

Evaluating acute effects of potential reduced-exposure products for smokers: Clinical laboratory methodology

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Harm reduction for tobacco smokers may involve reducing their exposure to lethal smoke constituents. Assessing smoke constituent exposure and any resulting harm reduction from a potential reduced-exposure product (PREP) will involve preclinical, clinical, and epidemiological research. The purpose of this study was to evaluate a clinical laboratory model for assessing the acute effects of PREPs for smokers. Philip Morris' Accord and R.J. Reynolds' Eclipse were used as examples. Twenty overnight-abstinent smokers (> 15 'light' or 'ultra-light' cigarettes/day) participated in 4 Latin-square ordered, 2.5-hr sessions in which they completed an 8-puff smoking bout every 30 minutes. Sessions were separated by at least 24 hours and differed by product used: own brand, denicotinized tobacco cigarettes, Accord, or Eclipse. Tobacco withdrawal and carbon monoxide (CO) were assessed before and after smoking, heart rate was assessed before and during smoking, and puff volume, duration, and interpuff interval were assessed while subjects smoked. Blood was sampled at the beginning and end of each session. Relative to normal cigarettes, Accord was less effective at suppressing withdrawal and produced minimal CO boost despite the fact that, when using Accord, subjects took bigger and longer puffs. Eclipse suppressed withdrawal fully and increased CO boost by approximately 30%. Own brand, Accord, and Eclipse, but not denicotinized cigarettes, increased plasma nicotine concentration. Taken together, these results suggest that neither Accord nor Eclipse is likely to be an effective reduced-exposure product for smokers and that this clinical laboratory model is valuable.

Introduction

Tobacco smoking causes cancer, stroke, respiratory illness, and cardiovascular disease (e.g., CDC, 1996; U. S. Department of Health and Human Services [USDHHS], 1989) and accounts for 430,700 deaths in the U.S. annually (Centers for Disease Control and Prevention [CDC], 1994). These harmful effects are due

to tobacco smoke's potentially lethal constituents, including carbon monoxide (CO) (Lakier, 1992) and carcinogens like nitrosamines and polycyclic aromatic hydrocarbons (e.g., Hecht, 1999). The best method of reducing smoking's harm is cessation (e.g., Russell et al., 1998; Stratton, Shetty, Wallace, & Bondurant, 2001), though abstinence-induced tobacco/nicotine withdrawal (e.g., anxiety, restlessness, insomnia) makes quitting difficult (e.g., Hughes & Hatsukami, 1986). Because universal cessation is unlikely in the near term, harm-reduction strategies that support use of potential reduced-exposure products (PREPs) may help to reduce smoking's enormous costs (Stratton et al., 2001).

Several PREPs for smokers have been introduced recently (e.g., Philip Morris' Accord; RJ Reynolds' Eclipse). According to industry tests, these products

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produce smoke with low levels of CO, nicotine, 'tar', and/or carcinogens (e.g., Bombick, Ayres, Putnam, Bombick, & Doolittle, 1998; Terpstra, Reininghaus, & Solana, 1998). Past experience with PREPs for smokers suggests that careful evaluation is required. For example, 'lower yield' cigarettes also produce smoke with low levels of CO, 'tar,' and nicotine when machine-smoked. However, despite wide-scale acceptance among U.S. smokers (Federal Trade Commission [FTC], 2000), these cigarettes have not been associated with decreased rates of smoking-related death and disease (Stratton et al., 2001), perhaps because smokers alter their behavior to compensate for reduced nicotine yield (e.g., Baldinger, Hasenfratz, & Battig, 1995a; Hoffmann, Djordjevic, & Hoffmann, 1997). These behavioral alterations may reflect inadequate suppression of tobacco/nicotine withdrawal; thus evaluating PREPs for smokers means, in part, assessing withdrawal suppression, nicotine delivery, and smokers' behavior.

While industry research focuses on smoke constituents (e.g., Bombick et al., 1998; Terspra et al., 1998), other work evaluating PREPs emphasizes withdrawal suppression—the amelioration of tobacco withdrawal symptomatology via PREP use. For example, Accord, a hand-held, puff-activated chamber that heats pressed tobacco, was examined in two laboratory studies (Buchhalter & Eissenberg, 2000; Buchhalter, Schrinel, & Eissenberg, 2001). Relative to own brand cigarettes, Accord failed to suppress withdrawal fully and led to minimal CO exposure. While reduced CO exposure is encouraging, inadequate withdrawal suppression may lead to behavioral compensation and/or supplementation with normally marketed cigarettes. Indeed, in a recently completed outpatient study, Accord users continued to smoke their usual brand (Keely, Hughes, & Hirsch, 2001), suggesting that this product may be ineffective at reducing smoking-related risks. Also, Eclipse, a paper-encased tobacco plug heated by a carbon element, is marketed explicitly as a less lethal smoking system. Little non-industry research has examined this claim, though in one outpatient study where smokers used Eclipse for 2 weeks, CO levels increased more than 50% (Fagerström, Hughes, Rasmussen, & Callas, 2000). Increased exposure to lethal smoke constituents is not a strong indicator of an effective harm-reduction strategy.

The effects of PREPs on withdrawal, physiological response, behavior, and CO and nicotine levels can be assessed efficiently in the clinical laboratory. The purpose of this study is to evaluate a clinical laboratory procedure for assessing two PREPs concurrently. Twenty smokers participated in four Latin-square ordered, 2.5-hr sessions in which they used either their own brand, denicotinized tobacco cigarettes (to control for smoking behavior and CO exposure), Accord, or Eclipse. Based on previously reported results (Buchhalter et al., 2001; Fagerström et al., 2000), we hypothesized that, relative to own brand cigarettes, Accord use would produce less withdrawal suppression, physiological response, and CO

and nicotine exposure, while Eclipse use would lead to equivalent or greater responses on these measures.

Method

Subjects and setting

Advertisements and word-of-mouth were used to recruit 10 women and 10 men who completed this IRB-approved study. Volunteers were excluded from participation if they reported previous Accord or Eclipse experience, past or current cardiovascular disorders, current pregnancy or breastfeeding, or current attempts at smoking cessation or reduction.

Volunteers were included if they were 18 to 50 years of age (mean = 21.6 yr, SEM = 1.1), reported smoking 15 or more king-sized, non-mentholated, 'light' or 'ultra-light' cigarettes daily (mean = 18.9 cigarettes/day, SEM = 0.7), and provided a breath sample ≥ 15 ppm CO at screening (mean = 24.3 ppm, SEM = 2.0). Many smokers of 'light' and 'ultra-light' cigarettes are aware of smoking's health risks (Giovino et al., 1996) and thus may be most likely to use PREPs. Participants had smoked the same number of cigarettes per day for a mean of 4.2 yr (SEM = 0.6) and were nicotine dependent, as indicated by a mean score of 5.6 (SEM = 0.3) on the Fagerström (1978) nicotine tolerance questionnaire. They reported an average of 3.8 quit attempts (SEM = 1.5), and 5 of the 20 subjects reported previous use of a smoking cessation pharmacotherapy. Men and women did not differ on body mass index [women's mean = 23.4, SEM = 1.2; men's mean = 26.4, SEM = 1.5; $t(18) = 1.5$, n.s.] or any other demographic measure except for the Fagerström tolerance questionnaire [women's mean = 5.0, SEM = 0.4; men's mean = 6.2, SEM = 0.3; $t(18) = 2.4$, $p < .05$]. All subjects provided written, informed consent before, and were paid \$240 after participating.

Materials

Cigarettes were provided to subjects; own brand cigarettes were identified, purchased, and prepared (see below) before a subject's participation. By the FTC method (FTC, 2000), on average, own brand cigarettes yielded 0.8 mg nicotine and 10.2 mg tar, while denicotinized cigarettes (Denic; Ultratech Corporation, Lafayette Hill, PA) yielded 0.07 mg nicotine and 12.1 mg tar (Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999). Accord (Philip Morris Inc., Richmond, VA) uses a cigarette-like tube that is 62 mm long and 8 mm in diameter and consists of 7 mm of filter plug, 30 mm of hollow tube, and 25 mm of pressed tobacco. The tube is inserted into a hand-held chamber that contains 8 puff-activated heater blades that heat the tobacco at a lower temperature than conventional cigarettes. (Terpstra et al., 1998; Stratton et al., 2001). By the FTC method, Accord yields 0.1 mg nicotine and 2 mg tar. Eclipse (R.J. Reynolds, Inc., Winston-Salem, NC) is 83 mm long and consists of 10 mm of filter, 61 mm of tobacco (in 2

plugs), and 12 mm of carbon heating element at the tip (Brown et al., 1998). The heating element is lit as with a conventional cigarette, though Eclipse does not burn down. By the FTC method, Eclipse yields 0.2 mg nicotine and 4.0 mg tar.

Subjects were aware when they were using Accord or Eclipse but were blind to own brand and Denic. Opaque tape was used on Eclipse, own brand, and Denic to cover any filter vent holes, because estimates suggest that approximately 57% of smokers cover vent holes at least partially when they smoke (Kozlowski, Pope, & Lux, 1988), thus potentially increasing their smoke constituent exposure (e.g., Stratton et al., 2001). No attempt was made to control for brand preference (i.e., by including a 'not own brand' condition), because previous research indicates that subjective and physiological responses to own brand and not own brand cigarettes are nearly identical (Buchhalter et al., 2001).

Subject-rated measures. All subject-rated measures were computerized. Visual analog scale (VAS) items consisted of a word or phrase centered above a horizontal line anchored on the left with 'not at all' and on the right with 'extremely.' Subjects responded to these items by moving a mouse-controlled cursor to any point on the line and clicking, thus producing a vertical mark; this mark could be further adjusted if necessary. The score for each scale was the distance of the vertical mark from the left anchor, expressed as a percentage of the total length of the horizontal line. The VAS items used in this study, derived from previous research describing tobacco withdrawal (e.g., Hughes & Hatsukami, 1986), included 'Urges to smoke,' 'Irritability/frustration/anger,' 'Anxious,' 'Difficulty concentrating,' 'Restlessness,' 'Hunger,' 'Impatient,' 'Craving a cigarette/nicotine,' 'Drowsiness,' 'Depression/feeling blue,' and 'Desire for sweets.' Another measure was the Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991), which consists of 32 smoking-related items that are rated on a 7-point scale ranging from 0 (Strongly disagree) to 6 (Strongly agree). The QSU yields 2 factors defined by previous factor analysis: Factor 1 (intention to smoke) and Factor 2 (anticipation of relief from withdrawal). VAS items allow for assessment of individual withdrawal symptoms while the QSU provides 2 more global measures of withdrawal-related symptomatology.

Physiological measures. Heart rate and skin temperature were monitored continuously (Monitor 507E, Criticare Systems, Waukesha, WI) and were recorded every 20 s. Carbon monoxide was measured before and at least 5 min (mean = 5.5 min) after each cigarette (Breath CO, Vitalograph, Lenaxa, KS).

Plasma nicotine measure. Blood samples were centrifuged immediately, and the plasma was removed and stored at -70°C . Plasma samples were analyzed for nicotine concentration using GC/MS, as described elsewhere (Jacob, Yu, Wilson, & Benowitz, 1991). The lower

limit of quantification (LOQ) of the assay was 2.5 ng/ml.

Puff topography measures. As described elsewhere (Eissenberg, Adams, Riggins, & Likness, 1999), topography data collection was computerized (Plowshare Technologies, Baltimore, MD). Cigarettes were smoked through a mouthpiece that was connected to a pressure transducer, and pressure changes created by an inhalation were amplified, digitized, and sampled at a rate of 1000 Hz. Software converted signals to airflow (ml/sec) and integrated the data over time for each puff, producing several measures including puff volume, duration, and interpuff interval (IPI).

Procedure

Participants were screened, provided informed consent, and were acclimated to the testing environment, equipment, and questionnaires at least 1 day before participating. Eight hours or more of objectively verified cigarette abstinence (i.e., CO level of ≤ 10 ppm; in previous work, overnight abstinence has been verified with CO levels ranging from 10 to 20 ppm; Buchhalter et al., 2001; Schuh, Schuh, Henningfield, & Stitzer, 1997; Zacny, Stitzer, Brown, Yingling, & Griffiths, 1987) was required before each of the four Latin-square ordered, approximately 2.5-hr experimental sessions; sessions were separated by at least 24 hr. Sessions differed by product used: own brand, Denic, Accord, or Eclipse.

After a subject met the abstinence criterion, each session began with blood sampling (10 ml) via forearm venipuncture. Next, non-invasive, computerized recording of physiological measures (i.e., heart rate, skin temperature) commenced and continued throughout the session. The participant then began the first of four smoking bouts, which were separated by 30 min and consisted of pre-smoking CO and subjective-effect measurement, eight self-paced puffs from the product assigned to that session, and post-smoking subjective effect and CO measurement. The number of puffs taken within each smoking bout was counted manually. The session ended with collection of another blood sample (mean = 12.7 min after the 8th puff of the fourth smoking bout).

Data analysis

Prior to analysis, heart rate and skin temperature data were averaged to produce a single value for each measure for each of four pre-smoking periods (10 min prior to smoking) and four smoking periods (time during which subjects were actually smoking; Buchhalter & Eissenberg, 2000). Topography data were examined for closely-spaced puffs (i.e., inter-puff intervals < 300 ms). Such puffs were assumed to be part of the preceding puff and the recorded volume and duration values were added to that preceding puff (e.g., Baldinger et al., 1995a). For example, if the first puff of an eight-puff bout had a

volume of 45 ml and a duration of 1.5 s and was followed 200 ms later by a puff with a volume of 1 ml and 0.1 s duration, software (PuffCleanUp, Plowshare Technologies, Baltimore, MD) changed the first puff to a volume of 46 ml and duration of 1.6 s and omitted the second puff. After this procedure, any puffs less than 5 ml were considered artifacts (e.g., as might occur when the subject tapped the cigarette on an ashtray; Eissenberg et al., 1999) and discarded. Remaining data for each of the four cigarettes were averaged for each subject using all remaining values for puff volume, duration, and inter-puff interval. For the plasma nicotine analysis, values below the LOQ were replaced with a value of 2.5 ng/ml.

All data were entered into a mixed analysis of variance (ANOVA), with subject gender as a between-subjects factor and tobacco product type (own brand, Denic, Accord, Eclipse), smoking bout (1 to 4; except for plasma nicotine data), and time (except for topography data) as the within-subjects factors. For all repeated-measures factors, significance levels were adjusted for violations of the sphericity assumption using Huynh-Feldt corrections (e.g., cited in Keppel, 1991). The mean square error terms for the overall interaction were used to conduct Tukey's honestly significant difference test (e.g., cited in Keppel, 1991); comparisons for which $p < .05$ are reported as significant.

Results

Statistical analysis results of subjective and physiological measures, excluding gender effects, are shown in Table 1. Gender effects are omitted because, of the more than 100 F tests including this factor (i.e., main effects and interactions), only nine were statistically significant, as described below. Unless otherwise noted, data are collapsed across gender, and reflect the mean of all 20 subjects. Effects of greatest interest include interactions involving the type and/or time factors, indicating that outcome measures were influenced by product used and/or pre- versus post-smoking timepoint.

Subjective measures

Significant product-type by smoking-bout by time interactions were observed for 'Urges to smoke,' 'Anxious,' 'Drowsiness,' and both QSU factors [$F(9,162) > 2.1, p < .05$]. For these measures, scores decreased relative to baseline (i.e., data collected before the first smoking bout) by the end of the 2.5-hour sessions, though there were fewer significant decreases when subjects used Accord. For example, Figure 1 (top) shows data from the 'Urges to smoke' VAS (the measure with the largest type by bout by time F value). Scores decreased significantly relative to baseline (i.e., before the first bout) after all bouts for own brand, Denic, and Eclipse, but only after the second, third, and fourth bouts for Accord. Figure 1 (bottom) displays data from QSU Factor 1, on which scores decreased significantly relative to baseline after

each bout for all products. Importantly, post-smoking scores were similar when subjects used own brand, Denic, and Eclipse, while post-smoking scores were significantly higher (relative to own brand, $p < .05$, Tukey's HSD) when subjects used Accord. From before the first smoking bout to after the fourth smoking bout, QSU Factor 1 scores decreased from baseline by 44.6% for own brand, 45.3% for Denic, and 43.6% for Eclipse, relative to 31.2% for Accord.

Significant smoking-bout by time interactions were noted for 'Restlessness,' 'Impatient,' 'Craving a cigarette/nicotine,' and 'Depression/feeling blue' [$F(3, 54) > 3.4, p < .05$]; a type by bout interaction was also observed for 'Restlessness' [$F(3, 54) = 2.5, p < .05$]. With the exception of 'Depression/feeling blue,' these interactions reflected larger decreases after the first smoking bout relative to subsequent bouts. For example, for the craving VAS, scores decreased by 24.8 (SEM = 5.3) after the first smoking bout, and then 18.1 (SEM = 3.8) after the second, 16.3 (SEM = 3.4) after the third, and 12.3 (SEM = 3.8) after the fourth smoking bouts. For 'Depression/feeling blue,' decreases of equal magnitude for the first and second smoking bouts and smaller decreases for subsequent bouts were observed. On measures where no interactions were observed ('Irritability/frustration/anger,' 'Difficulty concentrating,' 'Hunger'), a main effect of time indicates that product use, independent of type or bout, reduced scores. No significant main effects or interactions were observed for only one measure: the 'Desire for sweets' VAS.

Gender by smoking-bout by time interactions were observed for the VAS items 'Anxious' and 'Restlessness,' and QSU Factor 2 [$F(3, 54) > 4.2, p < .05$]. For these measures, men's scores decreased by a consistent amount after each of the 4 bouts, while women's scores tended to decrease more after the first relative to subsequent bouts. For example, for the 'Restlessness' VAS, men's scores decreased by 7.3 (SEM = 4.8) after the first bout and then by 5.7 (SEM = 4.1), 4.5 (SEM = 5.1), and 6.5 (SEM = 3.6) after subsequent bouts. Women's scores decreased by 20.4 (SEM = 8.6) after the first bout and then by 5.0 (SEM = 5.4), 0.3 (SEM = 5.2), and 5.3 (SEM = 4.1) for subsequent bouts. A similar pattern was observed for the gender by smoking-bout interactions for 'Impatient' and 'Craving a cigarette/Nicotine' [$F(3, 54) > 3.4, p < .05$]. A significant gender by time interaction was observed for 'Hunger' [$F(1, 18) = 5.7, p < .05$] on which men's scores decreased after smoking while women's scores did not.

Physiological measures

Table 1 shows a significant type by smoking-bout by time interaction for heart rate [$F(9, 162) = 5.5, p < .001$]; these data are shown in Figure 2 (top). Relative to baseline, heart rate was elevated during each of the 4 smoking bouts when subjects used own brand, Eclipse, and Accord. For Denic, however, heart rate increased significantly during the first smoking bout only. For the

Table 1. Statistical analysis results for subjective effects and physiological measures collected during four smoking bouts.

	Type ^a		Bout ^a		Time ^b		Type × Bout ^c		Type × Time ^a		Bout × Time ^a		Type × Bout × Time ^a	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p
<i>Subjective effects</i>														
<i>VAS items</i>														
Urges to smoke	4.0	<.05	43.1	<.001	35.9	<.001	0.5	n.s.	1.2	n.s.	7.6	<.01	3.2	<.01
Irritability/frustration/anger	0.8	n.s.	12.9	<.001	12.5	<.01	0.9	n.s.	1.2	n.s.	0.6	n.s.	1.4	n.s.
Anxious	1.4	n.s.	33.1	<.001	15.3	<.01	1.6	n.s.	0.9	n.s.	7.9	<.01	2.2	<.05
Difficulty concentrating	0.9	n.s.	14.2	<.001	14.1	<.01	1.5	n.s.	2.3	n.s.	0.0	n.s.	1.2	n.s.
Restlessness	0.2	n.s.	8.5	<.01	18.6	<.001	2.5	<.05	0.9	n.s.	8.1	<.01	0.5	n.s.
Hunger	0.8	n.s.	2.7	n.s.	7.9	<.05	1.8	n.s.	0.8	n.s.	0.6	n.s.	1.2	n.s.
Impatient	0.2	n.s.	10.0	<.001	21.4	<.001	1.3	n.s.	1.2	n.s.	8.2	<.01	1.2	n.s.
Craving a cigarette/nicotine	6.5	<.01	41.3	<.001	46.7	<.001	0.2	n.s.	1.1	n.s.	8.8	<.001	1.0	n.s.
Drowsiness	0.1	n.s.	7.0	<.01	8.6	<.01	1.0	n.s.	0.6	n.s.	0.2	n.s.	2.1	<.05
Depression/Feeling blue	0.0	n.s.	3.8	<.05	6.0	<.05	0.6	n.s.	0.6	n.s.	3.5	<.05	1.3	n.s.
Desire for sweets	0.8	n.s.	0.2	n.s.	0.5	n.s.	1.1	n.s.	2.4	n.s.	0.5	n.s.	2.2	n.s.
<i>Tiffany Drobes QSU</i>														
Factor 1	5.5	<.01	20.1	<.001	26.9	<.001	0.9	n.s.	1.0	n.s.	0.6	n.s.	2.3	<.05
Factor 2	3.1	<.05	13.0	<.01	28.4	<.001	0.6	n.s.	0.4	n.s.	1.4	n.s.	2.7	<.05
<i>Physiological measures</i>														
Heart rate	10.7	<.001	0.7	n.s.	52.0	<.001	5.7	<.001	5.9	<.01	29.5	<.001	5.5	<.001
Skin temperature	3.8	<.05	42.0	<.001	18.6	<.001	2.8	<.05	1.3	n.s.	7.3	<.01	1.0	n.s.
Expired air CO	26.8	<.001	76.7	<.001	118.5	<.001	24.0	<.001	36.0	<.001	4.0	<.05	0.3	n.s.

^adf = 3,54

^bdf = 1,18

^cdf = 9,162

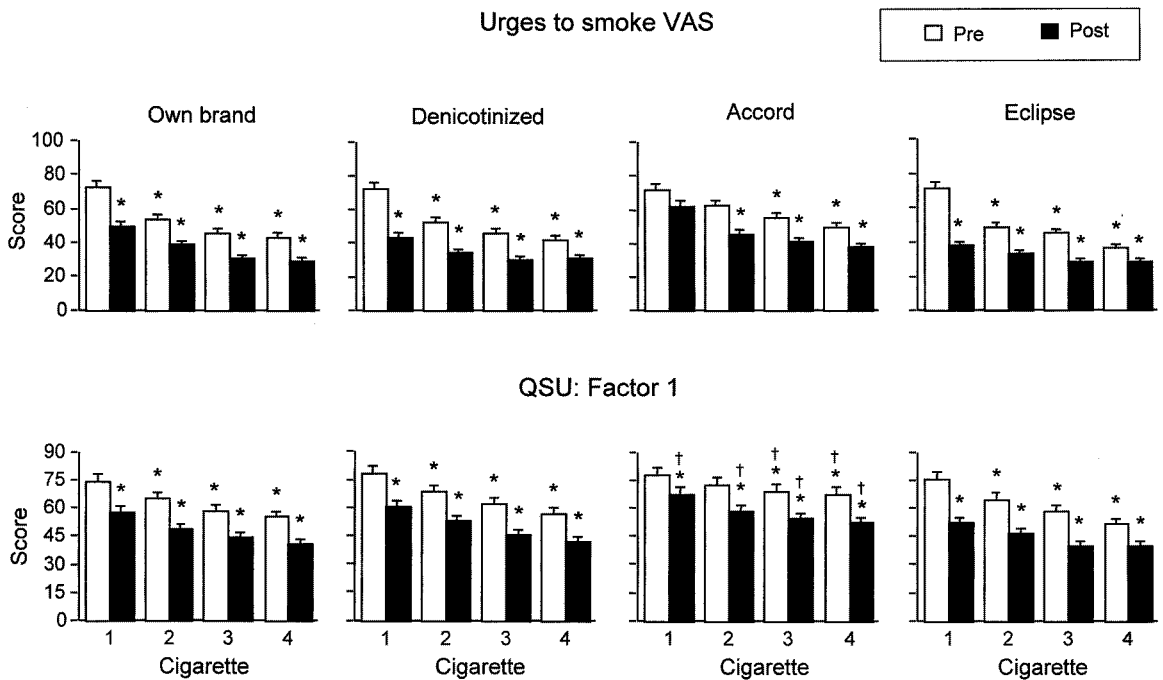


Figure 1. Averaged data (plus one SEM) from 20 subjects on the “Urges to smoke” VAS (top panels) and Factor 1 of the Tiffany-Drobes (1991) Questionnaire of Smoking Urges (bottom panels) when subjects were using own brand, denicotinized cigarettes, Accord or Eclipse. Y axis shows maximum possible score. Open bars represent data collected before and filled bars data collected after an 8-puff smoking bout. Asterisk (*) indicates a significant difference from baseline (i.e., before the first smoking bout), sword (†) indicates a significant difference from own brand at that time point (All $p < .05$, Tukey’s HSD).

first bout, heart rate increased, on average, by 13.0 bpm for own brand (SEM = 1.5) and by 11.4 bpm for Eclipse (SEM = 1.5), but by only 5.9 bpm for Accord (SEM = 1.5) and 5.2 for Denic (SEM = 1.1). Heart rate was significantly lower relative to own brand during every Denic bout, the first and 4th Accord bouts, and the third Eclipse bout.

Significant bout by time [$F(3, 54) = 7.3, p < .01$] and type by bout [$F(9, 162) = 2.8, p < .05$] interactions were observed for skin temperature. Temperature tended to decrease during each bout, with decreases of lesser magnitude across subsequent bouts. For example, collapsed across type, subjects’ skin temperature decreased 1.0°C (SEM = 0.2) in the first, 0.5°C (SEM = 0.2) in the second, 0.4°C (SEM = 0.2) in the third, and 0.4°C (SEM = 0.2) in the 4th bout.

Figure 2 (bottom) shows the data for expired air CO for which significant bout by time [$F(3, 54) = 4.0, p < .05$], type by time [$F(3, 54) = 36.0, p < .001$], and type by bout [$F(9, 162) = 24.0, p < .001$] interactions were observed. A CO level below or equal to 10 ppm was required for each session; the mean pre-smoking CO collapsed across all conditions was 6.3 ppm (SEM = 0.3). After smoking, CO depended on product and bout. For example, after the first bout with own brand, CO increased on average by 5.6 ppm (SEM = 0.6) as compared to 5.6 ppm (SEM = 0.5) for Denic, 1.6 ppm (SEM = 0.7) for Accord, and 8.0 ppm (SEM = 1.1) for Eclipse. By session’s end, mean CO was 23.6 ppm (SEM = 1.9) for own brand, as compared to 24.0 ppm (SEM = 1.7) for Denic, 8.2 ppm (SEM = 0.7) for Accord, and

31.4 ppm (SEM = 4.0) for Eclipse. Relative to own brand and at every post-smoking time point, Accord delivered significantly lower amounts of CO and Eclipse delivered significantly higher amounts of CO.

A significant main effect of gender [$F(1, 18) = 6.3, p < .05$] and interaction of gender by bout was observed for heart rate [$F(3, 54) = 5.3, p < .01$]. Overall, women’s heart rate was higher (mean = 82.4 bpm, SEM = 2.1) than men’s (mean = 75.1 bpm, SEM = 2.1). This difference became more pronounced across bouts. Also, a significant interaction of gender by type by smoking-bout was observed for skin temperature [$F(9, 162) = 2.3, p < .05$]. Generally, women’s temperature decreased more after the first smoking bout for each type than did men’s, for every type except Denic.

Plasma nicotine measure

As shown in Figure 3, pre-session nicotine level (mean = 2.7 ng/ml, SEM = 0.1) was indicative of smoking abstinence. Analysis of nicotine data revealed a significant product by time interaction [$F(3, 54) = 71.6, p < .001$]. Relative to pre-session data, significantly higher mean post-session plasma nicotine levels were observed for own brand (18.9 ng/ml, SEM = 1.4), Accord (8.7 ng/ml, SEM = 0.9), and Eclipse (13.3 ng/ml, SEM = 1.3) but not Denic (2.6 ng/ml, SEM = 0.6). Own brand delivered significantly more nicotine than Eclipse, which delivered significantly more than Accord, which delivered significantly more than Denic (Tukey’s HSD, $p < .05$).

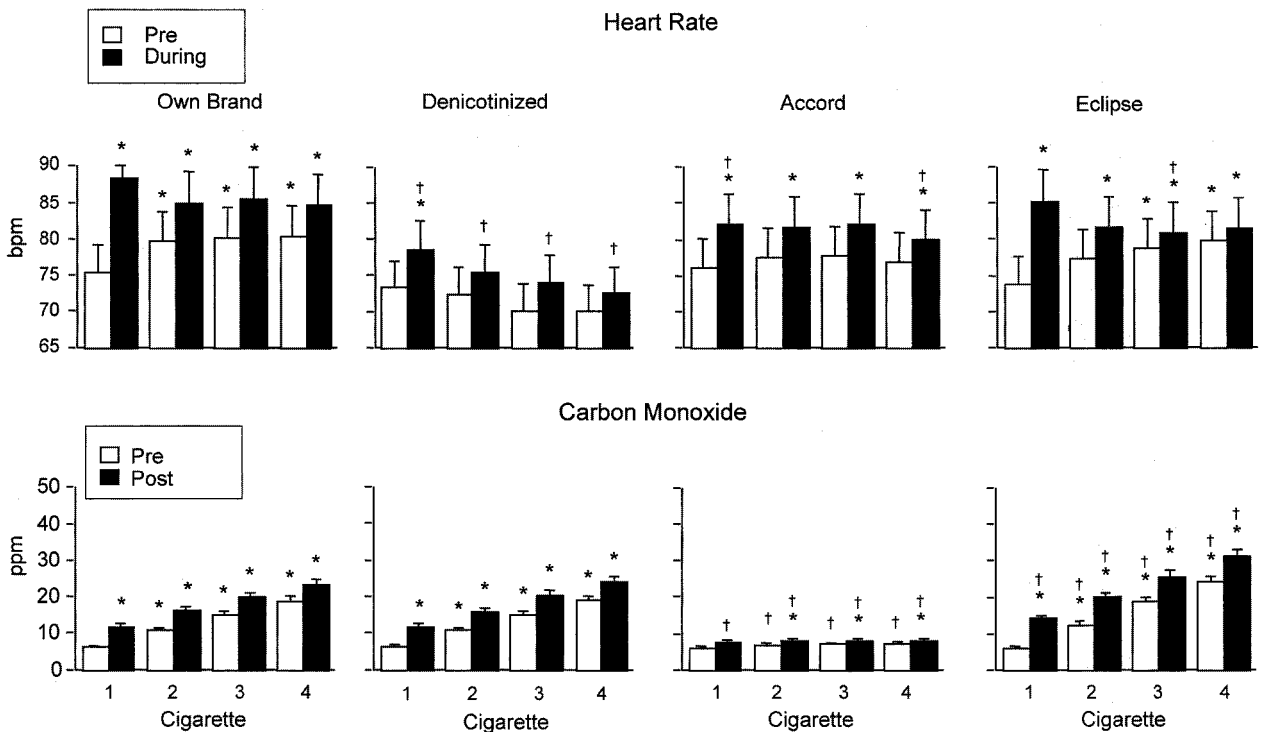


Figure 2. Averaged data (plus one SEM) from 20 subjects on heart rate (top panels) and expired air CO (bottom panels) for own brand, denicotinized cigarettes, Accord, or Eclipse. Open bars are data collected before an 8-puff smoking bout, and filled bars are data either collected during a smoking bout (heart rate) or at least 5 min after a smoking bout (CO). In all other respects the figure is identical to Figure 1.

Topography measures

For puff volume, duration, and IPI, significant main effects of type and bout were observed [$F(3,54) > 3.0$; $p < .05$]. For volume, *post hoc* tests revealed that, collapsed across bouts, mean volume was similar for own brand (49.8 ml, SEM = 3.3), Eclipse (53.3, SEM = 4.3), and Denic (52.8, SEM = 3.2), but larger for Accord (61.8 ml, SEM = 4.0). Collapsed across type, subjects tended to take smaller puffs in subsequent bouts. A nearly identical pattern was observed for puff duration. On average, puffs were similar for own brand (1.7 sec, SEM = 0.1), Eclipse (1.7, SEM = 0.1), and Denic (1.9, SEM = 0.1), but longer for Accord (2.4 sec, SEM = 0.2). Collapsed across type, subjects tended to take shorter puffs in subsequent bouts. Subjects tended to have shorter IPIs when using Accord and also in later bouts, though these differences were not significant.

Discussion

Judging by recently released or announced products, the U.S. tobacco industry (e.g., R.J. Reynolds, Philip Morris, Star Scientific, Vector Group) has a growing interest in marketing PREPs to smokers. Like the public health community, tobacco industry-sponsored harm reduction may be motivated by the potential to decrease smoking-related death and disease. Unlike the public health community, the industry may also be motivated by maintaining or increasing profits from tobacco sales.

This profit motive, coupled with a history of PREPs that failed to decrease smoking's lethality (i.e., lower yield "light" and "ultra-light" cigarettes) highlights the need for careful, objective evaluation of current and future industry-sponsored PREPs. This study demonstrates that clinical laboratory research can be a valuable tool in an ongoing evaluative process of PREPs for smokers. Specifically, laboratory studies can be used to examine if, relative to normally marketed cigarettes, PREPs suppress withdrawal adequately and expose smokers to lower levels of harmful smoke constituents. A PREP's susceptibility to compensatory behavioral changes can also be measured in the laboratory; compensatory smoking behavior in response to PREP use has been measured in sessions as short as 1.5 hours (e.g., Zacny, Stitzer, & Yingling, 1986).

In this acute laboratory study, Accord and Eclipse were examined in comparison to subjects' own brand of cigarettes; denicotinized cigarettes controlled for the effects of smoking behavior and CO exposure without nicotine. As reported previously using similar methods, Accord produced less subject-rated withdrawal suppression, heart rate increase, and CO boost as compared to subjects' own brand of cigarettes, while subjects took larger and longer puffs when using Accord (see Buchhalter & Eissenberg, 2000; Buchhalter et al., 2001). These changes in puff topography may be a behavioral indicator of inadequate withdrawal suppression, though they may also be related to the fact that the device is puff-activated. Accord also delivered significantly less

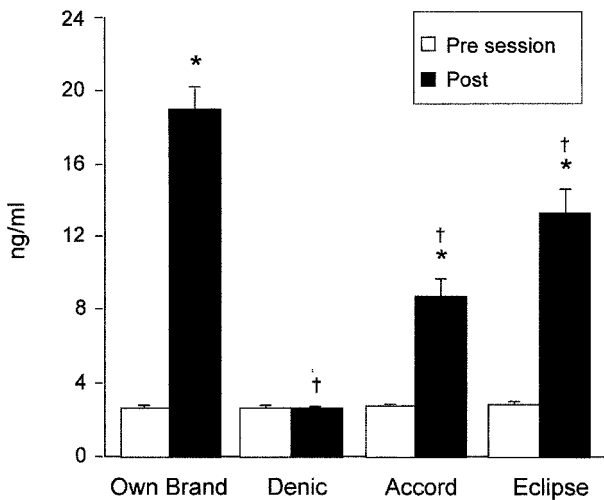


Figure 3. Averaged data (plus one SEM) from 20 subjects for plasma nicotine concentration for own brand, denicotinized cigarettes, Accord, or Eclipse. Open bars are data collected before each session, and filled bars are data collected after each session. In all other respects the figure is identical to Figure 1.

nicotine than subjects' own brand of cigarette: After four 8-puff smoking bouts, Accord increased plasma nicotine by 6.1 ng/ml on average, as compared to 16.3 ng/ml for own brand. Failure to suppress withdrawal fully may reflect Accord's fewer smoking-related stimuli (e.g., lighter, smoke, ashes), and/or lower nicotine delivery. Whatever the reason, inadequate withdrawal suppression may lead to increased use of the product (i.e., behavioral compensation) or continued use of normally marketed cigarettes. In fact, results of a longer-term study suggest that, even when using Accord 15 times/day, subjects supplemented that use with their own brand of cigarettes (Keely et al., 2001). If Accord is used as an adjunct to normally marketed cigarettes, rather than a replacement for them, its potential effectiveness as a harm-reduction strategy is lessened.

In contrast to Accord, Eclipse suppressed withdrawal and increased heart rate similarly relative to subjects' own brand, but delivered on average 33.3% more CO. Eclipse also delivered significantly more nicotine on average than Accord (i.e., 10.5 ng/ml). These results suggest that Eclipse may not lead smokers to alter their smoking behavior or supplement its use with normally marketed cigarettes. However, the increased levels of CO associated with Eclipse, also observed elsewhere (Fagerström et al., 2000), are inconsistent with a harm-reduction strategy where the goal is to lessen smokers' exposure to potentially lethal smoke constituents.

Interestingly, both Accord and Eclipse delivered more nicotine than is suggested by their FTC yields. The FTC nicotine yield of Accord is 0.1 mg/cig and Eclipse is 0.2 mg/cig as compared to the 0.8 mg/cig average FTC nicotine yield of own brand cigarettes in this study; thus, relative to own brand, these products might be expected to deliver 1/8 to 1/4 the dose of nicotine. In fact, as seen in Figure 3, Accord delivered about 1/2 and Eclipse

about 3/4 the nicotine of own brand cigarettes. These results highlight the difficulty in using FTC smoking-machine analysis to predict the delivery of smoke constituents to users of traditional cigarettes or PREPs (e.g., Buchhalter et al., 2001; Djordjevic, Stellman, & Zang; 2000; FTC, 2000).

Based on these results, neither Accord nor Eclipse is likely to be an effective reduced-exposure product. Accord's inability to suppress withdrawal effectively could translate to increased use, behavioral compensation, or, most likely, continued use of normally marketed cigarettes. Eclipse's greater CO is troublesome, as CO has been implicated in cardiovascular disease (Lakier, 1992) and fetal tobacco syndrome (Nieburg, Marks, McLaren, & Remington, 1985). Given that Eclipse may also contain harmful glass fibers not found in normally marketed cigarettes (Pauley et al., 1998) this product may add risks not usually faced by smokers. These increased risks are particularly noteworthy, given that Eclipse marketing materials explicitly state that it is a tobacco product with fewer health risks than cigarettes.

There are several advantages to using this clinical laboratory model in a comprehensive evaluation of PREPs for smokers. First, cross-study comparisons indicate that results are reliable: Over the 3 studies conducted with the Accord (Buchhalter & Eissenberg, 2000; Buchhalter et al., 2001; this study), similar findings regarding subjective effect, physiological response, and CO boost were obtained. Reliability is also evidenced by the observation that denicotinized tobacco cigarettes suppress withdrawal; placebo-induced withdrawal suppression has been reported in laboratory and outpatient studies of tobacco users (e.g., Baldinger, Hasenfratz, & Battig, 1995b; Brauer et al., 2001; Buchhalter et al., 2001; Butschky, Bailey, Gire & Eissenberg, 2000; Henningfield, & Pickworth, 1995). Second, laboratory results predict those of longer-term outpatient studies: Accord's failure to suppress withdrawal probably drives continued cigarette use in Accord users (Keely et al., 2001), while Eclipse's greater CO delivery has also been reported in an outpatient study (Fagerstrom et al., 2000). Finally, results from the clinical laboratory provide an opportunity to measure smoking behavior, thus assessing potential compensatory changes in puff topography that may underlie the failure of "light" and "ultra-light" cigarettes as reduced-exposure products. Taken together, these advantages suggest that clinical laboratory methods have an important role to play in evaluating PREPs for smokers.

One limitation to the current model as currently described includes the relatively short evaluation period (i.e., 2.5 hours, or four 8-puff smoking bouts). This short-term evaluation strategy makes measuring exposure to some carcinogens difficult, and may also limit the likelihood of measuring some behavior changes. For example, the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is thought to play a central role in lung cancer in human smokers

(Hecht & Hoffman, 1989), and the smoke produced by Accord, Eclipse, and Star Scientific's Advance are all thought to produce lower NNK levels than normally marketed cigarettes (Djordjevic, 2000; Terpstra et al., 1998; Eclipse Expert Panel, 2000; see also Labstat, 2000). NNK's metabolites can be measured in human urine, decline during abstinence, and have a distribution half-life of more than 3 days (e.g., Carmella et al., 1995; Carmella et al., 1999); thus, longer-term exposure periods may be required to assess any potential reduction in carcinogen delivery. In addition, some changes in smoking topography may become more pronounced after longer periods of PREP use, again suggesting that longer observation periods may be valuable.

In summary, there is increasing interest in effective harm-reduction strategies for cigarette smokers. As noted by the Institute of Medicine (Stratton et al., 2001), identifying these strategies is likely to be complex and involve preclinical, clinical, and epidemiological research. We present a short-term clinical laboratory model for assessing some important characteristics of industry-sponsored PREPs, using Accord and Eclipse as examples. While neither Accord nor Eclipse appears suitable as a reduced-exposure product, the acute clinical laboratory model is reliable and predicts the results of longer-term studies. It can be improved with the inclusion of longer-term exposure periods, thus allowing assessment of carcinogen delivery and behavioral adaptation to novel smoking systems.

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