Acute Effects of Transdermal Nicotine on Sleep Architecture, Snoring, and Sleep-disordered Breathing in Nonsmokers

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Previous research has suggested that nicotine may be therapeutically useful in the treatment of sleep-disordered breathing. The development of transdermal nicotine delivery systems has allowed us to test the overnight effectiveness of nicotine. Twenty nonsmoking subjects (10 men, 10 women) were recruited on the basis of a history of habitual snoring that was confirmed by overnight laboratory monitoring. Subjects were then randomized (double-blind crossover design) to receive either placebo or an active patch that delivers 11 mg of nicotine over a 24-h period. Patches were applied at 6 P.M. and removed at 6 A.M. the following morning, at which time venous blood was obtained for determination of serum nicotine concentrations. Polysomnography was performed using standard techniques to assess sleep architecture and sleep-disordered breathing. Snoring was monitored with a sound-level meter and quantitatively analyzed to determine the snoring index (SI) (number of snores per hour of sleep) and mean and maximum snoring intensities. The age of the subjects was 46.9 ± 11.4 yr (mean ± SD) and their mean body mass index (BMI) 33.3 ± 4.6 kg/m^2. A mean nicotine level was nondetectable with placebo and 7.8 ± 2.3 ng/ml with wearing of an active patch. Nicotine decreased total sleep time (TST) by 33 min ($p \leq 0.01$), sleep efficiency from 89.7 to 83.5% ($p \leq 0.01$), and percent rapid eye movement (REM) sleep from 18.8 to 15.1% ($p \leq 0.01$), and prolonged initial sleep latency (ISL) from 6.7 to 18.2 min ($p \leq 0.01$). No significant changes in non-rapid eye movement (NREM) sleep stages 1, 2, 3–4, or arousal index were detected. Although the SI was unchanged (602 ± 177 versus 607 ± 205/h), mean snoring intensity decreased by 1.1 dB, $p \leq 0.01$, with nicotine. A 1.4-dB reduction in maximum snoring intensity with nicotine was not significant. Although the decrease in disordered-breathing-event (DBE) frequency from 13.6 ± 15.4 to 11.4 ± 12.5/h with nicotine was not significant, a highly significant negative correlation ($r = -0.71$, $p \leq 0.001$) was detected between nicotine level and DBE duration during the active-patch night. In addition, lowest Spo_2 was positively correlated ($r = 0.52$, $p \leq 0.05$) with serum nicotine level. Nausea and emesis were the predominant side effects and were experienced by 50 and 20% of the subjects, respectively. In conclusion, transdermal nicotine significantly disrupted sleep architecture and produced no clinically significant improvements in either snoring or sleep-disordered breathing in this group of 20 nonsmoking snorers with mild sleep-disordered breathing. Increasing levels of nicotine were associated with a shorter DBE duration and less severe reductions in lowest Spo_2. **Davila DG, Hurt RD, Offord KP, Harris CD, Shepard JW Jr. Acute effects of transdermal nicotine on sleep architecture, snoring, and sleep-disordered breathing in nonsmokers. Am J Respir Crit Care Med 1994;150:469–74.**

Snoring and sleep-disordered breathing are two common conditions that disrupt the quality of sleep in bedmates and individuals, respectively. Between 3 and 31% of the adult population are habitual snorers (1). In men and women between the ages of 41 and 61 yr, the prevalence of snoring may reach 60% in men and 40% in women (2). Obstructive sleep apnea (OSA) is thought to affect from 1 to 6% of the working male population, with estimates ranging between 26 and 42% in the elderly (3, 4). Both conditions are thought to result in part from the sleep-related narrowing and collapse of pharyngeal tissues.

Nasal continuous positive airway pressure (CPAP), which prevents airway narrowing and collapse, is currently the treatment of choice for clinically significant OSA, and is equally effective for snoring (5, 6). However, this mechanical system is cumbersome, not tolerated by 20 to 40% of patients (7, 8), and generally not indicated for snoring alone (9). Weight loss, avoidance of sedatives, and maintenance of nasal patency are palliative measures that are appropriate for some individuals, but do not reliably af-

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fect snoring and apnea. Devices, such as oral prostheses, have been tried with mixed results (9).

Pharmacologic treatment in the form of ventilatory stimulants has been employed in the treatment of snoring and OSA in an attempt to increase upper-airway muscle tone sufficiently to prevent pharyngeal narrowing and collapse (10–15). Most such treatments, however, have met with limited success, either because of minimal efficacy or excessive toxicity. In animal studies, nicotine has been shown to increase muscle tone and decrease resistance to airflow in the upper airway (16–18). In eight human subjects with OSA, Gothe and colleagues (19) reported that 14 mg of nicotine gum chewed over a 6-h period prior to bedtime significantly decreased obstructive, mixed, and total apneas as compared with a control night. Because of the rapid elimination of nicotine, only the initial 2 h of sleep were compared for the nicotine and control nights. Although no differences in central apneas, sleep architecture, or arousal frequencies were detected, oxyhemoglobin saturation was increased during sleep in seven of eight subjects following nicotine administration. Snoring variables and nicotine levels were not measured during the study.

The development of the transdermal nicotine patch permits the delivery of nicotine over the time the patch is applied (20). This delivery system makes therapy with the drug pharmacologically possible throughout the nocturnal sleep period. We hypothesized that if an adequate serum nicotine concentration could be delivered throughout sleep, a sustained increase in upper-airway muscle tone, stability, and patency could be achieved. Therefore, the present study was conducted to determine whether a single dose of transdermally delivered nicotine would decrease the severity of snoring, sleep-disordered breathing, or both in a group of nonsmoking snorers.

METHODS

Subjects

Snoring subjects in good general health were recruited by public advertisement to participate in a study of the effects of transdermally delivered nicotine on sleep and snoring. Respondents were between the ages of 28 and 70 yr and willing to abstain from alcohol and caffeinated beverages during the study. Respondents were excluded if they had a medical condition that was known to specifically affect sleep (exceptions: nasal obstruction, snoring, or OSA), were taking any medications known to significantly affect sleep, were current smokers, or consumed more than two alcoholic or four caffeinated beverages per day on average. All subjects signed written informed consent documents prior to participating in this study, which was approved by the Mayo Clinic Institutional Review Board. A total of 24 subjects were entered into the study.

Protocol

The first night of study served as an adaptation night as well as a screening night to ensure that all subjects snored with a frequency of more than 60 snores per hour of sleep. Overnight polysomnography was performed using a multichannel polygraph (Model 78-D; Grass Instruments, Inc., Quincy, MA) to record electroencephalographic (EEG) activity from three lead locations (C_3–A_2 or C_4–A_1, F_z–C_z, O_z–C_z), electromyographic (EMG) activity of the submental and anterior tibialis muscles, and electrooculographic (EOG) activity. Pulse oximetry (Biox 3700; Ohmeda, Louisville, CO) was used to monitor oxyhemoglobin saturation (Spo_2). Oral and nasal airflow were monitored with thermocouples, thoracoabdominal movement by inductive plethysmography (Respitrace; Ambulatory Monitoring, Inc., Ardsley, NY), and electrocardiographic (ECG) activity by bipolar chest leads. Sleep architecture was scored in 30-s epochs according to standard scoring criteria (21). The scoring was separated into the two sleep position categories of on-back and off-back. The percentage of sleep observed in each sleep stage was computed as a proportion of total sleep time.

An apnea was defined as a cessation in airflow lasting 10 s or more. Hypopnea was defined as a decrease in oxyhemoglobin saturation of 2% or more, associated with a qualitative reduction in airflow. The disordered-breathing-event (DBE) index was calculated using the following formula: total number of apneas plus hypopneas observed/total sleep time. The DBE index was calculated for the two sleep-position categories of on-back and off-back.

Snoring was recorded using a microphone (Model EM-23; Quest, Oconowoc, WI) that was secured in an ADAM circuit CPAP headstrap system at the level of the nasion and placed in-line with an impulse sound-level meter (Model 2700; Quest, Oconowoc, WI). Standard calibration procedures were followed using a sound generator (Model CA-12B; Quest, 110 dB-1000 Hz). The sound-level signal was recorded directly on the polysomnographic record as well as on a Macintosh IIcx computer using LabVIEW 2 (National Instruments Corp., Austin, TX). LabVIEW 2 was used to develop a program to record, display, and analyze snoring. Criteria employed to identify episodes of sound as a snoring event included an intensity greater than 50 dB, duration greater than 0.3 s but less than 10 s, and time interval of more than 0.5 s between sounds. The accuracy of this custom-designed instrument was tested and found to be within 3% of a manually counted frequency and within 1 to 2 dB using a standard sound-level meter. Snoring index (SI) was computed as the number of snores per sleep hour. In addition, mean and maximal dB levels were computed, along with standard deviations and the coefficient of variation in snoring intensity.

Upon completion of the screening-adaptation night, two subjects were eliminated for insufficient snoring. A third subject's participation was terminated for beginning a new medication (lithium carbonate), and a fourth participant who was accepted into the patch phase of the study voluntarily withdrew.

The remaining 20 subjects (10 men and 10 women) advanced into and completed the double-blind crossover patch phase of the study. A balanced randomization procedure was used to ensure that five men and five women each received the placebo patch on study Night 2 and the active nicotine containing patch on study Night 3. The remaining five men and five women received the active patch on Night 2 and placebo patch on Night 3. Neither the subjects nor the investigators were aware of the randomization order. The active and placebo patches were applied at 6 P.M., approximately 4 h before bedtime. All patches were removed 12 h later, at 6 A.M. Venous blood was obtained at the time of patch removal for measurement of the serum nicotine concentration. Nicotine levels were measured by gas chromatography/mass spectrometry using a deuterated nicotine internal standard. The active patch contained 15 mg of nicotine and delivered 11 mg of nicotine over a 24-h period (Elan Pharmaceutical Research Corp., Gainesville, GA).

Data Analysis

Descriptive statistics were prepared and comparisons made analyzing the order effect and active-patch versus placebo differences (22). Active-patch versus placebo-night comparisons were made using the nonparametric signed-rank test. Linear and rank correlations were computed to assess relationships between sleep, snoring, sleep-disordered breathing variables, and serum concentrations of nicotine. Two-tailed p values ≤ 0.05 were considered evidence of a significant difference. Data are presented as mean ± SD.

RESULTS

The anthropomorphic data for the men and women enrolled in the study are presented in Table 1. Sleep architecture was similar for the men and women, Table 2, with the exception that women spent more time in NREM stages 3–4 than did men under both placebo (23.0 ± 5.3% versus 15.3 ± 7.1%, $p \leq 0.01$) and active-patch (23.7 ± 6.5% versus 12.6 ± 9.3%, $p \leq 0.01$) conditions. No significant differences were detected in SI or the mean or maximum intensity of snoring between men and women. Although there were no gender differences in snoring, the DBE index was greater in the men (16.0 ± 19.2 versus 11.2 ± 10.7 DBE/h, $p \leq 0.05$) dur-

TABLE 1

INDIVIDUAL AND MEAN ANTHROPOMORPHIC, DISORDERED BREATHING INDEX, AND NICOTINE LEVEL IN 10 MEN AND 10 WOMEN SNORERS

	Age (*yr*)	Height (*m*)	BMI (kg/m^2)	DBE Index, (*DBE*)		Nicotine level (*ng/h/ml*)	
				Placebo	Active	Placebo	Active
Men							
1	34	1.70	25.6	3.0	6.0	< 3.0	5.4
2	42	1.73	31.5	59.0	36.0	< 3.0	4.4
3	58	1.73	33.4	3.0	5.0	< 3.0	4.7
4	39	1.79	35.1	0.0	0.0	< 3.0	10.7
5	42	1.94	30.6	38.0	44.0	< 3.0	8.9
6	42	1.69	32.9	13.0	8.0	< 3.0	10.6
7	62	1.71	29.9	11.0	34.0	< 3.0	6.6
8	66	1.81	24.9	4.0	6.0	< 3.0	3.4
9	47	1.73	32.7	25.0	16.0	< 3.0	6.5
10	57	1.67	37.8	4.0	5.0	< 3.0	5.8
Mean	48.9	1.75	31.4	16.0	16.0	< 3.0	6.7
SD	10.9	0.08	4.0	19.2	15.9		2.6
Women							
1	46	1.70	29.0	3.0	1.0	< 3.0	8.4
2	38	1.65	35.6	12.0	7.0	< 3.0	9.0
3	49	1.64	39.7	22.0	21.0	< 3.0	9.0
4	57	1.54	30.7	37.0	4.0	< 3.0	9.0
5	47	1.73	33.7	12.0	6.0	< 3.0	9.4
6	41	1.74	32.9	6.0	9.0	< 3.0	11.6
7	38	1.74	42.3	7.0	5.0	< 3.0	5.6
8	35	1.71	36.3	5.0	5.0	< 3.0	8.5
9	28	1.67	40.6	5.0	5.0	< 3.0	8.4
10	70	1.71	30.0	3.0	4.0	< 3.0	9.3
Mean	44.9	1.68	35.1	11.2	6.7	< 3.0	8.8
SD	12.0	0.06	4.6	10.7	5.4		1.5

TABLE 2

NICOTINE AND POLYSOMNOGRAPHIC DATA FOR PLACEBO VERSUS ACTIVE PATCH

	Women		Men	
	Placebo	Active	Placebo	Active
Nicotine level, ng/ml	< 3.0	8.8 ± 1.5*	< 3.0	6.7 ± 2.6*
Sleep architecture				
Total sleep time (TST), min	371 ± 34	349 ± 51	385 ± 37	342 ± 43
Sleep efficiency (TST/TIB), %	90.3 ± 10.0	83.8 ± 12.3	89.1 ± 4.3	83.1 ± 6.2
Initial sleep latency (ISL), min	5.6 ± 6.5	15.4 ± 23.3	7.8 ± 6.2	20.7 ± 14.9
Initial REM latency (IRL), min	82.0 ± 19.7	86.2 ± 41	72.8 ± 37.2	76.7 ± 36.2
NREM stage 1, % of TST	8.2 ± 3.9	8.4 ± 4.2	8.2 ± 4.6	10.7 ± 4.2
NREM stage 2, % of TST	51.0 ± 4.1	52.5 ± 10.8	57.0 ± 8.6	61.8 ± 9.6
NREM stage 3–4, % of TST	23.0 ± 5.3	23.7 ± 6.5	15.3 ± 7.1	12.6 ± 9.3
REM, % of TST	18.1 ± 3.3	15.3 ± 6.7	19.6 ± 4.0	14.8 ± 4.4
Arousal index (Arl), n/h	19.3 ± 5.6	18.8 ± 8.0	20.9 ± 14.6	29.2 ± 22.4
PLM index, n/h	5.5 ± 9.8	5.6 ± 9.8	14.1 ± 16.6	13.2 ± 22.2
Snoring				
Snoring index, n/h	605 ± 207	635 ± 229	600 ± 154	580 ± 186
Mean intensity, dB	60.8 ± 3.2	60.1 ± 3.1	63.5 ± 4.1	62.0 ± 4.1
Maximum intensity, dB	81.8 ± 5.6	80.2 ± 6.9	84.2 ± 6.7	83.0 ± 8.9
Disordered breathing				
Cental apnea index, n/h	0.3 ± 0.9	0.2 ± 0.4	0.3 ± 0.7	0.3 ± 0.5
Obstructive apnea index, n/h	3.9 ± 8.3	1.2 ± 2.3	6.0 ± 8.8	5.6 ± 10.0
Hypopnea index, n/h	6.9 ± 3.5	5.3 ± 4.0	9.4 ± 11.2	10.2 ± 10.8
DBE index, nDBE/h	11.2 ± 10.7	6.7 ± 5.4	16.0 ± 19.2	16.0 ± 15.9
DBE duration, s	17.7 ± 3.7	16.2 ± 2.9	18.4 ± 4.9	18.6 ± 5.1
Mean Spo_2%	92.7 ± 1.8	92.7 ± 2.1	91.9 ± 1.8	92.5 ± 1.2
Lowest Spo_2%	84.2 ± 7.0	83.1 ± 6.3	80.9 ± 7.2	79.2 ± 8.1

Definition of abbreviations: TIB = time in bed; PLM = periodic leg movement; DBE = disordered breathing events; Spo_2 = oxyhemoglobin saturation by pulse oximetry.

Data are mean ± SD.

* $p < 0.001$.

ing the placebo condition. A trend toward an increased DBE index was also observed for the men compared with the women during the active-patch night (16.0 ± 15.9 versus 6.7 ± 5.4 DBE/h, $p = 0.10$).

Nicotine levels were undetectable in both men and women during placebo and were significantly increased on the active-patch night (range, 3.4 to 11.6 ng/ml). Although serum nicotine levels were greater in women than men (8.8 ± 1.5 versus 6.7 ± 2.6 ng/ml, $p \leq 0.05$), they were not significantly correlated with age, height, weight, or BMI. No significant differences in sleep architecture, snoring, or sleep-disordered breathing were detected between placebo and active-patch nights for either gender group.

Effects of Nicotine on Sleep Architecture (Combined Group)

Because of these findings, the data for both gender groups were combined and the results are presented in Table 3. With the added statistical power provided by 20 subjects, several significant effects were detected. For the total group, the active patch was associated with a significant 33-min reduction in TST ($p \leq 0.01$). Because time in bed was unchanged, nicotine decreased sleep efficiency from 89.7 to 83.5% ($p \leq 0.01$). The reduction in TST was due in part to a significant prolongation of ISL from 6.7 to 18.1 min ($p \leq 0.01$). Percent REM sleep was found to decrease from 18.8 to 15.1% of TST with nicotine, $p \leq 0.01$, but no significant changes in NREM stages 1, 2, or 3–4 were detected. Nicotine had no significant effect on arousal index, periodic-leg-movement (PLM) frequency, or the percent of PLMs associated with arousal.

Effects of Nicotine on Snoring (Combined Group)

Although nicotine failed to decrease snoring frequency, mean snoring intensity was significantly reduced by 1.1 dB ($p \leq 0.01$). Maximum snoring intensity showed a similar small decrease of 1.4 dB, but this was not statistically significant. To determine whether or not nicotine would affect the variability in snoring intensity, coefficients of variation in snoring intensity were compared and found not to differ between placebo and active-patch nights. In addition, no significant correlations between serum nicotine levels and snoring frequency, intensity, or variability were detected.

TABLE 3

EFFECTS OF NICOTINE ON SLEEP ARCHITECTURE AND SNORING IN THE COMBINED GROUP OF 20 SNORERS

	Placebo	Nicotine	p Value
Nicotine level, ng/ml	< 3.0	7.8 ± 2.3	0.0001
Sleep architecture			
Time in bed (TIB), min	422 ± 35	414 ± 39	NS
Total sleep time (TST), min	378 ± 35	345 ± 46	0.006
Sleep efficiency (TST/TIB), %	89.7 ± 7.5	83.5 ± 9.5	0.007
Initial sleep latency (ISL), min	6.7 ± 6.3	18.1 ± 19.2	0.002
Initial REM latency (IRL), min	77.4 ± 29.4	81.5 ± 38.0	NS
NREM stage 1, % of TST	8.2 ± 4.2	9.6 ± 4.3	NS
NREM stage 2, % of TST	54.0 ± 7.3	57.2 ± 11.1	NS
NREM stage 3–4, % of TST	19.0 ± 7.3	18.2 ± 9.6	NS
REM, % of TST	18.8 ± 3.6	15.1 ± 5.5	0.007
Arousal index (Arl), n/h	20.1 ± 10.8	24.0 ± 17.2	NS
PLM index, n/h	9.8 ± 14.0	9.4 ± 17.1	NS
Snoring			
Snoring index, n/h	602 ± 177	607 ± 205	NS
Mean intensity, dB	62.2 ± 3.9	61.1 ± 3.7	0.009
Maximum intensity, dB	83.0 ± 6.1	81.6 ± 7.9	NS
Intensity, %CV*	9.7 ± 2.2	9.3 ± 2.6	NS

Definition of abbreviations: PLM = periodic leg movement; CV = coefficient of variation.
Data are mean ± SD.

Effects of Nicotine on Sleep-Disordered Breathing (Combined Group)

The effects of nicotine on sleep-disordered breathing are presented in Table 4. On placebo, the group as a whole exhibited a mildly elevated total DBE index of 13.6 ± 15.4 DBE/h (range, 0 to 59 DBE/h). These events included predominantly hypopneas (60% of total DBEs), followed by obstructive apneas (37%), and only a small number of central apneas (3%). Nicotine produced no significant changes in the frequency of hypopneas, central apneas, obstructive apneas, or the total DBE index.

When classified according to sleep position, the DBE indices were from three to fivefold greater in the on-back as compared with the off-back position. When classified according to sleep stage, DBE indices were one to twofold greater during REM than NREM sleep. Although significant effects of position and to a lesser extent sleep stage existed, nicotine did not alter the DBE index in any subclass of sleep stage or position.

In the paired active-patch-versus-placebo analysis, DBE duration was not decreased with nicotine. However, a highly significant correlation ($r = -0.71$, $p \leq 0.001$) was detected between nicotine concentration and mean DBE duration on the active-patch night (Figure 1). There was a significant correlation ($r = 0.52$, $p \leq 0.05$) between serum nicotine concentration and lowest Spo_2. Mean Spo_2 during sleep was unchanged by the nicotine patch, and no significant correlation with serum nicotine was detected.

A subgroup analysis was performed to examine the effect of nicotine in subjects with high (DBE index > 10 DBE/h) versus low (DBE index < 10 DBE/h) levels of sleep-disordered breathing. The nine snorers (five men, four women) with a DBE index > 10 DBE/h with placebo showed a small but nonsignificant decrease in DBE index with nicotine (25.4 ± 16.4 versus 19.6 ± 15.0 DBE/h). Similarly, there were no significant changes in SI (601 ± 190 versus 624 ± 213/h) or mean snoring intensity (63.7 ± 4.9 versus 62.0 ± 4.6 dB) with nicotine in this subgroup. The 11 snorers (five men, six women) in the subgroup with a DBE index < 10 DBE/h with placebo also failed to show any significant changes in DBE index, snoring index, or mean snoring intensity on the active-patch night.

Side Effects of Nicotine

The side effects reported with both the placebo and active patches are presented in Table 5. Nausea was the predominant side effect and was exclusively associated with the active patch. Ten (50%) of the subjects (four men and six women) experienced nau-

TABLE 4

EFFECTS OF NICOTINE ON SLEEP DISORDERED BREATHING IN THE COMBINED GROUP OF 20 SNORERS

	Placebo	Nicotine	p Value
Cental apnea index, n/h	0.3 ± 0.8	0.3 ± 0.4	NS
Obstructive apnea index, n/h	5.0 ± 8.4	3.4 ± 7.4	NS
Hypopnea index, n/h	8.2 ± 8.2	7.8 ± 8.3	NS
DBE index, n/h			
Total	13.6 ± 15.4	11.4 ± 12.5	NS
NREM on back	28.3 ± 33.9	24.9 ± 29.9	NS
NREM off back	6.0 ± 13.2	5.2 ± 10.2	NS
REM on back	32 ± 41.5	29.4 ± 38.9	NS
REM off back	9.7 ± 17.4	10.5 ± 19.6	NS
DBE duration, s	18.1 ± 4.2	17.4 ± 4.2	NS
Mean Spo_2	92.3 ± 1.8	92.6 ± 1.6	NS
Lowest Spo_2	82.6 ± 7.1	81.2 ± 7.3	NS

Definition of abbreviations: DBE = disordered breathing events; Spo_2 = oxyhemoglobin saturation by pulse oximetry.
Data are mean ± SD.

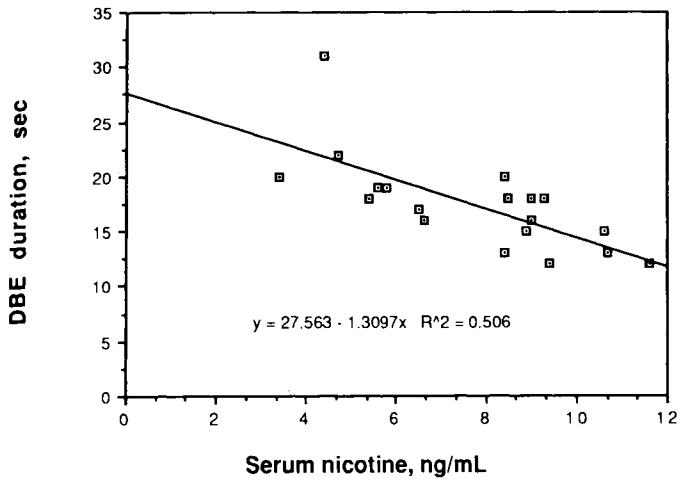

Figure 1. Plot of serum nicotine level against mean DBE duration on active-patch night.

TABLE 5

REPORTED SIDE EFFECTS WITH PLACEBO AND ACTIVE (NICOTINE) PATCHES IN 10 MEN AND 10 WOMEN

Symptom	Men (P/A)	Women (P/A)
Headache	0/1	5/3
Lightheadedness	0/2	2/3
Local irritation	1/0	0/2
Nausea	0/4	0/6
Sweating	0/1	1/2
Tremor	0/0	0/1
Vomiting	0/1	0/3
Dropped out	0	1

* P/A = placebo/active or nicotine patch; each value represents the number of participants who experienced the symptom.

sea. This was of sufficient severity to be associated with emesis in four subjects.

DISCUSSION

The results of the present study indicate that the acute administration of nicotine to nonsmoking snorers has adverse effects on sleep architecture. The reduction in TST and sleep efficiency was attributable to an increase in both ISL and waking after sleep onset. This effect is consistent with the known stimulant effects of nicotine and data documenting increased catecholamine release following nicotine administration (23, 24). Soldatos and colleagues (25) found that active smokers had decreased sleep efficiency due to increased ISL and waking after sleep onset as compared with age- and sex-matched nonsmoking controls. In addition, a subgroup of eight smokers studied immediately after smoking cessation demonstrated a significant decrease in ISL. In combination, these results suggest that elevated serum levels of nicotine (either acute or chronic) are associated with increased alertness, prolonged ISL, and decreased sleep efficiency. In the present study we also detected a decrease in percent REM sleep on the active-patch night. This preliminary finding is of interest because cholinergic mechanisms are known to be important to the generation of REM sleep (26). Although chronic smokers have shown no reduction in REM sleep as compared with control subjects, a small increase in percent REM sleep has been reported following smoking cessation (25).

Nicotine administration decreased mean snoring intensity from 62.2 ± 3.9 to 61.1 ± 3.7 dB ($p = 0.009$), but did not change snoring frequency. Although the human ear is capable of detecting a difference in sound pressure level of 0.5 dB during wakefulness (27), the 1.1-dB reduction in snoring intensity found in our study is considered unlikely to be clinically important. The intensity of the sound generated depends on the complex interaction of multiple variables that include the pressure generated across the pharynx as well as the shape, resistive, and compliance characteristics of the tissues of the upper airway. Because upper-airway muscle activity, resistance, and transpharyngeal pressures were not directly measured, our data do not allow us to determine the relative roles of muscle activity (EMG), resistance, or respiratory effort (transpharyngeal pressure) in the small decreases in mean intensity that we observed. A second factor that affects the perception of snoring is the frequency spectrum of the sound produced. The human ear is most sensitive to sounds between 2,000 and 5,000 Hz, and higher sound pressure levels (dB) are required at lower frequencies in order for them to be perceived as equally loud. Snoring sounds generally consist of a mixture of frequencies ranging from 60 to 10,000 Hz (28). Although snoring loudness was decreased only slightly with nicotine, it is possible but unlikely that a shift in the frequency of snoring sounds could have occurred that would have decreased the perception of snoring by listeners. Frequency (spectral) analysis was not performed in this study.

The results of the present study failed to document a clinically beneficial effect of nicotine on sleep-disordered breathing. This negative result is in contrast to the reduction in obstructive, mixed, and total apneas reported by Gothe and colleagues (19). Differences in study design and subject groups (snorers versus OSA) may have accounted for the discrepant results. In the present study, a transdermal nicotine delivery system was employed. This patch, which contains 15 mg of nicotine, delivers 11 mg over a 24-h period. With its use, serum nicotine concentrations approach 75% of maximal values 4 h after patch application, with peak concentrations being achieved at 8 h (20). Thereafter, serum levels decline slowly. Consequently, the serum level measured at the end of the sleep study (i.e, 12 h after application) should have closely approximated the mean serum concentration and remained relatively constant throughout the nocturnal sleep period. In contrast, the subjects studied by Gothe and colleagues were studied after chewing gum containing a total dose of 14 mg of nicotine. Because serum levels of nicotine peak within 5 to 10 min of chewing nicotine gum, decline with a half-life of approximately 0.5 h over the next 30 min (tissue-distribution phase), and then decline with a half-life of about 2 h (23, 25), these subjects were studied during a non-steady-state period of declining serum nicotine concentration.

The finding of a DBE index exceeding 10 DBE/h in nine (45%) of the 20 snoring subjects was not unexpected, since previous studies of habitual snorers have found that 35 to 64% may have clinically occult OSA (29–31). Although there were no significant changes in the DBE indices with nicotine compared with placebo, dose-related effects of nicotine were detected on the active-patch night. Increasing serum concentrations of nicotine were significantly associated with decreases in DBE duration and increases in lowest Spo_2. Because no difference in DBE frequency was detected, these results suggest that higher serum concentrations of nicotine may lower the arousal threshold and thereby decrease DBE duration, which in turn would diminish the decrease in Spo_2.

Among individual subjects, serum nicotine was uniformly undetectable at the end of the placebo patch night, confirming abstinence from other sources of nicotine. In those subjects who received the active patch on the first night, 16 h elapsed before the start of the second night of polysomnography with the placebo patch. Since this would have allowed approximately eight half-

lives for the clearance of nicotine, it is unlikely that any significant level of nicotine was present to exert a carryover effect. Despite the low levels of serum nicotine among the nonsmokers relative to smokers in this study, the nonsmoking subjects experienced substantial gastrointestinal side effects. Interestingly, these symptoms were experienced within 1 to 4 h of active-patch application, when serum levels of nicotine would not have been maximal. Tolerance to nicotine is known to develop rapidly, and this is probably the reason that these side effects did not persist throughout the night (32).

In this study, an 11-mg nicotine patch was used because prior experience has indicated that a 22-mg patch would produce intolerable side effects when acutely administered to nonsmokers. In a group of 24 smokers, serum nicotine levels averaged 25 ng/ml on admission to a smoking-cessation program and decreased to a stable trough level of 12 ng/ml upon treatment with a 22-mg transdermal nicotine patch each day (33). These results indicate that the mean nicotine level of 7.8 ± 2.3 mg/ml in the present study is well below levels that can be obtained with chronic dosing. Whether snoring and sleep-disordered breathing would respond to higher serum concentrations of nicotine with chronic administration remains a matter of speculation.

In summary, the transdermal administration of nicotine to 20 nonsmoking snorers resulted in significantly disrupted sleep architecture but no clinically significant effects on either snoring or the frequency of sleep-disordered breathing. DBE duration decreased and lowest Spo_2 increased in association with increasing serum concentrations of nicotine. Despite the achievement of relatively low serum nicotine levels, there were frequent gastrointestinal side effects in this group of nonsmokers acutely exposed to nicotine.

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