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Racial differences in propranolol enantiomer kinetics following simultaneous i.v. and oral administration

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1 Racial differences in propranolol enantiomer kinetics following oral dosing were previously documented in our laboratory. The purpose of this study was to more completely describe propranolol kinetics in black and white subjects with the goal of gaining a better understanding of the mechanism(s) responsible for racial differences in oral propranolol kinetics.

2 Twelve white and 13 black healthy males were included in the study. Poor metabolizers of dextromethorphan and mephenytoin were excluded. Subjects took oral propranolol 80 mg every 8 h for 16 doses and received an intravenous dose of radiolabelled propranolol with the 16th dose. Serum and urine samples were collected for 24 h after the 16th dose. Serum concentrations of R- and S-propranolol and urine concentrations of its three primary metabolites were determined by h.p.l.c.

3 Apparent oral clearances of R- and S-propranolol were higher ($P<0.05$) in blacks than whites (R-propranolol: 5036 ± 4175 ml min^{-1} *vs* 2854 ± 879 ml min^{-1}; S-propranolol 3255 ± 1723 ml min^{-1} *vs* 2125 ± 510 ml min^{-1}; blacks *vs* whites).

4 R- and S-propranolol clearances were higher in blacks than whites (R-propranolol 1069 ± 316 ml min^{-1} *vs* 841 ± 161 ml min^{-1}; S-propranolol 947 ± 271 ml min^{-1} *vs* 771 ± 142 ml min^{-1}; blacks *vs* whites, $P<0.05$).

5 There were trends ($P>0.05<0.10$) toward higher side chain oxidation, 4-hydroxylation and R-propranolol glucuronidation in blacks compared with whites. Ethnic differences in the enantiomeric ratios of partial metabolic clearance values were not observed.

6 We conclude the higher propranolol oral clearances in black subjects are explained by blacks having slightly higher hepatic metabolism via all three of its major metabolic pathways. Higher propranolol clearances among black subjects were also observed and we conclude this finding is explained largely by the higher hepatic metabolism, but also by slightly higher liver blood flow among black subjects.

Keywords propranolol racial differences pharmacokinetics drug metabolism blacks whites

Introduction

We have previously shown that following administration of equal oral doses of propranolol, black subjects have significantly lower plasma concentrations of both enantiomers of propranolol [1]. The lower concentrations translated into 51% and 34% higher apparent oral clearances (CL_o) of R- and S-propranolol, respectively, in black subjects as compared with white subjects. These racial differences were consistent with previously published reports [2,3]. Propranolol is completely absorbed

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after oral administration and is metabolized almost exclusively by the liver [4]. For a drug with these characteristics, the venous equilibration model predicts that CL_o of unbound drug is the same as intrinsic clearance [4,5]. Thus, the higher CL_o values of propranolol observed in our previous study suggested there may be racial differences in its hepatic drug metabolism. The overall objective of the current study was to describe more adequately the pharmacokinetics of propranolol in blacks and whites with the goal of gaining a better understanding of the mechanism responsible for the racial differences in kinetics following oral propranolol administration.

Propranolol is metabolized to at least 14 metabolites through three major pathways: glucuronidation, side chain oxidation and ring oxidation (Figure 1) [6]. The major urinary metabolites of these pathways are propranolol glucuronide (PG), naphthoxylactic acid (NLA) and 4-OH propranolol (HOP), respectively, with HOP undergoing further conjugation to 4-OH propranolol sulfate (HOPS) and 4-OH propranolol glucuronide (HOPG) [6]. These metabolites (PG, NLA, HOPS and HOPG) have been shown to account for approximately 70% of a propranolol dose and are excellent markers for their respective pathways [6]. We hypothesized that racial differences in propranolol CL_o were a result of differences in hepatic enzyme activity through one or more of the major metabolic pathways and so in the current study we characterized metabolism through these pathways.

Racial differences in hepatic enzyme activity would also be expected to produce racial differences in first pass metabolism, absolute bioavailability and probably clearance (CL) [5]. Thus we evaluated both intravenous (i.v.) and oral pharmacokinetics so that all these parameters could be determined. Because propranolol exhibits nonlinear hepatic first pass metabolism [7,8], calculations of propranolol bioavailability and clearance would be flawed unless concentrations of drug in the liver were identical following administration by oral and i.v. routes. In order to accomplish this experimental condition, we simultaneously administered unlabelled oral propranolol and ^{3}H-labeled i.v. propranolol.

Methods

Subjects

Thirteen African-American males and 13 Caucasian males participated in the study. Women were excluded because of restrictions on administering a radiolabelled compound to women of child-bearing potential. Subsequent to completion of the study, it was learned that one Caucasian subject was a smoker and his data were excluded from the analysis of the study. All other subjects were non-smokers and healthy as determined by medical history, physical examination, routine laboratory evaluation and 12 lead electrocardiogram. Subjects gave written, informed consent prior to participation in the study. The study was approved by the Institutional Review Board at The University of Tennessee, Memphis.

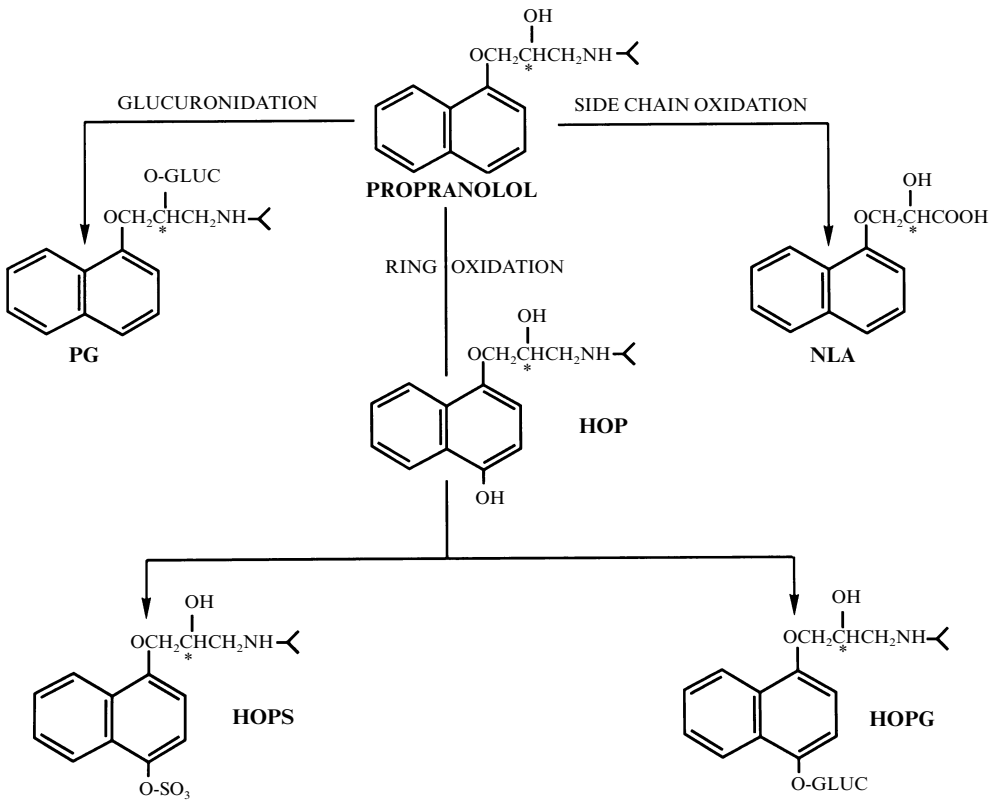

Figure 1 Schematic of propranolol's metabolism through three primary metabolic pathways. Chiral centres are depicted by the asterisk (*). Abbreviations: PG, propranolol glucuronide; HOP, 4-OH propranolol; HOPS, 4-OH propranolol sulphate; HOPG, 4-OH propranolol glucuronide; NLA, naphthoxylactic acid.

All studies were conducted at the University of Tennessee General Clinical Research Center.

Pharmacogenetic phenotyping

CYP2D6 (debrisoquine hydroxylase) and CYP2C19 (mephenytoin hydroxylase) appear to be important enzymes responsible for ring oxidation (formation of HOP) and side chain oxidation (formation of NLA) of propranolol, respectively [9]. Since both enzymes are known to exhibit genetic polymorphisms [10], the pharmacogenetic phenotypes for both enzymes were determined in all subjects prior to their inclusion in the study. Pharmacogenetic phenotypes for CYP2D6 and CYP2C19 were determined using dextromethorphan and *rac*-mephenytoin, respectively, as probes, using slight modifications of previously published methods [11,12]. Extensive metabolizers (EMs) of dextromethorphan were identified by a dextromethorphan/dextrorphan ratio <0.3 and EMs of mephenytoin were identified by a S/R mephenytoin ratio <0.8. Subjects phenotyped as poor metabolizers (PMs) for either enzyme were excluded from the study.

Study protocol

Subjects took oral *rac*-propranolol HCl 80 mg every 8 h for 14 doses on an out-patient basis and recorded the time at which each dose was taken. Subjects abstained from alcohol or caffeine containing food or beverages for 24 h before and during the in-patient study period. Subjects also refrained from using any other medications during the entire study. On the night before the study, subjects were admitted to the Clinical Research Center and received the 15th oral dose of propranolol 80 mg at 23.00 h. The following morning, one indwelling venous catheter was inserted into a forearm vein of each arm. One catheter was used for infusion of radiolabelled propranolol (described below) and the second catheter was used to obtain blood samples. Subjects received the 16th oral dose of propranolol 80 mg at 07.00 h. Subjects fasted from 8 h before until 4 h after receiving the 16th dose.

An intravenous dose of radiolabeled *rac*-propranolol (*rac*-[4-^{3}H] propranolol HCl, specific activity 19.4 Ci mmol^{-1}, radiochemical purity determined by h.p.l.c.: 98.7%, Amersham Life Science, Arlington Heights, IL, USA) was infused over 2 min just prior to 16th dose. The radiolabelled propranolol was diluted in normal saline prepared for parenteral administration in 10 ml, single dose vials by the Sterile Products Laboratory, Department of Pharmaceutical Sciences, University of Tennessee College of Pharmacy. Two 10 µl aliquots were taken from each vial and the radioactive content determined by liquid scintillation counting. Approximately 10 ml of radioactive drug solution was then withdrawn from the vial into a plastic syringe. The syringe was weighed before and after administration to determine the exact volume of radioactive solution administered. The radioactive dose was calculated based on the radioactivity present in the 10 µl samples and the total volume of solution injected. The mean $\pm$s.d. dose of *rac*-[^{3}H]-propranolol administered was 232 ± 28 µCi.

A 10 ml blood sample was obtained immediately before the intravenous dose for use in protein binding studies. Blood samples (20 ml) were collected immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15 and 24 h after the 16th dose. Samples were collected into non-heparinized blood collection tubes, allowed to clot, centrifuged and the serum separated and stored at -20°C until analysis. An additional 10 ml blood sample was collected at 4 h into a heparinized blood collection tube for determination of blood concentration. The blood–serum ratio (B/S ratio) was calculated as the ratio of the concentration of propranolol in blood and serum at the 4 h time point. Urine was collected for the same 24 h period (in two 12 h collections) into bottles containing 2 g of (-)ascorbic acid to prevent oxidation of the hydroxylated metabolites. Total urine volume from each collection period was measured and an aliquot frozen at -20°C until analysis.

Assay methods

Propranolol enantiomer serum concentrations were determined by h.p.l.c. with a chiral stationary phase, using a published method from our previous study; pronethalol was used as the internal standard [1]. The lower limit of detection was 5 ng ml^{-1}; within day CVs were $<2\%$ and between day CVs were $<5\%$ for low and high controls. Eluent fractions corresponding to R- and S-propranolol chromatographic peaks were collected into individual scintillation vials and samples were counted for radioactivity present by liquid scintillation counting (Beckman LS 6000TA, Beckman Instruments Inc., Fullerton, CA, USA). Radioactive counts from liquid scintillation counting were used to determine concentrations (d min^{-1} ml^{-1}) from the [^{3}H]-propranolol i.v. dose.

Urine concentrations of R- and S-PG and R- and S-HOP were determined by h.p.l.c. with slight modifications of an assay published from our laboratory, using pronethalol as the internal standard [13]. Lower limits of detection were 0.1 µg ml^{-1} (5 ng) for PG enantiomers and 0.2 µg ml^{-1} (10 ng) for HOP enantiomers. Within day CVs were all $<5\%$ and between day CVs were all $<10\%$. HOPG, HOPS and PG were deconjugated with 200 µL of a β-glucuronidase/aryl sulphatase mixture (Sigma G-0751, Sigma Chemical Company, St Louis, MO, USA) containing 20 000 units β-glucuronidase and 740 units of sulphatase activity per ml of solution at 37°C for 12–14 h to release the glucuronide and sulphate conjugates. Preliminary experiments suggested that deconjugation of glucuronide conjugates was complete within about 1 h of incubation while deconjugation of sulphate reached a plateau after 8 h. Other experiments showed the amounts of 4-OH propranolol and propranolol were stable from 12 to 24 h of incubation (data not shown).

Urine concentrations of NLA were measured by a

previously published h.p.l.c. technique [14] which was validated in our laboratory. The lower limit of detection for this assay was 0.1 μg ml^{-1} (5 ng) and within day and between day CVs were $<3\%$ and $<6\%$, respectively. Individual enantiomer concentrations of NLA were not determined because Ward *et al.* [9] have shown that metabolism via this pathway is not stereoselective. Serum protein binding of R- and S- propranolol was determined by equilibrium dialysis as previously described [1]. Unbound fraction in blood ($f_{u,b,}$) was calculated as $f_{u,s}$/B:S ratio.

Serum and blood concentration data

Propranolol serum concentrations following intravenous (labelled-[^{3}H]-propranolol) and oral (unlabelled-propranolol) administration were plotted against time and the number of coefficients and exponents were estimated by the method of residuals. The following equation was fitted to serum [^{3}H]-propranolol concentration-time data:

$$C_{\text{i.v.}}(t) = \sum_{i=1}^{n} C_{\text{i.v.}_i} \cdot e^{-\lambda_i \cdot t} \qquad \text{(equation 1)}$$

where $C_{\text{i.v.}_i}$ and λ_i are the ith coefficient and exponent following intravenous administration of [^{3}H]-propranolol. The following equation was fitted to serum propranolol concentration-time data:

$$C_{\text{p.o.}}(t) = \sum_{i=1}^{n} C_{\text{p.o.i}} \frac{e^{-\lambda_i \cdot (t - t_{\text{lag}})}}{(1 - e^{-\lambda_i \cdot \tau})} \qquad \text{(equation 2)}$$

where $C_{\text{p.o.i}}$ is the ith coefficient following administration of the 16th oral dose of propranolol, t_{lag} is the absorption lag time and τ is the dosing interval (8 h). λ_1 was designated as k_a (apparent first order absorption rate constant). Equations 1 and 2 were fitted simultaneously to the intravenous and oral serum concentration time data by weighted least squares regression using the computer program NONLIN (Vax Version 3.0, SCI Software, Lexington, KY, USA). Concentrations of R- and S-propranolol enantiomers were fitted separately. Weights were assigned as 1/observed concentration. NONLIN provided estimates of the coefficients, exponents and t_{lag}. The coefficients were converted from serum to blood concentrations using the B/S ratio. Clearance (CL), volume of distribution at steady-state of total drug (V_{ss}), and elimination half-life ($t_{1/2}$) were calculated by standard equations [15]. Apparent oral clearance (CL_o) and systemic bioavailability (F) were determined as follows:

$$CL_o = \frac{\text{Dose}_{\text{p.o.}}}{\int_0^{\tau} C_{\text{p.o.}}(t)\,dt} \qquad \text{(equation 3)}$$

$$F = \frac{\text{Dose}_{\text{i.v.}} \cdot \int_0^{\tau} C_{\text{p.o.}}(t)dt}{\text{Dose}_{\text{p.o.}} \cdot \int_0^{\infty} C_{\text{i.v.}}(t)dt} \qquad \text{(equation 4)}$$

Volume of distribution at steady-state of unbound drug ($V_{ss,u}$) was calculated as $V_{ss}/f_{u,b}$, hepatic extraction ratio (E) was calculated as 1-F and hepatic blood flow (Q_H) was calculated by $Q_H = CL/E$. The assumptions made in performing these final two calculations were that propranolol is completely metabolized by the liver (e.g. that $CL = CL_H$) and that the fraction absorbed is 1. Data from Kornhauser *et al.* [4] support these assumptions.

Urinary metabolite data

The amount of metabolite (PG, HOP, NLA) excreted in urine from 0 to 12 h ($Ae_{0,12h}$) was determined for the three primary metabolic pathways of propranolol. Partial metabolic clearances of propranolol (CL_m) to each metabolite (PG, HOP, NLA) were calculated from the equation:

$$Cl_M = \frac{Ae_{0,12h}}{\int_0^{12} C_{\text{p.o.}}(t)dt} \qquad \text{(equation 5)}$$

Assumptions implicit to the use of this equation are those above plus that all propranolol metabolites are eliminated renally, and that renal clearance of each metabolite is linear. The sum of $Ae_{0,24h}$ for the three metabolites was related to the 80 mg propranolol HCl dose as per cent dose recovered to obtain a relative estimate of the fraction of drug absorbed (f_a) for comparison between black and white subjects. The purpose of estimating a relative f_a in the current study was not to determine an accurate value for f_a, but rather to be able to assess whether the fraction absorbed was similar in the two groups. Finally, S/R enantiomeric ratios were calculated for CL_o, CL, V_{ss}, $V_{ss,u}$, $t_{1/2}$, F, Q_H, CL_m (HOP, PG), and $f_{u,b}$.

Statistical methods

The sample size was determined by statistical power analysis assuming an α of 0.05 and a β of 0.20 to detect a 35% difference in CL_o, based on data from our previous study [1]. Statistical comparisons between black and white subjects were made using a one-tailed, unpaired t-test with equal or unequal variances, as appropriate. A one-tailed t-test was performed because the direction of the difference between black and white subjects was known to us *a priori*, based on data from our previous study [1]. 95% confidence intervals for the difference in the means were calculated using equal or unequal variance equations, as appropriate. Stereoselectivity was determined by comparing enantiomeric (S/R) ratios to unity. The relationship between CL_o and CL_m to each metabolite (PG, HOP, NLA) was assessed by correlation analysis. Normally distributed data are presented as mean ± s.d. Statistical significance was defined as $P < 0.05$.

Results

The ages (25.4 ± 3.6 years *vs* 25.4 ± 3.3 years, black *vs* white) and weights (84.2 ± 9.2 kg *vs* 79.7 ± 10.1 kg, black *vs* white) of subjects did not differ between groups. Individual fits for R- and S-propranolol serum concentration *vs* time data in a representative subject are shown in Figure 2. For all subjects, 33% of the fitted data points were within 5% of the observed data points, 60% were within 10%, 74% were within 15%, 83% were within 20% and 89% were within 25%.

Mean pharmacokinetic parameter estimates for propranolol are shown in Table 1. Mean CL_o values for R- and S-propranolol were 76% and 53% higher ($P < 0.05$), respectively, in black subjects than white subjects. CL of R- and S-propranolol were 27% and 23% higher ($P < 0.05$), respectively, in black subjects as compared with white subjects. Median and range values of k_a for R- and S-propranolol were 1.04 (0.54–9.48) and 1.06 (0.65–6.97) h^{-1} in black subjects and 1.26 (0.87–2.09) and 1.55 (1.02–2.23) h^{-1} in white subjects. Median and range values of t_{lag} for R- and S-propranolol were 0.55 (0.36–1.47) and 0.49 (0.38–0.99) h in black subjects and 0.46 (0.34–0.92) and 0.43 (0.27–1.32) h in white subjects. Mean B/S ratios for S-propranolol were 0.86 in both

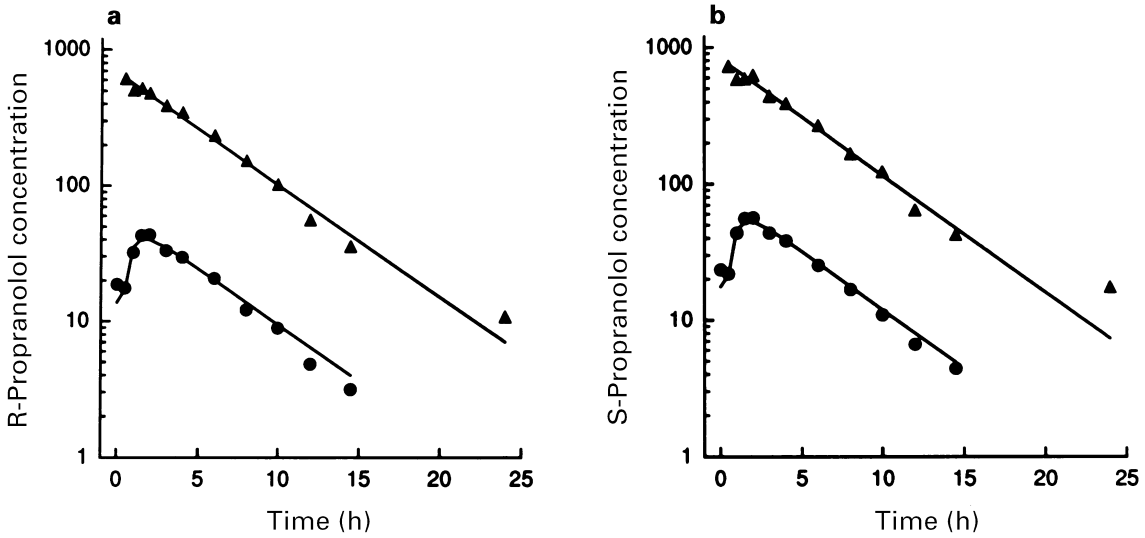

Figure 2 Individual pharmacokinetic model fits for R-propranolol (panel a) and S-propranolol (panel b) in a representative subject. The closed triangles (▲) represent the observed data points from the intravenous dose (d min^{-1} ml^{-1}) and closed circles (●) represent observed data points from the oral dose (ng ml^{-1}). The solid lines represent the fitted line to the data sets.

Table 1 Pharmacokinetic parameter estimates and blood to serum ratios of propranolol enantiomers based on propranolol blood concentrations

		Blacks (n = *13*)	*Whites* (n = *12*)	*95% CI (difference between means)*
CL_0 (ml min^{-1})	S-propranolol	3255 ± 1723	2125 ± 510*	+239 to +2021
	R-propranolol	5036 ± 4175	2854 ± 879*	+69 to +4295
CL (ml min^{-1})	S-propranolol	947 ± 271	771 ± 142*	+26 to +326
	R-propranolol	1069 ± 316	841 ± 161*	+54 to +402
F	S-propranolol	0.34 ± 0.10	0.37 ± 0.07	−0.09 to +0.03
	R-propranolol	0.29 ± 0.11	0.31 ± 0.08	−0.09 to +0.05
Relative f_a		0.80 ± 0.20	0.87 ± 0.11	−0.18 to +0.04
V_{ss} (l)	S-propranolol	329 ± 98	273 ± 32*	+5 to +107
	R-propranolol	397 ± 119	303 ± 45*	+31 to +157
$V_{ss,u}$(l)	S-propranolol	1960 ± 553	1960 ± 491	−360 to +360
	R-propranolol	2220 ± 595	2110 ± 595	−298 to +518
$f_{u,b}$	S-propranolol	0.169 ± 0.030	0.146 ± 0.034*	+0.001 to +0.045
	R-propranolol	0.174 ± 0.036	0.152 ± 0.034	−0.002 to +0.046
$t_{1/2}$ (h)	S-propranolol	4.2 ± 0.79	4.1 ± 0.47	−0.35 to +0.55
	R-propranolol	4.3 ± 0.89	4.2 ± 0.32	−0.37 to +0.57

CI, confidence intervals; CL_0, apparent oral clearance; CL, clearance; F, systemic bioavailability; Relative f_a, fraction of dose accounted for by three major urinary metabolites in 24 h; V_{ss}, volume of distribution at steady-state; $V_{ss,u}$, volume of distribution at steady-state of unbound drug; $f_{u,b}$, unbound fraction of propranolol in blood; $t_{1/2}$, elimination half-life.
Mean ± s.d.
*$P < 0.05$, comparison of black subjects *vs* white subjects.

blacks and whites and for R-propranolol were 0.87 in blacks and 0.89 in whites.

Partial metabolic clearances (CL_m) of propranolol to its three major metabolites after oral dosing are shown in Table 2. These data reveal there were trends (P values between 0.05 and 0.10) toward higher CL_m to R- and S-HOP, NLA and R-PG in black subjects compared with white subjects. Metabolism to both HOP and PG exhibited significant stereoselectivity in both groups.

Figure 3 depicts the relationship between S-propranolol CL_o and CL_M to S-HOP. The relationship was highly correlated and statistically significant in black subjects but not white subjects. Similar observations were made for the relationship between R-propranolol CL_o and CL_m to R-HOP (data not shown). The opposite was seen for the relationship between propranolol CL_o and CL_m to NLA (blacks: $r=0.243$, $P=0.45$; whites: $r=0.837$, $P=0.001$). Significant correlations between propranolol CL_o and CL_m to PG, for both R and S enantiomers were observed in both groups and there were no racial differences in these correlations (data not shown).

Calculation of Q_H based on racemic propranolol kinetics reveals estimated Q_H of 1241 ± 277 ml min^{-1} in white subjects versus 1449 ± 327 ml min^{-1} in black subjects ($P<0.05$). Although CL and CL_o remained different when corrected for body weight, the difference in Q_H was largely explained by the small (non-significant) differences in body weight between the two groups. When Q_H was corrected for body weight, racial differences in Q_H were no longer significant (17.1 ml min^{-1} kg^{-1} in blacks *vs* 15.7 ml min^{-1} kg^{-1} in whites).

V_{ss} of both R- and S-propranolol were higher in blacks than whites. Unbound fraction of propranolol was also higher in black subjects than in white subjects ($P<0.05$ for S-propranolol and $P=0.056$ for R-propranolol). When the contribution of plasma protein binding on V_{ss} was taken into account, the V_{ss} of unbound propranolol ($V_{ss,u}$) was not different between the two groups, suggesting that tissue binding of propranolol does not differ between black and white subjects.

Stereoselectivity was observed in several of the kinetic parameters of propranolol (specifically CL_o, CL, F, V_{ss}, CL_m-HOP and CL_m-PG) however, there were no racial differences in any of the enantiomeric ratios.

Table 2 Estimates (mean $\pm$ s.d.) of partial metabolic clearances of propranolol to its three major metabolites after oral dosing

		Blacks	*Whites*	*95% CI (difference between means)*
CL_m (ml min^{-1})	S-HOP	522 ± 404	338 ± 160	-32 to $+400$
	R-HOP	1430 ± 1690	783 ± 364	-209 to $+1503$
	S/R-ratio	0.44 ± 0.12§	0.44 ± 0.13§	
CL_m (ml min^{-1})	S-PG	692 ± 330	610 ± 148	-96 to $+259$
	R-PG	509 ± 239	392 ± 79	-8 to $+242$
	S/R-ratio	1.42 ± 0.39§	1.58 ± 0.32§	
CL_m (ml min^{-1})	NLA	611 ± 308	453 ± 131	-9 to $+324$

CI, confidence intervals; CL_m, Partial metabolic clearance of propranolol to individual metabolites; HOP, 4-hydroxypropranolol; PG, propranolol glucuronide; NLA, naphthoxylactic acid.
§ $P<0.05$ compared to unity, suggesting stereoselective metabolism.

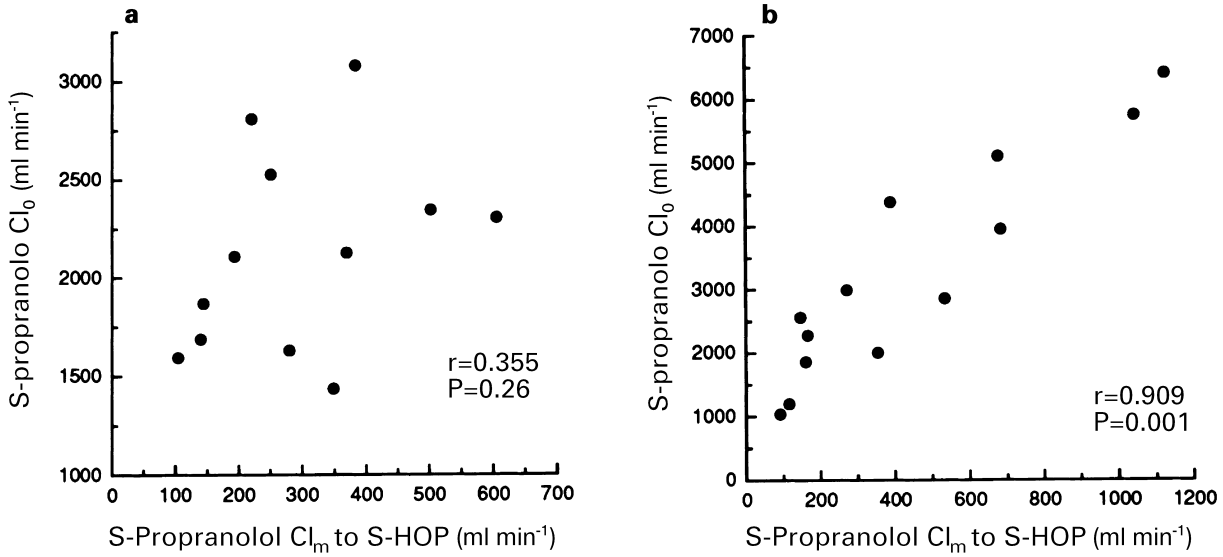

Figure 3 Relationship between S-propranolol oral clearance and partial metabolic clearance to S-4-OH-propranolol in white subjects (panel a) and black subjects (panel b). Individual data points are depicted by the closed circles (●).

Discussion

In the current study we confirmed the results of our previous study [1] that CL_o for both propranolol enantiomers was higher in healthy black men than in healthy white men. Based on the results of our original study, our hypothesis for the current study was that the racial differences in CL_o were due to differences in hepatic drug metabolism. To assess differences in metabolism in the current study, we determined partial metabolic clearances for propranolol's three major metabolites. We originally anticipated the observed racial differences in CL_o would be explained by large differences in one metabolic pathway. However, rather than observing large differences in a single pathway, we observed smaller differences in all three pathways. All three metabolic pathways (NLA, R- and S-HOP and R-PG) exhibited trends toward higher activity in blacks than whites (P values between 0.05 and 0.10). These data suggest that racial differences in CL_o are likely explained by slightly higher hepatic metabolism via all three propranolol metabolic pathways among blacks.

These findings of slightly higher metabolism lead to questions about specific enzymes which may exhibit different activities between black subjects and white subjects, particularly the cytochrome P450 enzymes. As described earlier, CYP2D6 is an important enzyme responsible for metabolism of propranolol to HOP. Data from other studies suggest that CYP2D6 accounts for 50 to 90% of total propranolol 4-hydroxylation, with the remaining 10–50% of propranolol 4-hydroxylation occurring via another CYP enzyme(s) [9,16–18]. Based on this, one reasonable hypothesis is that there may be racial differences in CYP2D6 activity. To test this hypothesis, we recently completed a study in which we compared CYP2D6-mediated metabolism in blacks and whites, using metoprolol with and without quinidine as the probe drug [19]. Data from that study suggest that there are no racial differences in metabolism via CYP2D6. The other cytochrome P450 enzyme(s) responsible for propranolol 4-hydroxylation have yet to be identified. However, based on the above data, it seems reasonable there may be differences between blacks and whites in the activity of this enzyme. We are currently working to identify this enzyme and characterize its activity in human liver microsomes from black and white donors.

Several CYP enzymes are also probably involved in the side chain oxidation of propranolol. Recent studies have shown that CYP1A2 is the major enzyme responsible for formation of the initial product of side chain oxidation (desisopropylpropranolol, DIP) (not shown in Figure 1) [17,18]. Differences in urinary NLA concentrations between CYP2C19 (mephenytoin hydroxylase) EMs and PMs suggest CYP2C19 may be responsible for conversion of the initial metabolite (DIP) to NLA [9]. Racial differences in the activity of either of these enzymes may be responsible for the observation in the current study of trends toward higher CL_m to NLA among blacks.

The relationships between CL_o and CL_m to HOP (shown in Figure 3 for S-propranolol) and to NLA are striking. While the variability in CL_m to HOP accounted for 83% of CL_o variability among blacks, the same relationship was non-significant among whites. Conversely, variability in CL_m to NLA accounted for 70% of CL_o variability among whites, yet was a non-significant relationship among blacks. The precise meaning of these racial differences in correlations is unclear.

As could be predicted from the venous equilibration model, CL of both propranolol enantiomers was higher in black subjects than in white subjects. Since propranolol is a moderately high extraction drug, its CL is dependent on both hepatic metabolism (intrinsic clearance) and also on liver blood flow [4,5]. We conclude that most of the observed difference in CL is explained by differences in hepatic metabolism. However, the small (approximately 9%) differences in weight-corrected Q_H also appear to contribute to the racial differences in propranolol CL.

Somewhat surprising was the lack of difference in absolute F. Since the aspect of F we expected to differ between blacks and whites was first pass metabolism, we needed to determine that extent of absorption of propranolol was similar in the two groups. The per cent of dose accounted for (relative fa) was not significantly different between groups and averaged 80% in blacks and 87% in whites. Since relative fa and absolute F were not different between the two groups, we conclude there were also no differences in hepatic first pass metabolism. The determinants of first pass metabolism are intrinsic clearance and Q_H in the following relationship (according to the venous equilibration model): $f_{fp} = Q_H/(CLint + Q_H)$. We conclude the lack of difference in F between blacks and whites is the consequence of differences in Q_H partially offsetting the differences in intrinsic clearance or drug metabolism.

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