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Assessment of the exposure to harmful and potentially harmful constituents in healthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence

Dai Yuki*, Yuki Takeshige, Kyoko Nakaya, Yasuyuki Futamura

Scientific Product Assessment Center, R&D Group, Japan Tobacco Inc., Japan

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ABSTRACT

The objectives of this clinical study were to demonstrate a reduction in exposure to selected harmful and potentially harmful constituents (HPHCs), and to assess product use behavior, in Japanese healthy adult smokers who switched to a novel tobacco vapor product (NTV). 60 smokers were randomly assigned for 5 days to either (a) a group who switched to an NTV (n = 20), (b) a group who continued to smoke their own brand of conventional cigarettes (CC, n = 20) or (c) a smoking abstinence group (SA, n = 20). Fifteen biomarkers of exposure (BoEs) to 14 HPHCs and pyrene were measured at baseline, day 3 and 5. Product use behavior was assessed by measuring product consumption, nicotine uptake and puffing topography. During investigations, increases were observed in product consumption and total puff volume in NTV group subjects as compared to baseline. Additionally, nicotine uptake in the NTV group was approximately half that observed in the CC group. BoE values were significantly reduced in the NTV group as compared to those in the CC group. Significantly, the magnitude of the reduction in exposure to HPHCs observed in the NTV group (49–94%) was close to that observed for the SA group (39–95%).

1. Introduction

Previous studies have reported that cigarette smoking is a risk factor for several diseases such as lung cancer, pulmonary disease and cardiovascular disease (Forey et al., 2011; U.S. Department of Health and Human Services, 2004; Benjamin et al., 2017). The use of other traditional tobacco products, such as cigars, pipes, and nasal or oral snuff, have also been identified as a risk factor for diseases such as cancer and cardiovascular disease (IARC, 2004, 2007).

In recent years, there has been an increasing interest in the development of novel tobacco products that could achieve tobacco risk reduction. In the first report, the Institute of Medicine (IOM, 2001) reviewed the scientific basis for tobacco harm reduction and came to the conclusion that reducing the risk of disease by reducing exposure to tobacco toxicants is a feasible goal. The IOM went further by defining the key characteristics of a potential reduced-exposure product (PREP). In 2009, the U.S. Family Smoking Prevention and Tobacco Control Act defined a modified risk tobacco product (MRTP) as any tobacco product that is sold or distributed for use to reduce harm or the risk of particular diseases related to marketed tobacco products. The Food and Drug Administration (FDA, 2012a) issued draft guidance for industry on regulatory applications for MRTP, in which the FDA recommended that human studies should be conducted to evaluate the exposure of harmful substances or to evaluate the impact of tobacco products on health. In addition, the FDA (2012b) published a preliminary list of the harmful and potentially harmful constituents (HPHCs) of tobacco products.

Recently, several European countries, such as Italy, Bulgaria, and Cyprus, have incorporated reduced-risk approval provisions into their national transpositions of EU Directive 2014/40/EU. Similar to the USA, these provisions state that human studies should be conducted to evaluate the reduced-risk potential of a particular product.

Some novel tobacco and nicotine containing products, such as electronic vapor products (D'Ruiz et al., 2016; O'Connell et al., 2016), electronically heated tobacco products (Haziza et al., 2016a; b; Lüdicke et al., 2017; Gale et al., 2017) and carbon-heated cigarette products (Sakaguchi et al., 2014; Ogden et al., 2015; Lüdicke et al., 2016), have been designed to reduce exposure to tobacco toxicants. Furthermore, many human clinical studies have been done for such novel products, and these studies have reported reduction in some biomarkers of exposure (BoEs) to selected HPHCs who switched to use the novel product from conventional cigarettes (D'Ruiz et al., 2016; O'Connell et al., 2016; Haziza et al., 2016a; Lüdicke et al., 2016, 2017).

* Corresponding author. JT International SA, Scientific & Regulatory Affairs, 8 rue Kazem Radjavi, 1202, Geneva, Switzerland. Tel.: +41 22 703 0680.
E-mail address: dai.yuki@jti.com (D. Yuki).

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The novel tobacco vapor product (NTV) evaluated in the present study is a new form of electronically heated tobacco product developed by Japan Tobacco Inc. Takahashi et al. (2017) reported results of the chemical analysis and *in vitro* toxicity testing of aerosol generated from the NTV and showed that most of the measured selected cigarette smoke constituents were below quantifiable levels. In addition, no measureable genotoxicity or cytotoxicity was found following *in vitro* testing of the NTV aerosol, in contrast to results obtained using the standard Kentucky reference 3R4F cigarette. Such results would suggest that switching from conventional cigarettes to the NTV examined in the present study reduces exposure to cigarette smoke constituents. Furthermore, switching from conventional cigarettes to the NTV could potentially result in a reduced health risk to the user as compared to the risk associated with conventional tobacco use.

The primary objective of the present study was to determine the exposure to selected HPHCs when subjects were switched from their own brand of conventional cigarettes to an NTV for 5 days. Smoking abstinence was used as a benchmark for exposure to HPHCs. Secondary objectives were to investigate the nicotine uptake, product consumption, and puffing behavior of the examined NTV as compared to conventional cigarettes.

2. Material and methods

2.1. Study design

This study was a controlled, randomized, 3-arm parallel, single-center study. The study was conducted at Fukuoka Mirai Hospital in Japan under confined conditions. 60 eligible smokers checked into the clinic in the evening of Day −2 and were randomly assigned into one of the three study groups (a group who switched to an NTV, a group who continued to smoke their own brand of conventional cigarettes [CC], and a smoking abstinence group [SA]) with similar gender ratio on Day −1 after the inclusion/exclusion criteria had been assessed. During the study period, all tobacco products were dispensed by the site staff one by one and subjects' instructed product consumption was individually managed. On Day −1, subjects smoked their own brands of CC *ad libitum* within ± 10% of their self-reported daily consumption. From Day1 to Day5, subjects in the CC and NTV groups were allowed to use their assigned tobacco product in separate rooms from 9:00 a.m. to 10:30 p.m. Subjects in the NTV group used the NTV *ad libitum* but limited to 10 tobacco capsules per day to reflect usual smoking frequency. Subjects in the CC group continued to smoke their own brands of CC *ad libitum* within ± 10% of their self-reported daily consumption. Subjects in the SA group abstained from smoking and were denied access to all smoking rooms. On Day 6, subjects were discharged during the morning after undergoing safety assessment procedures.

The study was approved by the Institutional Review Board of Japan Tobacco Inc. and the medical institution, conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and registered at the UMIN Clinical Trials Registry (UMIN000025777). All participants provided written informed consent to participate in the study.

2.2. Subjects

Healthy male and female Japanese adult smokers aged 21–65 years were eligible to participate if they smoked an average of 11 or more manufactured cigarettes per day at screening, had smoked for at least 12 months before entering the trial and had a positive result for a urinary cotinine test (One Step Cotinine Test Device, Accuracy-One Inc., California, USA). Before enrollment, the health conditions of participants were confirmed by physical examination, medical history, vital signs, electrocardiogram and clinical laboratory tests. Pregnant or breast-feeding females were excluded from this study. Males having a body mass index (BMI) of less than 18.5 or greater than 27.7 kg/m^2 and females having a BMI of less than 16.8 or greater than 26.1 kg/m^2 were excluded. Participants were also excluded if they had used any prescription drugs, over-the-counter medications (including smoking-cessation medications) or dietary supplements within 2 weeks prior to the investigational period; or if they had used any tobacco products other than commercial cigarettes (i.e., hand-rolled cigarette, cigarillo, cigars, pipes, snuff tobacco, chewing tobacco, etc.) within 1 week before screening.

A previous study found that delivered vapor chemistry from the NTV examined in the present study showed similar trends to vapor chemistry results obtained for another non-combustion inhaler type tobacco product (Takahashi et al., 2017; Miura et al., 2015). Therefore, sample size determination for the present study was based on the levels of biomarkers of exposure observed in subjects who previously used the non-combustion inhaler type of tobacco product used in the Miura et al. (2015) study. A sample size of 20 subjects in each group was considered sufficiently powered for detecting a relative effect between the NTV and CC groups with a two-sided probability of 5% for type I error and an 80% for type II error.

2.3. Test tobacco product

The NTV consists of a battery, a cartridge with a heater and liquid, and a tobacco capsule filled with tobacco blend (Supplementary Fig. 1). The NTV generates a nicotine-free vapor via electrical heating of a liquid, which contains glycerin, propylene glycol, triacetin and water and does not contain nicotine and flavor unlike many other major e-liquids for electronic cigarettes. The vapor then passes through the tobacco capsule. In doing so, evaporated constituents arising from the tobacco blend, including nicotine and flavors, pass into the vapor, which can then be inhaled by the user. The vapor chemistry of the NTV has been reported previously (Takahashi et al., 2017).

The sensor unit of the battery accumulates the total puffing duration, and the LED, which is located at the tip of the battery, indicates the replacement timing of the tobacco capsule by blinking when the tobacco capsule requires replacing i.e. when the cumulative puffing duration reaches 120 s. A single tobacco capsule can persist for approximately 50 puffs depending on users puffing duration, and one cartridge can be used for five tobacco capsules. The visibility of the LED blinking has been improved from the prototype NTV used in previous study (Yuki et al., 2017).

2.4. Assessment

2.4.1. Baseline characteristics

The baseline characteristics of subjects, included gender, age, BMI, smoking history, the ISO tar yield of the subject's usual brand of CC, daily cigarette consumption and score on the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991) were all recorded at screening.

2.4.2. Biomarkers of exposure

BoEs to selected HPHCs published by the Food and Drug Administration (FDA, 2012b) were chosen. 14 HPHCs (acrolein, acrylonitrile, 4-aminobiphenyl [4-ABP], 1-naphthylamine (1-NA), 2-naphthylamine (2-NA), benzene, benzo[*a*]pyrene [BaP], 1,3-butadiene, carbon monoxide [CO], crotonaldehyde, ethylene oxide, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK], N-nitrosonornicotine [NNN], *o*-toluidine) were selected. These HPHCs were selected because: (a) these constituents (or their metabolites) are easily detectable using validated, reliable, reproducible, and precise analytical methods; (b) the levels of BoEs to these constituents are well described in smokers and non-smokers; and (c) the BoEs to these constituents are widely used for assessing exposure in humans as a result of using tobacco products (Scherer, 2005; U.S. Department of Health and Human Services, 2010; Gregg et al., 2013; Chang et al., 2017; Schick et al., 2017). Although not listed as a HPHC by the FDA, pyrene is widely used as an alternative

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