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Zolpidem-Polysomnographic Study of the Effect of a New Hypnotic Drug in Sleep Apnea Syndrome

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CIRIGNOTTA, F., S. MONDINI, M. ZUCCONI, R. GERARDI, A. FAROLFI AND E. LUGARESI. *Zolpidem-polysomnographic study of the effect of a new hypnotic drug in sleep apnea syndrome.* PHARMACOL BIOCHEM BEHAV **29**(4) 807–809, 1988.—Clinical studies have shown that zolpidem, an original imidazopyridine derivative, induces and maintains sleep and does not have daytime side-effects. Polysomnography has revealed that this drug has several interesting qualities that benzodiazepines do not possess: stages 3–4 increase, stage 2 is unchanged or slightly reduced and no abnormal changes are detected on the EEG tracing. Like benzodiazepines, zolpidem slightly reduces REM sleep. The Multiple Sleep Latency Test confirmed that the drug does not cause daytime drowsiness. All the hypnotic drugs studied up to now worsen heavy snoring and obstructive sleep apnea syndrome. A controlled double blind cross-over trial assessed the effects of a single dose of zolpidem 20 mg on nocturnal breathing in patients with mild forms of sleep apnea syndrome. The results indicate that, at this dose, the drug does not overcome the existing contraindications to the use of hypnotics in this syndrome.

Zolpidem Sleep apnea syndrome Snoring

MAJOR discoveries over the last thirty years have demonstrated that sleep is not a "passive" uniform state, but a complex active event organized in stages and cycles which form sleep architecture. Changes in EEG tracings, submental muscle tone and eye movements distinguish REM sleep from non-REM sleep (NREM) which in turn can be divided into four stages.

Vegetative functions behave differently in the various sleep stages. During stages 1–2 NREM, or light sleep, the EEG tracings present continuous fluctuations in amplitude and frequency corresponding to synchronous oscillations in breathing, heart rate, arterial pressure and muscle tone.

Stages 3–4 NREM, or deep sleep, are characterized by marked functional stability, while phasic breathing and circulatory changes occur during REM sleep.

Any evaluation of hypnotic drugs must take into account that sleep involves all bodily functions, in particular the respiratory and cardiocirculatory system.

Zolpidem, an imidazopyridine, is an hypnotic drug developed by LERS Synthelabo in 1980. This drug is highly specific for BZD_2 receptors [3]; compared with benzodiazepine hypnotics, zolpidem's active spectrum presents several specific features. Firstly, it has virtually no muscle relaxant effect. Secondly, in corticograms recorded in rat, spectral analysis reveals a peak in the frequency band 1–4 Hz without the prolonged energy increase in the beta band typical of the benzodiazepines [2].

Polysomnographic studies, mostly performed in healthy subjects, have investigated the effect of zolpidem on sleep architecture [1, 7, 9]. The following results have been obtained administering 10–20 mg zolpidem:

—reduced sleep latency;
—less nocturnal awakenings;
—increased percentages of stages 3–4 NREM;
—no effect on the percentage and latency of REM sleep.

The original structure and effect of this hypnotic make zolpidem a noteworthy new drug from the therapeutic standpoint. For the first time in testing a new hypnotic, the effects of zolpidem on breathing during sleep have been evaluated alongside standard sleep parameters.

The study was based on the following premises:

(1) It has been shown that hypnotics can provoke obstructive sleep apneas in heavy snorers [8];

(2) Heavy snorers represent 19% of the population [4];

(3) Snoring is the first symptom of obstructive apnea syndrome [5]; and

(4) Besides being a risk factor for the heart and circulation, apneas lead to continuous arousal and in some cases are responsible for insomnia.

In view of this, any hypnotic drug must also be assessed in terms of its effect on breathing during sleep.

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TABLE 1

Sleep Parameters	ZOL	FLUR	PLAC	ANOVA *p*	Friedman *p*
TST	396.4	404.2	352.4	0.0414	0.0003
SE	84.4	93.7	81.9	0.1960	0.0024
SL	2.58	7.75	8.75	0.0589	0.0005
WASO	21.33	16.92	49.67	0.0601	0.0278
AW	5.41	3.83	7.83	0.0083	0.0109

Sleep parameters: TST=total sleep time (min); SE=sleep efficiency (%); SL=sleep latency (min); WASO=wakefulness after sleep onset (min); AW=number of awakenings; ZOL=zolpidem; FLUR=flurazepam; PLAC=placebo.

TABLE 2

Sleep Parameters	ZOL	FLUR	PLAC	ANOVA *p*	Friedman *p*
ST 1%	17.07	14.96	18.02	0.0813	0.1054
ST 2%	62.23	61.53	57.79	0.0769	0.0131
ST 3%	6.34	6.78	6.35	0.8540	0.9200
ST 4%	0.72	1.99	1.87	0.1657	0.3679
REM %	13.66	14.66	15.89	0.3979	0.2053
REM Lat.	138.08	96.00	81.25	0.0682	0.0123

Sleep Parameters: % of sleep stages and REM latency (min).

TABLE 3

Snoring	ZOL	FLUR	PLAC	ANOVA *p*	Friedman *p*
Percent of TST	36.1	47.2	43.6	0.2130	0.3679
Lowest SaO_2	88.67	90.2	91.0	0.1702	0.2185
Mean SaO_2	93.81	94.00	94.68	0.1553	0.2806

Percent of TST=time spent in snoring with respect of total sleep time. SaO_2=arterial oxygen saturation (%).

TABLE 4

Apnea + Hypopnea	ZOL	FLUR	PLAC	ANOVA *p*	Friedman *p*
Duration	21.29	21.30	19.22	0.1891	0.5580
Index	29.97	21.45	16.97	0.1222	0.4724
Lowest SaO_2	76.83	81.67	85.17	0.0024*	0.0278
Mean low SaO_2	88.57	90.78	91.66	0.0019*	0.0169

*ZOL vs. PLAC, ZOL vs. FLUR.
Duration: Mean duration of apneas and hypopneas (sec).

METHOD

Zolpidem is an hypnotic drug which has been proven devoid of myorelaxant properties in animal models. Assuming that zolpidem would have less hypotonic effect on the oropharyngeal muscles, we administered this drug to patients with mild forms of sleep apnea syndrome.

The trial included 12 patients: 11 males and 1 female with an average age of 49; 5 patients were in stage 0 and 7 in stage 1 of obstructive sleep apnea syndrome according to the criteria of Lugaresi *et al.* [6]. Informed consent on the modality and aims of the trial were obtained from all patients beforehand.

We compared the effects of a single oral dose of 20 mg zolpidem, 30 mg flurazepam and placebo administered in randomized double blind cross-over trail according to a Latin square design.

Each patient underwent four polysomnographic recordings: night 0 was for diagnosis and adaptation; eligible patients entered the study which consisted of polysomnographic recordings on each of the three treatments; 6 days of drug free wash-out at home were interposed between each recording.

Polysomnographic recording included EEG, EOG, submental EMG, oro-nasal, thoracic and abdominal respirogram, ear oxymetry, intercostal electromyography, monitoring of snoring noise and sleep position. In particular, the time spent on the back and that spent on the side was kept separate in all calculations. The standard sleep parameters were assessed.

As far as breathing is concerned we evaluated total snoring time, percentage of snoring time compared with total sleep time, and the lowest SaO_2 values during snoring.

For apneas and hypopneas, we calculated the number, duration, index, lowest SaO_2 and mean low SaO_2 values.

RESULTS

No significant differences in the amount of time spent on the back and the side were found in the nights with placebo, zolpidem and flurazepam.

Sleep Parameters

Both drugs determined an increase in total sleep time and sleep efficiency together with a decrease in sleep latency, WASO and number of awakenings (Table 1). The percentage of different sleep stages did not show relevant modification although REM latency tended to increase with zolpidem (Table 2).

Breathing Parameters

Zolpidem reduced snoring time and SaO_2 during snoring, but this did not reach statistical significance (Table 3). Both drugs, but especially zolpidem, increased the apnea index, though not significantly; with zolpidem, the apneas did not last longer, but they provoked greater O_2 desaturation than flurazepam and placebo (Table 4).

CONCLUSION

The outcome of our study indicates that 20 mg zolpidem fails to overcome the existing contraindications to administration of hypnotic drugs in patients with heavy snoring and

obstructive sleep apnea syndrome. However, the protocol we adopted does not allow any comparison between zolpidem and flurazepam, owing to the different pharmacokinetics of these two drugs.

Further studies using lower doses of zolpidem would be useful. Furthermore not all patients showed the same behaviour. In some of them only very slight changes occurred with the three treatments. The aim of future research would be to determine which factors characterize subjects who are susceptible to drug-induced sleep apneas.

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