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Clonidine in the management of mild hypertension in twenty-two patients

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CLONIDINE* (ST-155) is an imidazoline derivative [2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride] which has been reported to have depressor action in animals[1-4] and in man.[5-7] Its hypotensive effect is mediated by central suppression of the sympathetic nervous system.[1-4] Davidov, Kakaviatos, and Finnerty[5] reported that oral administration of clonidine produced a slight increase in cardiac output and a decrease in peripheral resistance in six hypertensive patients; whereas, Onesti and associates[7] found that clonidine given orally resulted in a consistent reduction in cardiac output with no change in peripheral resistance in seven hypertensive patients. Kroetz and colleagues[8] reported that intravenous administration of clonidine produced a decrease in cardiac output with no change in peripheral resistance in six hypertensive patients.

This report presents an analysis of a program of therapy consisting of the oral administration of clonidine to 22 mildly hypertensive patients for periods of from 2 to 26 months.

Selection of patients and design of study

Patients with mild hypertension were selected for this study on the basis of their willingness to cooperate. Many of the patients had participated in previous drug studies and had proved to be reliable with regard to the taking of medication and the keeping of appointments. Patients with severe hypertension or those with impending complications were not included in this study.

There were 9 men and 13 women—5 Caucasian and 17 Negro. The ages of the patients ranged from 38 years to more than 70 years (*Table 1*).

All the patients underwent extensive diagnostic evaluation and it was concluded that 21 had essential hypertension and one patient had hypertension secondary to chronic glomerulonephritis, although her renal function was normal. The duration of hypertension ranged from 1 year to 29 years or an average of 11 years. Seven patients had hypertension for less than five years, while nine had hypertension for more than 10 years.

All patients had mild hypertension (*Table 2*). None of the patients had diastolic blood pressures higher than 120 mm Hg in the supine position,

* *Supplied as Catapres in 0.075-mg and 0.3-mg tablets through the courtesy of Paul Kennedy, Jr., M.D., of Geigy Pharmaceuticals, Ardsley, New York.*

Table 1.—*Age ranges of 22 patients who received clonidine for mild hypertension*

Age range, years	Patients, number
38–50	10
51–70	11
>70	1
(Average, 55 yr)	Total 22

Table 2.—*Severity of hypertension of 22 patients before therapy with clonidine*

Supine diastolic blood pressure* before treatment, mm Hg	Number of patients				
	Keith-Wagener-Barker group				
	1	2	2+	Not done†	Total
90–100	1	6	0	1	8
101–110	2	6	1	1	10
111–120	1	3	0	0	4
Total	4	15	1	2	22

* Seven patients recorded blood pressures at home; 15 patients received placebos.

† Fundus examination was not done because of cataracts.

and none had retinopathy of group 3 or group 4 (Keith-Wagener-Barker criteria). Of the eight patients who had supine diastolic blood pressures between 90 and 100 mm Hg, all had either systolic blood pressures higher than 160 mm Hg in the supine position or diastolic blood pressures higher than 100 mm Hg in the erect position, or both.

Of the 22 patients, seven had no cardiovascular or renal complications from the hypertension (*Table 3*). Fifteen patients had evidence of cardiovascular complications, four of whom also had evidence of renal complications (*Table 3*). Abnormalities in the electrocardiogram included nonspecific ST-T changes, left ventricular hypertrophy and/or strain, evidence of previous myocardial infarction or left bundle branch block.

For all 22 patients, therapy was started with clonidine as the sole agent, usually with a dosage of 0.075 mg, four times daily (*Tables 4 and 5*). Seven patients received clonidine only for periods of from 2 to 19 months (*Table 4*). For 15 patients a diuretic was added to the regimen after they had been receiving clonidine for periods of from 2 weeks to 11 months. Combination

Table 3.—*Complications of hypertension in 22 patients* before treatment with clonidine*

Complications, type	Complications, number	Patients, number
None	0	7
Cardiovascular	24	15
Electrocardiographic abnormalities	12	
Arteriosclerotic heart disease	5	
Congestive heart failure	2	
Cardiomegaly	2	
Peripheral arteriosclerosis obliterans	2	
Remote cerebrovascular accident	1	
Renal	5	4
Proteinuria	4	
Azotemia	1	

* Five patients were diabetic.

Table 4.—*Duration of treatment with clonidine of 22 patients with mild hypertension*

Regimen	Patients, number: Duration of therapy, months <6	6–12	>12	Duration of therapy, months: Range	Average
Clonidine only	3	2	2	2–19	8
Combined:					
First clonidine only	9	6	0	½–11	5
Then, clonidine plus diuretic	6	7	2	1–25	8

therapy with clonidine and a diuretic was continued for from one month to 25 months (*Table 4*). For seven patients therapy with the diuretic was continued after therapy with clonidine had been stopped. The average dose of clonidine when used as the sole agent throughout the study was 0.6 mg daily, while the average dose when used with a diuretic was 1.2 mg daily (*Table 5*). Except for minor adjustments in two cases, the dosages of clonidine were not changed after the diuretic was added to the regimen. The maximal daily dose of clonidine was 2.4 mg. The oral diuretics added to the regimen included in 12 cases, chlorthalidone (Hygroton), and in one case each chlorothiazide (Diuril), hydrochlorothiazide (Hydrodiuril), and methychlothiazide (Enduron).

Seven patients took their blood pressures at home, and for all of them the

Table 5.—*Dosages of clonidine given to 22 patients with mild hypertension*

Regimen	Patients, number: Maximal daily dose, mg <0.5	0.5–1.0	>1.0	Daily dose, mg: Range	Average
Clonidine only	4	1	2	0.3–1.2	0.63
Combined:					
Clonidine	0	5	10	0.6–2.4	1.2
Plus diuretic	1	3	11	0.4–2.4	1.2

Table 6.—*Hypotensive effect of clonidine as sole agent given to 22 patients with mild hypertension*

Position	Average blood pressure, mm Hg: Control	Last month of therapy	Reduction in mean blood pressure,* %
Supine	180/105	172/101	4
Standing	180/112	160/101	10

* Mean blood pressure = diastolic pressure + ⅓ pulse pressure.

Table 7.—*Hypotensive effect of clonidine as sole agent given to 22 patients with mild hypertension*

Position	Number of patients: Reduction in mean blood pressure,* % <5	5–15	>15	Blood pressure, <150/100 mm Hg on treatment
Supine	10	11	1	2
Standing	6	9	7	4

* Mean blood pressure = diastolic pressure + ⅓ pulse pressure.

blood pressures taken in the supine and standing positions were averaged separately for at least two weeks immediately before therapy was started. In some cases the control period was as long as six weeks before therapy was started. When the control period exceeded four weeks, only the blood pressures taken in the four weeks immediately preceding initiation of therapy were averaged to determine the pretreatment level of blood pressure. The effect of the drug was judged by comparing the average blood pressure obtained during the last month of therapy with the pretreatment average.

Fifteen patients received placebos during the pretreatment period, and blood pressures obtained during the period of placebo administration were used as the control pressures.

For the 15 patients who had blood pressures recorded only at the Cleveland Clinic, the last four readings before initiation of therapy were averaged and compared with the average of the last four readings during any treatment period. Since most of the patients came in once weekly to have their blood pressure checked, this amounted to a four-week control period compared to a four-week treatment period. For patients who came in every two weeks the control period was eight weeks and the treatment period was eight weeks.

Results

Clonidine as sole agent. When used as the sole antipressor agent, clonidine had only a modestly hypotensive effect which was more pronounced in the erect position than in the supine position (*Table 6*). The average reductions in mean blood pressure for all 22 patients while receiving clonidine only was 4 percent in the supine position and 10 percent in the erect position. Despite the greater effect of clonidine on erect blood pressure, it did not induce orthostatic hypotension. Ten of the patients experienced less than 5 percent reduction in supine mean blood pressure as a result of therapy with clonidine as the sole agent, while only one patient had a reduction of more than 15 percent in supine mean blood pressure (*Table 7*). Of 22 patients only two had normal supine blood pressure (<150/100 mm Hg) while on therapy with clonidine alone. Six of the patients had less than a 5 percent reduction in standing mean blood pressure while therapy consisted of clonidine only, while seven patients had a reduction in standing mean blood pressure of more than 15 percent (*Table 7*). Of the 22 patients, four had normal blood pressure (<150/100 mm Hg) in the standing position, while receiving clonidine as the sole therapeutic agent.

Clonidine and an oral diuretic. Observations were made of the effect on blood pressure of adding an oral diuretic to the regimens of 15 patients who

Table 8.—*Hypotensive effect of clonidine and oral diuretic given to 15 patients with mild hypertension*

	Average blood pressure, mm Hg			Reduction in mean blood pressure* on treatment, %	
		Treatment			
Position	Control	Clonidine	Combined	Clonidine	Combined
Supine	181/105	176/102	151/89	2	15
Standing	184/113	163/101	140/91	11	22

* Mean blood pressure = diastolic pressure + ⅓ pulse pressure.

Table 9.—*Hypotensive effect of clonidine and oral diuretic given to 15 patients with mild hypertension*

Position	Treatment	Number of patients			
		Reduction in mean blood pressure,* %			Blood pressure, <150/100 mm Hg on treatment
		<5	5–15	>15	
Supine	Clonidine	8	7	0	0
	Combined	1	9	5	8
Standing	Clonidine	4	5	6	1
	Combined	0	2	13	10

* Mean blood pressure = diastolic pressure + ⅓ pulse pressure.

Table 10.—*Hypotensive effects of clonidine and diuretic given to 7 patients*

Position	Control blood pressure, mm Hg	Treatment					
		Clonidine		Clonidine and diuretic		Diuretic	
		Blood pressure, mm Hg	Reduction in mean blood pressure,* %	Blood pressure, mm Hg	Reduction in mean blood pressure,* %	Blood pressure, mm Hg	Reduction in mean blood pressure,* %
Supine	175/103	173/103	1	140/85	19	154/93	11
Standing	184/115	164/103	11	134/88	25	156/102	13

* Mean blood pressure = diastolic pressure + ⅓ pulse pressure.

had been receiving clonidine alone for periods of from 2 weeks to 11 months (*Tables 8 and 9*). The average reduction in supine mean blood pressure was 2 percent while clonidine was the sole therapeutic agent, and 15 percent after the addition of a diuretic (*Table 8*). Clonidine alone produced an average reduction in standing mean blood pressure of 11 percent, and after the addition of a diuretic the average reduction in standing mean blood pressure was 22 percent.

Combination therapy with clonidine and a diuretic produced more than a 15 percent reduction in supine mean blood pressure for five patients; and eight patients had normal blood pressure (<150/100 mm Hg) in the supine position (*Table 9*). Combination therapy produced a reduction of more than 15 percent in mean blood pressure in the standing position for 13 patients. Despite the fact that the combined regimen had a greater effect on standing blood pressure than on supine blood pressure, orthostatic hypotension did not occur in any case.

For seven patients who had been on combination therapy, clonidine was

discontinued while therapy with the oral diuretic agent was continued (*Table 10*). For those seven patients, clonidine alone had almost no effect on the supine blood pressure; whereas the combination regimen of clonidine and a diuretic produced an average reduction of 19 percent in mean blood pressure in the supine position. After therapy with clonidine was stopped, the oral diuretic alone produced an average reduction of 11 percent in mean blood pressure in the supine position for the seven patients.

Clonidine alone produced an average reduction in mean blood pressure of 11 percent for those seven patients in the erect position; whereas the combination regimen of clonidine and a diuretic produced an average reduction of 25 percent in mean blood pressure in the erect position. After therapy with clonidine was discontinued, the diuretic alone produced an average reduction in mean blood pressure of 13 percent. According to the data in *Table 10,* clonidine and an oral diuretic seemed to have additive effects on the standing blood pressure, but the combination of drugs seemed to have a synergistic effect on the supine blood pressure.

Effect of clonidine on pulse rate. The effect of clonidine on the pulse rates of 21 patients (in one patient pulse rates before and during therapy with clonidine were not measured) is shown in *Table 11.* There was a slight reduction, probably not significant, in average pulse rates both in the supine and standing positions. The pulse rates in the supine position actually increased for five patients while on therapy with clonidine, and decreased for 14 patients; there was no change for two patients. Pulse rates in the standing position increased for eight patients and decreased for 13 patients during therapy with clonidine.

Adverse effects. Of 22 patients, only six escaped adverse effects that possibly might be attributed to therapy with clonidine (*Table 12*). Fourteen patients noted drowsiness, and in five it was so severe that it limited the dosages that these patients could tolerate, and therefore prevented the administration of optimal doses of clonidine. Dryness of the mouth was mentioned by nine patients. For some patients the drowsiness and the dryness

Table 11.—*Effect of clonidine on pulse rates of 21 patients* with mild hypertension*

Position	Average pulse rate		Percentage change, %
	Control	During treatment	
Supine	76	73	−4
Standing	82	78	−5

* One patient did not have pulse rates recorded during therapy.

of the mouth persisted throughout the period of therapy; whereas in others it was temporary and tended to decrease in severity or disappear entirely despite continued therapy.

Increases in serum content of creatine phosphokinase were observed on at least one occasion during the period of therapy with clonidine for each of seven patients. The increases were usually temporary, as subsequent values were normal despite the continuation of therapy. The significance of the increase is not known, but it did not appear to be a serious problem.

In two patients there was objective evidence of fluid retention manifested by weight gain. One patient gained 12 pounds and went into mild congestive heart failure during the first 10 days after initiation of therapy with clonidine. This patient had hypertensive heart disease and had had an episode of congestive heart failure. One patient became depressed while taking clonidine, but it is doubtful that the drug was responsible for depression even though therapy was then discontinued. This patient had been depressed before and has been depressed since she took clonidine, and I am reluctant to attribute this episode to therapy with clonidine. In one patient toxic hepatitis developed, proved by biopsy, after she had received clonidine for 14 months. Elevated values for serum alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic-oxalacetic transaminase, and sulfobromophthalein retention, returned to normal within three months after therapy was discontinued. Serum bilirubin concentration was not increased. Without rechallenging the patient with clonidine, the role

Table 12.—*Adverse effects of therapy with clonidine given to 22 patients with mild hypertension*

Adverse effect	Patients, number
None	6
Drowsiness	14*
Dry mouth	9
Increase in serum creatine phosphokinase content	7
Constipation	3
Nausea	3
Nasal congestion	3
Unpleasant taste	3
Fluid retention	2
Agitation and insomnia†	2
Depression (incapacitating)	1
Toxic hepatitis	1

* Incapacitating in five patients.
† After abrupt cessation of therapy.

of the drug in the production of hepatitis remains uncertain, but no other cause was apparent.

Two patients became agitated and had intractable insomnia when therapy with clonidine was discontinued abruptly. One patient had received clonidine for 12-½ months and was taking 0.3 mg daily when therapy was stopped. The other patient had received clonidine for 28 months and was taking 0.3 mg daily at the time of cessation of therapy. For each patient withdrawal symptoms subsided within 24 hours after therapy with clonidine was resumed in a reduced dosage.

Comment

In this group of 22 patients with mild hypertension, therapy with clonidine as the sole agent produced only a slight reduction in blood pressure in the supine position. The depressor effect of the drug was greater in the standing position, but it did not cause orthostatic hypotension. These findings substantiate those of Davidov, Kakaviatos, and Finnerty[5] and of Onesti and colleagues,[7] although the former group reported an average reduction of 23 percent in mean blood pressure in the seated position when clonidine was administered as the sole agent to 25 hypertensive patients. Davidov, Kakaviatos, and Finnerty[5] reported tolerance to the antihypertensive effect of clonidine when given as the sole agent, while neither Onesti and colleagues[7] nor I encountered this phenomenon. Davidov and colleagues[5] attributed the development of tolerance to sodium retention induced by therapy with clonidine, because the addition of a diuretic to the regimen promptly induced weight loss and restored the hypotensive effect of clonidine.

The addition of a diuretic to the regimens of 15 patients of my series who were already receiving clonidine had an appreciable depressor effect, rendering eight of them normotensive in the supine position, and 10 normotensive in the erect position. Onesti and colleagues[7] also reported that combination therapy with clonidine and a diuretic was much more effective than therapy with clonidine alone.

Drowsiness and dryness of the mouth have also been the most frequently encountered adverse effects of therapy with clonidine in the previously reported studies.[5, 7]

To my knowledge, hepatotoxicity from therapy with clonidine has not been reported previously, and the role of this drug in the toxic hepatitis encountered in one patient in my series remains questionable. A withdrawal syndrome characterized by agitation and insomnia was experienced by two patients who stopped taking clonidine abruptly. A similar syndrome was described by Batterman.[9]

It is my impression from my previous similar studies that clonidine in the dosages used in my investigation reported here was not so effective as a

hypotensive agent as were reserpine, whole-root Rauwolfia, methyldopa, or a variety of oral diuretics when used as sole agents. However the hypotensive effect of combination therapy with clonidine and a diuretic is comparable to the combined effect of Rauwolfia compounds and a diuretic, or hydralazine and a diuretic, but is not so great as that observed from combination therapy with methyldopa and a diuretic.

Summary

In a study of 22 mildly hypertensive patients, clonidine in dosages of from 0.3 to 2.4 mg daily had little depressor effect on supine blood pressure (average reduction of 4 percent in mean blood pressure). The hypotensive effect of clonidine was somewhat greater on erect blood pressure, producing an average reduction of 10 percent in mean blood pressure for 22 patients. The addition of an oral diuretic to the regimens of 15 patients rendered 8 of them normotensive in the supine position and 10 of them normotensive in the standing position. An average reduction of 15 percent in mean blood pressure occurred during combined therapy in the supine position, and of 22 percent in the standing position. The most troublesome adverse effects were drowsiness, and dryness of the mouth.

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