A CLINICAL TRIAL OF ALPHA-METHYLDOPA (ALDOMET) AND HYDROCHLORTHIAZIDE (DICHLOTRIDE) ALONE AND IN COMBINATION IN HYPERTENSION*

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Introduction of newer hypotensive agents from time to time is a pointer to the unsolved problem of the treatment of hypertension. Severe hypertension (grades III and IV) is still a challenging problem for the physician. In the therapeutic armamentarium of hypertension some new drugs have disappeared faster than they were introduced because of their serious hazards or limitations. A clinician has, therefore, to continue trying established drugs singly in varied doses or in combination (3).

Guanethidine is powerful drug, but quite often postural hypotension limits its clinical usefulness (5). Alpha-methyldopa (4, 5, 7) and thiazide diuretics (6) are smooth acting hypotensive agents of mild to moderate efficacy. In the present study alpha-methyldopa (Aldomet) and a thiazide diuretic, hydrochlorothiazide (Dichlotride) were tried separately and in combination. It was expected that a combination of the two would yield information which could be of use for the better management of severe hypertension.

MATERIALS AND METHODS

Patients with high blood pressure as recorded in the outpatient department were admitted to the medical wards of S.S.G. Hospital. The patients had complete bed-rest and phenobarbitone 30 to 60 *mg* was administered at bed time every night for three nights to ensure proper sleep. At the end of three days patients who showed early morning systolic pressure of 170 mm Hg or more and diastolic pressure of 110 mm Hg or more, were selected for the trial. A total of 46 patients (29 male and 17 female) ranging in age from 22 years to 60 years were taken up for the study. The incidence and distribution of age and sex are shown in Table I. The symptoms associated with hypertension were headache, anorexia, palpitations, dizziness, giddiness, vertigo, weakness, dryness of mouth, dimness or vision, hiccough, anginal pain, dyspnoea on exertion and nocturnal dyspnoea. All patients were given salt-poor (sodium chloride 600 *mg* daily) diet supplied by the hospital. No patient was on any anti-hypertensive drug treatment for at least a fortnight prior to the start of the trial.

*Received 5-1-1971

TABLE I

Age and sex distribution of hypertensive patients employed in the study.

Age group in years	*Male*	*Female*	*Total*
21—30	3	3	6
31—40	2	3	5
41—50	6	4	10
51—60	18	7	25
Total	29	17	46

Blood pressure was messured by the method as suggested by the Committee for the Standardisation of Blood Pressure Readings (2). Blood pressure was recorded for 3 min every morning in supine and erect positions.

Aldomet was used as 250 *mg* tablets and Dichlotride as 50 *mg* tablets. The patients were divided into 3 groups. One group of 16 patients received Aldomet; another group of 13 patients received Dichlotride and the third group of 17 patients received a combination of the two drugs. The order of drug administration was according to a design of Latin Squares. The initial dose of Aldomet was 250 *mg* thrice daily. If the response was unsatisfactory, the dose was increased by 250 *mg* exery fourth day, till a satisfactory response was obtained. The initial dose of Dichlotride was 50 *mg* thrice daily and in case the response was unsatisfactory increment was effected by 50 *mg* every fourth day. In the case of combination therapy, Aldomet was given in a dose of 250 *mg* twice daily and Dichlotride in a dose of 50 *mg* twice daily. If the response was not satisfactory increment in the doses of the drugs was effected by one 250 *mg* tablet of Aldomet and one 50 *mg* tablet of Dichlotride every fourth day till a satisfactory response was obtained. Observations were made over a period of 30 days.

Investigations comprised haemogram, urinanalysis, blood urea, fasting blood sugar, fundoscopy, chest x-ray, blood cholesterol, erythrocyte sedimentation rate, urine culture, serum potassium levels, liver function tests (serum bilirubin, S.G.O.T., S.G.P.T. and alkaline phosphatase), plain x-ray of abdomen and aortography where indicated. All the investigations were done in the beginning and at the end of the trial.

Mean blood pressure was used for assessing the effects of therapy on blood pressure. Mean blood pressure was calculated by adding 1/3 of pulse pressure to diastolic pressure. Fall or rise of mean blood pressure was given scores. For every 10 mm Hg fall of mean blood pressure, the score was +1 and for every 10 mm Hg rise of mean arterial pressure the score was —1. Postural hypotension was calculated as the difference between the supine and the erect diastolic pressure. Difference of every 5 mm Hg of postural pressure beyond the initial 10 mm Hg was given a score of —1. For each side effect other than postural hypotension a

score of —1 was given. The scores for each drug were pooled and the response was designated as *excellent* if the total score was 4 or more; *good* if the total score was 3; *fair* if the total score was 2 and *unsatisfactory* if the total score was 1 or less than 1.

Each morning when the investigator recorded the blood pressure, enquiries about the relief of symptoms or appearance of side effects were made.

RESULTS

The results are summarized in Table II.

TABLE II

Effect of Aldomet, Dichlotride and combination therapy on mean blood pressure and serum potassium level.

ALDOMET			*DICHLOTRIDE*			*ALDOMET and DICHLOTRIDE*		
Patient	*% fall (or rise indicated by *) of mean blood pressure.*	*Difference between serum potassium level at the start and termination of therapy (meq/L)*	*Patient*	*% fall (or rise indicated by *) of mean blood pressure.*	*Difference between serum potassium level at the start and termination of therapy (meq/L)*	*Patient*	*% fall (or rise indicated by *) of mean blood pressure.*	*Difference between serum potassium level at the start and termination of therapy (meq/L)*
I	27	+0.6	XVII	28	—0.6	XXX	2.6	—0.2
II	19	+0.5	XVIII	45	—0.5	XXXI	5.4	+0.4
III	13	—1.1	XIX	16	—1.0	XXXII	9.0	—0.9
IV	18	0.0	XX	20	—2,1	XXXIII	20	—1.4
V	8*	—0.2	XXI	30	—1.2	XXXIV	20	—1.2
VI	5	—0.5	XXII	16*	—0.6	XXXV	41	+0.3
VII	22	—0.4	XXIII	35	—	XXXVI	27	—0.9
VIII	24	—0.3	XXIV	15	—1.3	XXXVII	22	—0.9
IX	26	0.0	XXV	11	—0.7	XXXVIII	11	—
X	13	—0.2	XXVI	25*	—2.0	XXXIX	23	—0.7
XI	11.8	+0.1	XXVII	7.3	—0.3	XXXX	5.4	—0.8
XII	17.0	+0.8	XXVIII	23.0	—0.7	XXXXI	9.5	+0.7
XIII	13.9	—0.8	XXIX	13.5	—0.4	XXXXII	25.7	+0.4
XIV	9.3*	—0.2				XXXXIII	11.6	—1.4
XV	3.3	—0.6				XXXXIV	8.7	+0.2
XVI	22.8	—1.0				XXXXV	4.6*	+0.2
						XXXXVI	3.5*	0.0
Mean ±S.E.	13.6±1.9	—0.11±0.143		15.4±3.4	—0.88±0.17		13.7±2.5	—0.48±0.19

\+ indicates the rise of serum potassium level.
— indicates the fall of serum postassium level.

Effect on mean blood pressure :

Aldamet : The response was *good* in 5, *fair* in 6 and *unsatisfactory* in 5 patients. Fall in mean blood pressure was recorded on the 7th day in 3, 10th to 12th day in 9 and 22nd to 27th day in 2 patients. In 6 patients (II, V, VI, VII, IX and XV) there was affection of the heart (left ventricular hypertrophy and strain on E.C.G. and enlarged heart on chest x-ray) and mild degree of nephropathy (albumin, red corpuscles, pus cells and few casts in the urine). The response was unsatisfactory in 3 of these 6 patients (V, VI and XV).

The average daily dose was 1.6 *g*.

Dichlotride : Of the 13 patients treated with Dichlotride, the response was *excellent* in 1, *good* in 4, *fair* in 3 and *unsatisfactory* in 5. In 2 patients (XXII and XXVI) there was a rise in blood pressure inspite of treatment. Of the 11 who exhibited a fall in blood pressure, the fall occured on the 8th day in 7, 18th day in 2 and 26th day in 2 patients.

Of the 2 patients who showed a rise in blood pressure inspite of treatment, in one (XXII) the pressure at the start of treatment was 172/112 mm Hg and at the end it was 181/136 mm Hg. In this patient blood urea level rose from 64 to 250 *mg*% Fundi were normal in the beginning but showed evidence of haemorrhages during treatment. The left ventricle was hypertrophied. This patient was subsequently given combination therapy (Patient XXX) which resulted in a definite arrest in the rise of blood pressure. In fact there was now a slight fall in mean blood pressure (10 mm Hg). Blood urea however, ranged from 286 to 302 mg%. Fundal pathology was not affected by the treatment. The second patient (XXVI) in whom the blood pressure rose from 170/110 mm Hg to 211/120 mm Hg, had gross nephropathy (blood urea rose to 98 *mg*% from an initial level of 56 *mg*%), cardiopathy and fundal pathology. During trial the patient developed cardiovascular crisis. The fact that the complications of hypertension (in the form of cardiovascular accidents) are due to hypertension is well illustrated by the poor response of this patient to the therapy.

The average daily dose was 0.17 *g*.

Aldomet and Dichlotride : Of the 17th patients treated with a combination of Aldomet and Dichlotride the response was *excellent* in 2; *good* in 4; *fair* in 3 and *unsatisfactory* in 8 patients. In 2 patients (XXXXV and XXXXVI) there was a rise in blood pressure inspite of treatment. Fall in blood pressure began on the 4th day in 3 patients and from the 11th to 13th days in 6 patients. In others the fall started in the last week. The fall in blood pressure was maintained during the rest of the observation period. The 3 patients (XXX, XXXI and XXXII) in whom the fall in mean blood pressure was less than 10% and the 4th (Patient XXXVIII) in whom the fall was a little more than 10% (11%), had gross nephropathy including high blood urea, fundal haemorrhages, exudates and blurred discs and marked cardiopathy as indicated by left ventricular enlargement on chest x-ray and left ventricular hypertrophy and strain on E.C.G. Patient XXXV, in whom the fall in mean blood pressure was of the order of 41% developed cerebral apoplexy (though the blood pressure was now normal).

The average daily doses of Aldomet and Dichlotride were 0.70 *g* and 0.11 *g*, respecttively.

Effects on complications :

None of the complications of hypertension were affected by any of the three types of therapy. For an assessment of the beneficial effects of antihypertensive therapy on the complications of hypertension, observations extending over prolonged periods are necessary. Some of the complications of hypertension take a long time to set in. Viewed in this light antihypertensive activity of the three types of therapy studied in the present investigation was not expected to have any beneficial effect on the complications of hypertension.

Effects on symptoms :

The symptomatic relief usually preceded the reduction or normalisation of blood pressure. In some patients the fall in blood pressure and symptomatic relief were related to each other.

During trial with Aldomet, 9 patients (III, VI, VII, VIII, IX, XI, XII, XIII and XVI) had complete relief, 3 patients (II, IV and X) had partial relief and 4 patients (I, V, XIV and XV) had no relief of symptoms. Five patients (VII, VIII, IX, XII and XVI) of the 9 patients who had complete relief of symptoms exhibited moderate to good fall in blood pressure. During trial with Dichlotride 7 patients (XVII, XVIII, XX, XXI, XXIII, XXIV and XXIX) had complete relief, 2 patients (XXV and XXVIII) had partial relief and 4 patients (XIX, XXII, XXVI and XXVII) had no relief of symptoms. Of the 4 patients who had no relief of symptoms 2 patients (XXII and XXVI) showed a rise in blood pressure. Of the 7 patients who had complete relief of symptoms, 4 showed a good hypotensive response.

During trial with Aldomet and Dichlotride 4 patients (XXXII, XXXVI, XXXVII and XXXXII) had complete relief, 4 (XXX, XXXIX, XXXX and XXXXIII) had partial relief and 9 patients (XXXI, XXXIII, XXXIV, XXXV, XXXVIII, XXXXI, XXXXIV, XXXXV and XXXXVI) had no relief of symptoms. Of the 9 patients who had no symptomatic relief, 3 showed a good hypotensive response.

Side effects :

During treatment with Aldomet minor side effects such as nausea, headache, constipation, diarrhoea and nasal stuffiness were noted. Drowsiness was seen in the first week of therapy. Postural fall of more than 15 mm Hg in diastolic pressure was present in 5 patients (II, III, IV, V and XVI). Giddiness did not always go pari passu with postural. For example, giddiness was absent in patients (V and XVI) in whom postural fall was 18 and 20 mm Hg respectively. The other 3 patients had postural giddiness. Drowsiness in the first week was a desirable effect rather than an undesirable side effect since the patients were tranquilised and got good sleep. There was no significant fall (0.11 ± 0.143 *meq/L*) in serum potasssium level with Aldomet.

The mean fall in serum potassium level during treatment with Dichlotride was 0.88±0.17 *meq/L*. One patient (XVII) had postural giddiness. In this patient the postural fall in systolic pressure was 17 mm Hg. There was no postural fall in diastolic pressure in this patient.

With combination therapy postural giddiness was observed in 2 patients (XXXIII and XXXVIII). The postural fall in diastolic pressure in these patients was more than 15 mm Hg. The mean fall in serum potassium level was 0.48±0.19 *meq/L*.

DISCUSSION

The present study shows that the per cent fall in mean blood pressure with Aldomet (13.6±1.9) or Dichlotride (15.4±3.4) or combination therapy (13.7±2.5) was more or less identical but postural hypotension and hypokalaemia were much less with combination therapy.

Aldomet produced a significant fall in blood pressure but the effects of postural hypotension were disturbing because locomotion and physical activities of the patients became limited and they felt miserable. Dichlotride given alone was capable of producing serious biochemical disturbances in the form of hypokalaemia.

Combination of the two drugs gave promise of hypotensive activity of significant degree with the minimal of side effects. This could be attributed to the potentiating effect of Dichlotride on the antihypertensive action of Aldomet as suggested by Bayliss and Smith (1). The average daily doses of Aldomet and Dichlotride used singly were 1.6 *g* and 0.17 *g*, respectively. However, comparable degree of fall in blood pressure was obtained with relatively small doses of Aldomet (0.70 *g*) and Dichlotride (0.11 *g*) given together. Moreover, combination was effective when a single drug had failed. This was well highlighted in one patient in whom a single drug (Dichlotride) was used in the beginning (XXII). The blood pressure in this patient not only did not fall but rose to higher level. Subsequently when combination therapy was instituted, the rise in pressure was arrested (patient XXX).

Admittedly till a powerful and a safe hypotensive drug is available, the treatment of grade III and grade IV hypertension will depend upon a combination of the currently available hypotensive drugs. Synergism of the hypotensive effects and reduction of the side effects is the cornerstone of combination therapy. With combination therapy doses of the individual drugs are reduced leading to a diminution of the side effects.

SUMMARY AND CONCLUSIONS

Alpha-methyldopa (Aldomet) and hydrochlorothiazide (Dichlotride) have been tried singly in 16 and 13 patients respectively and in combination in 17 patients each of hypertension. Using the criteria detailed under "Results" the response to Aldomet was *good* in 5, *fair* in 6 and *unsatisfactory* in 5 patients. The response to Dichlotride was *excellent* in 1, *good* in 4, *fair* in

3 and *unsatisfactory* in 5 patients. The response to combination therapy was *excellent* in 2, *good* in 4, *fair* in 3 and *unsatisfactory* in 8 patients. Complications associated with hypertension were not reduced. The symptomatic relief was correlated with the hypotensive response only in some patients. Hypokalaemia was the major drawback of Dichlotride and orthostatic hypotension was the major drawback of Aldomet. With combination therapy these drawbacks were reduced.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the gifts of alpha-methyldopa (Aldomet) and hydrochlorothiazide (Dichlotride) By Dr. K. Kanwar of Merck Sharp and Dohme (Bombay). This work was supported in part by a research grant from the Council of Scientific and Industrial Research, New Delhi.

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