Psychopharmacology (1992) 108:507–511

Psychopharmacology

Nicotine intake and dependence in Swedish snuff takers

Herman Holm[1], Martin J. Jarvis[2], Michael A.H. Russell[2], and Colin Feyerabend[3]

[1] Department of Psychiatry, Kalmar Hospital, S–Kalmar, Sweden
[2] ICRF Health Behaviour Unit, Institute of Psychiatry, 4, Windsor Walk, London SE5 8AF, UK
[3] Poisons Unit, New Cross Hospital, London, UK

Received August 19, 1991 / Final version October 28, 1991

Abstract. Two studies examining nicotine intake in users of Swedish moist oral snuff are reported. Absorption form a single pinch (2 g) in ten users after overnight abstinence was fairly rapid. The increment in plasma nicotine concentrations averaged 9.9 ng/ml (SD 6.5) after 10 min and peaked at 14.5 ng/ml (SD 4.6) shortly after discarding at 30 min. Among groups of habitual snuff takers ($n=27$) and cigarette smokers ($n=35$) studied on a day of normal snuffing/smoking, peak blood nicotine levels after use were similar [averaging 36.6 ng/ml (SD 14.4) and 36.7 ng/ml (SD 16.1), respectively], but there was a tendency to higher cotinine levels in the snuffers (399.2 ng/ml versus 306.3 ng/ml). The snuff takers and cigarette smokers reported similar levels of subjective dependence on tobacco. Epidemiological study of Swedish snuff users could clarify whether the cardiovascular risks of tobacco are attributable to nicotine or to other smoke components, as in their case nicotine intake is not accompanied by combustion products.

Key words: Snuff – Nicotine – Cotinine – Dependence

Nicotine intake from different forms of tobacco use is of interest for both theoretical and practical reasons. Nicotine is the major psychoactive substance found in tobacco and plays a crucial role in the maintenance of smoking behaviour and in the difficulties of withdrawal (US Surgeon General 1988). Considerable data have now accumulated on nicotine intakes in cigarette, pipe and cigar smokers (Wald et al. 1984; Russell et al. 1986; Benowitz 1988). Snuff users are of particular interest, since in their case nicotine intake is not accompanied by any combustion products, such as tar or carbon monoxide. Studies have been conducted on dry nasal snuff users in the UK (Russell et al. 1980, 1981), and on snuff dippers in the USA (Gritz et al. 1981; Benowitz et al. 1988). Sweden is unique in the developed world in having a substantial proportion of the adult population using moist oral snuff (snus). About 20% of Swedish men regularly take snuff (Nordgren and Ramstrom 1990). There appear to be no published reports of nicotine absorption in users of Swedish snuff.

One of the major unresolved issues relating to tobacco and health concerns the role of nicotine in smoking related disease. Nicotine has numerous effects on the cardiovascular system, and must come under suspicion of involvement in the risks of smoking for the heart. But in cigarette smoke, delivery of nicotine is confounded with that of tar and carbon monoxide, making it impossible to identify the role of nicotine per se. The relatively low risk of cardiovascular disease in noninhaling pipe and cigar smokers may indicate that nicotine is of concern only in combination with carbon monoxide or other smoke components, or when absorbed in bolus form from inhaled cigarette smoking. Epidemiological study of a group of tobacco users with substantial nicotine absorption but without exposure to tobacco combustion products should help to clarify the cardiovascular risks of nicotine. One purpose of the present study was therefore to examine the rate of absorption of nicotine in Swedish snuff users, and the blood levels maintained by regular users, in order to provide preliminary data which might inform epidemiological investigation of the relation between snuff and heart disease.

Among cigarette smokers, dependence as indexed by consumption, time to first cigarette of the day, and perceived difficulty in giving up smoking bears a positive relation to nicotine intake. How far this is determined by rate of absorption as opposed to plateau levels of circulating nicotine is unclear. A second purpose was therefore to gather questionnaire measures of dependence in snuff users, and to compare both dependence and nicotine intakes in snuff users with those in cigarette smokers.

Study 1

Ten regular users of snuff (nine men, one woman, mean age 32.6 years) were recruited to participate in a study

Correspondence to: M.J. Jarvis

examining nicotine absorption from a single pinch (2.0 g) of snuff. All were daily users, and their weekly snuff consumption averaged 160 g. Nine were nonsmokers, while one smoked two or three cigarettes at weekends. The study was conducted at Kalmar Hospital in southern Sweden, and was approved by the hospital's ethical committee.

Following overnight abstinence from snuff, subjects came to the laboratory at 1.30 p.m. An expired air carbon monoxide specimen confirmed nonsmoking status (mean 3 ppm, range 2–4). Each subject took 2.0 g snuff, placing it in their mouth in their usual way, and keeping it there for 30 min. before discarding. The same brand ("Ettan") was used for all subjects, always from a freshly opened tin. Venous blood specimens were taken via an indwelling cannula prior to dosing and at 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 30, 35, 40, 45, 50, and 60 min after placing the snuff in the mouth. Plasma specimens were frozen within 1 h and were subsequently assayed for nicotine and cotinine using a gas chromatographic method (Feyerabend and Russell 1990).

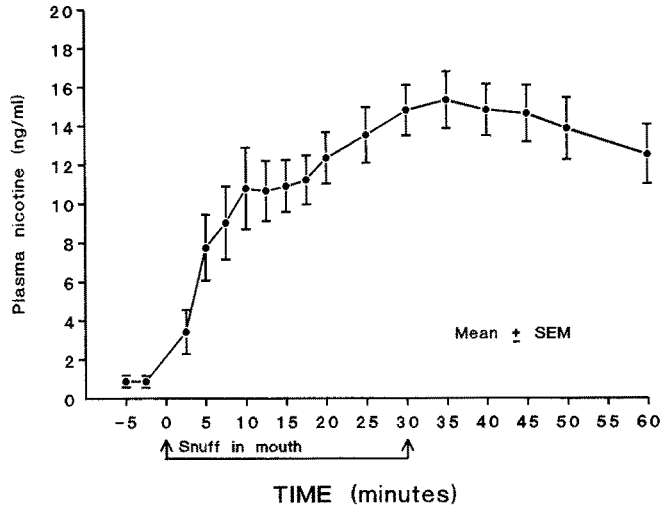

Fig. 1. Plasma nicotine concentrations from a single dose of 2 g Swedish oral snuff taken after overnight abstinence

Results

Individual blood nicotine concentrations from taking the snuff are given in Table 1 and the mean values are shown in Fig. 1. The mean increment over the first 10 min was 9.9 ng/ml, rising more slowly thereafter to peak at 14.5 ng/ml at 35 min shortly after the snuff was discarded. Average C_{max} was 17.0 (SD 5.6), T_{max} 35.5 min (SD 11.7), and AUC (0–60 min) 747.4 ng/ml.min (SD 243.0). As would be expected, cotinine concentrations showed little change over the one hour period of sampling.

Study 2

Thirty-four regular snuff users and 35 cigarette smokers responded to an article in an internal hospital newsletter seeking volunteers to participate in a study examining nicotine intake from habitual snuff use/smoking and its relation to questionnaire measures of dependence. Seven of the snuff users reported some current use of cigarettes, and these were excluded from the study. Among the remaining 27, the mean age was 28.6 and usual snuff consumption averaged 152 g/week. There were 16 never smokers and 11 ex-smokers. All were male. Among the cigarette smokers there were 12 men and 23 women

Table 1. Plasma nicotine concentrations following a single dose of 2 g Swedish snuff

Time (min)	Subject number											
	1	2	3	4	5	6	7	8	9	10	Mean	SD
−5	0.6	2.3	0.6	0.8	0.6	1.2	0.7	0.5	0.6	1.0	0.9	0.5
−2.5	0.5	2.2	0.6	0.8	0.6	1.1	0.8	0.6	0.5	1.0	0.9	0.5
2.5	11.7	6.4	1.2	4.5	0.6	2.5	1.1	0.7	0.5	5.0	3.4	3.6
5	13.3	11.9	4.7	10.9	1.9	7.8	4.8	3.0	1.9	17.2	7.7	5.3
7.5	15.7	8.6	5.4	10.4	3.6	10.7	5.7	4.9	3.4	21.8	9.0	5.9
10	20.4	10.8	6.5	11.8	4.4	15.0	6.0	5.1	5.3	22.6	10.8	6.6
12.5	17.1	13.0	7.0	11.9	5.3	15.2	7.6	5.8	5.4	14.6	10.3	4.7
15	14.9	12.6	7.4	12.3	6.1	18.2	9.1	6.9	6.7	14.8	10.9	4.2
17.5	17.5	12.3	8.8	13.3	6.7	17.7	9.5	9.1	7.8	15.8	11.9	3.8
20	20.0	12.5	8.9	15.1	8.1	16.1	8.8	9.8	8.3	15.9	12.4	4.2
25	19.6	12.5	10.0	17.1	8.3	19.2	8.6	12.2	9.7	18.1	13.5	4.5
30	18.7	15.0	11.5	20.3	9.2	18.1	9.8	14.7	11.7	19.1	14.8	4.1
35	23.1	15.8	11.5	21.7	10.1	15.7	10.6	12.5	13.2	19.2	15.3	4.6
40	16.9	16.9	11.6	23.0	10.3	15.9	10.1	11.1	14.0	18.4	14.8	4.2
45	16.8	17.5	11.7	24.8	9.4	14.3	9.8	11.4	13.9	16.8	14.6	4.6
50	15.4	15.6	11.5	25.9	8.9	13.5	9.0	9.4	13.7	15.8	13.9	5.0
60	12.1	14.7	10.8	24.8	8.7	10.9	7.7	9.6	13.1	12.9	12.5	4.8
Plasma cotinine												
−5	124.8	448.9	173.9	424.1	140.2	393.3	336.8	153.6	163.6	318.8	267.8	129
60	143.2	456.7	176.4	453.0	148.1	405.3	328.4	156.1	171.3	351.4	279.0	133

Note: The time of discard was 30 min, except in the case of subject 4, where it was 45 min

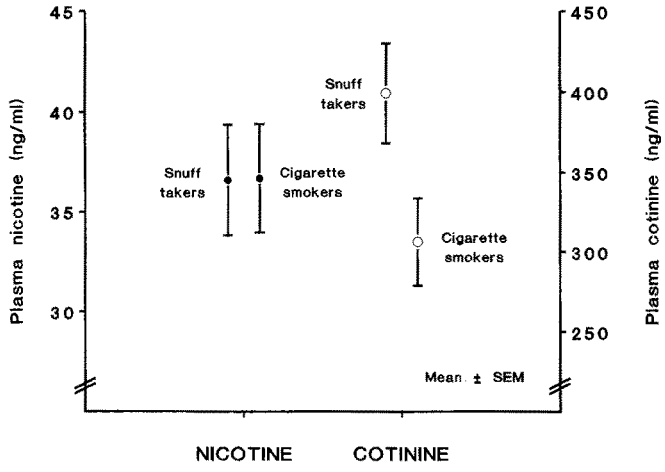

Fig. 2. Plasma nicotine and cotinine concentrations in Swedish snuff takers ($n=27$) and cigarette smokers ($n=35$). Samples were taken after snuffing/smoking during the afternoon of a day of normal use

(mean age 39.7), averaging 17 cigarettes per day, none of whom had ever been regular snuff users.

Subjects were studied on a day of normal snuff use/smoking, without prior abstinence. On arrival at the laboratory they completed a questionnaire and took a pinch of their usual snuff or smoked one of their usual brand of cigarette. A venous blood sample was taken 1 min after extinguishing the cigarette, and 5–15 min after discarding the snuff. After separation the plasma was analysed as previously for nicotine and cotinine.

The wording of questionnaire items, which enquired about current and past tobacco use and subjective aspects of dependence, was similar for the snuffers and smokers, with the exception that references to snuffing were altered to smoking in the version completed by the cigarette smokers. Responses were on anchored 3-, 4-, or 5-point scales (e.g. "Do you think that you are addicted to snuff/smoking?" Extremely/Fairly/Slightly/Not at all).

Results

In view of the differences between the snuffers and cigarette smokers in terms of age and the male/female proportion, statistical comparisons between the two groups controlled for these variables by analysis of covariance.

The mean plasma nicotine after dosing was 36.6 ng/ml (SD 14.4) in the snuffers and 36.7 (SD 16.1) in the smokers (NS). The corresponding cotinines were 399.2 ng/ml (SD 160.5) and 306.3 (SD 162.5). On a univariate analysis, this difference was statistically significant ($P=<0.05$), but was no longer so after controlling for age and sex ($F=3.44$, $P=0.07$). There was no significant difference in plasma nicotine between never smokers and ex-smokers among the snuffers (32.4 ng/ml and 42.6 ng/ml, respectively).

On questionnaire measures of dependence, there was no difference between smokers and snuffers in self-assessed addiction, craving for tobacco, or difficulty in giving up (Table 2). The great majority in each case rated themselves as fairly or extremely addicted, frequently or always craved when without their snuff/cigarettes, and anticipated that giving up would be very difficult. The snuff users rated enforced abstinence for an hour or two as more unpleasant ($t=2.81$, $P<0.01$), but this effect was no longer significant after controlling for age and sex ($F=1.56$, NS) However, the snuff users found their habit much more enjoyable ($F=7.33$, $P<0.01$). For their part, the smokers were significantly more likely to have their first cigarette of the day before tea or coffee than were the snuffers ($F=6.67$, $P<0.01$).

Discussion

Our two studies provide data on the rate of absorption of nicotine from Swedish oral snuff and the steady-state blood nicotine levels of regular users during usual everyday use. The 14.5 ng/ml average increase in blood nicotine concentration produced by the 2 g dose is similar to that found in an earlier study of American oral snuff (Benowitz et al. 1988). Slightly higher levels would have been obtained had the snuff been kept in the mouth for longer than 30 min. Nicotine absorption was more rapid during the first 10 min, the average increment at this point being 9.9 ng/ml.

A nicotine boost of around 10 ng/ml in 10 min or less, measured in mixed venous blood, may have some psychopharmacological significance. A mean trough-peak difference of this order has been found in regular

Table 2. Ratings of dependence and enjoyment in Swedish snuff takers and cigarette smokers

	Snuffers ($n=27$)	Smokers ($n=35$)	Univariate P value	P value controlling for age and sex
Unpleasantness of abstaining for an hour or two	2.48	2.03	<0.01	NS
Self-perceived addiction	3.07	2.86	NS	NS
Craving for tobacco when without it	4.38	4.03	NS	NS
Difficulty of giving up for a month	3.41	3.42	NS	NS
Enjoyment of snuffing/smoking	2.59	2.05	<0.0001	<0.01

Note: Responses were on 3-point (enjoyment), 4-point (addiction, unpleasantness, difficulty giving up), and 5-point (craving) scales. Replies have been coded so that higher values represent more extreme scoring on each dimension

smokers smoking their usual brand of cigarette during a typical smoking day, and in daily users of dry nasal snuff whose blood was sampled within 10 min of taking a pinch of their usual brand (Russell et al. 1981). A rate of absorption of this order is also required to produce the acute subjective feeling of lightheadedness or slight dizziness commonly reported after injection or nasal administration of nicotine, but not after slower absorption from nicotine chewing gum (Russell 1988). The significance of this particular effect as a reinforcer is unknown. Due to rapid desensitisation it is transient and commonly experienced only after the first cigarette of the day or after 2–3 h abstinence.

Like the boost from a single dose, the peak blood nicotine levels of regular users during typical everyday use of Swedish oral snuff were strikingly similar to the steady-state peak levels of smokers just after a cigarette, the average levels being 36.6 and 36.7 ng/ml, respectively. Similar findings have been reported for American oral tobacco users (Gritz et al. 1981). Likewise, the results of a similar comparison of British dry nasal snuff users and cigarette smokers could hardly have been closer to those of our present study, the average peak levels in daily nasal snuff users being 36.1 ng/ml compared with 36.7 ng/ml in a sample of 136 heavy smokers (Russell et al. 1981).

It is remarkable that tobacco products that deliver nicotine in ways as varied as smoke for inhalation to the lungs, dry powder for sniffing up the nose, and moist grounds or dry strips for holding in the mouth are used by regular users in ways contrived to produce the same increases in nicotine concentrations over 10 min in mixed venous blood, and the same steady-state peak levels after dosage during typical everyday use. This is powerful evidence that it is nicotine intake that controls tobacco use. The higher cotinine levels associated with nicotine absorption by the buccal route reflect the loss of availability due to swallowing and first-pass metabolism, and offer further evidence that it is the systemic availability of nicotine that governs the behaviour. However, it is not clear to what extent reinforcement and level of dependence are determined by steady-state peak levels, trough levels or the rate of nicotine absorption.

Blood nicotine concentrations in mixed venous blood obviously fail to detect the transient high nicotine boli that follow each inhaled puff of cigarette smoke and exceed 100 ng/ml when measured in arterial blood (Isaac and Rand 1969; Rand 1989). It has been suggested that the lack of bolus effects (whatever they may be) and the lower frequency of reinforcement from smokeless tobacco may give rise to lower levels of dependence and make it easier to quit than cigarettes (West and Krafona 1990; Hatsukami 1991). On these grounds DSM–III–R (1987, p 181) states that the use of snuff and chewing tobacco is less likely than cigarette-smoking to lead to nicotine dependence. DSM–III–R also refers elsewhere (p 150) to the mild symptoms of withdrawal that may occur after stopping use of smokeless (chewing) tobacco. The main evidence for this appears to be a single study which found a lower incidence and intensity of withdrawal effects in abstaining smokeless tobacco chewers compared with cigarette smokers (Hatsukami et al. 1987). In a subsequent study the same researchers have demonstrated significant withdrawal effects including decrements in performance following abstinence from chewing tobacco (Keenan et al. 1989).

Despite the imbalance in age and sex, our samples of smokers and regular snuffers were remarkably similar in both nicotine intake and questionnaire measures of dependence. The fact that the smokers were significantly more likely to have their first cigarette earlier in the day, before having tea or coffee, may reflect the incompatibility between taking snuff and ingesting food and drink. The lack of enjoyment of smoking compared with snuff use may be attributable to the guilt of continued smoking in the face of known health risks rather than to differences in pharmacological factors. Some caution in generalising from our results is called for in view of the relatively small sample size and possible volunteer bias in recruitment. Nevertheless, the data suggest that dependence among Swedish snuff users is of a similar order to that in cigarette smokers and that cessation and withdrawal may not be as trivial a matter as implied by the comments in DSM–III–R.

A major purpose of our study was to provide data on nicotine intake that might contribute to interpretation of epidemiological data on the cardiovascular risks of snuff use compared with those of cigarette smoking. If the risks are similar, carbon monoxide and other combustion products could be ruled out as causal agents and nicotine would be strongly implicated. Indeed, nicotine is likely to be implicated in any degree of cardiovascular risk of snuff use that can be demonstrated. To our knowledge, none have yet emerged (US Surgeon General 1986). The fact that smokeless tobacco causes short-term nicotine effects on heart rate and blood pressure (Squires et al. 1984; Benowitz et al. 1988) does not in itself implicate it as a cause of cardiovascular disease.

In conclusion, nicotine is absorbed quite rapidly from Swedish oral snuff. As with cigarette smoking, the majority of regular snuff users are dependent on nicotine and have blood nicotine levels similar to those of smokers. Epidemiological investigations are required to ascertain whether or not the substantial nicotine intake from smokeless tobacco use poses any risk to health. Studies of this kind could do more to increase understanding of the cardiovascular risks of smoking than is likely to be obtained by further studies confined to the risks of smoking alone.

Acknowledgements. We thank the UK Medical Research Council and the Imperial Cancer Research Fund for financial support.

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