Regulatory Toxicology and Pharmacology 63 (2012) 166–170

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Menthol smoking in relation to time to first cigarette and cotinine: Results from a community-based study

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ARTICLE INFO

Article history:
Received 31 October 2011
Available online 2 April 2012

Keywords:
Nicotine
Dependence
Menthol
Cotinine
Tobacco

ABSTRACT

Smokers who have their first cigarette shortly after waking, an indicator of nicotine dependence, have substantially higher cotinine levels. There is controversy regarding the role of menthol in nicotine dependence. We hypothesized that menthol smokers have a shorter time to first cigarette (TTFC), and tested whether any statistical association actually reflects increased dependence by measuring nicotine uptake (e.g. cotinine) in the same group of smokers. A cross-sectional community-based study was conducted that included 495 black and white daily cigarette smokers. Results showed a trend between menthol smoking and a shorter TTFC ($P < 0.04$ in blacks). Menthol was not an independent predictor of cotinine or an effect modifier with TTFC on cotinine levels in blacks and whites. These results show that while menthol in tobacco is associated with an indicator of nicotine dependence in blacks, menthol was not associated with biological uptake of nicotine in black and white smokers.

1. Introduction

The 2009 Family Smoking Prevention and Tobacco Control Act gave the Food and Drug Administration (FDA) the authority to regulate the advertising, marketing and tobacco content of cigarettes including the characterization of tobacco by flavor. The Tobacco Products Scientific Advisory Committee (TPSAC) made no specific policy recommendations to the FDA in 2011, and left opens the question of whether menthol in cigarettes should be banned. The panel noted that menthol facilitated nicotine dependence in some groups.

The role of menthol cigarettes in nicotine addiction has been extensively studied (Ahijevych and Garrett, 2010; Heck, 2010), yet many aspects of its effects are still not well understood and remains uncertain (Hoffman and Simmons, 2011). There has been a growing interest in studying the effects of menthol on the time to first cigarette (TTFC) since this measure is associated with many of the behavioral dimensions of nicotine dependence including smoking amount (Heatherton et al., 1989; Kozlowski et al., 1994), inability to quit (Baker et al., 2007; Kabat and Wynder, 1987; Kozlowski et al., 1994; Li et al., 2011), smoking relapse (Toll et al., 2007), tolerance (Pillitteri et al., 1997) and nighttime smoking (Bover et al., 2008). The TTFC accounts for much of the predictive validity of the Fagerstrom test for Nicotine Dependence (Baker et al., 2007).

Initial studies of menthol and TTFC found a shorter mean TTFC in menthol vs. non-menthol smokers in 95 black and white women (Ahijevych and Parsley, 1999) and in 600 black smoking cessation trial participants (Okuyemi et al., 2003). In contrast, menthol was not associated with a TTFC $\leqslant$ 10 min in 13,268 black and white participants in the Community Intervention Trial for Smoking Cessation (Hyland et al., 2002), and with a TTFC $\leqslant$ 30 min in daily smokers aged 18–24 years participating in the Tobacco Use Supplements to the Current Population Surveys (TUS CPS) (Ahijevych and Ford, 2010). Menthol was associated with a TTFC $\leqslant$ 30 min in nondaily smokers 18–24 years old. In a separate analysis of all adult TUS CPS participants, menthol was associated with a TTFC $\leqslant$ 5 min in smokers consuming 6–10 cigarettes per day (Fagan et al., 2010). Race-specific results were not presented. In a tobacco treatment clinic that studied 1699 patients, menthol was associated with a shorter TTFC (Gandhi et al., 2009). The inconsistency in the TTFC findings might be due to differences in subject characteristics such as age, race, study population (e.g. randomized trial vs. population-based), and categorical vs. continuous measures of TTFC.

Even if menthol is associated with a shorter TTFC, it is uncertain what this statistical relationship means with respect to the effects of menthol on nicotine dependence. A shorter TTFC has been

Abbreviation: TTFC, Time to first cigarette.

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http://dx.doi.org/10.1016/j.yrtph.2012.03.012

associated with increased nicotine uptake as determined by increased levels of cotinine (Muscat et al., 2009b; Fu et al., 2011), but the effects of menthol on the relationship between TTFC and cotinine have not been established. An assessment of this association by menthol might help to understand the potential effects of menthol on nicotine uptake (Fagan et al., 2010). Statistical associations between menthol and TTFC may not be informative by itself without contextualizing these findings with respect to physiological/biochemical measures of dependence (e.g. nicotine uptake). The association between TTFC and cotinine might be expected to differ by menthol since menthol has anesthetic and pharmacologic properties that possibly result in greater tobacco smoke exposure, although a review of this literature indicated that studies are inconclusive (Hoffman, 2011; Henningfield et al., 2003; Benowitz et al., 2004). In the current study, wefirst examined the association between menthol and TTFC in a biracial middle-class community.

2. Methods

2.1. The Mount Vernon CARES study

The Mount Vernon CARES program was a community-based health promotion and education program that was conducted in conjunction with business, community, and religious leaders in the town of Mt. Vernon, NY (Muscat ref). The original focus was on cardiovascular disease screening and prevention, but expanded to a larger effort on the health effects of tobacco, including cigarette smoke exposure. Small research laboratories were established in the town for study recruitment and sample collection. The methods for smoking assessment were previously described (Muscat et al., 2009b). Briefly, all participants were interviewed using a structured questionnaire that contained detailed items on smoking habits and sociodemographics. A smoking history was obtained including for each brand, brand name, type of cigarette, age started smoking, frequency and duration of smoking. Venipuncture blood samples were processed and blood fractions were stored in a −80 degree freezer. The study was open to residents of Mt. Vernon from 1990–2001. This is a middle-class community with middle or lower income census tracts that is approximately 50% black and 50% white, located about 15 miles north of New York City. The study was also open to other smokers who resided elsewhere and worked in Mt. Vernon, or to residents of other nearby towns who heard of the study through word of mouth or other media. Current cigarette smokers aged 18–55 years old were included and an institutionally-approved consent form was signed by all volunteers. All subjects were required to have been daily smokers and have smoked at least five cigarettes per day for one or more years. This cut-point was established to insure exclusion of non-smokers/passively exposed smokers since tobacco smoke biomarker levels may be similar for passive and light smokers (e.g. 1–5 cigarettes) depending on how cigarettes are smoked in active smokers, and environmental factors in passive smokers such as room ventilation, the proximity to smokers and other factors (Benowitz, 1996).

Nicotine uptake was determined by measuring plasma cotinine (ng/mL). In a preliminary analysis based on data available for 252 black and white smokers, there was a significant linear trend between a shorter time to first cigarette after waking and cotinine levels. The current study updated these findings with the completion of data entry for all subjects (an additional 243 subjects for a total of 495 subjects) and an assessment of the effects of menthol.

2.2. Statistical analysis

All analyses were performed using Statistical Analysis System software (version 9.1.2). Descriptive statistics included means and standard deviations, proportions and percents. The time to first cigarette was ascertained using four categories: $\leqslant$15 min, 16–30 min, 31–60 min, and >60 min. These categories were selected to be compatible with another study using these cutpoints, and differ slightly from the Fagerstrom Test for Nicotine Dependence that has as its first two categories "within 5 min" and "6–30 min." The Cochran-Armitage trend test was used to determine a trend in the proportions of TTFC categories between menthol and nonmenthol smokers. Separate trend tests were also conducted by categories of race and cigarettes per day (e.g. 5–10 CPD, 11–20 CPD, and >20 CPD). For the CPD >20 category, Fisher's Exact test was calculated to compare proportions.

Linear regression analysis was performed to obtain mean cotinine levels by categories of TTFC, adjusted for the covariates cigarettes per day, sex and race. A test for linear trend in cotinine levels by TTFC was conducted using a single ordinal term for the TTFC.

The hypothesis that menthol is an effect modifier for the relationship between TTFC and cotinine was tested using log-transformed values of plasma cotinine using general linear models. We used the PROC GLM procedure to model log-transformed cotinine values. The model covariates included cigarettes per day (continuous), a squared term for cigarettes per day, menthol, age, sex, and race. A term was also included for body mass index, which was previously shown to be inversely correlated with cotinine in this data. A few subjects had missing BMI, which was imputed using the average value for men or women depending on the gender of the subject with missing data. The TTFC was modeled as an ordinal variable with four levels. To test for effect modification, we used the interaction term TTFC $*$ menthol. Models are presented that include the interaction term and one model without the interaction term. Finally, separate general linear models were run for blacks only and for whites only. Statistical tests were two-sided and significance levels were set at 0.05, except for the Cochran-Armitage trend test which was one-sided and set at 0.05 significance. There was no missing data in the current analysis.

2.3. Theory

This setting is unique from previous studies in that it includes blacks and whites, and also allows us to study this association where environmental and sociocultural influences on smoking are similar between smokers. In addition, several previous analyses of TTFC were conducted within a smoking cessation setting, where motivational factors may have affected the findings. Secondly, if an association between menthol and TTFC exists, it needs to be determined whether menthol would affect the relationship between TTFC and cotinine. This information would then provide a stronger biological basis for assessing the effects of menthol on nicotine addiction, and could therefore be informative for policy decisions.

3. Results

The study included 242 men and 253 women. The mean age was 34.9 ± 10. More than half of all subjects (n = 259) smoked their first cigarette within 15 min after waking. The number of menthol and non-menthol smokers was about the same (n = 221 vs. 274).

Table 1 shows the relationship between TTFC categories by menthol status. Overall there was a trend between menthol smoking and a shorter TTFC ($P < 0.02$). When analyzed by race, the trend was significant in black subjects ($P < 0.04$). In black subjects, 61% of menthol smokers smoked within the first 15 min, compared to 44% of nonmenthol smokers. Eleven percent of menthol smokers waited more than one hour after waking, compared to 18% of nonmenthol smokers. In whites, the corresponding percentages were 52% vs. 48% (within 15 min) and 11% vs. 15% (more than one hour).