Guanethidine

By EDWARD D. FREIS

GUANETHIDINE is widely used for the treatment of severe hypertension. This compound produces a selective blockade of sympathetic nerve impulses without inhibition of the parasympathetic system. Guanethidine represents an improvement over the pre-existing ganglion blocking agents which inhibited indiscriminately the entire autonomic nervous system thereby producing many unpleasant side effects. Guanethidine possesses characteristic pharmacologic and hemodynamic actions that are pertinent to an understanding of its clinical effects when the drug is used in the treatment of patients with hypertension.

PHARMACOLOGICAL ACTION

Intravenous administration of large doses of guanethidine in animals produces an initial brief fall followed by a rise of blood pressure lasting 30 to 45 minutes, which is followed in turn by a prolonged reduction to well below control levels lasting 4 to 10 days or longer.[1,2] Further studies by Maxwell and his associates[3] indicated that the hypertensive phase was due to sympathetic nerve stimulation and the prolonged hypotensive phase to sympathetic atony.

Since Maxwell found no interference with nerve transmission along the pre- or postganglionic nerve fibers or in the sympathetic ganglia, he concluded that guanethidine blocked the release of norepinephrine at the sympathetic nerve endings or else produced depletion of this substance in some unknown fashion. It was later demonstrated that guanethidine does indeed block the release of radioactive labeled norepinephrine which normally occurs following either sympathetic nerve stimulation or reserpine treatment.[4] Guanethidine also blocks completely the accelerator response to cardiac sympathetic nerve stimulation before producing measurable myocardial depletion of norepinephrine.[5]

In addition to blocking the release of norepinephrine following sympathetic nerve stimulation, guanethidine also causes a partial depletion of norepinephrine stores. The transient hypertensive phase which follows intravenous guanethidine suggests norepinephrine release and is associated with a rise in the norepinephrine concentration of coronary sinus blood.[6] Partial depletion of catecholamine stores in the myocardium, aorta and spleen of animals has been found after intravenous guanethidine.[6-8]

Recent evidence indicates that in the myocardium there are 2 norepi-

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From the Veterans Administration Hospital and the Department of Medicine, Georgetown University School of Medicine, Washington, D. C.

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EDWARD D. FREIS, M.D.: *Senior Medical Investigator, Veterans Administration, and Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.*

nephrine pools which are in equilibrium. The norepinephrine in one of these pools is readily mobilizable and released by substances such as tyramine.[9] The other, which is considered to be a reserve pool, is not affected by tyramine but is partially depleted by guanethidine.[10] The guanethidine depletion can be prevented by the prior administration of sympathetic blocking agents of the bretylium type.[11] Both pools, however, can be depleted by reserpine.[11] The concept of 2 catecholamine pools, one released by tyramine, the other by guanethidine, is consistent with the observation that in man the tyramine pressor response was unaffected by both intravenous or chronic oral administration of guanethidine.[12]

The considerable hypotensive potency of guanethidine may be explained by its dual action of producing both a partial depletion of catecholamine stores, and probably more importantly, by blocking the release of catecholamines following sympathetic nerve stimulation. Other modes of action have been proposed but their importance has not been established. For example, injection of guanethidine directly into the cisterna magna produced hypotension, bradycardia and inhibition of sympathetic reflexes.[13] A major central action seems unlikely because guanethidine does not cross the blood-brain barrier; however, it is possible that with chronic administration small amounts may enter the brain and contribute to the antihypertensive effect by a central mechanism. There also is some evidence to indicate that guanethidine has a direct depressive effect on the myocardium,[14] and on vascular smooth muscle.[15,16] The evidence, in general, however, favors the view that the primary site of action of guanethidine is at the sympathetic nerve endings.

Hemodynamic Effects

Richardson and his associates[17] were the first to report on the hemodynamic effects of oral guanethidine in hypertensive patients. They found that the antihypertensive effect was associated with a fall of cardiac output averaging 10 per cent in the supine position and 33 per cent in the 40 degrees head-up tilt. Total peripheral resistance was only slightly reduced. Bradycardia occurred and because of this cardiac stroke volume was unchanged even though the minute output of the heart was reduced.

As would be expected with an agent which reduces cardiac output, renal plasma flow and glomerular filtration rate both decreased following guanethidine, the reduction being most marked in the tilt-up position.[17] Renal vascular resistance was unchanged. These results have since been confirmed by others.[18,19]

Following intravenous guanethidine in man, Cohn and his associates[12] observed a transient pressor phase lasting about 15 minutes, similar to that which had been seen previously in animals. During the pressor reaction the cardiac output rose in some and remained unchanged in others while total peripheral resistance usually increased. The subsequent and long-lasting depressor phase was characterized by a reduction in cardiac output and total peripheral resistance.[12,18] The pressor phase of guanethidine is not seen after oral administration of the drug.

In hypertensive patients with cardiac decompensation, the depressor phase

following guanethidine was accompanied usually by a rise rather than a fall in cardiac output.[12,20] This difference between compensated and decompensated hypertensive patients had been observed previously with ganglion blocking agents.[21] The improvement in cardiac output in the decompensated patient probably is due to the reduction in aortic pressure and hence in work demand imposed on the failing left ventricle, and possibly also to reduction in right heart filling pressures. In contrast to these beneficial effects on the cardiac failure associated with hypertension, Gaffney and Braunwald reported worsening of congestive failure following guanethidine in normotensive patients with functional classes III and IV rheumatic valvular and primary myocardial disease.[22] The discrepancy may be due to the differing hemodynamic factors producing heart failure in hypertension as opposed to valvular heart disease.

Right heart and pulmonary arterial pressures fall in guanethidine-treated patients[12,20] probably because of peripheral venodilatation. Mason and Braunwald[23] demonstrated abolition or marked inhibition of reflex venopressor responses in the human forearm following guanethidine administration. Imhoff and his associates[24] prevented the orthostatic hypotension induced by guanethidine by having the patient wear a pressurized antigravity suit. Thus, it seems clear that venodilatation and consequent venous pooling are important mechanisms in the production of orthostatic hypotension.

In other vascular regions hepatic-portal blood flow decreases considerably[12] while cerebral blood flow falls only moderately with a parallel decline in cerebrovascular resistance.[18] With regard to sympathetic vascular reflexes in man, the Valsalva and tilt-back "overshoots" as well as the cold pressor test were abolished or significantly inhibited.[24] However, despite complete abolition of the Valsalva "overshoot" and severe orthostatic hypotension after guanethidine, reflex vasoconstriction in the digit following a deep breath, although usually inhibited, was at times maintained.[12] Since the digital vascular reflex is under sympathetic control these results suggest that severe orthostatic hypotension and blockade of the Valsalva "overshoot" may occur although some sympathetic reflexes are still present.

The effects of guanethidine on cardiac output, right heart pressures, venous capacity and regional blood flows resemble those previously described following ganglion blocking drugs.[21,25] They explain why guanethidine has such a potent antihypertensive effect. The drug by its sympathetic blocking action influences all components of the cardiovascular system. Not only is there arteriolar dilatation but also venodilatation with a consequent decrease in right heart filling, particularly when the patient assumes the erect position. In addition, sympathetic stimulation of the heart itself is inhibited which results in a decrease in cardiac rate and probably in ventricular contractility.

Factors Influencing Responsiveness to Guanethidine

Blood and Extracellular Fluid Volumes. There is a reciprocal relationship between the level of plasma and extracellular fluid volumes and the responsiveness of patients to sympathetic blocking agents such as guanethidine. The antihypertensive effects of the blocking drugs are enhanced by reduction in

plasma and extracellular fluid volumes produced either by diuretic agents or by dehydration resulting from excessive vomiting or diarrhea.[26-28] Similarly, the appearance of edema often is accompanied by a reduced responsiveness to guanethidine and other blocking drugs.

The inhibition of sympathetic vascular constriction produced by blocking agents results in greatly enhanced blood pressure fluctuations in response to changes in total blood volume.[29] Reflex homeostatic adjustments to blood volume changes which tend to maintain the blood pressure at a constant level are prevented. Thus, small decreases in blood volume in "blocked" patients can produce considerable falls in blood pressure.

As described in the section on hemodynamic changes, guanethidine, in common with other agents which block sympathetic nerve transmission, produces venodilatation. This results in venous pooling when the patient assumes the erect position. External counterpressure on the lower extremities and abdomen, such as can be produced by a pressurized suit,[24] or by having the patient stand in water to the level of his chest, will entirely prevent the orthostatic hypotension.

A similar effect, although lesser in degree, may be produced by the normal diurnal shifts in extracellular fluid volume. During the day when the patient is in the upright position extracellular fluid is drawn by gravity to the lower extremities. At night when the patient is supine this fluid is redistributed generally over the body. These diurnal fluid shifts may explain why the orthostatic hypotension tends to be most severe in the morning. When the patient first arises there is less extracellular fluid in the legs, tissue pressure is low, and venous pooling is not prevented. As fluid accumulates in the lower extremities during the day, tissue pressure increases and orthostatic hypotension becomes less severe. Diurnal fluctuations in blood pressure are commonly seen during guanethidine treatment with the lowest pressure levels in the morning followed by higher pressures in the afternoon and evening.[30,31] An additional reason for the afternoon rise of blood pressure has been suggested by Cranston[32] who has observed that the plasma volume of hypertensive patients increases during the daytime hours.

Emotion. It has long been recognized that fear and anger will raise blood pressure. Despite the fact that the cardiovascular response to such emotions are mediated at least in part over sympathetic pathways, the pressor response to disturbing emotions is not prevented by blocking drugs.[33] In fact, pressor responses to epinephrine and norepinephrine are potentiated after ganglion blocking agents[34] or guanethidine.[3,35]

In clinical practice these emotionally induced pressor responses may present a problem when only casual office or clinic readings are used as a guide to adjusting doses of guanethidine. In patients treated with blocking agents, blood pressures recorded in the clinic may be much higher than those recorded at home.[36] If the clinic or office pressures are used as the sole guide to treatment, the physician may be encouraged to raise the dose beyond the therapeutic range thus precipitating hypotensive reactions.

The physician can be guided to some extent by the patient's symptoms. If

there are complaints of orthostatic faintness, particularly in the morning, it is probable that the maximum tolerable dose has been obtained or exceeded regardless of the level of blood pressure recorded in the office. Also, because of the diurnal fluctuation in blood pressure described in the previous section, the earlier in the day the patient is examined by the physician the lower the readings are apt to be. The ideal guide to treatment is to have the patient keep a record of twice daily recordings of blood pressures taken in the sitting or preferably the erect position at home by the patient himself or a member of his family. This is particularly useful during the period of dose adjustment.[30]

Vasodilator Influences. In the normal individual with intact sympathetic reflex activity, vasodilatation produced by various influences is compensated for by homeostatic vasoconstriction and cardiac activation mediated reflexly over the sympathetic nervous system. By this mechanism acute reductions in blood pressure are prevented. When the sympathetic system is inhibited, however, as by guanethidine, compensatory cardiovascular adjustments are depressed and hypotensive episodes may be precipitated. During febrile illnesses, for example, there is considerable vasodilatation in the large renal and hepatic-portal vascular beds.[37] Under these conditions guanethidine-treated patients may exhibit increased responsiveness to the drug requiring temporary omission or reduction in doses.

Patients undergoing treatment with blocking agents including guanethidine occasionally experience hypotensive symptoms after the ingestion of alcoholic beverages. This reaction probably is due to the vasodilator action of alcohol. The occurrence of hypotension depends both on the degree of sympathetic blockade imposed to control the blood pressure and on the alcohol blood level. The customary 1 or 2 cocktails before dinner are usually well tolerated and, in fact, aid in combatting the usual evening upswing in blood pressure.

Although moderate exercise, such as hiking or golf, usually is well tolerated in guanethidine-treated patients, strenuous exercise may precipitate hypotensive reactions.[38] The hypotension is due not only to vasodilatation in the exercising muscles with failure of reflex vasoconstriction in other vascular areas, but also to inhibition of the sympathetic drive to the heart so that cardiac output does not rise sufficiently to meet the demands imposed by the increase in muscle blood flow. Again, it should be emphasized that complete sympathetic blockade is not essential to obtain adequate blood pressure control. The fact that the cardiac sympathetics are not completely blocked is indicated by the fact that heart rate increases normally when the guanethidine-treated patient rises from the supine to the erect position.[30] Thus, the majority of patients are able to carry out their usual physical activities without symptoms.

Methods of Administration

Duration of Action. The original pharmacologic investigations of Maxwell and his associates[3] indicated that guanethidine had a prolonged duration of action lasting more than 1 week when large doses were injected intravenously. Following oral ingestion in man, Dollery[39] observed that peak urinary excretion occurred between 2 and 4 hours but that only 36 per cent was excreted by 72 hours and that urinary excretion continued beyond that time. Since excretion is so slow and the action of the drug so prolonged, it follows

that the dose intervals need not be more frequent than once daily. Even with once daily doses a cumulative effect will be obtained over a period of 5 to 7 days until the rate of excretion and destruction comes into balance with the rate of ingestion.

Dose Adjustment. Because of the cumulative effect of guanethidine it has become common practice to raise the doses rapidly only in hospitalized patients who are under close observation. In outpatients the drug is begun at a low level and increased slowly and by small increments.[30,40,41]

In hospitalized patients with severe hypertension, an initial dose of 25 mg. is appropriate with increases of 12.5 to 25 mg. every day or every other day depending on the urgency of the clinical situation. The blood pressure usually is recorded with the patient in both the supine and erect positions 3 or 4 times daily. When symptomatic orthostatic hypotension appears the dose should be reduced by 25 mg. and further adjustments made from that level by 5 to 12.5 mg. increments.

Page and his associates[40] advise elevation of doses until the supine blood pressure is controlled or no further decreases in supine blood pressure occur. Orthostatic hypotension was not used as the criterion for adequate response. Such intensive treatment is useful in producing a rapid reversal of the malignant phase of hypertension but will lead to obvious difficulties in the less severely ill patient who is not confined to bed. Also, in the presence of severe renal impairment, profound reduction of blood pressure will lead to further reduction in glomerular filtration rate and increasing azotemia. In the latter patients the blood pressure should be lowered gradually and cautiously in order to avoid oliguria.

The range of effective doses of guanethidine varies widely from as little as 5 to as much or more than 500 mg./day in different patients. Since there are no known criteria for predicting the response of individual patients the dose must be titrated in each case as a separate therapeutic experiment.

In outpatients the starting dose usually is 10 mg. once daily[40,41] and this is increased by 5 to 10 mg. every week or two until the blood pressure is reduced or symptoms of orthostatic hypotension appear. When titrating guanethidine the physician should consider the percentage change rather than the absolute change in dose. Increases should be about 20 to 30 per cent of the previous dose. Patients should be instructed regarding the symptoms of orthostatic hypotension and told to lie down if faintness occurs. The dose of guanethidine can be omitted for the next day and then begun usually at a 5 to 12.5 mg. lower level (fig. 1). When symptomatic hypotension appears the dose of guanethidine should be reduced by no more than 10 to 20 per cent of the amount which produced this side effect. Further small adjustments can then be made as necessary from that level.

As mentioned previously, the patient should be seen by the physician preferably early in the day when the orthostatic hypotension is most prominent. Home blood pressure recordings can be helpful, especially when the patient is complaining of faintness and other hypotensive symptoms despite high office blood pressure recordings.

Diuretics as Adjunctive Therapy. Guanethidine has been used effectively alone but in most patients administration of the drug with an oral diuretic agent leads to better control of the blood pressure and fewer side effects. Maronde[42] has reported that the combination results in a greater reduction in supine blood pressure for the degree of orthostatic hypotension produced than does guanethidine alone. Since symptomatic orthostatic hypotension is the most frequent and troublesome of the side effects produced by guanethidine, any measure which will reduce the differential between supine and erect blood pressure is worthwhile.

Guanethidine in common with certain other antihypertensive agents produces fluid retention and dependent edema in occasional patients.[40,43] An increase in total blood volume also has been reported.[44,45] Such fluid accumulation reduces the antihypertensive responsiveness to the blocking agent and also may lead to wider diurnal fluctuations of blood pressure. Thiazides prevent this fluid accumulation and also reduce somewhat the normal extracellular fluid and plasma volumes thereby leading to greater responsiveness to guanethidine and some reduction in diurnal as well as day-to-day fluctuations in blood pressure.[46]

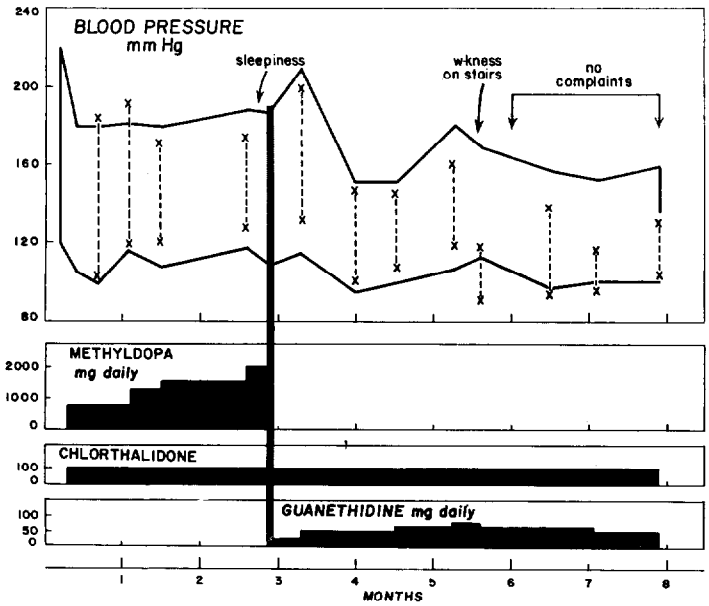

Fig. 1.—Chart of patient J. S., 42 year old male with essential hypertension. Treatment with methyldopa plus chlorthalidone and prior treatment with oral diuretics, reserpine and hydralazine (not shown) failed to reduce blood pressure significantly. Methyldopa was then discontinued and guanethidine substituted. The dose was raised gradually to 75 mg. daily at which level symptomatic orthostatic hypotension appeared. The dose of guanethidine was then reduced to 62.5 mg. and later to 50 mg. daily. The continuous line represents blood pressure in the supine position and the vertical broken lines blood pressure in the erect position.

By producing increased responsiveness the diuretic agents lower considerably the effective antihypertensive dose of guanethidine.[42,47] This is of importance because blood pressure control can be achieved without inducing as high a degree of sympathetic blockade. Certain side effects of guanethidine, such as diarrhea, are thereby minimized.

Adjunctive treatment with oral diuretics should precede or begin simultaneously with the initiation of guanethidine treatment. If thiazides are added after a partial antihypertensive effect has been achieved with guanethidine, severe hypotension may be precipitated. This is due to the considerable potentiation of the antihypertensive effects of blocking drugs produced by diuretic agents.[26,27,47] In such circumstances the dose of guanethidine should be halved for one week preceding the administration of thiazides and further adjustments in the dose of guanethidine made from this reduced level until optimal blood pressure control is achieved.

For the reasons stated above, it is generally a simpler task to achieve and maintain blood pressure control with guanethidine when diuretics are used as the background medication. There are, nevertheless, patients who can be managed quite satisfactorily with guanethidine alone; and in special cases, such as in gouty patients, an attempt should be made to control the blood pressure without thiazides.

Side Effects

The principal side effects produced by guanethidine are orthostatic hypotension, bradycardia, diarrhea and failure of ejaculation.[30,40,41] These probably are all related directly to the basic sympathetic blocking action of the drug.

Orthostatic hypotension and its associated symptoms of weakness, faintness and occasionally syncope, are the result of failure of reflex homeostatic vasoconstriction, especially venoconstriction when the patient assumes the erect position. Factors influencing the degree of orthostatic hypotension obtained with guanethidine have already been discussed in the previous sections.

Bradycardia probably is the result of blockade of sympathetic impulses to the sino-atrial node. Both the bradycardia and the orthostatic hypotension are desirable therapeutically and only become "side effects" when the dose of guanethidine is raised to the point of producing unpleasant symptoms. The diarrhea probably is due to sympathetic block with resulting parasympathetic dominance of intestinal motility. As would be expected under such conditions, atropine and related drugs are effective counteragents.

Guanethidine does not decrease libido nor does it usually prevent orgasm. There is rather ejaculation into the urinary bladder due to failure of reflex sphincteric closure of the proximal urethra at the time of orgasm. This sphincter is under the control of the sympathetic nervous system. Because of the failure of ejaculation male patients will remain impotent for as long as they are receiving blocking doses of guanethidine.

Patients treated with blocking agents may complain of easy fatigue and of dyspnea or faintness on moderate exercise such as on climbing stairs. These symptoms are probably due in part to orthostatic hypotension, and in part to a diminished cardiac response to exercise secondary to inhibition of the cardiac sympathetics.

It might be expected that guanethidine would aggravate angina by reducing aortic pressure and hence coronary artery blood flow. In a few patients angina is produced or aggravated by guanethidine but in the majority of hypertensive patients with this complaint angina is improved.[40] While reduction in aortic pressure should diminish coronary inflow it is also evident that the lower arterial pressure reduces the work of the heart and the myocardial demand for oxygen. The bradycardia produced by guanethidine also tends to alleviate angina. Page[40] has cited evidence which indicates that relief of angina in guanethidine-treated patients is due to the prevention of the rise of blood pressure that normally occurs with exercise.

Indications for Use of Guanethidine

Most authorities agree that guanethidine should be reserved for the treatment of patients with evidence of severe hypertension including diastolic blood pressures of 120 mm. Hg or above, who cannot be controlled satisfactorily using other antihypertensive agents. The reasons for this selectivity are the necessity for painstaking titration of doses and the frequent occurrence of orthostatic hypotension. Guanethidine has been used effectively in the control of mild and moderate hypertension[48] but the effort required on the part of both physician and patient hardly seems worthwhile if adequate blood pressure reduction can be obtained using antihypertensive agents which do not produce orthostatic hypotension.

Guanethidine, especially when given in conjunction with oral diuretics, con-

trols blood pressure in a larger percentage of patients with severe hypertension than does any other antihypertensive drug. It is for this reason a valuable therapeutic agent.

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