Circulatory Effects of Guanethidine
Clinical, Renal, and Cardiac Responses to Treatment with a Novel Antihypertensive Drug

By D. W. Richardson, M.D., E. M. Wyso, M.D., J. H. Magee, M.D., and G. C. Cavell, M.D.

Ganglionic blockade, though an effective method of lowering blood pressure in hypertensive patients, is frequently accompanied by many unpleasant effects attributable to blockade of the parasympathetic nervous system. These side effects limit the reduction in blood pressure practically attainable.

The development of a new hypotensive agent that reduces sympathetic nervous discharge without inhibiting parasympathetic activity has provided a promising approach to the management of hypertensive vascular disease. This drug, which has the chemical structure shown below and the chemical title

\[
\text{H}_2\text{SO}_4
\]

2-(octahydro-1-azocinyl)-ethyl guanidine sulfate, has been assigned the generic name guanethidine.

Pharmacology

Guanethidine, a synthetic antihypertensive agent developed by Ciba Pharmaceutical Products, Inc., was shown by Maxwell et al. to cause marked and prolonged reduction of blood pressure in dogs with renal and neurogenic hypertension. With regard to its mechanism of action, the drug is thought to interfere with release of norepinephrine from sympathetic nerve endings. Evidence to support this mechanism has been as follows: guanethidine produces marked and prolonged relaxation of the nictitating membranes of dogs and cats. This relaxation cannot be overcome by electric stimulation of the preganglionic cervical sympathetic nerves, but it is readily reversed by infused norepinephrine. The drug does not interfere with transmission of impulses along preganglionic nerve fibers or across the superior cervical ganglion. It seems reasonable to infer that the drug does not make effector cells unresponsive to the chemical mediator of neuro-effector activity, nor does it interfere with nerve or transganglionic transmission, but that it inhibits release of the mediator from sympathetic nerve endings.

In the early phases of its action, lasting 30 to 60 minutes, guanethidine demonstrates sympathomimetic effects such as contraction of the nictitating membrane and pilo-erection. These effects have suggested the possibility that guanethidine may release stores of the transmitter substance normally present in sympathetic nerves. This suggestion is supported by the observation of Sheppard that the drug reduced catecholamine levels in the hearts and spleens of rats.

Clinical Effects of Guanethidine

Reduction in Blood Pressure

Twenty-five male patients, hospitalized with severe hypertensive disease, have been treated with guanethidine* for periods up to 6 months. The drug was commonly given in doses of 150 to 200 mg. on the first day, half of this dose on the second day, and 25 to 75 mg. daily thereafter, the maintenance dose being adjusted to give maximum reduction in blood pressure without intolerable side effects. Striking reduction in pressure was achieved

*Supplied as Ismelin® through the courtesy of Dr. Harold Bornhold, CIBA Pharmaceutical Products, Inc., Summit, N. J.
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in every case, was maximum within 48 to 72 hours after the beginning of treatment, and was maintained at lowest levels for 3 to 4 days after administration of the drug was stopped. Blood pressure gradually returned to pretreatment levels in 7 to 21 days following omission of the drug. Figure 1 shows consistent reduction in blood pressure observed in the first 18 patients treated. Similar results were noted in the remaining 7 patients. Standing pressures decreased more than supine values, and pulse pressure decreased in the standing position. Diastolic pressure decreased an average of 23 mm. Hg supine and 45 mm. Hg standing.

Guanethidine has a "steep" dose-response relation, 25-mg. increments or decrements in maintenance dose frequently being accompanied by changes of 20 to 30 mm. in pressure.

Blood pressure can be reduced to extremely low levels in the standing position. Orthostatic dizziness or fainting occurred in 15 of the first 25 patients studied. Symptoms were relieved at once by lying down, and pressure rose to normal or high levels within 1 minute after resuming the supine position.

Side Effects

Orthostatic dizziness and fainting were the most common and troublesome untoward effects of the drug. The only "side-effect" commonly observed was mild diarrhea, 2 to 4 loose stools daily, which was poorly controlled by atropine, but easily controlled with paregoric. None of the parasympatholytic effects of ganglionic-blocking drugs, such as constipation, impairment of near vision, dry mouth, urinary retention, or impotence, was observed. Failure

\[\text{Figure 1}\]

Blood pressure response to guanethidine. Control pressures are averages of 12 values recorded on each patient on the fourth through sixth hospital day. "SU 5864" values are averages of 20 pressures recorded in each patient on 5 consecutive days during maximum effect of the drug. Arrows indicate mean value in each vertical column.

\[\text{Circulation, Volume XXII, August 1960}\]
of ejaculation without failure of erection occurred in 2 subjects.

Results similar to those presented above have been reported by Page and Dustan.5

Long-Term Administration

Eleven patients have been followed for 2 to 6 months after discharge from the hospital. These patients all had severe hypertensive disease (7 had grade 3 or 4 retinopathy, 11 had enlarged hearts, and 9 had diastolic pressures before treatment averaging more than 120 mm. Hg). They recorded their blood pressures twice daily in the sitting position at home. Average maintenance dose of guanethidine has been 50 mg. daily, though individual patients took from 25 to 300 mg. daily. As shown in figure 2, satisfactory reduction in blood pressure occurred in 9 of the 11, and in 2 orthostatic dizziness prevented adequate control. No abnormalities occurred in repeated determinations of hematocrit, white blood cell count, serum bilirubin, serum glutamic oxalacetic acid transaminase or in urinalysis.

Circulatory Changes with Guanethidine

Cardiac Output

Measurements of cardiac output were made by the indicator-dilution technic, with a continuously recording densitometer (Colson), and injection of indocyanine green dye into an antecubital vein. Details of the technic and comparison of the peripheral injection site with central injection and with simultaneous direct Fick estimates of cardiac output have been presented previously.6 Prior to treatment with guanethidine, 2 determinations of cardiac output in the supine position were followed by measurements made 1 and 5 minutes after tilting the head of the fluoroscope table up 40° from horizontal. When maximum reduction in pressure was achieved by guanethidine administration, usually 5 to 7 days later, duplicate determinations in the supine and 40° tilted position were repeated. Table 1 presents the average values of blood pressure, cardiac output, and calculated peripheral resistance that were observed. Blood pressure fell with guanethidine, mean pressure during treatment being 21 per cent lower in the supine position and 33 per cent lower in the standing posture. Cardiac output also fell, being reduced an average of 10 per cent in the lying and 33 per cent in the standing position, as compared with supine values before treatment.

Peripheral resistance, the quotient of mean arterial pressure divided by cardiac output, did not change greatly during the fall in blood pressure produced by guanethidine (fig. 3). During guanethidine treatment assumption of the semi-standing position reduced blood pressure 21 per cent without altering peripheral resistance. Though resistance was slightly (14 per cent) lower in the supine position during guanethidine administration than prior to
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Table 1

Effects of Guanethidine on the General Circulation

<table>
<thead>
<tr>
<th></th>
<th>Off</th>
<th>Supine</th>
<th>On</th>
<th>Off</th>
<th>40° Tilt</th>
<th>On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure mm. Hg</td>
<td>(17)* 157 ± 24 (20) 126 ± 16† (23)</td>
<td>150 ± 24 (21)</td>
<td>99 ± 22†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output L./min.</td>
<td>(21) 6.6 ± 1.7 (20) 5.9 ± 1.7 (23)</td>
<td>5.5 ± 1.8 (21)</td>
<td>4.4 ± 1.2‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total peripheral resistance dynes cm.⁻² sec.</td>
<td>(21) 2144 ± 801 (20) 1846 ± 642 (23)</td>
<td>2450 ± 943 (21)</td>
<td>1875 ± 531‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate beats/min.</td>
<td>(21) 75 (20) 61 (23)</td>
<td>76 (21)</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume ml./min.</td>
<td>(21) 91 (20) 98 (23)</td>
<td>72 (21)</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The numbers in parentheses are the number of determinations from which the mean values were calculated, and the results are reported as mean ±1 standard deviation.
†Mean values that are significantly different from the control mean in the same position at the p < .01 level.
‡Denotes differences significant at the p < .05 level.

Insofar as the changes in calculated total peripheral resistance can be assumed to represent changes in the average caliber of arterioles, it appears that reduction in blood pressure accompanying guanethidine administration is not brought about by relaxation of arteriolar constriction, since peripheral resistance decreased only slightly. Thus guanethidine, like ganglionic-blocking drugs, presumably lowers blood pressure by reduction in cardiac output, possibly by inhibition of sympathetic vasoconstrictor mechanisms with resultant pooling of blood in peripheral veins, especially in the standing position. The orthostatic hypotension and reduction in pulse pressure accompanying the use of guanethidine support the view that pooling of blood in leg veins with decrease in venous return and hence in cardiac output is responsible for the reduction in blood pressure. There is no direct evidence from the available data, however, that eliminates the alternate hypothesis that guanethidine primarily affects myocardial contractility rather than venous return.

As shown in table 1, reduction in cardiac output in association with use of guanethidine was accompanied by decrease in heart rate such that the volume of blood pumped per beat of the heart remained relatively constant. This observation suggests that guanethidine inhibits sympathetic cardio-accelerator stimuli. The absence of changes in stroke volume argues against a primary effect of guanethidine on myocardial contractile force.

Renal Circulation

Inulin clearance (Cᵢₙ) was used to estimate glomerular filtration rate (GFR), and clearance of para-aminohippurate (Cₑₚₐₙ) to estimate renal plasma flow (RPF) in 11 hypertensive patients. In 7 of these, observations were made in the supine and 40° head-up tilted positions both before and during guanethidine administration. In all subjects, control measurements, made while the patient received no hypotensive drugs, were compared with measurements made during the height of the hypotensive effect of guanethidine, about 1 to 2 weeks following or preceding the control determinations.

Table 2 presents average changes in renal circulation and figure 4 the individual variations in renal vascular resistance. Prior to treatment, glomerular filtration rate in these hypertensive patients averaged about 70 per cent of normal, and renal plasma flow was even lower, the average of the group being 45 per cent of normal. Before guanethidine, head-
up tilt to 40° reduced \( C_{\text{IR}} \) and \( C_{\text{PAH}} \) by about 30 per cent, despite lack of significant change in blood pressure. Administration of guanethidine was accompanied by reduction in GFR and RPF in both lying and "standing" positions in 7 individuals. These measurements were unchanged in 3 and rose slightly in 1.

Blood pressure decreased proportionately more than did renal plasma flow, so that calculated renal vascular resistance diminished slightly as compared to pretreatment values in either position. This slight decrease in renal vascular resistance was minor in comparison with the reduction in the absolute values for glomerular filtration rate and renal plasma flow accompanying administration of the drug. During guanethidine treatment, GFR averaged one third and RPF one fourth of the pretreatment values in the "standing" (40° tilted) position. Filtration fraction, the ratio of GFR to RPF, decreased under the influence of guanethidine, indicating proportionately greater fall in filtration than in blood flow. This observation suggests that the reduction in arterial pressure is primarily responsible for the observed changes in GFR and RPF.

Guanethidine treatment impairs renal function, presumably because the minimal reduction in vascular resistance that accompanies its use is inadequate to permit maintenance of blood flow and filtration in the face of the marked reduction in blood pressure. Similar changes have been observed acutely during parenteral administration of ganglionic blocking agents by Ford,\(^1\) who suggests, apparently from detailed experience with one patient, that initial impairment of renal function returns to pretreatment levels within 10 days of treatment with hexamethonium despite continuing reduction in blood pressure. This return of renal function to pretreatment values during continued reduction in pressure did not occur in our patients, 5 of whom had been receiving guanethidine 20 or more days before renal function was measured.

It is not surprising in view of these marked reductions in renal function to find that determinations of blood urea nitrogen rose during treatment with guanethidine in about half of the patients studied, but only if the blood urea nitrogen exceeded 25 mg per cent in the control period. Elevation of blood urea

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**Figure 3**

Changes in calculated total peripheral resistance accompanying guanethidine administration. Arrows point to the mean of each vertical column.

**Figure 4**

Changes in renal vascular resistance accompanying guanethidine administration.
nitrogen during guanethidine administration was of moderate magnitude, the largest change being from 46 to 78 mg. per cent. In no case was cessation of drug therapy required because of oliguria or progressive azotemia. As judged by the blood urea nitrogen, renal function returned to pretreatment levels soon after the drug was stopped.

Summary

Guanethidine, a new synthetic hypotensive drug that probably interferes with release of norepinephrine from sympathetic nerve endings and that does not inhibit parasympathetic activity, has proved an effective agent in reducing blood pressure in 25 hypertensive patients studied for periods up to 6 months. Untoward effects have been limited to orthostatic hypotension and mild diarrhea.

The drug apparently lowers blood pressure by reduction in cardiac output rather than by relaxation of the arterioles. Reduction in renal blood flow and glomerular filtration rate accompanied administration of the drug, but in no case did progressive azotemia or oliguria occur.

This agent is an extremely potent hypotensive drug with a remarkably prolonged duration of action and with none of the parasympatholytic side effects produced by ganglionic-blocking agents.

Acknowledgment

Grateful appreciation is expressed to Mrs. M. P. Stephenson, Mrs. Virginia Stewart, Mrs. Betty Cauthorne, and Misses Mary Andre and Carol Alcock for expert technical assistance.

Circulation, Volume XXII, August 1960

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Lying, no drug</th>
<th>Lying, guanethidine</th>
<th>40° tilt, no drug</th>
<th>40° tilt, guanethidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>ml/min.</td>
<td>70 ± 43</td>
<td>58 ± 35</td>
<td>44 ± 28</td>
</tr>
<tr>
<td>CNAV</td>
<td>ml/min.</td>
<td>258 ± 158</td>
<td>231 ± 125</td>
<td>185 ± 121</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>mm. Hg</td>
<td>157 ± 24</td>
<td>127 ± 16</td>
<td>151 ± 24</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>mm. Hg</td>
<td>.86 ± .72</td>
<td>.81 ± .69</td>
<td>1.15 ± .76</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>ml/min.</td>
<td>.28 ± .09</td>
<td>.25 ± .05</td>
<td>.31 ± .19</td>
</tr>
</tbody>
</table>

Figures are mean ±1 standard deviation; CNAV, clearance of inulin; CNAV, clearance of para-aminohippurate.

*Significantly different from values supine without drug (p < .05).

Summario in Interlingua

Guanethidina—un nove droga hipotensive synthet que probabilmente inhibi le liberation de norepinephrina per le terminos sympathico-nervose e che demonstratamente non inhibi le activitate parasympathic—se ha provate capace a effecuemente reducere le tension del sanguine in 25 patientes hypertensive qui esseva studiate durante periodos de usque a 6 menses. Le adverse effectos lateral esseva restringite a hypotension orthostatic e leve grades di diarrhea.

Apparentemente le droga reduce le tension del sanguine per reducere le rendimento cardiac plus tosto que per relaxar le arteriolas. Le administratone del droga esseva accompaniante de reductiones in le fluxo de sanguine renal e in le intensitate del filtratone glomerular, sed azotemia progressive o oliguria non occurveva in ulle del casos.

Iste agente es un potenissime droga hipotensive. Le duration de su effecto es remarcalemente longe. Iilo es charaterisate per nulle del effectos lateral parasympatholytic que es producede per le agentes de blockage ganglionic.

References

Medical Eponyms

By Robert W. Buck, M.D.

Schonlein's Purpura. In 1837 there was published at Wurzburg a work entitled Allgemeine und specielle Pathologie und Therapie. This consisted of students’ transcripts of lectures delivered by Johann Lucas Schonlein (1793-1864), Professor of Internal Medicine at Zürich. The following description of peliosis rheumatica is taken from the third edition, volume 2, pp. 48-49, Würzburg, 1837.

"The spots are never confluent as they often are in Wehrholf’s (sic) Disease . . .

"The patients have either previously suffered with rheumatism, or rheumatic symptoms appear coincidently.

"The characteristic spots of the disease appear first on the extremities in the majority of cases, especially the lower, rarely the upper ones, and here only up as far as the knee. The spots are small, the size of a lentil or a millet seed, bright red, not raised above the skin, and disappear on pressure by the finger. They gradually become dirty brown or yellow, and the skin over them undergoes a somewhat branny desquamation. The eruption follows a sporadic course, often over a period of several weeks . . .

"This disease has been confused with the morbus maculosus Wehrhofti. The absence of the so-called purpuric phenomena in the mouth . . . the lack of all hemorrhage, the peculiarity of the eruption . . . the joint involvement (which does not occur in that disease), and the absence of nervous phenomena, such as marked prostration and weakness, further assure the diagnosis.”
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Circulation. 1960;22:184-190
doi: 10.1161/01.CIR.22.2.184

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