Hemodynamic Effects of Guanethidine in Man

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Guanethidine is a potent antihypertensive agent with selective inhibitory effects on the sympathetic nervous system.1 It provides effective reduction of blood pressure without the troublesome side effects of parasympathetic blockade associated with ganglionic blocking drugs.2

Decreased blood pressure in supine patients following guanethidine has been associated with a fall in cardiac output in some studies.3,4 Other investigators, however, have reported unchanged cardiac output and diminished peripheral resistance.5,6 Glomerular filtration rate and renal plasma flow fall after guanethidine3,7 and a slight reduction in renal resistance may occur.3,8 Adequate studies on the effect on splanchnic blood flow have not been reported.

Guanethidine administered in large doses to animals produces interference with sympathetic reflexes,3 blockade of the tyramine pressor response,9,10 and depletion of catechol amines in the myocardium, aorta and spleen.11,12 These observations have suggested to some that guanethidine, like reserpine, exerts its antihypertensive effect by depleting the tissues of catechol amines.13

Because of species and dosage differences, the results of pharmacological studies in animals may not be related directly to clinical responses in man. The present study was undertaken in order to clarify some of the effects of guanethidine in man on the systemic and splanchnic circulations, the sympathetic nervous system and vascular catechol amine stores.

Methods

The subjects were 16 hypertensive and eight normotensive male patients admitted to the Veterans Administration Hospital, Washington, D.C. and 13 out-patients followed in the Hypertension Clinic. They were maintained in the supine position during all studies. In acute studies, guanethidine* 0.5 to 1.0 mg/kg was diluted with 100 ml of 5% dextrose in water and administered intravenously over a five- to ten-minute period. In chronic studies, patients received guanethidine orally in doses ranging from 30 to 125 mg daily.

Brachial arterial, hepatic venous and right heart blood pressures were recorded using Statham strain gauges (model P23D). Mean arterial pressure was recorded either by electronic averaging or by calculation from the formula MAP = 0.436(pulse pressure) + diastolic pressure. Cardiac output was determined by the dye dilution method utilizing indocyanine green. The dye was preloaded in a catheter and flushed rapidly into the subclavian vein or right atrium with isotonic saline solution. The brachial arterial dye concentration curve was recorded by a Gilford spectrophotometer. Two or more consecutive determinations were carried out prior to guanethidine as well as at periodic intervals after the drug. The average of the pretreatment values was taken as the control cardiac output.

Estimated hepatic blood flow (EHBFF) was determined by the method of Bradley et al.14 utilizing hepatic clearance of bromosulphthalein. The right hepatic vein was catheterized by the right antecubital approach. BSP was infused into an antecubital vein at a constant rate by a Harvard pump and samples of hepatic venous and brachial arterial blood were analyzed for BSP colorimetrically. Control values given for EHBFF represent the averages of three 10-minute clearance periods. In four subjects cardiac output and hepatic blood flow were determined in close succession. In these studies indocyanine green was injected in the right atrium for control cardiac output determination. The catheter was then advanced to the hepatic vein, and after a thirty-minute delay to allow excretion of the indocyanine green, collec-

*Supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.
HEMODYNAMIC EFFECTS OF GUANETHIDINE

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General Hemodynamic

Patient Age

Effects of

Time after drug

min

TABLE 1

Intravenous Guanethidine in

Arterial pressure (mean) mm Hg

Heart rate per min

Cardiac index liters/min/m²

Peripheral resistance units*

Essential Hypertension

1 32 Control 217/127 (166) 78 2.31 .073

15 255/139 (190) 88

40 178/100 (134) 70 1.88 .071

2 39 Control 210/118 (152) 56 2.68 .057

10 269/131 (190) 60

60 160/100 (128) 70 3.06 .041

3 61 Control 178/94 (130) 76 1.57 .083

10 245/122 (175) 80

35 111/67 (86) 75 1.18 .073

4 54 Control 222/132 (172) 64 2.04 .065

10 242/121 (173) 72

50 189/105 (142) 68 2.51 .057

5 45 Control 200/127 (159) 76 2.37 .067

15 140/116 (120) 80

25 100/75 (86) 56 1.60 .051

6 68 Control 236/125 (179) 90 2.74 .065

10 200/111 (150) 102 3.21 .047

30 134/78 (102) 102 2.23 .046

7 67 Control 216/95 (148) 64 1.93 .077

15 273/111 (182) 76

50 222/105 (156) 68 1.78 .088

Hypertension: congestive heart failure

8 50 Control 150/91 (117) 76 1.49 .079

10 155/100 (124) 104

40 111/72 (88) 96 1.46 .060

9 37 Control 200/132 (162) 88 3.24 .050

10 222/145 (178) 104 3.34 .059

30 183/116 (145) 88 3.84 .038

10 34 Control 160/100 (137) 112 2.07 .066

10 183/138 (158) 120 2.07 .076

40 154/100 (124) 96 2.58 .048

*Mean arterial pressure (mm Hg)

Cardiac index (ml/min/m²)

Results

1. GENERAL HEMODYNAMIC EFFECTS

Early Pressor Phase

A rise in mean arterial pressure occurred soon after the intravenous administration of guanethidine in 12 of the 16 hypertensive and in all eight of the normotensive subjects (tables 1 and 2). The blood pressure reached a peak about 10 minutes after the infusion was begun and returned to control levels at 15 to 20 minutes, or about 10 minutes after the in-
### Table 2

Effects of Guanethidine on Estimated Hepatic Blood Flow

<table>
<thead>
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<th>Patient No.</th>
<th>Age (years)</th>
<th>S.A. (m²)</th>
<th>Time after drug</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>EHBF (ml/min)</th>
<th>Splanchnic vascular resistance units*</th>
<th>Cardiac output (ml/min)</th>
<th>EHBF/CO</th>
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*Mean arterial pressure (mm Hg)

\[
\frac{EHRF}{EHBF} \quad (ml/min)
\]

†May be inaccurate because of rapidly changing arterial BSP concentration.
fusion was completed. Systolic pressure rose an average of 21% and diastolic 18%. The elevation of blood pressure was usually associated with a slight tachycardia in the hypertensive group (mean +14%) and a bradycardia in the normotensive group (mean -13%).

Cardiac output was determined during the pressor phase in three hypertensive and four normotensive subjects. Cardiac output rose slightly in two and remained unchanged in one of the hypertensive patients. In the normotensive group it rose moderately in two, remained unchanged in one and decreased slightly in one. The total peripheral resistance increased in five of the seven subjects. Right ventricular systolic pressure rose and diastolic pressure fell in the two patients in which this was measured, changing from 27/0 to 33/-2 mm Hg in patient 1 and from 58/28 to 62/24 mm Hg in patient 10.

Depressor Phase

Blood Pressure and Heart Rate (hypertensive patients). Soon after the pressor effect had subsided, the arterial pressure fell gradually to below control values in 14 of the 16 hypertensive patients (tables 1 and 2). The greatest fall occurred 30 minutes or more after administration of guanethidine, when there was a mean decrease of 23% systolic and 22% diastolic pressure. Some patients had a more striking hypotensive effect after returning to the ward one to three hours after the drug, perhaps related in part to the exercise hypotension previously noted with guanethidine. A significant but lessening hypotensive effect was maintained in some cases for as long as 72 hours.

One of the two hypertensive patients who failed to exhibit a fall in blood pressure (patient 14) was normotensive at the time the study was initiated. The other (patient 7) was an elderly man with primarily systolic hypertension who had a marked pressor response to the drug and whose blood pressure was still above control levels 50 minutes after the infusion when the study was discontinued.

Changes in heart rate during the depressor phase were variable. A slight increase from control rate was noted in three subjects, a decrease in three and no significant change in four others. There was no relationship between hypotensive effect and changes in heart rate.

Cardiac Output (hypertensive patients). Changes in cardiac output during the depressor phase were studied in 10 hypertensive subjects (table 1 and fig. 1). In those without congestive heart failure, the output decreased from control values in six and rose slightly in one. The mean decline for the entire group was 13%. In the three hypertensive subjects with congestive heart failure, cardiac output remained unchanged in one and increased in two despite decreases in both systemic and right heart pressures. Total peripheral resistance (TPR) fell in nine of the ten subjects, the mean decrease being 17.7% and the sd 14.0 (P<0.01).

Right Heart Pressures (hypertensive patients). Mean right atrial pressure decreased from an average of 5 to 3 mm Hg during the depressor phase following guanethidine. Right ventricular systolic and diastolic blood pressures fell in five subjects, including two with congestive heart failure. Right ventricular
pressure in the compensated hypertensive patients decreased from an average of 28/2 to 21/0 mm Hg and in the decompensated patients from 61/19 to 46/13 mm Hg. Pulmonary arterial pressures were measured in three of the subjects. In two compensated hypertensive patients mean PA pressure fell from 16 to 11 and from 20 to 13 mm Hg respectively. In one patient with congestive heart failure the mean PA pressure fell from 47 to 35 mm Hg.

Responses in Normotensive Subjects. A significant hypotensive effect following guanethidine was not noted in the normotensive subjects. Systolic blood pressure remained above the control level in one patient, was unchanged in one and fell slightly in three. Diastolic blood pressure rose in one and remained almost constant in the other four. Three other subjects are not reported because their responses may have been influenced by the prolonged effect of ephedrine administered prior to the guanethidine. Heart rate increased slightly in one subject, fell in two and remained unchanged in two. Cardiac output fell slightly in four of the normotensive subjects (average decrease 9%) and TPR increased (average 10%) (fig. 1). Right heart blood pressures were not determined.

2. ESTIMATED HEPATIC-PORTAL BLOOD FLOW

Estimated hepatic-portal blood flow (EHBF) was measured in 10 hypertensive patients before and after guanethidine (table 2). In seven patients studied during the pressor phase, EHBF increased in four, decreased in two and remained unchanged in one. During the brief pressor response rapid
TABLE 3
Hemodynamic Changes Induced by Tyramine and Ephedrine Before and After Guanethidine

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number studied</th>
<th>Pressor amine</th>
<th>Medication</th>
<th>Change in mean arterial pressure per cent</th>
<th>Change in cardiac output per cent</th>
<th>Change in heart rate per cent</th>
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<tbody>
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<td>Normotensive</td>
<td>6</td>
<td>Tyramine</td>
<td>Control</td>
<td>+21.5 ± 11.9</td>
<td>0 ± 13.8</td>
<td>-16 ± 8.7</td>
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<td>Intravenous guanethidine</td>
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<td>-5.7 ± 6.8</td>
<td>-23.8 ± 3.2</td>
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Changes in arterial BSP concentrations occasionally were observed and may have introduced errors in EHBFP measurements.

During the hypotensive effect of the drug, 30 to 60 minutes after the infusion, there was a decrease in EHBFP in all of the eight patients who exhibited a significant fall in blood pressure. Patient 1, who responded with only a slight decrease in mean arterial pressure, had an increase in hepatic blood flow. In patient 14, whose blood pressure rose after the guanethidine, there was no change in hepatic blood flow. The average decrease in EHBFP for the 10 subjects was 27.8%. Estimated splanchnic (excluding renal and adrenal) vascular resistance rose in seven with an average increase of 26.1%.

The cardiac output and hepatic blood flow were measured in close succession in four subjects. The fraction of total output perfusing the hepatic-portal bed decreased in three of these patients and remained unchanged in one. Hepatic blood flow averaged 33.5% of the cardiac output before guanethidine and fell to 20.7% during the depressor phase after the drug.

3. SYMPATHETIC NERVOUS SYSTEM EFFECTS

Sympathetic Vasoconstrictor Reflexes

The blood pressure "overshoot" following the Valsalva maneuver was completely blocked by guanethidine in 15 of 17 patients in whom this reflex was tested (fig. 2). Some inhibition appeared soon after the infusion of guanethidine was completed and occasionally preceded the hypotensive effect of the drug. The vasoconstrictor reflex in the digit following a deep breath often was not completely blocked (fig. 2). Marked inhibition of the reflex occurred in five subjects, moderate inhibition in one, and no significant change from control in three others. In three subjects, blockade of the Valsalva "overshoot" occurred despite persistence of the digital vasoconstrictor reflex. Orthostatic hypotension was demonstrated one hour after guanethidine in all of these patients.

Responses to Tyramine and Ephedrine

The circulatory responses to intravenous infusions of tyramine or ephedrine were studied before and up to six hours after the intravenous administration of guanethidine in eight normotensive subjects (table 3). A blocked Valsalva "overshoot" after guanethidine was demonstrated in all eight subjects and an orthostatic drop in blood pressure occurred in six. Tyramine elicited a slightly greater pressor effect after guanethidine than before in every subject. The difference, however, was not statistically significant. Changes in cardiac output and heart rate were variable, showing no consistent or significant response to tyramine either in the control or post-guanethidine periods.

The usual response to ephedrine was an increase in mean arterial pressure and cardiac output. This response was not signifi-
FIGURE 3

Digital plethysmographic and Valsalva responses recorded in a 52-year-old negro male who entered the hospital with hypertensive encephalopathy and blood pressure of 270/170. At the time of the above studies he had been receiving guanethidine 37.5 mg and chlorthalidone 100 mg daily for nine weeks. Blood pressure supine was 190/100, standing 120/90 with mild symptoms of orthostatic hypotension. A brisk digital vasoconstrictor response to a deep breath occurs despite block of the Valsalva "overshoot." Infusion of 10 mg of tyramine hydrochloride resulted in an 18% rise in mean arterial pressure.

Ephedrine appeared to elevate cardiac output for several hours. Effects of one injection were sometimes still present at the time of the second injection and could have influenced the results obtained; however, the existence of a prolonged ephedrine effect indicated that guanethidine exerted no blocking activity against this pressor amine.

4. EFFECTS OF ORAL GUANETHIDINE

Thirteen hypertensive out-patients maintained on oral guanethidine for periods of 3 to 86 weeks (mean 31 weeks) were studied. Daily dosage of guanethidine ranged from 30 mg to 125 mg with a mean of 52 mg. Some of the patients also were receiving thiazide diuretics. All patients were receiving the maximum tolerated dose of guanethidine at the time of their study, and an orthostatic drop in blood pressure with or without hypotensive symptoms was demonstrated in each subject. Four of the patients also had been studied prior to initiation of guanethidine therapy. The Valsalva "overshoot" was blocked in all 13 patients receiving guanethidine. The digital vasoconstrictor reflex was blocked in four of the subjects, markedly inhibited in three and moderately inhibited in three. In three others, however, a brisk vasoconstrictor reflex persisted (fig. 3).

Tyramine induced a pressor response in all of the subjects (table 3). The per cent increase in blood pressure following tyramine was slightly less in these hypertensive patients compared to the normotensive subjects, at least in part because of the higher baseline pressure levels. The tyramine response following guanethidine again was greater than in the control period, although the number of control observations is small.

Discussion

The transient pressor response following intravenous administration of guanethidine in man is of much shorter duration than that seen in animals, perhaps owing to the considerably smaller doses used in these human studies. A pressor response was observed in

Circulation Research, Volume XII, March 1963
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all normotensive subjects in the present series and in 80% of the hypertensive patients. It has been suggested that the pressor phase is produced by peripheral release of catechol amines. Increased coronary sinus norepinephrine concentration has been reported, and the early pressure elevation has been prevented in animals by pretreatment with reserpine and phentolamine. Catechol amine release could account for the hemodynamic effects noted during the pressor phase. Thus, systolic and diastolic arterial pressures both rose to a similar degree, cardiac output was not strikingly altered, total peripheral resistance increased, right ventricular systolic pressure rose while the diastolic fell, and changes in hepatic blood flow were variable.

The decreased blood pressure in supine hypertensive patients without cardiac decompensation was associated with a slight fall in cardiac output similar in degree to that noted by Richardson and his associates after oral guanethidine. The present observation of a consistent decrease in total peripheral resistance following guanethidine differs from results seen after intravenous hexamethonium, which produces no consistent change in peripheral resistance. The reduced pressures in the right heart suggest that the decreased cardiac output, like that following hexamethonium, was caused by diminished venous filling pressures. This could result from dilatation of venous capacity vessels associated with inhibition of sympathetic vasoconstrictor impulses. Previous reports of unchanged cardiac output following guanethidine might be explained by the smaller doses used in those studies and/or failure to distinguish patients with cardiac decompensation.

The increase in cardiac output which accompanied the hypotensive effect in two of the three patients with congestive heart failure has been reported previously following guanethidine, and also has been observed in such patients following hexamethonium. The improved cardiac function in these cases probably is the result of both a decrease in right heart filling pressure, due to increased capacity of the peripheral venous system, and a reduction in systemic peripheral vascular resistance.

The normotensive subjects responded differently than the hypertensive patients to guanethidine. Blood pressure was not significantly lowered, but a slight fall in cardiac output indicated a small increase in peripheral vascular resistance. Similar results have been reported in a series of patients with mitral stenosis. Various other antihypertensive agents also produce less depressor effects in normotensive individuals, suggesting that the hypertensive individual may have less efficient baroreceptor control.

Bradycardia has been described as a frequent clinical side effect of oral guanethidine therapy. The absence of definite cardiac slowing during the first hour following intravenous guanethidine, despite significant reduction in blood pressure, indicates that bradycardia is not essential for the hypotensive action of the drug.

The decrease in estimated hepatic blood flow was out of proportion to the fall in blood pressure in most of the subjects, thus indicating an increase in splanchnic vascular resistance. A considerable reduction in the fraction of the cardiac output perfusing the hepatic-portal bed was observed in three of four subjects in whom both parameters were determined in close succession. These results suggest that this vascular area did not share or at least was not the primary site of the decrease in total peripheral resistance and that blood was shunted away from the splanchnic area to other vascular beds. Similar effects on hepatic blood flow have been reported in a group of normotensive subjects given a short course of oral guanethidine, although the colloid method used for determining hepatic blood flow in that study has been shown to be inaccurate in assessing changes induced by guanethidine. Hexamethonium, in contrast to guanethidine, causes a decrease in estimated hepatic blood flow in proportion to the reduction in blood pressure without significant change in calculated splanchnic vascular resistance.

The effects of guanethidine are frequently
likened to those of bretylium tosylate, since both drugs cause selective inhibition of the sympathetic nervous system;29 guanethidine is also similar to reserpine, since depletion of tissue catechol amines has been reported following administration of both agents.11-13 More detailed pharmacological studies, however, indicate that these drugs each have unique actions. In contrast to guanethidine, bretylium produces a rise in cardiac output and an increase in pulmonary arterial pressure.29 Bretylium causes a dose-dependent parallel inhibition of the Valsalva "overshoot" and digital vasoconstrictor reflexes,15 whereas guanethidine blocked the Valsalva "overshoot" but frequently had only a partial effect on digital vasoconstrictor responses.

Although large doses of guanethidine (15 mg/kg) may deplete tissue catechol amines in some animals, clinical doses apparently do not do so in man, as evidenced by persistence of pressor responses to ephedrine and tyramine after both acute intravenous and prolonged oral administration. Vernikos-Danellis and Zaimis30 have reported the persistence of ephedrine and amphetamine pressor responses in cats with adrenergic blockade produced by guanethidine, and Rokseth et al.22 observed a prompt pressor effect of ephedrine in subjects who became hypotensive after intravenous guanethidine. Since the doses of guanethidine used in the present study were sufficient to produce significant reduction of blood pressure, postural hypotension and blockade of the Valsalva "overshoot," it is apparent that the inhibitory effects of the drug on sympathetic nervous system responses are not dependent on depletion of the vascular stores of catechol amines.

Guanethidine may act by blocking postganglionic sympathetic transmission at the nerve terminals proximal to the site of norepinephrine release.1 The persistence of some sympathetic vasoconstrictor reflexes, however, makes it attractive to postulate an additional non-adrenergic mechanism of action. There is some evidence that guanethidine has a direct effect on the myocardium and on smooth and striated muscles.10,26,31

Summary

Guanethidine was administered in a single intravenous infusion to supine hypertensive and normotensive subjects. Hemodynamic changes during the transient pressor phase were consistent with catechol amine effect. The later hypotensive effect occurred only in the hypertensive subjects and was usually associated with a slight decrease in cardiac output in patients without cardiac decompensation and a slight increase in output in those with congestive heart failure. Total peripheral resistance decreased although there was an increase in splanchnic vascular resistance and a decrease in the percentage of the cardiac output perfusing the hepatic-portal bed.

Tests of sympathetic nervous system activity revealed that, although the Valsalva "overshoot" usually was blocked, complete inhibition of digital vasoconstrictor reflexes did not always occur and vascular responsiveness to tyramine and ephedrine was not diminished up to six hours following intravenous guanethidine. Tyramine responses were also demonstrated in a group of patients on effective long-term oral therapy with guanethidine.

These studies suggest that guanethidine has unique hemodynamic effects not necessarily shared by ganglionic blocking agents, bretylium tosylate, or reserpine. Catechol amine depletion probably is not important in the mechanism of the antihypertensive and sympathetic inhibitory actions in man, and the possibility of an additional non-adrenergic effect is considered.

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Hemodynamic Effects of Guanethidine in Man

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doi: 10.1161/01.RES.12.3.298

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