Nicotine delivery of a menthol-flavored heat-not-burn tobacco product during directed use

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Introduction

IQOS was authorized by the Food and Drug Administration (US FDA) as a modified risk tobacco product (MRTP). We conducted a pharmacokinetic study evaluating the nicotine delivery and subjective effects of IQOS use among current menthol cigarette smokers to better understand if IQOS is an acceptable cigarette alternative in light of the proposed menthol cigarette ban.

Methods

Participants were adult smokers of >4 menthol cigarettes per day (CPD). After 14-hour nicotine abstinence, participants were provided an IQOS device and menthol heatstick to puff every 20 seconds for a total of 14 puffs. Blood samples were collected at baseline and during active use to calculate nicotine boost from baseline to peak concentration. Nicotine withdrawal symptoms were collected before and after IQOS use. In addition, a modified Product Evaluation Scale for IQOS was collected after use.

Results

Participants (n=8) were a mean age of 43.9 years, 63% were female, 88% identified as White, and they smoked a mean of 17.1 menthol CPD. After IQOS use, the mean nicotine boost obtained was 15.96 ng/mL (SD=6.91) (range 9.31 to 30.55ng/ml). Most (75%) participants reported enjoying use of the product “a lot” or greater and more than half (62.5%) reported reduced cigarette cravings. Most participants reported no side effects after use, however, 2 experienced dry mouth, 3 experienced dizziness, 1 experienced throat irritation, and 1 experienced headache.

Conclusion

We found that directed use (14 puffs) of menthol IQOS delivered a mean nicotine boost of 15.96 ng/ml which reduced craving for a cigarette. The majority of participants enjoyed use of IQOS and reported mild side effects.

Implications

Menthol IQOS delivered a sufficient dose of nicotine perceived as satisfying by menthol cigarette smokers and it reduced craving with mild side effects. Menthol IQOS has potential to serve as a less harmful alternative for menthol cigarette smokers. The availability of modified risk products like IQOS should be considered by FDA's Comprehensive Plan for Tobacco and Nicotine Regulation.

Declaration of Interests

JF has done paid consulting for pharmaceutical companies involved in producing smoking cessation medications, including GSK, Pfizer, Novartis, J&J, and Cypress Bioscience. There are no other competing interests to report.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author, JY, upon reasonable request.

Introduction

The availability of new and potentially less harmful tobacco products provides an opportunity for current smokers to reduce their harms from tobacco use. IQOS, a heat not burn (HnB) tobacco product, heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol. IQOS was recently approved for marketing and sale in the United States (US) by the Food and Drug Administration (FDA), through the pre-market tobacco product application pathway (PMTA), and is one of only three products approved to be marketed as modified risk tobacco products (MRTPs) (although currently not available for sale in the United States due to patent lawsuit).[1] This is because of preliminary evidence suggesting that IQOS users are exposed to fewer toxicants during use, compared with cigarette use, mainly due to the lack of combustion when using IQOS.[2-5] For example, one study has shown that IQOS (12 pmol/puff) produces >50-fold lower free radicals than conventional cigarettes per puff.[2]

While IQOS use is associated with exposure to fewer toxicants, it is not known whether smokers find IQOS to be an acceptable replacement for cigarette smoking. One aspect of acceptability is nicotine delivery; the product's ability to deliver a satisfying dose of nicotine to relieve withdrawal. Industry studies, which provided data for the MRTP application, reported that ad libitum IQOS use had a similar pharmacokinetic (PK) profile as cigarette use, in regards to time to maximum nicotine concentration (Tmax) and maximum nicotine concentration (Cmax), among adults who were experienced with cigarettes, but naïve to IQOS. However, in contrast, results from an independent study, also focusing on naïve IQOS users, found that IQOS was associated with significantly lower nicotine exposure compared to an own brand cigarette during a controlled puffing protocol. This study reported a Cmax of 20.7ng/ml (SD=11.4) for cigarettes after a 10 puff bout, and a Cmax of 12.7ng/ml (SD=6.2) for IQOS. This study also reported that IQOS reduced craving for a cigarette, after one bout of use.[6]

Understanding the acceptability of alternative tobacco products like IQOS will be important as the FDA moves forward with new tobacco product standards to improve public health and reduce the burden of tobacco use. For example, the FDA recently announced a ban on menthol flavored cigarettes. Because menthol smokers will no longer have access to menthol cigarettes, it will be important to understand whether they find menthol IQOS, a potentially less harmful product, to be an acceptable alternative. The purpose of this study was to evaluate the nicotine delivery profile and subjective effects associated with naïve IQOS use among current menthol cigarette smokers.

Methods

Participants were recruited from the Penn State Center for Research on Tobacco and Health's central recruitment repository. Participants who were identified as potentially eligible for this study were contacted via telephone to explain study procedures and to confirm further eligibility criteria. Inclusion criteria included: adults (21 years to 60 years), current cigarette smoker (>4 cigarettes per day; CPD), and willing to abstain from cigarettes and other nicotine products for 14 hours prior to study visit. For the current analysis, only participants who smoked menthol cigarettes were included. Participants were excluded if they experienced any of the following: unstable or significant medical conditions in the past 12 months, severe immune system disorders, history of seizure disorder or had a seizure in the last 12 months, history of difficulty or unwillingness to provide blood samples, current IQOS users, and women who were pregnant, trying to become pregnant, or nursing.

Participants deemed eligible at the phone screen were first scheduled to consent to the study via Zoom prior to their arrival at the study center. Once consented, participants were asked to complete baseline questionnaires prior to their study visit regarding their demographic information, tobacco use, nicotine dependence (Penn State Cigarette Dependence Index; PSCDI), and withdrawal symptoms, rated on a scale of 0, none, to 4, severe (Minnesota Nicotine Withdrawal Scale; MNWS). A total MNWS score was calculated by summing the first 8 items. Participants also completed a

modified version of the product evaluation scale[7] which asked participants to rate subjective effects for their own brand cigarettes on a scale from 1 not at all to 7 extremely. Questions were evaluated as sub-scales, including satisfaction, psychological reward, aversion, relief, and future use.

Upon arrival to the study facility, each participant was asked to complete an exhaled carbon monoxide test to verify abstinence from cigarettes (≤ 15 parts per million; ppm)[8] using the PICO+ Smokerlyzer. Once nicotine abstinence was confirmed, participants completed baseline measures including a nicotine withdrawal questionnaire (MNWS). Next, a trained nurse inserted a catheter into the participant's arm to facilitate frequent blood draws. A 7ml blood sample was taken at baseline. Participants were then provided with an IQOS device and a heatstick matched to the flavor of their own brand cigarette (fresh menthol).

Participants were instructed by a computer to take one puff on their IQOS device every 20 seconds for a total of 14 puffs (4 minutes, 20 seconds of use). The duration and volume of each puff was determined by the participant. This puffing protocol was designed to mimic cigarette smoking patterns[9-11] within the limitations of the IQOS device (IQOS lasts for 14 puffs or 6 minutes, whichever comes first) and also utilized a similar puffing protocol to our previous work.[12,13] Blood was drawn during and after IQOS use at 1, 2, 4, 6, 8, 10, 12, and 15 minutes after the first puff. Next the catheter was removed and participants completed post-use measures including an exhaled carbon monoxide test, the MNWS,[14] a side effects questionnaire, and the modified product evaluation scale[7] for IQOS.

The blood samples were processed at the completion of the visit and blood serum was frozen at -80°C until processed and analyzed for nicotine using a modification of the method of Jacob et al.[15] Nicotine levels were determined by liquid chromatography (Agilent 1100 HPLC system)/mass spectrometry (AB Sciex 4500 QTrap) using a Phenomenex Synergi Polar RP column, 4.6 x 150 mm. Solvent A was 5mM ammonium acetate with 0.1% acetic acid added. Solvent B was 5mM ammonium acetate in methanol with 0.1% acetic acid added. The initial solvent composition was

90% solvent A and 10% solvent B. A gradient of 5% solvent B/minute was run for 12 minutes to reach a composition of 30% solvent A/70% solvent B, which was held for one minute. Under these conditions nicotine eluted at approximately 5.3 minutes. The column was washed at 95% solvent B for 3 minutes before equilibrating at initial conditions for 10 minutes. Nicotine was quantified using positive ion electrospray, monitoring the transition from m/e 163 → 130. The transition for the internal standard (d4 nicotine) was m/e 167 → 134. The temperature was 550° C and the ionspray voltage was 1800 V. The limit of quantitation was 200pg/ml.

Study data were managed using REDCap and analyzed using SAS 9.4 Statistical Package. Cmax was defined as the maximum serum nicotine concentration and Tmax was defined as the time to reach maximal concentration. Nicotine boost was calculated as the concentration maximum minus the baseline nicotine concentration. Means and frequencies were used to describe the characteristics of the sample and the outcome measures. Paired t-tests were utilized to determine differences in pre and post withdrawal symptoms and between subjective ratings of own brand cigarettes and IQOS.

Results

Participants (n=8) were a mean age of 43.9 (SD=10.4) years, 63% (n=5) were female, and 88% (n=7) were White (Supplemental Table 1). All participants smoked menthol cigarettes at baseline, with a mean of 17.1 (SD=3.9) cigarettes smoked per day. At baseline, the mean CO was 9.5ppm (SD=3.5), ranging from 5-14ppm, and the mean blood nicotine level was 1.29 ng/ml, with a range of 0.73 to 2.34 ng/ml, confirming abstinence from nicotine prior to the visit.

After IQOS use, the concentration maximum was 17.25 ng/mL (SD=6.87), with a mean nicotine boost of 15.96 ng/mL (SD=6.91) (median=13.96) (range 9.31-30.55ng/ml). The mean time to maximal concentration (tmax) was 5.25 minutes (SD=2.38) (range 4-10 minutes) (Supplemental Table 1). Exhaled CO did not increase after use (Mean 9.0ppm, SD=2.8, range 5-12ppm) (p=.3). The nicotine delivery profile for each participant is displayed in Figure 1.

Participants experienced an overall reduction in total withdrawal score (9.86 to 3.57, p<.01), as well as significant decreases in several nicotine-related withdrawal symptoms from pre to post use including anger (1.43 to .57, p=.02), depressed mood/sad (2.71 to .57, p<.01), restlessness (1.43 to .29, p=.03), and desire or craving to smoke (1.71 to .43, p<.01). The majority of participants reported no side effects on the side effects questionnaire (62.5%, n=5). Among those who reported side effects (n=3), 2 reported dry mouth, 1 reported throat irritation, 3 reported dizziness, and 1 reported headache.

Participants reported that IQOS use was moderately satisfying (mean satisfaction subscale score 4.53, SD=.98) and rewarding (mean reward subscale score 3.35, SD=1.25), while providing a lot of relief (mean relief subscale score 4.97, SD=.74), with no aversion (mean aversion subscale score 1.16, SD=.30). Scores on the evaluation subscales were not significantly correlated with nicotine boost (all p>.1). Comparing own brand cigarettes with IQOS, there were no significant differences in ratings for satisfaction (4.53 vs. 3.93, p=.41) or reward (4.19 vs. 4.81, p=.32) respectively. However, users rated their cigarettes as more aversive than IQOS (2.22 vs. 1.16, p<.01). Individual IQOS evaluation items are presented in Figure 2.

Discussion

In this small sample of adult menthol cigarette smokers, we found that directed use of one IQOS menthol heatstick delivered a mean nicotine boost 15.96 ng/ml. We found variations in nicotine delivery across participants, which could be attributed to differences in the way participants puffed on the IQOS device. While participants were instructed to puff once every 20 seconds, they were able to control the puff duration and depth, which would allow for titration of nicotine, meaning that users could control their intake of nicotine to maximize satisfaction.[16] This behavior has been commonly reported with electronic nicotine delivery systems (ENDS).[16-18] It is also possible that the participant's nicotine metabolism was responsible for differences in nicotine boost, with faster metabolizers clearing the nicotine at a faster rate.[19]

The concentration maximum found in our study is higher than the mean concentration maximum reported in Maloney et al,[1] which was also conducted among IQOS naïve cigarette smokers. Differences in nicotine absorption between these two studies may be due to the more intensive puffing protocol utilized in the current study (10 puffs with 30s interpuff interval vs. 14 puffs with 20s interpuff interval). In addition, our study reported a much higher concentration maximum after IQOS use compared with Phillips-Waller et al (median C_{max} of 8.3 ng/ml), which recruited current e-cig users (with occasional cigarette dual use) to participate in the trial.[20] This difference in nicotine delivery suggests that cigarette smokers may obtain more nicotine from IQOS compared with e-cig users, possibly due to the similarities between cigarette smoking and IQOS use. For example, a recent qualitative study reported that IQOS users found the "overall sensory experience of using IQOS" equivalent to smoking.[21] More research is needed to understand differences in IQOS nicotine delivery for naïve and experienced users as well as for cigarette and e-cigarette users.

Compared with cigarettes, we found that IQOS appears to deliver slightly less nicotine, which has been reported previously in other studies.[6,20] While the current study did not measure nicotine delivery from an own brand cigarette, other studies have reported plasma nicotine concentrations of about 20 ng/ml for both directed and ad libitum use of one cigarette.[6,22] For example, in our previous work, smokers were asked to smoke one of their own brand cigarettes ad libitum in the lab. We found that after overnight abstinence, participants obtained a mean nicotine boost of 19.0 ng/ml after a mean of 14.9 puffs.[11] Together these studies suggest that cigarette use is associated with greater nicotine delivery compared with IQOS. However, IQOS nicotine delivery was similar to another popular cigarette alternative, JUUL. In a previous study,[12] we measured the nicotine delivery of JUUL (59 mg/ml e-liquid) using a very similar puffing protocol (ie. one puff every 20 seconds and blood collection at baseline and 1, 2, and 4 minutes after the first puff). After 12 puffs with a 20 second interpuff interval, experienced JUUL users obtained a nicotine boost of 12.9 (SD=9.8) ng/ml. In this study, after 12 puffs, naïve IQOS users obtained a nicotine boost of 15.58

(SD=7.31) ng/ml. This difference was not significant (p=.59). This finding is also supported by Maloney et al., which found no significant differences in nicotine delivery between IQOS and JUUL.[6]

Finally, we utilized a modified version of the product evaluation scale to understand subjective effects associated with IQOS use. We found that IQOS use was satisfying, rewarding, and provided relief from withdrawal symptoms, without causing aversion. Compared with ratings of own brand cigarettes, IQOS provided similar satisfaction and reward, but less aversion. In addition, compared with other cigarette alternatives like the 5% nicotine JUUL, subjective ratings are similar.[23,24] However, it appears that alternatives like oral tobacco products, such as Camel Snus, are associated with only very little to a little satisfaction, reward, and relief when sampled by naïve users.[7] Interestingly, this study found that oral tobacco products with more nicotine were rated as the least satisfying and the most aversive, suggesting that an appropriate balance of nicotine, as well as other product characteristics, is related to satisfaction with initial use.[7] This data suggests that IQOS provides similar subjective effects to cigarettes and other popular alternatives.

Strengths of this study include the collection of blood samples during active use. However, our study was limited by the timing of the blood draws. Blood samples were collected during active use at 1, 2, and 4 minutes after the first puff, then again after use at 6, 8, 10, 12 and 15 minutes after the first puff. It is possible that we missed the true nicotine peak as the 6 minute blood sample was collected 1 minute and 40 seconds after the last puff. In addition, our study did not measure nicotine delivery of own brand cigarettes, meaning that we could not draw within-subject comparisons between products. Finally, our study was limited by the small, primarily White sample, thus this data may not be generalizable to black smokers who are the most likely to report menthol cigarette use.[25]

In conclusion, we found that directed use of menthol IQOS was associated with few side effects and no increase in exhaled CO, while delivering a satisfying dose of nicotine to relieve cigarette craving. As the US FDA moves forward with a ban on menthol cigarettes, it will be important to understand how potentially less harmful cigarette alternatives like IQOS will fit into the

landscape. While some menthol smokers may quit smoking, others may switch to non-menthol cigarettes or other available tobacco products. The availability of acceptable cigarette alternatives like IQOS could help promote switching to a potentially less harmful product, rather than switching to non-menthol cigarettes, among those who do not want to quit tobacco.

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Figure 1: Blood nicotine delivery profile during active IQOS use

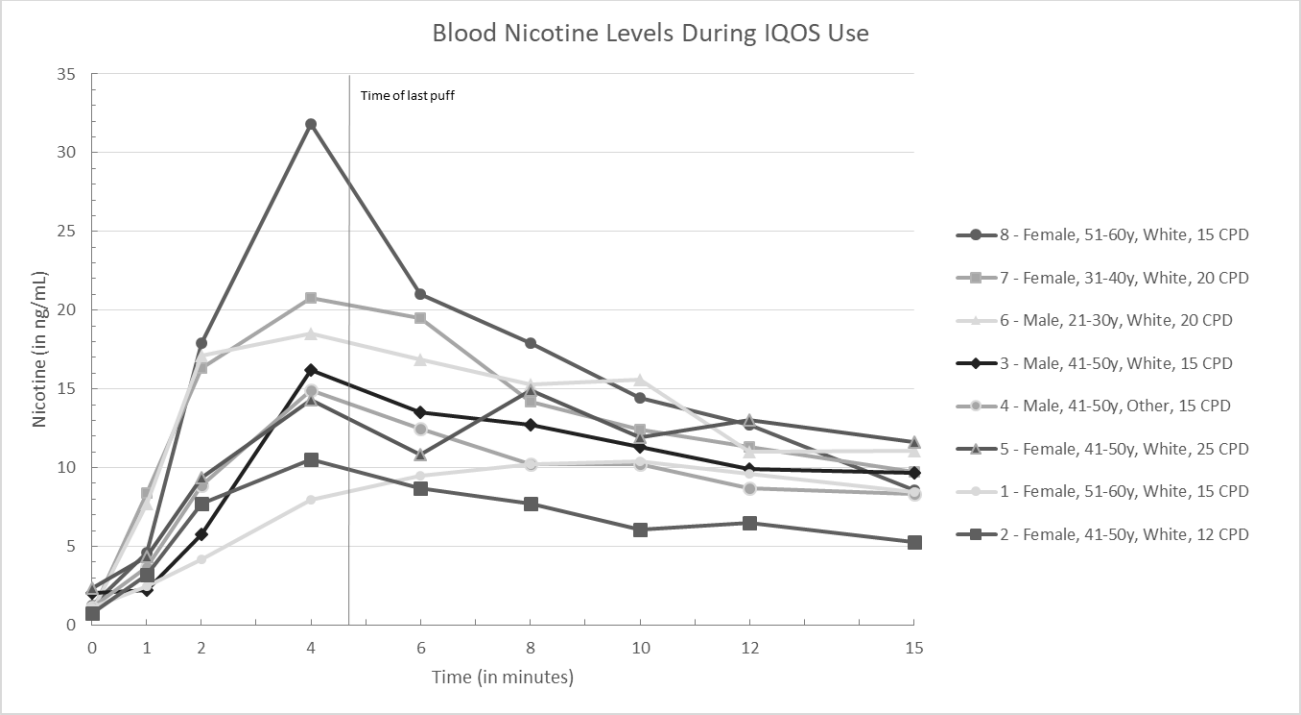

Figure 2: Subjective Ratings After IQOS Use