Nicotine delivery from e-cigarettes part II: data and learnings from two pharmacokinetic studies.

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Content

Part I
• E-cigarettes
• Introduction to nicotine PK studies
• Study design for two e-cigarette nicotine PK studies
  • Belfast, U.K.
  • Burbank, U.S.A.

Part II
• Data from U.K. and U.S.A. nicotine PK studies
• Discussion
  • What do our data tell us about nicotine delivery?
  • How can our data inform future study design?
  • Can we do it differently?
Interpreting PK data 101

![Graph showing serum drug concentration over time](image)

- $C_{\text{max}}$: maximum achievable concentration of drug in serum
- $T_{\text{max}}$: time needed to reach $C_{\text{max}}$

AUC = area under time-concentration curve

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British American Tobacco
BAT PK study #1 - data

Defined puffing period (10 puffs 30s apart)
## BAT PK study #1 - data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Period#</th>
<th>Cigarette $(n=24)$</th>
<th>e-cigarette $(n=23)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>LS Geometric mean</td>
<td>Controlled</td>
<td>13.0</td>
<td>2.5*</td>
</tr>
<tr>
<td></td>
<td>Geometric mean</td>
<td></td>
<td>13.4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Geometric CV (%)</td>
<td></td>
<td>51.4</td>
<td>67.8</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td>13.5</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Range (min – max)</td>
<td></td>
<td>5.3 - 35.5</td>
<td>0.5 - 6.9</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>LS Geometric mean</td>
<td>Ad libitum</td>
<td>14.1</td>
<td>5.8*</td>
</tr>
<tr>
<td></td>
<td>Geometric mean</td>
<td></td>
<td>14.9</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Geometric CV (%)</td>
<td></td>
<td>45.7</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td>14.7</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Range (min – max)</td>
<td></td>
<td>6.9 - 40.6</td>
<td>1.6 - 12.5</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>Median</td>
<td>Controlled</td>
<td>7.0</td>
<td>6.0$^{\text{NS}}$</td>
</tr>
<tr>
<td></td>
<td>Ad libitum</td>
<td></td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>$\text{AUC}_{0-14.5}$</td>
<td>LS Geometric mean</td>
<td>Controlled</td>
<td>2.1</td>
<td>0.4*</td>
</tr>
<tr>
<td></td>
<td>Geometric mean</td>
<td></td>
<td>2.2</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Geometric CV (%)</td>
<td></td>
<td>45.5</td>
<td>60.5</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Range (min – max)</td>
<td></td>
<td>1.0 - 5.0</td>
<td>0.1 - 1.2</td>
</tr>
</tbody>
</table>
BAT PK study #1 - data

Heart rate (% of baseline)

- cigarette
- e-cigarette

Defined puffing period (10 puffs 30s apart)
BAT PK study #1 summary

- E-cigarette nicotine delivery much lower than that of a cigarette under defined use conditions
- Potential for heart rate as a surrogate for blood nicotine
- Other data can be gained in these studies – smoking urges, satisfaction, cigarette consumption
  - be wary of subject overload
BAT PK study #2 - data

Blood nicotine (ng/ml)

- cigarette
- rechargeable
- cig-a-like

Time (minutes)

Ad libitum puffing period

Subject 1012

Subject 1018
## BAT PK study #2 - data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Cigarette (n=18)</th>
<th>Vype vPro e-cigarette (n=18)</th>
<th>Nicolites e-cigarette (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C_{max} (ng/mL)</strong></td>
<td>LS Geometric mean</td>
<td>7.2</td>
<td>8.8(^{\text{NS}})</td>
<td>4.7(^{\text{#NS}})</td>
</tr>
<tr>
<td></td>
<td>Geometric mean</td>
<td>7.2</td>
<td>7.8</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Geometric CV (%)</td>
<td>130.8</td>
<td>108.2</td>
<td>93.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.2</td>
<td>9.2</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Range (min – max)</td>
<td>0.7 - 37.6</td>
<td>0.0 - 40.2</td>
<td>1.2 - 18.2</td>
</tr>
<tr>
<td><strong>t_{max} (min)</strong></td>
<td>Median</td>
<td>6</td>
<td>6(^{\text{NS}})</td>
<td>9(^{\text{NS}})</td>
</tr>
<tr>
<td><strong>AUC_{0-60.0} (ng.h/mL)</strong></td>
<td>LS Geometric mean</td>
<td>3.4</td>
<td>2.9(^{\text{NS}})</td>
<td>2.2(^{\text{#NS}})</td>
</tr>
<tr>
<td></td>
<td>Geometric mean</td>
<td>3.4</td>
<td>2.9</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Geometric CV (%)</td>
<td>(\dagger)</td>
<td>(\dagger)</td>
<td>(\dagger)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>4.0</td>
<td>4.6</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Range (min – max)</td>
<td>0.2 - 11.5</td>
<td>0.0 - 15.6</td>
<td>0.0 - 6.3</td>
</tr>
</tbody>
</table>

\(\dagger\), unable to determine
BAT PK study #2 - summary

• Blood nicotine elevation far greater in vapers than in ‘naïve’ e-cigarette users

• Far greater variability seen in this cohort
  • puffing/inhalation behaviour

• Potential need for better screening to ensure subjects meet study criteria
Is there a need for a standardised PK study protocol?

• How you design and run the study will impact the data you generate
  • Subject demographics
  • Product use
  • Measurement times and tools

• Will this generate a headache for manufacturers and regulators as they try to assess products, potentially against one another?

• Do we need, therefore, a standardised way of running nicotine PK studies, as far as is practically possible?
A potential alternative approach using PBPK modelling

- Nicotine PK studies run according to GCP are expensive
- These studies are also resource-intensive
- Heart rate may be a potential surrogate
  - Product assessment
  - Not for regulatory submission
  - Still expensive and time-consuming
- Can we accurately model blood nicotine levels for assessment purposes?
A potential alternative approach using PBPK modeling

Commentary

Electronic Cigarette Effectiveness and Abuse Liability: Predicting and Regulating Nicotine Flux

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Abstract

Electronic cigarettes (ECIGs) comprise an aerosolized nicotine delivery product category that provides consumers with probably unprecedented control over extensive features and operating conditions, allowing a wide range of nicotine yields to be obtained. Depending on the combination of such ECIG variables as electrical power input, geometry, liquid composition, and puff behavior, ECIG users can extract in a few puffs far more or far less nicotine than with a conventional combustible cigarette. These features of ECIG design and use present challenges for public health policy, central among which is the question of how to regulate nicotine delivery. In this commentary, we propose a conceptual framework intended to provide a convenient approach for evaluating and regulating the nicotine emitted from ECIGs. This framework employs nicotine flux to account for the total dose and rate at which nicotine reaches the user, 2 key factors in drug abuse liability. The nicotine flux is the nicotine emitted per puff second (e.g., mg/s) by a given ECIG design under given use conditions, and it can be predicted accurately using physical principles. We speculate that if the flux is too low, users likely will abandon the device and maintain conventional tobacco product use. Also, we speculate that if the flux is too high, individuals may suffer toxic side effects and/or the device may have higher-than-necessary abuse liability. By considering ECIG design, operation conditions, liquid composition, and puff behavior variables in combination, we illustrate how ECIG specifications can be realistically mandated to result in a target flux range.
A potential alternative approach using PBPK modelling
In 2011 we supported development of a physiologically-based pharmacokinetic (PBPK) model for nicotine.

- The original nicotine model had three routes of exposure: IV dosing, inhalation and oral (from chewing gum; Teeguarden et al, 2012)

- Development work being carried out to incorporate additional routes of exposure into the PBPK model
A potential alternative approach using PBPK modelling

- Multi-compartment nicotine model
- Cotinine sub-model
- Renal and metabolic clearance applied to kidney and liver
Predicting blood nicotine from PK study #1

**Inputs:**
- Estimated puff nicotine yields; puff counts
- Average study body weight (76.4 kg)
- Nicotine cartridge weights

**Assumptions:** 30% mouthspill

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**Cigarette**

**e-cigarette**
Summary

• Nicotine PK studies have provided us with a wealth of insight into e-cigarette performance

• Such studies help us understand our products and may be a requirement for regulatory submissions and/or claims

• Standardised protocol will help compare products

• For product development purposes, there might be potential surrogates
  • heart rate
  • PBPK modelling
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Stacey Fiebelkorn
Chris Proctor

Don Graff
Kirsten Gill

Mitch Nides
.......... told me the other day that champions don't get nervous in tight situations. That really helped me a lot. I decided I shouldn't get nervous and just do the best I can.
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An overview of our research activities

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