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Report

Racial Differences in Drug Response: Isoproterenol Effects on Heart Rate in Healthy Males

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It was the purpose of this study to investigate racial alterations in β-adrenoceptor response. Two groups of healthy, male volunteers gave their consent. There were eight black Americans (mean age, 26.1 ± 2.5 years) and eight white/Caucasian Americans (mean age, 24.4 ± 1.8 years). Each subject underwent an isoproterenol sensitivity test. There was a significant ($P < 0.05$) decrease in the ratio of E_{max} to ED50 in the white group (25.3 ± 6.4) compared with the black group (37.1 ± 12.4). Over the dose range of 0.1 to 1.0 μg there was a significant increase in response at both the 0.25- and the 0.5-μg dose ($P < 0.05$), with the black American group appearing to respond with a greater rate of rise in heart rate following the initial doses.

KEY WORDS: isoproterenol; cardiovascular reactivity; heart rate; pharmacodynamics; American Negroes; American Caucasians.

INTRODUCTION

It has been recognized for many years that racial factors may influence responsiveness to drugs, such as impaired mydriasis following standard doses of ephedrine and cocaine in blacks (1) and an insensitivity to atropine (2). Recently, emphasis has been given to the need for more information regarding cardiovascular disease in black patients. It has been observed that the adult black population has a much higher prevalence of hypertension than the adult white population (3–8). Studies have shown that black hypertensives respond differently to antihypertensive medication than do white hypertensives (9–15). This observation may arise partially from the pathophysiologic basis of the disease. However, physiologic mechanisms must also be investigated. Therefore, it was the hypothesis of this study that altered adrenoceptor function between races may exist. To test this hypothesis, the isoproterenol sensitivity test was used to evaluate heart-rate responses between two racial groups (16–20). To eliminate alterations in drug response that may have a pathophysiological basis, healthy, adult male volunteers were studied. The safety, reproducibility, and sensitivity of the test have been described previously (17,18).

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MATERIALS AND METHODS

Subjects

Approval for the study was obtained from the Wayne State University Human Investigation Review Board. A written informed consent was obtained prior to participation. Two groups of healthy, male volunteers gave their consent. There were eight black Americans aged 23 to 29 years (mean, 26.1 ± 2.5 years) weighing 64 to 90 kg (mean, 73.6 ± 9.5 kg) and eight white/Caucasian Americans aged 23 to 27 years (mean, 24.4 ± 1.8 years) weighing 69 to 120 kg (mean, 85.2 ± 16.3 kg). There were no significant differences in age or weight. All subjects were in good health as determined by history, physical examination, electrocardiogram, 24-hr urinary sodium excretion, and standard blood indices. All subjects were nonsmokers and without a history of drug abuse or dependence. The subjects were drug and alcohol free for at least 1 week prior to and throughout the duration of the investigation. The studies were carried out in the same room with the same personnel between 7 AM and 9 AM. Subjects were studied in the supine position to aid in relaxation and to avoid changes in heart rate. Each subject relaxed for 30 to 45 min prior to participation. After an overnight fast, the procedure, including a description of the likely subjective effects, was explained in detail. Subjects were warned that an intense desire to inhale may occur after isoproterenol administration and that they should try and relax and breathe normally, in an attempt to prevent the effect of hyperventilation on heart rate response. Thereafter, conversation was reduced to a minimum.

Isoproterenol Challenge

An intravenous infusion of 5% dextrose in water was

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begun at least 15 min prior to the isoproterenol challenge. Isoproterenol hydrochloride (HCl) was prepared under sterile conditions at concentrations of 10 and 1 μg/ml. The electrocardiogram (MAC I, Marquette Electronics Inc., Milwaukee, Wis.) began recording 30 sec before and recorded for 2 to 3 min after the isoproterenol injection. Blood pressure (DYNAMAP 1846 SX/P, Critikon, Inc., Tampa, Fla.) was measured continuously. Isoproterenol HCl was given as a rapid injection of no more than 1 ml into the tubing of the fast-running 5% dextrose-in-water drip and flushed with 5 ml of 0.9% saline. Because of individual differences in sensitivity, doses of isoproterenol could not be safely randomized. Routinely, 0.1 μg was the initial dose. If no response was obtained or once the baseline heart rate was reestablished, then 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, and 6.0 μg were given in a stepwise fashion until an increase in heart rate of 30 to 45 beats per minute (bpm) above baseline or an absolute tachycardia of about 145 bpm was achieved. The heart rate was allowed to return to baseline before each injection, which usually required 4 to 5 min. One or two placebo injections were given randomly.

The heart rate before each isoproterenol injection was determined as the mean over 15 consecutive R–R intervals (lead II) of the electrocardiogram. Sinus arrhythmia results from a cyclical variation in heart rate in response to respiration. Therefore the resting heart rate before isoproterenol was computed over a relatively long time period including several respiratory cycles. The peak heart-rate response after the isoproterenol injection was determined as the three consecutive shortest R–R intervals (lead II). The increase in heart rate was calculated as the difference between the mean of the three shortest R–R intervals and the mean baseline R–R intervals.

Pharmacodynamic Analysis

Two pharmacodynamic models were used to fit the increase in heart rate over baseline data (21,22). In practice, it is frequently impractical to estimate E_{max}, i.e., the maximum effect. Therefore, if the isoproterenol doses were low in relation to the ED50 (the dose required to produce 50% of the E_{max}), the effect became proportional to the dose and the linear model was used:

$$E - E_o = S \times D \quad (1)$$

where E is the observed effect following a particular dose (D), E_o is the baseline effect, and S is the slope of the dose versus effect relationship and is a constant value (E_{max}/ED50). Therefore, the essentially nonlinear pharmacodynamic relationship can be approximated by a linear, straight-line relationship. The slope (E_{max}/ED50) may then be used to describe the drug effect in the dose range observed.

If a plateau in the isoproterenol dose versus change in heart rate was achieved in the individual, then the E_{max} model was used. The following equation was used to fit the data:

$$E - E_o = \frac{E_{max} \times D}{ED50 + D} \quad (2)$$

The two models were fit to the data using iterative nonlinear least-squares regression techniques (PCNONLIN, Statistical Consultants, Lexington, Ky.). When a plateau was observed, the ability of each model to describe the dose versus response profile of isoproterenol was compared with the Akaike's information criterion (23).

Statistical Analysis

The data are expressed as the mean ± SD. Comparisons between the two racial groups were performed using an unpaired t test corrected for unequal variance. Statistically significant difference between racial groups was defined as a $P < 0.05$.

RESULTS

Subjective Complaints

Regarding safety, the only untoward effect of isoproterenol noted was the subjective complaint of having the intense desire to inhale. This usually was followed by the observed increase in a "pounding" heart rate. Not all complained of the desire to inhale, but all noticed the increase in heart rate at the upper end of the dosing schedule.

Most subjects required 2 μg of isoproterenol. There were no differences in the mean isoproterenol dose required to achieve the prestudy goal of a 30- to 45-bpm increase in heart rate above baseline. Final isoproterenol doses in the black group ranged from 1.0 to 6.0 μg (mean, 2.4 ± 1.8 μg) and doses in the white group ranged from 1.0 to 4.0 μg (mean, 2.0 ± 1.0 μg).

Resting Heart Rate

Mean resting heart rates were not statistically different between the two groups (Fig. 1). The heart rate at baseline in the black group ranged from 61 to 82 bpm (68.4 ± 7.8 bpm) and that in the white group ranged from 59 to 92 bpm (74.6 ± 12.1 bpm).

Goodness of Fit

In all but three cases, a plateau in response was not achieved and the linear pharmacodynamic model was used to fit the linear portion of the curve. The specific E_{max} and ED50 parameters could not be estimated with confidence, therefore the single parameter of the ratio of the two was calculated. Two black subjects and one white subject, however, had responses that curved toward plateau and therefore the weighted sum of the square deviation was sufficiently reduced to justify fitting the isoproterenol dose versus response data to the E_{max} model. In this case, the E_{max} and ED50 parameters were estimated and the ratio was calculated and used for comparisons between the groups.

Racial Differences in E_{max}/ED50

Table I depicts the comparison of E_{max}/ED50 between racial groups. There was a significant ($P < 0.05$) decrease in the ratio of E_{max}/ED50 in the white group (25.3 ± 6.4) compared with the black group (37.1 ± 12.4). The reason for this is unknown but may be explained partially by presuming that the greater degree of heart-rate change in blacks reflects

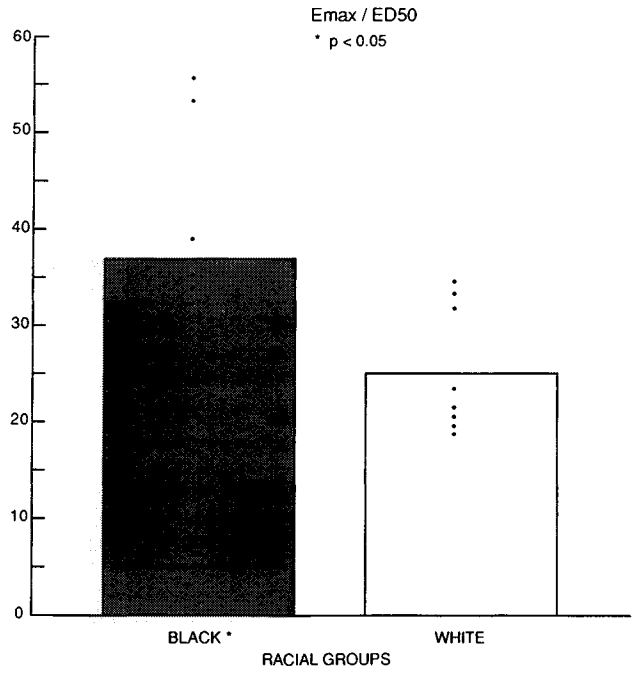

Fig. 1. Baseline heart rates between racial groups. The shaded bar is the black American group and the open bar is the white American group. Data are reoprted as mean ± SD along with the individual data points.

simply a higher degree of β-adrenoceptor activity, i.e., adrenoceptors or events "downstream."

Figure 2 illustrates the isoproterenol dose versus change in heart rate curve of the representative groups over the 0.1- to 1.0-μg dose range. This relationship is graphically displayed because all subjects received the isoproterenol dose up to 1.0 μg. Inclusion of mean data points after this dose would tend to bias the results toward those individuals that required more isoproterenol in order to reach the desired prestudy end point of 30 to 45 bpm above baseline. The rightward shift of the curve in the white subjects suggests that there is a slower rate of rise in heart-rate response over baseline response following exogenous stimulation with isoproterenol. There was a statistically significant difference in response at both the 0.25- and the 0.5-μg dose ($P < 0.05$), which further indicates that the black group as a whole appeared to show a more rapid increase in heart rate following initial isoproterenol dosing.

When simulating a fit of the mean data points in Fig. 2 to the E_{max} model, differences in parameter estimates, i.e., E_{max} and ED50, are observed. The E_{max} estimate for the black population was 43.8 bpm, and that for the white subjects was 37.8 bpm. Larger differences in ED50 are seen, i.e., 0.35 and 0.55 μg for the black and white groups, respectively. It is recognized that fitting mean data like this may be somewhat misleading, in that the individual fits are far more relevant, i.e., Table I. Therefore, it is not the purpose of this simulation to compare the E_{max}/ED50 ratios derived here with the slopes obtained from the best fit of the linear portion of the individual curves. We illustrate only that differences in response between all subjects in each group at the dosing range of 0.1 to 1.0 μg occur and appear to be related primarily to differences in the rate of rise of the dose response curve.

DISCUSSION

While the E_{max} model is considered the basic pharmacodynamic model, the linear model becomes a useful approximation when no maximum effect can be obtained. The present data confirm the hypothesis that racial differences in response to β stimulation exists. This preliminary report is a rather small study, and the bulk of its conclusions of significance rests on two high data points (in blacks) in Fig. 1. However, it should be noted that the white group had over half of the participants in the E_{max}/ED50-ratio range of between 19 and 25, compared to only one in the black group. Clearly, differences in response were observed between the groups and variability appeared to be greater in the black group.

Cardiac vagal activity during intravenous isoproterenol administration is dependent on the method by which the isoproterenol is given. With bolus injections, as in this study, there is a withdrawal of vagal tone (24), but with continuous infusions there is an increase in vagal tone (25). It is not unreasonable to suggest that there may also be different degrees of vagal withdrawal between races since differences in response to atropine have been reported (2).

It is difficult to conclude which parameter shows racial variation since the data are reported here in the form of the ratio of E_{max} to ED50. It is quite possible that differences in both may exist. Recent *in vitro* studies report racial differences in response of the adrenergic α-2 receptors on platelets and adrenergic β-2 receptors on lymphocytes (26). Both lymphocyte and platelet basal cyclic AMP levels were lower in black subjects, as were the responses to either isoproterenol-induced cyclic AMP accumulation in the lymphocytes or inhibition of prostaglandin E_2-induced cyclic AMP accumulation in the platelets.

In summary, there are modest differences in β-receptor responses to exogenous isoproterenol as measured by heart-rate increases above baseline values. Whether

Table I. E_{max}/ED50 Ratios of Each Subject in the Two Racial Groups

	Change in heart rate at an isoproterenol dose of (μg)[a]				
	0.1	0.25	0.5	0.75	1.0
Blacks	8.0 ± 4.0	18.6 ± 6.0	28.0 ± 6.7	29.0 ± 9.2	32.0 ± 11.2
Whites	7.5 ± 3.9	11.5 ± 4.0	16.5 ± 4.3	22.4 ± 4.4	24.7 ± 5.8
t test	NS	$P < 0.05$	$P < 0.05$	NS	NS

[a] Data are expressed as mean ± SD.

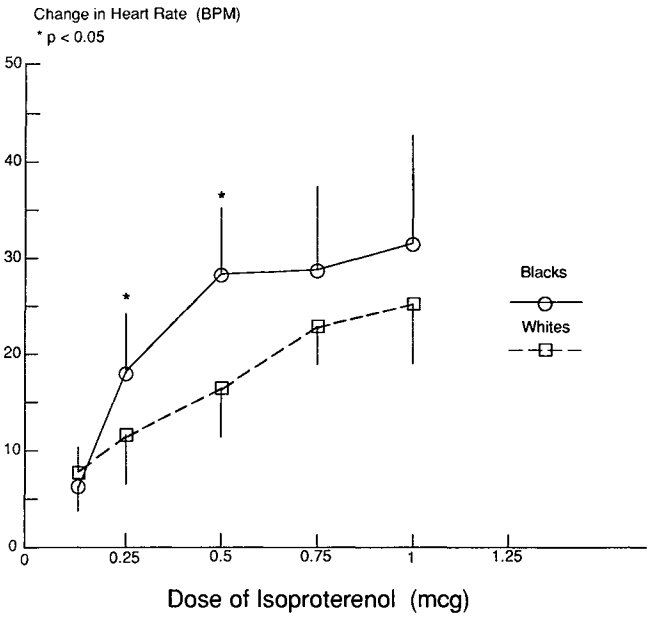

Fig. 2. Change in heart-rate response between the black (○) and the white (□) group over the dosing range of 0.1 to 1.0 μg of isoproterenol.

these differences exist between genders or in patients with disease is unknown.

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