Propranolol Effects on Hypertension and the Arterial Wall Beyond the Treatment Period in Turkeys

CHARLES F. SIMPSON, D.V.M., PH.D., AND W. JAPER TAYLOR, M.D.

SUMMARY To determine if the effects of propranolol on hypertension and the arterial wall persisted for a significant time after the medication was discontinued, various parameters were compared at 16 weeks in control turkeys (CC), in birds on the medication from 3 days to 16 weeks (PP), and in others that were treated only from 3 days to 10 weeks (PC). At 16 weeks, arterial blood pressure, maximum rate of pressure increase (dp/dt max), and aortic intimal hyperplasia were lowest in the PP group, intermediate in the PC birds, and highest in the CC turkeys. Likewise, the vascular wall constituted 61% of the radius of the coronary arteries in the CC group, but only 52% and 45% in the PC and PP groups, respectively. At 16 weeks, heart rate was lowest and aortic tensile strength highest in the group that was treated for the entire period, at the end of which the average plasma propranolol level was 97 ng/ml. At the same age, heart rate and aortic tensile strength were approximately the same in the CC and PC groups, and propranolol was not detectable in the plasma. It is concluded that the administration of propranolol to hypertensive turkeys early in life reduced blood pressure, aortic intimal hyperplasia, and arterial wall thickness and that these effects persisted to a significant degree for at least 6 weeks after the medication was discontinued. The higher aortic tensile strength that was produced by propranolol did not persist. (Hypertension 5: 442-445, 1983)

KEY WORDS • heart rate • blood pressure • maximum rate of pressure increase (dp/dt max) • tensile strength • intimal hyperplasia • propranolol • turkey

ALTHOUGH the pathologic effects of systemic hypertension in humans generally become clinically manifest in later life, it is a disorder that may develop at an early age. Serial epidemiological studies of school children in biracial communities of Bogalusa, Louisiana, and St. Louis, Missouri, have demonstrated that hypertension sometimes can be detected in the first decade of life and, contrary to earlier views, is usually not associated with an identifiable cause.1,2 Usually, essential hypertension is present before the fourth decade. Compelling physiologic, biochemical, and pathologic evidence indicates that hypertension, regardless of cause, induces an increase in the mass of vascular smooth muscle and collagen, thereby augmenting peripheral resistance and making it self-sustaining.3,4

To a degree, therefore, the long-term prognosis in hypertension is dependent on the extent to which these structural vascular changes can be prevented or reversed. In genetically hypertensive rats, regression has been induced in regional vascular beds that have been protected from hypertension.5 In these rats, the early systemic administration of a variety of antihypertensive agents (hydralazine and guanethidine, captopril, and various beta-blockers) has been shown to inhibit the development of secondary structural changes in the vessels with the result that blood pressure may remain low even after the cessation of therapy.6-11 However, response to treatment is not uniform in various strains of spontaneously hypertensive rats when drug therapy is introduced at an older age and in renal hypertension.12-14 Studies in humans have been limited, but it appears that the structural component of peripheral resistance may also regress after prolonged drug therapy.15,16

In view of the variability of responses to drugs in the hypertensive rat model, we elected to explore the effects of propranolol on the hemodynamics and arterial wall 6 weeks after cessation of therapy in the hypertensive broad-breasted white turkey (BBW). The systemic arterial pressure is higher in the male of this strain of turkey than in any other common experimental animal,
but responds to many of the same agents that are used in human hypertension, including reserpine,17 β-blockers,18 hydralazine,19 and captopril.20 In addition, a spontaneous fibrous plaque develops in the abdominal aorta of this strain by approximately 5 weeks of age, which becomes frankly atheromatous by about 12 weeks of age21 and resembles closely that seen in humans.22 Accordingly, hemodynamic measurements and quantitation of aortic intimal hyperplasia and tensile strength along with coronary artery thickening were determined in turkeys 6 weeks after cessation of treatment with propranolol from the age of 3 days to 10 weeks.

Methods

Two experiments were conducted. In each trial, three groups of 12 male BBW from a commercially available hypertensive strain were randomized into three study protocols at 3 days of age, except that Groups 2 and 3 were not separated until the age of 10 weeks; hemodynamic data at 10 weeks were pooled from those two groups. The duration of the study period was 16 weeks, with Group 1 receiving the control diet (CC) for the entire time. Group 2 was fed the control diet containing 0.04% propranolol from 3 days until 10 weeks of age and the control diet alone for the remaining 6 weeks (PC). Group 3 received 0.04% propranolol for the total period, 3 days to 16 weeks of age (PP). At 10 weeks of age, and an average weight of 3.5 kg, the turkeys were consuming an average of 110 mg/day of propranolol; at 16 weeks of age, the average weight was 7.4 kg, and they were consuming 165 mg/day of propranolol.

Arterial blood pressure, heart rate, and maximum rate of pressure increase (dp/dt max) were determined in each turkey at 10 and 16 weeks of age by cannulation of the carotid artery following local anesthesia with lidocaine hydrochloride. Blood pressure and heart rate were obtained by using a linear-core P1000 transducer and dp/dt max by use of a differentiator coupler-730 (Narco Bio-Systems, Houston, Texas). All turkeys were sacrificed at 16 weeks of age, and at necropsy two small rings (2.9 mm wide) were removed from each turkey. Aortic tensile strength was determined on the distal ring by a previously described methodology.18 The proximal ring was fixed in 10% neutral formalin, embedded in paraffin, and sectioned at 5 μm. Sections were stained with the orcein Van Gieson elastic fiber stain to outline the intimal plaque so that the length, depth, and elliptical area of aortic intimal hyperplasia could be determined. A microscope stage micrometer was employed for measurement of the dimensions of the ellipsoidal intimal plaques. A section of left ventricle from each turkey was also embedded in paraffin and stained with the orcein Van Gieson stain. The percentage of the radiiuses of four coronary branches per turkey that constituted vascular wall was determined from such tissue sections.

Plasma propranolol concentrations were determined by a fluorometric technique23 for each bird at 10 and 16 weeks of age.

Results

At 10 weeks of age, arterial blood pressure, heart rate, and dp/dt max were higher in the CC than the PP and PC groups of turkeys (table 1). At 16 weeks of age, heart rate and aortic tensile strength (tables 1 and 2) were essentially the same in the CC and PC groups, but aortic tensile strength was highest and heart rate lowest in the PP group. However, at this same age, blood pressure and dp/dt max were highest in the CC group, considerably lower in the PC group and lowest in the PP group (table 1).

The depth of intimal hyperplasia of the abdominal aorta, and therefore the elliptical area, varied at 16 weeks of age among the three treatment groups. This area was largest in the CC group, intermediate in the PC group, and smallest in the PP group (table 2).

From the measurement of the width of the wall and the radius of coronary arteries in sections of myocardium, it was determined that 61% of the radius constituted vascular wall in the CC group, and 52% and 45% in the PC and PP groups, respectively (table 2).

Plasma levels of propranolol varied among the three treatment groups and the age at sampling. At 10 and 16 weeks of age, the CC group had no detectable levels of plasma propranolol. The PP and PC groups at 10 weeks of age contained an average of 12.2 ng/ml of propranolol in the plasma. The plasma of the PC turkeys at 16 weeks of age did not contain detectable

### Table 1. Effect of Treatments with Propranolol on Hemodynamics

<table>
<thead>
<tr>
<th>Diet</th>
<th>Systolic Blood Pressure (mm Hg) 10wks</th>
<th>Diastolic Blood Pressure (mm Hg) 10wks</th>
<th>Systolic Blood Pressure (mm Hg) 16wks</th>
<th>Diastolic Blood Pressure (mm Hg) 16wks</th>
<th>Heart Rate (bpm) 10wks</th>
<th>Heart Rate (bpm) 16wks</th>
<th>DP/DT max (mm Hg/sec) 10wks</th>
<th>DP/DT max (mm Hg/sec) 16wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>203 ±4.8* 152 ±6.1*</td>
<td>225 ±7.4* 167 ±7.0*</td>
<td>303 ±5.9* 280 ±3.9*</td>
<td>1447 ±49.1* 2247 ±93.0*</td>
<td>973 ±63.2*</td>
<td>1307 ±52.4*</td>
<td>1473 ±57.9*</td>
<td>1765 ±57.9*</td>
</tr>
<tr>
<td>PP</td>
<td>134 ±3.3† 103 ±2.8†</td>
<td>143 ±5.8† 105 ±5.7†</td>
<td>236 ±3.4† 232 ±6.2†</td>
<td>793 ±63.2† 1307 ±52.4†</td>
<td>973 ±63.2†</td>
<td>1307 ±52.4†</td>
<td>1473 ±57.9†</td>
<td>1765 ±57.9†</td>
</tr>
<tr>
<td>PC</td>
<td>134 ±3.3† 103 ±2.8†</td>
<td>177 ±6.0† 127 ±5.5†</td>
<td>236 ±3.4† 280 ±7.2†</td>
<td>793 ±63.2† 1307 ±52.4†</td>
<td>973 ±63.2†</td>
<td>1307 ±52.4†</td>
<td>1473 ±57.9†</td>
<td>1765 ±57.9†</td>
</tr>
</tbody>
</table>

C = control diet to 16 weeks of age; PP = propranolol, 3 days to 16 weeks of age; PC = propranolol, 3 days to 10 weeks of age, control diet 10 to 16 weeks of age.

* † ‡ Numerals with different superscripts are significantly different (p < 0.05) from each other.
Discussion

The persistent lowering of blood pressure 6 weeks after the cessation of propranolol administration and the attendant effects of the reduced blood pressure on the arterial wall were striking findings. This continuing influence of the drug long after its discontinuation is similar to that which has been found in spontaneously hypertensive rats and probably was due to an inhibition of the development of smooth muscle cell hypertrophy and increase in collagen which serves to perpetuate, and, perhaps, accentuate hypertension.

Propranolol was effective in inhibiting the development of hypertension and it is of interest that significant decreases in heart rate, blood pressure and dp/dt max were produced with a mean plasma propranolol concentration of 12.2 ng/ml at 10 weeks of age. Indeed, this concentration which is in the lowest range of therapeutic effectiveness in humans was equivalent in action to the much higher drug concentration at 16 weeks. The concentration of propranolol in the feed remained the same for the entire trial of 16 weeks in the case of the turkeys in the PP group; therefore, the high plasma values at 16 weeks probably were a reflection of an increased consumption of feed relative to body weight, or diminished hepatic metabolism.

Serial determinations of plasma propranolol levels and heart rate were not performed between 10 and 16 weeks so that it is impossible to be certain how long a direct pharmacologic effect of propranolol persisted. Indeed, data on plasma or tissue concentrations of the drug after its discontinuation are not available in birds. In humans it is known that propranolol is not detectable in plasma or left atrium and that the responsiveness of cardiac tissue to norepinephrine is normal 48 hours after discontinuation of chronic propranolol therapy. It seems very unlikely that a pharmacologically effective quantity of propranolol was present in the turkeys for more than a few days after the drug was discontinued.

Hypertension has been long known to be one of the major factors for the subsequent development of atherosclerosis. The intimal plaques of the abdominal aortas of turkeys are comparable to the early lesions of human atherosclerosis. Profound retardation of the progression of this lesion was induced by propranolol and the effects persisted after the period of drug administration. This is in contrast to the influence of the agent on aortic tensile strength. Tensile strength relates primarily to the elastic and collagenous tissue of the aorta and although it is clear that propranolol improved tensile strength, this effect was not persistent. The rate of arterial pressure development reflects not only contractile velocity of the heart, but also the degree of elasticity of the arterial wall. It is notable that dp/dt max was lower 6 weeks after cessation of treatment with propranolol in the PC than the CC turkeys. Sympathetic blockade, as judged by heart rate, was no longer present in turkeys 6 weeks after cessation of drug administration, ruling out a form of delayed B-receptor activity. Accordingly, it is probable that the continued reduction in dp/dt max indicated greater distensibility of the arterial wall, probably reflecting decreased collagen deposition.

Since propranolol was started in the two treatment groups at 3 days of age, this study relates most directly to the prevention or amelioration of hypertension rather than to the treatment of established hypertension. It provides evidence that early intervention has a continuing effort not only on the blood pressure alone, but also on the development of aortic intimal plaque formations, coronary artery thickening, and on the preservation of a distensible vascular wall.

Acknowledgments

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References


Table 2. Effect of Treatments with Propranolol on Aortic Plaques, Coronary Artery Walls, and Aortic Tensile Strength

<table>
<thead>
<tr>
<th>Diet</th>
<th>Plaque size (m)</th>
<th>Area plaque (mm²)</th>
<th>Aortic tensile strength (g/mm²)</th>
<th>Coronary artery Wall thickness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Length</td>
<td>Depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2515 ± 151.7*</td>
<td>183 ± 14.5*</td>
<td>0.355 ± 0.03*</td>
<td>123.3 ± 2.3*</td>
</tr>
<tr>
<td>PP</td>
<td>1692 ± 79.2†</td>
<td>127 ± 6.3†</td>
<td>0.138 ± 0.01†</td>
<td>139.4 ± 1.8†</td>
</tr>
<tr>
<td>PC</td>
<td>2366 ± 155.4*</td>
<td>110 ± 11.8†</td>
<td>0.231 ± 0.02‡</td>
<td>124.3 ± 2.5*</td>
</tr>
</tbody>
</table>

C = control diet to 16 weeks of age; PP = propranolol, 3 days to 16 weeks of age; PC = propranolol, 3 days to 10 weeks of age. * † ‡ Numerals with different superscripts are significantly different (p < 0.05) from each other.
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