Patient Acceptance of Guanethidine as Therapy for Mild to Moderate Hypertension

A Comparison with Reserpine

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SUMMARY The relative benefits and risks of reserpine and guanethidine were compared in patients with thiazide-treated mild to moderate hypertension (diastolic pressure 95–115 mm Hg). Forty-nine ambulant patients (30 men, 19 women) were treated throughout the study with hydrochlorothiazide, 50 mg/day. In this double blind crossover study each drug was added in graded increments until a predetermined therapeutic response was obtained, blood pressure measurements and side effect scores were evaluated biweekly. Major conclusions of the study were: 1) guanethidine, as well as reserpine, will reduce mild to moderate blood pressures to normal; 2) in most cases, side effects which did occur while taking guanethidine or reserpine were well tolerated and neither drug was clearly superior. Side effects associated with larger doses of guanethidine employed in severe hypertension were absent or only slightly bothersome. Thus, guanethidine appears to have a good benefit-to-risk ratio in the therapy of mild to moderate hypertension and offers a number of advantages over drugs commonly used in this syndrome. This study refutes the common belief that guanethidine must be reserved only for the treatment of more severe degrees of hypertension.

CONTINUOUSLY EFFECTIVE ANTIHYPERTENSIVE THERAPY requires drugs that are not only effective but also well-tolerated. Lack of patient compliance is the major problem in drug therapy of mild-moderate hypertension since the disease is usually asymptomatic. An ideal drug should be free of serious or annoying side effects and should have kinetic properties that allow simple dosage regimens.

In spite of these considerations, the choice of therapy for hypertension is hampered by a lack of studies comparing the relative clinical efficacy of drugs available. For years reserpine has been considered by authorities to be the antihypertensive drug of choice for treatment of mild to moderate hypertensives who have an inadequate response to thiazide diuretics. In addition to its demonstrated efficacy, reserpine can be given in a single daily dose. However, reserpine can cause several troublesome or serious side effects. These not only limit patient acceptability of the drug but restrict the useful dosage range, so that alternative therapies may be required.

Although many other antihypertensive drugs are available, all except guanethidine must be given more than once daily, and many share with reserpine side effects related to the central nervous system. Guanethidine is not distributed to the brain as readily and has a long half-life allowing once daily dosage. However, guanethidine has traditionally been reserved for use in severely hypertensive patients who have failed to respond to less effective agents. In these patients with very high blood pressure, guanethidine in large doses often produces a number of side effects related to essentially complete sympathetic blockade. Data do not exist to indicate whether guanethidine is as effective and well tolerated as other commonly used drugs in patients with less severe hypertension.

This study was designed to compare reserpine with guanethidine in patients who have persistent mild to moderate hypertension during treatment with hydrochlorothiazide alone. Criteria for efficacy were defined prospectively and each drug was given in the dose necessary to achieve this goal. Particular attention was paid to undesirable effects with each drug, which were evaluated in a standard fashion after the blood pressure had been lowered to the predefined level. This method allowed comparison of acceptance of the two drugs at equi-effective doses. We found that guanethidine is an acceptable alternative to reserpine for patients with mild-moderate hypertension.

Methods

Patients

Fifty-four patients with a sustained standing diastolic blood pressure of 95–115 mm Hg on hydrochlorothiazide, 50 mg/day, participated in this study. Patients were studied by a common protocol at Vanderbilt University, Nashville, Tennessee, and at Michigan State University, East Lansing, Michigan. With one exception, all patients were classified as having essential hypertension on the basis of compatible history and normal physical examination, and normal results for urinalysis, serum sodium, serum potassium, serum creatinine, VMA, rapid-sequence pyelogram and in some cases renal arteriograms. One man had stable chronic renal disease as evidenced by history, elevated blood urea nitrogen (50 mg%), and granular casts in the urine. The average age of the patients was 43 years (range 26–66). There were 19 white and 13 black men, 11 white and 11 black women in the study. Informed, written consent was obtained from each individual following a careful explanation of the nature and purposes of the study.

All antihypertensive drugs were discontinued; other drugs were either discontinued or kept constant for the duration of the study. All patients were instructed to follow a no-added salt diet (2-3 g sodium daily) during the study, but no

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attempt was made to measure the amount of sodium they were ingesting.

Patients with congestive heart failure resistant to digitalis and thiazides, blood urea nitrogen greater than 50 mg%, clinical depression prior to therapy, active peptic ulcer, or concurrent fatal disease such as malignant neoplasm were excluded from the study. Also excluded were patients who were pregnant or who were taking oral contraceptives, those who were unwilling or unable to attend clinic at scheduled times, or those who concomitantly were taking other drugs that might influence blood pressure.

The following determinations were done within one week of admission to the study and at the end of the study: hemoglobin, hematocrit, total and differential white blood cell count, blood urea nitrogen, serum creatinine, uric acid, serum potassium and sodium, fasting blood sugar, urinalysis, SGPT, and direct and indirect serum bilirubin. A chest X-ray and electrocardiogram were obtained unless done within one year of admission to the study and the results were available. Each patient received a complete history and a thorough physical examination.

Study Design

This study was performed with a double-blind two cell crossover design with random allocation of treatments to patients. Patients were seen at two week intervals throughout the investigation. Each patient received hydrochlorothiazide, 50 mg daily, throughout the study. During the six-week hydrochlorothiazide-placebo periods at the beginning, middle, and end of the study, the patients took one placebo tablet per day during the first two-week period, two tablets per day during the second two-week period, and three in the third two-week period to simulate the dosage increments of the study drugs. Drug compliance was checked in two ways. One was by pill counts made on returned medication at each visit. The other was by urinary fluorescence to check for riboflavin that was contained in the placebo tablet. Randomization of patients into the study was performed only after the first six week placebo period when compliance had been assured, the patients' standing diastolic blood pressure on hydrochlorothiazide alone had been documented to be 95–115 mm Hg, and the diastolic pressure at two successive visits did not vary by more than 15 mm Hg.

The therapeutic goal was defined as a standing diastolic pressure of less than 95 mm Hg in addition to a decrease of at least 10 mm Hg from the preceding placebo period. Test medications, identical in appearance to the placebo tablets, were initiated at a single daily dose of 0.1 mg reserpine or 10 mg of guanethidine sulfate, in addition to the continued treatment with hydrochlorothiazide. The single daily doses of guanethidine and reserpine were adjusted at two-week intervals until the therapeutic objective was attained, until side effects limited further dosage increments, or until the arbitrary maximum of 0.6 mg reserpine or 60 mg guanethidine was reached. When the therapeutic goal had been reached, the drugs were maintained at the effective dose for a total of six weeks so that repeated observations could be made. The drug regimen was similar in the second test-period except that each patient received the alternate test drug. All drugs were dispensed by a pharmacist and provision for emergency drug decoding was made.

Observations

At each visit, three supine blood pressure readings, at least two minutes apart, were determined in the right arm after an initial 10 min rest period. The patient then assumed a standing position and after two minutes three additional blood pressure readings were recorded at one minute intervals. The three blood pressure readings for each position were averaged and the values used for dosage adjustments of each test drug. Diastolic pressure was measured by the disappearance of sound. Supine and standing pulse rates and body weight also were measured and recorded. In six patients ambulatory plasma renin activity was measured at the final visit of a placebo period and at the final visit of each drug period when the therapeutic goal had been reached.

Side effects were evaluated by a clinical symptom questionnaire which was completed for each patient. The patient was asked to rate each of the 30 symptoms or symptom complexes for the previous two-week period on a scale of 0 to 5 (0-not present, 1-slightly bothersome, 2-moderately bothersome, 3-severe, and 5-intolerable). Space for comments and other symptoms also was provided. In addition, each patient was seen by a physician who asked general questions related to well-being and overall satisfaction.

Each patient's score for each side effect was determined by subtracting the maximum score during the final two visits of the preceding and succeeding placebo period from the corresponding score during the final two visits of the drug period when blood pressure had reached the therapeutic objective.

Statistical Analysis

The Student's t-test for paired observations was used to compare the blood pressures, weights, and heart rates for the last two visits of each control period with the corresponding values during the final two visits of the following test drug periods, when the therapeutic goal had been attained. Drug doses required for blood pressure control were compared for an effect of order of administration by t-test for unpaired observations. Hypotensive dose-response curves were calculated for each drug and analyzed by Finney's method of probit analysis. Correlation coefficients were determined for the relationships between standing diastolic pressure while on hydrochlorothiazide plus placebo and the maximal dose of reserpine or guanethidine required. Side effects were evaluated by the signed rank test, using the total scores for each patient for each drug. In the case where side effects precluded reaching the therapeutic objective with one drug, a score one larger than the highest score in the comparison group was assigned, thereby giving that score the highest rank.

Results

Dropouts

Forty-nine patients completed the study. One man withdrew following the reserpine test period with complaints of numbness and tingling of the hands and general dis-
satisfaction with the medication in spite of good blood pressure control. One man died suddenly during his sleep; he had previously completed the guanethidine period and was under control with 0.4 mg reserpine at the time of death. One man was in an automobile accident requiring prolonged hospitalization which occurred while he was receiving 0.2 mg reserpine with blood pressure control. One woman was hospitalized with hemiplegic migraine on 0.2 mg reserpine after having completed the guanethidine test period satisfactorily. One woman quit the study during the guanethidine test period after she developed overt diabetes mellitus. Her blood pressure was well controlled at the time with 10 mg of guanethidine. These five patients are not included in the subsequent analysis.

Hypotensive Effects

Of the remaining 49 patients who completed the study, blood pressure control was attained with reserpine in 43 patients and with guanethidine in 43. There was no significant effect of the order of drug administration, and the data for each drug were pooled. The systolic and diastolic pressures at the therapeutic objective are compared with the pressures in the preceding placebo period in figure 1. Blood pressures during the placebo periods were statistically identical as was the control of the standing diastolic pressure achieved with each drug. With this equivalent lowering of the standing diastolic pressure, guanethidine produced more orthostatic fall in both the systolic and diastolic pressures than reserpine. The orthostatic change corrected for the placebo period (drug period minus placebo period) is shown in figure 2 for all patients who achieved a therapeutic response with both drugs.

The drug doses required to control the blood pressure are shown in figure 3. The dose-response curves for the two drugs have slopes which are not significantly different (reserpine slope = 2.43; guanethidine slope = 3.38). The median effective dose for reserpine was 0.16 mg (95% confidence interval 0.14 to 0.19 mg) and for guanethidine was 19 mg (95% confidence interval 17.1 to 21.0 mg). There was no correlation between the blood pressure during the placebo period and the effective dose of either drug. The number of clinic visits after initiation of drug therapy until the therapeutic objective had been reached was 3.5 ± 0.3 for reserpine and 4.3 ± 0.3 for guanethidine.

Relative Efficacy

The most effective drug in each patient was the one which lowered blood pressure to the therapeutic objective with the lowest total side effect score. Neither drug proved to be superior by signed rank analysis of side effect scores. Except for seven patients with dose-limiting side effects (see below) both drugs were well tolerated at the effective dose. Twenty-seven of the 49 patients while taking guanethidine and 28 while taking reserpine had no side effects rated greater than 1 (slight bother). In the 38 patients in whom a direct comparison of side effects was possible, i.e., patients who achieved blood pressure control with both drugs, reserpine was better tolerated in 12, guanethidine was better tolerated in 11, and for 15 the drug tolerances were equal.

In spite of equal overall satisfaction with the two regimens, the spectrum of side effects was different and one

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![Graph](image-url)  
**Figure 1.** Blood pressures in all patients obtaining a therapeutic effect with reserpine or guanethidine as compared with the preceding control period. The top of the bars represents the systolic pressure ± standard error of the mean (SEM) and the bottom of the bars the diastolic pressure ± SEM. The crosshatched bars represent supine and dotted bars upright pressure. Significant differences from control are indicated by *(P < 0.01).*

![Graph](image-url)  
**Figure 2.** Orthostatic effects of reserpine and guanethidine in patients achieving pressure control with both drugs. The effects of the drugs are evaluated by subtracting the orthostatic change during treatment with placebo-thiazide (control period) from the orthostatic change during therapy with drug-thiazide. Significance between reserpine and guanethidine is indicated on the figure (Student's t-test for paired observations).
drug or the other was preferable for some patients (table 1). While taking reserpine, more patients were bothered by drowsiness, mental changes, epigastric distress, and nasal congestion than in the control periods immediately preceding and succeeding; while with guanethidine, more patients had complaints of weakness and fatigue, dizziness, diarrhea and inhibition of ejaculation.

Eleven of the 49 patients did not achieve satisfactory blood pressure control for three consecutive visits with one of the drugs; only one patient was not adequately controlled with either regimen. The reason and the dose of each drug at discontinuation are shown in table 2. Two men did not achieve adequate blood pressure control with reserpine because of intolerable side effects. Four patients failed to achieve satisfactory control at the maximal dose of reserpine of 0.6 mg daily, and one of these also did not respond to 60 mg guanethidine daily. Five patients required discontinuation of guanethidine because of side effects. One man who required discontinuation of guanethidine at 5 mg/day in spite of adequate lowering of pressure was the patient with stable chronic renal disease. His BUN also increased from 45 to 60 mg% during this period and he later developed gouty arthritis.

The supine heart rate decreased 8.1 ± 1.3/min ($P < 0.001$) with reserpine and 6.6 ± 1.4/min ($P < 0.001$) with guanethidine. The changes in standing heart rate were similar ($−8.3 ± 1.6$ with reserpine and $−7.2 ± 1.4$ with guanethidine). Body weight increased slightly with reserpine ($+2.4 ± 0.7$ pounds $P < 0.01$) but was unchanged with guanethidine ($+0.9 ± 0.8$ pounds). The ambulatory plasma renin activity was significantly ($P < 0.05$) higher during blood pressure control with guanethidine (3.6 ± 1.6 ng/ml/hr) than with reserpine (1.8 ± 1.0 ng/ml/hr), which was no different from thiazide alone (2.0 ± 1.0 ng/ml/hr).

There were no major changes in the laboratory values obtained at the beginning and end of the study for any patient. Five patients, however, were provided potassium chloride supplementation due to low serum potassium concentrations while taking hydrochlorothiazide. One patient developed a nasal hemorrhage during a control period that required treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Patient Age/Sex</th>
<th>Reason for failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>0.2</td>
<td>20/M</td>
<td>Nasal congestion, decreased mental function</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>42/M</td>
<td>Nightmares, insomnia</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>56/M</td>
<td>Upright BP 147/104 on maximal dose. Responded to 20 mg guanethidine.</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>49/F</td>
<td>Upright BP 137/103 on maximal dose. Responded to 20 mg guanethidine.</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>34/M</td>
<td>Upright BP 137/96 on maximal dose. Responded to 50 mg guanethidine.</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>47/M</td>
<td>Upright BP 154/106 on maximal dose. Did not respond to guanethidine 60 mg/d (BP 160/108).</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>5</td>
<td>62/M</td>
<td>Fatigue, inhibition of ejaculation</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>55/M</td>
<td>Impotence, tinnitus, lethargy</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>66/F</td>
<td>Lethargy, weakness, anxiety</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>42/M</td>
<td>Severe epigastric pain</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>38/M</td>
<td>Depression, impotence, fatigue.</td>
</tr>
</tbody>
</table>

*Number of patients complaining of increased symptoms during drug period.
†Total symptom score + number of patients with symptom.

![Figure 3. Dose-response curves of guanethidine and reserpine. Cumulative percent response (percent of patients achieving the therapeutic objective) is plotted versus the dose required. The dose response curves are not significantly different from being parallel and are plotted with a common slope. * The relative potency is 110. Values in parentheses represent 95% confidence limits.](http://circ.ahajournals.org/)
Discussion

Drug choices in mild to moderate hypertension unresponsive to thiazide diuretics are dictated as much by tradition and advertising as by controlled trials comparing clinical efficacy of drugs. Reserpine traditionally has been a drug of choice in such patients. However, for a number of reasons, reserpine may not be used, and it is in this situation that methyldopa, clonidine, propranolol, and multiple drug combinations are considered.

Guanethidine traditionally has been reserved for patients refractory to other drugs because it is felt to cause high incidence of severe side effects. However, there are a number of theoretical reasons why guanethidine might be preferable to the usual drugs for mild hypertension including once daily dosage, lack of central nervous system depression or sedation, and few or no toxic effects. The side effects are a direct extension of the pharmacologic blockade of the sympathetic nervous system. Reported efficacy and side effects of guanethidine in the severely hypertensive individual cannot be extrapolated to patients with mild-moderate hypertension. Moreover data obtained by comparison of two drugs at fixed doses are not helpful in defining relative efficacy.

To test the possibility that guanethidine might be useful in mild-moderate hypertension, the present study directly compared patient acceptance of guanethidine and reserpine at doses effective in lowering blood pressure to a predetermined value. The study was designed to simulate the manner in which physicians would use these drugs clinically. It must be emphasized that the findings in this study are limited to patients with asymptomatic essential hypertension who do not have cardiovascular, cerebrovascular, or renal complications of hypertension.

In patients with standing diastolic pressures of 95-115 on hydrochlorothiazide, both guanethidine and reserpine were effective in decreasing standing diastolic pressures at least 10 mm Hg and to 95 mm Hg or below in the majority of the patients. These therapeutic effects occurred at doses of these drugs ordinarily prescribed. In four patients the therapeutic objective was not achieved with 0.6 mg reserpine and in one of these patients 60 mg of guanethidine also was ineffective. In clinical practice, the dose of reserpine is usually limited to less than 0.6 mg whereas there is no dose limitation with guanethidine. This result in less flexibility with reserpine use, in that patients who do not respond must be switched to another drug rather than merely adjusting the dose, a disadvantage guanethidine does not present.

Since both drugs were effective, the relative efficacy must be based on the side effects present at an equi-effective dose. In this respect neither drug was superior. Intolerable side effects were infrequent; they occurred in two patients with reserpine and five with guanethidine. Over half the patients had no side effects greater than “slight bother” with either drug. On the other hand, the types of side effects produced were different with the two drugs, so that patients intolerant of one could usually tolerate the other.

As expected, reserpine produced bothersome nasal stuffiness, drowsiness, mental slowness, and a “let down” feeling more frequently than did guanethidine. Interference with ability to do mental work and/or increased anxiety were considered less tolerable in patients who performed mainly mental tasks in their jobs. In this study, depression associated with reserpine treatment was not a significant problem, probably because of the relatively short duration of therapy (6-16 weeks) at the doses administered. Freis found that depression is likely to occur with larger doses of reserpine; Simpson and Waal-Manning report that it becomes a problem mainly during long-term therapy with the doses we used.

Guanethidine produced slightly more weakness and fatigue than reserpine but was better tolerated than one might expect from previous studies of severely hypertensive patients requiring larger doses. In spite of a greater orthostatic fall in blood pressure with guanethidine, symptoms of dizziness were rarely a problem. Only five patients reported moderately bothersome postural symptoms, probably because the orthostatic fall in blood pressure in our patients was relatively small as contrasted with severely hypertensive patients treated with guanethidine. Similarly, diarrhea was also infrequent and mild in this study.

Men were specifically asked about impairment of sexual function. None of the 29 males complained of some impairment of ejaculation during treatment with guanethidine which was severe in four and only slightly troublesome in three. Impotence was a problem with one patient on reserpine and two on guanethidine.

Six patients had ambulatory plasma renin activity determined. In all six the plasma renin activity increased during therapy with guanethidine whereas values during reserpine and control periods were similar. These data are consistent with the findings of Lowder and Liddle who found guanethidine to potentiate the renin response to furosemide and upright posture in patients with “low-renin” essential hypertension. Guanethidine appears to be the only antihypertensive drug which blocks the sympathetic nervous system and raises plasma renin activity during successful therapy.

The success achieved with guanethidine in this study can be partly attributed to the manner in which it was administered. Since there was no correlation between the height of blood pressure while taking hydrochlorothiazide and the dose of drug required to lower the blood pressure, the dose must be arrived at empirically. Side effects may also occur at low doses. Thus in ambulatory patients the dosage of guanethidine should be carefully adjusted by increments; good results with guanethidine seem to us to depend on this approach.

Both drugs have the advantage of once daily administration, moderate cost, and low incidence of side effects over the short term. However, long term use of reserpine occasionally produces the serious side effect of depression and there is the possible association between reserpine and breast cancer, although this is disputed. There is no suggestion that long term guanethidine will produce unexpected side effects.

Compared with other antihypertensive drugs guanethidine has a notable lack of side effects relating to the central nervous system and allergic or toxic side effects are essentially unknown. The disabling side effects related to sympathetic blockade by guanethidine were uncommon in

nasal packing. No other major complications or events occurred during the study.
our study. This illustrates the fallacy of extrapolating results obtained in patients with severe hypertension to patients with milder hypertension and emphasizes the necessity for carefully designed studies comparing side effect of drugs at equally effective doses in the same population.

Acknowledgment

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References


The Protective Effect of Glucose-Insulin-Potassium on the Response to Atrial Pacing

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SUMMARY The effects of glucose-insulin-potassium infusion (GIK) on atrial pacing-induced angina, ST depression, abnormal left ventricular end-diastolic pressure during pacing interruption (LVEDP) and lactate metabolism (L), were studied in 18 patients: ten had angina during pacing = Ischemic group, and eight (5 normals and 3 with coronary artery disease) remained asymptomatic = Non-ischemic group. The study consisted of 8–10 minute periods of control, pacing, recovery, pacing, and before and after GIK. No untoward effects were observed. Comparison of the pacing responses (GIK vs pre-GIK states) showed that during GIK, angina occurred in only 4 patients, while significantly less severe changes were observed in ST depression (1.4 ± 0.5 vs 2.4 ± 0.4 mm) and LVEDP (16 ± 3 vs 23 ± 3 mm Hg). Lactate extraction was also higher (8.1 ± 10.9 % vs 5.2 ± 11.1 %), but not significantly so, although L became normal in 4 subjects and improved in another. These results indicate that GIK infusion was well tolerated and had a beneficial effect on pacing-induced myocardial ischemia.

IN 1962 SODI-PALLARES reported that the administration of glucose-insulin-potassium (GIK) was beneficial in the treatment of cardiac arrhythmias in the acute phase of myocardial infarction. This has become a highly controversial issue and reports both in favor and against this therapy have subsequently appeared in the literature. More recently, GIK has been found to decrease infarct size after coronary artery occlusion in dogs, but it has also been reported to be ineffective in increasing tolerance to pacing-induced myocardial ischemia. The objective of this preliminary study was to assess the influence of GIK on the pacing-induced myocardial ischemic syndrome which consists of chest pain, ST depression and abnormalities in left ventricular end-diastolic pressure and myocardial lactate extraction. An abstract of this work has been published recently and our detailed observations constitute the basis of this report.

Methods

This study was performed in 18 patients referred for investigation of chest pain suspected to be due to coronary artery disease (Table 1). None of the patients had clinical diabetes mellitus, cardiac arrhythmias, cardiomegaly or cardiac failure and none was receiving digitalis or diuretics at the time of study. Informed consent was obtained in all subjects.

Patients were studied in the fasting state one hour after the oral administration of 10 mg of diazepam. Under local

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