2 Synopsis

Title of the study:

Effect of pantoprazole on sleep-related breathing disorders. Monocenter, double-blind, randomized, placebo-controlled, stratified parallel-group comparison. EPOS-Study

Study center:

Zentrum für Schlafmedizin, Hörder Burgstraße 18, 4426 Dortmund, Germany

Publication (reference):

Not applicable

Studied period:

20-Sep-2005 (first patient in) to 14-Nov-2006 (last patient out)

Clinical phase:

II

Objectives:

This proof-of-concept study was to assess the potential benefit of pantoprazole for patients with and without evidence of GERD and sleep-related breathing disorders

Methodology:

The study was designed as a monocenter, double-blind, randomized, placebo-controlled, stratified parallel-group comparison.

The duration of the study for each patient comprised about 2-4 weeks, ie a pre-treatment period of 17 days (maximum) and a treatment period of 2 weeks. The patients had to take either 40 mg pantoprazole-Na or placebo twice daily.

Schedule of Visits

Pre-treatment Visit V-2	Adaptation PSG Visit V-1*	Baseline PSG Visit V0	Treatment Period	
			Baseline Visit V1	Final Visit V_{end}
Day -17 to Day -3	V-2 to V0	Day -2	Day 0 ± 1 day	Day 14 + 2 days

* If a PSG has been performed prior to inclusion in the study this might be accepted as adaptation for the study, provided that it has been done within 6 months before intake of the first study medication. In this case, V-1 can be skipped.

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No. of patients (total and for each treatment) planned and analyzed:

As this was a pilot project, no formal sample size calculation was made. Approximately 60 ITT patients were planned to be included into the study in order to obtain data from 48 PP patients. The analyzed sets are presented below:

Analyzed sets

	Enrolled	Safety Set	Full Analysis Set	Valid Cases Set
Pantoprazole-Na, 40mg, twice daily		30	26	23
Placebo, twice daily		30	29	29
Total	81	60	55	52

Diagnosis and main criteria for inclusion:

Outpatients fulfilling following criteria were considered for study inclusion:

- Written informed consent by the patient for study participation, prior to protocol specific procedures
- Male and female outpatients of at least 18 years of age
- Patients suffering from sleep-related breathing disorders / Upper airway resistance syndrome for at least 3 months prior to start of the study who are seeking help for their snoring
- Stratum I: Patients with evidence of GERD
  Stratum II: Patients without evidence of GERD

Test product, dose, mode of administration, batch no.:

Pantoprazole-Na (tablets), 40 mg , twice daily, po, batch numbers BY1023-529, BY1023-514

Reference product, dose, mode of administration, batch no.:

Placebo (tablets), twice daily, po, batch numbers BY1023-529, BY1023-514

Duration of treatment:

One treatment period of two weeks

Criteria for evaluation:

Primary variable:

Comparison of the ratio of snoring time over sleeping time (Snoring Index)

Secondary variables:

- Change in ventilation (oral / nasal flow) including
  → Peakflow V_{max}
  → Tidal volume (V_t)
- Change in Apnea-Hypopnea index
- Comparison of the ratio of respiratory cycles with and without snoring
- Changes in Polysomnography
  →EEG
  →EOG
  →EMG
  →ECG
  → Blood Gas Analysis
- Proportion of REM phases
- Proportion of NREM stage 3 and 4
- Arousal Index (according to ASDA criteria)
- Calgary Sleep Apnea Quality of Life Index
- Stanford Sleepiness Scale (SSS)
- Epworth Sleepiness Scale (ESS)
- ReQuest™

- Safety: adverse events, laboratory, physical examination

Statistical methods:

Efficacy

The primary variable was analyzed within an analysis of covariance using a model including stratum (GERD status), treatment group, treatment * stratum, patients' sex, BMI and age as main effects. The calculated treatment effects were compared using the F-test. Superiority of pantoprazole treatment was concluded if the p-value was below 0.05 and the two-sided 95% confidence interval lay completely below zero. The primary analysis was based on the Full Analysis Set. The additional analysis of the Valid Cases Set was supportive.

The secondary variables ReQuest™, Stanford Sleepiness Scale, and Epworth Sleepiness Scale were analyzed descriptively. All other secondary variables were analyzed analogously to the primary variable.

Safety

Adverse events were coded according to MedDRA. The adverse events were summarized by treatment, System Organ Class, preferred-term and intensity. Nature, incidence, and intensity, as well as the investigator's and the sponsor's causality assessment were reported for each treatment-emergent adverse event. The number of treatment-emergent adverse event were compared between the two treatment groups by means of Fisher's exact test. Laboratory values and vital signs were compared descriptively.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

The Full Analysis Set comprised 55 patients, 44 were male (80%) and 11 were female (20%). The mean age was 47.3 years (SD: 8.5). The pantoprazole-treated group consisted of 26 patients, 22 were male (84.6%) and 4 were female (15.4%). The mean age was 46.5 years (SD: 7.9). The placebo-treated group consisted of 29 patients, 22 were male (75.9%) and 7 were female (24.1%). The mean age was 48.0 years (SD: 9.1).

All patients included into the study suffered from sleep-related breathing disorders and had a Snoring Index $\geq$ 15 and a Respiratory Disturbance Index of $\leq$ 10 / h. The Safety Set comprised 30 patients with evidence of GERD (stratum I) and 30 patients without evidence of GERD (stratum II).

Study results

Efficacy

The primary efficacy variable Snoring Index of patients with and without GERD after 2 weeks of treatment with pantoprazole 40 mg (P_{40mg}) or with placebo ($P_{Placebo}$) was analyzed within an analysis of covariance. Results of the primary variable are presented in the following table:

Analysis of Snoring Index by an Analysis of Covariance

	p-Value final model[a]	Factors selected for final model[b]	p-Value factors[c]	Treatment difference[d] (95% CI)	p-Value for treatment difference
Full Analysis Set	0.0584	- stratum	0.0888	2.59	0.6781
(N = 55*)		- bmi	0.0167	(-9.87, 15.05)	
		- treatment	0.6781		
Valid Cases Set	0.1383	- bmi	0.0490	3.13	0.6393
(N = 52*)		- treatment	0.6393	(-10.23, 16.50)	

* Due to missing values, only 54 observations could be used for analysis of the Full Analysis Set and 51 observations for the Valid Cases Set.
[a] Significance level 5.0%.
[b] The factor treatment was included into the final model regardless its p-values in the selection process.
[c] P-value for the respective factor within the final model.
[d] Treatment difference was calculated as difference between treatment least square means of the respective variable.
CI = confidence interval. Data source: Table 15.2.2.1

Superiority of pantoprazole treatment was not concluded since the calculated p-value was not below 0.05 and the two-sided 95% confidence interval did not lie completely below zero.

Further 36 objective variables and the Calgary Sleep Apnea Quality of Life Index (SAQLI), which is based on the patient's self-assessment, were analyzed analogously to the primary variable. Superiority of treatment was shown for 3 out of 20 analyzed polysomnographic variables. These variables were Heart Rate (awake), Heart Rate (sleep) and EMG Diaphragm absolute (wake). Superiority of treatment was not shown for 10 ventilation-related parameters, for 6 other sleep-related variables (Apnea-Hypopnea Index, Ratio of Respiratory Cycles with and without Snoring, Proportion of REM Phases, Proportion of NREM Phases Stage 3 and 4, Arousal Index) as well as for SAQLI.

Additionally, the scores of the Stanford Sleepiness Scale (SSS), Epworth Sleepiness Scale (ESS) and ReQuest™ and its subscales were evaluated descriptively. In both treatment groups the mean sum scores of SSS and ESS were lower at study termination compared to baseline which reflects reduced daytime sleepiness. With respect to SSS, the score reduction was higher for the P_{40mg} group. With respect to ESS, the score reduction was higher for the $P_{Placebo}$ group. Mean sum scores of the ReQuest™ total and its subscales were low and did not change remarkably during treatment.

Safety

A summary of the number of patients with adverse events is presented in the following table:

	n (%)[a]			
	P_{40mg} (N = 30)		$P_{Placebo}$ (N = 30)	
AEs	9	(30.0)	4	(13.3)
SAEs	-	-	-	-
Deaths	-	-	-	-
AEs with causality[b] suggested by the investigator	2	(12.5)	1	(14.3)
AEs leading to discontinuation	-	-	1	(3.3)

[a] Percentages are based on the total number of patients in a treatment group.
[b] AEs assessed by the investigator as "likely" or "definitely" related to the study medication.
AE = adverse event, N = number of patients in each treatment group, n = number of patients with events, P_{40mg} = pantoprazole 40 mg, $P_{Placebo}$ = placebo, SAE = serious adverse event.

No death and no serious adverse event occurred during the course of this study.

In total, 23 treatment-emergent adverse event symptoms were recorded for 13 patients (21.7%) of the Safety Set. In the P_{40mg} group, 9 patients (30.0%) experienced 16 different adverse event symptoms, in the $P_{Placebo}$ group 4 patients (13.3%) experienced 7 different adverse event symptoms.

The intensity of 22 AE symptoms (P_{40mg}: N = 15, $P_{Placebo}$: N = 7) as reported by the investigator was 'mild', only one AE symptom of a patient in the P_{40mg} group was 'moderate' in intensity.

In total, the investigator assessed 3 of 23 AE symptoms (13.0%) as 'likely related' to study medication, 2 symptoms (12.5%) in the P_{40mg} group and 1 symptom (14.3%) in the $P_{Placebo}$ group. The symptoms assessed as 'likely related' to the intake of P_{40mg} were 'abdominal discomfort' and 'abdominal pain lower'. The symptom assessed as 'likely related' in the $P_{Placebo}$ group was 'dizziness'. No symptoms were assessed as 'definitely related' to study medication.

The most often stated treatment-emergent AE symptoms as coded by MedDRA were 'abdominal pain lower', 'nasopharyngitis', 'pharyngolaryngeal pain', 'rhinitis', and 'vomiting' which were reported 2 times each. The other AE symptoms occurred only once in all patients.

One patient of the $P_{Placebo}$ group prematurely discontinued the study due to a treatment-emergent AE. The respective symptom 'dizziness' was assessed as 'likely related' to study medication by the investigator as well as by the sponsor.

Changes in physical examination at V_{end} were observed in 2 patients (7.1%) of the $P_{Placebo}$ group. No clinically relevant changes in parameters of vital signs occurred during the course of the study.

In conclusion, treatment with pantoprazole was well tolerated and safe.

Conclusions:

This study did not provide evidence that pantoprazole treatment improves sleep-related breathing disorders.

Pantoprazole treatment was well tolerated and safe. The adverse events observed during this study did not rise any suspicion of hitherto unknown risks of the study drug.