infarcts and sudden deaths in people treated with thiazide diuretics, the reason is not clear. It could be due to subtle alterations in K⁺ and/or Mg⁺⁺ content of the cell, although we could not show any alteration in serum K⁺. Alternatively, treatment with thiazide diuretics and relative sodium and volume depletion may cause activation of the sympathetic nervous system, which may be responsible for arrhythmias and sudden death. This may be supported by the apparent protective effect exerted by both β-blocking drugs and centrally acting neuron-blocking drugs.

Monotherapy for treatment of mild hypertension has a theoretic attractiveness but it is essential to evaluate critically the best drug to use.

ACKNOWLEDGMENTS: The help of W. Adam, S. Carney, A. Gillies, J. Myers, M. Wilson, G. Morgan, and S. Waga in these studies is acknowledged.

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Use of Clonidine and Propranolol As Monotherapy in Borderline Hypertension

Christopher Cottier, M.D., and Stevo Julius, M.D.

The effect of clonidine (average 0.24 mg/day) and propranolol (average 105 mg/day) on home blood pressure readings in 16 patients with borderline hypertension was investigated in a randomized, double-blind, placebo crossover design. Patients could detect small but significant decreases of blood pressure with both active compounds (-5/-5 with propranolol and -11/-7 with clonidine). The sympatholytic agents might control the blood pressure in patients with borderline hypertension, and the home blood pressure technique is a convenient tool to detect and monitor such changes. Biochemical predictors of the responsiveness to clonidine were investigated. There was no difference in placebo norepinephrine and renin values between better and lesser responders to clonidine. Plasma norepinephrine fell with clonidine treatment, but with no relationship to the blood pressure response. Plasma norepinephrine response to clonidine might reflect not only the central withdrawal of sympathetic tone, but also, in part, the effect of clonidine on peripheral presynaptic α₂-receptors.

In view of the recent results of the Hypertension Detection and Follow-up Program Cooperative Group (HDPF) and of the Australian National Blood Pressure Study, the recommended level at which hypertension should be treated has been substantially lowered. Consequently, serious consideration is given to providing treatment even at lower blood pressure levels, ie, in patients with borderline hypertension (oscillating above and below 150 mm Hg or 90 mm Hg). We do not suggest treating all patients with borderline hypertension, but believe that treatment should be attempted in the group that is at the highest risk for hypertension and for its complications.

It stands to reason that diuretics which cause a number of chemical side effects may not be an ideal choice for treatment of borderline hypertension in young patients who would be committed to a lifetime of treatment. At these low levels of blood pressure, and over a long period, the chemical side effects may outweigh the positive effect of the lowered blood pressure. Furthermore, patients with borderline hypertension show a strong autonomic nervous involvement in the maintenance of elevated blood pressure. On theoretic grounds, therefore, antiadrenergic agents that decrease either the central sympathetic outflow or block the peripheral receptor responses may be advantageous for the treatment of borderline hypertension.

The major clinical problem in the treatment of borderline hypertension is the variability of clinical blood pressure readings. The problem of separating spontaneous blood pressure variability from the effects of treatment are so large that in all three recent studies of mild hypertension, the authors found it necessary to remove from the trial those patients with occasionally normal readings. We have been advocating the use of home blood pressure readings to aid in the management of borderline hypertension. First, it was found that with simple instruction a large number of subjects can be taught to measure blood pressure accurately. Later, normal values for home blood pressure readings were established, and it was found that about 30 percent of patients with borderline hypertension maintain hypertensive readings at home. The question of whether patients are able to detect small changes of blood pressure at home has not, to our knowledge, been investigated. This is important, since even
study to investigate: (1) whether patients with borderline hypertension are able to detect small changes in home blood pressure readings; (2) whether blood pressure can be lowered with small doses of adrenergic agents given as monotherapy; and (3) whether, among patients with borderline hypertension, one can identify a subgroup particularly prone to respond to adrenolytic agents.

**Materials and Methods**

Thirty-three outpatients were enrolled in the study and taught to measure their blood pressure at home. They were asked to obtain blood pressure reading at home twice a day and return to the clinic after three weeks. Those whose average blood pressure of the last week at home was over 130 or 85 were considered "hypertensive at home" and enrolled in the study. There were 16 such patients (one woman). Four were black Americans. The age was 29 ± SE 1.5 years (range 24 to 47 years). Their first clinic blood pressure readings were 144/96 ± 5/5 mm Hg. None had target organ damage as judged by ECG, serum creatinine, and funduscopic examination.

This was a two-period, double-blind crossover design with a baseline and washout period of placebo before treatment with active compounds. Each period lasted three weeks. Each subject was randomly assigned to either clonidine or propranolol in the first treatment period. The physicians knew that the second period after baseline was placebo. Drugs were either 0.1 mg of clonidine or 40 mg of propranolol. The shapes of all pills including placebo were identical. Treatment was started with two pills, and if the blood pressure did not decrease during the first week, the dose was increased to three pills.

Plasma norepinephrine after 15 minutes in recumbency and plasma renin activity after 30 minutes in upright position were determined at the end of each treatment period. A radioenzymatic assay for catecholamines and radioimmunoassay for plasma renin activity are utilized for assays in our research laboratory.

All patients read, discussed, and signed an informed consent form outlining the purpose and design of the study, including the knowledge that one of the treatment periods would be placebo. The study was approved by the Institutional Committee for Use of Human Subjects for Experimental Purposes.

An analysis of variance for repeated measures with an experiment-wise significance of alpha + 1 percent for multiple comparison was used for statistical assessment of the blood pressure results. When appropriate, paired t test was used for nonrepeated measures.

**Results**

**Blood Pressure Effects**

The average of the last seven days of home blood pressure readings untreated at the entry into the study and later during placebo were practically identical (Fig 1). Each time an active compound was given, this group of patients was able to detect a decrease of average home blood pressure. A further measure of the ability to detect small changes in the average blood pressure readings by the home blood pressure technique can be found in the fact that compared with placebo, in 31 of 32 readings (16 systolic and 16 diastolic) the patient reported lower readings while receiving clonidine. One diastolic reading remained unchanged.

With the doses used in this study, clonidine was more effective than propranolol in lowering blood pressure (Fig 2). This small but significant difference in blood pressure readings with two compounds again attests to the patient's ability to record accurate readings. Overall, there was a good correlation between the blood pressure response to clonidine and to propranolol (r = 0.76), but the formula read: \[ \Delta \text{ mean BP clonidine} = 2.2 \pm 1.03 \Delta \text{ mean BP propranolol} \]. Thus, the blood pressure response was shifted in a parallel fashion toward the clonidine axis across the whole range of blood pressure decreases observed in this study.
Table 1—Response to Clonidine Administration by Diastolic Pressure Decrease

<table>
<thead>
<tr>
<th>Regimen*</th>
<th>Best Responders</th>
<th>Other Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 4)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA, ng/ml/hr</td>
<td>1.50 ± 1.3</td>
<td>1.66 ± 0.86</td>
</tr>
<tr>
<td>PNE, pg/ml</td>
<td>197 ± 99</td>
<td>245 ± 98</td>
</tr>
<tr>
<td>Change from placebo to clonidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA, ng/ml/hr</td>
<td>−0.32 ± 1.3</td>
<td>−0.59 ± 1.1</td>
</tr>
<tr>
<td>PNE, pg/ml</td>
<td>−45.2 ± 46.5</td>
<td>−72.0 ± 119</td>
</tr>
</tbody>
</table>

*PRA = plasma renin activity; PNE = plasma norepinephrine.

Prediction of Response to Clonidine

Patients were divided into those responding to clonidine (diastolic decrease >9 mm Hg, n = 4) and lesser responders (diastolic decrease <9 mm Hg, n = 11). Table 1 shows the characteristics of these two groups.

During placebo phase, plasma norepinephrine and plasma renin levels and changes were similar in both groups. Surprising was that the best responders tended to have lower norepinephrine suppression when receiving clonidine. To analyze this trend further, patients were divided into those whose plasma norepinephrine on clonidine fell most (∆ PNE >100, n = 4) and those whose PNE decrease was less pronounced (∆ PNE <100, n = 12). Blood pressure changes in these two groups were very similar.

DISCUSSION

This study shows that sympatholytic monotherapy in small doses can be used effectively to control the blood pressure in patients with borderline hypertension. Overall the side effects were minor and similar in active compound and placebo groups. However, five of 16 patients taking placebo complained of headaches. Five of the 16 receiving clonidine noted dry mouth, in one this symptom was rather bothersome. None of the subjects complained of sexual dysfunction; tiredness was reported in four subjects taking placebo, five taking propranolol, and five taking clonidine. With the exception of one case of dry mouth, the side effects were considered by the patients to be trivial and would not have interfered with patient compliance had we elected to maintain them further in the study.

We are not advocating therapy in all patients with borderline hypertension. However, it is reasonable to consider treatment in subjects who are at highest risk for future acceleration of hypertension and for cardiovascular complications of hypertension. Criteria for choosing patients for treatment are given elsewhere. In the aftermath of the HDFP and Australian Mild Hypertension studies, many physicians may also decide to treat patients with borderline hypertension. It is, therefore, important to ask whether sympatholytic therapy, which is associated with fewer chemical side effects, is feasible and effective in borderline hypertension. The answer is affirmative.

A major clinical problem in the management of borderline hypertension is the notorious variability of clinical blood pressure, making it nearly impossible to detect small changes in blood pressure in office readings when patients with borderline hypertension are given antihypertensive medication. Yet the goal of treatment is a small change in blood pressure, since these patients have near-normal readings. We earlier demonstrated that about one third of the patients with borderline hypertension show hypertensive readings with the home blood pressure technique. Such patients, in our opinion, are candidates for antihypertensive treatment if the blood pressure can be lowered with small doses that do not cause side effects. Whereas the reliability and prognostic importance of repeated noninvasive blood pressure readings outside the physician’s office has already been documented, it was not clear whether this method will be sufficiently sensitive to depict blood pressure changes resulting from small doses of antihypertensive therapy. The present study demonstrates that patients with borderline hypertension are able to detect small but significant treatment-induced changes in average home blood pressure readings.

In our study, treatment with clonidine (Catapres) resulted in significantly lower blood pressure readings than treatment with propranolol. It must, however, be recognized that the average difference between blood pressure values on the two regimens was small. It is not certain that this statistical significance can be translated into clinical importance. Furthermore, the two drugs were compared within a narrow therapeutic range and with a fixed upper limit of dosage. A different dosage may lead to different results.

This study was, in part, designed to test the hypothesis that patients with neurogenic borderline hypertension, those marked by high plasma renin and high plasma norepinephrine values, will be particularly responsive to the treatment with Catapres. This did not prove to be the case. "Lesser responders" to clonidine had similar plasma norepinephrine and renin values during placebo treatment similar to those of responders. We have no explanation for this observation. Our previous research on markers of neurogenic involvement in borderline hypertension suggests that patients with borderline hypertension who have high renin and high plasma norepinephrine have a higher neurogenic tone. If the observation in the present study is confirmed on a larger sample, this would mean that clonidine is equally effective in borderline hypertensive subjects who do or do not have the stigmas of sympathetic overactivity. The finding that the norepinephrine lowering and blood pressure lowering effects of clonidine do not correlate is not as surprising as it would appear to be. Plasma norepinephrine changes do not necessarily reflect changes of the vascular sympathetic tone. By altering the transmural pressure of carotid baroreceptors, Mancia et al were able to affect substantial changes in total vascular resistance without causing a change in plasma norepinephrine values. Furthermore, a similar lack of correlation between blood pressure and norepinephrine decrease was reported by Schoeppe and Brecht with guanfacine, another hypotensive α-agonist, in the course of chronic treatment of mild hypertension.

Table 2—Changes in Blood Pressure From Placebo to Clonidine

<table>
<thead>
<tr>
<th>Pressure Measurement</th>
<th>NE Responders* (n = 4)</th>
<th>NE Nonresponders (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic, mm Hg</td>
<td>−11.2 ± 5.3</td>
<td>−13.5 ± 8.4</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>−7.0 ± 1.8</td>
<td>−7.5 ± 5.9</td>
</tr>
</tbody>
</table>

*NE = norepinephrine.
Clonidine possesses central and peripheral effects on sympathetic activity. It is conceivable that plasma norepinephrine changes on clonidine reflect not only the central withdrawal of the sympathetic tone, but also in part the peripheral effects of clonidine in presynaptic α₂ receptors.

ACKNOWLEDGMENT: We are grateful to Dr. Stanley Garbus, Boehringer Ingelheim Ltd., for providing the compounds used in this study.

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The Use of Clonidine Monotherapy in Adolescent Hypertension*

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The effect of a centrally acting agent (clonidine) vs a diuretic as a single agent was studied in a group of hypertensive adolescents. Following placebo therapy, adolescents with blood pressure >95th percentile were randomized to clonidine 0.1 mg or hydrochlorothiazide 25 mg, each given twice daily. Following 12 weeks' active treatment, those who had not achieved blood pressure goals proceeded to clonidine 0.2 mg or hydrochlorothiazide 50 mg twice daily. Blood pressure and clinical assessment was performed at two-week intervals. Cardiovascular response to mental stress and pre-post stress catecholamines were obtained prior to active therapy and during therapy. Clonidine therapy significantly lowered systolic and diastolic pressure and heart rate (p <.01). Hydrochlorothiazide significantly lowered systolic pressure only. Mental stress testing resulted in a lower diastolic pressure and heart rate response (p <.01), with lower norepinephrine in the clonidine-treated group. The diuretic group had higher plasma norepinephrine and no significant reduction in stress response. Hypertensive juveniles may be more sensitive to central control of blood pressure and more resistant to diuretics.

Recent blood pressure screening programs in the young have demonstrated that primary hypertension in adolescence is a recognizable entity. A number of adolescents who are unresponsive to nonpharmacologic therapy will require specific pharmacologic intervention to achieve recommended blood pressure goals. Pharmacologic data are sparse regarding the use of antihypertension agents in this age and phase of essential hypertension. Issues to be resolved include the comparative effectiveness of individual antihypertension agents on various parameters of physiologic and cognitive function in juveniles. The purpose of this study was to compare the effectiveness of clonidine vs a diuretic as single-agent therapy in hypertensive adolescents.

METHODS

Participants in the treatment program consisted of adolescents 13 to 19 years of age with fixed hypertension (blood pressure >95th percentile). Secondary causes of hypertension were clinically excluded, and nonpharmacologic maneuvers were ineffective. Each participant received placebo (1 tablet twice daily) for four weeks. During the placebo phase and prior to active therapy, blood specimens were obtained for determinations of electrolytes, creatinine, complete blood cell count, and biochemical profile. Also during the placebo phase, testing of cardiovascular response to mental stress was performed. Plasma catecholamines were determined before and after each stress test. Those adolescents whose blood pressure (systolic or diastolic or both) remained above the 95th percentile after placebo treatment were randomized double-blind to clonidine or hydrochlorothiazide therapy. Active therapy was initiated with clonidine 0.1 mg twice daily or hydrochlorothiazide 25 mg twice daily (low dose). Patients were evaluated clinically at two-week intervals throughout the study. Following 12 weeks of therapy, blood chemistry studies were repeated. Those who had achieved treatment goals (blood pressure <90th percentile) remained at the low-dose schedule. In those who had not achieved treatment goals, the dosage was increased to clonidine 0.2 mg twice daily or hydrochlorothiazide 50 mg twice daily (high dose). Mental stress testing was repeated at 16 to 18 weeks of therapy. Following 24 weeks of total therapy, the blood chemistry studies were repeated, and therapy was discontinued. Individual treatment plans were developed after one month without active therapy.