Original Investigation

Effects of Menthol on the Pharmacokinetics of Bupropion Among Black Smokers

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Received June 8, 2011; accepted October 17, 2011

Abstract

Introduction: Despite the widespread use of mentholated cigarettes, lower cessation rates, and disproportionately high smoking-related morbidity among Blacks, the possible role of menthol in smokers' response to pharmacotherapy has not been well-studied. This study examined the effects of menthol on the pharmacokinetic (PK) profiles of bupropion and its principal metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion among Black smokers.

Methods: After a 7-day placebo run-in period, participants received 150 mg bid sustained-release bupropion for 20–25 days. Blood samples were drawn for PK analysis on 2 occasions, 10–15 days after the commencement of bupropion while participants were still smoking (smoking phase) and at days 20–25 when they were asked not to smoke (nonsmoking phase).

Results: 18 smokers of nonmenthol cigarettes and 23 smokers of menthol cigarettes were enrolled in this study. No differences were found by menthol smoking status in the C_{max} and area under the plasma concentration versus time curve (AUC) of bupropion and its metabolites in the smoking or nonsmoking phases. However, among menthol smokers, the AUC ratios of metabolite/bupropion were lower in the nonsmoking phase compared with the smoking phase (hydro/bup = 31.49 ± 18.84 vs. 22.95 ± 13.27, *p* = .04; erythro/bup = 1.99 ± 1.02 vs. 1.76 ± 0.75, *p* = .016; threo/bup = 11.77 ± 8.90 vs. 10.44 ± 5.63, *p* = .034). No significant differences were found in the metabolite/bup ratios between smoking and nonsmoking conditions among nonmenthol smokers.

doi: 10.1093/ntr/ntr268

Advance Access published on February 8, 2012

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Conclusions: We did not find a significant effect of menthol compared with nonmenthol cigarette smoking on the PKs of bupropion and metabolites at steady state. More research is needed to advance the understanding of mechanisms underlying disparities in smoking cessation outcomes related to smoking of menthol cigarettes.

Introduction

Blacks are more likely to attempt to quit smoking than Whites in any given year, however, the success rate is lower for Blacks than it is for Whites (Fiore et al., 1989; Fu et al., 2008; Giovino et al., 1994). One of the most striking differences in the smoking patterns between Blacks and Whites is the preference for mentholated (menthol) cigarettes among Blacks. While only 20% of White smokers use menthol cigarettes, prevalence of menthol use among Black smokers is more than 70% (Caraballo & Asman, 2011; Cubbin, Soobader, & LeClere, 2010; Fagan et al., 2010; Giovino et al., 2004; Lawrence et al., 2010). Because of their high preference for menthol cigarettes, it has been suggested that the disparity in cessation success may be in part due to effects of the menthol in the smoke.

While some studies have reported that menthol smokers have lower quit rates than nonmenthol smokers (Foulds, 2006; Gandhi, Foulds, Steinberg, Lu, & Williams, 2009; Okuyemi et al., 2003; Okuyemi, Faseru, Sanderson Cox, Bronars, & Ahluwalia, 2007), others have failed to show differential quit rates (Blot et al., 2011; Hyland, Garten, Giovino, & Cummings, 2002; Muscat,

Richie, & Stellman, 2002). Smoking cessation clinical trials do not routinely report outcomes based on whether participants smoked mentholated cigarettes. Consequently, little published information is available about whether menthol smokers have higher quit rates than nonmenthol smokers in smoking cessation trials. We previously reported (Okuyemi et al., 2003) that bupropion had lower efficacy for smoking cessation among menthol cigarette smokers younger than 50 years of age compared with nonmenthol smokers. Of the 600 smokers enrolled in the study, 471 (78.5%) smoked mentholated cigarettes, whereas 129 (21.5%) smoked nonmentholated cigarettes. Overall 28.3% of menthol smokers were abstinent at 6 weeks compared with 41.5% of nonmenthol smokers ($p = .006$). When separated by treatment, among those who received bupropion, the 7-day point prevalence abstinence rate at 6 weeks for nonmenthol smokers (60.3%) was significantly higher than for menthol smokers (36.2%, $p < .01$). Abstinence rates did not differ by menthol status among those who received placebo (23.3% nonmenthol vs. 20.5% menthol; $p = .63$). This study suggested that mentholated cigarettes attenuate the effect of bupropion for smoking cessation among Blacks (Okuyemi et al., 2003).

The mechanism by which bupropion enhances ability of smokers to quit smoking is not completely known but is presumed to involve both dopaminergic and adrenergic mechanisms and possibly nicotine receptor antagonism (Haustein, 2003). The elimination kinetics of bupropion are biphasic, with mean half-lives for the distribution and terminal phases of approximately 3–4 hr and 21 hr, respectively (Physicians' Desk Reference, 2011). In humans, bupropion is extensively metabolized with less than 1% of the oral dose excreted unchanged in urine (Hsyu et al., 1997). Bupropion has three principal metabolites: hydroxybupropion, produced through hydroxylation of the *tert*-butyl group and threohydrobupropion and erythrohydrobupropion, which result from reduction of the carbonyl group (Physicians' Desk Reference, 2011). The mean elimination half-lives for these metabolites are estimated to be 20 hr for hydroxybupropion, 37 hr for threohydroxybupropion, and 33 hr for erythrohydrobupropion. Steady-state plasma concentrations of bupropion and metabolites following 150 mg of sustained-release bupropion every 12 hr are reached within 7–8 days.

The relative activity of the three bupropion metabolites is not well-established. Johnston et al. (2001) reported that hydroxybupropion is more active than threohydrobupropion and erythrohydrobupropion. In vitro studies indicate that cytochrome P450 2B6 (CYP2B6) is the principal isoenzyme involved in bupropion metabolism, particularly in the formation of its primary metabolite, hydroxybupropion. Other enzymes that have been reported to be involved to a lesser extent in bupropion metabolism include CYPs 1A2, 2A6, 2C9, 2E1, and 3A4 (Haustein, 2003). The different biological activities of bupropion and the three primary metabolites suggest that an alteration of bupropion metabolic pathways would alter the effects of drug treatment. Menthol might affect the enzymes involved in bupropion metabolism and thus alter the efficacy of the drug.

Metabolic interactions have been reported between menthol and nicotine. Menthol inhibits the metabolism of nicotine to cotinine in liver microsomes (MacDougall, Fandrick, Zhang, Serafin, & Cashman, 2003). In a crossover study of people smoking menthol versus nonmenthol cigarettes, menthol smoking was shown to inhibit the metabolism of nicotine, both by oxidative and

by glucuronide conjugation pathways (Benowitz, Herrera, & Jacob, 2004). Thus, it is plausible that menthol might affect the metabolism of bupropion. Although only limited data are available on the metabolism of bupropion following concomitant administration with other drugs, there is evidence that certain drugs (e.g., carbamazepine, phenobarbital, phenytoin) induce bupropion metabolism, while other drugs (e.g., cimetidine) inhibit its metabolism (Physicians' Desk Reference, 2011). The reduction of bupropion concentration by carbamazepine an inducer of CYP3A4 and CYP2C19, but not CYP2B6, has been tentatively explained by the increased activity of one of the pathways of bupropion metabolism (Golden et al., 1988; Ketter et al., 1995). Despite the widespread use of mentholated cigarettes, lower cessation rates, and disproportionately high smoking-related morbidity among Blacks, the possible role of menthol in smokers' response to pharmacotherapy has not been well-studied. Understanding the effects of menthol in cigarettes on bupropion pharmacokinetics (PKs) has potential for improving smoking pharmacotherapy, especially among Blacks. We therefore conducted a study to examine the effects of menthol on the PK profiles of bupropion and its three principal metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, among Black smokers.

Methods

This study was conducted within the General Clinical Research Center (GCRC) at the University of Kansas Medical Center, and the protocol was approved and monitored by the University of Kansas Medical Center Human Subjects Committee.

Recruitment

Recruitment of participants into the study has been previously reported in detail (Faseru et al., 2010). Participants were recruited using clinic-based and community-based strategies. Study eligibility criteria included self-identifying as Black, aged 18 years or older, smoked 10 cigarettes per day or more, have body mass index between 18 and 45 kg/m², and have smoked either mentholated or nonmentholated cigarettes exclusively for the past year. Consistent with contraindications for bupropion use, exclusion criteria included predisposition to seizures, a diagnosis of bulimia or anorexia nervosa in the past year, an unstable medical or psychiatric illness, alcohol dependency within the last year, or a myocardial infarction in the last month. In addition, individuals who had used bupropion or forms of tobacco other than cigarettes in the past 30 days were excluded, as were those currently using any prescription or other medications contraindicated or with known interaction with bupropion, and women who were pregnant, breastfeeding, or contemplating pregnancy in the next month. Eligibility screening was multistaged: Telephone eligibility screening was followed by in-person medical screening and then, lastly, by screening for adverse events with medication and adherence to medication.

Study Procedures

Phone-eligible individuals came to the GCRC after an overnight fast and signed a written informed consent form. They provided a 20 ml blood sample for a complete blood count, a complete metabolic profile, and cotinine analysis. Women also gave a urine sample for a pregnancy test. Participants underwent a

medical history and physical examination by a GCRC nurse and completed a baseline smoking history questionnaire. Further eligibility was confirmed if history, physical examination, and test results were within normal limits. Eligible participants were then given a sterile container for collecting urine beginning 24 hr prior to the next visit to verify menthol status.

Study Design

The PK parameters of bupropion and its three principal metabolites, hydroxybupropion, threohydrobupropion, and erythrohydrobupropion, were assessed at steady state under smoking and nonsmoking conditions. During the smoking condition that lasted 10–15 days, participants smoked their usual brand of cigarettes. This period was followed by a nonsmoking condition lasting another 10–15 days during which participants were asked to not smoke any cigarettes. The PK parameters were then compared between (a) menthol and nonmenthol smokers and (b) smoking and nonsmoking conditions. Participants were given \$50 gift cards for each screening visit and \$150 gift cards for each PK study visit. Fifty-dollar gift cards were given to the participants for the use of Medication Event Monitoring System (MEMS) devices. Additional \$50 gift cards were given to participants who were able to abstain from smoking during the nonsmoking phase (cotinine verified with Nic check).

Reporting Adverse Events and Verifying Medical Adherence

At the first visit, medically eligible participants were given a 7- to 10-day supply of placebo in a container with a MEMS cap, an adherence verification device (AARDEX, Union City, CA). On their second visit, participants were asked about adverse events using the Common Terminology Criteria for Adverse Events, version 3.0 (National Cancer Institute). Unused study medication was collected and counted, and data were downloaded from the MEMS cap. Individuals who did not tolerate the placebo medication or used less than 75% of the prescribed dose were excluded from continued participation. Such individuals were excluded with the rationale that they were unlikely to take the active medication as prescribed during the entire study. Participants were enrolled in the PKs phase of the study. The participants continued to use the MEMS cap for the entire study to monitor bupropion use. The study staff instructed participants to bring MEMS cap and all medications to each GCRC visit.

PK Study Phase

Procedure Overview

After a 7-day placebo run-in period and an initial 3-day dosing period of 150 mg/day, participants were given 300 mg/day (150 mg bid) sustained-release bupropion for 20–25 days. Participants were asked to smoke their usual brand of cigarettes ad lib for the first 10–15 days (smoking condition) and to quit smoking for the remaining 10–15 days of the study (nonsmoking condition). Blood samples were drawn for PK analysis on two occasions, 10–15 days after the commencement of bupropion while participants were still smoking (PK 1) and again at Days 20–25 (PK 2) when they were asked not to smoke (nonsmoking condition). The blood samples at Visit 3 (PK 1) provided PK parameters when participants were exposed to both bupropion and cigarette smoke (menthol or nonmenthol). Samples at Visit 4 (PK 2) provided PK parameters when participants were exposed

to bupropion but not to cigarette smoke. At each PK visit, approximately 10 ml of blood for PK were taken through an intravenous line inserted into the participant's arm prior to and at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 12 hr after ingestion of the first daily dose of 150 mg bupropion-SR. Use of the second dose of bupropion for the day was delayed until after all blood draws were completed.

Blood samples were drawn into tubes containing Ethylenediamine tetra-acetic acid, immediately iced, and centrifuged at 4 °C to separate the plasma. Plasma samples were then frozen at –20 °C. Plasma samples were thawed at room temperature and then assayed by solid phase extraction followed by Liquid Chromatography/Mass Spectrometry. Plasma concentrations were determined, and PK parameters of bupropion and its metabolites at steady state were calculated. This protocol and PK analyses are similar to those used in a previous study (Johnston et al., 2001; Palovaara, Pelkonen, Uusitalo, Lundgren, & Laine, 2003). Assays for bupropion and metabolites were performed by the Clinical Pharmacology Laboratory at the San Francisco General Hospital, University of California, San Francisco using liquid chromatography–tandem mass spectrometry (Hsyu et al., 1997).

Statistical Methods

The study's primary hypothesis was that at steady state in the smoking condition, the mean area under the plasma concentration versus time curve (AUC) of bupropion for menthol smokers will be significantly lower than that of nonmenthol smokers. The secondary hypothesis was that at steady state in the smoking condition, the mean AUC of bupropion metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion) for menthol smokers will be significantly higher than that of nonmenthol smokers. The exploratory hypothesis was that among menthol smokers at steady state, the mean AUC of bupropion in the smoking condition will be significantly lower than that in the nonsmoking condition and that the AUC for the metabolites will be significantly higher in the smoking than nonsmoking condition. PK parameters were summarized by *Ms* and *SDs* for each group. Corresponding 95% *CI*s are also presented and differences in these parameters between the two groups were compared using the two-sample *t* test assuming nonconstant variance. A similar analysis was performed comparing the ratios of these parameters to determine if stopping smoking had an effect between menthol and nonmenthol smokers. All *p* values reported are unadjusted for multiple testing, and all confidence intervals are at the nominal 95%.

Results

Eighteen smokers of nonmenthol cigarettes and 23 smokers of menthol cigarettes were enrolled in this study. There were technical problems in sample collection and storage for six nonmenthol smokers and four menthol smokers, and these subjects' bupropion data were not included in the analysis. Bupropion metabolites' measurements were valid from those participants. In addition, one nonmenthol smoker did not provide plasma samples for the nonsmoking period and another nonmenthol smoker showed no quantifiable bupropion or any of its metabolites in any of the smoking-condition plasma samples. Participants with missing samples or no detectable bupropion or metabolites in plasma were not included in our analysis of data, as reflected by the different *n* values in Table 1.

Table 1. Bupropion and Bupropion Metabolite Pharmacokinetics in Active Smokers of Nonmenthol and Menthol Cigarettes

Metabolite AUC	AUC nonmenthol hr × ng/ml	Menthol hr × ng/ml	<i>p</i> Value	Cmax nonmenthol ng/ml	Menthol ng/ml	<i>p</i> Value
Bupropion	482 ± 159 (11)	466 ± 152 (19)	.78	72 ± 23 (11)	69 ± 25 (19)	.77
Upper and lower 95% CI of mean	375; 589	392; 539		56; 87	57; 81	
Hydroxy-	9,625 ± 4,771 (17)	10,114 ± 5,319 (23)	.76	936 ± 436 (17)	1,002 ± 515 (23)	.66
Upper and lower 95% CI of mean	7,172; 12,078	7,813; 12,414		711; 1,160	780; 1,225	
Erythro-	886 ± 271 (17)	831 ± 303 (23)	.55	85 ± 24 (17)	80 ± 27 (23)	.56
Upper and lower 95% CI of mean	747; 1,025	700; 962		72; 97	68; 92	
Threo-	5,548 ± 2,248 (17)	4,507 ± 2,024 (23)	.14	538 ± 205 (17)	439 ± 186 (23)	.13
Upper and lower 95% CI of mean	4,392; 6,704	3,632; 5,383		433; 644	359; 520	

Notes. AUC = Area under the curve. Data presented as $M \pm SD$, number of evaluable participants in parentheses. *p* values calculated by two-sample *t* test.

The first question was whether the Cmax and AUC of bupropion and its metabolites differed between smokers of nonmenthol versus menthol cigarettes. As shown in Table 1, no differences were found between smokers of nonmenthol and menthol cigarettes in these measures.

The second question was to determine the effects of smoking abstinence on the PKs of bupropion and its metabolites and to see if this differed between nonmenthol and menthol cigarette smokers. Forty-three percent (10/23, 9 cotinine verified) menthol smokers and 29% (5/17, 4 cotinine verified) nonmenthol smokers reported 7-day abstinence from smoking at end of non-smoking condition. Of this number, only three nonmenthol and four menthol participants had evaluable plasma samples. Due to the small number of abstinent participants with evaluable data, analysis of the nonsmoking condition was conducted for exploratory purposes to inform future studies. There were no differences between menthol and nonmenthol smokers in the AUC of bupropion or its metabolites in the nonsmoking condition. However, among menthol smokers, the AUC ratios of metabolite/bupropion were lower in the nonsmoking compared with the smoking condition (hydro/bup = 31.49 ± 18.84 vs. 22.95 ± 13.27 , $p = .04$; erythro/bup = 1.99 ± 1.02 vs. 1.76 ± 0.75 , $p = .016$; threo/bup = 11.77 ± 8.90 vs. 10.44 ± 5.63 , $p = .034$). The differences in ratios between the two conditions ranged 13%–17%. No significant differences were found in the metabolite/bup ratios between smoking and nonsmoking conditions among nonmenthol smokers.

Discussion

The aim of our study was to determine if smoking menthol cigarettes affects the metabolism and PKs of bupropion and its metabolites in a way that could explain lower rates of smoking cessation with bupropion treatment of menthol cigarette smokers compared with nonmenthol cigarette smokers. A comparison of menthol versus nonmenthol cigarette smokers demonstrated no difference in bupropion or metabolite levels in steady-state conditions of dosing, suggesting that the menthol does not alter bupropion PKs.

While we did not find group differences between menthol and nonmenthol cigarette smokers, we did observe in a subgroup analysis that among menthol cigarette smokers, stopping smoking was associated with a small statistically significant increase in bupropion concentrations. This finding suggests that among menthol smokers, smoking may induce bupropion metabolism to a small extent such that bupropion levels rise after stopping smoking. However, the magnitude of the change ranged 13%–17%, which is not likely to be pharmacologically significant. The enzymes and mechanisms by which menthol might produce such an effect are unknown and require further study. The relationship between the plasma concentrations of bupropion and metabolites and smoking cessation has been examined in a study of 519 smokers (Johnston et al., 2001). In that study, the highest predicted probability of quitting was observed at the highest erythro-metabolite concentrations.

A limitation of our study is that we measured total bupropion. Bupropion as provided for medical use is a racemic mixture, and the rate of elimination and the pharmacologic activity of the different stereoisomers of bupropion and its metabolites differ from one another. Thus it is possible that finding little or no change in total bupropion and metabolite concentrations might miss stereoselective changes in concentrations that could be selective for one enantiomer but not for total analyte. Measuring the enantiomers of hydroxybupropion may also be important because animal studies show that 2S,3S-hydroxybupropion is much more active on nicotinic receptors and on behavioral models of depression and development of nicotine reward compared with the 2R,3R-hydroxybupropion isomer (Damaj et al., 2004, 2010). In addition, without knowing the intake dose of menthol in the smokers, we were not able to normalize our results to plasma levels of menthol or its metabolite. Also, the small sample size with resultant large SDs may have contributed to lack of statistical significance in observed changes. It could be possible for a study with a larger sample size to reach different conclusions. In addition, although participants were instructed and incentivized to quit smoking during the nonsmoking phase of the study, most participants were not abstinent, and this may have contributed to finding a lack of significant differences by menthol status. Nevertheless, being the first to examine the

effects of mentholated cigarettes on the PKs of bupropion, a Food and Drug Administration–approved smoking pharmacotherapy, this study provided estimates of plasma concentrations of bupropion and metabolites that would inform design of future studies assessing interactions between menthol and other drugs.

In conclusion, we did not find a significant effect of menthol compared with nonmenthol cigarette smoking on the PKs of bupropion and metabolites at steady state. It is possible that the adverse effect of menthol cigarettes on bupropion-aided smoking cessation is a pharmacodynamic one, perhaps acting via addiction-related sensory or neurochemical pathways. Given poorer smoking cessation outcomes observed among menthol smokers in some studies, research is needed to advance the understanding of mechanisms underlying disparities in smoking cessation outcomes related to smoking of menthol cigarettes.

Funding

This work was supported by the National Institutes of Health (R21DA018720 and M01 RR0239410).

Declaration of Interests

Dr Benowitz has been a consultant to several pharmaceutical companies that are developing or market smoking cessation medications and has been a paid expert witness in litigation against tobacco companies. All other authors have no competing interests to declare.

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