Pressor Responses to Noxious Stimuli in Hypertensive Patients

Effects of Guanethidine Sulfate and Alpha Methyldopa

By Alvin P. Shapiro, M.D., and Emanuel Krifcher, M.D.

In previous studies, pressor reactivity to several standardized noxious stimuli was evaluated quantitatively, and increased responsiveness was demonstrated in hypertensive as compared with normotensive subjects. The stimuli employed in these studies included simple psychologic provocation as well as the cold pressor test and the intravenous injection of a small dose of angiotensin II. Differences in the physiologic mechanisms of response were suggested from examination of the influence of diabetes mellitus on pressor reactivity to these stimuli. Since alteration by hypotensive drugs of the blood pressure response to noxious stimuli represents a clinically important but usually undetermined pharmacologic function, evaluation of the effect of several of these agents also was undertaken. In an earlier study it was reported that chlorothiazide and reserpine, in their usual therapeutic doses in hypertensive patients, failed to diminish the degree of pressor response to several of the aforementioned stimuli, despite lowering of the basal pressure. The present study was designed to test the reactivity of hypertensive patients before and during therapy with two more potent hypotensive agents, guanethidine sulfate and alpha methyldopa. The data also were examined for information pertinent to the questions of the clinical pharmacology and mechanism of action of these compounds.

From the Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

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Methods and Materials

Twenty-eight studies were done in subjects with moderate to severe hypertensive vascular disease, before and during therapy. Thirteen were in patients receiving guanethidine sulfate and 15 in patients on alpha methyldopa. The severity of the hypertensive disease and the average dose and duration of therapy in each group are indicated in Table 1.

Patients were either ambulatory and seen regularly in the Hypertension-Renal Clinic or were hospitalized on the Clinical Research Unit* of the Presbyterian-University Hospital. All were receiving the medications for therapeutic indications.

Four noxious stimuli that have been described in detail previously were administered to study pressor responses. They consisted of (1) the intravenous injection of 10 ml. of normal saline during which the patient is asked "to count backwards from 100 as rapidly as possible" (saline); (2) a standard cold pressor test; (3) the reading of a confusing color chart (color); (4) the intravenous injection of 0.03 μg./Kg. body weight of angiotensin II over a period of 1 minute. In the group of 13 patients receiving guanethidine sulfate, only the last eight were tested with angiotensin. Of the 15 on alpha methyldopa, one was not tested with angiotensin. The four tests were administered at 15-minute intervals after an initial rest period of 15 to 30 minutes.

The order of administration of the stimuli was the same in all subjects, as follows: saline, cold pressor, angiotensin, color. In most subjects, the first testing was before therapy. In a few, the first set of tests was performed while subjects were receiving medication and, in these instances, a minimum of 2 weeks was allowed to elapse before re-testing. Tests were done in the morning, usually with the patients in a fasting state, but at least 1 hour after the most recent dose of medication. All blood pressures were recorded with the patient supine during the rest periods and the tests, but at the end of the study the

* Supported by Clinical Research Center Grant FR-56.
patients were tilted to the upright position and an erect blood pressure was determined when it had stabilized (i.e., after 3 to 5 minutes in the erect posture).

Blood pressures were determined on the Gilford automatic indirect recorder; pulse rates were registered simultaneously by means of a Gilford cardiotachometer operating from a photoelectric cell attached to the ear of the subject. The pretest baselines and the maximum responses of blood pressure and pulse rate for each test were determined as described previously. Systolic and diastolic values were converted to a calculated mean blood pressure

\[
\text{Mean blood pressure} = \frac{\text{diastolic} + \frac{\text{pulse pressure}}{3}}{}
\]

to simplify subsequent statistical calculation.

### Results

The resting blood pressures and pulse rates (pretest baselines) and the responses to each test, before and during therapy with either guanethidine sulfate or alpha methyldopa, are presented in tables 2 and 3. Comparison of the responses to each test are depicted in figure 1 (guanethidine sulfate group) and figure 2 (alpha methyldopa group). The declines in pretest baselines and erect blood pressures are also illustrated in these figures. The method of paired differences was used to test the significance of the changes in both pretest levels and responses.

### Table 1

**Clinical Data**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of patients</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Guanethidine sulfate</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Alpha methyldopa</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 2

**Baseline Blood Pressures and Pressor Responses Before and During Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Guanethidine sulfate (n = 13)</th>
<th>Alpha methyldopa (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean blood pressure (mm. Hg)</td>
<td>Mean blood pressure (mm. Hg)</td>
</tr>
<tr>
<td></td>
<td>Pre-test baseline</td>
<td>Response</td>
</tr>
<tr>
<td>Saline</td>
<td>Before Rx</td>
<td>150.0</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>144.0</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−6.0</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.1 &gt; 0.05</td>
</tr>
<tr>
<td>Cold pressor</td>
<td>Before Rx</td>
<td>150.5</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>145.2</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−5.3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Angiotensin †</td>
<td>Before Rx</td>
<td>150.5</td>
</tr>
<tr>
<td>(0.03 µg./Kg.)</td>
<td>During Rx</td>
<td>139.1</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−11.4</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt; 0.01 *</td>
</tr>
<tr>
<td>Color</td>
<td>Before Rx</td>
<td>153.7</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>147.0</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−6.6</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

* Significant difference.

† With angiotensin test; n = 8 for guanethidine sulfate, n = 14 for alpha methyldopa.

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Table 3

Baseline Pulse Rates and Responses Before and During Therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Guanethidine sulfate (n = 13)</th>
<th>Alpha methyldopa (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulse rate (beats/minute)</td>
<td>Pulse rate (beats/minute)</td>
</tr>
<tr>
<td></td>
<td>Pre-test baseline</td>
<td>Response</td>
</tr>
<tr>
<td>Saline</td>
<td>Before Rx</td>
<td>68.4</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>59.1</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-9.3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt; 0.01 *</td>
</tr>
<tr>
<td>Cold pressor</td>
<td>Before Rx</td>
<td>69.1</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>58.0</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-11.1</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt; 0.01 *</td>
</tr>
<tr>
<td>Angiotensin†</td>
<td>Before Rx</td>
<td>74.0</td>
</tr>
<tr>
<td>(0.03 μg./Kg.)</td>
<td>During Rx</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-13.6</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt; 0.01 *</td>
</tr>
<tr>
<td>Color</td>
<td>Before Rx</td>
<td>68.2</td>
</tr>
<tr>
<td></td>
<td>During Rx</td>
<td>57.9</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-10.3</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.01 *</td>
</tr>
</tbody>
</table>

* Significant difference.
† With angiotensin test; n = 7 for guanethidine sulfate, n = 10 for alpha methyldopa.

Figure 1

Effects of therapy with guanethidine sulfate on the resting (pre-test baseline) pressures and pulse rates, and the responses to noxious stimuli before and during therapy. The last column in the chart (MBP erect) indicates the fall in erect pressure produced by therapy. The vertical lines indicating pulse rates are all depicted in solid black, but refer to response before, decline in resting, and response during, respectively, in the same order from left to right as for the larger bars preceding them which indicate mean blood pressures.
It is apparent that both drugs caused only a modest decline in the supine pretest baseline pressures. In fact, with guanethidine sulfate, the average fall was of questionable significance. The erect blood pressures, however, were lowered significantly with both compounds.

The effect of therapy on pressor responsiveness essentially was similar with both drugs. The most striking feature was the contrast between the cold pressor response, which was decreased markedly with therapy, and the angiotensin response, which was unaffected by guanethidine and indeed significantly increased, albeit a modest amount, in the subjects receiving alpha methyldopa. The responses to the venipuncture (saline test) and to the color test tended to follow the pattern of the cold pressor response in this study, both showing a decline during therapy with each compound.

The contrast between the effects of therapy on the responses to angiotensin and to the cold pressor stimulus also can be shown by the device of comparing the ratio, angiotensin to cold pressor (A/CP), before and during therapy.² The median * A/CP ratios before therapy were 1.31 for guanethidine sulfate and 1.57 for alpha methyldopa; during therapy, they rose to 2.41 and 3.18, respectively. With use of the Wilcoxon rank test,⁴ the increases in ratio were highly significant (p < 0.01). Similarly, the average differences between angiotensin and cold pressor responses (A – CP) were 8.3 and 12.1 mm Hg before therapy for guanethidine sulfate and alpha methyldopa, respectively, increasing to 19.7 and 26.0 mm Hg during therapy; these differences also were highly significant (p = 0.02).

A dose-dependent relationship of the fall in cold pressor response was noted with alpha methyldopa; this was suggested by the data for guanethidine sulfate, but was not as clear-cut (fig. 3).

The patterns of the changes in pulse rate were similar to those for blood pressure. Pretest baseline rates declined during therapy

* The median was determined rather than the mean because these are ratios and accordingly do not follow a normal distribution.
PRESSOR RESPONSES IN HYPERTENSION

with both compounds but this effect appeared greater with guanethidine sulfate than with alpha methyldopa. With guanethidine, the pulse rate increments with the saline, cold pressor, and color tests were significantly less during therapy. With alpha methyldopa, the differences in pulse rate responses to these three stimuli were small and significant statistically only for the saline test. Angiotensin produced a slight fall in pulse rate, unaffected by therapy with either compound.

**Discussion**

In contrast to the results achieved in our previous study with chlorothiazide and reserpine in therapeutic doses, the two more potent agents, guanethidine sulfate and alpha methyldopa, caused a decline in reactivity to the cold pressor test. The response to angiotensin, the result of a direct vasoconstricting effect on the peripheral vascular bed, was not reduced by treatment and indeed was increased in some subjects. Since the effector arc of the cold pressor response is probably the sympathetic nervous system, these findings are in keeping with the concept of sympatholysis by the drugs and hypersensitivity of the denervated arterioles to humoral vasoconstrictors. Preservation of angiotensin response after sympatholysis also has been observed by Brown and Wood, who used a ganglion-blocking agent, and argues against any significant role of the autonomic nervous system in the pressor response to angiotensin. Likewise, Dollery, Harington, and Hodge recently have demonstrated an increased responsiveness to norepinephrine in

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Figure 3

*Effect of treatment with alpha methyldopa (left) and guanethidine (right) on mean blood pressure response to cold pressor test. The per cent decline is calculated from the ratio:*  

\[
\frac{\text{Response before therapy} - \text{Response during therapy}}{\text{Response before therapy}} \times 100.
\]
patients receiving alpha methyldopa.\(^8\) As suggested in our report of angiotensin and cold pressor reactivity in normal and diabetic subjects,\(^2\) an elevation of the "A/CP ratio" above 2.0, although this is an empirically derived figure dependent on conducting both tests according to the described protocol, may serve clinically to indicate impairment of sympathetic innervation of peripheral vasculature.

A significant decline was noted in both the saline and color responses with guanethidine, and in the saline test only with alpha methyldopa. In the previous study with chlorothiazide and reserpine, these responses, as well as the cold pressor response, did not decline.\(^3\) In diabetic subjects with sympathetic impairment, however, in whom the cold pressor response was decreased, responses to these psychological stimuli also were not diminished and it was proposed that they could operate alternatively through humoral or "angiotensin-like" mechanisms.\(^2\) The data in the present study, indicating that with the sympatholysis induced by these potent compounds the psychophysiologic responses were depressed, would suggest that our previous observation in diabetic subjects was dose dependent, i.e., a less complete sympathetic denervation was present in the diabetic subjects than in the present group of patients on drugs. On the other hand, the difference between the two groups could be interpreted as time dependent, i.e., alternative response pathways may represent a gradually developing adaptive mechanism to spontaneous acquisition of sympathetic impairment, and thus may be absent with the relatively acute sympatholysis produced by drugs. Such concepts, however, are inferred from hemodynamic measurements that are influenced by a variety of factors and remain speculative.

The hypothesis that peripheral mechanisms alternative to the autonomic nervous system, such as the elaboration of vasoactive polypeptides, could mediate cardiovascular responsiveness, is attractive, but its exploration requires the development of technics for measuring the humoral biochemical changes acutely accompanying responses to noxious stimuli.

The study was not designed and the patients were not selected specifically to compare differences between the effects of guanethidine sulfate and alpha methyldopa, but several observations can be noted. Pharmacologically the two compounds act differently on the autonomic nervous system. Guanethidine sulfate appears to deplete norepinephrine stores or to interfere with norepinephrine release at peripheral sites, possibly by blocking acetylcholine.\(^9\) Alpha methyldopa theoretically could interfere with norepinephrine synthesis by competitive inhibition at the decarboxylase step. Some investigators have reported a decrease in the excretion of the urinary metabolite vanilmandelic acid,\(^10\) but others have not.\(^11,12\) Tissue depletion of norepinephrine occurs, but neither the persistence of this depletion nor the hypotensive effects of the compound correlate with the duration of decarboxylase inhibition.\(^12\) It has been suggested, therefore, that the amine metabolites of alpha methyldopa themselves are responsible directly for norepinephrine depletion.\(^12\) Alternatively, Day and Rand have argued that alpha methylnorepinephrine, itself a pressor material but less potent than norepinephrine, becomes a "false transmitter" after administration of alpha methyldopa and hence responses to sympathetic stimulation are damped.\(^13\) The situation remains uncertain as is emphasized by a comprehensive recent study of the metabolism of alpha methyldopa in man by Buhs and co-workers. The data of these investigators indicate no apparent correlation between the variations in the metabolic fate of the drug and its degree of hypotensive action.\(^14\)

Clinically, however, the two drugs produced qualitatively similar effects in the present study, effects that demonstrate at least a functional sympatholysis. The effect of guanethidine sulfate on the pulse rate seemed more pronounced, a finding which may indicate that although both drugs deplete cardiac tissue of catecholamines,\(^15\) the clinical
effect on the heart is more pronounced with guanethidine than with alpha methyldopa. Alpha methyldopa lowered the supine pressure to a greater extent than did guanethidine sulfate, which is in keeping with the impression that this drug has a greater potential to lower blood pressure by actually decreasing peripheral resistance.8 Nevertheless, as these observers, and others,16,17 pointed out, an additional and quite significant postural hypotension is present, as usually occurs with drugs that are operationally sympatholytic, and is the result of fall in cardiac output in the erect position. The dose-dependent relationship of the depression of the cold pressor response with alpha methyldopa was indicative of increasing sympatholyis with increasing dosage.

The results, as did those with chlorothiazide and reserpine,9 have certain therapeutic implications. Obviously, a decrease in the blood pressure “ceiling” in response to stimulation occurred; this may have therapeutic value, since hypertensive patients are rarely in a basal state but are exposed continually to noxious stimuli of various types. It is equally clear, however, that increments in blood pressure during any particular period of observation may occur despite effective therapy with potent drugs, and in some instances reactivity may be enhanced. Elevations of blood pressure during drug therapy thus can represent reactive responses rather than therapeutic failures. Accordingly, they should suggest search for sources of such stimulation, which are frequently psychophysiologic,18 rather than constitute immediate indications for changes in type or dose of medication.

Summary

The pressor and pulse rate responses to several standardized stimuli were determined in hypertensive patients receiving guanethidine sulfate or alpha methyldopa in therapeutic doses. Despite differences between the two compounds in their mode of action, both demonstrated functionally sympatholytic effects. Both drugs produced a greater blood pressure fall in the erect posture than in the supine and impaired the pressor response to the cold pressor test. The pressor reactivity to intravenous angiotensin, however, persisted. Responses to psychophysiologic stimuli were decreased. The implications of these findings for both therapy and for understanding of physiologic mechanisms of pressor reactivity are discussed.

Acknowledgment

Guanethidine sulfate and angiotensin II (as valyl-5-angiotensin-II) were supplied by Ciba Pharmaceutical Company; alpha methyldopa was obtained from Merek, Sharp and Dohme, Inc. The assistance of Miss Eileen Tyrrell in the statistical analyses of the data is gratefully acknowledged.

References

11. Cannon, P. J., Whitlock, R. T., Morris, R. C.,


Observations on Treatment

By Richard Bright—1827

One of the most important questions in the treatment of this class of dropsies, is the propriety of employing Mercury. It is consistent with the most successful treatment of many forms of inflammatory disease, that we should have recourse to the valuable combination of Calomel with Opium; and it is consistent with what is generally deemed good practice, that by the cautious use of mercury we should endeavour to produce more healthy action, and to promote absorption when there is reason to believe that disease has left any chronic morbid action tending to produce unhealthy deposit in glandular structures. Still however, the cases which have proved most successful in my own practice, have generally been those in which I have rigidly abstained from the use of mercury. In some cases I have seen the good effects of other remedies entirely interrupted by the mercurial action; and I have likewise seen several instances in which the cure, when mercurials have formed part of the plan, has been protracted to a great length; and a great many in which the full action of mercury has not prevented the regular progress of the disease, and its fatal termination.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, pp. 74-75.
Pressor Responses to Noxious Stimuli in Hypertensive Patients: Effects of Guanethidine Sulfate and Alpha Methyldopa

ALVIN P. SHAPIRO and EMANUEL KRIFCHER

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