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Short communication

Stimulus effects of propylene glycol and vegetable glycerin in electronic cigarette liquids

Arit Harvanko^{a,b,*}, Richard Kryscio^c, Catherine Martin^d, Thomas Kelly^{a,b,d}^a Department of Psychology, University of Kentucky, Kastle Hall, 171 Funkhouser Drive, Lexington, KY 40506-0044 United States^b Department of Behavioral Science, University of Kentucky, Medical Behavioral Science Building, Lexington, KY 40536-0086 United States^c Department of Statistics, University of Kentucky, 725 Rose Street Multidisciplinary Science Building 0082, Room 311, Lexington, KY 40536-0082 United States^d Department of Psychiatry, University of Kentucky College of Medicine, 245 Fountain Court, Lexington, KY 40509-1810 United States

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ABSTRACT

Background: Little is known about the behavioral effects of non-nicotine ingredients in electronic cigarette liquids. Propylene glycol (PG) and vegetable glycerin (VG) are the most common humectants used in electronic cigarette liquids. These ingredients may influence stimulus effects (e.g., visibility of exhalant, taste, or smell), which have played a role in the abuse liability of conventional cigarettes. In the current study, the stimulus effects of aerosol from liquids varying only in PG and VG content were assessed.

Methods: Sixteen electronic cigarette users completed five sessions (one practice and four testing sessions). Following one hour of nicotine deprivation, two sampling puffs from liquid formulations containing 100/0, 75/25, 50/50, 25/75, and 0/100% PG/VG concentrations were administered in random order during five assessments, each separated by 20 min. Measures included self-reported stimulus effects and breakpoint on a multiple-choice procedure with options consisting of sampled puffs or varying amounts of money.

Results: VG content was associated with greater reports of visibility of the exhalant (i.e., “cloud”). Liquids with only PG or VG engendered lower reports of inhalation sensations (e.g., throat hit) and greater reductions of systolic blood pressure compared to mixtures of PG and VG. There was no effect of liquid formulation on the multiple-choice procedure, but puffs were rarely chosen over even the smallest monetary option (\$0.05), suggesting minimal reinforcing efficacy.

Conclusions: Liquids containing greater concentrations of VG are more capable of producing visible exhalant and mixtures of PG and VG engender greater airway sensory effects than either ingredient alone.

1. Introduction

Electronic cigarette (EC) use has been continually increasing in the United States (Bao et al., 2018), and there is debate on the extent ECs reduce harms associated with conventional tobacco smoking relative to causing new public health problems. Most EC liquids comprise of propylene glycol (PG) and vegetable glycerin (VG) (e.g., 80–97%, Han et al., 2016). Stimulus effects from conventional cigarettes (CCs), such as airway sensory effects (e.g., strength of the puffs in the chest, throat), are associated with subjective liking (Westman et al., 1996), and PG/VG may alter stimulus effects of ECs. If PG and VG influence the stimulus effects of ECs, they could be important regulatory targets, and harm-reduction efforts could better tailor ECs to increase smoking cessation efficacy. The current study tested whether EC user perceptions (e.g., Harvanko et al., 2017) of greater VG engendering desirable

stimulus effects (i.e., good taste, good smell, large cloud), and greater PG engendering undesirable stimulus effects (i.e., sore throat, headache, dizziness), could be replicated under controlled conditions.

2. Methods

2.1. Participants

Recruitment included online and radio advertisements, and word-of-mouth referrals. Volunteers reporting use of an EC at least 20 of the past 30 days and answering affirmatively to “do your liquids typically contain nicotine” were invited to participate. Individuals were excluded if they used CCs more frequently than ECs (determined using Timeline Follow-Back Assessments), planned to cut-down or cease their EC usage, or reported any condition that would increase risk for study

* Corresponding author at: University of California San Francisco, 530 Parnassus Ave, Suite 366 Library, San Francisco CA 94143-1390 United States.

E-mail addresses: Arit.H@uky.edu, Arit.Harvanko@ucsf.edu (A. Harvanko), Kryscio@email.uky.edu (R. Kryscio), Cmartin@uky.edu (C. Martin), thkelly@uky.edu (T. Kelly).

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Table 1
Demographic and Clinical Variables.

	N = 16
Age, mean (SD)	24.8 (3.65)
Sex, N (%)	
Male	12 (75.0)
Female	4 (25.0)
PSCDI Score, ^a mean (SD)	14.8 (3.8)
Typical electronic cigarette nicotine concentration (mg/ml), mean (SD)	7.13 (5.2)
Typical electronic cigarette nicotine wattage, mean (SD)	64.5 (33.4)
Milligrams of electronic cigarette liquid per day, mean (SD)	6.6 (7.5)
Years of electronic cigarette use, mean (SD)	2.7 (1.8)
Use of other tobacco products in the past month, N (%)	
Conventional Tobacco Cigarettes	2 (12.5)
Chewing Tobacco	1 (6.3)
Hookah	1 (6.3)

^a PSCDI = Penn State Cigarette Dependence Index (Foulds et al., 2015).

participation (e.g., recent use of psychoactive drugs other than caffeine or alcohol) as determined by the study physician (CA Martin). Sixteen volunteers provided informed consent and completed the study (see Table 1 for volunteer demographics, nicotine dependence scores, tobacco usage history, and typical device parameter setting use). This study was approved by the University of Kentucky's Institutional Review Board and accorded with the Declaration of Helsinki.

2.2. Procedures

An EC with a refillable tank (Nautilus, Aspire, Shenzhen, China) and adjustable power supply (iStick TC100 W, Eleaf, Shenzhen, China) were used for aerosol administration. Liquids were provided by a commercial vendor (Nude Nicotine, San Diego) who also provided gas chromatography and mass spectrometry verification of formulation compositions. All liquids were devoid of flavorants. Parameter settings were 10 W (the setting most often used by regular EC users (Harvanko et al., 2017)) and 12 mg/ml nicotine concentration (the most popular concentration by the vendor) for the administration of all study aerosols. Participants completed one practice day to acclimate them to study procedures, followed by four identical test days (to increase statistical sensitivity and reliability of estimates) each approximately 3 h long. Each day five liquid formulations (100/0, 75/25, 50/50, 25/75, 0/100 PG/VG) were assessed in a random order that was balanced between the 5-days and participants to control for order effects. Data from the practice day were collected but not analyzed.

To standardize nicotine conditions and EC use prior to testing each day, 10 three-second puffs with 30-second inter-puff intervals were administered from an EC containing liquid with 50/50 PG/VG and 12 mg/ml nicotine concentration, followed by a one-hour deprivation period. In order to focus on effects of PG and VG under controlled puffing conditions, while engendering minimal acute nicotine effects (puff topography and nicotine effects were assessed by the *control measures* described below), puffing bouts consisted of two three-second sample-puffs with 30 s inter-puff intervals, controlled by computer prompts to “inhale” and “exhale.” Twenty minutes separated each assessment, with a different liquid formulation tested during each assessment.

2.3. Measures

2.3.1. Control measures

Cardiovascular Measures (Dinamap Pro 200, General Electric)

Heart rate and blood pressure were recorded using an automated blood pressure monitor.

Puff topography (spa-D; sodim, France)

Puff topography (volume and duration) was recorded with a

volumetric transducer.

Questionnaire of smoking urges-brief (QSU-B) (Cox et al., 2001)

This 10-item questionnaire focused on nicotine withdrawal and was used to monitor nicotine withdrawal effects on a 100-unit visual analog scale (VAS).

Visual analog scale - smoking effects (VAS-SE) (Blank et al., 2008)

This ten-item measure was used to monitor acute nicotine effects on a 100-unit VAS scale.

2.3.2. Outcome measures

Duke sensory questionnaire (DSQ) (Westman et al., 1996)

This seven-item questionnaire asks participants to rate sensory effects on a 7-point Likert scale. Items include: “how much nicotine do you estimate was in the last puffs,” “how similar were those puffs to your typical electronic cigarette,” “what was the strength of the puffs on your tongue,” “what was the strength of the puffs in your nose,” “what was the strength of the puffs in the back of your mouth and throat,” “what was the strength of the puffs in your windpipe,” and “what was the strength of the puffs in your chest?”

Visual analog scale - post sampling (VAS-PS)

This 12-item questionnaire assesses stimulus effects on a 100-unit VAS scale. Items included: “feel stimulated,” “like the effects,” “want to use the electronic cigarette again,” “enjoy the electronic cigarette,” “crave the electronic cigarette,” “get pleasure from the electronic cigarette,” “produce a large vapor cloud,” “experience a throat hit,” “feel dry-mouth,” “feel sore-throat,” “enjoy the smell,” and “enjoy the taste?”

Multiple choice procedure (MCP) (Griffiths et al., 1993)

This computerized form of the MCP was comprised of 21-choices between: two more three-second puffs of the sampled liquid formulation or an amount of money beginning at \$.00 and increasing in increments of \$.05 until \$1.00 was reached. The computer randomly selected one of the choices, and if two more puffs were selected, two more puffs from the same formulation were administered following *control* and *outcome* measures. If money was selected, that amount was added to the compensation provided at the end of the session. The dependent variable on this measure was the breakpoint at which participants chose money over two more puffs.

2.4. Data analysis

Mixed models (PROC MIXED) examined differences among liquid formulations with PC-SAS, version 9.3 (SAS Institute Inc., Cary, NC) and alpha set at $p \leq 0.05$. All models used participant as the repeated variable, liquid formulation the fixed independent variable, and compound symmetry as the covariance structure. For control measures, change scores were calculated for each formulation (post- minus pre-sampling values). Since heart rate and blood pressure were taken at the beginning of each session and following each puff bout, change relative to that day's baseline was calculated to account for daily fluctuations in resting heart rate and blood pressure. Scores on all measures were averaged across the four test sessions. Contrasts for linear and quadratic “dose-response” relationships across the formulations were used to examine main effects.

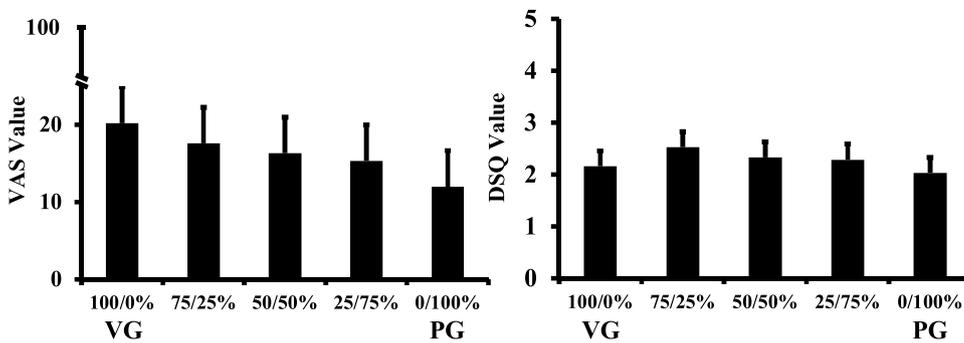
3. Results

3.1. Smoking puff topography

The average volume of each puff was 168.13 ($SE = 20.30$) ml and lasted 4.10 ($SE = .30$) seconds. Expectedly, there were no significant effects of liquid formulation on volume or duration of the puffs.

3.2. Control measures

Heart rate significantly decreased an average of 6.07 ($SE = 1.90$)



[60] = 10.59, $p = .002$). A significant main effect of liquid condition was indicated on “strength on the tongue” ($F[60] = 3.98, p = .006$) and post-hoc tests indicated a significant quadratic relationship ($F[60] = 9.78, p = .003$).

beats per minute from session baseline for all of the liquid formulations ($ps < .05$) and, as expected, there was no significant effect of formulation. There was a significant change in systolic blood pressure (SBP) ($F[55] = 3.67, p = .010$) with a significant quadratic relationship among formulations ($F[55] = 12.66, p < .001$), such that SBP decreased significantly more following 100/0 PG/VG ($m = -6.55, SE = 1.60$) and 0/100 PG/VG ($m = -4.47, SE = 1.47$) compared to 50/50 PG/VG ($m = -6.5, SE = 1.60$).

Expectedly, mixed models for QSU-B or VAS-SE items did not indicate significant effects of liquid formulation.

3.3. Outcome measures

For DSQ items, there was a significant effect of liquid formulation on “how much nicotine do you estimate was in the puffs” ($F[60] = 3.05, p = .023$), “what was the strength of the puffs on your tongue” ($F[60] = 3.98, p = .006$), and “what was the strength of the puffs in your chest” ($F[60] = 3.52, p = .012$). There were significant quadratic relationships between liquid formulation and these items, such that mixtures of PG/VG were rated more highly than PG or VG alone (e.g., right panel, Fig. 1). Magnitudes of these effects, however, were small (Cohen’s f^2 s < 0.15).

For VAS-PS items, significant effects of liquid formulation were indicated on “did the e-cig produce a large cloud” ($F[60] = 2.77, p = .035$) and “did you experience a throat hit” ($F[60] = 3.43, p = .014$). A linear relationship was indicated on large cloud ($F[60] = 10.59, p = .002$) (left panel, Fig. 1) and a quadratic relationship on throat hit ($F[60] = 7.66, p = .008$), such that throat hit was rated slightly lower on formulations containing 100% VG (36.4, $SE = 5.7$) or 100% PG (32.4, $SE = 5.7$) compared to formulations with 50/50% PG/VG (38.0, $SE = 5.7$). No effects of formulation were observed on the MCP. Notably, the monetary value of the breakpoint for these formulations was low ($\$0.04 + 0.02$, mean + SE).

4. Discussion

Consistent with our hypotheses, greater VG was associated with greater visibility of exhalant. Unexpectedly, liquids with equal concentrations of PG and VG mixtures were associated with greater strength on the tongue and other inhalation sensations, and smaller reductions in systolic blood pressure compared to liquids with solely PG or VG, although the magnitude of these effects was small.

Visibility of exhalant has been noted as an important factor for mimicking the experience of using a conventional cigarette (Barbeau et al., 2013). Results show that greater concentration of VG is associated with this effect, confirming anecdotal reports by EC users (Harvanko et al., 2017) and replicating recent laboratory research (Spindle et al., 2018). Past research has shown that EC users associate throat hit with smoking cessation efficacy of the EC (Etter, 2016) and similarity to CC smoking (Barbeau et al., 2013). Results of this study

Fig. 1. Ratings of “did the electronic cigarette produce a large cloud?” and “what was the strength of the puffs on your tongue?”.

Note: Fig. 1. Ratings of “did the electronic cigarette produce a large cloud” on the Visual Analog Scale (left) and “what was the strength of the puffs on your tongue” rated on the Duke Sensory Questionnaire (right). Values represent least-squares mean estimates and standard error bars derived from the mixed model. A significant main effect of liquid condition was indicated on “large cloud” ($F[60] = 2.77, p = .035$) and post-hoc tests indicated a significant linear relationship (F

indicate throat hit and other inhalation sensations are associated with PG/VG mixtures (e.g., 50/50 PG/VG), which is consistent with anecdotal reports by EC users (Harvanko et al., 2017). These results, however, differ with other laboratory research (Spindle et al., 2018) and anecdotal reports (Chen and Zeng, 2016) suggesting PG concentration and throat hit are positively correlated. Disparity among results could be due to differences in device and liquid parameters across studies, or use of controlled puffing bouts or exclusion of flavorants in the current study.

This study was designed to assess stimulus and reinforcing effects of EC liquid formulations under controlled flavorant, puffing, nicotine concentration, and nicotine withdrawal conditions. Plasma nicotine was not measured, but there was no influence of formulation on control self-report measures (i.e., VAS-SE, and QSU-B). Also, the average heart rate following puffing did not change as a function of liquid formulation, suggesting that nicotine delivery was not significantly different between formulations under these conditions. There was, however, an interesting quadratic relationship between formulations and SBP. Previous research has indicated that PG and VG can influence nicotine delivery (Spindle et al., 2018), although nicotine generally produces more potent effects on heart rate rather than blood pressure (e.g., Benowitz et al., 1982). Further research on the potential sympathomimetic effects of PG/VG mixtures is warranted.

Breakpoints on the MCP were low for each of the liquid formulations, indicating a floor effect that limits interpretation of these data. The modest monetary value of these formulations may be due to the omission of flavorants, which has been previously associated with decreased reports of liking EC aerosol (Audrain-McGovern et al., 2016; Goldenson et al., 2016). Indeed, reports of ‘good taste’ were low following puffing (< 15 on a 100-unit scale), and spontaneous reports by participants indicated dissatisfaction with the flavor. Although EC parameters for this study were carefully chosen, they were not the same as those typically used by these participants (e.g., 10 versus typical $m = 64.5$ W or 12 versus typical $m = 7.12$ mg/ml nicotine concentration), which could explain the low subjective and reinforcing effects observed in this study.

5. Conclusion

These data confirm anecdotal reports that VG is associated with greater cloud compared to PG. PG and VG mixtures are associated with greater inhalation sensations than either ingredient alone. Neither ingredient was related to reinforcing effects (e.g., liking), but formulations used in the current study, devoid of flavorants, had little monetary value.

Contributors

Mr. Harvanko designed this study, managed data collection, and prepared the first draft of the manuscript. Dr. Kryscio assisted in the

statistical analyses for this study and assisted in manuscript preparation. Dr. Martin served as the study physician and assisted in manuscript preparation. Dr. Kelly assisted in the design of this study and manuscript preparation. All authors read and approved the final manuscript.

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Conflict of interest

No conflict declared.

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