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Pharmacokinetic analysis of nicotine when using non-combustion inhaler type of tobacco product in Japanese adult male smokers

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ABSTRACT

In a clinical study, the pharmacokinetics of nicotine were investigated using the prototype of a non-combustion inhaler type of tobacco product (PNCIT) with comparison to a 1 mg tar conventional cigarette (CC). The study was conducted in 12 healthy adult Japanese male smokers with an open-label non-randomized design to make an intra-subject comparison of the use or smoking of these products. Subjects used a single piece of PNCIT with 80 aspirations or smoked a CC with 10 puffs every hour, for a total of 12 PNCITs or CCs on each study day. Under this study regimen, the steady state plasma nicotine concentration was not significantly different between the test tobacco products. The time to reach the maximum plasma nicotine concentration was longer for PNCIT compared to CC, suggesting that nicotine delivered from PNCIT was absorbed primarily in the upper airway, not in the pulmonary sites as cigarette smoking. The relative bioavailability of nicotine for PNCIT compared to CC was 0.92 ± 0.32, indicating similar nicotine bioavailability for both forms. The difference in the elimination half-lives between the test products was not significant, suggesting that the elimination of nicotine from blood is not affected significantly by the difference in the nicotine absorption sites.

1. Introduction

Throughout the history of tobacco, various kinds of tobacco products have been used. Although the cigarette is the predominant form used today, many other kinds of tobacco products, such as cigars, pipes, and nasal or oral snuff are used in various regions of the world. With the increasing awareness of the health concerns associated with smoking, interest has grown in tobacco products other than cigarettes. Given these circumstances, some non-traditional forms of tobacco product, such as electrically heated cigarettes (Buchhalter and Eissenberg, 2000) and dissolvable tobacco tablets (Rainey et al., 2011), have been introduced in recent decades. Of these new forms, some were aimed at reducing exposure to those chemicals for which health concerns have been raised (Frost-Pineda et al., 2008).

The non-combustion inhaler type of tobacco product is a new form of smokeless tobacco product (this type of product has been marketed under the name Zerostyle in Japan). This smokeless tobacco product consists of a tapered mouthpiece and cartridge filled with fine cut tobacco leaves (Fig. 1). The flavor components can be delivered from the tobacco leaves not by burning or heating but just by the air flow when users aspirate through its mouthpiece. Although the motion for using the non-combustion inhaler type of tobacco product, i.e., aspiration through the mouth, is similar to that of smoking a conventional cigarette, the degree of user exposure to chemicals derived from the product is unclear.

The investigation of the intake and pharmacokinetics of chemicals derived from various kinds of tobacco products has given us valuable information that has clarified the degree to which humans are exposed to chemicals when those tobacco products are used. The composition and amount of chemicals derived from a tobacco product are variable and the intake of them depends on both its form of use and how it is used by individual consumers, even if each product consists of the same tobacco leaves. Additionally, the increase in the blood concentration of nicotine, one of the chemical components of tobacco, is slower when oral moist snuff and chewing tobacco are used than it is when cigarettes are smoked, as in the former case absorption takes place through the oral mucosa (Benowitz et al., 1988; Foulds et al., 2003). Given these previous studies, different types of tobacco products may have different absorption sites for these chemicals and this could change the pharmacokinetic profile, such as the rate of absorption of these chemicals. Among these chemicals, nicotine is one of the most characteristic compounds contained in tobacco leaves, and its pharmacokinetics have been studied extensively in relation to the use of existing tobacco products.

Accurate estimation of the intake of chemicals would contribute to more precise evaluation of the pharmacokinetics of such chemicals. Methods used to estimate the amount of smoke constituents

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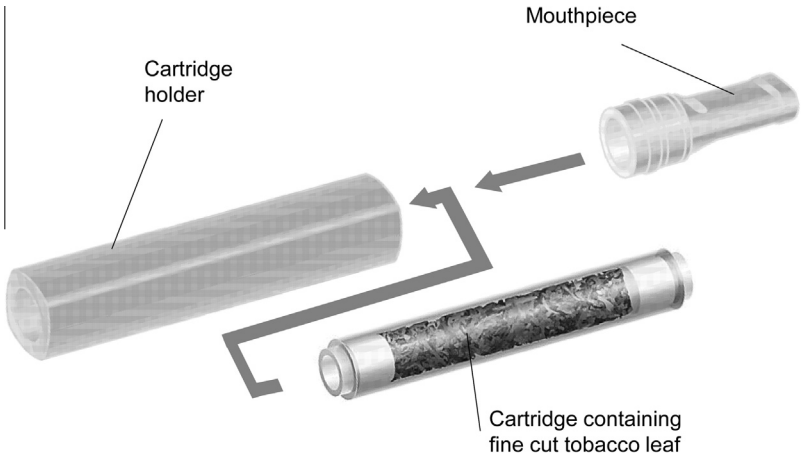

Fig. 1. Representation of non-combustion inhaler type of tobacco product. The prototype (PNCIT) used in this study did not have flavorings added.

delivered from conventional cigarettes during smoking (mouth level exposure, MLE) have been thoroughly studied (Watson et al., 2004; Shepperd et al., 2006, 2009). However, there are few methods for estimating the intake amount of chemicals from tobacco products other than cigarettes, therefore it is necessary to improve existing estimation methods or develop new methods for estimation of the intake of chemical components including nicotine.

The objective of the present study was to investigate the pharmacokinetics of nicotine when using the prototype non-combustion inhaler type of tobacco product (PNCIT) in comparison with smoking 1 mg tar conventional cigarette. In this study, the MLE of nicotine delivered from PNCIT during use was calculated from the aspiration volume and the ambient room temperature measured, which is a different way of estimating the MLE of chemicals from cigarettes during smoking. To investigate the pharmacokinetics of nicotine, the estimated MLE of nicotine from tobacco product was regarded as the dose and the blood nicotine and cotinine concentrations were measured for both PNCIT use and cigarette smoking in the same subjects.

2. Materials and methods

2.1. Study design and subjects

This study was an open-label, non-randomized design to make an intra-subject comparison between the nicotine pharmacokinetics associated with using PNCIT and smoking conventional cigarettes (CC, 1 mg machine-smoked tar yield under the protocol standardized by the International Organization for Standardization (ISO)). The CC chosen for the study is one of the most popular brands in Japan. The entire study period comprised nine consecutive days and subjects stayed in a medical institution throughout the study. All subjects used PNCIT on Day 4 after a 3-day washout period, followed by another 3-day washout period prior to smoking CC on Day 8. During the washout period, subjects did not use any nicotine-containing products. The clinical staff observed and recorded any adverse events, and ensured that the subjects abstained from using nicotine-containing products except for the tobacco products specified for the study. The study was conducted at Maruyama Hospital, Hamamatsu, Japan, in accordance with Good Clinical Practice (GCP) and principles that have their origin in the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board of Japan Tobacco Inc. and Maruyama Hospital.

Twelve healthy Japanese male smokers aged 21–40 years who reported smoking at least 12 non-mentholated cigarettes per day for at least one year prior to the study were enrolled. Subjects were also required to have a body mass index in the range of 18.5–25.0 kg/m^2. The health of subjects was checked before their entry into the trial by physical examination, medical history, vital signs, 12-lead electrocardiogram and laboratory tests. Serum cotinine concentrations were measured and had to exceed 14 ng/ml to prevent the entry of non-smokers into the trial (Pérez-Stable et al., 1992). All volunteers were paid for participating and provided written informed consent before the enrollment.

2.2. Study procedure

Subjects were given one new piece of the test tobacco product every hour for 12 h: a total of 12 pieces are used or smoked on their study days. Regulated multiple aspirations or puffs were employed for both PNCIT and CC; the aspiration frequency for PNCIT was set at 80 times with 15-s intervals in each hour. The puff frequency for a CC was set at 10 times with the same intervals as PNCIT (15 s). Twelve PNCIT and 12 CC were set in order to achieve a steady state plasma concentration of nicotine. During use of PNCIT or CC, the aspiration or puff volumes for each subject were recorded using a puff profiler (CReSSmicro™, Plowshare/Borgwaldt-KC), and the ambient temperature was measured with a temperature datalogger (TR-72U, T&D Corporation). Additionally for CC, the spent filters from the CC that the subjects had smoked were collected.

2.3. Test tobacco products

PNCIT consists of a cartridge filled with ground tobacco leaf and a tapered mouthpiece (Fig. 1). Volatile substances, including nicotine, are delivered from tobacco leaves not by burning or heating but just by the air flow when users aspirate the air through the PNCIT mouthpiece. Water, flavorings, potassium carbonate and propylene glycol were added to the tobacco leaves. The recipe of flavorings for the commercial version of the product depends on the each brand character, while flavorings were not added to PNCIT used in this study in order to simplify the flavor composition derived from the product.

For measuring the amount of nicotine derived from PNCIT by machine aspiration, the following regimen was set; 70 ml aspiration volume, 2 s aspiration duration with 15-s intervals between each aspiration and a total of 80 aspirations. The aspiration volume was set based on the results of the in-house preliminary study conducted in 60 participants. The results showed that the mean inhaled volume was 68 ml per aspiration (range: 25.5–157). The intervals and the number of aspirations were set based on the