Nicotine & Tobacco Research, 2015, 175–179
doi:10.1093/ntr/ntu153
Advance Access publication August 13, 2014
Original investigation

OXFORD

Original investigation

Nicotine Intake From Electronic Cigarettes on Initial Use and After 4 Weeks of Regular Use

Peter Hajek PhD[1], Maciej L. Goniewicz PharmD, PhD[2], Anna Phillips MSc[1], Katie Myers Smith PhD[1], Oliver West MSc[1], Hayden McRobbie PhD[1]

[1]Tobacco Dependence Research Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK; [2]Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, NY

Corresponding Author: Maciej L. Goniewicz, PharmD, PhD, Department of Health Behavior, Division of Cancer Prevention and Population Science, Roswell Park Cancer Institute, Elm and Carlton Sts, Buffalo, NY 14263, USA. Telephone: 716-845-8541; Fax: 716-845-1265; E-mail: maciej.goniewicz@roswellpark.org

Abstract

Introduction: Electronic cigarettes (EC) have the potential to generate a substantial public health benefit if there is a switch from smoking to EC use on a population scale. The nicotine delivery from EC is likely to play a major role in their attractiveness to smokers. We assessed nicotine delivery from a first-generation EC and the effect of experience with its use on nicotine intake.

Methods: Six smokers provided pharmacokinetic (PK) data after their first use of EC and again following 4 weeks of use.

Results: The peak nicotine levels were achieved within 5 min of starting the EC use, which suggests that EC may provide nicotine via pulmonary absorption. There were large individual differences in nicotine intake. Compared with the PK profile when using EC for the first time, 4 weeks of practice generated a 24% increase in the peak plasma concentrations (from 4.6 to 5.7 ng/ml; nonsignificant) and a 79% increase in overall nicotine intake ($AUC_{0\rightarrow inf}$ increased from 115 to 206 ng*min/ml; $p < .05$).

Conclusions: First-generation EC provide faster nicotine absorption than nicotine replacement products, but to compete successfully with conventional cigarettes, EC may need to provide higher doses of nicotine. Nicotine intake from EC can increase with practice, but further studies are needed to confirm this effect.

Introduction

Electronic cigarettes (EC) are a developing technology aiming to provide nicotine without the harmful chemicals produced by tobacco combustion.[1] EC have the potential to generate a substantial public health benefit if there is a switch from smoking to EC use on a population scale.[2] So far, however, only some 12%–14% of smokers who tried EC progress to using them daily.[3,4] This suggests that the current generation of EC products does not yet match combustible tobacco closely enough in providing smokers with what they want from their tobacco cigarettes. The nicotine delivery profile is likely to play a major role.

Early studies of EC pharmacokinetics (PK) detected very low nicotine delivery to users.[5–7] This could be due to inclusion of EC brands with poor nicotine delivery and/or due to the fact that study participants were instructed to puff at pre-specified, relatively long intervals (e.g., taking 10 puffs with 30-s inter-puff intervals). More frequent puffing may be needed to heat the element that vaporizes the nicotine solution. Later studies of experienced users using their own EC brands recorded much higher plasma nicotine levels.[8–11] It is possible that this was due to EC brands with better nicotine delivery, but it may also be that EC users improve their nicotine intake from the device with practice. However, it is also possible that there are

persistent individual differences in smokers' ability to obtain nicotine from the device and that being able to obtain a good nicotine level from EC early on leads to frequent use, rather than the other way round. There are no data available on changes in nicotine intake from EC following practice.

Little data exist on how quickly EC deliver nicotine to users and whether this happens primarily via buccal absorption, as with nicotine inhalator, or whether there are any signs that pulmonary nicotine absorption is involved. This study had two objectives: it aimed to examine nicotine delivery from EC used ad lib after overnight abstinence and it assessed the effects of 4 weeks of EC use on nicotine intake from the device.

Materials and Methods

The experiment was a part of a larger study of exposure to a carbonyl compound acrolein, which is generated by cigarettes and can be also produced by EC containing glycerin. The results of the acrolein study are being reported separately.[12]

Subjects

A total of 40 adult smokers interested in stopping smoking were recruited through advertisements in local newspapers and took part in the acrolein study (see above). We excluded women who were pregnant or breast feeding, smokers with any current serious illness, and those who had used EC for more than one week in the past. A subsample of 10 volunteers who agreed to venipuncture took part in the PK study. Two participants did not attend the follow-up session and two provided less than five consecutive blood samples so their results could not been used for PK modeling. The remaining six participants provided at least five consecutive blood samples on each occasion, and their data were used to analyze the PK parameters.

Study Procedures

The study was approved by the National Health Service (NHS) Health Research Authority, National Research Ethics Service (NRES) Committee London (12/LO/1987) and registered at ClinicalTrials.gov (NCT01714778). Participants were screened over the telephone and attended a preparation session 1 week prior to their target quit date (TQD), where they provided written informed consent and baseline measures. They attended the laboratory in between their preparation and TQD sessions after overnight abstinence from smoking for the first PK assessment. The sessions took place between 7:30 and 9:30 a.m., depending on the participants' availability, and took about 90 min.

On the TQD, participants were provided with an EC and 15 cartridges and instructions on its use, and attended standard withdrawal-oriented behavioral support weekly for 4 weeks.[13] Further supplies of cartridges were available at each session as needed. The instructions suggested that smokers usually find their own way of using EC; that EC can be puffed on for 5–10 min and may require a few more and longer puffs than cigarettes; and that smokers typically use one cartridge per day, but enough cartridges are provided to use up to two per day.

Participants attended the second PK assessment 4 weeks later, again between 7:30 and 9:30 a.m. after overnight abstinence from both smoking and EC use. All six participants were smoking and using EC during the week of their second assessment. One participant reported smoking less than five cigarettes over the previous week; the others smoked more than five cigarettes. At the two PK sessions, a blood sample was taken after which participants were asked to smoke a fully charged EC ad lib for 5 min. Further blood samples were taken at 5, 10, 15, 20, 30, and 60 min after starting the use of EC. Participants received £120 on completion of the second PK session.

Measures

Demographic and smoking history data were collected at baseline. At each visit, participants reported on their cigarette and EC use, and provided an end-expired carbon monoxide (CO) reading collected using a CO monitor.

Three to five milliliters of blood were collected at each time point via a 20-gauge intravenous catheter that was placed in the dorsal aspect of the participants' nondominant hand. The blood was immediately transferred to a heparinized tube. At the end of each session, all samples were centrifuged and 1–2 ml of plasma frozen at −20 °C. At the end of the study, the frozen plasma samples were air freighted to ABS Laboratories for measurement of plasma nicotine concentration. Samples were prepared as described previously by Feyerabend and Russell.[14]

The plasma samples were assayed for nicotine using a liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay developed and validated by ABS Laboratories using d_4-nicotine as the internal standard. The LC chromatography was performed on a HILIC-PFP column, 4.6 × 50 mm from Thermo-Fisher and the multiple reaction monitoring (MRM) transitions used for the MS/MS analysis were m/z 163–130 for the analyte and m/z 167–134 for the internal standard. The analysis was performed using 96-well plates. Each batch included double and single blank samples and seven calibration standards in duplicate and duplicate low-, medium-, and high-quality control samples. The lower limit of quantification was 0.5 ng/ml.

Study Product

The study used a Green Smoke EC with cartridges labeled 2.4% nicotine. This was a first-generation "cig-a-like" re-chargeable device. EC were purchased from the manufacturer. The selected product was tested in our previous study.[15] The labeling of nicotine content was accurate and the model had good consistency in nicotine delivery. It delivered 9 mg of nicotine in vapor more than 300 puffs, which was in the middle of the range of the products tested. Cartridges used in this study were tobacco flavored and contained nicotine dissolved in a mixture of propylene glycol and vegetable glycerol.

Pharmacokinetics

All PK analyses were performed using PCModfit for Excel v. 4.0 software.[16] The following PK parameters (a) time at which the highest nicotine concentration occurred in plasma following EC use (T_{max}); (b) the highest drug concentration observed in plasma following EC use; (c) estimated area under the plasma nicotine curve concentration from time 0 to 60 min ($AUC_{0\rightarrow60}$); and (d) estimated area under the plasma nicotine curve concentration from time 0 to infinity ($AUC_{0\rightarrow inf}$) were estimated using a noncompartmental model and trapezoidal rule. In order to analyze changes in nicotine plasma concentration, all measures were corrected for baseline values. We used fixed value correction and did not account for the half-time. The same correction procedure was used for the data obtained during initial and follow-up visits.

A single-dose PK concentration-time analysis was performed for each subject using a two-compartment model with an iteratively Weighted Least Squares approach without constraints. The weighting scheme used in this approach was $1/conc^2$. The results from a two-compartment modeling are presented for individual participants in Supplementary File.

Statistical Analysis

To estimate the effect of experience with EC use on nicotine delivery, we compared baseline (first EC use) and follow-up (after 4 weeks of use) sessions pairwise on the following PK parameters: T_{max}, C_{max}, $AUC_{0\rightarrow60}$, and $AUC_{0\rightarrow inf}$. All statistical comparisons were performed using Statistica 9.0 software. Differences were considered statistically significant when $p < .05$, two-tailed.

Results

The average age of the six participants was 52 years (*SD* = 16, range 32–74); five were female and all except one were White British. At the beginning of the study, they smoked on average 25 cigarettes/day (*SD* = 16, range 10–60) and scored 5.7 (*SD* = 3.2, range 1–9) on Fagerström Test for Nicotine Dependence.[17] During the study, they reported using on average 1.2 EC cartridges per day (*SD* = 0.7, range 0.7–2.5).

Figure 1 shows the PK data on the two occasions, that is, when the participants were new to EC use and after using EC for 4 weeks. Table 1 presents the nicotine delivery parameters at the two timepoints. T_{max} was reached at 5 min at both timepoints. C_{max} was 24% higher at follow-up (nonsignificant). Nicotine delivery profiles of individual participants are presented in Supplementary File. Four participants increased their nicotine intake at the second test, whereas two participants showed a decrease. At 4-week follow-up, four participants reported using 7 cartridges over the past week, one used 10, and one used 14 cartridges. Cartridge use was highly correlated with C_{max} at follow-up ($r = 0.93$; $p < .01$). It also showed a moderate correlation with C_{max} at baseline, though this did not reach statistical significance ($r = 0.55$; $p = .26$).

At 4-week follow-up, AUC_{0-60} increased by 50% (nonsignificant). Using AUC_{0-inf} statistics which extrapolates the nicotine absorption curve beyond 60 min shows an increase by 79% ($p < .05$). This suggests that practice may have increased the amount of nicotine users obtained from their EC. We estimated the dose of nicotine taken systemically from the EC for three participants for whom we had information about their weight. We used the plasma nicotine AUC and a population-averaged nicotine clearance value of 16.7 ml/min/kg for men and 17.7 ml/min/kg for women as follows: Dose = AUC × CI.[18] The estimated doses were 0.11, 0.22, and 0.26 mg at baseline and increased at follow-up to 0.43, 0.44, and 0.32 mg, respectively.

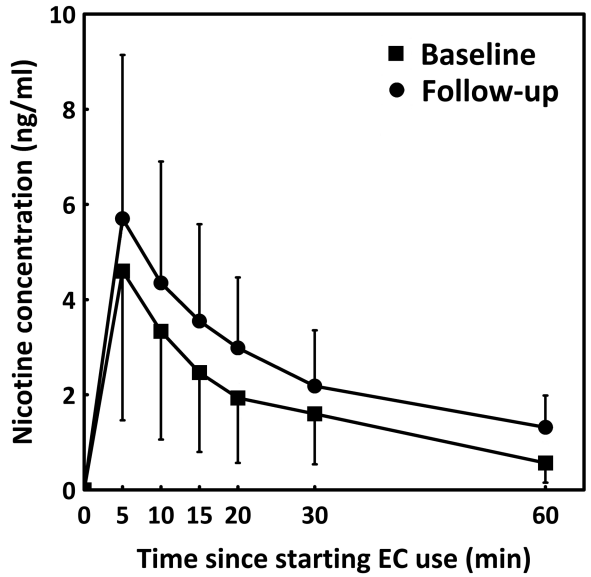

Figure 1. Plasma nicotine concentrations after 5 min of ad lib electronic cigarette use at baseline and at 4-week follow-up.

Table 1. Changes in PK Profile After 4 Weeks of EC Use ($N = 6$)

PK parameters	Mean ± *SD* (range)		p^a
	Baseline	Follow-up	
C_{max} (ng/ml)	4.6 ± 3.0 (0.9–9.0)	5.7 ± 3.3 (1.9–11.0)	.3525
T_{max} (min)	5.0 ± 0.0	5.0 ± 0.0	1.0000
$AUC_{0\rightarrow60}$ (ng*min/ml)	96 ± 70 (12–198)	142 ± 80 (56–234)	.1159
$AUC_{0\rightarrow inf}$ (ng*min/ml)	115 ± 81 (15–239)	206 ± 96 (80–300)	.0464

EC = electronic cigarette; PK = pharmacokinetic.
$AUC_{0\rightarrow60}$ is estimated area under the plasma nicotine curve concentration from time 0 to 60 min; $AUC_{0\rightarrow inf}$ is estimated area under the plasma nicotine curve concentration from time 0 to infinity; C_{max} is the highest drug concentration observed in plasma following EC use; T_{max} is time at which the highest nicotine concentration occurred in plasma following EC use.
[a]Nonparametric Wilcoxon paired test.

The mean baseline nicotine level was 2.3 ng/ml (*SD* = 0.6, range 1.2–2.7) during the first study session and 1.6 ng/ml (*SD* = 0.6, range 0.8–2.6) at follow-up ($p = .12$). We examined whether any changes in nicotine levels at the start of the two testing sessions affected changes in C_{max}. There was no relationship between the two variables ($r^2 = 0.14$; $p = .79$).

Discussion

Compared with the PK profile when using EC for the first time, 4 weeks of practice generated a 24% increase in the peak plasma concentrations (from 4.6 to 5.7 ng/ml, NS) and a 79% increase in overall nicotine intake (from $AUC_{0\rightarrow inf}$ 115 to 206 ng*min/ml; $p < .05$). We were unable to assess effects of practice on T_{max} because that has already been achieved at the first blood sampling at 5 min in all participants at both timepoints. An important limitation of our study is that blood samples were collected for only 60 min, thus the accuracy of the $AUC_{0\rightarrow inf}$ estimate may be less than optimal due to short period of blood sampling. The study generated several new results, but it need to be interpreted with caution because of the small sample size. Several findings can guide future replications.

This study used an ad lib puffing paradigm as opposed to scheduled puffing because we wanted to see the effects of any user-generated adjustments of EC use. Some participants learned to use EC more effectively, but it is not clear at which point in time this happened. It could have happened within the first few hours after trying the device for the first time, or may have needed more time. Future studies should consider scheduling the follow-up testing within 24 hr of the first-time use. The improvement was most likely achieved by deeper and/or more frequent inhalations. We did not monitor smoking topography as the use of the topography apparatus can influence smoking behavior. Once the effect of practice we observed has been replicated, further studies should consider including such measures.

The peak plasma nicotine levels were recorded at 5 min after starting the EC use. The real peak could have taken place before 5 min

or in between 5 and 10 min when the next sampling took place. This is much faster than nicotine absorption from oral NRT products (~30 min for nicotine chewing gum)[19] or from nicotine nasal spray (~10 min)[20] and suggests that in some users at least, EC may provide nicotine via pulmonary absorption. Future studies should schedule additional blood sampling points within the initial 10 min.

Little data exist on EC PK profile. In our previous study using an EC with a poor nicotine delivery, we observed a slower T_{max} (20 min) and very low C_{max} (1.3 ng/ml).[5] Two other studies looked at experienced EC users using their own EC brands. After 10 puffs over 5 min, blood nicotine levels were 10.3 ng/ml at the first sampling at 5 min in one of them,[9] and 6.8 ng/ml at the first sampling at 10 min in the other (also with 10 puffs over 5 min).[10] The present results suggest that the sample taken at 10 min was likely well past the C_{max}. All existing studies including ours used small samples and future experiments should include larger sample sizes.

The peak plasma nicotine levels achieved with this particular EC model were fairly low, comparable with the low end of oral NRT products and much lower than peak levels achieved with a cigarette.[21,22] This corresponds with our previous study where Green Smoke EC vapor contained 0.46 mg of nicotine per 15 puffs,[15] which is about 3 times less than obtained from smoking a typical tobacco cigarette.[23] The second-generation "tank system" EC now on the market may generate better nicotine delivery[11] and further developments are likely.

There were large individual differences in nicotine intake from the same EC. C_{max} values differed up to 5-fold after 4 weeks of practice. Different users have different needs and use the product differently. Participants who used more EC cartridges per day during the practice period had higher C_{max} values. It is possible that more frequent EC use led to higher nicotine intake, but there was a trend for those with a higher C_{max} at baseline to use EC more frequently later on, so an alternative and perhaps more likely explanation is that participants who were able to derive higher nicotine levels from EC from the start used the device more and improved their nicotine intake further. The finding that practice improves nicotine delivery from EC is only tentative. It did not apply to two out of six participants, and the result requires further confirmation.

In summary, in some EC users, nicotine intake from EC increased with practice. Smokers trying EC for the first time should be informed that nicotine delivery from the device may increase as they learn how to use it. The first-generation EC model used in this study delivered only low levels of nicotine, but did so very quickly compared with the speed of nicotine delivery from nicotine replacement therapy. Fast nicotine absorption is considered essential for smokers' satisfaction.[24,25] Our finding may explain some of the EC appeal to smokers, and it suggests that if EC manage to provide higher doses of nicotine as well, they may have the potential to replace conventional cigarettes.

Supplementary Material

Supplementary file can be found online at http://www.ntr.oxfordjournals.org

Funding

This study was funded by the UK Medicines and Healthcare Products Regulatory Agency. The study sponsor had no role in the collection, analysis, or interpretation of the data; in writing or approving the manuscript; or in the decision to submit for publication.

Declaration of Interests

PH, MLG, and HM received research funds and/or consultancy fees from manufacturers of smoking cessation medications.

References

1. Etter JF. *The Electronic Cigarette: An Alternative to Tobacco?* 3rd ed. Geneva, Switzerland: CreateSpace Independent Publishing Platform; 2012.
2. Hajek P. Electronic cigarettes for smoking cessation. *Lancet*. 2013;*382*:1614–1616.
3. Douptcheva N, Gmel G, Studer J, Deline S, Etter JF. Use of electronic cigarettes among young Swiss men. *J Epidemiol Community Health*. 2013;*67*:1075–1076.
4. Kralikova E, Novak J, West O, Kmetova A, Hajek P. Do e-cigarettes have the potential to compete with conventional cigarettes? A survey of conventional cigarette smokers' experiences with e-cigarettes. *Chest*. 2013;*144*:1609–1614.
5. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e-cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised crossover trial. *Tob Control*. 2010;*19*:98–103.
6. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control*. 2010;*19*:87–88.
7. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev*. 2010;*19*:1945–1953.
8. Etter JF, Bullen C. Saliva cotinine levels in users of electronic cigarettes. *Eur Respir J*. 2011;*38*:1219–1220.
9. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res*. 2012;*15*:267–270.
10. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)*. 2013;*231*:401–407.
11. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific Reports*. 2014;*26*:4133.
12. McRobbie H, Goniewicz ML, Phillips A, Myers-Smith K, West O, Hajek P. *Effects of the Use of Electronic Cigarettes With and Without Concurrent Smoking on Acrolein Delivery. Report to MHRA*. London: Queen Mary University of London; 2014.
13. McEwen A, Hajek P, McRobbie H, West R. *Manual of Smoking Cessation: A Guide for Counsellors and Practitioners*. Oxford: Blackwell Publishing; 2006.
14. Feyerabend C, Russell MA. A rapid gas-liquid chromatographic method for the determination of cotinine and nicotine in biological fluids. *J Physiol Pharmacol*. 1990;*42*:450–452.
15. Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour, and its consistency across batches: regulatory implications. *Addiction*. 2014;*109*:500–507.
16. Allen GD. MODFIT: a pharmacokinetics computer program. *Biopharm Drug Dispos*. 1990;*11*:477–498.
17. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström K-O. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991;*86*:1119–1127.
18. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P III. Female sex and oral contraceptive use accelerate nicotine metabolism. *Clin Pharmacol Ther*. 2006;*79*:480–488.

19. Benowitz NL, Porchet H, Sheiner L, Jacob P III. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*. 1988;*44*:23–28.
20. Fishbein L, O'Brien P, Hutson A, Theriaque D, Stacpoole PW, Flotte T. Pharmacokinetics and pharmacodynamic effects of nicotine nasal spray devices on cardiovascular and pulmonary function. *J Investig Med*. 2000;*48*:435–440.
21. Benowitz NL, Hukkanen J, Jacob P III. Nicotine chemistry, metabolism, kinetics and biomarkers. *Handb Exp Pharmacol*. 2009;*192*:29–60.
22. Hukkanen J, Jacob P III, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*. 2005;*57*:79–115.
23. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J Natl Cancer Inst*. 2000;*92*:106–111.
24. McRobbie H, Thornley S, Bullen C,et al. A randomized trial of the effects of two novel nicotine replacement therapies on tobacco withdrawal symptoms and user satisfaction. *Addiction*. 2010;*105*:1290–1298.
25. Caldwell B, Sumner W, Crane J. A systematic review of nicotine by inhalation: is there a role for the inhaled route? *Nicotine Tob Res*. 2012;*14*:1127–1139.