

THE EFFECT OF NASAL APPLICATION OF ASONOR AND POLYGLYCOSIDE 80 ON SNORING AND SLEEP APNEA

A double blind controlled study and an acceptance study

By

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Document Log: Address information updated, the abbreviation P-80 is corrected to the full name (Polysorbate or P-80), the full composition incl. the Asonor preservative is disclosed exclusive g/30ml.

SUMMARY

Earlier small, open human and animal studies have indicated, that nasal application of long acting polyglycols might reduce snoring. In order to characterize the effect of Asonor and polysorbate 80 (P-80), a long acting tissue-lubricating polyglycols, on snoring and sleep apnea, two studies were performed: 1) a double blind controlled study with 50 every-night snorers, and 2) an open acceptance study with 218 every night snores.

218 male, self-reported every-night snorers, age 50-65, participated in an open, acceptance study with a daily use of 1.2 mg Asonor. All participants were instructed to use Asonor freely. After 6 months 67.9% were still using Asonor. A significant improvement in self or bed-partner reported snoring, and a significant improvement in sleep quality, daytime tiredness and sleepiness were observed compared to baseline values.

In the double blind controlled study, 50 every-night male snorers, age 50-65 were included. All were using a nasal application of 1.2 mg Asonor every night or a control preparation which was of a chemical exact the same composition, but without P-80. No differences were found in self-reported snoring, in bed-partner reported snoring, in sleep quality, daytime symptoms or in laryngeal sound measurements between the polysorbate 80 and the control period. The respiratory parameters Respiratory Distress Index (RDI) and Respiratory Time Index (ATI) (both: apnea + hypopnea) were slightly reduced during the treatment nights, but no differences was found compared to the control solution.

The study shows, that nasal installation of a solution of Asonor improves snoring in an open study.

The effect of nasal installation of lubricating agents on snoring can probably not be related to P-80 alone in humans.

Side effects are minimal and no serious side effects were observed. No differences in the side effects were observed between the control or the ASONOR treated group.

Key words

Snoring, snoring sounds, frequency analysis, respiratory pattern, methods, computing, inductive plethysmography, treatment, nasal resistance, lubricating agents, polyglycols, surfactans

INTRODUCTION

Epidemiological studies have shown, that snoring is very prevalent in the adult population. Snoring is more common among men and increases with age, until the age of 60-70. Snoring has been found to imply social and family welfare (difficulties in maintaining work, family problems, e.g. because of separate bed rooms, hypersomnia, sexual dysfunction). Snoring has been found to be a risk factor for cardiovascular and cerebrovascular disorders and complications, including high blood pressure, angina pectoris, myocardial and cerebral infarction (1-5).

Surgical treatment (UvuloPalatoPharyngoPlastic (UPPP), Mandibular advancement e.g.) are effective in some patients but are associated with operative and postoperative complications and risk for side effects. Nasal CPAP (Continuous Positive Airway Pressure) is very effective in reducing sleep apnea in patients suffering from severe sleep apnea, but most people suffering from simple snoring do not accept this treatment. Non-surgical and non-CPAP interventions, e.g. position training, tongue or dental devices have been found to be able to reduce snoring in some patients but their use has been debated and disputed (6, 7). Because most of the snorers does only have "simple snoring" any simple treatment of the snoring problem are of major interest.

In 1987 new data showed that nasal application of tissue-lubricating agents might reduce snoring in humans (8, 9) and in dogs as well (10) probably because of increased inspiratory muscular tone in the upper airway muscles and by reduced nasal and pharyngeal resistance. The human studies relied on small (8) or open (9) studies and further controlled studies with objective measurements were needed in order to characterize: 1) the subjective effect of nasal application of Asonor and P-80, 2) the snoring and respiratory changes associated with nasal application of Asonor and P-80, and 3) the acceptance rate, subjective well-being and possible side effect in an open, non-controlled study.

Asonor and P-80 was used in the former studies, and was not associated with any major side effects. The Asonor solution contained P-80 and the control solution contained Asonor without P-80 (table 1). The dosis used was 4 drops in each nostril from a bottle containing 30 ml. The daily dosis of Asonor was 1.2 mg. The drug was supplied from Boehringer Ingelheim, Germany.

SUBJECTS AND METHODS

Study population

The study population was selected from a large-scaled epidemiological study performed in 1986 in the Copenhagen area involving 3439 men, age 50-75 (5). Of those 49.9% reported every night or nearly every night snoring according to the questionnaire. 550 were selected by the following criteria:

1. Age 50-65,
2. Every night snoring according to the questionnaire
3. Abnormal ENT-findings, acute nasal allergies, alcoholism,

abuse of sleeping tablets, major cardiovascular, cerebrovascular and psychiatric diseases were exclusion criteria.

Controlled and stable cardiovascular diseases were accepted. Former cerebrovascular disorders were excluded.

All persons were invited by postal invitation. Of the 550 invitations 278 accepted entry into the study and were found to fulfill the inclusion criteria. This population was divided in 224 persons to the acceptance study and 54 persons to the controlled study.

All were invited to the hospital. A standardized questionnaire was given. All participants underwent a general physical examination and a otolaryngological examination. Blood pressure was measured on the left arm after at least 10 minutes at rest in sitting position. Weight and height were determined and body mass index (BMI) was calculated using Quetelets index (weight / height²).

All participants received written and oral information about the study. Written informed concensus was given by all participants. The study was accepted by the local ethical committee.

THE MEASUREMENTS

a) The controlled study

The following measurements were performed:

1. Nocturnal respiratory measurements by use of inductive pletysmography (11,12).
2. Laryngeal sound measurements.
3. A questionnaire in both treatment periods.

The nocturnal measurement was performed on day 1, 2, 15, 16, 29 and 30. The treatment periods were in periods A day 2 to day 15, and in periods B day 16 to day 29. Day 1 and day 30 were without any treatment in order to reduce the influence of the first night effect and to characterize the period effect.

The laryngeal sound was determined by use of a laryngeal microphone (Senheiser). The sound was amplified and subdivided in the following frequency responses: 0.25-0.75 KHz (mean: 0.5 KHz), 0.75-1,5 (mean: 1.0 KHz) and 1,5-3.0 (mean: 2.0 KHz). The frequency responses were separated by analog filters. The signals were smoothed with an integration time of 35 mseconds. The selection of the frequency responses were performed based on a former study of the frequency responses during snoring (13), showing that the main part of the frequencies is within the range of 250-3000 Hz (figure 1). A lower frequency component exists, however, in this frequency major noise from movements and artefact arose, why frequencies below 250 Hz were not included.

Laryngeal sound and inductive pletysmography were sampled on a portable microcomputer (Olivetti) using a 12 bit analog-digital converter (Data Translation). The sampling rate was 10 Hz (S -1) on all

channels. An example of normal respiration is shown on figure 2, of respiration and laryngeal sounds during a snoring episode is shown on figure 3 and an example of respiratory movements and laryngeal sounds is shown in figure 4.

The microphones and amplifiers were calibrated every month using a Brüel and Kjær (B&K 4230, Copenhagen, Denmark) equipment. Data range within a distortion less than 1% was 24-98 dB for the microphone, amplifiers and the analog-digital converter. It was ensured that the same participants always used the same equipment.

Before start of the study measurements with a microphone 50 cm from the persons head were compared with a laryngeal position in three measurements in different rooms. It was found, that in traditional bed rooms and in traditional hospital rooms major noise arose and disturbed the measurements, thereby decreasing the reliability of the measurements of the respiratory sound measurements. Based on these data it was decided to use a laryngeal position of the microphone instead of a room microphone.

All nocturnal recordings were performed ambulatorily with a portable equipment. All participants were visited by the same technician, who set up the equipment in the bed room and gave further instructions about the study and the equipment. The measurements started automatically. At the termination of the recordings the participants just had to stop the sampling by pressing on the computerboard in the morning. Then the following measurements were written to the file: time of start and stop of the sampling and the recording-date. The equipment was collected after the recording nights. All data were analysed for invalid and missing data. If any data were insufficient they were recollected if possible or the patient were excluded. In two patients the data were insufficient (2 out of 54) and these patients were excluded. One patient had a myocardial infarction and 1 patient denied to participate before entry to the study. In total 50 participants finalized the study and the data were used in the results given here.

According to a double blind randomisation design the technician brought the medications to the participants and collected them after each period.

Respiratory Distress Index (RDI) were determined by the total apnea and hypopnea determinations which were based upon visual analysis (11, 12).

The following measurements were determined: apnea, hypopnea, RDI, the mean respiratory time index (RTI) the mean and maximum values of the sound measurements of the laryngeal microphone subdivided in the three octaves recorded.

Because the nasal clearance is few hours (< 1 – 2 hours), the data has been further recalculated for respiratory sounds and apnea within the periode 30 – 90 minutes of sleep, in order to characterize the effects of respiratory abnormalities and changes within this first periode of sleep.

b. The acceptance study

All participants were treated with the solution containing Asonor, in total 1.2 mg every night (table 1). The study period was 6 months. Every month new bottles containing 30 ml were sent by mail to the participants and the used bottles were collected. A questionnaire with questions about subjective and bed partner reported snoring pattern, sleep quality, daytime symptoms (sleepiness and tiredness), side effects and whether the persons wanted to continue the use of the solution was enclosed.

After 6 months of treatment the participants were invited to the clinic and were asked about the treatment effect, side effects and possible other (positive) effects. Blood pressure, weight and height were measured. If any participants wanted further treatment two bottles were given free to the participants.

218 out of 224 (97.3%) started in the acceptance study after the first visit to the clinic.

Statistics

Mean and Standard Deviation (SD) or median and range were calculated on all data. Data were compared using non-parametric statistics (Mann Whitney). Level of significance was $p < 0.05$.

RESULTS

BMI (Body Mass Index), Systolic and diastolic blood pressure are significantly higher in the study population compared to the representative Danish background population which the population was selected from (table 2).

Complaints of snoring, prevalence of every night snoring, disturbances of the bed partner and daytime symptoms (sleepiness and tiredness) were significantly more prevalent in the study population compared to the background population. Separate bed rooms because of the snoring was significantly more common in the study population compared to the background population (table 3).

ENT-findings in between the two populations are shown in table 4.

In the acceptance study, after 6 months of treatment 66.1% were still using the Asonor solution. A significant reduction in snoring was reported by the participants and by the bed partner and a significant improvement

were reported in sleep quality and daytime symptoms in the treatment period compared to baseline values (table 5).

In total 88.4% used the solution daily more than 5 times per week after 6 months of active treatment. In 7.9% snoring totally disappeared, in 40.4% an improvement appeared, no effect was observed in 43.6% and 8.1% did not know which effect appeared. These data were consistent with the report from the bed partner though snoring was reported to disappear in 7.6%, improved in 40.7%, no changes were observed in 37.2%, deteriorate in 3.6% and 10.9% did not know whether any effect appeared. Sleep quality improved in 40.0% and sleepiness was reduced in 81.4% during the treatment period compared to baseline values.

In the controlled study, a significant improvement was found in self and bed partner reported snoring, tiredness, sleepiness and in sleep quality both in the control and in the test period compared to baseline values. However no significant differences were found between the two groups, neither in the use of medication, in self reported snoring, in bed-partner reported snoring, in sleep quality or in daytime symptoms: tiredness and sleepiness (table 6).

No differences were found in the respiratory or laryngeal sound measurements between the control and the test period (table 7). A slight but non-significant improvement between baseline values, the control and the test period was found in the sound measurements as well as in the number of apneas/hypopneas (RDI, RTI) (table 8).

Between 30 to 90 minutes of sleep (in total 60 minutes of observation), a significant reduction in snoring sound appeared compared to baseline values. This was especially true for the lower frequencies (0.25 – 1.5 KHz) (table 7). A reduction in laryngeal sound appeared between the first day of treatment and the baseline values, both day 1 and 30. However no difference were observed in laryngeal sounds between the ASONOR and the period with the control solution.

The respiratory parameters calculated as RDI and ATI were improved within the test period compared to control, but this effect showed no statistical significance. No difference were observed between RDI and RTI if RDI was further subdivided slight, moderate or severe sleep apnea. No difference in any of these measurements were noted if the first period of sleep were taken into consideration (table 8).

No significant association between the reduction snoring sound from night 1 to the ASONOR treated night or between ASONOR and the nights with treatment with the control solution were noted in BMI, Systolic Blood Pressure, Diastolic Blood Pressure or in the following otolaryngological measurements: tonsillar hypertrophy, uvula size, nasal resistance (diameter of condensed humidity of the glass plate after expiration through one nasal opening).

No significant period or threshold effect (14) was found.

Few side effects were reported using the Asonor solution (table 9). Two of the three participants reporting nasal hemorrhage suffered from intermittent nasal hemorrhage before entering to the study. Some participants reported

spontaneous positive effects using Asonor, namely decreased nasal resistance (improved nasal air flow), less tendency during the winter and spring to common cold and less tendency to allergic and vasomotor rhinitis (table 10).

DISCUSSION

In the open study, approximately 2/3 of snoring population continuously used a solution containing Asonor. Approximately 2/3 of this population (in total 50% of all snorers) reported reduced snoring.

In the controlled study, however, minor differences were found in subjective or bed partner reported snoring or in any of the laryngeal nocturnal sound measurements between the control and the ASONOR treated period. A slight reduction were noted with the first period of sleep, between baseline values and ASONOR treated values, but this also appeared between the baseline values and the control solution. Therefore the difference between the ASONOR treated night and the control night did not appear.

Hoffstein et al. Reported in 1987 (8) a significant decrease in that snoring measured by a microphone. This study was performed as an open controlled but not a randomized study with 6 snorers in two groups: one group was treated with phosphocholinamin, a long-acting tissue-lubricating agents, the other group was treated with a tap of water were used as a control. No dose or composition of the solution was given. Though no comparative placebo was used, this can explain the apparent positive effect of nasal installation of phosphocholinamin in this study. Until now a further confirmation of these results based upon a very small sample is totally lacking.

In an earlier open study a significant reduction of snoring using Asonor with nocturnal respiratory measurements was found (9) compared to baseline. This actually is confirmed by this study, because a reduction compared to baseline values were found. Because no difference was found between control and ASONOR in this study, the questions could be raised, whether the reduction in laryngeal sounds is related to an unspecific effect of nasal or pharyngeal stimulation, rather than P-80 itself.

The use of Asonor both in the test and the control-solution could have decreased the difference of the activity additionally. This is further supported by the findings, that Asonor reduce laryngeal resistance in dogs. (Widdicombe et al., 1988, oral information).

The mechanism for the effect of nasal application of liquids installed in the nose might be a local or a neural reflex mechanism, increasing the upper airway tone, decreasing the nasal and pharyngeal resistance and probably a lubricating effect (10). It is not known which of these factors is active in the responders. Surgical or pharmacological treatment of decreased nasal resistance can reduce snoring in patients suffering from nasal obstruction (septum deviation, allergic and vasomotoric rhinitis) (6, 7). It is probably that the responders in this study respond by changes in nasal or pharyngeal resistance.

The study shows that polysorbate 80, by itself does not effectively treat snoring in a representative selection of male snorers, age 55-65. However approximately 50% of the every night snorers reported a significant improvement of the snoring problem, approximately 8% had a total disappearance of the snoring

problem and no serious side effects were reported. This indicates that some snorers might benefit from using ASONOR. Moreover people suffering from rhinitis (allergic, vasomotoric) and from dry mouth might benefit using the ASONOR solution.

FIGURES

Figure 1.

Frequency analysis (Fast Fourier Transform, FFT) during a snoring episode from a male every night snorer, age 55. The sampling rate was 20 KHz, 12 bit (Jennum & Hansen 1987)

Figure 2.

Normal respiration.

The thoracic and abdominal movements are determined by inductive plethysmography. The laryngeal sound is subdivided in: 250-750, 750-1500 and 1500-3000 Hz.

Figure 3.

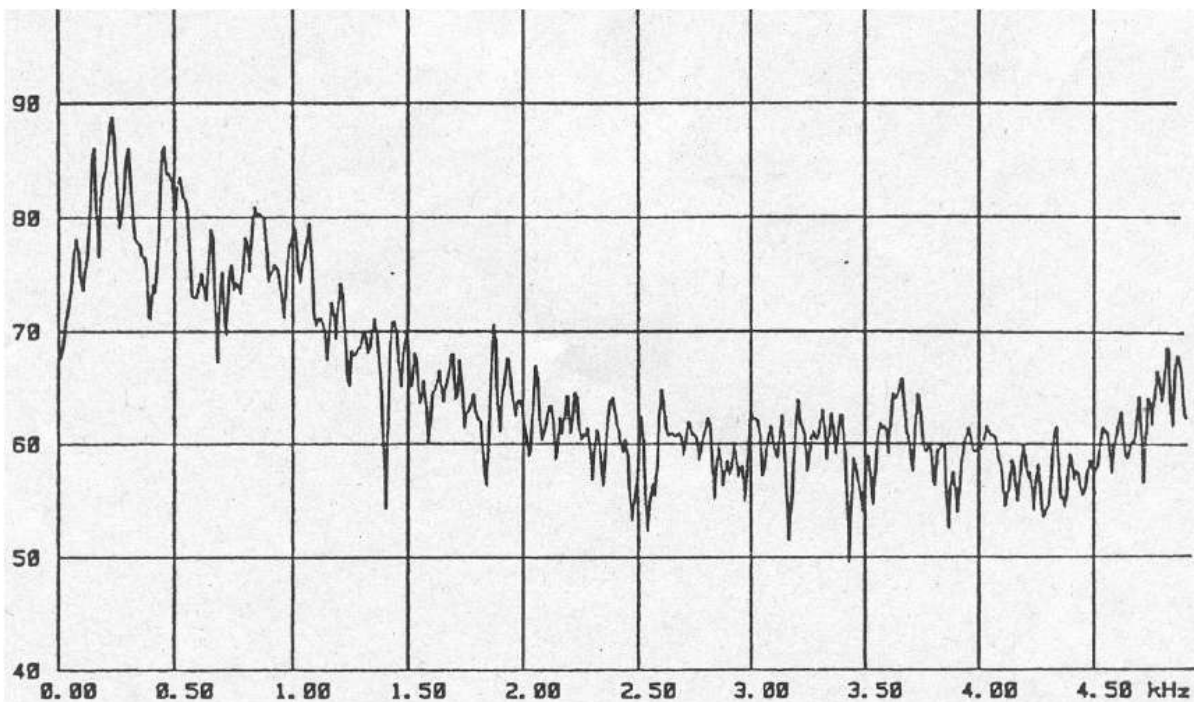
A snoring episode without any apnea and hypopnea.

The thoracic and abdominal movements are determined by inductive plethysmography. The laryngeal sound is subdivided in: 250-750, 750-1500 and 1500-3000 Hz.

Figure 4.

An apneic episode with intermittent snoring.

The thoracic and abdominal movements are determined by inductive plethysmography. The laryngeal sound is subdivided in: 250-750, 750-1500 and 1500-3000 Hz.



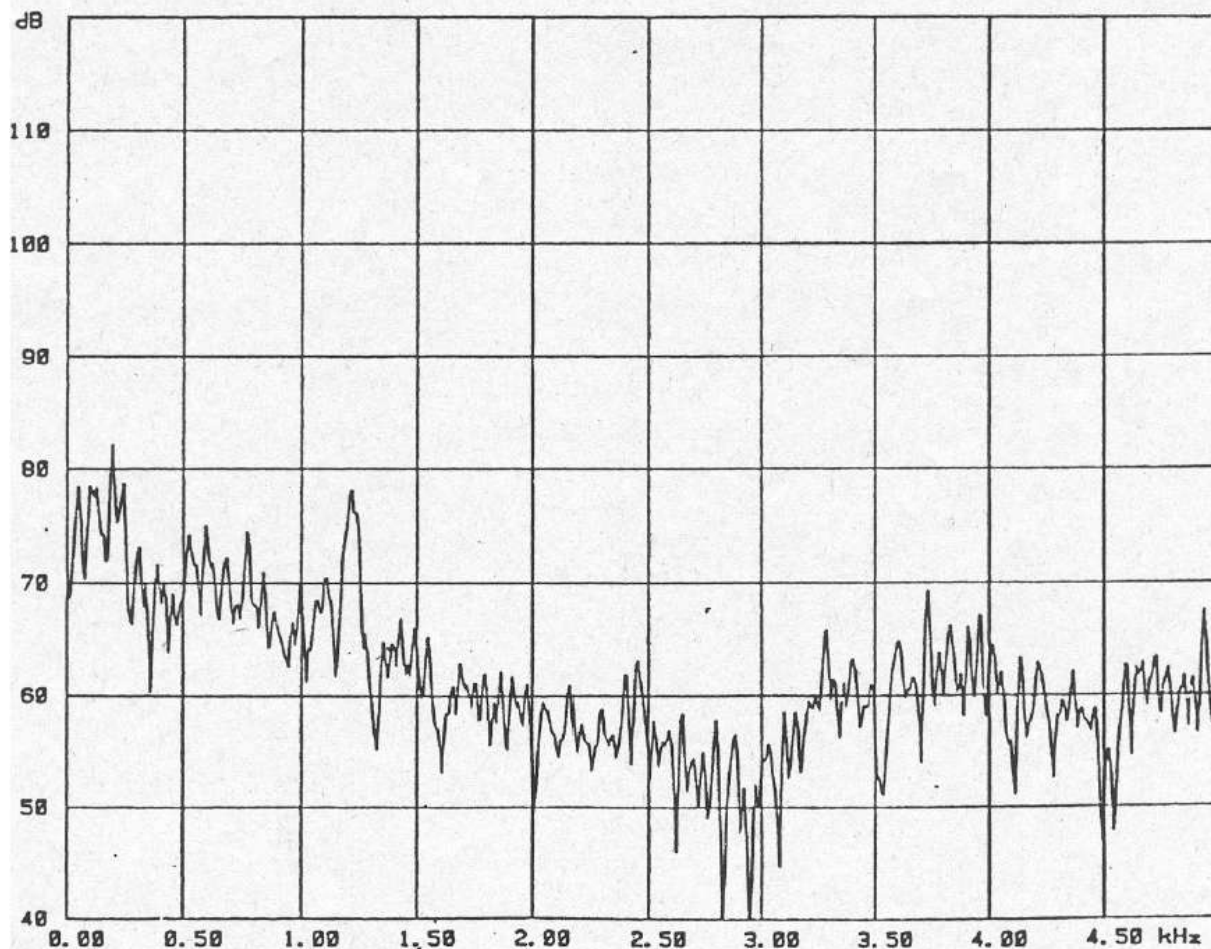
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Danish Acoustical Institute

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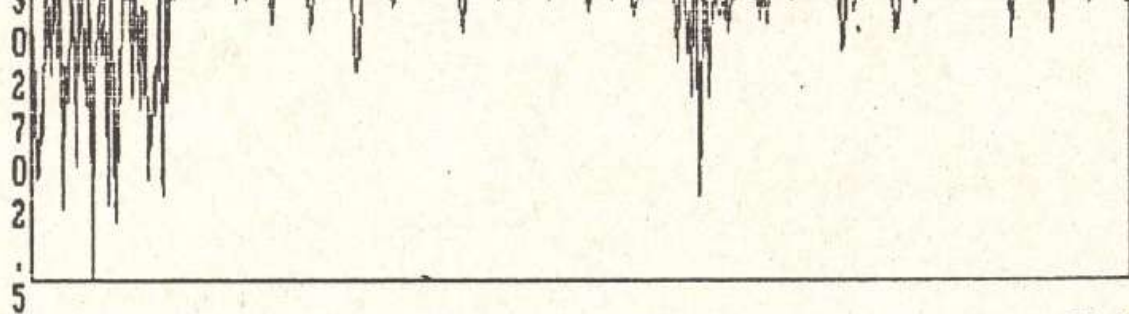
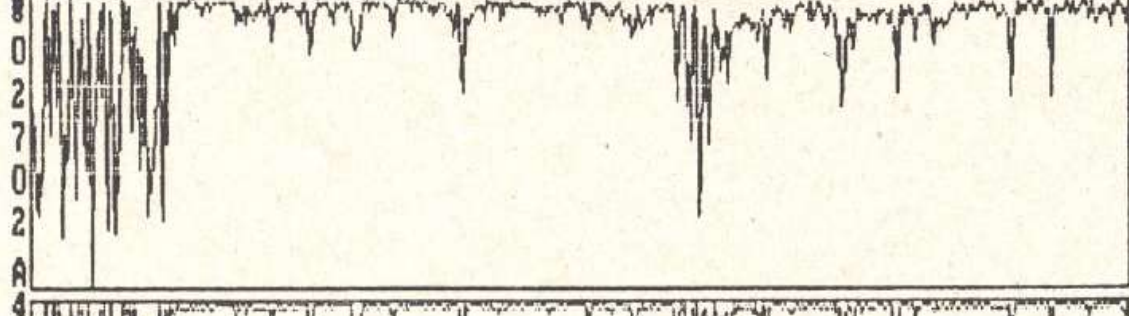
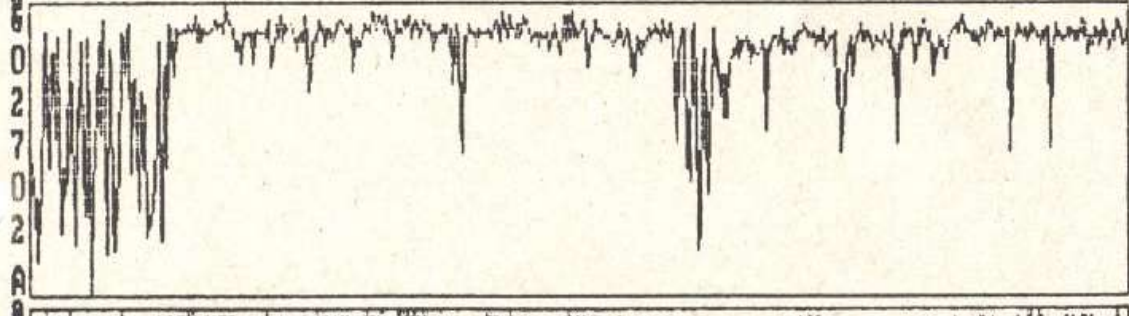
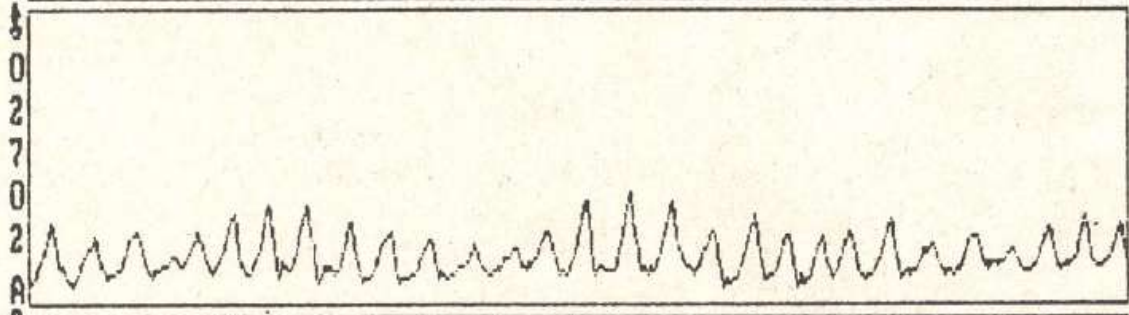
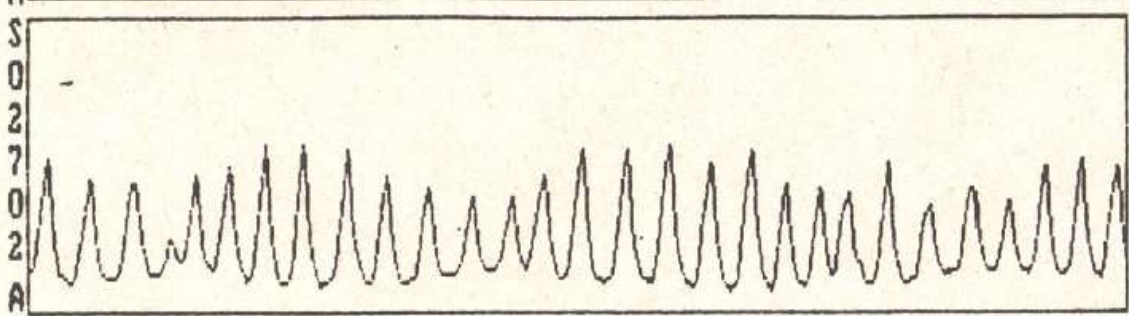
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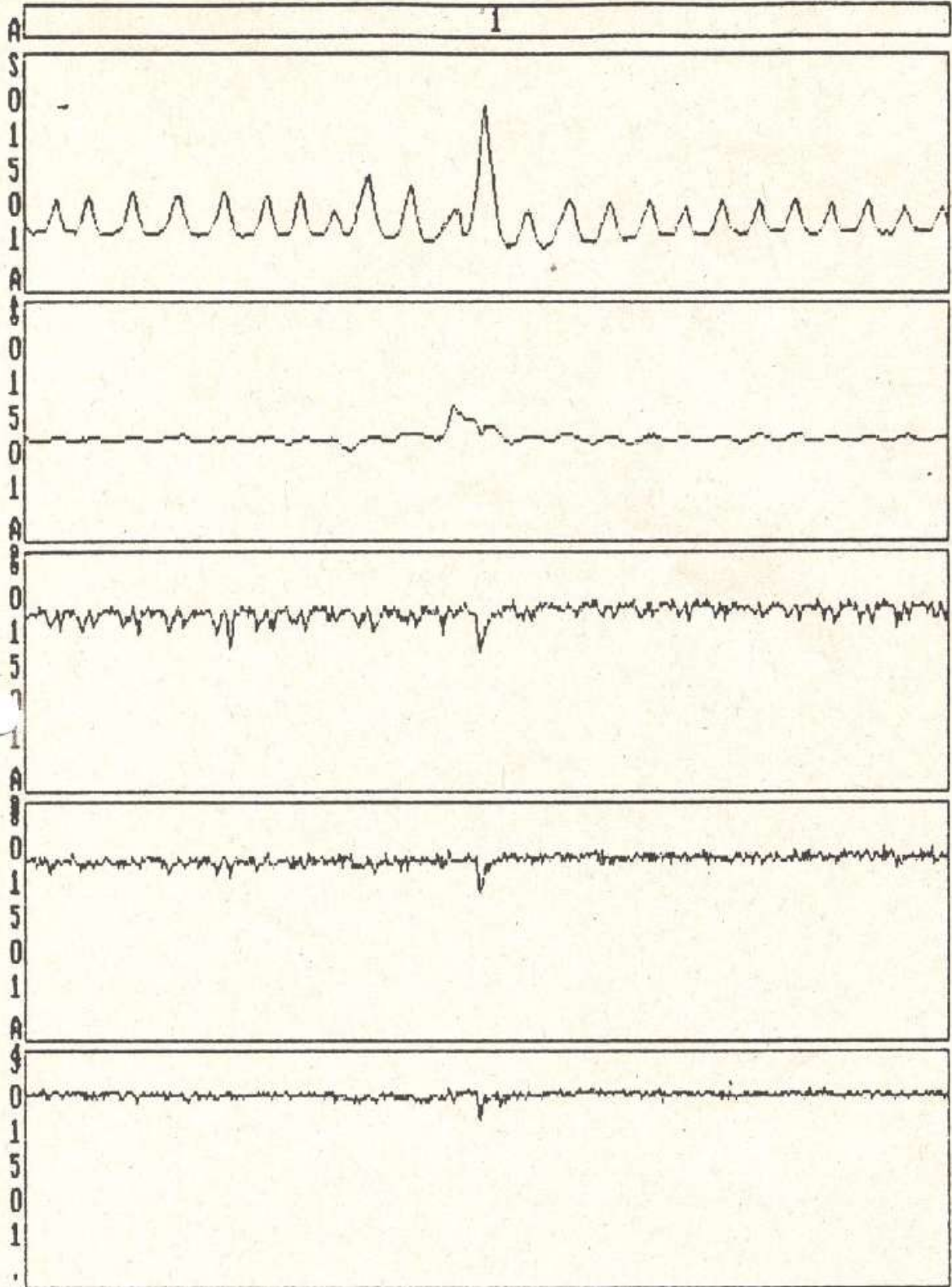
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Table 1. The composition

	<u>Test solution</u>	<u>Control solution</u>
Sodium Chloride	incl.	incl.
Glycerole 85%	incl.	incl.
Polysorbate 80	incl.	excl.
Potassium sorbate	incl.	incl.
Edetatesodium	incl.	incl.
Purified Water	incl.	incl.

Table 2. Systolic (SBP) and diastolic (DBP) blood pressure and body mass index (BMI) in the background population (self reported non-snorers and snorers) and the studied snoring population

	<u>The background population</u>		<u>The study population</u>
	non-snores	every-night snorers	
number	1723	1716	278
SBP ¹	116.9	121.6*	150.1\$
DBP ¹	72.9	75.1*	93.6\$
BMI ²	24.7	24.7	26.3\$

1 mmHg

2 kg/sqm

* p<0.0001 between snorers and non-snorers in the background population

\$ p<0.0001 between the study population and the total background population

Table 3. Differences in snoring pattern and daytime symptoms between the background population and the study population

	<u>The background population</u>		<u>The study population</u>
	non-snores	every-night snorers	
number	1723	1716	278
Intermittent daytime sleepiness	59.6%		72.8%\$
Imperative sleepiness	4.3 %		9.9 %\$
Every night snoring	29.9%		52.6%\$
Disturbed bed partner because of snoring		44.5%	85.1%\$
Separate sleeping places because of snoring		4.3%	14.4%\$

\$ p<0.0001 between the study population and the total background population

Table 4. ENT findings in the study population: the controlled population and the population for the acceptance study. The values are given as pct. of the study population or median (range)

	Controlled study N=224	Acceptance study N=54
Deviation of nasal septum	4.5%	5.8%
Nasal Polyps	1.8%	0.0%
Atrophy of the tonsils	89.3%	23.1%
Hypertrophy of the tonsils	3.6%	0.0%
Uvula, oedema	3.8%	3.8%
Uvula length	9 mm (4-19)	9 mm (6-16)
Uvula thickness	9 mm (4-24)	9 mm (5-17)
Velopharyngeal distance	12 mm (6-20)	12 mm (6-20)
Rhinopharynx, normal	100%	100%
Pharynx oedema	8.3%	0.0%
Tounge, hypertrophic	1.0%	0.0%
Epiglottis, normal	100%	100%
Ramus, height	70 mm (60-105)	69 mm (56-80)
Angle of angulus	120 ^o (108-138)	120 ^o (110-134)
Double skin of the neck	95.9%	94.2%
Skinfoldthickness, neck	5 mm (2-15)	6 mm (3-16)
Retrognatia/micrognatia	0.0%*	0.0%*

* Cause of exclusion

None of the differences are statistical different ($H(0) : p < 0.05$), chisquare (X^2) or Mann-Whitney tests

Table 5. Number of persons using Asonor and the self reported effects in the acceptance study.

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Number of users	224	216 (97.3%)	185 (82.6%)	171 (76.3%)	161 (71.9%)	148 (66.1%)	148 (66.1%)
Use of Asonor. ¹	(0)	6.07	6.48	6.33	6.23	6.36	6.03
Self rep.snor ²	5.0	6.09	6.10	6.20	6.22	6.40	6.42
Bed.part.rep ²	5.0	6.10	6.07	6.19	6.19	6.37	6.37
Sleep quality ²	5.0	5.58	5.88	6.06	6.06	6.20	6.13
Tiredness ³	7.22	7.79	7.71	7.49	7.86	8.12	7.78
Sleepiness ³	7.41	8.21	8.26	8.23	8.31	8.50	8.23

1 times per week (= 7 days)

2 0 = worsened, 5 = no changes, 10 = improvement

3 0 = daily, 10 never

Table 6. Self reported symptoms between the control-periode and the ASONOR treated periode.

	Control ex. P-80	ASONOR incl. P-80	Baseline
Use of med. ¹	6.93	6.89	(0)
Self rep.snor ²	5.78	5.82	5.0
Bed.part.rep ²	5.83	6.02	5.0
Sleep quality ²	5.51	5.57	5.0
Tiredness ³	8.21	8.30	7.22
Sleepiness ³	8.95	8.98	7.41

1 times per week (= 7 days)

2 0 = worsened, 5 = no changes, 10 = improvement

3 0 = daily, 10 never

Table7. The effect of Asonor and control solution on the control the laryngeal sound measurement (db(A)), divided into the whole night and the first hour of sleep (from 30 to 90 minutes of the recording). Mean (Standard Deviation). N=50.

	U1	A1	A2	P1	P2	U2
<u>0.25-0.75 KHz</u>						
Mean	45.6	46.1	44.8	45.6	46.4	46.5
Maximum	86.5	82.6	85.7	83.8	85.2	86.7
Mean, 1 st hour	45.3	43.5	43.8	45.5	46.4	44.7
Max, 1 st hour	84.9	79.6	81.7	82.5	83.9	86.1
<u>0.75-1.5 KHz</u>						
Mean	38.9	40.4	38.7	38.8	39.0	38.9
Maximum	82.0	76.2	80.8	80.6	78.4	80.6
Mean, 1 st hour	39.3	38.2	37.6	39.4	39.6	39.3
Max, 1 st hour	80.6	73.6	77.5	79.2	77.7	79.2
<u>1.5-3.0 KHz</u>						
Mean	34.6	34.1	34.3	35.1	34.3	35.7
Maximum	77.2	73.3	75.4	74.8	73.1	75.0
Mean, 1 st hour	34.2	34.9	32.9	34.5	33.8	35.6
Max, 1 st hour	75.9	70.9	72.8	73.4	72.1	73.6

U1 and U2: Baseline nights day 1 and 30

A1 and A2: Asonor treated nights

P1 and P2: Control solution nights

Table 8. The effects of Asonor on respiratory parameters, apnea and hypopnea, during the first and 14 th night of treatment in the double blind controlled study. Apnea/hypopnea time => 10 seconds. Apnea time index (ATI): mean apnea time longer than 10 seconds.

	U1	A1	A2	P1	P2	U2
RDI	16,2	15.3	16.4	18.1	17.7	17.6
RDI, 1 st hour	9.3	11.2	10.1	10.8	10.8	11.2
ATI	17.2	14.5	15.5	19.7	18.3	17.6
ATI, 1 st hour	14.3	13.8	14.9	15.7	15.9	14.8

Statistics: Wilcoxon matched paired tests, level of significance is $p < 0.05$

Table 9. Reported side effects from acceptance study

Effects	Number	Pct
Dry mouth and throat	11	5.0%
Nasal hemoragi	3	1.3%
Nasal or throat irritation	5	2.3%
Nasal rhinitis	9	4.1%
Dry nose or throat during the day	9	4.1%
Stomach pain	2	0.9%
Sneeze	2	0.9%

Table 10. Reported other (positive) effects.

Effects	Number	Pct
Increased nasal air flow	15	6.9%
Reduced dry mouth	30	13.8%
Decreased vasomotoric or allergic rhinitis	14	6.4%

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