TREATMENT OF HYPERTENSION WITH RESERPINE, THIAZIDE DERIVATIVES, AND GUANETHIDINE

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Hypertension is not uncommon at King Edward VIII Hospital, over 600 patients having been seen at the Hypertension Clinic in the past 3 years. As the side-effects of treatment not infrequently produce symptoms worse than those of the disease it was decided to use those drugs that in our experience produced minimal side-effects. Reserpine and thiazide were used in combination because together they have a greater hypotensive action than when used alone. Guanethidine was used because it does not produce the side-effects of ganglionic blockade or depression of the central nervous system. This paper summarizes our experience in the treatment of hypertension at the Hypertension Clinic over the past 3 years with reserpine and thiazide derivatives together or this combination with guanethidine.

Material and Methods

Patients were referred to the clinic from the medical outpatients department and from the wards. Only those with diastolic blood pressures of 120 mm.Hg or more at rest, or greater than 110 in young patients, each taken on 2 separate occasions, were selected for the study. In addition they had to fulfil at least one of the following conditions:

1. Retinal changes of grades 2 - 4.
2. Clinical, radiological or ECG changes in the heart compatible with hypertension.
3. Renal involvement consisting of albuminuria, haematuria, or casts in the urine.

Based on the above criteria, 238 patients out of a total of 600 were selected for the study. Only those with a reasonably good follow-up were included.

All the patients had the following investigations done initially: urine examination, blood-urea estimation, chest X-ray, and ECG. These were repeated and further investigations were done only where indicated. The patients were treated initially with a combination of reserpine, 0·25 mg. 3 times a day, and chlorothiazide derivative, usually cyclopenthiazide, 0·5 mg. daily. Patients who failed to respond to this combination and patients with malignant hypertension were given guanethidine in addition. Guanethidine was also used for patients referred to us while on ganglion-blocking drugs who were complaining of distressing side-effects.

Patients were seen at weekly intervals until their blood pressures were satisfactorily controlled, and thereafter at intervals of 4 - 7 weeks.

Results with Reserpine and Thiazide Combination

There were 201 patients on this form of treatment. In 25 of them the blood urea was between 40 and 100 mg. per 100 ml. Duration of therapy varied from 1 to 25 months, 30 patients being controlled for 6 - 12 months and 28 patients for 13 - 25 months. Patients were regarded as being satisfactorily controlled when the blood pressure, either supine or erect, was maintained at 160/100 or less. Table I

TABLE I. RESPONSE TO RESERPINE PLUS THIAZIDES

	Age in years	No. and Race of Patients	Primary resistance	Inadequate Response	Tolerance	Finally controlled		Mean initial BP	Mean control blood pressure	
						No.	%		Supine	Erect
Males	< 46	18 A	7	4	2	5	27·8	220/130	165/100	155/100
		13 I	7	2	0	4	30·8	200/125	135/90	130/90
	> 46	26 A	8	2	2	14	53·9	205/130	155/100	135/90
		33 I	11	2	4	16	48·5	210/135	150/95	145/95
Females	< 46	23 A	4	1	1	17	73·9	205/130	150/100	140/90
		32 I	6	2	2	24	75·0	210/130	155/95	145/90
	> 46	25 A	6	2	4	13	52·0	215/130	155/95	130/85
		31 I	8	0	4	19	61·3	220/130	160/100	150/95
Total		201	57	15	19	112	55·7	210/130	150/95	140/90

A = Africans I = Indians

shows that 112 patients (55·7%) were finally controlled. The average drop in diastolic pressure was 30 - 40 mm.Hg, although in African females over the age of 46 years a mean reduction of 45 mm.Hg was recorded. Postural differences of 5 - 10 mm.Hg in the diastolic pressures were found. Control in relation to fundal grades are shown in Table II. The best results are obtained with minimal fundal

TABLE II. FUNDAL CHANGES IN PATIENTS CONTROLLED ON RESERPINE PLUS THIAZIDES

Fundal grade	0	I	II	III	IV	Total
No. of patients ..	21	46	103	25	6	201
No. controlled ..	18	29	50	14	1	112
Percentage control ..	86%	63%	49%	56%	17%	56%

changes. One patient with malignant hypertension who is now maintained on this combination alone was initially controlled on large doses of mecamylamine. To this combination young females respond well (75% control), young males respond poorly, and patients over 46 years of age respond moderately.

Resistance and tolerance. Primary resistance, i.e. a diastolic BP drop of less than 20 mm.Hg, was seen in 57 patients, while inadequate response, i.e. diastolic BP drop of more than 20 mm.Hg but not to 100 mm.Hg, occurred in 15 patients. Tolerance, i.e. the BP rising above control limits after initial control, was seen in 19 patients—most of these developed tolerance within the first month, but 5 did so after as long as 1 year.

Side-effects were uncommon, occurring in 11 patients. Only 3 complained of nasal congestion, and one developed galactorrhoea, these being side-effects of reserpine. Five complained of dizziness and one had marked postural hypotension, the BP falling from 280/120 mm.Hg to 160/95 supine and 110/50 erect.

Results with added Guanethidine

There were 94 patients in the series, all treated as outpatients. The initial dose was 10 or 12·5 mg. daily. Two patients failed to respond, and in another response was inadequate. The fourth patient showed tolerance after 3 months of good control on 50 mg. of guanethidine. He has not attended the clinic since and is regarded as a failure. This is at variance with the work of Turner[1] in East Africa, who found resistance to guanethidine in 41%

TABLE III. RESPONSE TO GUANETHIDINE + RESERPINE + THIAZIDES

No. of patients	Primary resistance	Inadequate response	Tolerance	Finally controlled		Mean initial BP	Mean Control BP	
				No.	%		Supine	Erect
94	2	1	1	90	95·7	230/145	170/110	135/90

of his African patients. The dosage of guanethidine varied from 5 mg. to 200 mg. daily (Table IV) and 74 of the 90 patients under good control received 50 mg. or less. This compares favourably with the doses used by Bauer *et al.*[2] (25 - 75 mg. daily, the majority being controlled on 25 - 50 mg. daily), Turner[1] (mean dose 147 mg. daily), Dollery *et al.*[3] (10 - 750 mg. daily, the majority being controlled on 30 - 120 mg. daily), Evanson and Sears[4] (5 - 80 mg. daily,

TABLE IV. DAILY DOSAGE OF GUANETHIDINE (mg.) IN 90 CONTROLLED PATIENTS

Daily dosage of guanethidine	5 to 12½	25 to 25	30 to 50	62½ to 75	100	125	200
No. of patients	25	28	21	11	3	1	1
Percentage ..	28%	31%	23%	12%	3%	1%	1%

the majority receiving 40 mg. daily), and Leishman *et al.*[5] (60 mg. or less daily as maintenance, the blood pressure being reduced with higher doses initially). It is possible that the relatively low dosage in this series was due to the additive effects of reserpine and thiazide. On control of BP, average postural differences in diastolic pressure of 15 - 25 mm.Hg and in systolic pressure of 20 - 40 mm.Hg were recorded.

Discussion

A favourable aspect of guanethidine is the absence of serious tolerance, a major obstacle to the use of bretylium tosylate. An increase of 10 mg. in the daily requirement of guanethidine indicated tolerance if the blood pressure was under good control previously on a fixed dose of guanethidine. Tolerance occurred in 8 patients and in only one after the 5th month. Tolerance was overcome by an increase in the dose of guanethidine and it was not serious enough to warrant a change of therapy. One patient was well controlled on 10 mg. guanethidine daily, but the dose was inadvertently increased. A marked rise in blood pressure ensued until control was finally re-established with 75 mg. guanethidine daily. It has been suggested by Zaimis[6] (1961) that acquired resistance to guanethidine is due to sensitization of the peripheral arterioles to the local effects of circulating catecholamines, and she warns against the excessive use of guanethidine.

Side-effects occurred in 26 (18 males) of the 94 patients on guanethidine, but not sufficiently severe to withhold the drug except in 2 cases. Seventeen patients experienced early-morning giddiness—the commonest side-effect. Leishman *et al.*[5] have demonstrated that large initial doses of guanethidine (50 - 100 mg. daily) produced postural hypotension in 50% of their patients. The same observers found that when initial doses of 10 - 30 mg. were given and

gradually increased the incidence of postural hypotension was minimal. The relatively low incidence in our series is possibly due to the low initial dosage (10 - 12·5 mg. daily). Failure of ejaculation occurred in 3 patients. Three developed bradycardia on guanethidine and digitalis. Four patients showed significant weight gain (more than 10% of body weight) despite the use of diuretics. One patient complained of dizziness with a normal blood pressure. Another developed diarrhoea, and yet another collapsed after exercise. Other side-effects such as mental depression, dyspepsia, shivering, and basal congestion, which have been described with guanethidine, did not occur.

Conclusion

An adequate control of blood pressure was obtained with a combination of thiazide and reserpine. Nearly 60% of all patients have been controlled with this combination, which we recommend as a first line of therapy. The advantages are (1) gradual drop in blood pressure, (2) fewer side-effects, (3) rare toxicity, (4) fewer tablets used, (5) cheapness, and (6) that failures are easily controlled on the addition of guanethidine, which is required in a smaller dose than if it were used alone.

Summary

A series of 238 hypertensive patients treated with a combination of thiazide and reserpine, and some with the addition of guanethidine, is analyzed. Of 201 patients treated with reserpine and thiazide alone, 112 patients were controlled, and with the addition of guanethidine a further 90 were successfully treated. After a follow-up extending to 33 months, guanethidine has proved to be an effective hypotensive agent.

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