Effects of Clonidine on 24-Hour Hormonal Secretory Patterns, Cardiovascular Hemodynamics, and Central Nervous Function in Hypertensive Adolescents

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SUMMARY To assess the potential of antihypertensive drugs for interference with somatic growth and sexual development in hypertensive children, the effect of clonidine therapy on various endocrine, cardiovascular, and neuromuscular functions has been examined in five male adolescents with idiopathic hypertension. In studies done before and at the end of 4 weeks of twice-daily clonidine therapy, in an average daily dose of 0.31 mg, no significant effects were noted in the secretory patterns of growth hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, cortisol, aldosterone, or testosterone, measured in blood obtained every 20 minutes for 24 hours. In blood obtained while the patients were supine and then erect, plasma renin activity and norepinephrine levels were significantly lowered after clonidine therapy. Cardiovascular responses to dynamic exercise were little altered beyond a 17% decrease in maximal oxygen consumption. The performance of fine motor skills was minimally altered. These data provide preliminary evidence that clonidine, an antihypertensive drug that affects the adrenergic nervous system, may not interfere with normal growth and maturation in adolescent males. (Hypertension 2: 83-89, 1980)

KEY WORDS • adolescents • clonidine therapy • idiopathic hypertension • hormonal secretion • hemodynamics

THE majority of postpubertal hypertensive adolescents with elevated blood pressures are considered to have idiopathic or essential hypertension, since their high blood pressures have no recognizable, reversible cause.1, 2 Assuming that the elevated blood pressure will usually persist, and knowing that untreated hypertension in adolescents may quickly lead to serious cardiovascular complications,3 we find the use of antihypertensive therapy in such patients of increasing interest.

The various antihypertensive drugs available have similar antihypertensive potency, so their suitability depends mainly on their propensity toward side effects. In children and adolescents, another factor must be considered: the effect of the drugs on various hormones involved in somatic growth and sexual maturation. Effects of these drugs on growth and maturation should be determined before they are given to large numbers of adolescents for prolonged periods of time.

Clonidine is widely used for hypertension in adults. Being a centrally acting α-adrenergic agonist, this drug could affect growth and maturation by altering the level of hormones whose secretion is influenced by α-adrenergic mechanisms. Clonidine has been shown to affect various hormones acutely. After a single intravenous or oral dose of clonidine, growth hormone rises in various animals 4-6 and normal adult humans; 7, 8 prolactin rises in rats 9 and in adult humans; 10 and stress-induced ACTH secretion is inhibited in dogs.11 Moreover, studies in monkeys have shown that pulsatile luteinizing hormone (LH) secretion is under the control of α-adrenergic stimulation: blockade of α-adrenergic tone by phenolamine stops pulsatile LH secretion.12

Since there are no data available on the effects of any antihypertensive agent in adolescent hypertensives, and since clonidine is more likely than most other agents to affect hormonal secretion, we have examined the effects of this drug on various hormones in five male hypertensives aged 14-16 years over a 5-week treatment period. To ensure that the drug would
not interfere with the desire of adolescent boys to engage in strenuous athletics, we determined the cardiovascular responses to maximal physical exercise. Since the most frequent side effect of clonidine is drowsiness, we also assessed the performance of fine motor tasks. The results show little, if any, alteration in hormonal secretory patterns, cardiovascular function, and motor coordination. They provide some assurance for at least the short-term safety of such therapy in male adolescents.

Methods

Subjects

Five adolescent males with systolic blood pressures exceeding 140 mm Hg on four separate examinations over an 18-month period were identified during a screening program of 10,641 eighth-grade children in the Dallas public schools. These readings were above the 99th percentile for age in this population. We obtained approval of the Human Research Review Committee and informed consent of the adolescent and his parent.

The clinical characteristics of the five adolescents are shown in table 1. They were all well into puberty. Secondary forms of hypertension were excluded by the normal results of these procedures: urine analysis; analysis of serum creatinine, blood urea nitrogen, sodium, potassium, cholesterol, and urine metanephrine; assessment of plasma renin activity while the patient was supine and after he remained upright 2 hours; chest roentgenogram, rapid-sequence intravenous pyelogram, electrocardiogram, and echocardiogram.

The adolescents were made to feel comfortable with the personnel and surroundings by repeated contacts prior to the study.

Protocol

Pretreatment Studies

The five adolescents underwent cardiovascular function studies and tests of fine motor skills on separate days prior to clonidine therapy. Subsequently, they were admitted to the Clinical Research Center of the University of Texas Health Science Center at Dallas for a 24-hour, 20-minute-interval blood-sampling study with monitoring of the stages of sleep. That evening, surface electrodes were fitted to monitor the electroencephalogram, electro-oculogram, and electromyogram during sleep. The following morning, a 21-gauge needle was inserted into a forearm vein and attached to a polyethylene catheter that extended into an adjoining room. There blood samples were withdrawn every 20 minutes over the ensuing 24 hours without disturbing the patient who remained in his room reading, watching television, eating at usual times, and sleeping from about 10 p.m. to 6 a.m.

At the beginning of the 24-hour interval, blood samples were obtained with the patient supine and twice during quiet standing: after 5 minutes for catecholamines and after 60 minutes for renin activity. Thereafter, 5 ml of blood were withdrawn every 20 minutes. The samples were centrifuged immediately, an aliquot of each combined to form an integrated 24-hour pool for assays of cortisol, testosterone, and aldosterone, and the remainder frozen for assays of LH, follicle-stimulating hormone (FSH), prolactin, and growth hormone. A 24-hour urine and blood sample was obtained before and at the end of the study for measurement of electrolytes, creatinine, and glucose.

The sleep record was scored and the plasma hormone levels plotted against the sleep histogram.

Drug Therapy

After completion of the pretreatment studies, clonidine was started at a dosage of 0.05 mg at 8 a.m. and 0.15 mg at 10 p.m. in an attempt to minimize drowsiness during school time. On weekly visits, the clonidine dosage was increased by 0.05 mg if the systolic or diastolic pressures remained above the 95th percentile for age and if drowsiness was not a problem.

Posttreatment Study

After 4 weeks on clonidine, the patients were re-admitted to the Clinical Research Center for a second 24-hour study. Drug therapy was continued for another week, when the tests of fine motor skills and cardiovascular function were performed. Therapy was then gradually tapered without incident and the patients kept under observation.

Techniques

Hormone Assays

To minimize interassay variability, radioimmunoassays for LH, FSH, growth hormone, and sodium, potassium, cholesterol, and urine metanephrine; assessment of plasma renin activity while the patient was supine and after he remained upright 2 hours; chest roentgenogram, rapid-sequence intravenous pyelogram, electrocardiogram, and echocardiogram.

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Techniques

Hormone Assays

To minimize interassay variability, radioimmunoassays for LH, FSH, growth hormone, and
prolactin were done simultaneously on all 72 samples from both studies of each patient. Standards, antibodies, highly purified human growth hormone, LH, and FSH for iodination were obtained from the National Pituitary Agency and the National Institute of Arthritis Metabolic and Digestive Diseases. With the techniques used, \(1\) mIU of LH is equivalent to 3.1 mg LER 907 utilizing LH antibody batch No. 2, and 1 mIU of FSH is equivalent to 17 mg LER 907 utilizing LH antibody batch No. 4. The intra-assay variability was 5% to 7%.

Radioimmunoassays for cortisol, \(^{17}\) testosterone, \(^{18}\) and aldosterone \(^{19}\) were done on all 10 integrated plasma pools. To minimize interassay variation, radioimmunoassay for plasma renin activity \(^{20}\) and radioenzymatic assay for plasma epinephrine and norepinephrine \(^{21}\) were done on the four samples from both studies of each subject during the same run.

**Cardiovascular Function**

Echocardiograms were obtained with an EkoLine 20 ultrasonoscope interfaced to an EkoLine 21 strip chart recorder. Studies were obtained from the third or fourth intercostal space and the left parasternal edge, with the subject in the supine position. Dimensions of the left ventricle, septum, and posterior wall were obtained at the onset of the QRS complex with the ultrasound beam passing through the left ventricle at the tips of the mitral valve leaflets. For all dimensions, five consecutive complexes were measured and averaged.

Patients exercised dynamically on a mechanically-braked bicycle ergometer. A continuous-graded exercise program was used, with the workload starting at 300 kiloponometers and increased by 300 kiloponometers every 3 minutes. Blood pressures were measured using a mercury sphygmomanometer connected to a Narco Biosystems program electrophygmonanometer (model PE 300), which was used for semi-automatic cuff inflation. The cuff covered at least two-thirds of the left arm. Systolic and diastolic pressures were recorded at the appearance and disappearance of Korotkoff sounds. A Frank electrocardiogram was displayed continuously and the last minute of each work-load level recorded.

Oxygen consumption was measured continuously using a flow-through hood system. \(^{22}\) Each subject was urged to continue until complete exhaustion. In no case was it necessary to stop the exercise tests because of untoward reactions, arrhythmia, or blood pressures greater than 240 mm Hg systolic or 130 mm Hg diastolic. During the repeat-exercise stress test while on clonidine therapy, all subjects were exercised to the same work-load level for the same duration of exercise.

**Fine Motor Skills**

To assess the possible side effects of clonidine on perceptual-motor coordination, four tasks were used to represent various levels of cognitive demand on fine motor skills. The first consisted of 10 trials of a simple-reaction time task. The second was a choice-reaction task, where subjects were required to depress a microswitch in the presence of one visual stimulus and refrain from responding in the presence of a second stimulus. There were eight target trials embedded in a total of 16 experimental trials. For the third task, subjects were asked to place the tip of a metal stylus as rapidly as possible in a sequence of 28 holes ranging in size from 30 to 3 mm in diameter punched in the face of an upright rectangular easel, without touching the sides of the holes. The subjects' speed of performance, number of errors (defined as the number of times the stylus made contact with the side of the holes), and duration of errors were monitored electronically. The final task, designed to evaluate hand steadiness or tremor, was to place the tip of the stylus in the 3 mm hole of the easel at a given signal and keep it in place for 10 seconds without touching the sides of the hole.

During these four tasks, heart rate and basal conductance levels of electrodermal activity were monitored.

**Analysis of Data**

The individual values of each hormone measured every 20 minutes were plotted with the sleep histogram. The mean values of all 72 samples collected through the 24 hours were taken to compare the pre- and post-therapy levels. With the pooled specimens and the sets of supine and upright values, the data were compared using Student's \(t\) test. Comparison of the scores on the tests of motor skill were done by means of the Wilcoxon matched pairs signed-ranks test.

**Results**

During the 5-week period of clonidine intake, the patients remained active and in school. Their body weight, urinary and plasma electrolytes, and glucose and creatinine clearances were not significantly changed.

**Blood Pressure and Dose of Clonidine**

The systolic blood pressure of all five adolescents was above 140 mm Hg on four examinations over the preceding 2 years. The average diastolic blood pressure ranged from 58 to 89 mm Hg. Although these levels were not inordinately high, they are above the 95th percentile of the large population from which these subjects came, and the systolic pressure above the 99th percentile.

Clonidine was started at a dose of 0.05 mg at 8 a.m. and 0.15 mg at 10 p.m. The dosage was raised at weekly intervals to bring the blood pressure below the 95th percentile for age (table 2). The mean blood pressure levels were reduced from 145/69 to 131/67 with a mean daily clonidine dose of 0.31 mg. In three
TABLE 2. Blood Pressure and Dosage of Clonidine

<table>
<thead>
<tr>
<th>Patient Case no.</th>
<th>Pretreatment Blood pressure* (mm Hg)</th>
<th>Blood pressure (mm Hg) After 2-week therapy</th>
<th>Clonidine dose (mg) a.m.-p.m.</th>
<th>Blood pressure (mm Hg) After 4-week therapy</th>
<th>Clonidine dose (mg) a.m.-p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>142/80</td>
<td>135/80</td>
<td>0.1-0.2</td>
<td>129/76</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>2</td>
<td>148/68</td>
<td>136/70</td>
<td>0.1-0.2</td>
<td>124/72</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>3</td>
<td>142/67</td>
<td>122/66</td>
<td>0.05-0.2</td>
<td>135/80</td>
<td>0.05-0.2</td>
</tr>
<tr>
<td>4</td>
<td>146/58</td>
<td>141/57</td>
<td>0.1-0.2</td>
<td>141/56</td>
<td>0.1-0.3</td>
</tr>
<tr>
<td>5</td>
<td>148/72</td>
<td>120/54</td>
<td>0.1-0.2</td>
<td>126/52</td>
<td>0.1-0.2</td>
</tr>
</tbody>
</table>

*Average blood pressure of four examinations over 2-year period.

patients, moderate daytime drowsiness was noted but only in one (Case 4) did this preclude increasing the dose to lower the blood pressure to the desired level. One patient (Case 5) complained of dry mouth while on clonidine therapy for the first 2 weeks.

Heart rates did not significantly change, averaging 70.6 before therapy and 65.2 after 4 weeks of therapy.

Hormone Levels

The plasma levels of the various hormones of pituitary origin (e.g., LH, FSH, prolactin, and growth hormone) or adrenal origin (e.g., cortisol and aldosterone) and the hormone testosterone were not significantly changed after 4 weeks of clonidine therapy (table 3). Neither the mean levels nor the 24-hour secretory patterns of growth hormone (as measured by samples obtained every 20 minutes) were altered (fig. 1). The patterns of LH were those typical of mid-to-late male puberty, with LH secretory episodes being greater during sleep than while awake.

Although the pattern of growth hormone secretion was not significantly changed, and there was no consistent temporal relationship between clonidine intake and the episodic rises in growth hormone, clonidine therapy did reduce the mean levels of plasma renin activity and plasma norepinephrine in samples of both the supine and upright patients (table 4). The plasma epinephrine levels were not significantly changed.

Despite the significant fall in plasma renin activity, the mean aldosterone level in the plasma pooled from the 24-hour study period was not reduced.

Cardiovascular Function

The response to dynamic exercise before and during clonidine therapy is shown in table 5. Peak heart rates averaged 188 ± 5.8 after therapy, which is not a significant change. Peak systolic blood pressures averaged 208 ± 3.2 and 213 ± 6.6 respectively; diastolic pressures averaged 58.8 ± 19.2 and 49.6 ± 13.9; so neither systolic nor diastolic pressures were altered. The patterns of LH were those typical of mid-to-late male puberty, with LH secretory episodes being greater during sleep than while awake.

Probability values were not significant throughout.
showed a significant change. Endurance was unaffected, but oxygen consumption (ml/min/kg) during dynamic exercise stress fell from an average of 36.4 ± 2.6 to 30.1 ± 2.2 (p < 0.05).

Echocardiographic findings before and during clonidine therapy in these five patients are shown in table 6. No significant changes occurred in left ventricular diastolic dimension. Neither the left ventricular shortening fraction nor left ventricular velocity of circumferential fiber shortening was significantly affected by clonidine, which suggests that this antihypertensive agent does not significantly alter myocardial contractility.

Fine Motor Skills

No changes were observed in the performance of the reaction-time task, choice-reaction task, and rapid-sequence-movement task. Following clonidine, the subjects made significantly more errors on the task designed to evaluate hand steadiness or tremor, the mean number of errors rising from 2.25 to 11.2 (p < 0.05). The mean duration of errors also increased from 205 to 744 msec.

Discussion

Diuretics are likely to be the first drug chosen when antihypertensive drugs are prescribed for children, just as they are for adults. If additional therapy is needed, the next choice is likely to be one of the adrenergic neuronal blockers that either inhibit the neuronal release of catecholamines or block their actions upon the adrenergic receptors. Since the adrenergic nervous system is involved in the control of hypothalamic-pituitary function, these drugs may have various effects on the secretion of the hormones involved in somatic growth and sexual maturation. Therefore, before these drugs are administered for prolonged
TABLE 4. Individual Plasma Renin and Catecholamine Levels and 24-Hour Urine Sodium Excretion Before and During Clonidine Treatment

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Condition</th>
<th>Renin activity (ng/ml/hr)</th>
<th>Norepinephrine (pg/ml)</th>
<th>Epinephrine (pg/ml)</th>
<th>Urine sodium (mEq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>1 hr up</td>
<td>Supine 5 min up</td>
<td>Supine 5 min up</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td>3.19</td>
<td>5.87</td>
<td>168</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0.85</td>
<td>2.33</td>
<td>83</td>
<td>220</td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>0.77</td>
<td>0.43</td>
<td>118</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0.56</td>
<td>1.60</td>
<td>89</td>
<td>223</td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>0.62</td>
<td>1.40</td>
<td>137</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0.21</td>
<td>0.38</td>
<td>68</td>
<td>304</td>
</tr>
<tr>
<td>4</td>
<td>Control</td>
<td>1.98</td>
<td>5.03</td>
<td>152</td>
<td>463</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>1.09</td>
<td>1.60</td>
<td>56</td>
<td>166</td>
</tr>
<tr>
<td>5</td>
<td>Control</td>
<td>2.27</td>
<td>4.07</td>
<td>301</td>
<td>646</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>0.89</td>
<td>1.39</td>
<td>114</td>
<td>477</td>
</tr>
</tbody>
</table>

Mean ± SD
Control: 1.77 ± 1.1 5.16 ± 2.9 175 ± 74 427 ± 161 26 ± 20 23 ± 12 206 ± 37
Treatment: 0.74 ± 1.7 1.52 ± 0.7 82 ± 22 278 ± 121 11 ± 9 20 ± 12 183 ± 24

p values: p < 0.05  p < 0.05  p < 0.025  p < 0.05  n.s.  n.s.  n.s.

TABLE 5. Response to Dynamic Exercise

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Peak heart rate (bpm)</th>
<th>Peak blood pressure (mm Hg)</th>
<th>Peak oxygen consumption (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Treatment</td>
<td>Pretreatment</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>195</td>
<td>196/110</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>210</td>
<td>212/0</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>180</td>
<td>210/90</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
<td>175</td>
<td>214/44</td>
</tr>
<tr>
<td>5</td>
<td>184</td>
<td>170</td>
<td>210/50</td>
</tr>
</tbody>
</table>

TABLE 6. Echocardiographic Findings Before and During Clonidine

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Left ventricular diastolic dimension (cm)</th>
<th>Left Ventricular Shortening Fraction (%)</th>
<th>Left Ventricular Vcf (circ/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Treatment</td>
<td>Pretreatment</td>
</tr>
<tr>
<td>1</td>
<td>4.6</td>
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<td>2</td>
<td>4.9</td>
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<td>3</td>
<td>4.2</td>
<td>4.7</td>
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<tr>
<td>4</td>
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<td>5</td>
<td>5.4</td>
<td>5.6</td>
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</table>

periods to large numbers of children, studies need to be undertaken to determine these effects.

In this study, we have found that over a 4-week interval, therapy with the centrally-acting α-agonist antihypertensive drug clonidine did not alter the secretion of various pituitary, adrenal, and gonadal hormones in five male adolescents. Clonidine was chosen for this initial study because its major action is that of a central α-adrenergic agonist and because it has been shown in acute studies to cause changes in the levels of growth hormone and other pituitary hormones.4-11 The absence of discernible, significant effects in these five boys is reassuring, but obviously other adrenergic-blocking drugs should be tested in both prepubertal and pubertal children, whose responses may differ from these adolescents.

The lack of hormonal effects over 4 weeks of clonidine therapy differs from the changes seen in nor-
al humans and animals given single intravenous or oral doses. In one study on normal men, the intravenous administration of 0.15 mg of clonidine induced hyperglycemia in all subjects, maximal at 15 minutes. Despite the hyperglycemia, serum growth hormone levels rose in eight out of 12 studies. In our study, neither plasma growth hormone nor plasma glucose levels were altered at the end of 4 weeks. Since clonidine was administered over 4 weeks, any acute changes would have been observed had they occurred. Therefore, it is possible that such hormonal changes appear only with the first exposures to the drug.

The patients were receiving pharmacologic doses of clonidine, as shown by their lowered blood pressures and reduced levels of both plasma renin and norepinephrine, a response similar to that in adult hypertensives given the drug. The significant fall in plasma norepinephrine is in keeping with the central α-adrenergic agonist action of the drug to decrease sympathetic outflow. The lower levels of norepinephrine and suppression of adrenergic stimulation may be responsible for the decrease in renin release. Plasma epinephrine levels were unchanged, but the values were at the limit of sensitivity of the assay.

Despite these effects, the cardiovascular responses to maximal exercise were not altered by clonidine therapy in these young patients as shown by similar heart rate and blood pressure responses before and during therapy. The echocardiographic studies at rest demonstrated that the indices of myocardial contractility were not altered by clonidine.

Although some daytime sedation was observed, tests of fine motor skill were little affected by the 4- to 5-week course of therapy. In general, the sedative effects tended to be maximal at the start of therapy and diminished with time.

This study is the first to examine the effects of an antihypertensive drug on the hormonal secretory patterns and cardiovascular responses to exercise and motor skills of hypertensive children. Hopefully, additional data on other antihypertensive drugs will be forthcoming and in children of different ages so that, when therapy is indicated, it can be given with relative assurance that normal growth and development will not be affected.

Acknowledgments

We thank Scott Blackwell, Christy Raimey, Jack Ramsey, Tamara Segel, Tanya Murray, and Shirley Anderson, R.N., for expert technical assistance; Lindy Legler for secretarial work; and Dr. W. A. Pettinger for the assays of plasma renin activity and plasma catecholamines.

References

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_Hypertension_. 1980;2:83-89
doi: 10.1161/01.HYP.2.1.83

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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