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Evaluation of side effects after nicotine nasal spray in patients with chronic rhinitis*

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SUMMARY

Thirty-three subjects with chronic rhinitis used nicotine nasal spray in an open study as an aid in smoking cessation. Thirty-eight percent of them were completely abstinent at 12 weeks, whereas 35% were completely abstinent at 20 weeks. The nasal spray was associated with irritant nasal side effects, which occurred most often in the early stages of treatment. Clinical nasal examinations could not observe any significant impairment in nasal conditions following spray use. In conclusion, this study confirms the short-term safety of the nicotine nasal spray as an aid in smoking cessation.

Key words: chronic rhinitis, nicotine nasal spray

INTRODUCTION

Pharmacologic nicotine dependence is a major problem for smokers attempting to quit and nicotine nasal spray (NNS) was developed to provide a fast acting, flexible form of nicotine replacement therapy. NNS has been shown to approximately double the smoking cessation rates compared with placebo. The most commonly reported adverse effects with NNS are local irritant effects which occur most frequently during the first 48 hours of treatment. The recommended duration of treatment is 3 months, followed by a weaning-off period in which the dose is gradually reduced (Hjalmarson et al., 1994; Sutherland et al., 1992; Schneider et al., 1995). In the earlier performed major clinical trials with NNS, subjects with polyposis, vasomotor or perennial rhinitis and chronic sinusitis were excluded for safety reasons. The aim of this study was primarily to investigate the local nasal effects of NNS in smokers with chronic nasal disorders.

MATERIAL AND METHODS

The study was an open non-randomized study and each subject served as his/her own control. Subjects were recruited through an advertisement in a local newspaper after approval from the local ethical committee. Inclusion criteria were subjects over 18 years old with a well-documented clinical history of chronic rhinitis (polyposis, vasomotor rhinitis, perennial rhinitis) and/or chronic sinusitis, and having smoked 15 cigarettes or more per day for more than 3 years. A total of 40 subjects was motivated to stop smoking and gave informed consent, 17 men and 23 women, aged between 26 and 71, mean age 45. Seven subjects, all women, were withdrawn early due to loss of motivation to continue the study, and the results are therefore based on 33 subjects. They had been smoking for 28 ± 10 years (SD) and smoked regularly 22 ± 6 cigarettes per day. All suffered from chronic rhinitis and 8 of them also had recurrent sinusitis, 20 % regularly used topical nasal corticosteroids during the trial.

Procedure

The subject was examined and routine examinations on the nasal functions were performed: nasal expiratory peak flow (Wihl, 1996), acoustic rhinometry (Grymer et al., 1989), olfactory threshold test with butanol (Cain et al., 1988), and nasal brushing for cytology. The subject was then urged to stop smoking within the next couple of days with the help of NNS (see below). The subject was invited to re-visit the clinic at week 1, week 2, week 6, week 12 and week 20 and the subject's symptoms were registered. Smoking status was confirmed by carbon monoxide (CO) in expired air and compliance was confirmed by cotinine saliva sampling. More than 10 ppm CO categorized the subject as a smoker. At all visits nasal examination, nasal peak flow and acoustic rhinometry were performed and at the final visit in week 20 all examinations were repeated.

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Nasal cytology

Nasal brushings from the middle turbinate on the right side were air-dried and stained by the Giemsa method and the following blind countings were performed by the same pathologist in order to investigate the status of the nasal membrane:

1. Total cellular score (TCS) as defined by Chalon (1974). A score was used to evaluate the morphological integrity of the ciliated cells in nasal smears. The following scoring system was used (one point was given for each factor): presence of cilia, presence of end plate, normal cytoplasmic colour (blue), normal cytoplasmic shape and texture, normal nuclear size, and normal nuclear shape and texture. Two hundred cells of each smear were evaluated, therefore the score could vary from 0 to 1,200 points.
2. Percentage of goblet cells (PGC). The number of goblet cells in relation to all ciliated cells and goblet cells (300 cells counted).
3. Percentage of squamous cells (PSC). The number of squamous cells in relation to all columnar epithelial and squamous cells (300 cells counted).

An improvement in status results in a decrease in PGC and PCS which was the primary evaluation. An improvement in status results in an increase in TCS which was evaluated secondly.

Nicotine nasal spray

The active spray releases 0.5 mg nicotine per 50 µl shot. One dose is defined as two shots, one in each nostril. During the first week subjects were asked to use the spray at least once an hour in order to help them become accustomed to the sensation and master the technique. After the first week the use of the spray was *ad libitum*. They were advised that additional doses might be needed to control the urge to smoke with a maximum of 5 mg nicotine/h (10 shots) and 40 mg/day (80 shots/day). The subjects were asked about adverse events at each visit.

Statistics

Intra-individual changes from baseline values regarding the acoustic rhinometry measurements, the nasal peak flow values and the smell test scorings, were tested with the Wilcoxon signed rank test. Judgements (better, unchanged or worse) of changes in cytology status were evaluated with the two-sided sign test.

RESULTS

Subjects who reported complete continuous abstinence after the first two weeks of treatment were classified as non-smokers provided their carbon monoxide levels were below 10 ppm at endpoint. With this definition, 38 % were successful at the 12 week visit, whereas 35 % were successful at 20 weeks. Average daily doses of NNS decreased from around 15 doses/daily during the first week to about 10 doses daily at week 20. All of the abstinent subjects reported to use the spray regularly at the 6 weeks visit and 79 % still used the spray at the final visit after 20 weeks.

Irritation in the nose was the most frequent side effect of NNS. In Table 1 the frequency of various symptoms after the first week, and the visits at weeks 6 and 20 is illustrated.

Table 1. Frequency of subjective symptoms (%) after nicotine nasal spray during the trial.

Symptoms	week 1	week 6	week 20
nasal irritation	78	51	51
bleeding in the nose	22	21	20
irritation in the throat	62	30	10
sneezing	78	51	65
irritation in the eys	58	18	28
cough	54	27	17
nausea	25	6	10
sweating	47	28	17
headache	47	24	17

Acoustic rhinometry was evaluated by minimal cross sectional area and nasal volume. No clinically significant change of these parameters could be seen during the study as compared to baseline measurements. Nasal expiratory peak flow, however, increased significantly ($p < 0.01$) from initial 249 L/min with 52 L/min.

Smell test

The mean score value decreased with 0.14 threshold steps at the 20-week visit as compared to the baseline. Thus, no statistically significant change in olfactory function was found for this group of subjects following the use of NNS.

Nasal cytology

Nineteen out of 29 evaluable subjects (66 %) showed an improvement in the cytology/cell pattern. Five subjects (17 %) showed no change as compared to the baseline and five subjects showed a worse pattern than at the baseline. None of the subjects that showed a worsening in cell pattern had used extreme amounts of NNS, three subjects had stopped smoking and two were still smoking.

DISCUSSION

The rate of smoking cessation defined as complete abstinence (no slips allowed) from week 2 to endpoint at week 20 was 35 %. This result confirms earlier results from previous studies (Hjalmarson et al., 1994; Sutherland et al., 1992; Schneider et al., 1995). The use of NNS was on high level, also among the abstinent subjects.

The most commonly reported adverse effects of the nasal spray were the local irritant effects which occurred most frequently during the first period of treatment. Such effects were reported by 50-90 % of all subjects in the earlier placebo-controlled studies with the spray (Hjalmarson et al., 1994; Sutherland et al.,

1992; Schneider et al., 1995). The frequency of these effects tends to decrease with time, suggesting that there is some adaptation to them. The findings in the present study indicate that the subjects were more sensitive in the nose, explained by their medical histories.

No serious systemic effects have been reported following the use of NNS. The most common complaints have been headache and dizziness, experienced by 15-20 % of the subjects on starting the treatment but declining to approximately 8 % after 3 weeks (Hjalmarson et al., 1994; Sutherland et al., 1992; Schneider et al., 1995). The results from the present study confirm these findings, the extensive clinical nasal examinations performed could not prove any significant impairment in nasal condition following spray use at the last visit as compared to the baseline.

One earlier study has evaluated the NNS effects on the nasal mucosa after four weeks (Ödkvist et al., 1990). Biopsy samples showed an improvement in the subjects that stopped smoking, but not in those who continued to smoke. It was concluded that the nasal mucosa in smokers do not change when using NNS, but any previous abnormality due to smoking may diminish if the person stops smoking. The cytology in the nasal mucosa in the present study gave no indication of NNS having any negative effect on the mucosa.

Thus, all available information on the use of NNS by smokers trying to quit indicate the safety of the product when used as recommended in the patient information leaflet but also when used for a longer period of time. In conclusion, extensive examinations of 33 evaluable subjects (following 6 weeks' usage; 29 subjects following 20 weeks usage) with chronical nasal illnesses, confirm the safety of the nicotine nasal spray as an aid in smoking cessation. Furthermore, NNS is an effective help for subjects with chronic rhinitis/sinusitis in smoking cessation.

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Table 2. The results of nasal cytology after 20 weeks. Most subjects reacted positively to total cellular score (TCS), percentage of goblet cells (PGC) and percentage of squamous cells (PSC).

	better	worse
TCS	55 %	17 %
PGC	59 %	28 %
PSC	52 %	31 %

REFERENCES

1. Cain WS, Gent FG, Goodspeed RB, Leonard GL (1988) Evaluation of olfactory dysfunction in the Connecticut Chemosenory Clinical Research Center. Laryngoscope 98: 83-88.
2. Chalon J (1974) Changes in tracheobronchial cytology noted during anesthesia. NY State J Med 2185-2189.
3. Grymer LF, Hilberg O, Elbrönd O, Pedersen OF (1989) Acoustic rhinometry: evaluation of the nasal cavity with septal deviations, before and after septoplasty. Laryngoscope 99: 1180-1187.
4. Hjalmarson A, Franzon M, Westin Å, Wiklund O (1994) Effect of Nicotine nasal spray on smoking cessation. A randomized, placebo-controlled, double-blind study. Arch Int Med 154: 2567-2572.
5. Ödkvist LM, Hjalmarson A, Hellqvist H, Arheden L (1990) A morphological study on nasal mucosa in subjects using nasal nicotine solution in smoking cessation. In: T Sacrist†n, JJ Alvarez-Vicent, J Bartual, F Antolí-Candela et al. (Eds.) . Proceedings of the XIV World Congress of Otorhinolaryngology, Head and Neck Surgery. Kugler & Ghedini Publications, Amsterdam, Berhely, Milano, pp. 1583-1587.
6. Schneider NG, Olmstead R, Mody FV, Doan K, Franzon M, Jarvik ME, Steinberg C (1995) Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. Addiction 90: 1671-1682.
7. Sutherland G, Stapleton JA, Russell MA (1992) Randomized controlled trial of nasal nicotine spray in smoking cessation. Lancet 340: 324-329.
8. Wihl JÅ (1996) Assessment of nasal hyperactivity. Thesis, University of Lund, Sweden.

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