Antihypertensive Properties of Cryptenamine Used with Reserpine and Methyclothiazide

CHARLES C. KENNEDY*, RALPH E. SPIEKERMAN*, and LILA ELVEBACK†

Abstract □ By a double-blind crossover method, the hypotensive effects and side effects of cryptenamine were studied in 22 patients with Group 1 or 2 essential hypertension. The dosage administered was 2.5 mg. of methyclothiazide alone and a combination of 2.5 mg. of methyclothiazide and: (*a*) 2.0 mg. of cryptenamine, (*b*) 0.1 mg. of reserpine, and (*c*) 1.0 mg. of cryptenamine and 0.1 mg. of reserpine. Each preparation was administered four times each day for 8 weeks. The mean decrease in diastolic blood pressure with methyclothiazide alone was 10.5 mm. Hg; with methyclothiazide and cryptenamine, 15 mm. Hg; with methyclothiazide and reserpine, 21.6 mm. Hg; and with methyclothiazide, reserpine, and cryptenamine, 23.5 mm. Hg. Two patients receiving methyclothiazide and cryptenamine were unable to complete the study because of nausea or depression. Mild side effects were more frequent with the combinations. Hypokalemia was noted in 50% of the patients, and small increases in levels of uric acid, urea, and blood sugar were without complication.

Keyphrases □ Antihypertensive activity and side effects—cryptenamine, methyclothiazide, reserpine combinations □ Cryptenamine, methyclothiazide, reserpine combinations—hypotensive effects and side effects □ Methyclothiazide, cryptenamine, reserpine combinations—hypotensive effects and side effects □ Reserpine, cryptenamine, methyclothiazide combinations—hypotensive effects and side effects □ Veratrum alkaloids, cryptenamine—hypotensive effects, side effects, in combination with methyclothiazide and reserpine

When diuretics alone do not restore satisfactory blood pressure levels, an antihypertensive agent must be added. For many years, veratrum viride has been considered as a significant hypotensive agent. However, it has not been used extensively because of the small range between hypotensive and emetic doses. By means of an extraction process using nonaqueous benzene triethylamine, an alkaloid preparation called cryptenamine has been obtained from veratrum viride. With cryptenamine, studies in animals have demonstrated an appreciable difference between hypotensive and emetic doses.

The principal objective of the study was to determine the hypotensive effects and side effects of cryptenamine. As an aid in evaluating the effectiveness, a comparison was made with a drug of established efficacy, methyclothiazide. The agents used in combination with methyclothiazide were: (*a*) cryptenamine, (*b*) reserpine, and (*c*) cryptenamine and reserpine.

MATERIAL

Twenty-two ambulatory patients, who had essential hypertension of Group 1 or 2, were selected. Their average blood pressures all exceeded 160 mm. Hg systolic and 90 mm. Hg diastolic during a 1-month period in which they were receiving a placebo. Eighteen patients satisfactorily completed the study. No patient received specific antihypertensive medication other than that administered during the study, and each had clinical records verifying the presence of chronic and sustained hypertension that was not secondary to any known cause. Thirteen of the patients were women, five were men, and all were Caucasians. Their ages ranged from 41 to 71 years with an average of 55 years. The average blood pressure of these patients before treatment ranged from 120 to 240 mm. Hg systolic, with a mean systolic pressure of 179 mm., and from 76 to 126 mm. Hg diastolic, with a mean diastolic pressure of 104 mm.

Examination of the ocular fundi revealed that all 18 patients had hypertensive changes of Group 1 or 2 severity, according to the Keith–Wagener–Barker classification; that is, none had retinal exudates or hemorrhages. Renal function was apparently adequate, the concentration of blood urea being within or close to normal limits in all patients. None of the patients had congestive heart failure or edema, and none was taking digitalis. No patient had symptomatic cerebrovascular impairment or residue from previous injury to the brain.

METHODS

All patients underwent complete physical and appropriate laboratory examinations before beginning the study. Thereafter, they came to the clinic at weekly intervals at their convenience, almost invariably at the same time of the day each week. The examining physician did not know which preparation the patient was receiving. After the patient rested for a short period, the blood pressure was taken three times, first with the patient in the sitting position and then twice after the patient had been standing for 1 min. The two lowest values for blood pressure (sitting and standing), the pulse rate, and body weight were recorded, along with relevant notes regarding possible side effects.

At regular monthly intervals during the entire study, fasting blood samples were obtained in the clinic laboratory for determination of levels of serum sodium, serum potassium, serum chloride, carbon dioxide, blood sugar, urea, and uric acid. An excretory urogram was obtained on all patients prior to beginning the study, and none gave evidence of a renal cause for hypertension. At the beginning and at the end of the study, the following laboratory tests were obtained: leukocyte and differential counts, hemoglobin, serum GOT, serum alkaline phosphatase, urinalyses, urine amylase, and urine metanephrines. In addition, chest roentgenograms for each patient were obtained before and after the study. Additional examinations were done when needed.

The study was carried out as a double-blind crossover procedure. The medications and placebo were taken four times each day at approximately 4-hr. intervals. The use of all previous antihypertensive medications was stopped, and the patient was given a placebo during the 1st month of the study. Each of the four medications was then given for a period of 2 months. The active medication was dispensed under a code number in a sequence determined by a person who did not have contact with the patients. The study lasted 9 months. Blood pressure recordings during the first 2 weeks of each 2-month period were disregarded because of the possible sustained effect of reserpine. The amount of drug per dose was 2.5 mg. of methyclothiazide; 2.5 mg. of methyclothiazide with 0.1 mg. of reserpine; 2.5 mg. of methyclothiazide with 2.0 mg. of cryptenamine; and 2.5 mg. of methyclothiazide, 0.1 mg. of reserpine, and 1.0 mg. of cryptenamine.

As mentioned previously, 22 patients were initially included in the study. One patient was excluded from the study because of inconsistencies in taking the medication regularly. Another was excluded because of the need for more vigorous antihypertensive treatment. Two others experienced drug intolerance and were unable to finish the study. After the completion of the study, the code was revealed; the values obtained during the pretreatment, placebo, and treatment periods were tabulated.

RESULTS

Effect on Blood Pressure—All medications, when compared to methyclothiazide, produced an increased hypotensive effect. The

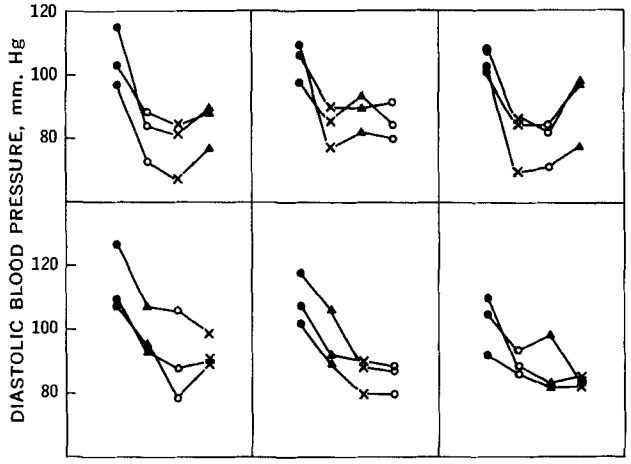

Figure 1—*Distribution of diastolic blood pressures for 18 patients in six orders of drug administration. Each of the six orders is represented by values from three patients. Each of the four medications was given for a period of 2 months. Key: ●, methyclothiazide alone; ▲, cryptenamine with methyclothiazide; ○, reserpine with methyclothiazide; and ×, combination of cryptenamine, reserpine, and methyclothiazide.*

mean decrease in diastolic blood pressure with methyclothiazide when compared with control levels was 10.5 mm. Hg. The effectiveness of the other drugs was compared with methyclothiazide. The mean diastolic blood pressure decreased an additional 5 mm. during treatment with methyclothiazide and cryptenamine (15 mm., as contrasted to control levels). The mean diastolic blood pressure decreased 11 mm. with methyclothiazide and reserpine (21.6 mm., as contrasted to control levels). The mean diastolic blood pressure decreased 13 mm. when the combination of methyclothiazide, reserpine, and cryptenamine was employed (23.5 mm., as compared to the control levels).

The sequence in which the medication was administered did not affect the therapeutic effectiveness (Fig. 1).

Effect on Pulse and Body Weight—The mean pulse rate was slowed with the methyclothiazide that contained cryptenamine, reserpine, or reserpine and cryptenamine, as contrasted to the rate

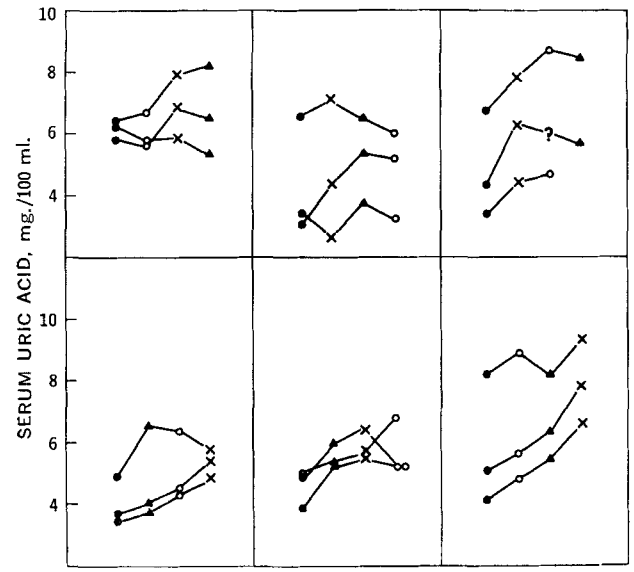

Figure 2—*Distribution of serum uric acid levels for 18 patients in six orders of drug administration. Each of the six orders is represented by values from three patients. Each of the four medications was given for a period of 2 months. Key: ●, methyclothiazide alone; ▲, cryptenamine with methyclothiazide; ○, reserpine with methyclothiazide; and ×, combination of cryptenamine, reserpine, and methyclothiazide.*

with methyclothiazide alone. The decrease ranged from 4 to 16 beats/min. The mean body weight was essentially unchanged with all medications.

Effect of Constituents on Blood—*Serum Potassium*—Nine of the 18 (50%) patients required an orally administered potassium supplement to maintain their serum potassium level in a normal range of 4–5 meq./l. Hypokalemia was consistently present with all medications in patients who required the supplemental use of potassium. The mean decrease in patients who required potassium was 0.5 meq., and the lowest potassium value was 2.9 meq./l. No symptoms could be attributable to hypokalemia in any of these patients. One patient was withdrawn from the study for evaluation of hyperaldosteronism, but the diagnosis could not be established, and antihypertensive treatment was reinstituted.

Serum Sodium—There was no significant change in mean serum sodium value during treatment with any of the medications, except for one patient. This patient persistently had a serum sodium level that ranged from 125 to 130 meq./l.

Serum Chloride—All patients tended to have serum chloride levels that were at the lower limits of normal. Four had mild hypochloremia in the range of 90–97 meq./l. The one patient with low levels of serum sodium also had slightly reduced levels of serum chloride; the values usually varied from 82 to 91 meq./l. No one medication consistently produced hypochloremia.

Plasma CO_2-Combining Power—Compared to that of patients taking methyclothiazide alone, CO_2-combining power was generally elevated a slight amount. In 60 of 144 determinations of CO_2-combining power, the values were elevated slightly above the normal range. The two highest levels were 37 and 36 meq./l. All medications produced mild elevation with equal frequency.

Serum Uric Acid—The serum uric acid levels increased during treatment in nine of the 18 patients, as compared with uric acid levels obtained when the patient was taking methyclothiazide alone (Fig. 2). Only three female patients and no male patient had mild elevations of the serum uric acid level while taking methyclothiazide alone. Six women and three men had mild hyperuricemia during combination treatment. The elevation in uric acid levels occurred with equal frequency with all three drugs given. The highest level of uric acid found was 9.5 mg./100 ml. in a female. There was no incidence of gouty arthritis or renal calculus during the study.

Blood Urea—Mild elevation of blood urea levels occurred in seven patients. The highest value was 55 mg./100 ml. (normal 20–40 mg./100 ml.). The majority of values ranged from 41 to 46 mg./100 ml. All medications produced this degree of elevation with equal frequency.

Blood Sugar—Nine patients had mild hyperglycemia which was not increased by the medication and which occurred consistently with all medications in the same patient.

Other Blood Counts—No abnormalities or significant changes were found in hemoglobin concentration, leukocyte counts, or differential blood cell counts when values before and after treatment were compared.

Side Effects—Two patients were unable to complete the study because of side effects. One of these patients had moderately severe nausea while taking methyclothiazide and cryptenamine. The nausea subsided after the use of the medication was discontinued and recurred when the dosage was resumed. The other patient had an agitated depression while taking this same combination of medication. The symptoms subsided within 10 days after the medication was discontinued and during the coincident administration of amytriptyline[1]. None of the other side effects was severe enough to preclude taking the drugs four times each day. A summary of side effects is listed in Table I. Three patients had no side effects during the entire study. Some of the more nonspecific complaints which could be associated with minor coincidental acute infections were not included as side effects.

The major side effects were weakness, fatigue, nausea or anorexia, and lightheadedness. Weakness and fatigue were complaints of equal frequency with any combination containing cryptenamine or reserpine or both and may well have been dose related inasmuch as these compounds were taken four times daily. Lightheadedness and nausea or anorexia occurred equally with all medications. These symptoms generally subsided in 2–3 weeks and would seem to be

[1] Elavil.

Table I—Side Effects in Drug Administration for Essential Hypertension

Side Effect	Placebo	Methyclothiazide	Methyclothiazide and Cryptenamine	Methyclothiazide and Reserpine	Methyclothiazide, Reserpine, and Cryptenamine
Lightheadedness	1	2	2	0	2
Nausea or anorexia	0	2	3	2	1
Weakness and fatigue	1	0	3	3	3
Nasal congestion	0	0	0	1	2
Thirst	0	1	0	0	0
Bloated	1	0	0	1	1
Total	3	5	8	7	9

related to the diuretic effect of methyclothiazide after the placebo period. These patients had a weight reduction of 1.49–2.98 kg. (4–8 lb.), and the symptoms may have been caused by a sudden decrease in plasma volume. Nasal congestion was experienced by three patients while receiving medication containing reserpine. No patients complained of diarrhea, palpitations, or blurred vision. In patients who were free of side effects, the medications containing reserpine or reserpine and cryptenamine in combination were considered to be the most satisfactory antihypertensive medications.

COMMENT

The pharmacodynamics of the hypotensive action of veratrum or of its active ester alkaloids have been considered by many investigators to constitute an ideal mechanism because blood pressure is lowered by dilatation of the arterioles without concomitant peripheral adrenergic or ganglionic blockade. Furthermore, the functioning of the autonomic nervous system remains unimpaired, even though the means by which the arterioles are dilated is essentially neurogenic. Thus, there is little likelihood of peripheral pooling of the blood (and orthostatic hypotension), and all or most of the normal vascular pathways remain intact. The basic mechanism by which the veratrum alkaloids produce their hypotensive responses was long believed to be primarily reflex in nature, whereby the reflex actions were initiated by stimulation of afferent fibers which run in the vagi aortic nerves (von Bezold-Jeriah) reflex. Although this mechanism undoubtedly has a role, several studies showed that the primary mechanisms of action are related to more direct central effects of these alkaloids, such as stimulation of the carotid sinus receptors, depression of the central vasomotor mechanism, or both of these mechanisms (1–3). More recently, studies by Jandhyala and Buckley (4) demonstrated that cryptenamine significantly decreased the epinephrine content of adrenal venous blood while increasing the norepinephrine content, thus suggesting that the drug may inhibit the methylation of norepinephrine in the adrenal medulla.

The data from the present study are interpreted as showing that in a wide range of patients with Group 1 or 2 essential hypertension, cryptenamine in combination with methyclothiazide was significantly effective in lowering blood pressure. Only a minimal additive hypotensive effect was obtained by adding cryptenamine to the reserpine–methyclothiazide combination. However, the dose of cryptenamine used was reduced to 1 mg. when given with reserpine. If the dose had been maintained at 2 mg., perhaps a more significant response would have been obtained. Although the drugs were administered four times each day in this study, a significant number of patients with essential hypertension of Grade 1 or 2 could be controlled by a twice daily dose. It would seem justifiable to make two similar trials of cryptenamine in patients with moderate hypertension, one utilizing a higher dose in combination with methyclothiazide (or ideally a potassium-sparing diuretic), given two to four times a day, and another utilizing a higher dose in combination with 0.1 mg. of reserpine and methyclothiazide (or a potassium-sparing diuretic), given two or four times a day. The optimal well-tolerated oral dose of cryptenamine should be determined. A better decision could then be made regarding the usefulness of the three drugs (methyclothiazide, cryptenamine, and reserpine) in combination.

The response of patients to methyclothiazide alone was similar to that previously reported by Spiekerman *et al.* (5). The changes in serum electrolyte levels were comparable to those reported previously with the administration of thiazide diuretics. In the present study, half of the patients required the supplemental use of oral potassium. Elevations of serum uric acid occurred in 50% of the patients (9 of 18) who were taking methyclothiazide with cryptenamine or reserpine, as compared to those taking methyclothiazide alone. The specific mechanism by which uric acid levels were increased is not known. However, it may be that cryptenamine and reserpine interfere with the reabsorption of filtered urate in the tubules or with the active secretion of urate in a manner such as that postulated for other drugs including the thiazide diuretics or pyrazinoid acid amide. Symptomatic gout did not develop in any of the patients who had hyperuricemia. Other small electrolyte changes noted were mild elevations of CO_2-combining power (60 of 144 determinations).

The medications generally were tolerated well. The two patients who stopped taking the combination of methyclothiazide and cryptenamine had a definite abrupt onset of symptoms (nausea and depression) which subsided when the use of the medication was withdrawn. These were the only serious side effects noted in the study and seemed to be drug related rather than dose related.

REFERENCES

(1) A. P. Richardson, H. A. Walker, C. B. Farrar, W. Griffith, E. Pound, and J. R. Davidson, *Proc. Soc. Exp. Biol. Med.*, **79,** 79 (1952).

(2) S. C. Wang, S. H. Ngai, and R. G. Grossman, *J. Pharmacol. Exp. Ther.*, **110,** 51(1954).

(3) L. Martini and L. Calliauw, *Arch. Int. Pharmacodyn. Ther.*, **101,** 49(1955).

(4) M. L. Jandhyala and J. P. Buckley, *J. Pharm. Sci.*, **57,** 1576 (1968).

(5) R. E. Spiekerman, R. W. P. Achor, K. G. Berge, and W. F. McGuckin, *J. Amer. Med. Ass.*, **184,** 191(1963).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 24, 1970, from the **Department of Internal Medicine* and the †*Section of Medical Statistics, Mayo Clinic and Mayo Foundation, Rochester, MN 55901*

Accepted for publication March 23, 1971.