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RESEARCH REPORT

The long-term effect of nicotine on the oral mucosa

MATS WALLSTRÖM,[1] LARS SAND,[1,3] FREDRIK NILSSON[2] & JAN-M HIRSCH[1,3]

[1]*Department of Oral and Maxillofacial Surgery, Faculty of Odontology, Göteborg University, Gothenburg.* [2]*Department of Clinical Research Pharmacia & Upjohn, Consumer Healthcare, Helsingborg &* [3]*Department of Oral and Maxillofacial Surgery, Uppsala University Hospital, Uppsala, Sweden*

Abstract

Aims. *Although nicotine replacement therapy (NRT) has been used to aid smoking cessation for the last 20 years, little information exists on the effect of nicotine products on the oral mucosa, particularly with regard to the direct effect at the site of application. This study aimed to assess the oral safety of a new sublingual tablet containing 2 mg nicotine with regard to lesions at the site of application.* **Design**. *Prospective follow-up to 12 months of smokers using the 2-mg sublingual tablet over a period of 3–6 months.* **Setting**. *A smoking cessation programme* **Participants**. *Thirty smokers.* **Measurements**. *Oral mucosa was inspected and photographed at each visit. At 6 months, subjects were asked for consent to take a biopsy from the site of application.* **Findings**. *Spontaneous smoking cessation outcome at 12 months was 27% allowing for lapses. At baseline 21 mucosal lesions were diagnosed in 15 subjects. After 6 months eight lesions were observed in six subjects. The predominant diagnosis at all visits was melanin pigmentation. Eight subjects had lesions in the floor of the mouth during the 6-month medication period, all of which appeared in the first 1–6 weeks of treatment. By the 6-month visit all such lesions had resolved. The local symptoms were all mild and tolerable.* **Conclusion**. *The sublingual tablet appears to be a safe form of administration of nicotine with mild and transient effects on the floor of the mouth.*

Introduction

Nicotine replacement therapy is now widely used to aid tobacco cessation. Various administration forms are available, including nicotine chewing gum, nasal spray, inhaler and transdermal patch, all of which involve absorption of nicotine through either the mucosal membrane or skin.[1–13] However, these products may not suit all users, so it is important to continue expanding the range of administration types. Against this background, a nicotine 2-mg tablet for sublingual administration, a well-recognized mode of administration, has been developed. The sublingual tablet has a pharmacokinetic profile that resembles that of the nicotine 2-mg chewing gum, and the plasma nicotine levels produced are similar.[14] One cross-over trial demonstrated the nicotine tablet to be comparable with nicotine gum in terms of nicotine delivery and the subject's perceived 'helpfulness' in controlling

Correspondence to: Dr Mats Wallström, Department of Oral and Maxillofacial Surgery, Box 450, Göteborg Universitet, S-405 30 Göteborg, Sweden. Tel: +46 31 7733212; fax: +46 31 826091. E-mail: odomawa@odontologi.gu.se

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tobacco withdrawal symptoms.[15] One *in vitro* study has shown nicotine to be more rapidly and completely absorbed through the mucosal membrane in the floor of mouth than through other parts of the mouth or the skin.[16] When smoking, venous plasma nicotine concentration peaks within 5 min of smoking a cigarette. This contrasts with NRT, where a period of 20–30 minutes is generally required to achieve plasma nicotine levels that are adequate to alleviate tobacco withdrawal symptoms.[13] A pharmacokinetic comparison between the nicotine 2-mg gum and the sublingual tablet showed no difference in plasma concentration after 30 minutes.[14] Whether the sublingual nicotine tablet offers potential therapeutic advantages because of the site of administration should be further investigated in a classical smoking cessation setting.

In the meantime, there is little published information regarding the direct effect of nicotine on the oral mucosa.[17–19] This study was therefore designed to evaluate the safety and long-term effects of locally applied nicotine on the oral mucosa.

Materials and methods

Subjects

Thirty healthy subjects, 20 years or older, who had smoked at least 10 cigarettes per day for the previous 3 years were recruited from the Smoking Cessation Clinic, Sahlgren's University Hospital, Gothenburg, Sweden. Any subjects with pre-existing pathological lesions on the floor of the mouth were excluded from the study. Other exclusion criteria included: individuals suffering from acute medical illness; with history of severe or symptomatic cardiovascular disease; requiring any form of regular psychotropic medication; or with a history of alcohol or drug abuse during the preceding 12 months. Pregnant or breast-feeding women were also excluded. This study was approved by the Ethics Committee of Sahlgren's University Hospital, Gothenburg, and all subjects gave informed consent before participating.

Study design

This was an open study. In order to retain the maximum number of subjects until study completion, complete abstinence was not stressed, in order to keep as many subjects as possible throughout the study period; none the less, achievement of abstinence was recorded. A total of nine visits were made during the study. The first visit (baseline) was made 2–4 weeks prior to quit day, and at the second visit (1 day before quit day) subjects were issued with the study medication. Further visits where made at 1, 2, 3 and 6 weeks, and at 3 and 6 months with the final follow-up visit at 12 months. All subjects were seen on a individual basis, and a guide to smoking cessation was provided at the baseline visit.[20]

Treatment administration

The sublingual nicotine tablet used contains 2 mg of nicotine bound to β-cyclodextrin. The mean decomposition time is 15–20 minutes. The recommended dosage was based individually upon the subjects' baseline nicotine dependence score, using the Fagerström Tolerance Questionnaire (FTQ; maximum score = 11).[21] Low nicotine-dependent smokers (those with a FTQ score < 7) were instructed to use one tablet/hour, up to a maximum of 20 tablets/day, whereas highly dependent smokers (FTQ $\geqslant$ 7) were instructed to use two tablets/hour, up to a maximum of 40 tablets/day. Subjects were instructed to place each tablet under the tongue until it disintegrated. For those subjects still using medication at 3 months, treatment was gradually tapered by reducing the dose by 25% each month (months 3–4, 4–5 and 5–6). No further medication was dispensed after 6 months.

The oral mucosa

The oral mucosa was visually examined at each visit. Any pathological findings were classified according to the World Health Organization international classification[22] and photo-documented. In order to evaluate the site of application further (i.e. the floor of the mouth), results were rated according to visual observations and any subjective symptoms recorded. Severity was graded as follows.

No reaction:	No symptoms and no visual change.
Mild:	No symptoms, but a visual change on inspection.
Moderate:	Slight irritation and burning sensation when exposed to the tablet plus a visual change.

Severe: Marked symptoms of irritation and a burning sensation even when not exposed to the tablet, with a clearly visible change. Precludes further use of trial medication.

Visual changes were classified as hyperplastic, hyperkeratotic, atrophic or erosive. The size of each lesion was measured in mm^2. The floor of the mouth was photo-documented throughout the study (even if no local reaction was noted), and all photographs were jointly re-examined by two of the authors on two separate occasions.

At 6 months the subjects were asked whether they would be prepared to undergo an optional biopsy of the oral mucosa at the site of tablet application. A specimen measuring 3 mm in diameter was taken under local anaesthesia (Xylocaine® 20 mg/ml plus adrenaline 12.5 μg/ml, Astra, Sweden), fixed in 4% of formaldehyde and transferred for routine analysis. Histological characteristics were evaluated and described on an escalating scale from normal mucosa, keratinized, proliferative to dysplasia. Any inflammation of the connective tissue was noted and recorded.

The total mucosal nicotine exposure of nicotine, the number of tablets × 2 mg used over time during the first 3 months, was also calculated for each subject.

Smoking cessation

Smoking status was checked at all visits using a carbon monoxide monitor (Bedfont Smokerlyzer, Technical Instruments Ltd, Kent, UK). Spontaneous smoking cessation outcome was recorded based on subject self-report and CO < 10 p.p.m. At 12 months a 3 ml saliva sample was analysed for cotinine levels,[23] for verification of complete abstinence.

Adverse events

All adverse events (AE), including those reported spontaneously and those elicited using an open-ended questionnaire, were recorded at each visit and classified according to intensity, duration and severity.

Results

Subjects

Thirty-two subjects were screened for eligibility at baseline, two of whom were rejected (antidepressant treatment 1, pathological lesions on the floor of mouth 1). A total of 30 subjects were therefore eligible, comprising 12 males (mean age 45.2 years, range 29.3–62.4) and 18 females (mean age 39.4 years, range 25.8–50.6); 23 subjects had a FTQ ⩾ 7 (11 M/12 F) and seven had a FTQ < 7 (1 M/6 F).

Smoking cessation

Spontaneous abstinence (allowing occasional slips throughout the study period and complete abstinence, no slips, after 2 weeks) were 73% at 6 weeks, 40% at 6 months and 27% at 12 months (Table 1).

Medication use

Compliance with the tablet use was high; at 6 weeks, 90% of the subjects were using at least one tablet every day. During the first week of treatment the daily dose ranged from seven to 38 tablets/day (mean = 23) in subjects with an FTQ ⩾ 7, and from three to 17 tablets/day (mean = 11) in those with an FTQ < 7. During the tapering-off period (from month 3 to month 6), the daily doses ranged from one to 18 (mean = 8), and two to 10 (mean = 4) tablets/day, respectively. Mean overall tablet consumption up to the 6-month visit was 7 and 12 tablets/day in the low and high dependent groups, respectively.

Oral lesions

The floor of the mouth. A total of 10 lesions were registered in the floor of mouth in eight subjects; these were clinically characterized as hyperplastic

Table 1. *Spontaneous smoking evaluation*

Visit	Complete abstinence, no slips, from 2 weeks % (*N*)	Abstinence with occasional slips % (*N*)
6 weeks	43 (13)	73 (22)
3 months	27 (8)	70 (21)
6 months	13 (4)	40 (12)
12 months	7 (2)	27 (8)

Table 2. *Mucosal lesions registered in the floor of the mouth*

Subject no.	Weeks/ months (smoking status*)	No. of tablets mean/day	Clinical type of lesion	Severity	Adverse events**
1	2W (AB)	35	Hyperplastic	Mild	Burning/ smarting
	3W (AB)	17	Hyperplastic	Mild	—
	6W (SL)	25	Hyperplastic	Mild	—
	3M (AB)	30	Hyperplastic	Mild	—
	6M (AB)	15	Normal	—	—
4	6W (AB)	31	Hyperplastic	Mild	Burning/ smarting
	3M (AB)	34	Normal	—	—
5	2W (AB)	16	Atropic	Moderate	Burning/ smarting
	3W (AB)	19	Hyperkeratotic	Mild	—
	6W (AB)	19	Normal	—	—
6	2W (AB)	22	Hyperkeratotic	Mild	Burning/ smarting
	3W (AB)	38	Normal	—	Burning/ smarting
	3M (SL)	37	Hyperkeratotic	Mild	—
	6M (SM)	—	Normal	—	—
8	2W (AB)	21	Hyperplastic	Mild	—
	3W (AB)	32	Hyperplastic/ hyperkeratotic	Mild	—
	6W (AB)	37	Hyperplastic	Mild	—
	3M (AB)	34	Normal	—	—
20	1W (AB)	36	Hyperplastic	Mild	—
	2W (AB)	36	Normal	—	—
23	2W (AB)	24	Atropic	Mild	—
	6W (AB)	19	Normal	Mild	—
31	6W (SL)	20	Hyperkeratotic	Mild	—
	3M (AB)	14	Normal	—	—

*Smoking status: AB-abstinence, SL-occasional slips, SM-smoking. ** Only AE from the area of application reported.

($n = 4$), hyperkeratotic ($n = 4$) and atrophic ($n = 2$; diagnosed on two occasions). All such lesions occurred during weeks 1–6 of treatment and were mild and transient; at the 3-month visit, all lesions except one had resolved. This lesion had, however, healed at the 6-month visit (Table 2).

The average area of the lesions over time was 4 mm^2. Subjects in whom lesions were observed were exposed to significantly greater total nicotine exposure ($p < 0.05$) compared to those subjects who remained free of lesions (Table 3).

No self-reported complaints or clinical alterations were noted either at 6 months, when tablet treatment discontinued, or at the 12-month follow-up (Table 2).

The clinical appearance and the appearance of the photographic documentation examined were consistent in all but three cases, where photographs indicated a lesion that was not clinically documented. In these cases, where there was some uncertainty, diagnoses were based on the

Table 3. *Cumulative nicotine exposure during the first 3 months in relation to mucosal lesion in the floor of the mouth during tablet medication*

	Mucosal lesion	No mucosal lesion
No. of subjects (N**)	8	21
Mean exposure (mg)	5460*	3174
Range	2732–9492	560–8218
SD	2281	1943

*$p < 0.05$, Mann–Whitney U-test. **One subject withdrawn from the study due to protocol violation.

Table 4. *Histological characteristics of mucosa from the floor of the mouth in patients using sublingual nicotine tablets*

Histological diagnosis	No. of biopsies	No. of patients showing lesions
Normal mucosa	6	0
Keratinized mucosa	4	1
Hyperplastic mucosa	1	1
Dysplastic mucosa	0	0

Four of the biopsies showed inflammatory cells in the connective tissue.

clinical appearance rather than photographic evidence. At 6 months, 11 subjects (36.7%) agreed on a biopsy taken from the site of application; these revealed the mucosa to be either normal or only slightly altered (Table 4).

Oral mucosa (excluding the floor of the mouth). A mean of 1.4 lesions was reported by 50% ($n = 15$) of subjects at baseline, and this was reduced to a mean of 1.0 lesions in 26% ($n = 6$) of subjects at 12-month follow-up. The predominant diagnosis at all visits was melanin pigmentation. One subject had a cavernous haemangioma excised during the study.

Adverse events

The most frequent self-reported adverse events during treatment with the nicotine sublingual tablet were hiccups ($n = 13$), burning/smarting sensation in mouth and sore throat ($n = 12$), coughing and dry lips ($n = 7$) and dry mouth ($n = 6$).

Discussion

Tablet use resulted in a total of 10 reversible lesions in eight subjects during the first 3 months of treatment. The lesions were mainly hyperplastic or hyperkerotatic in nature and small in size; all lesions observed during tablet use were considered clinically non-significant.

All lesions occurred in more highly dependent smokers (baseline FTQ $\geqslant$ 7) who were instructed to use two tablets/hour, and the total exposure to nicotine over the study period was significantly higher among these eight subjects than in subjects who did not experience any lesions. No clinical changes were observed in the floor of the mouth after treatment had been tapered off (at 6 months), and all lesions had resolved during the tapering-off period.

To date, little information has been published regarding the local effects of nicotine administration on the oral mucous membrane. Although a local perioral rash induced by nicotine gum has been reported,[24] a subsequent critical evaluation of the safety of nicotine gum did not report any such adverse reactions.[19] However, subjects were only instructed to chew the gum and not place it in prolonged contact with the mucous membrane. Optional biopsies, obtained from one-third of the study participants at the 6-month visit, confirmed that no serious changes had occurred at the microscopic level. All histological grading was performed by an experienced oral pathologist. Most of the application sites exhibited healthy mucosa throughout the study, and this corresponds well with the pathological reports. One report on the use of the nicotine nasal spray reported similar results following biopsy of the nasal mucosa.[25]

The incidence of oral lesions is higher among smokers than non-smokers,[26] probably as a result of the toxic combustion compounds contained in cigarette smoke. The predominant diagnosis of oral lesions reported in our study was smokers' melanosis, which confirms an earlier report.[27] In our study smoking cessation or a decrease in smoking had a positive impact on baseline mucosal lesions. In summary, the nicotine sublingual tablet did not aggravate any of these pre-existing lesions in the oral mucosa. In the floor of the mouth, however, no lesions were observed at baseline (one patient excluded at baseline due to a leukoplakia), nor did the tablet induce any lesions of clinical importance.

The subjective adverse events experienced during tablet use were mild and tolerable. Thirteen subjects reported a burning/smarting sensation in the mouth, either at the site of application or at the tip of the tongue. Five of these reports occurred in subjects who subsequently developed a lesion, with the burning sensation reported at the visit prior to that at which the lesion was observed. The burning sensation then diminished, and disappeared before the lesion resolved (Table 2), probably because of subject adaptation to the effect of nicotine and mucosal adaptation to the local nicotine concentration.

When recording oral symptoms, subjects ex-

perienced difficulty in distinguishing between soreness either at the site of application or in the surrounding tissue. All adverse events reported in this study have been described previously with nicotine gum use, and are recognized as being nicotine-related,[19,28] with the exception of dry lips (experienced by seven subjects). One reason for this difference may be that previous studies have placed less emphasis on the oral cavity and any specific changes found there. In other studies evaluating the efficacy and safety of NRT, adverse events related to specific body systems usually include any findings in the oral cavity under the major heading of 'gastrointestinal system disorder'. It is possible that dry lips may have previously been recorded as 'dry mouth' and that this may not be a new finding. As dry lips also resolved when treatment discontinued, this particular event may be explained by frequent licking of the lips, thereby exposing the lip surface to nicotine from the dissolved tablet. It may be interesting and worthwhile to list adverse events of the oral cavity under a separate heading in future studies in order to classify such events better.

Conclusion

In conclusion, the sublingual nicotine tablet is a safe administration form of NRT. The tablet had no adverse long-term effect on the oral mucosa; any lesions that did occur were transient and reversible. During the study, the only adverse events reported were mild and tolerable, and reflected those previously ascribed treatment with nicotine gum.

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