be indicated, a diuretic of the benzothiadiazine group was given in addition. The material was drawn from private consultant practice, and from European and African hospital practice. A total of 23 patients, 12 of them European and 11 African, were considered to be sufficiently studied and documented for inclusion in this paper. The diagnoses of the group are set out in Table I.

TABLE I. DISTRIBUTION OF CASES

	No.
Essential hypertension	16
Malignant hypertension	3
Primary nephrosclerosis	1
Diabetic nephropathy	1
Chronic pyelonephritis	2
Total	23

TABLE II. RESULTS OF FOLLOW-UP STUDIES

Case	*Age*	*Sex*	*Race*	*Diagnosis*	*Pre-treatment blood pressure (mm. Hg)*	*Duration of treatment in weeks*	*Additional therapy*	*Final daily dose (mg.)*	*Final blood pressure*	*Side-effects*
1	43	F	Eur.	Malignant hypertension	L 286/160 S 240/130	12	B	60	L 212/120 S 152/104	Nil
2	44	M	Eur.	Essential hypertension	L 230/140 S 210/130	16	Nil	25	L 116/88 S 104/82	Failure of ejaculation. Postural hypotension
3	71	M	Eur.	Diabetic nephropathy	L 210/140 S 208/140	6	B Insulin	25	L 136/90 S 112/70	Postural hypotension
4	68	M	Eur.	Essential hypertension. CHF. Previous CT.	L 202/132 S 196/124	10	B	12½	L 142/72 S 122/60	Nil
5	62	M	Eur.	Essential hypertension	L 202/130 S 172/120	15	Prednisolone (for asthma)	60	L 176/110 S 158/110	Slight postural hypotension
6	52	M	Eur.	Essential hypertension	L 232/160 S 224/154	5	B	25	L 182/112 S 146/90	Nil
7	53	M	Eur.	Essential hypertension. Recent hemiplegia	L 264/168	12	B	50	L 184/106 S 178/102	Nasal congestion
8	46	F	Eur.	Nephrosclerosis	L 260/160 S 232/152	16	B	37½	L 222/128 S 192/106	Nil
9	83	F	Eur.	Essential hypertension	L 232/140	9	Nil	25	L 182/108 S 160/108	Nil
10	68	F	Eur.	Essential hypertension, angina pectoris	L 194/130	4	Nil	37½	L 168/104 S 142/90	Status anginosus (treatment discontinued)
11	62	F	Eur.	Essential hypertension. HE, DU + haematemesis	L 256/150	9	Ac	37½	L 182/90 S 146/84	Nil
12	62	F	Eur.	Essential hypertension. Recent hemiplegia	L 268/170	2	B	40	S 190/110	Nil
13	50	F	Afr.	Essential hypertension. CHF.	S 240/140	3	Nil	30	S 175/95	Nil
14	21	M	Afr.	Essential hypertension	S 175/145	5	Nil	40	S 120/90	Nil
15	55	M	Afr.	Nephrosclerosis	S 220/140	6	Nil	60	S 220/120	Nasal discomfort, mild diarrhoea
16	40	M	Afr.	Malignant hypertension	S 220/180	3	Nil	50	S 190/130	Nil
17	46	M	Afr.	Malignant hypertension	S 250/170	11	Nil	75	S 175/110	Postural hypotension + mild diarrhoea
18	28	M	Afr.	Essential hypertension	S 200/130	9	Nil	20	S 170/100	Impotence (temporary)
19	50	F	Afr.	Essential hypertension. CHF.	S 200/120	10	Nil	30	S 120/90	Nil
20	42	F	Afr.	Essential hypertension	S 210/140	5	Nil	40	S 165/105	Nil
21	30	F	Afr.	Chronic pyelonephritis	S 230/140	12	Nil	70	S 190/130	Nil
22	70	M	Afr.	Chronic pyelonephritis	S 200/140	4	Nil	20	S 150/90	Nil
23	55	F	Afr.	Essential hypertension	S 175/130	5	Nil	40	S 140/100	Nil

L=lying; S=standing; B=diuretic of benzothiadiazine group; CHF=congestive heart failure; CT=coronary thrombosis; Ac=Anticholinergic; HE=hypertensive encephalopathy; DU=duodenal ulcer. **N.B.** Ages of African patients were approximate.

Patients were followed up for periods ranging from 2 to 16 weeks, and the results of the investigations are set out in Table II.

DISCUSSION

Although this is a limited trial, the results obtained to date (Table II) indicate that the use of guanethidine in the treatment of hypertension is a method of considerable promise.

Effects on Blood Pressure

It will be seen from the results tabulated that the drug caused a fall in blood pressure to satisfactory levels in 21 out of the 23 cases treated. The 2 exceptions were both African patients. Case 15 is an African male aged approximately 55, who is being treated as an out-patient with weekly increases of dosage as indicated. It is probable that the effective maintenance dosage has not yet been reached. Case 21 is an African female, aged 30, who showed little response to a dosage of 20 mg. daily, but who has not been followed up any further, since she defaulted from the trial.

The effect of the drug is cumulative, a fact which was demonstrated by the gradual fall of blood pressure in the standing position over several days on a constant dosage. For this reason the initial dosage should be low, and an increase should be made at intervals of several days, as indicated by blood-pressure readings. In this trial, the initial dosage in most cases was 10 mg. daily, given in the morning. This was increased by 10 mg. at a time, at intervals of 4 - 7 days, until a dosage was reached at which a satisfactory level of blood pressure was recorded. In most cases (18 out of the 23 cases) this maintenance dosage was between 25 and 60 mg. daily. The remaining 5 cases required doses that were either smaller or larger than those within this range.

Although the fall in blood pressure was largely a postural effect, there was in some cases an appreciable fall in the lying position as well after a few weeks' treatment. This phenomenon was more noticeable in the European than in the African patients (Table II). (Unfortunately no accurate records were kept of blood pressure in the recumbent position in African patients). This effect on blood pressure in the lying position has been noted in previous papers.[4,7]

The prolonged smooth effect of guanethidine, permitting its administration in a single daily dose which may be taken at any time during the day, is of considerable advantage. This is particularly so in dealing with African patients, where simplicity of dosage and administration is most desirable in a condition which requires treatment for an indefinite period. We did not find any evidence of appreciable diurnal variations in blood pressure, as may occur with ganglion-blocking agents, e.g. bretylium.

Effect on Electrocardiograph

As the blood pressure fell and was maintained at a near normal level, the ECGs of several of the patients showed considerable or almost complete reversal of the patterns of LV strain and hypertrophy which were present before treatment. In the short period of study T-wave changes reverted before the high-voltage pattern was reduced. More prolonged study is necessary before it will be known whether the ECGs, in any cases, will revert completely to a normal pattern.

The improvement in the ECG seems to be roughly parallel to the degree of objective improvement in the ocular fundi. Fig. 2 shows the left-pectoral leads of 2 patients who showed considerable improvement after a short period of treatment.

Side-Effects

Various side-effects have been described. These include diarrhoea, bradycardia, parotid tenderness, nasal obstruction, tremor, fluid retention, breathlessness, weakness, tiredness and depression, and failure of ejaculation.[10] Most of these are similar to the side-effects which have been found with bretylium.

The side-effects have not usually been severe. In particular, the parasympatholytic side-effects of the ganglion-blocking agents have been absent. Case 17 (African male, aged 46), who has been described in an earlier paper,[11] could not be treated with ganglion-blocking agents because of severe side-effects. He developed tolerance to bretylium, but has been well-controlled on guanethidine. Another

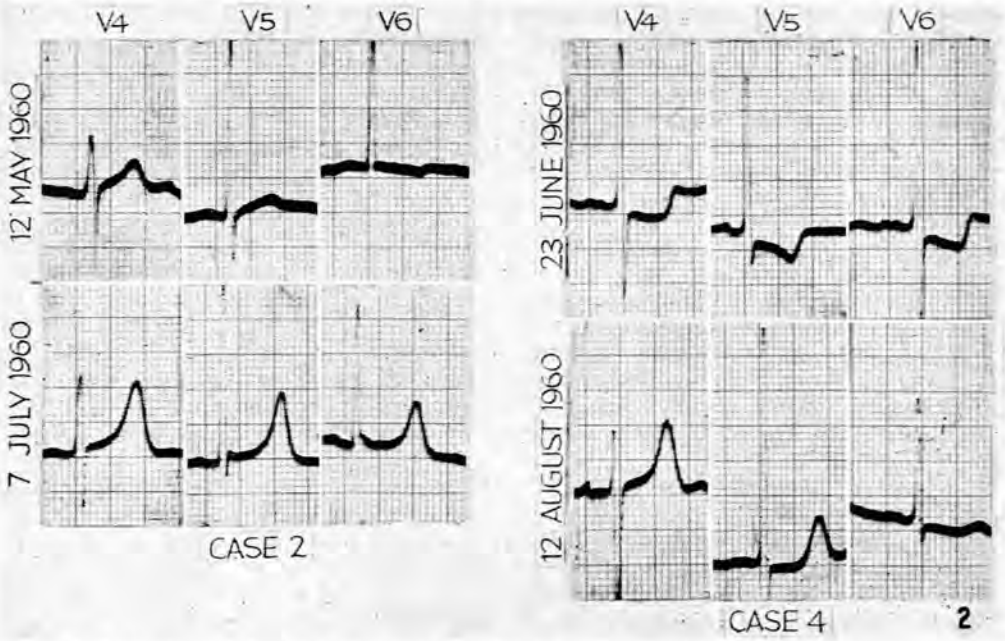

Fig. 2. Left pectoral leads from cases 2 and 4 showing considerable improvement in the T-wave changes after short periods of treatment.

patient, case 8 (European female, aged 46), was also treated originally with bretylium, but this was abandoned owing to episodes of severe postural hypotension. She has been controlled satisfactorily with guanethidine — without side-effects.

Faintness and dizziness as a consequence of postural hypotension was the most common side-effect in our series, but this was never severe enough to effect continuation of treatment. It was always relieved by adopting the recumbent position for a short while. Dollery *et al.*[10] have noted that this symptom is aggravated by exercise, and this is a factor which will undoubtedly need to be taken into consideration in future, particularly in the treatment of manual labourers.

Mild diarrhoea, which amounted only to the passage of 3 or 4 semi-formed stools per day, occurred in 2 African patients, who were receiving fairly high doses of the drug. The symptom was not considered severe enough to warrant special treatment. Where indicated, it may be controlled by kaolin, small doses of pempidine,[11] or anticholinergic drugs.

Nasal congestion and discomfort occurred in 2 patients, and failure of ejaculation in 1. Impotence occurred in an African male aged 28; this was a temporary symptom, lasting for 2 weeks only, and may not have been due to treatment. Treatment had to be discontinued in 1 patient because of persistent angina pectoris (case 10).

Tolerance to the drug has not yet developed in any case treated. Indeed, it is possible that the opposite may occur. Cases 2 and 3 in our series had their original maintenance dosage reduced, because of increasing symptoms of postural hypotension.

Addition of Benzothiadiazine Diuretics

Seven patients were given oral diuretics of the benzothiadiazine group. In most of them it was possible to reduce the daily dose of guanethidine for maintenance requirements, thereby reducing the incidence of side-effects. This finding agrees with a previous report on the use of diuretics in combination with guanethidine[7] and may be an advantage in patients in whom side-effects are troublesome. Combined therapy was not used in African patients, because it was felt that a multiplicity of tablets would lead to confusion.

Effect on Renal Function

Insufficient investigation has been carried out to comment fully on this factor, but no deterioration of renal function has been noted in any of our patients.

SUMMARY AND CONCLUSIONS

23 patients suffering from severe hypertension have been treated with guanethidine, a new adrenergic-blocking agent. The drug was used in both European and African patients. A satisfactory smooth reduction of blood pressure was obtained in 21 of the 23 cases, with minimal side-effects.

The main advantages of guanethidine in the treatment of hypertension are: ease of administration, lack of development of tolerance, freedom from parasympatholytic side-effects, and satisfactory reduction of blood pressure in most cases.

A possible disadvantage is the effect of postural hypotension, particularly in cases liable to myocardial ischaemia. These effects may be largely prevented by careful adjustment of dosage at suitable intervals, since the drug has a cumulative effect.

In spite of our limited experience we feel that guanethidine is the drug of choice, and that its use represents a major advance in the treatment of severe hypertension.

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