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A randomised, crossover study on an electronic vapour product, a nicotine inhalator and a conventional cigarette. Part B: Safety and subjective effects

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ABSTRACT

An Electronic Vapour Product (EVP) has been evaluated for short-term safety parameters and subjective effects in a 2-part study, in smokers. Part 1 compared the EVP with unflavoured (UF) and flavoured (FL) e-liquid at 2.0% nicotine to a conventional cigarette (CC; JPS Silver King Size, 0.6 mg) and a licensed nicotine inhalator (Nicorette®, 15 mg). Part 2 assessed the effect of increasing concentrations of nicotine in the e-liquid used with the EVP (0%, 0.4%, 0.9%, 2.0%). The study was designed as a randomised, controlled, crossover trial. Outcomes included adverse events (AEs), vital signs, exhaled carbon monoxide (CO), clinical laboratory parameters, smoking urges and withdrawal symptoms. In both study parts, only mild non-serious AEs were reported. No major differences were observed in AEs between the EVPs and Nicorette®. Exhaled CO levels only increased for CC. All products appeared to decrease smoking urges and nicotine withdrawal symptom scores to a similar extent. The EVP had a similar short-term safety profile to Nicorette® and relieved smoking urges and nicotine withdrawal symptoms to a similar extent as Nicorette® and CC. Unlike nicotine replacement therapies, the EVP may offer an alternative for those finding it difficult to quit the behavioural and sensorial aspects of smoking.

1. Introduction

Electronic vapour products (EVPs), also known as “electronic cigarettes” are a relatively new class of products. Even though the majority of EVPs are marketed as consumer products, they are often reported to be used as a means to stop smoking conventional cigarettes (Berg et al., 2015; Dockrell et al., 2013; Etter and Bullen, 2011). Any claims to cessation or harm reduction must require a medicinal license (MHRA, 2015). The few short-term studies performed to date suggest that EVPs have the potential for being safer alternatives to conventional cigarettes (CC) and at the same time satisfy the ritualistic elements of smoking. For example, EVPs do not increase exhaled carbon monoxide (CO) levels or white blood cell count, and do not have immediate effects on myocardial and lung functions (Farsalinos, 2012; Flouris et al., 2013, 2012; Vansickel et al., 2010; Vardavas et al., 2012). When smokers switch to use EVPs and are followed-up for prolonged periods, observations have included a progressive decrease in occurrences of adverse events (AEs) commonly reported by CC smokers, *e.g.* cough, dry mouth, shortness of breath, throat irritation and headache (Caponnetto et al., 2013; Farsalinos et al., 2014a; Polosa et al., 2014; van Staden et al., 2013). A higher frequency of mouth and throat irritation was observed in smokers switching to using a Nicorette® inhalator, compared to those using EVPs (Bullen et al., 2010). Few commercially available EVPs have been studied for their subjective effects such as the suppression of desire to smoke and tobacco or nicotine abstinence symptoms. Some studies have demonstrated that even with no nicotine present in EVP e-liquid, nicotine craving and withdrawal symptoms were alleviated albeit less compared to CCs (Bullen et al., 2010; Vansickel et al., 2010).

This study was conducted as part of a product stewardship evaluation of an EVP prototype. The evaluation of the product's plasma nicotine pharmacokinetic (PK) profile is reported elsewhere

Abbreviations: AE, Adverse event; CC, Conventional cigarettes; CO, Carbon monoxide; EVP, Electronic vapour product; NRT, Nicotine replacement therapy.

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(Walele et al., 2015). In this paper, the short-term health effects and the potential of the EVP for reducing smoking urges and withdrawal symptoms are described. The study consisted of two parts. Part 1 compared the EVP with an unflavoured (UF) and a flavoured (FL) e-liquid containing 2.0% nicotine to a nicotine replacement therapy (NRT) product and a commercially available CC. Part 2 investigated the effects of the EVP with unflavoured e-liquids containing increasing levels of nicotine (0%, 0.4%, 0.9% and 2.0%).

2. Materials and methods

2.1. Study design

This study was performed at a single clinical site (Simbec Research Ltd, Wales) in a confinement setting. A total of 24 healthy male subjects, recruited in the UK, participated in the study: 12 assigned to Part 1 and 12 to Part 2. Both study parts were designed as a randomised, controlled, four-way crossover trial. Part 1 was performed open-label and Part 2 was blinded. Following overnight abstinence from smoking or using EVPs, subjects used each different product for one daily use session.

The study was approved by the South East Wales Research Ethics Committees on 31 October 2013, and is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02032212. All procedures were performed in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP). The Medicines and Healthcare Products Regulatory Agency (MHRA)-UK granted Clinical Trials Authorisation (CTA) for the use of the NRT product in this study. All subjects signed an informed consent form prior to any study procedures being performed.

2.2. Study population

Detailed inclusion and exclusion criteria are presented in our paper reporting the plasma PK results (Walele et al., 2015). Subjects were 21–65 year old males and were confirmed smokers (5–30 cigarettes per day for at least one year). The subjects' smoking history was recorded using internal questionnaires and with the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). Subjects were excluded if they were taking or receiving any form of NRT, snuff or chewing tobacco or if they intended to stop smoking.

2.3. Products used in this study

The EVP prototype used in this study was developed by Fontem Ventures B.V. It consisted of a rechargeable battery, an atomiser and a capsule containing e-liquid (Fig. 1). The capsules were replaceable and the battery and atomiser were reusable. The base components of the e-liquids used are propylene glycol (70–75% w/w), glycerol (18–20% w/w) and water (5% w/w). Two e-liquids were used in Part 1 of the study, which differed solely in their flavour content: an unflavoured base e-liquid with 2.0% nicotine (UF2.0%; 2.7 mg/capsule) and a flavoured (menthol) e-liquid with 2.0% nicotine (FL2.0%; 2.7 mg/capsule). In Part 2, four unflavoured e-liquids were used, which differed in their nicotine content: 0% nicotine (UF0%), 0.4% nicotine (UF0.4%; 0.4%; 0.54 mg/capsule), 0.9% nicotine (UF0.9%; 1.22 mg/capsule) and UF2.0%. The EVP with UF2.0%, FL2.0% and UF0.4% delivers mean amounts of 0.013, 0.007 and 0.002 mg nicotine per puff, respectively (internal data, generated under Health Canada Intense smoking regime). Nicotine delivery with UF0.9% was not measured.

Fig. 1. Schematic of the external appearance and parts of the tested EVP. From left to right, pieces are: the housing, which contains the battery and has a LED indicator on the side, the atomiser, the capsule containing the e-liquid and the mouthpiece.

In Part 1 of the study, the NRT Nicorette® Inhalator (15 mg nicotine, manufacturer Johnson & Johnson; coded NIC15) was used as a comparator product and a JPS Silver King Size CC (0.6 mg nicotine; manufacturer Imperial Tobacco Group) was used as a control.

2.4. Study interventions and schedule

Subjects were admitted to the study site on the morning of Day −2 (baseline) for confirmation of eligibility and training on using the EVP or NIC15. Smoking status was verified by measuring the urinary cotinine levels in a spot urine sample (NicAlert strip), the exhaled CO levels (measured with a portable Bedfont Micro + Smokerlyser device) and blood carboxyhemoglobin (COHb) levels (2 mL sample, from a forearm vein, in lithium heparin, measured with a blood gas analyser system). A safety assessment was performed on Day −2, which included vital signs (blood pressure, heart rate and oral body temperature in supine position), AEs, a physical exam, a lung function test (spirometry) and a 12-lead electrocardiogram (ECG). Blood (7.6 mL, from forearm vein) and urine samples were taken to measure haematology, clinical chemistry and urinalysis parameters, for standard clinical laboratory evaluations. From the time of admission, subjects were not permitted to use any EVP, NRT or CC other than that assigned by the study design and were not allowed to consume alcohol. Subjects remained in confinement until the end of the study period, on the morning of Day 5. On Day −1, the revised Minnesota Nicotine Withdrawal Scale questionnaire (MWS-R) was administered to document nicotine withdrawal symptoms (Hughes, 2007) and the Brief Questionnaire of Smoking Urges (QSU-Brief), to measure craving (Cox et al., 2001). On Day −1, subjects were randomly assigned to one of four pre-defined sequences of product use within their allocated study Part, in a 3:3:3:3 ratio.

On study Days 1, 2, 3, and 4, after overnight smoking abstinence, subjects used the allocated product for four product administrations at 1-h intervals (0hr, 1hr, 2hr and 3hr). Each administration consisted of 10 inhalations at 30 s intervals. Each inhalation was monitored, and subjects were instructed to take 4-s puffs for the EVP and NIC15, and 2-s puffs for the CC (an electronic tablet was used instructing subjects when to inhale and exhale). Vital signs were recorded approximately 30 min before the first product administration, and 30 min after the fourth one. Exhaled CO was measured 5 min before and 25 min after each product administration. Subjects filled the MWS-R and QSU-Brief questionnaires approximately 30 min after the third administration, at a similar timing as on Day −1. These assessments were done 30 min after the fourth administration because priority was given to PK sampling (Walele et al., 2015). AEs were monitored on each study day.

On Day 5, safety assessment parameters were checked, and subjects answered both the MWS-R and QSU-Brief questionnaires for the last time. Subjects were also provided full verbal smoking cessation advice by the investigator and were discharged from the clinic after all study assessments were performed.