Characterization of Nicotine Pharmacokinetics and Pharmacodynamics During Use of Five Commercially Available Nicotine Pouches and Two Nicotine Lozenges in Adult Cigarette Smokers

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The College on Problems of Drug Dependence 84th Annual Scientific Meeting
June 11-15, 2022

Abstract

Oral tobacco-derived nicotine (OTDN) products are a rapidly emerging tobacco category that may offer noncombustible alternatives to adult smokers unable or unwilling to quit. In this study we characterized the nicotine pharmacokinetics (Nic-PK) and pharmacodynamics of five commercially available nicotine pouches (labeled nicotine: 4 mg, “medium”, 6 mg, 7 mg, 8 mg) and two nicotine lozenges (labeled: 2 mg and 4 mg). Adult cigarette smokers (n=34, 21 male) participated in a randomized crossover study that measured Nic-PK and heart rate assessments over a 120-minute period (product use for 30 minutes). Participants completed questions on the Tobacco Nicotine Withdrawal Questionnaire about “urges to smoke” and “craving cigarettes”, as well as the Direct Effect of Product Questionnaire about “how pleasant” they rated the products. Nicotine Cmax (Geometric Least Square Means, ng/ml) was 3.0 (4 mg pouch), 5.6 (medium), 11.4 (6 mg), 8.9 (7 mg), 15.0 (8 mg), 3.1 (2 mg lozenge) and 4.1 (4 mg lozenge). The median Tmax was slower than historical cigarette data (i.e., < 10min) and ranged from 30 to 35 minutes (pouches) and 36 minutes (2 mg) and 90 minutes (4 mg) (lozenges). Mean heart beats per minute (bpm) increase ranged from 9.2 to 14.4 bpm (pouches) and corresponded with the Cmax. Lozenges increased bpm by 8.8 (2 mg) and 10.3 bpm (4 mg). All products reduced ratings of urge to smoke and craving cigarettes; reductions generally followed Cmax, but were lower than reported cigarette values. All products increased ratings of “pleasant”, but with no clear relationship to Cmax. In general, nicotine delivery followed the labeled amount. However, product design can influence nicotine delivery, as illustrated by the 6 mg and 7 mg pouches and the Tmax for the lozenges. Based on the Nic-PK, nicotine appears to be absorbed primarily through the buccal mucosa for the pouches and through the buccal and the gastrointestinal tract for the lozenges. Overall, the oral nicotine products delivered a range of nicotine amounts and reduced the urge to smoke and craving a cigarette and may serve as alternative products for adult smokers to use in place of cigarettes.

Introduction

Background:
There is overwhelming scientific evidence regarding a risk continuum in the range of tobacco products currently available on the market. According to this body of evidence, combustible tobacco products such as conventional cigarettes are the most risky, whereas non-combustible tobacco products present relatively lower risks.[1] Many adult cigarette smokers and smokeless tobacco (ST) users (including dual users of cigarettes and ST products) seek alternatives to their current products. The oral tobacco-derived nicotine (OTDN) products used in this study are pouch and lozenge products containing flavors. These OTDN products are currently marketed for sale. OTDN products are innovative tobacco products that do not contain cut, ground, powdered, or leaf tobacco.

Objectives:
1. To characterize the Nic-PK profiles of seven OTDN products under controlled use conditions;
2. To characterize the subjective effects of seven oral TDN products under controlled use conditions;
3. To assess change-from-baseline in pulse rate of seven OTDN products under controlled use conditions.

Methods

Study Design

A randomized, controlled, crossover clinical study to characterize the Nic-PK and subjective effects of seven OTDN products in adult cigarette smokers

Key inclusion/exclusion criteria:
Inclusion criteria
- Voluntary consent
- Healthy adult males & females: 21 to 45 years of age
- Self-affirmed adult exclusive smokers of combustible manufactured cigarettes (at least 10 per day, for at least 12 months)
- Positive urine cotinine (≥ 500 ng/mL at screening

Exclusion criteria
- Use of any TDN pouch products within the 30 days prior to screening
- Attempted to quit smoking in the 3 months prior to Day -1
- Planning to quit smoking or postponement of quitting smoking

Products Assessed

Table 1. Study Products & Product Characterization

Product ID	Product Name	Flavor	Nicotine (labeled)	Measured Nicotine Concentration (mg)	pH
A	on!®	Mint	8 mg/pouch	7.81	8.11
B	Lyft	Mint	Medium Strength Pouch	4.26	7.79
C	Zyn®	Cool Mint	6 mg/Pouch	5.69	7.90
D	Velo®	Mint	4 mg/Pouch	3.76	7.33
E	Dryft	Spearmint	7 mg/Pouch	5.58	8.26
F	Velo®	Mint	2 mg/Lozenge	1.75	5.57
G	Rogue	Peppermint	4 mg/Lozenge	2.26	7.48

Table 2: Demographics

Enrolled	34
Female	13
Male	21
Completed	25
Age (yrs)	
Mean	33.8
SD	6.43
Weight (kg)	
Mean	92.15
SD	18.304
Height (cm)	
Mean	171.5
SD	9.64
# of Cigarettes Smoked per Day	
Mean	17.2
SD	6.55
Number of Years of Cigarette Use	
Mean	14.0
SD	9.32

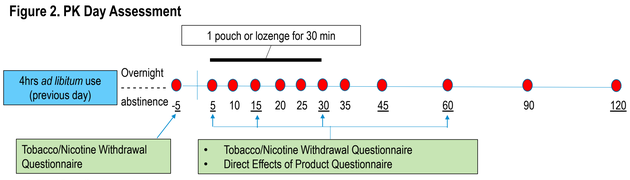
Statistical Method

A linear mixed model for analysis of variance (ANOVA) was performed on the log-transformed nicotine PK parameters AUC and Cmax. The model included sequence, study product, and period as fixed effects and subject-nested-within-sequence as a random effect. Sequence was tested using subject-nested-within-sequence as the error term. Geometric least square means (LSM) and 95% confidence intervals (CI) are provided below for the PK parameters of Cmax and AUC by study product.[2]

Figure 1. Study Design

Study Day		-2	-1	1	2	3	4	5	6	7
Randomization			X							
Study Product Use	X	X	X	X	X	X	X	X	X	
Controlled Study Product Use		X		X	X	X	X	X	X	X
PK Sampling				X	X	X	X	X	X	X
Questionnaire			X	X	X	X	X	X	X	X
Pulse Rate Measurement				X	X	X	X	X	X	X
Product Use Documentation		X		X	X	X	X	X	X	X

Figure 2. PK Day Assessment



Results

Figure 3. Plasma Nicotine PK Profile

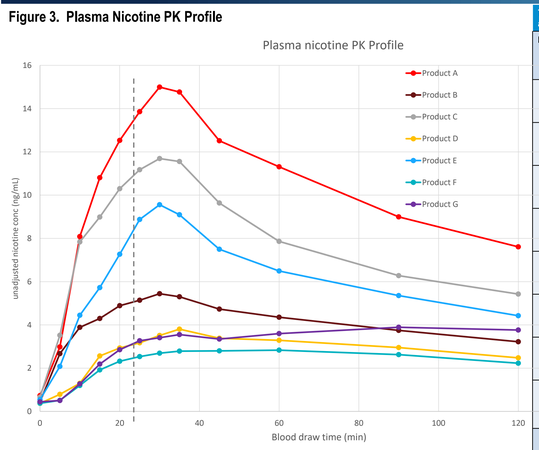


Table 3: Baseline-Adjusted Plasma Nicotine PK Parameters During and after Controlled Product Use Episode

Product ID	AUC (0-120) (ng*min/mL) Geometric LS Mean	Cmax (0-120) (ng/mL) Geometric LS Mean	Tmax (0-120) (min) Median
A	1081	15.00	34.967
	95% CI: 953.02,1225.48	95% CI: 12.88,17.47	
B	443.3	5.555	35.542
	95% CI: 399.66,491.61	95% CI: 4.97,6.20	
C	794.2	11.37	30.025
	95% CI: 681.07,926.23	95% CI: 9.59,13.49	
D	227.3	3.029	30.117
	95% CI: 170.96,302.13	95% CI: 2.30,3.98	
E	607.4	9.026	30.000
	95% CI: 515.10,716.29	95% CI: 7.77,10.48	
F	252.4	3.161	35.817
	95% CI: 226.43,281.30	95% CI: 2.80,3.57	
G	336.0	4.215	89.983
	95% CI: 299.73,376.69	95% CI: 3.78,4.70	
	AUC (0-180) (ng*min/mL) Geometric LS Mean	**Cmax (0-180) (ng/mL) Geometric LS Mean**	**Tmax (0-180) (min) Median**
Cigarette[3]	1008	16.32	7.467
	95% CI: 920.86,1103.84	95% CI: 14.38,18.52	

Figure 4. Change in Heart Rate Over Time

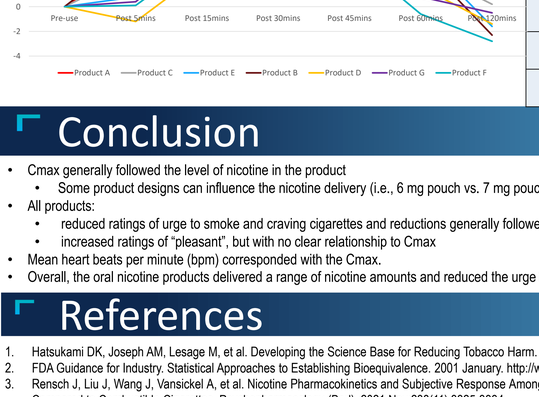
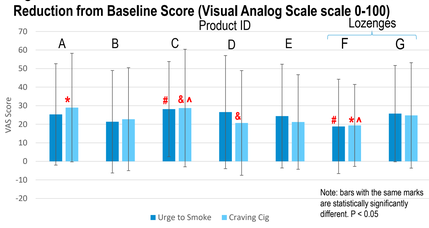


Table 4: Baseline-Adjusted Pulse Rate Parameters During and After the Controlled Product Use Episode (Pharmacodynamic Pulse Rate Population)

Product ID	AUEC0-120 (bpm*min) Mean	Emax-PR (BPM) Mean
A	997.4	17.71
	95% CI: 646.69, 1348.04	95% CI: 13.19, 22.24
B	589.6	11.68
	95% CI: 425.54, 753.64	95% CI: 9.10, 14.26
C	786.1	15.38
	95% CI: 582.76, 989.48	95% CI: 12.61,18.16
D	438.5	10.62
	95% CI: 289.60, 587.38	95% CI: 7.83, 13.41
E	679.5	13.38
	95% CI: 468.99, 890.00	95% CI: 10.24, 16.52
F	494.8	10.38
	95% CI: 284.27, 705.32	95% CI: 7.71, 13.05
G	494.6	11.24
	95% CI: 298.28, 690.89	95% CI: 8.24, 14.24

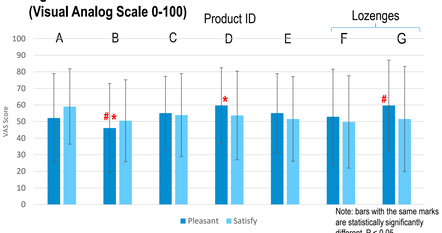
Figure 5. Tobacco Nicotine Withdrawal Questionnaire[4] - Maximum Reduction from Baseline Score (Visual Analog Scale scale 0-100)



Note: bars with the same marks are statistically significantly different. P < 0.05

Question		Product A	Product B	Product C	Product D	Product E	Product F	Product G	Cigarette[3]
Urges to Smoke	N	27	28	27	29	29	28	29	42
	Mean ± SD	25.3 ± 27.32	21.4 ± 27.64	28.1 ± 25.64	26.6 ± 30.49	24.4 ± 27.96	18.8 ± 25.44	25.7 ± 25.95	31.9 ± 28.47
	95% CI	14.5, 36.1	10.6, 32.1	18.0, 38.3	15.0, 38.2	13.7, 35.0	9.0, 28.7	15.9, 35.6	23.0, 40.8
Craving a Cigarette	N	27	28	27	29	29	28	29	42
	Mean ± SD	29.0 ± 29.27	22.7 ± 27.75	28.7 ± 31.66	20.7 ± 28.23	21.2 ± 25.52	19.4 ± 22.10	24.8 ± 28.43	35.4 ± 28.86
	95% CI	17.4, 40.5	12.0, 33.5	16.2, 41.3	10.0, 31.4	11.5, 30.9	10.8, 27.9	14.0, 35.6	26.4, 44.4

Figure 6. Direct Effects of Product Questionnaire - Maximum Score (Visual Analog Scale 0-100)



Note: bars with the same marks are statistically significantly different. P < 0.05

Question		Product A	Product B	Product C	Product D	Product E	Product F	Product G	Cigarette[3]
Is the Product “Pleasant” Right Now?	N	28	28	27	29	29	29	29	42
	Mean ± SD	52.1 ± 26.81	46.1 ± 26.79	55.1 ± 22.19	59.7 ± 22.74	55.1 ± 23.78	52.9 ± 28.68	59.7 ± 27.28	64.8 ± 25.90
	Median	57.0	50.5	54.0	65.0	58.0	53.0	61.0	70.5
	95% CI	41.7, 62.5	35.7, 56.5	46.3, 63.9	51.0, 68.3	46.1, 64.2	42.0, 63.8	49.3, 70.0	56.7, 72.9
Is the Product “Satisfying” Right Now?	N	28	28	27	29	29	29	29	42
	Mean ± SD	59.0 ± 22.74	50.5 ± 24.67	53.9 ± 25.03	53.7 ± 26.70	51.6 ± 25.46	49.8 ± 27.82	51.5 ± 31.68	65.2 ± 25.75
	Meadian	61.0	51.0	58.0	65.0	49.0	53.0	59.0	69.5
	95% CI	50.2, 67.9	40.9, 60.1	44.0, 63.8	43.5, 63.8	41.9, 61.2	39.2, 60.3	39.5, 63.6	57.2, 73.2

Conclusion

- Cmax generally followed the level of nicotine in the product
  - Some product designs can influence the nicotine delivery (i.e., 6 mg pouch vs. 7 mg pouch; pouch vs. lozenges)
- All products:
  - reduced ratings of urge to smoke and craving cigarettes and reductions generally followed Cmax, but were lower than reported cigarette values
  - increased ratings of “pleasant”, but with no clear relationship to Cmax
- Mean heart beats per minute (bpm) corresponded with the Cmax.
- Overall, the oral nicotine products delivered a range of nicotine amounts and reduced the urge to smoke and craving a cigarette and may serve as alternative products for adult smokers to use in place of cigarettes

References

1. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the Science Base for Reducing Tobacco Harm. Nicotine Tob Res 2007; Suppl 4:S537-53.
2. FDA Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. 2001 January. http://www.fda.gov/cder/guidance/index.htm.pdf.
3. Rensch J, Liu J, Wang J, Vansickel A, et al. Nicotine Pharmacokinetics and Subjective Response Among Adult Smokers Using Different Flavors of on!® Nicotine Pouches Compared to Combustible Cigarettes. Psychopharmacology (Berl). 2021 Nov;238(11):3325-3334.
4. Hughes JR, Hatsukami D (1986). Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 43(3):289-294.