Clinical Investigation

Nicotine Metabolism and Intake in Black and White Smokers

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Context.—Racial differences in tobacco-related diseases are not fully explained by cigarette-smoking behavior. Despite smoking fewer cigarettes per day, blacks have higher levels of serum cotinine, the proximate metabolite of nicotine.

Objective.—To compare the rates of metabolism and the daily intake of nicotine in black smokers and white smokers.

Design.—Participants received simultaneous infusions of deuterium-labeled nicotine and cotinine. Urine was collected for determination of total clearance of nicotine and cotinine, fractional conversion of nicotine to cotinine, and cotinine elimination rate. Using cotinine levels during ad libitum smoking and clearance data, the daily intake of nicotine from smoking was estimated.

Setting.—Metabolic ward of a university-affiliated public hospital.

Participants.—A total of 40 black and 39 white smokers, average consumption of 14 and 14.7 cigarettes per day, respectively, of similar age (mean, 32.5 and 32.3 years, respectively) and body weight (mean, 73.3 and 68.8 kg, respectively).

Main Outcome Measures.—Clearance (renal and nonrenal), half-life, and volume of distribution of nicotine and cotinine and the calculated daily intake of nicotine.

Results.—The total and nonrenal clearances of nicotine were not significantly different, respectively, in blacks (17.7 and 17.2 mL·min^{-1}·kg^{-1}) compared with whites (19.6 and 18.9 mL·min^{-1}·kg^{-1}) (P=.11 and .20). However, the total and nonrenal clearances of cotinine were significantly lower, respectively, in blacks (0.56 and 0.47 mL·min^{-1}·kg^{-1}) than in whites (0.68 vs 0.61 mL·min^{-1}·kg^{-1}; P=.009 for each comparison). The nicotine intake per cigarette was 30% greater in blacks compared with whites (1.41 vs 1.09 mg per cigarette, respectively; P=.02). Volume of distribution did not differ for the 2 groups, but cotinine half-life was higher in blacks than in whites (1064 vs 950 minutes, respectively; P = .07).

Conclusions.—Higher levels of cotinine per cigarette smoked by blacks compared with whites can be explained by both slower clearance of cotinine and higher intake of nicotine per cigarette in blacks. Greater nicotine and therefore greater tobacco smoke intake per cigarette could, in part, explain some of the ethnic differences in smoking-related disease risks.

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tality from lung cancer than do white men, while rates among women are similar in these 2 racial groups.[2,4] Differences in smoking rates and socioeconomic status between blacks and whites explain most of the observed differences in lung cancer incidence and mortality among men.[2] However, available evidence indicates that blacks have a lower risk of developing and dying from COPD compared with whites, and this discrepancy in racial differences in smoking-related diseases is unexplained.[2] In addition, the risk for low-birth-weight infants among black women is greater than that for white women after adjusting for cigarette consumption.[5,6]

Cigarette-smoking behavior differs substantially by race and sex in the United States.[7] Blacks have had an overall higher prevalence of cigarette smoking since 1965,[7] but data for 1994 show similar overall rates, with 26.3% of whites and 27.2% of blacks reporting current cigarette smoking.[8] However, sex differences persist as black men continue to smoke at higher rates than white men (33.9% vs 28.0%), while black women smoke at lower rates than white women (21.8% vs 24.7%).[8] Black smokers smoke differently than whites with consistently fewer reported cigarettes smoked per day compared with their white counterparts and a predominant preference for mentholated cigarettes.[7,9] Despite smoking fewer cigarettes per day, black smokers have higher levels of serum cotinine, the proximate metabolite of nicotine, after controlling for number and yield of cigarettes.[10] This observation raises the questions of racial differences in accuracy of self-reported number of

LUNG CANCER and chronic obstructive pulmonary disease (COPD) are primarily diseases of cigarette smokers, with estimated smoking-attributable mortalities in excess of 80% among both men and women.[1] The incidence and mortality of lung cancer and COPD differ by race and sex between blacks and whites.[2-4] Black men have a higher incidence of and mor-

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I suspect that the blacks extract more from their cigarettes then do the whites (eg. shorter butts) in a link to SES. Menthol involvement unclear.

Chris

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CHRIS COGGINS

cigarettes smoked,[11] in the intensity of smoking cigarettes, and whether nicotine and/or cotinine are metabolized differently in blacks compared with whites.

Racial differences in nicotine metabolism could be important in understanding differences in smoking behavior and rates of some smoking-related diseases. Cigarette smokers tend to regulate their tobacco consumption to gain the desired effects of nicotine, which are related to the levels of nicotine in the body.[12,13] Nicotine is extensively metabolized in the liver, and there is considerable individual variability in the rate of nicotine metabolism.[14-17] Persons who metabolize nicotine more rapidly would need to smoke more to maintain the same level of nicotine in the body than those who are slower metabolizers of nicotine.

The objective of our study was to compare the rates of metabolism of nicotine and its metabolite cotinine in black smokers and white smokers. Based on the metabolism data, we were also able to estimate the daily intake of nicotine from cigarette smoking, which presumably reflects the intake of other tobacco smoke toxins, in the same individuals.

METHODS
Participants

Volunteers were recruited through posted advertisements in the San Francisco, Calif, black community and at local community colleges. Eligibility criteria included (1) being in good health on the basis of history, physical examination, electrocardiogram, and blood chemistries; (2) age 21 to 64 years; (3) male or nonpregnant female defined by surgical sterilization or negative pregnancy test result; and (4) self-identified as non-Latino white or black. Exclusion criteria were habitual use of any prescription medication, narcotic or sedative drug addiction, or long-term alcoholism. Eligible subjects received $250 for completing the study successfully. Black subjects and white subjects were matched by sex and age within 5 years. Subjects were also stratified by self-reported cigarette consumption of 1 to 9 or 10 or more cigarettes per day.

Screening Procedure

Potentially eligible subjects completed a questionnaire on demographic items, smoking history, current smoking behavior, medical history, and habitual use of prescribed medications, alcohol, and other drugs. At the time of the eligibility evaluation, blood was collected and analyzed for serum cotinine as a measure of ad libitum nicotine intake from cigarette smoking and for routine screening tests (complete blood cell count, chemical analyses of the blood, evalua-

tion for hepatitis B antigen) to determine eligibility. The screening cotinine blood samples were collected from all participants in the afternoon. Results of the questionnaires and blood tests were reviewed by a physician prior to contacting the potential participant.

Experimental Procedure

Eligible subjects were asked to come to the clinical study center at San Francisco General Hospital between 7 and 8 AM, at which time they completed questionnaires on smoking behavior, including a scale to measure physical dependence on tobacco.[18] Subjects were asked to abstain from food and cigarette smoking from 10 PM the previous night until arrival at the clinical study center. Overnight abstinence from tobacco was assessed by measurement of plasma concentration of nicotine (unlabeled) prior to the infusion.

Venous catheters were placed in both forearms. Subjects received a simultaneous infusion of deuterium-labeled nicotine-d_2 (3',3'-dideuteronicotine) and cotinine-d_4 (2,4,5,6-tetradeuterocotinine) for 30 minutes. Smokers of 10 or more cigarettes per day received $2.0\,\mu g \cdot kg^{-1} \cdot min^{-1}$ of nicotine-d_2 and cotinine-d_4; infusions of this dose result in nicotine blood levels similar to those observed with cigarette smoking and are tolerated well by habitual smokers.[13,14] A modified dose of $1.5\,\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered to self-reported smokers of 1 to 9 cigarettes per day. During all infusions, subjects were monitored by continuous electrocardiography and frequent blood pressure measurements taken by an automated blood pressure machine. Two hours after the end of the infusion, subjects were given a light breakfast. Subjects were allowed to smoke their cigarettes freely after 1 PM or about 5 hours after the beginning of the labeled nicotine and cotinine infusion.

Blood samples (5 mL) for measurement of nicotine and cotinine levels were collected at 0, 10, 20, 30, 45, 60, 90, 120, 240, 360, and 480 minutes, and then 24, 48, 72, and 96 hours after the infusion to include at least 3 half-lives for cotinine.[13] Urine was collected during the infusion and up to 480 minutes thereafter. The study had approval of the University of California, San Francisco (UCSF), Committee on Human Research.

Analysis of Nicotine and Cotinine in Biological Fluids

Analysis of blood samples for concentration of nicotine and cotinine at the eligibility evaluation was performed by gas chromatography (GC) with nitrogen-phosphorus detection.[19] Assays of samples collected during and after infusion of

labeled nicotine and cotinine were performed by GC with mass-selective detection.[20] Gas chromatography–mass spectroscopy (GC-MS) was required because the metabolic studies were performed using deuterium-labeled nicotine and cotinine.[21] Labeled compounds are necessary for metabolic studies because smokers already have considerable levels of nicotine and cotinine in their bodies that would make measurements of clearance of unlabeled nicotine or cotinine impossible. Internal and external quality-control procedures are used routinely in the laboratory. Samples were frozen and assayed in batches. The GC-MS assay sensitivity is $0.003\,\mu mol/L$ (0.5 ng/mL) for nicotine and 28 nmol/L (5 ng/mL) for cotinine. The GC assay previously described[19] was modified for use with a capillary column and simultaneous extractions and chromatography of nicotine and cotinine.[20] The GC assay sensitivity for nicotine is $0.006\,\mu mol/L$ (1.0 ng/mL) and for cotinine is 57 nmol/L (10 ng/mL).

Nicotine and Cotinine Salts

Nicotine-d_2 tartrate and cotinine-d_4 base were synthesized as described previously and purified by multiple recrystallizations and purity certified by microanalysis (C,H,N), thin-layer chromatography, and GC-MS.[22] Deuterium-labeled nicotine and cotinine were made up in 0.9% sodium chloride, sterilized by autoclaving, and sealed under nitrogen in vials by the Pharmaceutical Preparations Laboratory at UCSF. Specimens were pyrogen tested, and concentrations of nicotine and cotinine were measured by GC prior to use in subjects.

Pharmacokinetic Analysis

Pharmacokinetic parameters were estimated from blood concentration and urinary excretion data using model-independent methods described previously.[23] The terminal elimination rate constant and half-life were determined from the slope of the terminal log blood concentration–time curve using linear least squares regression. Total clearances were computed as $CL_{nic} = Dose\,(nic - d_2)/AUC(nic - d_2)$ and $CL_{cot} = Dose\,(cot - d_4)/AUC(cot - d_4)$, where CL is clearance; AUC, area under the curve; nic, nicotine; and cot, cotinine. Renal clearances were calculated as urinary excretion of nicotine or cotinine divided by the AUC, on urine collected for the 8 hours during and after the infusion while subjects were on the research ward. Metabolic clearance was estimated as total clearance minus renal clearance.

Fractional conversion of nicotine to cotinine (f) was estimated using blood levels of cotinine generated from infused nicotine and the clearance of cotinine it-

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Table 1.—Smoking and Demographic Characteristics of Black and White Smokers*

Characteristic	Blacks (n = 40)	Whites (n = 39)	P Value
Age, y	32.5 (30.0-35.0)	32.3 (28.8-35.8)	.93
Male, %	50	51	>.99
Education, y	12.8 (11.7-13.8)	13.9 (13.2-14.6)	.08
Employed, %	45	64	.02
Body weight, kg	73.3 (69.0-77.6)	68.8 (65.0-72.5)	.11
Cigarettes per day	14.0 (11.4-16.6)	14.7 (11.0-18.3)	.75
Menthol brand, %	78	5	<.001
FTC nicotine, mg	1.1 (1.1-1.2)	1.0 (0.9-1.1)	.005
FTC tar, mg	15.9 (15.1-16.6)	14.1 (12.8-15.5)	.03
FTC CO, mg	16.4 (15.6-17.1)	14.0 (13.2-14.8)	<.001
Smoking history, y	15.2 (12.6-17.7)	15.3 (11.5-19.1)	.96
Fagerstrom Tolerance score	3.7 (2.9-4.5)	3.4 (2.2-4.7)	.68
Time to first cigarette of day, min	43.8 (20.3-67.2)	111.7 (53.7-169.8)	.03

*Values are mean (95% confidence interval) unless indicated otherwise. FTC indicates Federal Trade Commission method yields based on smoking-machine testing; CO, carbon monoxide.

Table 2.—Disposition Kinetics of Nicotine in Black and White Smokers*

	Blacks (n = 40)	Whites (n = 39)	P Value
Clearance			
mL·min^{-1}	1276 (339)	1328 (359)	.57
mL·min^{-1}·kg^{-1}	17.7 (4.9)	19.6 (5.7)	.11
Vss, L·kg^{-1}	2.92 (0.70)	3.09 (0.90)	.35
Nicotine t$_{1/2}$, min	134 (31)	129 (30)	.47
Renal clearance			
mL·min^{-1}	62 (51)	43 (39)	.09
mL·min^{-1}·kg^{-1}	0.89 (0.77)	0.66 (0.60)	.19
Nonrenal clearance			
mL·min^{-1}	1243 (358)	1282 (367)	.66
mL·min^{-1}·kg^{-1}	17.2 (4.8)	18.9 (5.9)	.20

*Values are mean (SD). Vss indicates steady-state volume of distribution; t$_{1/2}$, half life.

Table 3.—Disposition Kinetics of Cotinine in Black and White Smokers*

	Blacks (n = 40)	Whites (n = 39)	P Value
Clearance			
mL·min^{-1}	40 (13)	46 (15)	.07
mL·min^{-1}·kg^{-1}	0.56 (0.17)	0.68 (0.24)	.009
Vss, L·kg^{-1}	0.75 (0.11)	0.80 (0.19)	.16
Cotinine t$_{1/2}$, min	1064 (257)	950 (296)	.07
f Conversion	0.77 (0.08)	0.77 (0.11)	>.99
Renal clearance			
mL·min^{-1}	7.3 (2.9)	5.8 (2.3)	.02
mL·min^{-1}·kg^{-1}	0.10 (0.04)	0.08 (0.04)	.10
Nonrenal clearance			
mL·min^{-1}	34.1 (14.1)	41.2 (15.0)	.05
mL·min^{-1}·kg^{-1}	0.47 (0.18)	0.61 (0.25)	.009

*Values are mean (SD). Vss indicates steady-state volume of distribution; t$_{1/2}$, half life; and f, fractional conversion of nicotine to cotinine.

Table 4.—Nicotine Intake From Cigarette Smoking in Blacks and Whites*

	Blacks (n = 40)	Whites (n = 39)	P Value
No. of cigarettes per day	14.0 (8.2)	14.7 (11.2)	.75
Plasma cotinine			
nmol/L	1329 (774)	1005 (767)	.06†
ng/mL	234 (131)	177 (135)	.06†
Plasma cotinine per cigarette			
nmol/L	110 (58)	74 (44)	.003
ng/mL	19.3 (10.3)	13.0 (7.7)	.003
Daily nicotine intake, mg	16.7 (8.8)	15.0 (12.0)	.47
Nicotine intake per cigarette, mg	1.41 (0.89)	1.09 (0.74)	.02†

*Values are mean (SD).
†P = .02 with log transformation.

self, determined by infusion of cotinine: $f = [AUC(cot - d_2)/Dose(nic - d_2)]CL_{cot}$.

Daily intake of nicotine from tobacco was estimated based on knowledge of fractional conversion of nicotine to cotinine and total clearance of cotinine, as described and validated previously.[23] At steady state, the estimation was based on the following: $COT_{gen} = COT_{elim} = fD_{nic}$, where COT_{gen} is the amount of cotinine generated from nicotine; COT_{elim}, the amount eliminated from the body per day; f, the fractional conversion of nicotine to cotinine; and D_{nic}, the daily intake of nicotine. Cotinine elimination rate can be estimated as the product of average plasma cotinine concentration (C_{cot}) during habitual cigarette smoking and total body clearance of cotinine (CL_{cot}): $COT_{elim} = C_{cot} CL_{cot}$. Combining these 2 equations, $D_{nic} = C_{cot} CL_{cot}/f$. Based on each of these parameters, we estimated the daily intake of nicotine and, using the reported daily cigarette consumption, nicotine intake per cigarette for each subject.

Data Analysis

Means and SDs were calculated where appropriate and comparisons between blacks and whites were performed using the t test for continuous variables and χ^2 test for categorical variables.[24] Pharmacokinetic parameters were compared by a 2×2 analysis of variance, examining effects of race and sex.

RESULTS

A total of 79 subjects were studied. Demographic variables and smoking behavior are shown in Table 1. Mean age, the percentage of male participants, and average body weight were similar for blacks and whites. All participants had normal blood pressure, serum glucose and creatinine levels, and creatinine clearance. Blacks had fewer years of education (12.8 vs 13.9 years; P = .08) and were less likely to be employed (45% vs 64%; P = .02). Although the number of cigarettes smoked per day, years of smoking, and Fagerstrom Tolerance scores were similar by race, blacks on average reported a shorter time to first cigarette after waking up and smoked cigarettes with a higher content of nicotine, tar, and carbon monoxide as determined by machine testing using the Federal Trade Commission method. Most blacks reported smoking mentholated cigarettes, compared with only 2 whites.

Plasma concentrations of labeled nicotine and cotinine during and after intravenous infusion were similar to previous studies with smokers.[23] Pharmacokinetic parameters for nicotine among black and white smokers are shown in Table 2. The total and nonrenal clearance of nicotine was, on average, lower in blacks than in whites, but these differences were not significant. Volume of distribution of nicotine was similar for blacks and whites.

For cotinine, the total and nonrenal clearances were significantly lower for blacks than for whites (Table 3). Renal clearance of cotinine was higher in blacks than in whites. Half-life of cotinine tended to be longer for blacks, while volume of distribution was similar for both races. The fractional conversion of nicotine to cotinine was similar for both.

Blacks and whites smoked similar numbers of cigarettes per day, but blacks had higher baseline serum cotinine levels compared with whites (P = .06; Table 4). The serum cotinine concentration per cigarette was 50% higher in blacks than in whites (P = .003). The estimated daily intake of nicotine from cigarette smoke was slightly greater, and the nicotine intake per cigarette was 30% greater in blacks than in whites (P = .02, log transformed data).

No sex differences were found for nicotine or cotinine clearance or fractional conversion of nicotine to cotinine. The volume of distribution (Vss, measured in liters per kilogram) was greater respectively for men than for women, ie, $Vss = 0.83 \pm 0.17$ vs 0.72 ± 0.10 ($P<.001$), and the half-life ($t_{1/2}$, measured in minutes) of cotinine was also greater in men than in women, ie, $t_{1/2} = 1071 \pm 229$ vs 943 ± 315 ($P = .04$).

COMMENT

Our study confirms the observation made in previous studies that the serum cotinine concentration per cigarette

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smoked is significantly higher in black smokers than in white smokers.[10,25] Our pharmacokinetic analysis indicates that this difference is attributable to 2 factors. First, the clearance of cotinine is slower, leading to higher levels of cotinine for a given level of nicotine intake in blacks compared with whites. This difference is not attributable to systematic differences in renal function by race, since all participants had normal serum creatinine levels and blood pressure, and renal clearance is a minor pathway of nicotine or cotinine clearance. Second, the intake of nicotine per cigarette tended to be higher in blacks than in whites. Since intake of nicotine is highly correlated to exposure to tar and oxidant gases, the latter observation may help explain the higher smoking-related risks of lung cancer and reproductive disorders in blacks compared with whites. However, the lower rate of COPD among blacks is an unexplained paradox that may be related to other biological or environmental factors.[2]

Pharmacokinetic analysis indicates that the nonrenal or metabolic clearance of cotinine is significantly lower, and the metabolic clearance of nicotine tends to be lower in blacks than in whites. One possible explanation for these differences is that there may be a racial genetic difference in cotinine metabolism. Blacks have been shown to metabolize some drugs at different rates than whites.[26] Cotinine and nicotine appear to be metabolized primarily by the enzyme CYP2A6[27,28] with a lesser percentage conjugated via glucuronidation.[29] No prior studies have looked at racial differences in drug metabolism via CYP2A6 or glucuronidation. Our study represents the first reported racial difference in the activity of one or both of these drug metabolizing enzymes.

Racial differences in drug-metabolizing activity could also be attributable to environmental factors. One possible environmental explanation is that smoking mentholated cigarettes influences cotinine metabolism. Nearly all of the blacks and few of the whites in our study smoked mentholated cigarettes, which reflects national racial patterns of smoking behavior.[9,30] No data are available on the effects of menthol on drug metabolism, so further research is needed to address this possibility.

The reasons why blacks take in more nicotine and more cigarette smoke per cigarette are unclear. The most obvious possibility is that menthol via its cooling action facilitates deep inhalation. However, studies measuring puffing behavior and puff volumes after persons have smoked individual mentholated vs non-mentholated cigarettes have not supported this explanation.[31] Persons smoking mentholated cigarettes take fewer puffs with lower average total volume of smoke, but with an increased carbon monoxide boost compared with persons smoking regular cigarettes.[31,32] Whether these observations are related to racial differences in nicotine intake and cancer rates is not known.

Restriction of access to cigarettes has been shown to increase the intake of nicotine per cigarette, believed to be a compensatory response to maintain desired levels of nicotine in the body.[33] It is plausible to consider that economic constraints on purchasing cigarettes among blacks lead to greater smoking of each cigarette, thereby increasing intake of nicotine per cigarette compared with whites. However, cost of cigarettes has not been found to be an important factor in motivating adults of any ethnic group to quit smoking,[34] and the proportion of heavy smokers ($\geq$25 cigarettes per day) in the United States is highest among those with less than a high school education.[7]

Systematic differences in reporting number of cigarettes per day could theoretically explain the difference in estimated nicotine intake per cigarette by race. If blacks systematically underreported the number of cigarettes smoked per day and whites were always accurate, we could be overestimating the nicotine intake per cigarette by blacks. However, based on analyses from the National Health Interview Surveys in 1970 and 1980, no evidence was found of a systematic racial bias in self-reporting of cigarettes.[35]

The question of racial differences in self-reported use of cigarettes compared with biochemical measures has been addressed in several studies. Defining underreporting as a serum cotinine level of more than 142 nmol/L (25 ng/mL) per cigarette smoked, we found that among Mexican Americans up to 20% of men and 25% of women reporting 1 to 9 cigarettes per day were underreporters.[36] Subsequently, using our definition of underreporting, another study found that 75% of 95 black women smoking fewer than 20 cigarettes per day were classified as underreporters.[11] However, a recent study using carbon monoxide measures found no reporting artifacts comparing white, African American, and Hispanic adolescents.[37] Finally, 66 blacks and 97 whites were observed smoking 1 cigarette, had their cigarette butts counted for 1 week, and completed 2 self-reported measures of cigarette use 2 weeks apart, and the investigators concluded that there was no evidence that underreporting differed by race.[38] In that study blacks also had higher mean serum cotinine levels and reported smoking fewer cigarettes per day.[25]

In summary, our study demonstrates, we believe for the first time, that black smokers and white smokers differ in their metabolism of cotinine, as well as in the intake of nicotine per cigarette. These differences have implications in interpreting biomarkers of tobacco smoke exposure and possibly in explaining differences in smoking-related disease risks in blacks and whites. Further research in the possible role of mentholated cigarettes, differential effects of tobacco use on disease rates, and comparison among other ethnic and racial groups is needed.

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