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Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: A crossover study

Erik Lunell, Marianne Lunell

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The present study evaluated nicotine plasma levels achieved following 1 day's regular use of four commonly used brands of Swedish portion snus and 2-mg Nicorette chewing gum. The study also estimated the amount of sodium chloride extracted from each snus sachet to identify potential risks for exacerbation of heart failure and hypertension with the use of Swedish snus. Extracted dose of nicotine, area under the venous plasma concentration–time curve (AUC), maximum plasma nicotine concentration (C_{max}) of the last (12th) dosing interval, and the C_{max} and AUC ratios versus Nicorette were calculated. Relative bioavailable dose was calculated using AUC of 2-mg Nicorette gum as the reference. The mean extracted nicotine doses were 2.74 ± 0.80, 1.55 ± 0.68, 2.00 ± 0.56, and 1.08 ± 0.94 mg/sachet for General, Catch Licorice, Catch Mini, and Catch Dry Mini snus, respectively. The approximate bioavailable dose of nicotine from snus was 40%–60% of the extracted dose. The steady-state nicotine plasma concentration–time curve for the weakest brand, Catch Dry Mini portion snus, did not differ significantly from that of the 2-mg Nicorette gum. The AUC and C_{max} for Catch Licorice 1 g and Catch Mini 0.5 g portion snus were twice those for the 2-mg Nicorette gum; for the strongest brand, General, these values were 2½ times those for Nicorette gum. The differences in AUC and C_{max} versus the 2-mg Nicorette gum were statistically significant ($p = .020$). Nicotine plasma levels with General portion snus were sustained at higher levels than current nicotine replacement therapy products, peaking at 29.0 ± 8.5 ng/ml, and more closely mimicking cigarette smokers' nicotine plasma levels. The risks of aggravation of heart failure and hypertension with respect to increased salt load from the use of snus appeared to be negligible.

Introduction

Swedish oral moist snuff (snus) is the smokeless tobacco product most commonly used in Sweden. It is typically placed between the upper lip and the gum, toward the front of the mouth, for approximately 30 min before it is discarded. It comes in portions of 1 g or less, served in pouches or sachets. Snus availability in Sweden is claimed to have contributed to the unusually low rates of smoking among Swedish men by helping them transfer to a less harmful form of nicotine dependence (Bates et al., 2003; Foulds, Ramstrom, Burke, & Fagerström, 2003), although the causality associated with this claim has been questioned (Tomar, Connolly, Wilenfeld, & Henningfield, 2003).

The pH of Swedish snus is higher than in five comparison brands of U.S. smokeless tobacco (Brunneman & Hoffman, 1993) and therefore probably delivers nicotine more efficiently than the comparison brands. Snus typically has a pH in the range of 7.8–8.5 with only minor differences between brands (Andersson, Bjornberg, & Curvall, 1994). The pH is important because only in the free-base form is nicotine absorbed rapidly through the mucosal membrane. Moreover, snus may carry a lower risk for oral cancer than the U.S. moist snuff brands because of lower yields of tobacco-specific *N*-nitrosamines (Brunneman, Qi, & Hoffman, 2001).

The human pharmacokinetics and pharmacodynamics of four U.S. brands of oral moist snuff are well studied (Fant, Henningfield, Nelson, &

Erik Lunell, M.D., Ph.D., Department of Clinical Pharmacology, University Hospital, Lund, and CROEL AB, Helsingborg; Marianne Lunell, M.Sc., CROEL AB, Helsingborg, Sweden.

Correspondence: Marianne Lunell, CROEL AB, SE 252 84 Helsingborg, Sweden. Tel: +(46) 46 913 16; Fax: +(46) 42 913 92; E-mail: croel@swipnet.se

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Pickworth, 1999). The pharmacokinetics of Swedish snus, however, is less well studied. Only plasma nicotine levels resulting from a pinch of 2-g loose snus have been published (Holm, Jarvis, Russell, & Feyerabend, 1992; Larsson, Curvall, & Enzell, 1987). Each dose of the 2-g pinch typically produced a venous nicotine boost of about 15 ng/ml after half an hour. Steady-state levels of 2-g loose snus were approximately 30 ng/ml (Larsson et al., 1987). Although Holm et al. and Larsson et al. studied a high dose of loose Swedish snus (2 g), snus is currently used most often in 1-g or lower doses portion packed in sachets. We therefore investigated the plasma nicotine levels and relative bioavailability of four brands of snus compared with 2-mg polacrilex gum (Nicorette) in a crossover study.

Some studies suggest that snus use increases cardiovascular risk. Two studies reported higher daytime (but not nighttime) heart rate and blood pressure among both snus users and smokers as compared with non–tobacco users (Bolinder, Ahlborg, & Lindell, 1992; Bolinder & de Faire, 1998). The authors suggested that the effects of snus on blood pressure may be related to its sodium content (1.3%–3.5% sodium chloride and 1.5%–3.5% sodium bicarbonate). We therefore also investigated the in vivo extraction of sodium (presented as sodium chloride) from the same four brands of Swedish snus.

Method

Study design

The study used an open-label, partly randomized, crossover design and comprised a total of five 12-hr sessions. Healthy male regular snus users were randomly given 12 hourly repeated doses of four different types of snus. For practical reasons (the coordination of standardized chewing, using a metronome), 2-mg Nicorette gum as the reference was tested on a separate occasion. A minimum period of 5 days elapsed between the sessions. Serial blood samples were drawn to determine trough nicotine levels as well as nicotine levels during the last dosing interval. Analysis of residual nicotine and residual sodium chloride in each dose of snus was performed to calculate the extracted dose of nicotine and sodium chloride, respectively, from each type of snus. The approximate relative bioavailable dose of each type of snus was calculated using the AUC of 2-mg Nicorette gum as the reference and an approximate 55% bioavailability for the nicotine gum, which is in the lower end of the range found in the literature (Benowitz, Jacob, & Savanapridi, 1987).

Subjects

A total of 12 male nonsmoking regular (for at least 1 year) snus users, aged 18–23, years were selected for participation in the study. None of the subjects were current smokers; 10 subjects were ex-smokers, and 2 were never-smokers. They were healthy according to medical history, physical examination, and laboratory screening. The study was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association Assembly, Helsinki, Finland, 1964 (Declaration of Helsinki) and later revisions. The study was conducted in accordance with the principles of good clinical practice. Each subject was given full and adequate oral and written information about the nature, purpose, and possible risks of the study. Each subject's signed informed consent was obtained before any study procedures were conducted.

Treatments

The four snus preparations, General 1 g (pH=8.4), Catch Licorice 1 g (pH=8.5), Catch Mini 0.5 g (pH=8.4), and Catch Dry Mini 0.3 g (pH=7.3) portion snus, respectively, were given according to a computer-generated randomization list. Nicotine gum (2-mg Nicorette) was chewed on a separate occasion for practical reasons. The study products were given as multiple doses administered every hour (12 administrations). Only nonsmoking personnel were allowed to perform practical functions in the study. The nicotine content of the four snus preparations and the nicotine gum is given in Table 1.

Snus was used under standardized conditions as follows: One portion was placed and kept in the same place between the upper lip and the gum toward the front of the mouth for 30 min. Chewing of the gum was performed under standardized conditions as follows: One piece of chewing gum was chewed every 2 s for 30 min (using a metronome for standardization). Each dose of the snus products was administered under the supervision of the study nurse, as was the chewing of the nicotine gum. The subjects were instructed to abstain from any nicotine-containing products from 8 P.M. the night before each study day. Violation of this rule detected in the poststudy bioanalysis (baseline nicotine plasma concentrations exceeding 4 ng/ml) led to the exclusion of one subject's results from the statistical analysis. The results of another subject's chewing gum session were excluded from statistical analysis because of obvious noncompliance with the chewing instructions. The analysis of pharmacokinetic variables is thus based on 11 subjects and the ratios versus 2-mg Nicorette gum on 10 subjects.

Table 1. Nicotine content in 10 unused portions of snus and in vivo extraction ($N=12$); maximal nicotine plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) ($N=11$); ratio of C_{max} and AUC for the various snus preparations vs. 2-mg Nicorette chewing gum ($N=10$).

Study product	Nicotine content (mg)	Extraction (mg)	C_{max} (ng/ml)	C_{max} ratio	AUC (hours × ng/ml)	AUC ratio
General 1 g (pH=8.4)	8.84±0.40	2.74±0.18	29.00±8.53 (p=.0020)[a]	2.53±1.01	26.16±3.36 (p=.0020)[a]	2.55±1.03
Catch Licorice 1 g (pH=8.5)	7.04±0.12	1.55±0.18	23.79±8.60 (p=.0020)[a]	1.96±0.74	21.57±8.82 (p=.0020)[a]	1.98±0.76
Catch Mini 0.5 g (pH=8.4)	4.53±0.26	2.00±0.11	20.95±6.90 (p=.0039)[a] *ns* (p=.1602)[b]	1.80±0.60	19.02±6.69 (p=.0039)[a] *ns* (p=.2754)[b]	1.83±0.61
Catch Dry Mini 0.3 g (pH=7.3)	4.82±0.58	1.08±0.12	10.85±5.65 *ns* (p=.3223)[a]	0.94±0.50	9.81±5.12 *ns* (p=.3750)[a]	0.93±0.46
2-mg Nicorette gum	1.91±0.1	0.84±0.34	12.75±4.67	—	11.55±4.52	—

Note. All values are mean±standard deviation. *ns*=not significant.
[a]Versus Nicorette 2-mg gum.
[b]Versus Catch Licorice 1 g.

Nicotine plasma concentrations

Venous blood samples (5 ml) were collected in sodium heparinized glass tubes from an antecubital vein at the following timepoints: Before (0) and 1, 2, 4, 6, 8, 10, 11, and 12 hr after the first dose administration as well as at the five 10-min intervals between the 11- and 12-hr timepoints. The blood samples were centrifuged within 30 min and the plasma was transferred to plastic tubes, which were stored frozen (−20°C) pending analysis.

The determination of nicotine was performed at ABS Laboratories (London), using capillary gas chromatography with a nitrogen-selective detector after a single liquid-liquid extraction of a basified plasma sample (Feyerabend & Russell, 1990). The limit of quantification was 0.5 ng/ml. To quantify nicotine, a multilevel calibration at seven concentrations was performed. The calibration line was fitted by means of a power-curve-fitting regression model using the equation $y=ax^b$. The samples were assayed once. If the sample showed concentrations considered by the analyst to be outside those expected, the sample was reassayed. If the repeat assay gave a result greater than ±30% of the first result, a third analysis was performed until the assay results differed by less than 30%. The median of the multiple analysis results for each sample was used in the pharmacokinetic calculations.

Residual nicotine and sodium chloride in used snus

Each used portion of snus was placed in a sealed container, labeled with a unique number, frozen, and stored at −20°C pending analysis at the Research Department, Swedish Match (Stockholm, Sweden). Ten portions of unused snus of each preparation also were analyzed. The mean nicotine content of these portions was used for the calculation of extracted dose of nicotine. The same procedure was applied for the calculation of extracted sodium chloride.

Pharmacokinetic calculations

The pharmacokinetic calculations were carried out using the WinNonlin Pro computer system for pharmacokinetic data analysis (Pharsight Corporation, Mountain View, California). The maximum nicotine plasma concentration (C_{max}) and the time to peak plasma concentration (t_{max}) were determined from the observed plasma concentration–time curve after the last dose administration. The nicotine plasma concentrations were used for calculating the area under the plasma concentration–time curve of the last dosing interval (AUC_{11-12}) by the linear trapezoidal method.

A calculation of the approximate bioavailability (F%) of nicotine from each type of snus was made by comparing its AUC to the average AUC of 2-mg Nicorette gum and its extracted dose to the average extracted dose of 2-mg Nicorette gum, assuming an approximate 55% bioavailability for the nicotine gum (Benowitz et al., 1987). The following formula was used:

$$F = \mathrm{AUC}_{\mathrm{snus}} / \text{extracted dose} \times 55 / \mathrm{AUC}_{\mathrm{gum}} \times \text{extracted gum dose}.$$

Statistical analyses

All continuous variables were presented using descriptive statistics such as mean, standard deviation, median, minimum, maximum, and the like. Categorical variables were presented using frequency tables including number of observations and percentages. The ratios of pharmacokinetic parameters for snus versus 2-mg Nicorette gum were carried out within each patient. Statistical testing was performed using Wilcoxon's signed-rank test.

Results

Nicotine extraction from snus and gum

For General snus, the mean amount of nicotine extracted (i.e., the difference between the amount of nicotine in unused snus and the residual amount in used snus) was 2.74 ± 0.18 mg/portion, corresponding to an average 31% of the dose. The mean nicotine extraction from Catch Licorice snus was 1.55 ± 0.18 mg/portion, corresponding to an average 22% of the dose. The mean nicotine extraction from Catch Mini snus was 2.00 ± 0.11 mg/portion, corresponding to an average 44% of the dose. The mean nicotine extraction from Catch Dry Mini snus was 1.08 ± 0.12 mg/portion, corresponding to an average 22% of the dose. The interindividual variation was 50%–300% larger than the intraindividual variation. The nicotine content in unused portion snus and from the in vivo extraction is shown in Table 1.

The mean extracted amount of nicotine from Nicorette gum was 0.84 ± 0.34 mg/piece (range 0.42–1.37 mg/piece), corresponding to an average 44% of the dose. The interindividual variation was about three times larger than the intraindividual variation ($SD = 0.12$ mg/piece).

Sodium chloride extraction from used snus

The mean sodium chloride amount extracted (i.e., the difference between the amount of sodium chloride in unused snus and the residual amount in used snus) was 8.13 ± 7.33 mg/portion from General snus, 10.38 ± 6.83 mg/portion from Catch Licorice snus, 5.58 ± 4.49 mg/portion from Catch Mini snus, and 4.73 ± 6.61 mg/portion from Catch Dry Mini snus.

Maximal nicotine plasma concentration

The mean C_{max} obtained in the last dosing interval after use of the General portion snus was 29.00 ± 8.53 ng/ml. This value was significantly higher than for all other snus preparations ($p = .0020$). The corresponding value after use of the Catch Licorice portion snus was 23.79 ± 8.60 ng/ml. The mean C_{max} obtained in the last dosing interval after use of the Catch Mini portion snus was 20.95 ± 6.90 ng/ml. The corresponding value after use of the Catch Dry Mini portion snus was 10.85 ± 5.65 ng/ml. The mean C_{max} obtained after chewing of the 2-mg Nicorette gum was 12.75 ± 4.67 ng/ml. All C_{max} values differed significantly ($p < .020$) from the Nicorette gum except that of Catch Dry Mini ($p = .3223$). Maximal nicotine plasma concentration for the various snus preparations is shown in Table 1.

Time to maximal plasma concentration

The median t_{max} in the last dosing interval after use of snus was 30 min for all products. The median t_{max} after chewing of the 2-mg Nicorette gum was 30 min.

Area under the plasma concentration–time curve

The mean AUC of the last dosing interval after use of the General portion snus was 26.16 ± 3.36 hr $\times$ ng/ml. This value was significantly higher than for all other snus preparations ($p = .0020$). The corresponding value after use of the Catch Licorice portion snus was 21.57 ± 8.82 hr $\times$ ng/ml. The mean AUC of the last dosing interval after use of the Catch Mini portion snus was 19.02 ± 6.69 hr $\times$ ng/ml. The corresponding value after use of the Catch Dry Mini portion snus was 9.81 ± 5.12 hr $\times$ ng/ml. The mean AUC after chewing of the 2-mg Nicorette gum was 11.55 ± 4.52 hr $\times$ ng/ml. All AUC values differed significantly ($p < .020$) from the Nicorette gum except that of Catch Dry Mini ($p = .3750$). The AUC results for the various snus preparations are shown in Table 1.

C_{max} ratio of snus versus 2-mg Nicorette gum

The mean C_{max} ratio versus 2-mg Nicorette gum was 2.53 ± 1.01 for the General portion snus, 1.96 ± 0.74 for the Catch Licorice portion snus, 1.80 ± 0.60 for the Catch Mini portion snus, and 0.94 ± 0.50 for the Catch Dry Mini portion snus. The C_{max} ratios versus the 2-mg Nicorette gum for the various snus preparations are shown in Table 1.

AUC ratio of snus versus Nicorette gum

The mean AUC ratio versus 2-mg Nicorette gum for the General portion snus was 2.55 ± 1.03. The corresponding value for the Catch Licorice portion snus was 1.98 ± 0.76. The mean AUC ratio versus 2-mg Nicorette chewing gum for the Catch Mini portion snus was 1.83 ± 0.61. The corresponding value for the Catch Dry Mini portion snus was 0.93 ± 0.46. The AUC ratios versus the 2-mg Nicorette gum for the various snus preparations are shown in Table 1.

Relative bioavailability

The mean plasma nicotine concentration–time curves for all brands of portion snus investigated show the relative size of the dose absorbed into the systemic blood circulation and may be compared with that of the Nicorette chewing gum (Figure 1). The approximate relative bioavailable dose of each type of snus was calculated using the AUC of 2-mg Nicorette gum as the reference. In the present study, we assumed the

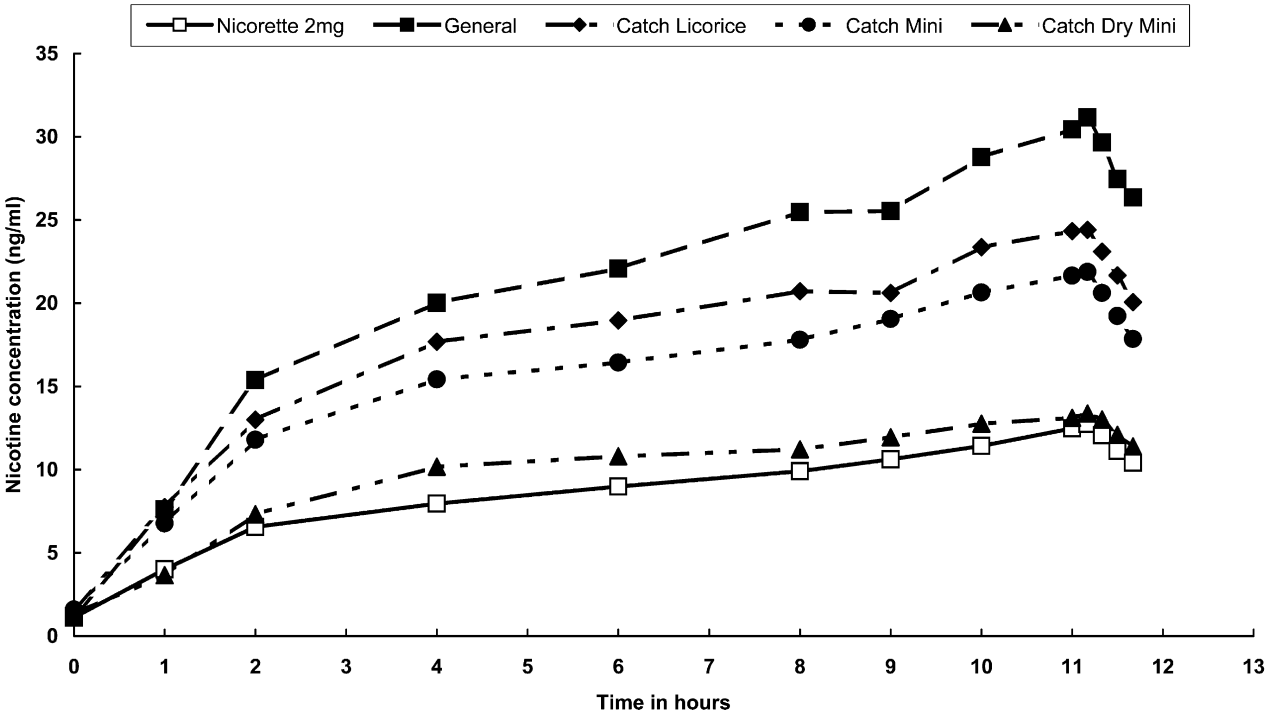

Figure 1. Mean nicotine plasma concentration–time curves obtained following hourly use of four different brands of Swedish snus and 2-mg Nicorette chewing gum.

bioavailability from Nicorette gum to be approximately 55%. This value is at the lower end of the 50%–70% range of bioavailabilities found in the literature for the extracted dose from nicotine gum (Benowitz et al., 1987). Based on the average extracted dose of 0.84 mg, the bioavailable dose of the gum was 0.46 mg. Using this figure for the calculations, we found approximate bioavailabilities of 40% for General, Catch Mini, and Catch Dry Mini portion snus, respectively, compared with 60% for Catch Licorice.

Adverse events

All snus brands were well tolerated and accepted. No adverse events were reported. Among the various brands of snus, based on spontaneous reports, General was most liked and Catch Dry Mini was least liked. Adverse events were reported by some subjects for the Nicorette chewing gum. They were generally mild. Most frequently reported were hiccups, headache, and irritated throat, with occasional reports of abdominal discomfort, cough, and nausea.

Discussion

The mean plasma nicotine concentration–time curve for the Catch Dry Mini portion snus showed great similarity to that of the Nicorette chewing gum (Figure 1). Catch Dry Mini was close to bioequivalent to the 2-mg Nicorette gum. Catch Licorice 1 g and Catch Mini 0.5 g were quite similar, with AUC and C_{max} values twice those of the 2-mg Nicorette gum. The AUC and C_{max} values for General were 2½ times those for the 2-mg Nicorette gum. Catch Dry Mini once hourly produced blood levels similar to the lower end of cigarette smoking (7–10 cigarettes/day), whereas Catch Licorice and Catch Mini once hourly showed blood levels similar to moderate cigarette smoking (15–20 cigarettes/day). Only General once hourly produced steady-state levels around 30 ng/ml, similar to the upper end of cigarette smoking (25–40 cigarettes/day) and similar to the results of Holm et al. (1992). As seen in Figure 1, a situation only close to steady state may be assumed. For some individuals a longer dosing period than 12 hr would be necessary to achieve a true steady state. Therefore, the systemic doses calculated in the present study should be viewed with caution.

Swedish snus generally has a higher pH (7.8–8.5) than most brands of U.S. smokeless tobacco (Brunneman & Hoffman, 1993). The exception is Catch Dry Mini portion snus, which has a slightly lower pH of 7.3. The free-base form of nicotine is absorbed rapidly through the mucosal membranes, and the proportion of free-base nicotine available from smokeless tobacco is determined by the pH level. Swedish snus, being basic, probably delivers nicotine more efficiently than do the U.S. smokeless tobacco brands. This may explain the comparatively high steady-state levels of around 30 ng/ml for the highest dose of snus, General, found in the present study.

The AUC and C_{max} values of Catch Licorice portion snus did not differ significantly from those of Catch Mini ($p=.2754$ and $p=.1602$, respectively) despite the twice-as-large dose of snus in Catch Licorice (1 g) versus Catch Mini (0.5 g). The approximate bioavailable dose of each type of snus, based on comparison with the AUC and bioavailable dose of 2-mg Nicorette gum leads to about 40% bioavailability for General, Catch Mini, and Catch Dry Mini portion snus, respectively, compared with about 60% for Catch Licorice. The higher bioavailability found for Catch Licorice compared with Catch Mini may be related to more efficient absorption of the extracted dose, about 1.5 mg, from Catch Licorice than of the 2-mg dose extracted from Catch Mini.

Whether snus is responsible for the very low smoking prevalence in Swedish men is a matter of controversy. Some authors suggest that snus may be an effective aid for smoking cessation (Bates et al., 2003; Foulds et al., 2003; Kozlowski, O'Connor, & Edwards, 2003). Other authors suggest that snus played a minor role in reducing smoking in Sweden and that smokeless tobacco may even be a causal gateway to cigarettes (Tomar et al., 2003). In Sweden, only 19% of the adult population smokes, compared with 31% in Norway and Denmark. The use of Swedish snus has increased steadily in Sweden whereas cigarette smoking has decreased, particularly among men (Foulds et al., 2003). However, Finland's per-capita cigarette consumption also has been declining since the early 1970s, despite low snuff usage for most of that period.

Some 47% of snus users in Sweden in 2001 were ex-smokers (Foulds et al., 2003). In a longitudinal study in southern Sweden, giving up smoking was associated with high snus use (Lindström & Isacsson, 2001). The most common snus brand in Sweden, General, produces nicotine plasma concentrations similar to those observed with cigarette smoking, as shown in the present study and the study by Holm et al. (1992).

Every other lifelong smoker dies prematurely with a lifespan shortened on average by 6–8 years (World Health Organization, 1997). The most common disease categories related to tobacco smoking are cancers followed by respiratory and cardiovascular disorders. Among smoke-free tobacco products, reports of the risks of oral, pharyngeal, and larynx cancers vary considerably (Critchley & Unal, 2003). A meta-analysis showed that the highest risk was associated with dry snuff and the lowest with moist snuff, which carried no increased risk (Rodu & Cole, 2002).

Differences in the manufacturing process—such as type of tobacco, curing, pasteurization, additives, and storage—may play a role in the harm profile of tobacco products. The manufacturing process used in the United States includes fermentation of the tobacco, resulting in microbial activation of nitrites to carcinogenic nitrosamines. Swedish snus is manufactured with a heating process with steam for 24–36 hr to approximately 100°C, killing bacteria, producing a relatively sterile product. The exposure to heat during manufacturing prevents microbial formation of carcinogenic nitrosamines (Brunneman et al., 2001). Snus is then kept refrigerated during storage, further reducing any microbial growth.

A slightly increased risk of myocardial infarction from the use of snus cannot be ruled out, however much smaller than the risk associated with smoking (Asplund, 2001). The average sodium chloride amount extracted from each portion of the various brands of snus in the present study was approximately 7 mg, with General snus close to the average at about 8 mg and Catch Mini snus and Catch Dry Mini at about 5 mg. Catch Licorice showed the highest sodium chloride amount extracted, about 10 mg per portion. About 900 sachets of snus thus correspond to 1 tablespoon of salt (6 g of sodium chloride), suggesting that the risks of aggravation of heart failure and hypertension related to increased salt load from the use of snus are negligible.

A need exists for the current, "cleaner" (i.e., pharmaceutical) nicotine sources to be made more effective; however, little improvement has been made since the first nicotine replacement therapy (NRT) was introduced 30 years ago. Odds ratios versus placebo for sustained abstinence for the various NRT products vary around 2.0 with little difference between inhaler, gum, patch, nasal spray, and sublingual tablet (Schneider, Olmstead, Franzon, & Lunell, 2001), with disappointingly low absolute success rates of only about 15% at 12 months. Is the nicotine substitution from these products too low or too slow? The present study demonstrated that steady-state nicotine may be sustained at higher levels and it may be speculated that novel NRT products could be targeted at such levels to be more effective. Results from prospective controlled clinical trials are needed to show whether stronger NRT products would be more effective for smoking cessation.

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References

Andersson, G., Bjornberg, G., & Curvall, M. (1994). Oral mucosal changes and nicotine disposition in users of Swedish smokeless tobacco products; a comparative study. *Journal of Oral Pathology and Medicine*, *23*, 161–167.

Asplund, K. (2001). Snus—How dangerous is it? The controversy continues. *Journal of Internal Medicine*, *250*, 457–461.

Bates, C., Fagerström, K., Jarvis, M. J., Kunze, M., McNeill, A., & Ramström, L. (2003). European Union policy on smokeless tobacco. A statement in favour of evidence-based regulation for public health. *Tobacco Control, 2003*, *12*, 360–367.

Benowitz, N. L., Jacob, P. III, & Savanapridi, C. (1987). Determinants of nicotine intake while chewing nicotine polacrilex gum. *Clinical Pharmacology and Therapeutics*, *41*, 467–473.

Bolinder, G. M., Ahlborg, B. O., & Lindell, J. H. (1992). Use of smokeless tobacco: Blood pressure elevation and other health hazards found in a large-scale population survey. *Journal of Internal Medicine*, *232*, 327–334.

Bolinder, G. M., & de Faire, U. (1998). Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. *American Journal of Hypertension*, *11*, 1153–1163.

Brunneman, K. D., & Hoffmann, D. (1993). Chemical composition of smokeless tobacco products. In: *Smokeless tobacco or health: An international perspective* (Smoking and Tobacco Control Monograph Number 2, pp. 96–106). Bethesda, MD: U.S. Department of Health and Human Services.

Brunneman, K. D., Qi, J., & Hoffmann, D. (2001). *Aging of oral moist snuff and the yields of tobacco specific N-nitrosamines (TSNA)*. Progress report prepared for the Massachusetts Tobacco Control Program. Department of Public Health, Boston, Massachusetts. Retrieved January 18, 2005, from http://www.tobacco.org/news/010622bostonre.html

Critchley, J. A., & Unal, B. (2003). Health effects associated with smokeless tobacco: A systematic review. *Thorax*, *58*, 435–443.

Fant, R. V., Henningfield, J. E., Nelson, R. A., & Pickworth, W. B. (1999). Pharmacokinetics and pharmacodynamics of moist snuff in humans. *Tobacco Control*, *8*, 387–392.

Feyerabend, C., & Russell, M. A. H. (1990). A rapid gas-liquid chromatographic method for the determination of cotinine and nicotine in biological fluids. *The Journal of Pharmacy and Pharmacology*, *42*, 450–452.

Foulds, J., Ramstrom, L., Burke, M., & Fagerström, K. (2003). The effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control*, *12*, 349–359.

Holm, H., Jarvis, M. J., Russell, M. A., & Feyerabend, C. (1992). Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology*, *108*, 507–511.

Kozlowski, L. T., O'Connor, R. J., & Edwards, B. Q. (2003). Some practical points on harm reduction: What to tell your lawmaker and what to tell your brother about Swedish snus. *Tobacco Control*, *12*, 372–373.

Larsson, I., Curvall, M., & Enzell, C. R. (1987). Disposition of nicotine and cotinine in plasma, saliva and urine of snuff-users. *Proceedings from the third European Congress of Biopharmaceutics and Pharmacokinetics*, pp. 318–324.

Lindström, M., & Isacsson, S.-O. (2001). The Malmö shoulder-neck study group. Smoking cessation among daily smokers, aged 45–69 years: A longitudinal study in Malmö, Sweden. *Addiction*, *97*, 205–215.

Rodu, B., & Cole, P. (2002). Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, *5*, 511–515.

Schneider, N. G., Olmstead, R. E., Franzon, M. A., & Lunell, E. (2001). The nicotine inhaler. Clinical pharmacokinetics and comparison with some other nicotine treatments. *Clinical Pharmacokinetics*, *40*, 661–684.

Tomar, S. L., Connolly, G. N., Wilkenfeld, J., & Henningfield, J. E. (2003). Declining smoking in Sweden: Is Swedish Match getting the credit for Swedish tobacco control's efforts? *Tobacco Control*, *12*, 368–371.

World Health Organization. (1997). *Tobacco or health: A global status report*. Geneva, Switzerland: Author.