TREATMENT OF HYPERTENSION WITH BETHANIDINE (ESBATAL)

By O. S. Yeoh, M.B., B.S., A.M., M.R.C.P.(Ed.), M.R.C.P. (Glas.)

and

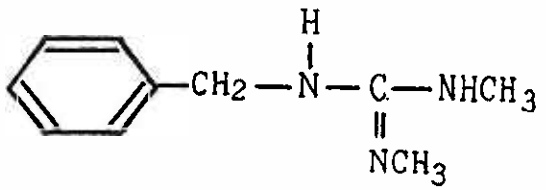
B. K. Chew, M.B., B.S., A.M., M.R.C.P. (Ed.)

(Department of Medicine, University of Singapore)

A wide variety of new hypotensive agents are now available for the treatment of hypertension. They differ in their modes of actions, usefulness and side effects. One of the recent potent hypotensive agents introduced is bethanidine sulphate (B.W.467C60), marketed by Burroughs and Wellcome under the trade name of "Esbatal". Favourable reports have been made on the effectiveness of this drug in the treatment of hypertension by Montuschi and Pickens (1962), Smirk (1963) and Johnston *et al* (1964). The purpose of this paper is to report the results of the treatment of hypertension with bethanidine sulphate on 25 patients for a period ranging from 9 days to 15 months.

CHEMISTRY AND PHARMACOLOGY

Bethanidine sulphate (B.W. 467C60) is a benzyl guanidine compound which is stable and colourless and has a metallic taste.



Boura *et al* (1961) and Boura and Green (1963) showed that it lowered the blood pressure by sympathetic blockade and selectively blocked impulses in the peripheral sympathetic nerves by inhibiting the releases of noradrenaline at the nerve endings.

In therapeutic doses, it has no effect on the para-sympathetic or the central nervous system. Large intravenous doses block autonomic cholinergic nerves and cause paralysis of voluntary muscles. Unlike guanethedine it does not bring about depletion of tissue catecholamine stores. It is also well absorbed orally. The hypotensive action of bethanidine is antagonized by those direct pressor substances which do not act through released noradrenaline.

MATERIAL AND METHODS

Twenty-five patients comprising 21 males and 4 females were studied; 16 were Chinese, 5 Malays and the rest were Indians. Their ages ranged from 26-67 years. Seventeen patients were newly diagnosed hypertensives and had not had previous therapy while 7 had been previously treated with guanethedine. They were given bethanidine because of difficulty in controlling the blood pressure and/or becuase of troublesome side effects. One patient had lumbar sympathectomy prior to this trial.

Of the 17 newly diagnosed hypertensives twelve were selected when their basal blood pressures remained persistently high after 2 days' stay in hospital. Five outpatients were included in the trial when after at least 5 minutes rest on the examining couch, their blood pressures taken by the same observer remained high on 2 consecutive visits. As these patients were referred to us for high blood pressure by other doctors, it could therefore be said that the blood pressure of these patients were taken on more than 2 occasions before inclusion into the trial.

Once it was decided that the patients were hypertensive both routine and special investigations, if indicated, were carried out in order to determine the aetiology. Haemoglobin, total white blood counts and platelet counts, biochemical estimations of blood urea and serum electrolytes, urinalysis, electrocardiogram, chest X-ray and intravenous pyelogram were done in all cases. Such special investigations like renal angiography and vanillyl mandelic acid determinations were carried out in cases where there were indications.

Of these 25 patients—19 had essential hypertension, 2 chronic nephritis (one proven at necropsy), 1 renal artery stenosis, 1 suspected but not proven renal artery stenosis, 1 ureteric stricture and 1 ureteric calculus.

The severity of hypertension was graded according to the fundal appearances as described by Keith, Wagener and Barker (1939). Three patients had no retinopathy, 6 patients belonged to Grade I, 13 Grade II and 3 Grade III. Even before treatment 6 of the patients had old hemiplegia or hemiparesis, 1 transient hemi-

SUMMARY OF PATIENTS TREATED WITH BETHANIDINE ("ESBATAL")

Case No	Sex	Age (yr)	Race	Diagnosis	Previous Therapy	Fundi Grading	Pre-Therapy B.P.	Post-Therapy B.P. Lying	Post-Therapy B.P. Standing	Daily Dose mg.	Duration of treatment (mths)	Result	Side Effects
1	M	51	Malay	Essential Hypertension	—	I	210/120	150/90	140/90	60	5	Good	—
2	M	43	Malay	Hypertensive heart failure	—	0	190/110	150/95	150/100	30	7	Good	—
3.	M	36	Malay	Hypertension Right renal artery & partial Left Renal Artery Stenosis	—	II	170/130	175/80	115/80	100	7	Good	Tolerance
4	M	35	Chinese	Hypertensive heart failure Chronic nephritis Uremia	—	III	230/135	150/100	120/100	20	1	Good but died of Uremia	
5	M	53	Indian	Essential Hypertension Old Hemiplegia	—	II	180/120	130/80	130/90	60	10	Good	—
6.	M	42	Indian	Hypertension Left Ureteric Stricture	—	0	170/120	140/90	140/90	40	9	Good	Postural Giddiness
7.	M	54	Chinese	Essential Hypertension Hemiparesis	Guanethidine Reserpine Chlorothiazide	II	220/120	200/110	200/100	70	6	Good	—
8.	M	41	Chinese	Essential Hypertension		II	160/120	150/100	140/100	20	5	Good	—
9	M	57	Malay	Essential Hypertension		I	240/140	180/110	170/105	30	9	Fair	—
10	M	65	Chinese	Essential Hypertension	Guanethidine Chlorothiazide	II	230/165	180/110	180/100	180	12	Poor	Postural Giddiness
11	F	65	Chinese	Old hemiparesis Essential Hypertension	—	I	230/140	220/120	230/120	260	8	Poor	Tolerance
12	M	58	Chinese	Hypertensive Heart Failure	—	II	250/150	190/120	180/120	140	8	Poor	Severe Postural Hypotension Tolerance
13	F	46	Chinese	Essential Hypertension Hemiparesis	—	III	250/150	130/80	not recordable	110	9 days	Abandoned	Severe Postural Hypotension. Died of Cerebral Haemorrhage
14	M	55	Malay	Hypertensive Heart failure	Guanethidine Chlorothiazide	I	210/115	200/120	200/120	450	9	Poor	—
15	M	37	Chinese	Essential Hypertension Diabetes Mellitus Myocardial Infarct.	Guanethidine Methyl Dopa	II	210/130	190/130	180/130	130	6	Poor	
16	M	26	Chinese	History of Nephritis Young hypertensive	—	II	195/140	150/100	150/100	100	1	Good	Defaulted
17	M	49	Chinese	Hypertensive Encephalopathy	—	III	260/140	150/110	120/70	60	4	Good	Marked Postural Hypotension
18.	M	63	Chinese	Hypertensive Heart failure	—	II	170/120	160/100	160/100	70	14	Good	—
19	F	54	Chinese	Essential Hypertension Hemiparesis	—	I	170/120	150/95	150/90	30	15	Good	
20	F	51	Chinese	Renal Hypertension Ureteric Calculi	Guanethidine Chlorothiazide	II	190/150	210/110	210/110	360	9	Fair	
21.	M	35	Chinese	Young Hypertensive Transient Hemiparesis	Guanethidine Chlorothiazide	I	150/130	150/110	140/110	360	13	Fair	Failure of ejaculation Tiredness
22	M	43	Chinese	Essential Hypertension Old hemiparesis	Guanethidine Chlorothiazide	II	200/150	180/140	90/60	40	7 days	Abandoned	Marked Postural Hypotension
23.	M	55	Sikh	Hypertensive Heart failure	—	II	170/110	140/90	160/90	20	1	Good	Defaulted
24	M	60	Chinese	Hypertensive Heart failure and Encephalopathy	—	II	210/130	160/80	130/100	40	1	Good	Defaulted
25	F	20	Chinese	Hypertensive Heart failure ? Renal stenosis	Lumbar Sympathectomy	0	170/140	170/110	180/130	30	1	Poor	Failed to attend follow-up clinic

paresis; 5 heart failure, 1 heart failure and encephalopathy, 1 uremia and 1 myocardial infarction. The only uremic patient died while this therapy was in progress, although the blood pressure response was good. There was no evidence to indicate whether this therapy caused an improvement or deterioration of hemiplegia or hemiparesis.

A normal diet was prescribed to all patients, unless there was an associated heart failure when salt had to be restricted. The initial dose of the drug was 10 mg. When there was no undue hypotensive reaction the dose was 10-20 mg given in 2 doses. The aim was to achieve a standing diastolic pressure of less than 100 mm. Hg. After discharge from the hospital, treatment was continued in our outpatients' clinic and the patients were instructed to take the drug in 2 divided doses—one at 8 a.m. and the other at 4 p.m. They were seen at weekly intervals until the blood pressure was satisfactorily controlled after which they were seen fortnightly. In some instances these visits caused a great deal of inconvenience and financial hardship to the patients, in which case monthly visits were arranged. During the weekly visits the drug was increased by 10-20 mg per visit if the blood pressure was not controlled.

In order to ensure that the drug had no hematotoxic or nephrotoxic effects, leucocyte and platelet counts and blood urea were done one month after treatment and repeated at 3 monthly intervals until the termination of the trial.

RESULTS

Responses were graded as good if the standing B.P. was less than 100 mm. Hg., fair if it was 100-110 mm. Hg. and little or no response if it was more than 110 mm. Hg.

TABLE I

	Good	Fair	Little or No Response	Abandoned
No Previous therapy	13	1	2	1
Previous therapy	1	2	4	1

Of the 17 patients without previous therapy, 13 showed good response, 1 fair and 2 little or no response. One patient (Case 13) was abandoned because of severe postural hypotension. Of the 8 patients who had other forms of treatment before the trial, only 1 had good response, 2 fair and 4 poor. One patient (Case 25) did not come for follow-up after 1 month's treatment and the dosage used was only 30 mg. It is therefore difficult to say if with increasing dosage and longer follow-up the response might have been different. One patient (Case 22) after 7 days of treatment had such severe postural hypotension that the therapy had to be abandoned.

The dose used in this series ranged from 20-450 mg. Inspite of fairly high doses, 5 cases had poor response.

DURATION OF ACTION—A study of three cases.

In order to assess the duration of action of the drug, a study of three in-patients was made. Two hourly blood pressure recordings were taken. Fig. 1 showed separate blood pressure recordings of the three cases and also their average blood pressure. It can be seen that the blood pressure began to fall in two hours and the maximum fall was at six hours and remained so for eight hours after which the blood pressure started to rise.

SIDE EFFECTS

The side effects were few and minor and no serious ill effects were encountered during this trial. Eight patients complained of weakness, which could not be explained by either electrolyte imbalance or any neurological deficit, however, it was not serious enough to incapacitate the patients and they were able to carry on with their usual work inspite of continuance of therapy. Dizziness which was not serious enough to cause a withdrawal of the drug occured in 6 hospitalised patients during the initial stage of therapy. It disappeared even when the drug was continued. Two to four months after the blood pressure had been satisfactorily controlled, 3 cases developed tolerance requiring bigger dose of bethanidine to control the blood pressure. One case had nasal stuffiness and the other had constipation. One had failure of ejaculation though erection was obtainable. When the drug was stopped or dosage reduced, however, ejaculation was possible. Postural hypotension tended to be troublesome initially but disappeared inspite of the drug being continued to be administered. However, in 2 cases (13 & 22) the postural hypotension was so severe that the drug had to be withdrawn.

DISCUSSION

The results of this study show that bethanidine sulphate is very effective in the treatment of hypertension. It acts within 2 hours and remains effective for 8 hours. The maximal effect is 4-6 hours. Obviously this is a very useful drug in the treatment of hypertensive emergencies when rapid lowering of blood pressure is desirable.

The side effects of the drug have been relatively minor in this series. Although Smirk (1963) reported that thrombocytopenia occured in two cases we did not get such a complication. There was not a single case of diarrhoea, which is common with guanethidine.

In our series the effective dose was in most cases not more than 100 mg a day, although the range was between 20-450 mg. This was less than that used by Montuschi and Pickens (1962) and Johntson *et al.*, (1964). On the other hand, the average dose used by Smirk was only 65 mg. but the range was 20-500 mg. As we wanted to assess the effect of bethanidine alone none of our cases had additional diuretic therapy. It is our opinion that if it is combined with thiazide derivatives or methyl dopa as reported by Wilson *et al*, (1965), the amount of bethanidine required to control the blood pressure will be much reduced. Weakness was one of the side-effects, the cause of which we are unable to explain. Two cases (13 &22) had to be abandoned because of severe postural hypotension, which occured inspite of only relatively small doses of bethanidine. The hypotensive effect persisted for several days even after the drug was withdrawn. It appeared that this was probably due to increased sensitivity of the patient to the drug.

SUMMARY AND CONCLUSION

1. Twenty-five patients suffering from hypertension were treated with bethanidine (Esba-

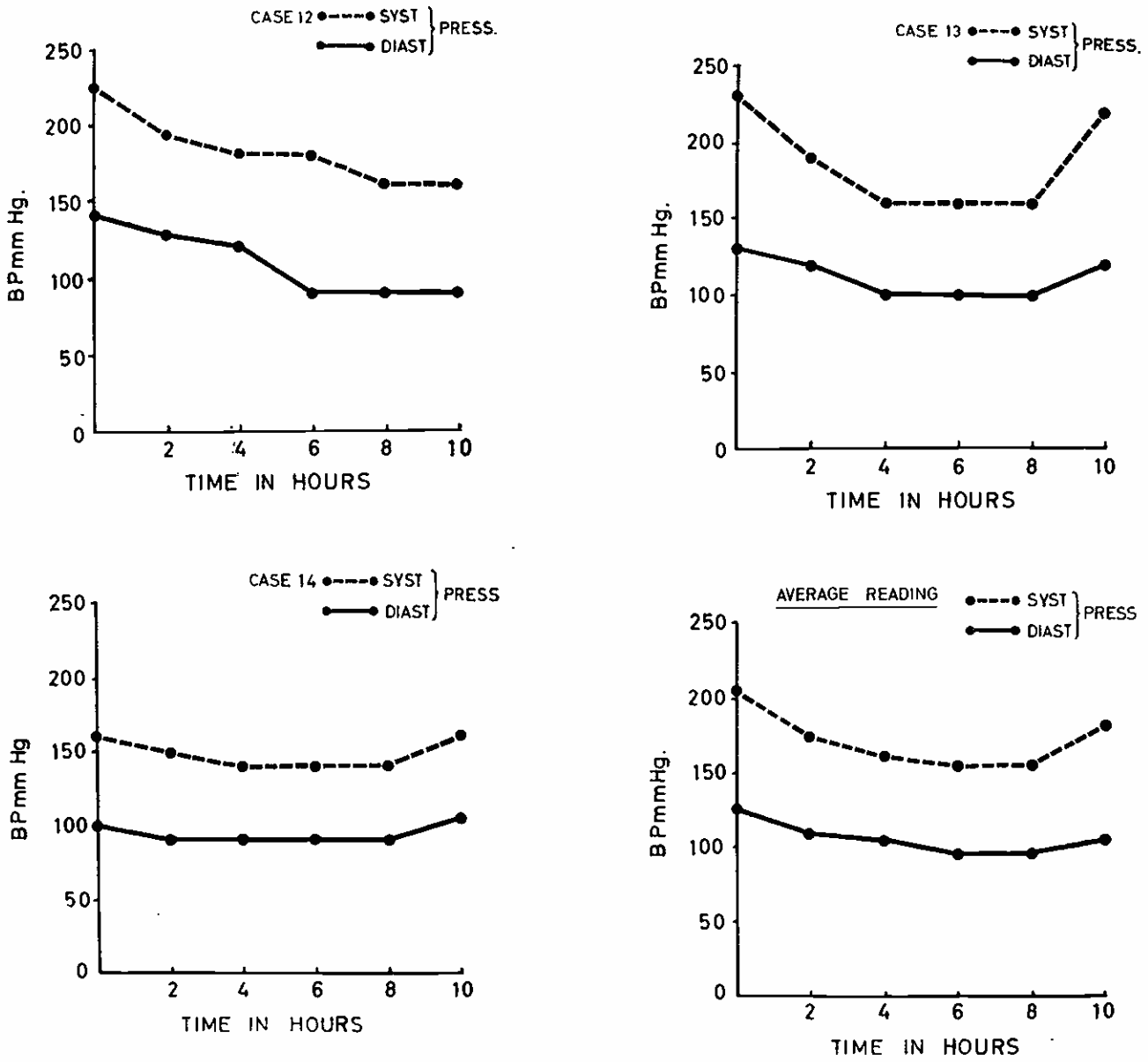


Fig. 1 - Show the blood pressure recordings of Case 12, 13 and 14 and their average readings.

tal) for a period ranging from 9 days to 15 months. Explanation was given for the short duration of study in six cases.

2. Of 17 patients who had no previous treatment, 13 had good response, 1 fair, 2 little or no response and 1 withdrawn from the trial because of severe postural hypotension. Of eight cases given other treatment for hypertension, 1 had good response, 2 fair and 3 failures. One was lost in the follow-up and 1 was withdrawn because of severe postural hypotension.
3. Three cases were studied to assess the duration of action of the drug. The drug acted within 2 hours and lasted 8 hours. The maximal effect took place within 4-6 hours.
4. The minor side effects were postural hypotension, dizziness, weakness, tolerance, nasal stuffiness, constipation and failure of ejaculation.
5. The conclusion is that this drug is effective in the treatment of hypertension. At present there is no ideal drug for the treatment of hypertension, the introduction of this potent and effective hypotensive agent is certainly an asset in the medical armamentarium for the treatment of hypertension. In view of its rapid action, bethanidine can be safely used in hypertensive emergencies. As there are some patients who might hyper-react to

the drug's hypotensive action, it is advisable that the starting dose be small especially in those cases treated as outpatients.

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REFERENCES

1. Boura, A.L.A., Copp, F.C., Greem, A.F., Hodson, H.F., Ruffell, G.K., Sim, M.F., Waltoe, E. & Grivsky, E.M. (1961): "Adrenergic neurone-blocking agents related to choline 2, 6-xylyl ether bromide (TM 10), bretylium and guanethidine," Nature, 191, 1312.
2. Boura, A.L.A. & Green, A.F. (1963): "Adrenergic neurone blockade and other acute effects caused by n-benzy-n^{1} n^{11}-dimethyl-guanidine and its ortho-chloro derivative," Brit. J. Pharmacol., 20, 36.
3. Johnston, A.W., Prichard, B.N.S. & Rosenheim, N.W. (1964): "The use of bethanidine in the treatment of hypertension," Lancet, 2, 659.
4. Keith, N.M., Wagener, H.P. & Barker, N.W. (1939): "Some different types of Essential Hpertension, their course and prognosis," Am. J. Med. Sci., 197, 332.
5. Montuschi, E. & Picken, P.T. (1962): "A clinical trial of two related adrenergic neurone-blocking agents—B.W. 392C60 and B.W. 467C60," Lancet, 2, 897.
6. Smirk, H. (1963): "The Hypotensive action of B.W. 467C50," Lancet, 1, 743.
7. Wilson, R., Long, C. & Jogoe, W.S. (1965): "The Hypotensive action of Bethanidine sulphate," J. Irish Med. Assn., 56, 9.