Antihypertensive Effect of Clonidine

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ABSTRACT
Clonidine hydrochloride is a sympathetic inhibitor with central site of action. The antihypertensive effect in man in the supine position is associated with a decrease in cardiac output and no consistent changes in total peripheral resistance. In the standing position, however, in addition to the decrease in cardiac output, a fall in total peripheral resistance becomes evident. The fall in blood pressure results in no significant alteration in renal blood flow or glomerular filtration rate in the supine position. In the standing position a consistent decrease in renal vascular resistance is seen.

In the anesthetized dog the intravenous administration of clonidine produces a significant reduction of renal vein plasma renin activity. Similarly, in patients with essential hypertension oral administration of the drug results in a decrease in peripheral plasma renin activity.

In ambulatory essential hypertensive patients treated with clonidine alone in doses of 400 to 900 μg per day, a modest antihypertensive effect is achieved. When clonidine is used with a diuretic, antihypertensive efficacy is achieved in 80% of the patients treated. In higher doses (up to 3,600 μg per day) and in combination with a diuretic, the antihypertensive effect appears to be superior to that of many of the standard agents. Drowsiness and dryness of the mouth are the most frequent and serious side effects with the higher doses.

KEY WORDS
hypertension clonidine sympathetic nervous system cardiac output renal blood flow renin
phentolamine abolished the early hypertensive response. It was therefore concluded that the initial vasopressor effect of clonidine was due to a direct stimulation of alpha-adrenergic receptors and was not related to the release of catecholamines.

The prolonged antihypertensive effect of clonidine has attracted the greatest attention in view of the possible therapeutic applications. Kobinger and Hoefke demonstrated that the prolonged vasodepressor effect of clonidine was prevented by pretreatment with reserpine or phenoxybenzamine. In addition, no vasodepressor effect was produced with clonidine administration to the spinal animal. Furthermore, experiments with electrical stimulation of sympathetic nerves excluded the possibility of clonidine blockade of the peripheral sympathetic nervous system. These observations suggested that the hypotensive effect was related to sympathetic inhibition but that the site of action was in the central nervous system. The hypothesis of a direct inhibition of the vasomotor centers was tested by Kobinger with injection of the drug into the cisterna magna of the anesthetized dog. The small dose of 1 μg/kg of clonidine injected into the cisterna magna resulted in a significant decrease in blood pressure and bradycardia. This effect on blood pressure and heart rate was similar to that observed with the systemic administration of 30 μg/kg clonidine. With the intracisternal administration, however, no pressor effect was seen. It was therefore concluded that the antihypertensive and bradycrotic effects of clonidine were due to a direct action on the vasomotor and cardiac centers. The studies of Sattler and Van Zwieten, Sherman and coworkers, and Schmitt and coworkers support these conclusions.

In summary, pharmacological studies imply that intravenous clonidine has a brief, direct, alpha-adrenergic stimulating effect followed by a prolonged suppression of the central nervous system's sympathetic centers. Only the latter effect is seen on oral administration of the drug.

**Cardiac Effects**

In 1966 Hoefke and Kobinger demonstrated that the initial, transient hypertensive effect of intravenous clonidine in the anesthetized dog was associated with a decrease in cardiac output, decrease in heart rate, and increase in total peripheral resistance. The subsequent prolonged fall in blood pressure was associated with a decrease in cardiac output and bradycardia, while the total peripheral resistance returned to control levels.

In 1967 Kobinger and Walland injected clonidine into the cisterna magna and demonstrated that the hypotensive effect was again accompanied by a decrease in cardiac output and a decrease in heart rate. There were no changes in total peripheral resistance. The decrease in cardiac output was secondary to the decrease in heart rate with no change in stroke volume.

Studies in hypertensive patients by Grabner and coworkers showed that acute administration of intravenous clonidine resulted in a fall in blood pressure associated with a decrease in cardiac output. There were no changes in total peripheral resistance, and the stroke volume remained unchanged. Calculated cardiac work was reduced proportionally more than was mean arterial pressure. Schneider and Gattenlohner also studied the cardiac effect of oral clonidine in hypertensive patients. Four hours after drug administration there was a fall in blood pressure, a fall in cardiac output, and a modest decrease in total peripheral resistance. The fall in cardiac output was due to a decrease in both heart

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rate and stroke volume. Circulation time was prolonged. Vorburger and coworkers\(^1\) investigated the acute effects of intravenous clonidine in hypertensive patients. As previously seen in the animal studies\(^1\),\(^5\),\(^6\) intravenous clonidine produced a brief hypertensive response in these patients; a long-lasting decrease in blood pressure followed. During the hypotensive response there was a decrease in cardiac output while the total peripheral resistance did not change. Heart rate decreased by 5 to 7% and stroke volume by 8 to 10%. Similarly, Michel and coworkers\(^14\) reported a decrease in blood pressure associated

Acute effects of clonidine in seven patients with essential hypertension in the supine position. The ordinate represents percentages, with the control being 100%. The numbers in parentheses represent changes (i.e., increase or decrease) from control. MAP = mean arterial pressure; CO = cardiac output; HR = heart rate; SV = stroke volume; TPR = total peripheral resistance; NS = not statistically significant.

Acute effects of clonidine in seven patients with essential hypertension in erect position (45° tilt). See legend in Figure 3.
with a decrease in cardiac output, stroke volume, and heart rate in hypertensive patients. The calculated total peripheral resistance was actually increased.

In the above experiments the patients were studied at rest in the supine position. Studies of the acute cardiac effect of oral clonidine (300 to 750 µg) in the supine and upright positions were conducted in our laboratory in patients with essential hypertension. In addition, the cardiac effects of passive head-up tilting were studied before and after drug administration. After oral clonidine the onset of antihypertensive effect was noted as early as 30 minutes. Significant blood pressure reduction occurred between one and four hours, with the peak effect occurring at two to four hours. Duration of the effect lasted from six to ten hours.

Figure 2 shows the cardiac effects in the supine position. Clonidine produced a consistent decrease in mean arterial pressure with an average reduction of 17% (P < 0.01). Cardiac output decreased in every case with an average reduction of 21% (P < 0.01). Both a decrease in heart rate (10%) and a decrease in stroke volume (15%) contributed to the reduction in cardiac output. There were no consistent changes in total peripheral resistance.

Figure 3 shows the cardiac effect in the upright position (45° tilt). The reduction in mean arterial pressure (33%, P < 0.01) was greater than that in the supine position. The reduction in cardiac output was 15% (P < 0.05). The heart rate decreased by 14% (P < 0.05) with no consistent change in stroke volume. In contrast to the supine response, there was a consistent and significant reduction in the total peripheral resistance, with an average decrease of 21% (P < 0.02). The upper portion of Figure 4 depicts the cardiac effects of control head-up tilting, i.e., before the administration of clonidine. Passive 45° head-up tilting resulted in a 24% decrease in cardiac output, 28% decrease in stroke volume, and a 6% increase in heart rate. There was a 27% increase in total peripheral resistance. This compensatory increase in peripheral resistance mediated by the sympathetic nervous system maintained the mean arterial pressure unchanged in the 45° tilted position. This is the physiological response to upright tilting. The cardiac changes with tilting during the period of maximum clonidine effect are reported in the lower portion of Figure 4. Passive 45° head-up tilting again resulted in the normal decrease in cardiac output (22%) and stroke volume (20%) and a modest increase in heart rate (5%). In contrast to the control studies no significant increase in total peripheral resistance occurred. This failure of compensatory arteriolar constriction produced a 21% orthostatic decrease in mean arterial pressure.

The effects of chronic clonidine therapy (several weeks) on cardiac output were studied by Schneider in 36 hypertensive patients. The decrease in blood pressure was less marked than in acute studies. After an initial antihypertensive response there was a tendency of the blood pressure to return toward control values. After several weeks of therapy, there was an 11% decrease in total peripheral resistance. It is apparent, however, that the over-all hemodynamic changes were too small to allow definite conclusions. In the same study normal subjects performed ergometer exercise before and two hours after clonidine administration. Exercise heart rate...
HYPERTENSION XIX—SALT, HORMONES, AND HYPERTENSION

Acute renal hemodynamic effects of clonidine in seven patients with essential hypertension in supine position. MAP = mean arterial pressure; RBF = renal blood flow; GFR = glomerular filtration rate; RVR = renal vascular resistance; NS = not statistically significant.

Renal Effects in Man

The acute renal effects of oral clonidine were studied in our laboratory in seven patients with essential hypertension. Renal blood flow was estimated by the clearance of para-aminomhippurate and the hematocrit. Glomerular filtration rate was measured by inulin clearance. Figure 5 shows the acute renal hemodynamic effects of oral clonidine in seven hypertensive patients in the supine position. The blood pressure reduction (17%, P < 0.01) was not associated with any significant alteration in renal blood flow or glomerular filtration rate. Sodium and chloride...
Renal hemodynamic effects of passive head-up tilting (45°) before and after administration of clonidine. MAP = mean arterial pressure; RBF = renal blood flow; GFR = glomerular filtration rate; RVR = renal vascular resistance; S = supine; T = tilted.

excretion decreased markedly, while excretion of potassium did not change.

Figure 6 shows the acute renal hemodynamic effects of oral clonidine with the patients in the erect position (45° tilt). Despite the substantial blood pressure reduction (33%, P < 0.001) in the erect position, there was no significant change in renal blood flow or glomerular filtration rate. The renal vascular resistance decreased in every case with an average reduction of 30% (P < 0.01). During the hypotensive response excretion of sodium and chloride decreased markedly, while there were no changes in excretion of potassium.

Figure 7 depicts the renal hemodynamic effects of tilting before the administration of clonidine (control study). Passive head-up tilting resulted in no changes in renal arterial pressure, a 16% reduction in renal blood flow, and a 15% reduction in glomerular filtration rate. Renal vascular resistance increased with tilting. After clonidine administration (Fig. 7, lower panel) head-up tilting resulted in a 21% orthostatic decrease in blood pressure. Despite the orthostatic blood pressure reduction the decrease in renal blood flow and glomerular filtration rate with tilting was the same as that of the control study. In contrast to the control period, tilting during clonidine effect resulted in a decrease in renal vascular resistance.

The effects of the prolonged administration of clonidine on renal hemodynamics of seven hypertensive patients were studied by Bock and coworkers. Administration of oral clonidine for periods from 11 to 110 days produced no significant change in renal plasma flow or glomerular filtration rate. The blood pressure
Effect of intravenous clonidine (30 μg/kg) on mean arterial pressure renal hemodynamics and renal vein plasma renin activity in 12 anesthetized dogs. All changes are expressed in percentage of control. The +10 on the ordinate represents an increase of 10% above control (100%). The numbers in parentheses represent the actual mean values of the respective parameters. The units for each parameter are listed in parentheses on the left of the figure. After control each parameter was determined at 10, 45, and 85 minutes after drug administration. GFR = glomerular filtration rate; TRBF = total renal blood flow; TRVR = total renal vascular resistance; U Na = urinary sodium excretion.

was significantly reduced in every case. Ludwig\(^\text{18}\) reported that in hypertensive patients the glomerular filtration rate was slightly decreased after one week of clonidine therapy but returned to the control levels after four weeks. A modest increase in renal plasma flow occurred while the blood pressure was consistently reduced. This again implies a reduction in renal vascular resistance.

Grabner\(^\text{11}\) also described minor and inconsistent effects on the clearance of para-aminobiphenyl and inulin in hypertensive patients administered a single dose of clonidine.

**Acute Effect on Renal Hemodynamics and Renin Release in Anesthetized Dogs**

The release of renin by the juxtaglomerular apparatus is regulated by several factors, including renal perfusion pressure, sympathet-
Representative experiment illustrating the effect of intracisternal injection of clonidine (1 μg/kg) on the blood pressure, renal hemodynamics, and renal vein plasma renin activity. After control each parameter was determined at 10, 45, and 85 minutes after drug administration. See legend in Figure 9.

In order to elucidate the action of clonidine on renin release, 12 anesthetized dogs (thiopental) were studied in our laboratory. Intraarterial pressure and heart rate were continuously monitored. The following parameters were determined: total renal blood flow (by para-aminohippurate clearance and extraction), glomerular filtration rate (by clearance of exogenous creatinine), sodium excretion, and renal vein plasma renin activity (method of Boucher). After control determinations these measurements were repeated 10, 45, and 85 minutes after intravenous clonidine. Figure 8 shows the effect of 30 μg/kg intravenous...
clonidine on renal vein plasma renin activity. A dramatic reduction occurred in every case ten minutes after clonidine administration with an average decrease of 48% (P < 0.02). Forty-five and 85 minutes after drug administration renin suppression persisted with an average reduction of 46% and 50% of control, respectively (P < 0.02). In Figure 9 the effects on renin are reported together with the effects on blood pressure, glomerular filtration rate, total renal blood flow, total renal vascular resistance, and sodium excretion. The mean arterial pressure was essentially unchanged ten minutes after drug administra-
tion. Forty-five minutes after clonidine, however, there was a consistent decrease in mean arterial pressure with an average decrease of 28% (P < 0.005). Eighty-five minutes after drug administration the average decrease in blood pressure was 33% (P < 0.005). Changes in glomerular filtration rate were minor. Total renal blood flow showed a 29% decrease at ten minutes, a 19% decrease at 45 minutes, and an 11% decrease at 85 minutes. These changes, however, were not statistically significant. Total renal vascular resistance increased in every case ten minutes after drug administration with an average increase of 16% (P < 0.02). Forty-five minutes after drug administration renal vascular resistance returned toward the control level, and 85 minutes after drug administration the renal vascular resistance was consistently decreased, averaging 29% (P < 0.005). Urinary excretion
Representative experiment illustrating the effects of four days clonidine administration on peripheral plasma renin activity, blood pressure, urinary sodium excretion, and creatinine clearance in a patient with essential hypertension. renal vein plasma renin activity was markedly suppressed. The timing and the magnitude of renin suppression were similar to the results observed with the systemic injection of 30 mcg/kg of clonidine.

Effects on Peripheral Plasma Renin activity

Studies on the effect of clonidine on peripheral plasma renin activity were conducted in four patients with essential hypertension in our laboratory. After four days on a constant sodium intake (30 mEq Na/day), peripheral plasma renin activity was first determined by the method of Boucher after nine hours rest in the supine position. A second renin determination was done after 30 minutes at 60° passive upright tilting. After this control study 100 mcg of clonidine were administered orally four times a day for four days. Constant sodium intake was continued. After four days of clonidine administration, peripheral plasma renin activity was measured again both after nine hours rest in the supine position and after 30 minutes tilting. The effects of four days of clonidine administration are depicted in Figure 11. Peripheral plasma renin activity was decreased in every case, both in the supine and in the tilted positions. The blood pressure was lower after four days drug administration in all patients. In Figure 12 a representative case is shown. Administration of clonidine (400 mcg/kg) resulted in a decrease in blood pressure and peripheral plasma renin activity. Sodium excretion remained constant until the third day of drug administration. On the third and fourth days of drug administration, a modest natriuresis occurred.

Clinical Efficacy

Our evaluation of the antihypertensive efficacy of clonidine in the treatment of ambulatory patients with essential hypertension has proceeded in three phases. During the first phase (1968), a group of ambulatory patients was treated with clonidine in doses between 150 and 900 mcg/day. Clonidine was used as the sole antihypertensive agent. During the second phase of our investigation (1968), the efficacy of clonidine in combination with the diuretic, chlorthalidone, was studied. Again the maximum dose of clonidine used was 900 mcg/day. Following the reports of Heimsoth and Bock of excellent results with much higher doses, the third phase of our investigation was started in 1969, with doses of clonidine up to 3,600 mcg/day alone and in combination with chlorthalidone.

The first study (1968) included 16 ambulatory patients with resting blood pressure...
The patients returned to clinic at weekly or biweekly intervals, at which time resting cuff blood pressure was recorded supine and erect. After the control period administration of clonidine was begun in an initial dosage of 75 μg daily. Thereafter, the dosage was increased at biweekly intervals to a maximum of 900 μg/day. Therapy was continued for 12 to 25 weeks. The blood pressure response of these 16 patients treated with clonidine alone is reported in Table 1. Of the 16 patients treated, three obtained a significant blood pressure reduction* in the supine position, and one of the 16 became normotensive. When the blood pressure was measured standing, six patients obtained a significant antihypertensive response. Side effects included drowsiness (11 patients), dryness of the mouth (5), and constipation.

*Significant blood pressure reduction = decrease in mean arterial pressure (diastolic + 1/3 pulse pressure) of 20 mm Hg or the achievement of normotension.

†Normotensive = blood pressure of 140/90 or less.

The drowsiness improved in three patients and cleared entirely in two others.

The second investigation included 34 patients with resting blood pressure greater than 150/100 mm Hg who after at least four weeks of placebo were given chlorthalidone alone in a single dose of 100 mg/day. After treatment with chlorthalidone, 20 of the 34 patients continued to have blood pressure consistently greater than 150/100 mm Hg. These 20 patients continued to receive chlorthalidone (100 mg/day), and in addition, clonidine was added to the therapeutic regime. The initial dose was from 75 μg to 150 μg/day. Thereafter, the dose was increased until satisfactory control of the blood pressure was achieved, or side effects became prohibitive, or a maximum daily dose of 900 μg/day was reached. The combination therapy was continued for from 20 to 37 weeks. The blood pressure response of these 20 patients treated with chlorthalidone in combination with clonidine is reported in Table 1. Of the 20 patients treated, 16 (80%) obtained a significant blood pressure reduction* in the supine position, and one of the 16 became normoten-

*Normotensive = blood pressure reduced to 140/90 mm Hg or less.
†Responsive = mean blood pressure (diastolic + 1/3 pulse pressure) reduced 20 mm Hg or more or normotension.

**TABLE 1**

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<th>Therapeutic regimen</th>
<th>No. patients</th>
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<th>Responsive†</th>
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<td>1</td>
<td>6</td>
<td>19</td>
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<tr>
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*Normotensive = blood pressure reduced to 140/90 mm Hg or less.
†Responsive = mean blood pressure (diastolic + 1/3 pulse pressure) reduced 20 mm Hg or more or normotension.
When the blood pressure was measured in the erect position, 16 patients (80%) obtained a significant blood pressure reduction,* and 2 of the 16 (10%) became normotensive.† Drowsiness, dry mouth, and constipation were the most common side effects encountered.

The third investigation with higher doses of clonidine started in 1969. After at least four weeks of placebo therapy, 45 ambulatory patients with blood pressure greater than 150/100 mm Hg were given clonidine alone, starting with 600 μg/day. Thereafter, the dose was gradually increased until satisfactory blood pressure reduction was achieved or the side effects became prohibitive. Maximum dosage employed was 3,600 μg/day. Clonidine alone was continued for four to eight weeks. The patients who did become normotensive or who had severe side effects with clonidine alone were subsequently given the combination of chlorthalidone and clonidine. The doses of chlorthalidone varied from 60 to 120 mg/day, while the doses of clonidine ranged between 400 and 1,200 μg/day. At the time of this writing, 21 patients have remained on clonidine alone, and 21 have remained on the clonidine-chlorthalidone combination for a long enough period of time to justify some clinical conclusion. The blood pressure response of the 21 patients treated with clonidine alone is reported in Table 2. Of the 21 patients treated with clonidine alone, 12 (57%) obtained a significant blood pressure reduction,* and 5 of the 12 became normotensive in the supine position.† When the blood pressure was measured in the standing position, 11 patients (52%) achieved significant blood pressure reduction,* and 3 of the 11 became normotensive.† The side effects were drowsiness (33%) and dryness of the mouth (21%). The drowsiness cleared after two to four weeks therapy in 70% of the cases.

Discussion and Conclusions

PHARMACOLOGY

It is now well established that clonidine exerts a biphasic cardiovascular effect: an initial transient rise of the blood pressure is followed by a sustained fall. This response appears to be the same in different species.†, 2, 5, 6, 21-23 The brief vasopressor effect shows the following characteristics: (1) It is not prevented by pretreatment with reserpine,5-6 (2) it is abolished by pretreatment with phentolamine,5-6 (3) it is still elicited in the spinal animal,5-6 and (4) it is accompanied by bradycardia.5 In addition, clonidine has been found to cause direct constriction of the isolated rabbit aorta.24 It is concluded, therefore, that the hypertensive effect of clonidine is due to direct sympathomimetic constriction of peripheral arterioles. Contrary to the initial vasopressor effect of guanethidine and bretylium, clonidine does not act by a discharge of catecholamines from the nerve ending but probably by direct alpha-adrenergic receptor stimulation.5, 22

Hemodynamic studies in the experimental animal have shown that the hypertensive phase is characterized by a decrease in cardiac output, bradycardia, and an increase in total peripheral resistance.1, 5, 7

The long-lasting antihypertensive phase of clonidine shows the following characteristics: (1) It is inhibited by pretreatment with reserpine or phentolamine,5-6 (2) it is absent in the spinal animal,5-6 (3) it is elicited by injection of the drug into the cisterna magna,7 and (4) it is accompanied by bradycardia.5, 6

It is concluded, therefore, that the most likely site of action of clonidine is at the level of the medullary vasomotor and cardiac centers.7, 22 Although the experimental evidence supports this conclusion, the ability of the drug to gain access to the subarachnoid space from the circulation awaits final demonstration.

HEMODYNAMICS

Hemodynamic studies in the dog have

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shown that the decrease in blood pressure is associated with a decrease in cardiac output and no changes in total peripheral resistance. The decrease in cardiac output is due primarily to a decrease in heart rate with no change in stroke volume.

Hemodynamic studies with human subjects in the supine position have demonstrated a response similar to the one observed in dogs. The decrease in blood pressure is associated with a decrease in cardiac output and no effect on the total peripheral resistance. The cardiac output fall is due to a combination of decrease in rate and stroke volume.

In the upright position, however, human hemodynamic studies have demonstrated that in addition to the fall in cardiac output, there is a definite decrease in total peripheral resistance. The precise reason for this difference between supine and standing positions is not clear. It may be postulated that clonidine exerts a more potent inhibition of the sympathetic stimuli to the "resistance vessels" during sympathetic overactivity in the upright position. It should also be noted that the peripheral resistance ought to rise in response to drug-induced reduction in cardiac output. This expected compensatory increase in resistance appears to be blocked by clonidine. This last effect, together with the obvious effect on peripheral resistance in man in the standing position, demonstrates that the hypotensive effect of clonidine is a decrease in peripheral arteriolar tone.

The studies of the cardiac effects of passive head-up tilting in man demonstrate that clonidine administration blocks the compensatory peripheral arteriolar constriction normally occurring in the upright position. Peripheral arteriolar constriction in the upright position is mediated by the sympathetic nervous system. This effect of clonidine is therefore in keeping with sympathetic inhibition. Failure of the normal orthostatic reflexes during tilting have been reported with clonidine in the monkey and to a lesser extent in the dog. Failure of compensatory arteriolar constriction results in orthostatic hypotension and has been previously reported with alphamethyldopa and pargyline hydrochloride.

RENAL EFFECTS

The acute renal hemodynamic studies in the anesthetized dog demonstrate an initial increase in renal vascular resistance followed by a progressive return to the control levels and subsequently by an actual decrease. Acute renal hemodynamic studies in man show that renal blood flow and glomerular filtration rate are maintained during the hypotensive response to clonidine. Renal vascular resistance is decreased. Prolonged administration of oral clonidine results in similar preservation of renal plasma flow and glomerular filtration rate. This renal effect is similar to the one previously reported with alphamethyldopa.

The renal hemodynamic effects of tilting appear to be altered by clonidine: the normal increase in renal vascular resistance observed...
in the upright position in man is abolished. The decrease in mean arterial pressure, seen with tilting under the effect of clonidine, is associated with an actual decrease in renal vascular resistance. It would appear that clonidine preserves the autoregulation of the kidney circulation. The same effect has been reported with alpha-methyldopa.28 A marked retention of sodium and chloride follows the acute administration of clonidine in both the experimental animal and in man. The retention occurs with a glomerular filtration rate which is usually unchanged but may be increased or decreased.18 The most likely mechanism of sodium retention is that the decrease in renal perfusion pressure stimulates enhanced tubular reabsorption of sodium.30

With respect to renin release in the anesthetized dog, intravenous administration of clonidine resulted in a consistent decrease in renal vein plasma renin activity. Ten minutes after drug administration the mean arterial pressure had not changed significantly. Forty-five and 85 minutes after drug administration there was a significant decrease in mean arterial pressure. Decrease in renal perfusion pressure is a known stimulus for renin release.19 Yet in our present study the clonidine-induced fall in perfusion pressure was associated with a significant decrease in renin release.16 Yet in our present study the clonidine-induced fall in perfusion pressure was associated with a significant decrease in renin release. Renal vasodilatation also results in renin stimulation. In our present study, however, decrease in renal vascular resistance was associated with a decrease in renin release, and the clonidine-induced sodium retention was associated with a consistent decrease in renin release. The most likely explanation of the renin suppression by clonidine is that it is due to sympathetic inhibition.9 The present study cannot exclude a possibly direct effect of clonidine on the juxtaglomerular apparatus. It is important to note that minimal doses of 1 \( \mu \text{g/kg} \) of clonidine injected into the cisterna magna result in the same decrease in renin release. This suggests the possibility of interference with a central mechanism of renin regulation. It is of interest to note that sympathetic inhibition by this drug represented the over-riding stimulus for renin suppression. Sympathetic inhibition was capable of overcoming the stimuli to increase renin release exerted by decreased perfusion pressure and alteration of renal circulation. In contrast to the effect of clonidine, Ayers and coworkers24 demonstrated that other sympathetic inhibitors (reserpine, trimethaphan) produce increases in plasma renin activity in renal hypertensive dogs. Furthermore, sodium nitroprusside,32 diazoxide,33 and hydralazine34 have each been shown to increase plasma renin activity in normotensive or hypertensive subjects or dogs. The renin release stimulation by these drugs is presumably due to the reduction in renal perfusion pressure. Only alpha-methyldopa has been reported to decrease plasma renin activity while activating a known stimulus for renin secretion, i.e., a decrease in mean arterial pressure.35

The suppressive effect of clonidine on renal release described in the anesthetized dog was confirmed in patients with essential hypertension to whom the drug was administered for four days. These results are entirely similar to the results observed with alpha-methyldopa.32 The observation that clonidine can decrease plasma renin activity raises the possibility that this effect may also contribute to the antihypertensive efficacy of the drug. The possibly therapeutic implication of the effect of clonidine on renin remains speculative at this time.

CLINICAL USEFULNESS

Various clinical trials have demonstrated the antihypertensive efficacy of clonidine.25-27, 29 Our first study in 196825 demonstrated that clonidine alone at doses between 400 and 900 \( \mu \text{g/day} \) produced only a modest clinical effect. Our second study in 196826 showed that the combination of clonidine-chlorthalidone is much more effective. Although evaluation of comparative efficacy of antihypertensive agents is difficult, a rough comparison may be attempted if the study is conducted in the same laboratory and with the same criteria. During the past few years guanethidine,28 pargyline,29 and alpha-methyldopa30 have
been evaluated in our clinic in the same hypertensive population and with the same criteria of effectiveness. A comparative impression will, therefore, be attempted.

The combination of clonidine-chlorthalidone with doses of clonidine not higher than 900 μg/day gave us significant antihypertensive response in 80% of the patients treated in both the supine and standing positions. The results in supine position appear to be superior to those observed with the combination of guanethidine-hydrochlorothiazide (52%), pargyline-hydrochlorothiazide (58%), and alpha-methyldopa-hydrochlorothiazide (63%). The results obtained with our most recent investigation are interesting because of the higher doses used without greater side effects. It is noteworthy that the combination of clonidine-chlorthalidone is now producing "significant blood pressure reduction" in all the patients treated. It is of particular importance that the satisfactory response is obtained in both the supine and standing positions. Although our acute hemodynamic studies have demonstrated orthostatic hypotension, there is no significant difference between supine and standing pressure in the patients on long-term therapy. The results observed with clonidine alone in higher doses (up to 3,000 μg/day) are superior to those observed with guanethidine, pargyline, and alpha-methyldopa used alone. A definite advantage of clonidine is the same antihypertensive effect in the supine and standing positions. The results with the combination of clonidine-chlorthalidone (with clonidine doses up to 1,200 μg/day) are very encouraging. The blood pressure is reduced in both the supine and standing positions. There is no orthostatic hypotension. Drowsiness and dry mouth are serious side effects. The drowsiness, however, decreased markedly in 70% of the cases after three to four weeks of therapy. Thus, it is very important that the patients are counseled regarding this side effect and its transient nature. There has been no evidence of unusual toxicity. Our experience has included patients with mild, moderate, or severe hypertension. Studies of the efficacy of clonidine in the malignant phase of hypertension are warranted, especially in view of the renin suppression induced by the drug. We predict that if unforeseen long-term side effects are not demonstrated, clonidine in combination with a diuretic will replace reserpine, guanethidine, and alpha-methyldopa as the standard antihypertensive regimen.

Acknowledgment

The authors wish to thank Prof. Dr. Med. Klaus D. Bock for advice and useful criticism. They also wish to acknowledge with thanks the invaluable assistance of Miss Ellen Lippmann and Mrs. Erme-linda Sgro for the determinations of renal functions and plasma renin activity and Miss Lillian Toriello for editorial assistance.

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Supplemental II to Circulation Research, Vols. XXVIII and XXIX, May 1971
Discussion

Dr. Frank A. Finnerty, Jr., Washington, District of Columbia: Prompted by the work of Dr. Bock in Germany, we administered clonidine intravenously in three patients with acute hypertensive crisis. The pressor reaction almost killed all three. Intravenous clonidine administered to such patients is followed by a purely pressor response; no depressor effect is noted. When clonidine is administered intravenously to patients with chronic, long-standing hypertension—not in the accelerated phase, a short pressor response lasting one to two minutes is followed by a prolonged fall in arterial pressure lasting six to eight hours. It would seem, therefore, that clonidine should not be administered intravenously to patients with accelerated hypertension.

We have just completed a double-blind study comparing clonidine plus chlorothalidone with methyldopa plus chlorothalidone over a two-year period. There were no significant differences in the two groups from the blood pressure standpoint. The side effects in both groups, drowsiness and dry mouth, were also similar. The side effects were less in the clonidine group during the second year of study, however. I was amazed to hear that you could give such enormous doses of clonidine without putting the patient to sleep.

Dr. Gaddo Onesti, Philadelphia, Pennsylvania: Thank you, Dr. Finnerty. I know that the short, initial hypertensive effect observed in the experimental animal with intravenous clonidine is also present in man. I also know, however, that with intramuscular or subcutaneous administration this hypertensive effect is not present, while the prolonged fall in blood pressure persists. For this reason there is a potential usefulness of intramuscular or subcutaneous clonidine in hypertensive emergencies. I would like to stress that with oral administration (even with high doses), there is no hypertensive phase.

As far as the drowsiness is concerned, I agree that this remains a problem in a number of patients. It is important to recognize, however, that the drowsiness is only transient in many cases. If the patient is warned about this side effect and its transient nature, it is possible to continue the drug in many instances.
Antihypertensive Effect of Clonidine
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Circ Res. 1971;28:II-53-II-69
doi: 10.1161/01.RES.28.5_Suppl_2.II-53

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