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Double Blind Control Study of Antihypertensive Agents

III. Chlorothiazide Alone and in Combination with Other Agents; Preliminary Results

VETERANS ADMINISTRATION
COOPERATIVE STUDY ON
ANTIHYPERTENSIVE AGENTS*
WASHINGTON, D. C.

The previous 2 reports of the Veterans Administration Cooperative Study on Antihypertensive Agents described the results obtained with reserpine, hydralazine, and 3 ganglion blocking drugs.[1,2] The present investigation is concerned with the evaluation of chlorothiazide both alone and in combination with the agents listed above and with cryptenamine, an alkaloid derived from Veratrum viride. Although these latter studies are still in progress, the results seemed of sufficient interest to warrant a preliminary report at this time.

Methods

This investigation used 2 separate protocols for each of 2 different groups of patients. The first (Group A) were untreated cases entering the study for the first time. The second (Group B) were patients who had been under treatment in the cooperative study for at least 1 year,[1,2] after which chlorothiazide was added to the regimens of the patients taking active medications.

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The criteria used for selecting patients and for classifying severity have been described in a previous communication.[1] The Group A patients entering the study for the first time were treated as follows:

Mild and moderately severe cases were assigned one of the following 4 regimens using a double blind, randomization method: (1) chlorothiazide 500 mg. with reserpine 0.25 mg. combined in a single tablet twice daily plus hydralazine 25 mg. 4 times daily for 1 week followed by hydralazine 50 mg. 4 times daily thereafter; (2) chlorothiazide without reserpine plus hydralazine, both drugs given as above; (3) chlorothiazide without reserpine plus placebo of hydralazine, given as above; (4) placebos of chlorothiazide-reserpine and of hydralazine, given as above.

Severe cases were assigned one of the following regimens: (1) chlorothiazide 500 mg. combined with reserpine 0.25 mg. in a single tablet twice daily; in addition, hydralazine 12.5 mg. (½ tablet) 3 times daily were given and the doses raised by 12.5 mg. increments to a total dose of 50 mg. 3 times daily or until the diastolic pressure fell below 100 mg. Hg, or else side-effects supervened; (2) same as above except that cryptenamine (an alkaloid derived from Veratrum viride) was substituted for hydralazine. Each tablet of cryptenamine contained 3 mg., and the initial dose was 1.5 mg. (½ tablet) 3 times daily.

The tablets of hydralazine and the Veratrum compound were made up to appear and taste the same. Chlorothiazide, reserpine, and hydralazine also were prepared to resemble their respective placebos. As in the previous study[1] 3 different code numbers were assigned to each preparation including the placebos.

The Group B patients were those who had been under treatment for more than 1 year with either reserpine, reserpine plus hydralazine, placebos, or reserpine plus ganglion blocking agents.[1,2] The

TABLE 1.—*Group A: Change in Blood Pressure from Pretreatment Hospital Average to Third-Month Home Pressure by Regimen and Severity*

Severity and Regimen	No. of Cases	Systolic: Pretreat. Level	Systolic: Difference at 3 Mo. Av.	Systolic: Difference at 3 Mo. 0.90 Confidence Limit	Diastolic: Pretreat. Level	Diastolic: Difference at 3 Mo. Av.	Diastolic: Difference at 3 Mo. 0.90 Confidence Limit
Mild and moderately severe							
Chlorothiazide+reserpine+hydralazine	23	163	−17.2	−10.4 to −24.0	108	−14.3	− 9.8 to −18.8
Chlorothiazide+hydralazine	37	156	−11.2	− 5.7 to −16.7	105	−11.8	− 7.9 to −15.7
Chlorothiazide	34	157	− 3.2	+ 0.8 to − 7.2	103	− 1.9	+ 1.2 to − 5.0
Placebo	32	166	− 0.9	+ 5.2 to − 7.0	105	0.0	+ 3.7 to − 3.7
Severe							
Chlorothiazide+reserpine+cryptenamine	15	179	−17.9	− 6.2 to −29.6	119	−16.4	− 9.3 to −23.5
Chlorothiazide+reserpine+hydralazine	25	186	−22.7	−14.2 to −31.2	118	−20.9	−15.8 to −26.0

cases had been divided so that all patients with mild and half of those with moderately severe hypertension received the reserpine, hydralazine, and placebo regimens. The addition of chlorothiazide was accomplished in these cases by substituting for the 0.25 mg. reserpine tablet a specially prepared tablet containing reserpine 0.25 mg. plus chlorothiazide 500 mg. A similar-appearing placebo also was manufactured. These tablets were given the same code number identifications as used in the prior study except that the letter "C" preceded the series of digits. By substituting the "C" series medication for the prior "A" series those patients taking either reserpine plus hydralazine or reserpine plus placebo of hydralazine had chlorothiazide 500 mg. twice daily added to their regimens, while those patients who were not treated with active preparations had only placebo of chlorothiazide added.

All of the patients with severe hypertension in prior treatment Group B and half of those with moderately severe hypertension had been treated with reserpine 0.25 mg. twice daily plus 1 of 3 ganglion blocking agents: mecamylamine, chlorisondamine, or pentolinium tartrate.[1,2] Chlorothiazide was added to their regimens by substituting a tablet containing 500 mg. of chlorothiazide and 0.25 mg. of reserpine for the prior 0.25 mg. of reserpine. This tablet was administered twice daily. At the same time the dose of the ganglion blocking agent was decreased to half the prechlorothiazide level because of the well-known enhancement of the antihypertensive effect of blocking drug induced by chlorothiazide. Further adjustments of the doses of the ganglion blocking agent were then made from this reduced level as seemed indicated for control of the blood pressure.

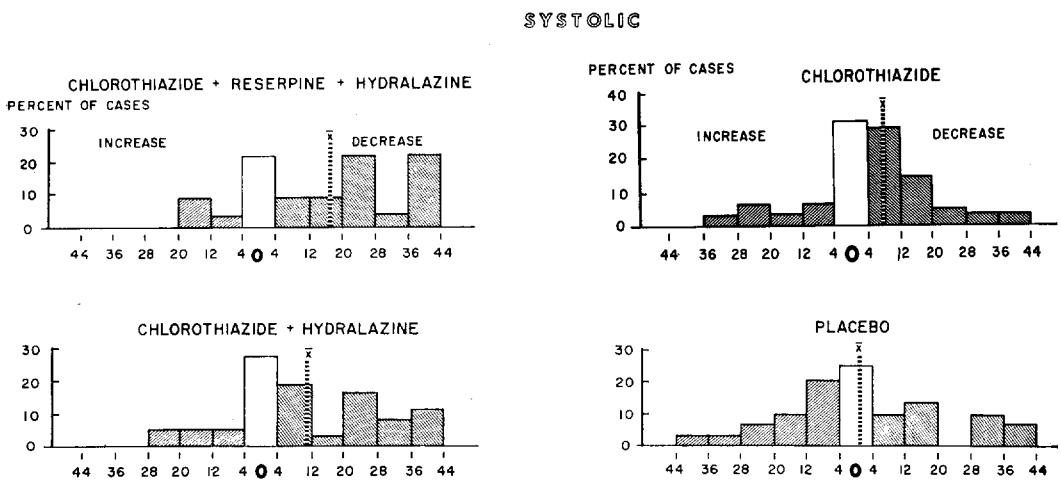

Fig. 1.—Percentage distribution curves of changes in systolic blood pressure at the end of 3 months of treatment in patients with mild and moderate hypertension. Changes in systolic pressure from pretreatment values are listed on the abscissae and percentage of patients on the ordinates.

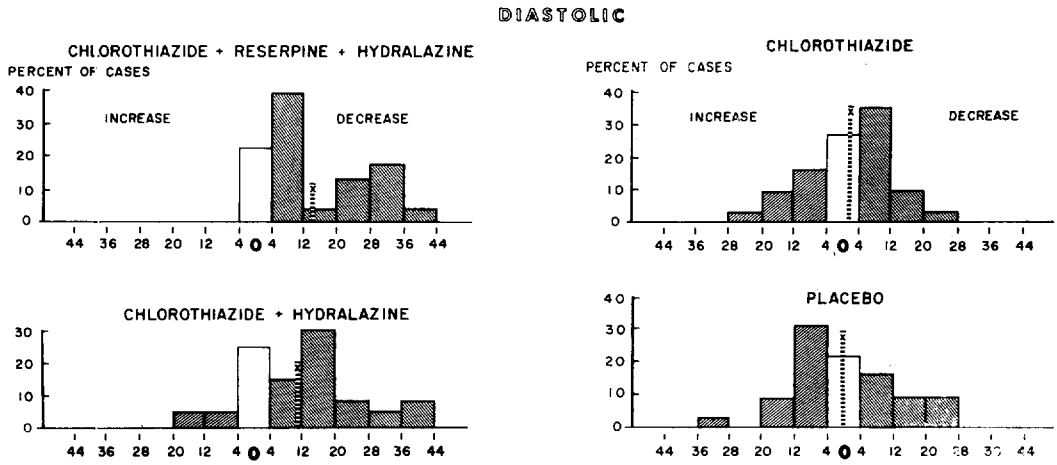

Fig. 2.—Percentage distribution curves of changes in diastolic blood pressure. Other notations are as in Figure 1.

Results

Group A (Previously Untreated) Patients. Chlorothiazide Regimens in Mild and Moderate Hypertension: The results in the mild and moderately severe groups suggested that the various agents have additive effects. The average reduction from the hospital basal pretreatment, systolic/diastolic blood pressure [1] to the average home blood pressure was 7.9/3.8 mm. Hg in the chlorothiazide-treated patients and 0.9/0.0 in the placebo-treated group (Figs. 1 and 2). The patients receiving chlorothiazide plus hydralazine exhibited an average reduction of 10.2/11.8 mm. Hg, and those taking chlorothiazide, hydralazine, and reserpine showed an average fall of 17.2/14.3 mm. Hg. None of the 23 patients receiving the 3-drug regimen (chlorothiazide, hydralazine, and reserpine) exhibited an increase in diastolic blood pressure (Fig. 2).

Chlorothiazide and Reserpine with Hydralazine or Veratrum in Severe Hypertension: In the Group A patients with severe hypertension, the 25 patients receiving reserpine and chlorothiazide plus a titrated dose of hydralazine exhibited a reduction of blood pressure averaging 22.7/20.9 mm. Hg (Figs. 3 and 4). These values are not significantly different from those which had been previ-

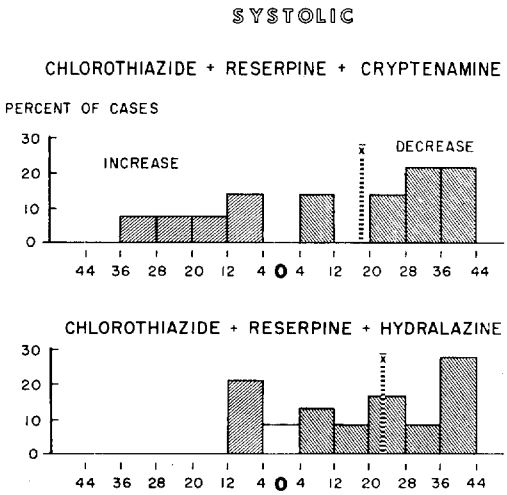

Fig. 3.—Percentage distribution curves of changes in systolic blood pressure at the end of 3 months of treatment in patients with severe hypertension.

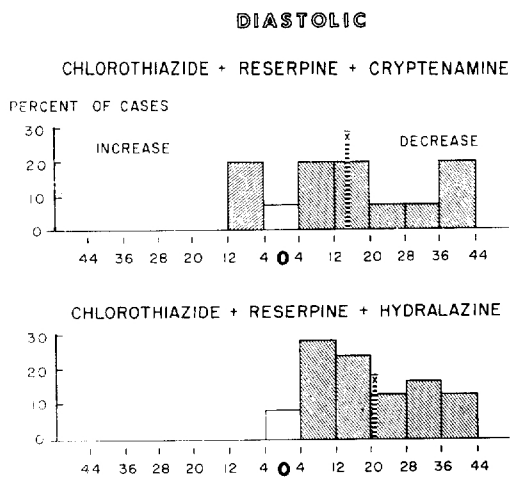

Fig. 4.—Percentage distribution curves of changes in diastolic blood pressure in patients with severe hypertension.

TABLE 2.—*Group B: Effect of Addition of Chlorothiazide After One Year of Treatment with Reserpine, Reserpine plus Hydralazine or Reserpine plus Ganglion Blocking Agents*

Antihyp. Regimen	No. of Cases	Av. Blood Pressure, Mm. Hg		
		Prior to Any Treat	Last Mo. Before Chlorothiazide	3 Mo. After Chlorothiazide
Chlorothiazide added to				
Reserpine	70	159/102	154/96	145/91
Reserpine & hydralazine	71	158/102	153/92	142/86
Reserpine & gang. block. agents	68	180/116	161/97	151/93
"A" placebo to "C" placebo	36	155/101	164/104	164/105

ously obtained with reserpine and ganglion blocking agents without chlorothiazide in severe hypertension.[2] The somewhat greater reduction of blood pressure in the severe as compared to the mild and moderate groups probably is related to the fact that the pretreatment levels of blood pressure were higher in the severe cases.[1,2] The distribution curve in this reserpine-, chlorothiazide-, and hydralazine-treated group showed no patients with a rise in diastolic blood pressure (Fig. 4). The average reduction of blood pressure in the severe patients treated with chlorothiazide, reserpine, and cryptenamine was 17.9/16.4 mm. Hg.

Group B (Previously Treated) Patients.—Addition of Chlorothiazide to Mild and Moderate Cases Previously Treated with Reserpine, Hydralazine: Chlorothiazide or its placebo was added to the regimens of 177 mild and moderately severe Group B patients who had been treated with reserpine, hydralazine, or placebo regimens for one year or longer.[1,2] In 71 patients receiving reserpine 0.25 mg. twice daily and hydralazine 50 mg. 4 times daily, the average reduction from pretreatment "basal" levels prior to chlorothiazide was 5/10 mm. Hg. During the 3 months after addition of chlorothiazide there was a further reduction of 11/6 mm. Hg or a total average fall of 16/16 mm. Hg from the mean pretreatment value. The post-treatment average diastolic pressure was 86 mm. Hg. In 70 patients receiving reserpine 0.25 mg. twice daily without hydralazine, a mean reduction of 5/6 mm. Hg from pretreatment basal values before chlorothiazide decreased further to 14/11 after the addition of chlorothiazide, an additional reduction of 9/5 mm. Hg. The average pressure of the 36 placebo-treated patients was unaffected by the addition of chlorothiazide placebo.

The reduction of diastolic blood pressure after the administration of chlorothiazide was correlated with the degree of elevation of these readings prior to chlorothiazide. The patients with elevations of diastolic above 90 mm. Hg exhibited the greatest response; those between 80 and 90, a lesser response, and the few below 80 mm. Hg showed essentially no change in average diastolic pressure after chlorothiazide was added.

Addition of Chlorothiazide to Moderate and Severe Cases Previously Treated with

TABLE 3.—*Group B: Average Change in Diastolic Blood Pressure, According to Average Diastolic Pressure Prior to Change*

Diastolic Pressure Prior to Change, Mm. Hg	Chlorothiazide Added to			
	Reserpine		Reserpine+Hydralazine	
	No. of Cases	Av. Change, Mm. Hg	No. of Cases	Av. Change, Mm. Hg
90 or higher	47	−7.4	36	−9.1
80 to 90	15	−5.4	27	−2.3
Less than 80	8	+3.7	8	+1.0
All cases	70	−5.7	71	−5.5

TABLE 4.—*Average Laboratory Values Before Therapy and at 3 and 12 Months, for Patients Receiving Chlorothiazide and Control Patients*

	Weight, Lb.	Na, MEq/L	K, MEq/L	Cl, MEq/L	CO_2, MEq/L	BUN, Mg. %	Uric Acid, Mg. %	FBS, Mg. %
Patients on chlorothiazide								
No. of patients tested	(208)	(216)	(209)	(217)	(211)	(214)	(65)	(41)
Pretreatment levels	172	139	4.5	104	27	16	5.5	100
Three-month levels	172	139	4.2	103	27	17	5.6	103
No. of patients tested	(95)	(101)	(101)	(100)	(95)	(102)	(22)	(8)
Pretreatment levels	168	139	4.5	104	27	16	5.6	102
Twelve-month levels	170	139	4.2	103	27	18	6.2	103
Patients on placebo								
No. of patients tested	(51)	(52)	(52)	(50)	(49)	(53)	(11)	(11)
Pretreatment levels	175	139	4.5	104	27	15	5.2	108
Three-month levels	174	140	4.6	103	27	15	5.4	95
No. of patients tested	(23)	(24)	(24)	(23)	(23)	(25)	(9)	(6)
Pretreatment levels	175	138	4.6	105	26	14	5.8	114
Twelve-month levels	174	140	4.5	103	27	13	5.8	97

Reserpine and Ganglion Blocking Drugs: Data were available on the addition of chlorothiazide to the regimens of 68 patients taking reserpine 0.25 mg. twice daily plus 1 of 3 ganglion blocking agents—mecamylamine, chlorisondamine, or pentolinium tartrate. Since the previous study failed to reveal significant differences in the antihypertensive effectiveness of the 3 blocking drugs, the 68 patients are reported as a single group. The average blood pressure in these patients was reduced from a basal pretreatment value of 180/116 to 161/97 after 1 year of treatment with reserpine and ganglion blocking drugs. The addition of chlorothiazide resulted in a further average reduction of 11 mm. systolic and 5 mm. diastolic, to 151/93 mm. Hg. In addition, doses of the blocking drug were reduced to one-half or less of the prechlorothiazide levels in approximately 45% of these patients.

Changes in Body Weight and Certain Blood Constituents

The average values for body weight, serum sodium and chloride, blood CO_2, and BUN in approximately 210 patients were essentially unchanged from pretreatment values when tested at the end of 3 months of therapy with chlorothiazide. There also were no significant changes in these parameters after 1 year of continuous treatment as determined in approximately 100 patients. The group treated with placebos also showed no significant changes. The average values of serum potassium were unchanged in the placebo group, but in the chlorothiazide-treated patients, the average serum potassium level fell from 4.5 pretreatment to 4.2 mEq. per liter both at 3 months and at 1 year after beginning administration of chlorothiazide. Serum potassium levels also were determined after

TABLE 5.—*Percentage of Patients Showing Abnormal Laboratory Values Before and After 3 Months of Treatment with Chlorothiazide or Placebo*

	Serum Sodium, <135 MEq/L	Serum Potassium, MEq/L			Serum Chloride, <90 MEq/L	Serum Uric Acid, >7.9 Mg. %	Fasting Blood Sugar, >120 Mg. %
		<3.5	<3.0	<2.5			
Patients on chlorothiazide							
Number of patients tested	(216)	(209)	(209)	(209)	(211)	(65)	(41)
% of patients with abnormal levels pretreatment	14.2	2.6	0.5	0.0	0.9	12.3	6.6
% at 3 months	10.6	8.7	0.5	0.0	0.5	12.6	17.0
Patients on placebo							
Number of patients tested	(52)	(53)	(53)	(53)	(53)	(14)	(14)
% of patients with abnormal levels pretreatment	15.3	1.9	0.0	0.0	0.0	7.2	21.4
% at 3 months	13.5	0.0	0.0	0.0	1.9	7.2	23.1

1 week of chlorothiazide treatment in 97 patients. The serum potassium in these 97 patients averaged 4.50 pretreatment, 4.06 at one week, and 4.06 mEq. per liter at 3 months, indicating that the reduction occurred during the first week of treatment.

The laboratory data also were analyzed for the percentage of patients exhibiting abnormal serum concentrations of sodium, chloride, and potassium. There was no significant difference between the number of patients exhibiting serum sodium levels below 135 mEq. per liter and serum chloride values below 90 mEq. per liter at 3 months after chlorothiazide as compared to before treatment. The incidence of serum potassium values below 3.5 mEq. per liter increased from 2.6% at pretreatment to 8.7% at 3 months, whereas in the placebo group the incidence decreased from 1.9% to 0.0%. There was no increase in the number of patients exhibiting potassium levels below 3.0 mEq. per liter, and there were no patients with levels below 2.5 mEq. either before or after treatment.

Changes in serum uric acid and in fasting blood sugar were determined in a smaller number of patients. The results obtained to date must be regarded as being preliminary. The average values for serum uric acid were essentially unchanged in 65 patients at the end of 3 months of treatment. At 1 year, the mean values increased in 22 patients from 5.6 to 6.2 mg. %. The average values for the fasting blood sugar in 41 patients were not significantly altered either at 3 months or at 1 year. The incidence of patients with levels above 120 mg. %, however, increased from 6.6% in the pretreatment period to 17.0% at 3 months. Data on a larger series of cases will be required to determine the significance of these trends.

Comment

Although the numbers of patients in some of the treatment groups are still too small to provide a final estimate of the comparative effectiveness of certain of the treatment regimens, particularly chlorothiazide alone and the combination of chlorothiazide and hydralazine, certain features seemed worthy of reporting at this time. There was a distinct trend indicating the additive effects of combining various drugs. Chlorothiazide plus reserpine resulted in a greater reduction of arterial pressure than either chlorothiazide or reserpine alone. The chlorothiazide, reserpine, and hydralazine combination was quite effective and, in fact, resulted in as great a reduction of blood pressure in the severe cases as reserpine plus ganglion blocking agents.[2] In the less severe groups this combination reduced the average diastolic blood pressure to normal. The chlorothiazide, reserpine, and hydralazine regimen did not require the careful dosage regulation needed with blocking agents, nor did it produce as high an incidence of disturbing side-effects.

Although not quite as effective as the chlorothiazide, reserpine, hydralazine regimen, it is of interest that the Veratrum compound plus the first 2 agents resulted in a significant reduction of both systolic and diastolic blood pressure. Since patients of comparable severity were not given chlorothiazide and reserpine without other agents, it is not possible to state how much of the antihypertensive effect was contributed by cryptenamine. The results obtained with this regimen will be reported in more detail, including incidence of nausea and vomiting and treatment failures, as more data become available.

The blood chemistry values indicated that the induction of hyponatremia or hypochloremia by chlorothiazide was rarely encountered in hypertensive patients. Mild to moderate hypokalemia was common, but serum potassium levels below 3.0 mEq. per liter were unusual. Potassium supplements were prescribed in only a few cases in this series, although many patients were advised to drink 1 glass of orange juice daily.

Individual patients often react differently from the average, the blood pressures of some being controlled on a regimen containing 1 or 2 antihypertensive drugs. Considering the extra cost and increased incidence of toxic effects as additional agents are prescribed, it would seem desirable in clinical

practice, in managing mild and moderate forms of hypertension requiring treatment, to begin with a single agent and add other drugs one at a time until the desired level of blood pressure is obtained.

Summary

Preliminary results of the effects on elevated blood pressure of chlorothiazide alone and in combination with various other agents are the subject of this report.

Mild to Moderate Hypertension.—Chlorothiazide in a dose of 500 mg. twice daily resulted in a reduction of blood pressure averaging 7.9/3.8 mm. Hg (systolic/diastolic) as compared to no change in the placebo-treated group.

The average reduction of blood pressure in previously untreated patients given chlorothiazide plus hydralazine 50 mg. 4 times daily was 11/12 mm. Hg, and in those taking chlorothiazide, hydralazine, and reserpine in a maintenance dose of 0.25 mg. twice daily, it was 17/11 mm. Hg.

Chlorothiazide also was added to the regimens of patients who had been treated previously with reserpine alone or in combination with hydralazine for 1 year. The reduction from average pretreatment levels of blood pressure was 14/11 mm. in the chlorothiazide plus reserpine group and 16/16 mm. in the patients receiving these 2 agents plus hydralazine.

Moderate and Severe Hypertension.—Chlorothiazide, reserpine, and hydralazine resulted in an average fall of 23/21 mm. Hg. This was not significantly different from the results previously obtained with reserpine and ganglion blocking agents in patients of similar severity.

Treatment with chlorothiazide, reserpine, and cryptenamine (an alkaloid of Veratrum viride) was associated with an average fall of 18/16 mm. Hg.

The addition of chlorothiazide after 1 year to the regimens containing reserpine plus ganglion blocking drugs resulted in an additional average reduction of 10/4 mm. Hg. In 45% of these patients, the doses of the blocking agents were reduced to half or less of the prechlorothiazide levels.

We wish to thank the representatives of Merck, Ciba, Irwin Neisler & Co., and Wyeth Laboratories who collaborated in the manufacture, labeling, and distribution of the special preparations of antihypertensive drugs and placebos used in this study.

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