Racial Differences in Drug Response: Isoproterenol Effects Before and After Propranolol

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The aim of this study was to determine in young, healthy men the relative contribution of pharmacodynamic factors inherent between two groups known to respond differently to hypertensive therapy. Black (n = 10) and white (n = 10) men received an isoproterenol sensitivity test before and after propranolol (0.1 mg/kg, then 50 μg/min). There were greater increases (twofold) in systolic BP following the 1.0- and 1.5-μg isoproterenol dose ($P < 0.05$) in the black group. During propranolol there were no differences in free (1)-propranolol concentrations between the groups; however, propranolol decreased resting heart rate in the white group more than in the black group ($P < 0.05$). Cardiac index decreased less in the black group compared to the white group ($P < 0.05$). Following the second isoproterenol challenge, there again were greater increases in systolic BP in the black group at both the 10- and the 20-μg isoproterenol dose ($P < 0.05$). Our study has highlighted the importance of cross-racial studies in evaluating drug effects.

KEY WORDS: cardiovascular reactivity; isoproterenol; propranolol; ethnic groups; nationality.

INTRODUCTION

Little information exists evaluating racial differences in either basic physiologic mechanisms, e.g., aldosterone excretion (1,2), or pharmacological response differences (3–5). Many of the data used to design pharmaceuticals and, eventually, therapeutic regimens in the United States have been obtained using white males. The results of these studies, when applied to other populations, have a probability of inaccurately predicting optimal therapeutic responses. It has been recognized for many years that racial factors may affect responsiveness to drugs, for example, impaired mydriasis following standard doses of ephedrine and cocaine in blacks (6) and an insensitivity to atropine (7). Black male hypertensive patients respond differently to antihypertensive medication than do white hypertensive patients (8,9). This disparity is most prominent with beta-adrenergic receptor blockers (10,11). Finally, men of Chinese descent have been shown to have at least a twofold greater sensitivity to the beta blocking effects of propranolol than white American men (3). Hence, investigators hypothesize that genetic factors may partially explain these differences. The aim of this study was to investigate in young, healthy men the relative contribution of pharmacodynamic factors inherent between two racial groups.

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METHODS

Experimental Subjects

Approval for the study was obtained from Wayne State University Human Investigation Review Board. Written informed consent was obtained from the subjects before the study was conducted between 7 and 10 AM. A total of 20 (n = 10 black, n = 10 white) healthy, nonsmoking, normotensive American male volunteers was recruited. Subject demographics are shown in Table I.

Drug Administration

An intravenous infusion of 5% dextrose in water was begun at least 15 min before the isoproterenol challenge. Racemic isoproterenol hydrochloride (HCl) (Lot 128215, Elkins-Sinn, Inc., Cherry Hill, NJ) was prepared under sterile conditions in concentrations of 100, 10, and 1 μg/ml and identified carefully. Doses were administered as previously described (4,5,12). Bioimpedance cardiac index monitoring (BoMed Medical Manufacturing Ltd., NCCOM3-R7, Irvine, CA) was begun 30 min before the initiation of isoproterenol and continued throughout the duration of the study at an intermittent rate of approximately every 30 sec. The electrocardiogram (MAC I, Marquette Electronics Inc., Milwaukee, WI) began recording 30 sec before and continued for 2 to 3 min after the isoproterenol injection. Blood pressure was continuously measured every 30 sec using the STAT mode of the Dinamap 1846 SX/P (Critikon, Inc., Tampa, FL).

Immediately after the standardized isoproterenol sensitivity test, racemic propranolol (0.1 mg/kg) (Lot 3890042, Ayerst Laboratory Inc., New York) was injected intravenously over 10 min by means of a syringe pump (SAGE Model 355, Orion Research Inc., Boston, MA). After the initial loading dose, the infusion was decreased to 50 μg/min. Approximately 15 min into the infusion, a second isoproterenol sensitivity test was performed. Blood samples were obtained prior to propranolol and every 20 min during the propranolol maintenance infusion both for the measurement of propranolol isomers by a modification of a previously published high-performance liquid chromatographic assay (HPLC) (13) and for the protein binding experiment. Separation of the enantiomers was accomplished without precolumn derivatization using a mobile phase of hexane:2-propranol:diethylamine (90:9:1, v/v) and a commercially available column with a cellulose tris (3,5-dimethylcarbamate) chiral stationary phase.

Pharmacodynamic Data Analysis

According to the classic receptor theory of drug antag-

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Table I. Subject Demographics and Pretreatment Values at Rest in the Supine Position*

	Height (cm)	Weight (kg)	VEPT** (ml)	BSA*** (m^2)	Age (yr)	Heart rate (beats/min)	Blood Pressure Systolic (mmHg)	Blood Pressure Diastolic (mmHg)	Cardiac index (liters/min/m^2)
Black	174.2 ± 8.5	73.0 ± 8.0	6229.0 ± 1100.6	1.9 ± 0.2	27.0 ± 3.4	62.8 ± 7.2	113.8 ± 8.5	60.9 ± 6.9	3.3 ± 0.8
White	181.3 ± 5.6	77.8 ± 7.3	7043.0 ± 850.0	2.0 ± 0.1	25.0 ± 2.5	63.6 ± 9.7	118.9 ± 4.3	60.0 ± 4.6	3.6 ± 0.9

* Values are mean (±SD). There were no significant differences between the groups.
** Volume of electrically participating tissue.
*** Body surface area.

onism, the following relationship should exist between dose ratio (DR) [i.e., dose of isoproterenol required to increase heart rate by 25 beats/min (CD_{25}) with propranolol divided by CD_{25} without propranolol] and drug concentration (P):

$$DR - 1 = K_a \times P \text{ or } K_a = (DR - 1)/P \quad (1)$$

in which K_a is the (apparent) affinity constant for the binding of propranolol to its receptor. The effectiveness of propranolol is estimated as the DR to isoproterenol. The "apparent" association constant, K_a, for propranolol binding to the receptor is a measure of propranolol sensitivity as greater values imply greater efficacy.

We did not measure systemic vascular resistance directly. Instead, we used (a) peak mean arterial pressures (MAP) and (b) peak cardiac output (CO) data and assumed (c) a right atrial pressure (RAP) of 4 mm Hg and simulated responses. Systemic vascular resistance (SVR) (dynes · sec/cm^5) can be defined as

$$\frac{(MAP - RAP)}{CO} \times 80 \quad (2)$$

Protein Binding

Free fraction was determined in the same samples used for HPLC analysis using standard equilibrium dialysis techniques with correction of volume shift (14). Free isomer concentrations were determined by multiplying the free fraction times the propranolol isomer serum concentrations.

Statistical Analysis

Data are expressed as the mean ± SD unless otherwise stated in the figure. Comparison between racial groups was examined using the Student t test for unpaired data corrected for unequal variance. A statistically significant difference was defined as $P < 0.05$.

RESULTS

Racial Pharmacodynamic Disparity

Isoproterenol Alone. The shared dosing range for isoproterenol was from 0.1 to 1.5 μg. Peak blood pressure responses following isoproterenol are shown in Fig. 1. In all cases there were immediate small decreases in systolic blood pressures following isoproterenol in both groups followed by increases in systolic blood pressures. There were no differences in acute diastolic blood pressure responses. The increase in blood pressure always followed the increase in heart rate and cardiac output. There was a significant difference in systolic pressure changes following the 1.0- and 1.5-μg dose ($P < 0.05$). The black group increased systolic pressures more than the white group at both doses. There were no differences in CD25 between the black and the white group, respectively (1.0 ± 0.7 and 1.1 ± 0.5 μg). There was a modest but significant difference (increase) in peak cardiac index changes from baseline between the two groups only at the 1.0-μg dose (1.6 ± 0.7 and 2.4 ± 0.7 liters/min/m^2, black and white, respectively; $P < 0.05$). There were no differences in calculated baseline SVR between the black and the white groups, 1081.8 ± 321.4 and 945.7 ± 225.4 dynes · sec/cm^5, respectively. SVR simulation demonstrated both groups "decreased" to the same degree.

Intravenous Propranolol. There were no differences between the two groups in either free fraction (0.14 ± 0.04 and 0.14 ± 0.02, black and white, respectively) or free l-propranolol (3.0 ± 0.6 ng/ml and 2.9 ± 0.4 ng/ml, black and white, respectively). If free concentrations (15) of the (l)-propranolol isomer are predominantly responsible for the pharmacological effect (16), then the two groups were studied at indistinguishable free isomer concentrations.

Following the administration of racemic propranolol, 15 min into the maintenance infusion, resting heart rate decreased more in the white group (11.7 ± 4.4 beats/min) compared to the black group (3.4 ± 2.1 beats/min) ($P < 0.05$). Although there were no differences in baseline cardiac indexes between the groups following the first isoproterenol challenge and prior to the propranolol infusion (3.7 ± 0.9 and 4.4 ± 0.8 liters/min/m^2, black and white, respectively), cardiac index decreased more in the white group (1.3 ± 0.3 liters/min/m^2) than in the black group (0.7 ± 0.4 liters/min/m^2) ($P < 0.05$). There were no differences in blood pressure responses.

Isoproterenol Following Propranolol. Over the shared isoproterenol dose range (0.1 to 20.0 μg), peak systolic blood pressure responses after isoproterenol stimulation (during the propranolol infusion) are shown in Fig. 1. There were no differences in diastolic blood pressures between the two groups. However, there were significant increases in peak systolic blood pressure changes at the 10-μg dose (14.6 ± 8.1 mm Hg in the black group, compared to 6.5 ± 3.6 mm Hg in the white group) ($P < 0.05$) and 20-μg dose (26.6 ± 11.3 and 15.0 ± 4.3 mm Hg, black and white, respectively; $P < 0.05$). There were no differences in CD_{25} (25.8 ± 11.6 and 21.6 ± 8.4 μg, black and white, respectively), heart rate, or cardiac index changes following ISO in the presence of pro-

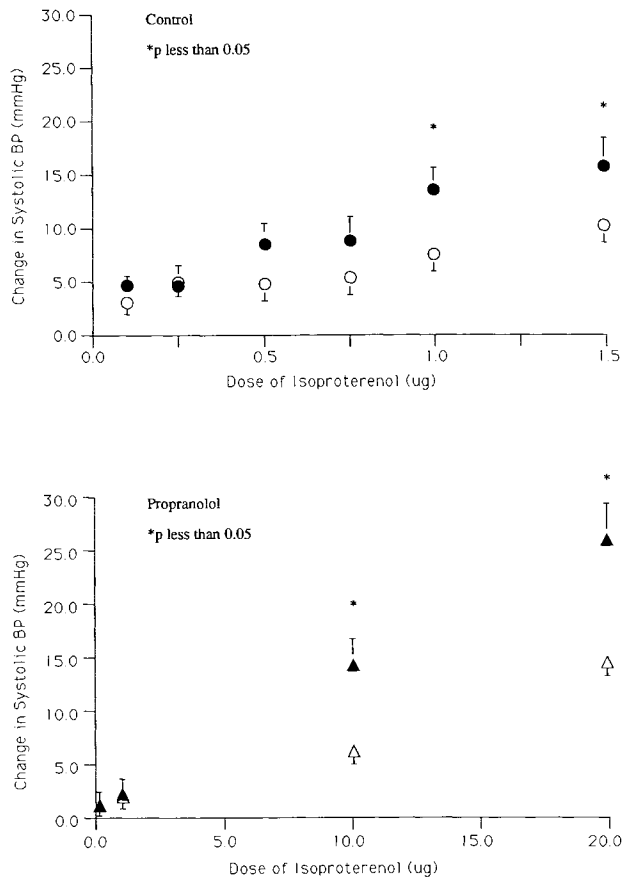

Fig. 1. Change in systolic blood pressures following isoproterenol before and after propranolol. Data are presented as mean (SE). Filled symbols represent the black group and open symbols represent the white group.

pranolol between the groups. Although wide variability occurred in the black group, there were no differences in dose ratio between the black (37.3 ± 28.7) and the white (21.4 ± 6.4) group. Due to the wide variability in physiologic responses, there were no differences in the apparent K_a for free (l)-propranolol binding between the black (12.1 ± 10.4 ml/ng; 95% confidence limits, 4.7 to 19.5 ml/ng) and the white (6.0 ± 2.4 ml/ng; 95% confidence limits, 4.3 to 7.7 ml/ng) groups. There were no differences in baseline SVR, 1098.7 ± 347.3 and 960.6 ± 291.1 dynes · sec/cm^5, black and white, respectively. However, there were larger decreases in the simulated SVR data in the white group (416.3 ± 267 dynes · sec/cm^5) compared to the black group (267.0 ± 193.2 dynes · sec/cm^5) at the 20-μg isoproterenol dose.

DISCUSSION

Young, healthy black and white males respond differently to both isoproterenol before and after propranolol and propranolol alone. Specifically, systolic blood pressures following isoproterenol before and after propranolol were higher in the black group. Propranolol decreased resting heart rate and cardiac index more in the white group.

Racial differences in heart rate responses from isoproterenol both before (4) and after metoprolol (5) have been reported. Racial differences in heart rate response following exercise has been reported (17), i.e., blacks required higher doses of propranolol and longer exercise times before significant reductions in heart rate occurred. It must be emphasized that elevation in plasma noradrenaline is known to occur after exogenous isoproterenol administration in humans (18).

We have not investigated specifically whether the differences we observed with isoproterenol or propranolol were of genetic, environmental, or mixed origin. The reasons for the reported differences are, without doubt, multifactorial. Our study has highlighted the importance of cross-racial studies in evaluating drug effects.

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