Two favourable aspects of guanethidine remain to be stressed. First, the absence of any significant development of drug tolerance, one of the major disappointments of bretylium tosylate therapy; and, secondly, the absence of any toxic drug effects on liver, kidney, or haemopoietic organs.

Comparison of guanethidine with the specific sympathetic blocker and other anti-adrenergic substance, bretylium tosylate, becomes unavoidable. Although in their main pharmacological action these two drugs appear to be essentially similar, there are certain differences which have an important bearing on their practical use in clinical medicine.

1. Each drug has been shown to have its own peculiar side-effects. Bretylium commonly causes parotid pain and muscle weakness, while guanethidine is more likely to induce diarrhoea and seems to be associated in some patients with the appearance of depressive symptoms.

2. Drug tolerance is a frequent problem with bretylium; with increasing length of observation it has become obvious that many patients require increasing quantities of the drug. This unfortunately necessitates frequent visits to the clinic or the physician's consulting-room, resulting in increased loss of time from work and domestic duties and leading to excessive economic burdens, as well as placing a great strain on the medical staff. So far, tolerance has not been a problem with guanethidine, although minor adjustments in drug dosage may occasionally be necessary.

3. The prolonged action of guanethidine makes it possible not only to administer the drug in a single daily dose but also to estimate its effectiveness with fewer blood-pressure readings. Bretylium has a shorter duration of action and is given in three divided doses a day. It is therefore essential to take several blood-pressure readings at various intervals after administration of the drug to assess its effectiveness.

4. Although neither drug is fully absorbed from the gastro-intestinal system, guanethidine is somewhat superior and gives more constant day-by-day blood-pressure reduction. The incomplete and irregular absorption of bretylium is partly responsible for the unpredictable hypotensive effects, not unlike those seen in the early days of oral hexamethonium treatment.

5. The number of tablets required is less with guanethidine than with bretylium; and this, in our opinion, is a definite advantage. The largest dose of guanethidine prescribed by us was 75 mg. a day—three 25-mg. tablets. With bretylium we have given up to 3,000 mg. a day, or 15 200-mg. tablets, and to many of our patients this has been a definite psychological hardship, quite apart from the bitter taste and large bulk of the tablets.

In summary it is felt that guanethidine is a more suitable drug for routine clinical use.

Summary

Guanethidine sulphate, a new potent oral hypotensive agent, was administered to 28 patients for a period of up to 12 months. This drug selectively blocks adrenergic nerve transmission, leading to sympathetic inhibition with marked postural falls in blood-pressure without any parasympathetic blocking effects such as blurred vision, dryness of mouth, constipation, and bladder atony. Its prolonged action makes it suitable for long-term out-patient treatment provided certain precautions

are taken. It is best given in conjunction with saluretic agents such as chlorothiazide or hydrochlorothiazide. Drug tolerance has not been a problem, and side-effects have been slight except for the appearance of depressive symptoms in four patients. Guanethidine has been compared with another adrenergic blocking agent and has been found to be a more suitable drug for routine clinical use.

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METHOSERPIDINE

A NON-DEPRESSANT ISOMER OF RESERPINE

BY

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In the treatment of moderate hypertension reserpine is often the drug of choice, particularly in the older patient in whom a precipitate fall in blood-pressure, such as can occur during administration of the ganglion-blocking and adrenergic blocking agents, may lead to coronary or cerebral thrombosis. Unfortunately, its usefulness may be limited by side-effects, which can be severe. Platt and Sears (1956), for example, were forced to discontinue treatment because of mental depression in 10 out of 54 cases, and found that over half the patients complained of drowsiness and nasal stuffiness. Palmer (1961) has pointed out that rauwolfia alkaloids may cause mild suppression of mental alertness and diminished intellectual capacity, which can be serious in brain workers. He believes this to be far more common, and therefore more important, than the occasional instances of serious mental depression and of the other well-known side-effects. Animal experiments and early clinical studies have suggested that the synthetic isomer of reserpine, methoserpidine

("decaserpyl"), is relatively free from these undesirable side-effects while retaining hypotensive potency.

The synthesis of methoserpidine (formerly named 10-methoxydeserpidine) was described by Velluz *et al.* (1958a), and subsequent animal studies with the drug showed that, whatever the dosage used, route of administration, or animal species, there was retention of the hypotensive action of reserpine with loss of the central depressant effect (Velluz *et al.*, 1958b). In rats made hypertensive by implantation of deoxycortone acetate and saline drinks, administration of methoserpidine over a period of a month produced a much more effective hypotensive response than was seen with reserpine (Peterfalvi and Jequier, 1960). In addition, methoserpidine is noticeably less toxic, its LD₅₀ being found by Mir and Lewis (1960) to be 82 mg./kg. in mice, whereas that of reserpine is 8 mg./kg. The greater chronic toxicity of reserpine has been demonstrated in animals by Peterfalvi and Jequier (1960). Ten rats were given 1 mg. of methoserpidine per kg. daily for two months and remained in good condition, whereas there was a 50% mortality among a second group receiving reserpine in the same dosage. Mir and Lewis (1960) confirmed the

dissociation between hypotensive and central depressant effects using methoserpidine. They observed that, in mice, drowsiness and reduction of motor activity were seen only with the higher doses, and were much less severe than with reserpine or deserpidine. Moreover, loose stools did not occur. Similarly, La Barre (1960) concluded from his experiments that methoserpidine had reduced toxicity and sedative properties without a concomitant reduction of hypotensive action, and also showed less tendency to produce gastric ulceration and vomiting.

Material and Methods

Thirty patients were studied (21 women and 9 men), their ages ranging from 44 to 86 years, with an average of 64 (see Table I). All were ambulant and treated entirely as out-patients. The series included every patient with hypertension referred to the physician's clinic of an eye hospital during an eight-month period in 1960, apart from one case of malignant hypertension treated as an in-patient and those whose rise in blood-pressure was considered insufficient to warrant specific therapy. All patients included in the trial had hypertension of essential type, and there was a high proportion

TABLE I.—Summary of Findings in 30 Patients Treated with Methoserpidine

Case No.	Age and Sex	Months of Observation	Initial B.P.	Final B.P.	Daily Dosage (mg.) _†	Response	Side-effects	Comments	Ocular State	
									Before Treatment	After Treatment
1	72 F	6	210/110	170/90	30→10	Good	Nasal stuffiness	Relieved by reduction dosage		
2	67 F	5	190/110	140/75	15	"			Secondary glaucoma	Eye painless
3	47 M	9	190/105	130/80	40→15	"			Grade III retinopathy	No change
4	61 F	9	210/115	160/90	20→10	"			Glaucoma	
5	74 M	5	190/110	200/90	15→60	"	Mild depression	Passed off with continued treatment	C.R.V.T.	"Visual" improvement
6	62 M	10	190/100	130/80	15→5	"			Grade III retinopathy	
7	44 F	7	190/120	130/80	30→10	"			C.R.V.T.	No change
8	68 F	7	200/110	160/90	40→15	"		Pre-existing anxiety depression unaffected	Grade III retinopathy	" "
9	56 M	5	200/120	140/80	30→45	"	Nasal stuffiness	Passed off with continued treatment	Grade III retinopathy	Grade I
10	70 F	7	170/120	130/85	20→10	"		Pre-existing anxiety state much improved	Grade II retinopathy	
11	53 M	7	210/120	170/95	30→20	"	Drowsiness	Passed off with continued treatment	" "	Normal fundi
12	69 F	5	190/110	180/90	15→60	"			Post-thrombotic optic atrophy	No change
13	64 M	2	250/130	190/110	30→60	Poor		After 2 months' treatment developed bronchial carcinoma	Grade III retinopathy	" "
14	71 F	7	210/120	190/110	30	"		Patient defaulted after 7 months		
15	54 F	1	180/100	170/110	10	"	Headache and nausea	Symptoms recurred after second attempt at treatment. Drug discontinued	C.R.V.T.	" "
16	64 F	6	260/140	150/90	40→30	Good		Pre-existing depression improved		
17	62 F	12	220/140	150/100	30→80	Poor	Fatigue at 80 mg. dosage	" " "	Vitreous haemorrhage	Partial clearing
18	65 F	3	220/110	160/90	30	Good		Pre-existing anxiety state improved	Subconjunctival haemorrhage	Cleared
19	51 M	1	200/125	160/100	15	Poor	Sweating. Fullness in head	Symptom recurred after second attempt at treatment. Drug stopped		
20	60 F	2	270/125	300/130	60	Fair		Therapy abandoned. Hypertension previously resistant to other hypotensive agents		
21	73 F	6	200/120	180/90	60→40	Good	Drowsiness	Relieved by reduction in dosage	Grade III retinopathy	Grade II
22	78 F	4	210/110	170/110	30→60	Fair			" "	No change
23	68 M	7	180/110	160/90	15→60	Good			Post-thrombotic optic atrophy	" "
24	86 F	4	280/110	195/90	30→60	"	Slight drowsiness	Passed off without change in dosage	Grade III retinopathy	" "
25	50 M	4	240/140	180/110	30→60	Poor			Specific choroiditis	" "
26	71 F	4	200/130	180/95	15→40	Good	Mild depression	Passed off with continued treatment		
27	68 F	3	240/140	200/105	60	Poor		Defaulted after 3 months' treatment	Myopic degeneration	" "
28	83 F	3	200/110	155/85	15→20	Good		Pre-existing depression improved	Grade II retinopathy	" "
29	60 F	3	200/110	200/105	15→60	Fair	Fatigue at 60 mg. dosage	Changed to guanethidine with satisfactory response	" "	Grade I
30	54 F	3	220/120	140/90	30	Good		Chronic anxiety state improved		

Response: G = Good; P = Poor; F = Failure. C.R.V.T. = Central retinal vein thrombosis.

of elderly and arteriosclerotic subjects. No attempt was made to exclude patients showing signs of mental depression.

It was realized in planning the trial that an appreciable number of the patients would inevitably present with acute retinal vascular lesions, in some cases threatening sight, and under these circumstances the use of a placebo was felt to be unjustifiable.

However, for purposes of comparison data were also collected regarding a consecutive series of 30 patients from the same clinic treated with reserpine during the period immediately preceding the methoserpidine trial. This group had an average age of 61.3 years, and included 19 women and 11 men. The findings with regard to hypotensive action and side-effects are summarized in Tables II and III.

TABLE II.—*Hypotensive Response in Two Groups of 30 Patients Treated with Methoserpidine and Reserpine Respectively*

Treated with Methoserpidine and Reserpine Respectively				
Response	No. of Cases	Average Fall in Blood-pressure (mm. Hg.)		Average Age in Years
		Systolic	Diastolic	
Methoserpidine (21 Females, 9 Males)				
Good	20	44.5	28.25	64.8
Poor	7	42.9	24.3	60
Failure	3	3.3	0	66
Reserpine (19 Females, 11 Males)				
Good	16	46.2	21	57
Poor	8	25	16	67.5
Failure	6	3.5	9	64

TABLE III.—*Side-effects in Two Groups of 30 Patients Treated with Methoserpidine and Reserpine Respectively. Numbers in Parentheses Show the Instances in which the Drug was Discontinued*

Side-effect	No. of Cases Affected	
	Methoserpidine	Reserpine
Depression	2	4 (4)
Fatigue or drowsiness	5	1
Muzziness	1 (1)	2 (2)
Nasal stuffiness	2	3 (2)
Nausea	1 (1)	0
Diarrhoea	0	1

Before starting treatment the blood-pressure was recorded on at least two separate occasions, the lowest figure obtained being taken as the pretreatment level. Patients attended at intervals of one or two weeks and were seen by me personally throughout the trial, the average period of observation being five and a half months. The examination was carried out at approximately the same time of day on each occasion, the blood-pressure being recorded in the sitting position, without prior sedation or prolonged rest. Information regarding side-effects was specifically sought at every visit.

Treatment was initiated with 15–30 mg. of methoserpidine daily, given in divided doses after the three main meals. Full therapeutic effect was obtained in two weeks in most cases, and the maintenance requirements varied considerably, ranging from 5 to 80 mg. daily. The concurrent use of other hypotensive agents was avoided, but weight reduction was advised where indicated.

Results

Hypotensive Effect.—A fall of diastolic blood-pressure of at least 20 mm. Hg with a final level of less than 100 mm. was accepted as a satisfactory response. Twenty cases, two-thirds of the total, fell into this category (see Table II). In a further seven patients the result was

classed as poor, the final diastolic pressure remaining at 100 mm. or above, although in many cases the fall was substantial. In the remaining three subjects methoserpidine in the maximum tolerated dosage failed to affect the blood-pressure level materially. One of these patients had already proved resistant to a wide range of other hypotensive agents. Generally the fall in blood-pressure was progressive, the full effect rarely being achieved in less than four weeks. No evidence of the development of drug tolerance was seen during this trial, but the period of observation was short, and to clarify this point a long-term follow-up is now in progress.

Relief of Symptoms.—There was symptomatic relief in a high proportion of cases, the improvement usually beginning within a few days after starting treatment, and preceding the fall in blood-pressure. Prior to treatment 11 patients showed depressive symptoms, usually associated with anxiety. All but one improved, and five commented spontaneously on an unusual sense of well-being. Of 10 patients complaining of headache and giddiness, eight were completely relieved (often before any effect on the blood-pressure was apparent), and effort angina was much improved in two of the three subjects in whom this symptom was present.

Cardiographic and Ocular State.—During the period of observation only 4 of the 10 patients with cardiographic evidence of hypertrophy ischaemia of the left ventricle showed any improvement, and improvement in retinal grading was found in only 5 of 11 cases showing retinopathy. However, two patients with glaucoma appeared to benefit from the treatment, and in no instance was there deterioration in cardiographic or ocular status.

Side-effects were infrequent and usually mild, necessitating termination of treatment in only two patients, both emotionally unstable individuals with a history of previous drug intolerance. One complained of muzziness in the head and sweating, and the other of headache and nausea, the symptoms in each case returning when the drug was given again after a temporary withdrawal. Mild transient nasal stuffiness which passed off without treatment occurred in three cases (10% of the subjects studied). No complaints of intellectual impairment or loss of mental alertness were received except for five patients (17%) who experienced drowsiness or fatigue. Four of these were taking relatively high doses of methoserpidine, 60 mg. or more daily, and in two the dose had to be cut down, but in the others the symptoms passed off without any change being made. Diarrhoea did not occur, and the fall in blood-pressure was gradual, there being no reports of any episode suggesting postural hypotension. No tendency to increase in weight was apparent, and loss of weight was maintained in those patients who were on reducing diets. As has been mentioned, depressive states present at the onset of treatment were often relieved. Only two patients developed depression during the course of the trial; in both instances the symptom could be adequately explained as a reaction to environmental circumstances, and in neither case was it necessary to stop the drug.

Discussion

The findings in previous clinical trials of methoserpidine are summarized in Table IV. In most the criteria for a satisfactory hypotensive response were similar to those used in the present study, and included

TABLE IV.—*Clinical Trials of Methoserpidine. Summary of Results*

Authors	No. of Cases	Daily Dose (mg.)		Cases Non-malignant Hypertension Showing Satisfactory Hypotensive Response	Side-effects	
		Initial	Maintenance		Depression	Others
Brun and Rondelet (1959)	21	10-30	20-100	76%	Nil	Nasal stuffiness in 2
Mériel <i>et al.</i> (1959)	30	10	30-100			Few minor digestive upsets
Mérlen and Gérard (1960)	43	30	20-80	66%	Nil	None
Gros <i>et al.</i> (1959)	230	15-30	15-60	58%	Nil	Occasional slight nausea
Tricot <i>et al.</i> (1960)	65	30	30-70	65%	Nil	Mild heartburn in 5 (also rhinitis in 2 subsequent to trial)
Read (1961)	15	15	5-15	75%	Nil	Fatigue, 1. Weight gain, 1. Nasal stuffiness, 1. Sense of unreality, 1. Nausea, 1
Present series	30	15-30	5-80	66%	2 mild	

a fall of at least 20 mm. in the diastolic pressure. It will be seen that in all the reported trials approximately two-thirds of the cases of non-malignant hypertension showed a satisfactory fall in blood-pressure, and it is of interest that, although only one trial was conducted with placebo control (Tricot *et al.*, 1960), the results here do not differ significantly from the others. In malignant hypertension either the drug has proved to be ineffective (Gros *et al.*, 1959) or a temporary improvement during hospitalization has not been maintained after discharge (Mériel *et al.*, 1959).

Good symptomatic relief has been reported in all the trials of methoserpidine, and Gros *et al.* (1959) note that this often precedes the hypotensive effect, a finding confirmed in the present study.

Most authors have found 30 mg. daily to be a suitable initial dose. Maintenance levels of up to 100 mg. daily have been well tolerated, but both Gros *et al.* (1959) and Tricot *et al.* (1960) feel that 60 mg. daily is probably the maximum effective dose and that patients whose hypertension is not controlled at this level are more satisfactorily treated by the addition of another hypotensive agent.

A study of the published work indicates that the toxic effects of methoserpidine are few, and seldom severe enough to require discontinuance of the treatment, mild nasal stuffiness and slight nausea being those most commonly recorded. No sharp fall in blood-pressure occurs, and, as Gros *et al.* (1959) comment, the drug is therefore particularly suitable for use in elderly arteriosclerotic subjects. More important perhaps is the freedom from mental depressant action, even in the higher dosage levels and after prolonged administration, which has been stressed in all the reported studies. In my own series it is doubtful whether the two mild depressive episodes which occurred were attributable to the action of the drug, and it is of interest that several patients with pre-existing anxiety and depressive symptoms were relieved by methoserpidine therapy. A beneficial action in patients with neurotic symptoms is also noted by Read (1961). The relative freedom from sedative action would seem to indicate a field of usefulness for this drug amongst hypertensive patients in

whom mental alertness is of particular importance for the performance of their normal activities.

Comparative figures indicate that methoserpidine is at least as effective as reserpine as a hypertensive agent, while showing a clear advantage in the absence of serious side-effects. A reduction in diastolic blood-pressure of 20 mm. or more was reported in 58-76% of patients in the previous methoserpidine trials (see Table IV), the corresponding figures for reserpine-treated cases ranging from 41.5% in the study by Platt and Sears (1956) to 53% in my own patients (Table II). Depression, which was virtually absent among patients treated with methoserpidine, occurred in 15% of Locket's (1955) series and forced the termination of treatment with reserpine in 18.5% of the cases reported by Platt and Sears (1956), the depression in two subjects being severe enough to lead to suicidal attempts. Nasal congestion, often severe in reserpine-treated cases, has been mild and infrequent among those receiving methoserpidine, and other reserpine side-effects such as gain in weight and diarrhoea seem to be extremely rare, although lethargy or drowsiness is reported in a few patients.

Summary

The report concerns a clinical trial of methoserpidine, a synthetic isomer of reserpine, which has been shown by pharmacological studies to retain the hypotensive action of reserpine without its central depressant effects.

The drug was administered to 30 ambulant patients with hypertension of moderate severity. Two-thirds of the cases showed a good hypotensive result, and serious side-effects were absent. Only two subjects showed depressive reactions, and these were mild and only doubtfully related to the action of the drug. On the other hand, 11 patients with anxiety depression prior to treatment were relieved of their symptoms, and several particularly commented on their sense of well-being.

Although relatively expensive, methoserpidine seems likely to prove a useful hypotensive agent for the patient who is unable to tolerate reserpine owing to side-effects or in whom depression makes the use of this drug unwise. The relative freedom from sedative effect suggests that methoserpidine may also be of value where diminution of mental alertness is particularly undesirable.

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