Regulatory Toxicology and Pharmacology 87 (2017) 30–35

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Pharmacokinetics of nicotine following the controlled use of a prototype novel tobacco vapor product

Dai Yuki*, Chikako Sakaguchi, Akira Kikuchi, Yasuyuki Futamura

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

ARTICLE INFO

Article history:
Received 13 January 2017
Received in revised form
28 April 2017
Accepted 3 May 2017
Available online 4 May 2017

Keywords:
Clinical study
Japanese healthy adult male smokers
Nicotine
Pharmacokinetics
Prototype novel tobacco vapor product
Mouth level exposure
Relative bioavailability

ABSTRACT

The objective of this clinical study was to investigate the pharmacokinetics of nicotine following the use of a prototype novel tobacco vapor (PNTV) product in comparison to a conventional cigarette (CC1). The study was conducted in Japanese healthy adult male smokers, using an open-label, randomized, two-period crossover design, to assess the pharmacokinetics of nicotine after controlled use of a PNTV product or CC1. During the study period, blood samples were drawn from subjects for the measurement of plasma nicotine concentrations and nicotine intake was estimated from the mouth level exposure (MLE). The C_{max} and AUC_{last} following the use of PNTV product were 45.7% and 68.3%, respectively, of those obtained with CC1 and there were no significant differences in the tmax and $t_{1/2}$ between PNTV product and CC1. The estimated MLE following the use of PNTV product was approximately two-thirds of that obtained following the smoking of CC1, but the relative bioavailability of PNTV product to CC1 was approximately 104%. The differences in C_{max} and AUC_{last} between PNTV product and CC1 therefore are explained by differences in nicotine intake. These results suggest that the PNTV product shows a similar pharmacokinetic profile to CC1, while delivering less nicotine following controlled use.
© 2017 Japan Tobacco Inc. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Many kinds of tobacco product, such as cigars, pipes, and nasal or oral snuff, are used throughout the world, though the cigarette is the predominant form used today. The past few years has seen a rapid increase in the availability of novel tobacco and nicotine containing products, in particular electronic cigarettes, known as electronic vapor products (Walele et al., 2016; Marsot and Simon, 2016), and heated tobacco products (Sakaguchi et al., 2014; Lüdicke et al., 2016; Haziza et al., 2016). Among these new product forms, some have been aimed designed to reducing smokers' exposure to chemicals for which health concerns have been raised (Frost-Pineda et al., 2008).

Nicotine is the major alkaloid in tobacco leaf and therefore present in tobacco products, and its pharmacokinetics has been studied extensively following cigarette smoking and the use of some other forms of tobacco product. The absorption rate of nicotine is slower with the use of oral moist snuff and chewing tobacco compared to smoking cigarettes, and this difference has been explained by the differences in the absorption site of nicotine: in the former cases, primary absorption site is the oral mucosa while in the latter it is the lungs (Benowitz et al., 1988; Foulds et al., 2003). Additionally, the absorption rate of nicotine following the use of electronic cigarettes is delayed compared with conventional cigarettes (Marsot and Simon, 2016). Given these previous findings, different forms of tobacco product may have different pharmacokinetic profiles due to the absorption site of nicotine.

The pharmacokinetics of nicotine demonstrated by various kinds of tobacco product has provided valuable information to clarify the extent to which individuals are exposed to nicotine when these tobacco products are used. Since nicotine intake delivered from tobacco products varies among smokers due to differences in their puffing behavior, accurate estimation of the intake of nicotine would contribute to a more precise evaluation of its pharmacokinetics. Methods for estimating the amount of nicotine delivered from conventional cigarettes during smoking (mouth level exposure [MLE]) have been thoroughly described (Watson et al., 2004; Shepperd et al., 2006, 2009). However, few methods have been reported for estimating the intake of nicotine from tobacco products other than cigarettes.

The objective of the present study was to investigate the pharmacokinetics of nicotine when using a prototype novel tobacco vapor (PNTV) product in comparison with smoking a conventional

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

http://dx.doi.org/10.1016/j.yrtph.2017.05.005
0273-2300/© 2017 Japan Tobacco Inc. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

cigarette. The pharmacokinetic parameters were calculated from the blood nicotine concentrations and the estimated MLE of nicotine following controlled product use. In this study, the MLE of nicotine from PNTV product use was estimated in a different way than the MLE of nicotine from cigarette smoking.

2. Material and methods

2.1. Study design

This study was employed an open-label, two-sequence, two-period, randomized crossover design to investigate the pharmacokinetics of nicotine following the use of a PNTV product in comparison with smoking a commercially available conventional cigarette (CC1: 1 mg tar and 0.1 mg nicotine values, measured by ISO machine-smoking (ISO 3308, 2000) and printed on the package). The study was conducted at a single center in Japan. 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 (UMIN000017297). All participants provided written informed consent to participate in the study.

2.2. Subjects

Healthy Japanese adult male smokers aged 21–65 years were eligible to participate if they smoked an average of 11 or more manufactured cigarettes per day at screening and had smoked for at least 12 months before entering the trial. Before entering the trial, the health conditions of subjects were confirmed by physical examination, medical history, vital signs, electrocardiogram, and clinical laboratory tests. Subjects were excluded if they had a body mass index (BMI) of less than 18.5 or of 25.0 kg/m^2 or more; a urinary cotinine level less than 200 ng/mL at screening, as determined using an immunoassay kit (One Step Cotinine Test Device, Accuracy-One Inc., California, USA); or had used any prescription smoking cessation treatment within the 4 week period before entering the study.

The target sample size was determined as 20 subjects according to the guidelines on the investigation of bioequivalence (MHLW, 2012), and 24 subjects were subsequently enrolled.

2.3. Procedure

On Day 1, Subjects checked in to the clinic and abstained from their regular tobacco product use. Days 2 and 3 were product use days. On each product use day, subjects used a PNTV product or smoked one CC1 under controlled use according to the randomization schedule. The controlled use of both PNTV product and CC1 consisted of 10 puffs for 3 min at approximately 20-s intervals. On Day 4, subjects were discharged following completion of health assessments.

2.4. Test tobacco product

The PNTV product consisted of a power supply unit, a cartridge with a heater and liquid, and a capsule filled with tobacco blend (Fig. 1). The PNTV product generates a nicotine-free vapor via electrical heating of a liquid, which contains glycerin, propylene glycol and water and does not contain nicotine and flavor unlike 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 nicotine yield of the PNTV product in 50 puffs, which is the intended puff number of one capsule, was 1.10 mg per capsule as measured by the Health Canada machine-smoking test regimen (puff volume: 55 mL, puff duration: 2 s, and puff frequency: 2/min) (Health Canada, 1999). In addition, we selected a CC1 as a comparator of PNTV product in this study, in order to approximate the estimated amount of nicotine delivered under the controlled use condition between investigational tobacco products from the above mentioned results of chemical analysis.

2.5. Measures

2.5.1. Baseline characteristics

The baseline characteristics of subjects, included gender, age, BMI, daily cigarette consumption, smoking history, and the ISO tar yield of the subject's usual cigarette brand, were recorded at screening. The *trans*-3'-hydroxycotinine:cotinine ratio, which is reported as an indicator of CYP2A6 activity (Mooney et al., 2008; Swan et al., 2009; Dempsey et al., 2004), was calculated by the plasma concentration of *trans*-3'-hydroxycotinine and cotinine on Day 2. Plasma concentrations of *trans*-3'-hydroxycotinine and cotinine were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using validated analytical methods with appropriate quality controls at LSI Medience Corporation (Tokyo, Japan). The limits of quantification for *trans*-3'-hydroxycotinine and cotinine were 0.500 ng/mL.

2.5.2. Estimation of mouth levels of nicotine exposure

The MLE of nicotine from CC1 smoking was estimated by using cigarette part-filter analysis, which is a method commonly used to estimate cigarette smoke constituent yield to smokers (Shepperd et al., 2009). Puff volume, puff duration, puff interval, and butt length were set as parameters for preparing a calibration curve, and machine smoking of CC1 was then conducted using combinations of these parameters (18 conditions in total), followed by analysis of the amount of residual nicotine contained in the 10 mm mouth-end section of the filter and the amount of nicotine delivered in the mainstream smoke. CC1 has the dual-filter consist from acetate filter and charcoal filter, and the mouth-end section of the 10 mm acetate filter from CC1 smoked by subjects were pulled out by tweezers. The filter then placed in glass jars by clinical staff immediately after smoking and sent to Japan Tobacco Inc. (Tokyo, Japan) for analysis. Each spent filter underwent an extraction process using 2.0 mL of methanol containing 10% acetic acid, and the amounts of nicotine contained in the extracts were measured by gas chromatography (7890, Agilent Technologies, California, USA) using a flame ionization detector. The MLE of nicotine during CC1 smoking was subsequently calculated from the calibration curve (Fig. 2(A)).

Since the PNTV product does not contain a filter to filtrate the chemical components in the vapor, the part-filter analysis method could not be used for it. In this study, the estimated MLE of nicotine during PNTV product use was calculated from the puffing topography data (puff volume and puff duration) recorded using the CReSSmicro device (Plowshare Technologies, Inc./Borgwaldt KC, Inc., Richmond, USA). Machine aspiration was performed under 15 conditions that consisted of combinations of the puff volume (ranging from 25 to 140 mL) and the puff duration (ranging from 1.5 to 2.5 s) during 10 puffs at 20-s intervals. This was followed by analysis of the amount of nicotine delivered in the vapor (Fig. 2(B)). Multiple regression analysis was conducted by using the amount of delivered nicotine in the vapor as an objective variable and the aspiration parameters as explanatory variables, and the estimate formula was selected the best relational expression from the result of multiple regression analysis. The MLE of nicotine during PNTV

Download English Version:

https://daneshyari.com/en/article/5561330

Download Persian Version:

https://daneshyari.com/article/5561330

Daneshyari.com