GUANETHIDINE IN HYPERTENSION

EXPERIENCES IN AN EAST AFRICAN HOSPITAL

BY

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The advent of the adrenergic fibre-blocking drugs—bretylum tosylate (Boura *et al.*, 1959) and guanethidine sulphate (Page and Dustan, 1959)—has been hailed as the greatest advance in the treatment of hypertension since Paton and Zaimis (1948) introduced hexamethonium. Bretylum has largely been discarded because of its irregularity of absorption and of action and because of the rapid manner in which tolerance develops. In this hospital it was discarded for these reasons and also because it is deliquescent in the climate of Mombasa and therefore difficult to handle.

Guanethidine has been used successfully by many, including Leishman *et al.* (1959, 1961), Dollery *et al.* (1960), Evanson and Sears (1960), and Bauer *et al.* (1961). It has been stated that in severe hypertension guanethidine is the drug of choice. My purpose here is to present the findings in a small series of Africans and to draw attention to certain differences in their response to this drug from that of other races; in particular, to draw attention to the higher doses required for maintenance, and to the problem of resistance to the drug, both initial and acquired.

Clinical Material

Of 100 hypertensive cases admitted to this hospital in 20 months 39 were selected as being severe enough to warrant the use of guanethidine. This selection was based on a persistent resting diastolic pressure of 120 mm. Hg or over. Mombasa, being a port, has a very mixed population. Only half of these patients were from Kenya coastal tribes, the others coming from farther afield, even from Nyasaland and Uganda. Five of the 39 patients died before treatment could properly be assessed, all within one month of its commencement. In none was there any evidence that guanethidine contributed to the deaths: they all died from uraemia, complicated in three cases by cardiac failure. The only two examples of malignant hypertension were among those who died.

Adequate follow-up of patients is very difficult, and of the 34 left only 22 have attended for a sufficient length of time. These have been followed for from 3 to 16 months—more than half for six months or longer. Fifteen were males, and seven females, the hospital adult medical ward male-to-female admission ratio being 2.8:1 (Turner, 1962). The assessed age range was from 26 to 70 years, with a mean of 44.5. Five cases were thought to be of renal origin and 17 essential hypertension. This reflects the approximately equal incidence of renal and essential hypertension in females in this hospital but exposes a considerable excess of male essential hypertensives (13 to 2), for the ratio should be two to one (Turner, 1962). This may be because essential hypertension is found in the older African male (Leather, 1961) and he may be less impatient and more willing to attend for prolonged treatment.

Methods

Before treatment was begun all patients were admitted to hospital and every effort was made to assess the severity of the condition and to discover its cause. Each patient was subjected to careful clinical examination, screening, electrocardiography, urine examination, and blood urea estimation; if the blood urea was under 60 mg./100 ml. pyelography was carried out. If his condition was severe enough guanethidine was given in a dosage of 25 mg. daily (Dollery *et al.*, 1960) at 6 p.m. except for a few of the earlier cases for which 10 mg. (Leishman *et al.*, 1959) was used. The dosage was increased by increments of 25 mg. or 12.5 mg. according to the response. Since this is a long-acting drug (Dollery *et al.*, 1960) increases were made at intervals of five to seven days. Only one drug was used, because it was found to be easier, particularly with simple people, to use several tablets of one drug, given once a day, than to use two or more drugs several times a day. This, of course, was not possible in the failures, who had to be put on to other drug regimes. Blood-pressure was measured in the standing position after the patient had been resting for at least half an hour.

After discharge from hospital patients were seen within two weeks and thereafter at intervals of one or two weeks as seemed appropriate. A few of the well-controlled patients were later seen only once a month.

Results

The results are given in Table I and in individual detail in Table II. A good initial response was obtained in 29 out of the 34 patients. By this is meant a persistent fall of the diastolic blood-pressure to 100 mm. Hg or below. This state of affairs was not maintained. After discharge from hospital an increase of dosage was required in most patients. Of the 22 available for follow-up over three months or longer, two showed initial resistance to the drug and a further seven developed resistance to it. Of the 13 patients in whom maintenance on guanethidine remained possible, one developed a freak sensitivity to the drug. Of the

TABLE I.—Results in 39 Patients Treated with Guanethidine

Died of uraemia and/or heart failure before treatment assessed	5 out of 39
Good initial response, diastolic pressure 100 mm. Hg or less	29 " 34 (85%)
Lost sight of or too short a follow-up	12 " "
Followed up for three months or longer	22 " "
Good result, diastolic pressure of 100 mm. Hg or less	13 " (59%)
Initially resistant to the drug	2 " "
Acquiring resistance to the drug	7 } 9 (41%)

TABLE II.—Details of 22 Cases Followed Up for Three Months or Longer

Case No.	Sex and Age	Diagnosis	Initial B.P.	Final B.P.	Daily Dose (mg.)	Follow-up Months	Resistance
5	F 52	Essential	240/125	130/95	100	9	Nil
7	M 45	"	190/130	160/120	375	12	Acquired
8	M 50	"	190/130	130/90	150	14	Nil
9	F 26	Renal	210/130	105/70	12.5	9	"
10	M 45	Essential	210/130	210/130	250	11	Acquired
12	F 32	"	180/125	140/90	100	3	Nil
13	M 45	"	190/120	120/90	150	4	"
14	M 28	Renal	220/150	220/165	375	11	Acquired
15	M 35	Essential	180/130	200/140	750	5	Initial
16	F 30	Renal	240/140	110/70	100	16	Nil
17	F 28	"	220/120	235/140	250	6	Acquired
18	M 45	Essential	180/130	130/90	250	13	Nil
19	M 50	"	220/130	120/90	250	13	"
21	M 28	"	210/150	140/95	100	7	"
22	M 60	"	180/120	190/120	250	3	Acquired
23	F 50	"	210/130	180/150	250	4	Initial
26	M 30	Renal	210/140	210/130	250	5	Acquired
30	M 40	Essential	200/130	120/80	37.5	5	Nil
31	M 55	"	240/120	190/90	200	6	"
35	M 65	"	220/140	130/90	200	4	"
37	F 70	"	210/140	180/100	125	4	"
38	M 50	"	230/140	230/160	250	5	Acquired

remaining 12, 8 (67%) needed increased dosage as out-patients. This is a common experience (Leishman *et al.*, 1959, 1961). Repeated increase of dosage such as is seen with bretylium is not a feature of guanethidine (Dollery *et al.*, 1960). These 12 patients were initially controlled on guanethidine with a range of 37.5 to 250 mg. (mean 113 mg., median 100 mg.) and their subsequent out-patient control was on a range of 37.5 to 250 mg. (mean 147 mg., median 137.5 mg.).

The patient, mentioned above, who developed a freak sensitivity to the drug was a young woman with severe renal hypertension (210/130 and grade 3 retinopathy). She was initially stabilized on 200 mg. of guanethidine and remained stable as an out-patient for three months. She then developed a profound hypotension (75/60). The dosage was gradually reduced and at the time of writing she has been controlled successfully for four months as an out-patient on 12.5 mg. daily. Her blood-pressure was of the order 140/90. No other patient has been controlled on so small a dosage.

Toxic effects were not a serious problem. Diarrhoea, muscle weakness, and fainting after exertion were seen occasionally; failure of ejaculation was complained of once. Parotid tenderness and mental symptoms were not met. Toxic effects were not seen in those with drug resistance even when on enormous doses.

Patients With Initial or Acquired Drug Resistance

Resistance to guanethidine was seen in 9 of the 22 patients (41%). In two of these the resistance to the drug was present from the beginning. One was male and one female, and both had essential hypertension. The dose in both patients was increased by 25 mg. at five-day intervals. When 250 mg. was reached in the woman without response, except that the diastolic pressure had climbed from 130 to 150 mm. Hg, the drug was abandoned. She never attended the out-patient department. The man eventually reached a daily dosage of 750 mg. without any effect on his blood-pressure. He was later successfully stabilized on 60 mg. of mecamylamine twice daily.

The other seven patients acquired resistance to the drug very rapidly. They responded initially as in-patients to a dosage range of 60 to 150 mg. (mean 95 mg., median 90 mg.), their initial requirement being no greater than that of the patients who remained sensitive. In five the blood-pressure was raised again at the first out-patient attendance two weeks later. In the other two the pressure became raised again two and three months after discharge. The dosage was increased by 25-mg. increments at intervals of one or two weeks until a total daily dosage of 250 mg. in five patients and 375 mg. in two patients was reached. At this stage the drug was abandoned. In two patients second attempts were made, after an interval on other drugs, beginning with small doses, but neither was successful. The pressure rose to its original level, where it remained in spite of increasing dosage.

The response in those with the expected early temporary increases in tolerance was quite different from that in those who had acquired resistance. In the latter the blood-pressure rose suddenly to the original level and remained at this level, or rose even further, despite increases of dosage. In four of the nine resistant patients the diastolic pressure seemed to be

increased even further by persistence with guanethidine (150 to 165, 120 to 140, 130 to 150, and 140 to 160) and fell to its original level after stopping the drug. Of the seven who acquired resistance, three were controlled, two on mecamylamine and one on reserpine with hydroflumethiazide. One patient has not been controlled even with large doses of mecamylamine given with various combinations of thiazide diuretics and reserpine. The other three resistant patients have discontinued attendance.

The nine resistant patients were six males, four with essential and two with renal hypertension, and three females, two with essential and one with renal hypertension. Thus male essential hypertensives are fewer as compared with the whole series. It is unlikely that this is of any significance.

The disease, as measured by the diastolic pressures at rest in the ward, is equal in severity in the sensitive and resistant groups. The mean diastolic pressure of the sensitive group was 132 mm. Hg and of the resistant group 132 mm. Hg. The severity of the disease thus seems to play no part in the development of resistance to the drug.

Discussion

A good and sustained response to guanethidine has been obtained in 59% of a mixed group of African hypertensives. This is a lower figure than that obtained in other published series, where figures around 90% are usual (Dollery *et al.*, 1960; Evanson and Sears, 1960; Leishman *et al.*, 1961; Bauer *et al.*, 1961), but similar to another independent series from East Africa (Somers, 1961b).

The dosage of the drug required for eventual stabilization was higher than that reported by other workers. Most of our patients required over 100 mg. daily (mean 147 mg.)—half of them 150 mg. or more. One patient needed only 37.5 mg., and one developed a freak sensitivity and needed only 12.5 mg. after having 200 mg. for three months. Most of the patients of Dollery *et al.* (1960) were controlled on 30 to 120 mg. daily, those of Evanson and Sears (1960) on 40 mg. daily, those of Leishman *et al.* (1961) on 60 mg. or less daily, and those of Bauer *et al.* (1961) on 50 mg. or less daily. Additional drugs were not given in this series nor in most of those with which it is compared. Bauer *et al.* (1961) gave a thiazide diuretic in addition to most of their cases, and lower doses of guanethidine are undoubtedly possible if this is done. The reasons for not doing so in the present series have already been given.

Increase of dosage in the first few weeks of out-patient treatment has been necessary in most series and this one is no exception. Once the maintenance dose has been reached further increases have seldom been required.

In contrast to experience with bretylium, resistance to guanethidine has not previously been reported as a serious problem. Resistance was not observed by Evanson and Sears (1960). Dollery *et al.* (1960) stated: "After nine months' experience it does not seem that tolerance to repeated administration is likely to be a major problem with guanethidine." Only 2 of their 80 patients were regarded as failures because of initial drug resistance and none because of acquired resistance. Leishman *et al.* (1961) observed tolerance only in the initial stages as described above, and this was as usual easily overcome. Resistance was no problem to Bauer

et al. (1961). In the present series it has been a serious problem—two patients being initially resistant and seven after a good initial response developing resistance and remaining so to increased doses. Thus resistance to the drug led to a failure of treatment in 9 (41%) of the 22 patients.

In a small personal series of 12 Indian and European hypertensive patients treated with guanethidine neither initial nor acquired resistance has been seen and dosage has been of the order of 25 to 75 mg. daily. Many of these patients have been satisfactorily controlled for many months.

That African patients from East Africa respond satisfactorily to ganglion-blocking drugs has been shown by Somers and Gitau (1959) with mecamlamine and by Somers (1961b) with pempidine. Experience in this hospital with mecamlamine, prior to using bretylium and guanethidine, was satisfactory.

Why this difference in response to treatment in these African patients occurs is obscure but is clearly a matter of great physiological and pharmacological interest. It has been suggested by Zaimis (1961) that acquired resistance to guanethidine is due to the sensitization of peripheral arterioles to the local effects of circulating catecholamines, and they warned against the use of excessive dosage. In this context it is of interest that in four of the resistant patients in the present series the diastolic pressure actually increased while dosage was being built up in an endeavour to gain control of the blood-pressure, and then fell when the drug was discontinued. Guanethidine is also known to cause increased noradrenaline release in animals. In man intravenous injection leads to an initial rise of blood-pressure without increase in the cardiac output. This is presumably due to muscle and visceral vasoconstriction (Dollery *et al.*, 1961).

The therapeutic efficiency of guanethidine may depend on the balance that is struck between its relaxant effect on peripheral blood-vessels from sympathetic-fibre blockade and the tendency towards sensitization of these vessels to circulating catecholamines, and possibly also to an increase in the amount of these amines. It may be that some dietary or metabolic factor in African subjects enhances, to a variable degree, these undesirable effects. It must be noted that unexpected increased sensitivity to guanethidine can occur, as is illustrated by the patient described above who after good control on large doses became very sensitive to the hypotensive effects of the drug and was then controlled on a very small dose.

The possible causes of this drug resistance can only be a matter for speculation at this stage. It is to be hoped that further studies will be made.

Summary

The use of guanethidine in a small series of African patients is described. Drug resistance as a serious problem has not previously been recorded, yet in this series it led to failure of treatment in 9 out of 22 (41%) patients. Two of these were initially resistant and seven developed resistance rapidly. Resistance to the drug has not been a problem in European and Indian hypertensives in Mombasa.

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TREATMENT OF PERFORATED DIVERTICULITIS COLI

BY

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Perforated diverticulitis of the colon is not a common condition. Martin and Adsit (1945) estimated that it occurred in 2% of cases of diverticulitis. With the increase in life expectancy of the community there is no doubt that the incidence of diverticulitis coli will also increase, and result in a corresponding rise in the number of cases with complications.

The following account is based on 14 cases of acute perforated diverticulitis of the colon treated at Morriston Hospital in the four years 1955–9. During this period 72 other cases of diverticulitis were admitted to the same hospital; thus 16.3% of cases of diverticulitis treated as in-patients presented with perforation. Smithwick (1960) estimated an incidence of 13.4% in a total of 545 cases.

The relative incidence is best arrived at by comparing the incidence of perforated diverticulitis coli with that of acute appendicitis: during the period under study 1,402 cases of appendicitis were operated upon, giving a relative incidence of 1 case of perforated diverticulitis coli to every 100 cases of appendicitis. MacLaren (1957), in Edinburgh, found 26 cases of perforated diverticulitis among 2,322 cases of acute appendicitis. He classified cases of perforated diverticulitis into those that give rise to a faecal peritonitis and those that give rise to peritonitis of a purulent nature. These differences are dependent on the size of the perforation—a large perforation allows the escape of faeces into the peritoneal cavity, while a pinhole perforation usually results in a purulent peritonitis. Another factor in the causation of purulent peritonitis is that an abscess in a diverticulum may rupture into the peritoneal cavity but, owing to the fact that the neck connecting the sac to the lumen of the bowel is occluded by inflammation,

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