ELSEVIER

European Neuropsychopharmacology 13 (2003) 111–115

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

Effects of zolpidem 10 mg, zopiclone 7.5 mg and flunitrazepam 1 mg on night-time motor activity

P. Denise[a,*], M.L. Bocca[b]

[a]*Service des Explorations Fonctionnelles Neurologiques, CHU Côte de Nacre,14033 Caen Cedex, France*
[b]*CRESS, UPRES EA 1609, Division STAPS, bât 335, Université Paris XI-Orsay, 91405 Orsay Cedex, France*

Received 27 December 2001; received in revised form 30 October 2002; accepted 30 October 2002

Abstract

The effects of a single dose of zolpidem (10 mg), zopiclone (7.5 mg) and flunitrazepam (1 mg) on motor activity the following 3 nights were compared to those of a placebo in a double-blind, crossover study. Thirty-three healthy subjects received medication between 10.30 and 11.30 p.m. and were asked to rise between 7.30 and 8.30 a.m. During the night under treatment, flunitrazepam, zopiclone and zolpidem significantly reduced motor activity. Changes in motor activity are quantitatively compatible with the hypothesis of reduced light sleep and wakefulness after sleep onset. During the first or second post-drug night, for zolpidem and zopiclone the opposite effect was observed, i.e. increased activity compared with placebo. These modifications cannot be explained by modified sleep structure. This last result underlines our inadequate understanding of the underlying mechanisms of motor activity during sleep. However, being sensitive and easy to use, actigraphy is an ideal technique to assess the effect of hypnotics on large populations and for long duration studies.

Keywords: Zolpidem; Zopiclone; Flunitrazepam; Actigraphy; Side-effect; Sleep

1. Introduction

The therapeutic aim of hypnotic drugs being to induce and maintain sleep, they should reduce both the latency of sleep onset and the number or duration of awakenings (wake after sleep onset, WASO). Along with these desired effects, hypnotics have side-effects on sleep structure. Thus, benzodiazepines, which are second generation hypnotics, increase stage 2 sleep and reduce REM sleep and slow wave sleep (stages 3 and 4) (for review see Parrino and Terzano, 1996). Moreover, rebound insomnia may be produced by discontinuation of benzodiazepine hypnotics even when taken for short periods of time (for review see Gillin et al., 1989). Conversely, zolpidem and zopiclone, third generation hypnotics, seem to induce only slight alterations to sleep structure and no rebound insomnia (Parrino and Terzano, 1996). However, this conclusion was drawn from a small number of studies, each only involving a small number of subjects, usually less than ten. These negative results may therefore be due to low statistical power. The small number of subjects is partly due to the fact that these studies used polysomnography (PSG), the reference technique for the study of sleep and the only one capable of describing its structure, but a costly and time-consuming one. Intra-subject variability in sleep episodes from one night to another is such that even a high precision method as PSG fails to highlight substantial effects in a small number of subjects.

Being cheap and easy to use, actigraphy, the continuous ambulatory recording of motor activity, has developed as a method for assessing sleep. Some polysomnographic parameters such as total sleep time, time in bed, and WASO are highly correlated with actigraphic measurements (for review, see Sadeh et al., 1995). Although the underlying mechanisms for motor activity during sleep are not fully understood, several studies have found a relationship between sleep structure and movements (Gimeno et al., 1998; Middelkoop et al., 1993). While actigraphy does not

*Corresponding author. Tel.: +33-231-064-528; fax: +33-231-068-219.
E-mail address: denise-p@chu-caen.fr (P. Denise).

0924-977X/02/$ – see front matter
doi:10.1016/S0924-977X(02)00153-0

reveal the fine structure of sleep, it does have definite advantages over polysomnography: it costs less in material and scoring time; it interferes less in the subject's normal life; it is ambulatory, so sleep characteristics can be observed in the person's normal habitat; it can be used for long periods of time. Thus, actigraphy would appear to be a technique well suited to detecting changes in sleep in a large number of subjects over an extended period.

All hypnotics studies using actigraphy reported a decrease in motor activity during sleep (Borbély et al., 1983, 1984; Borbély, 1984, 1986; Crowley and Hydinger-Macdonald, 1979; Mattmann et al., 1982). However, no research using actigraphy has been done with third generation hypnotics.

The first aim of the study was to look for the effects of zolpidem and zopiclone on night-time motor activity. Since the most appropriate role for hypnotics is in transient sleep disorders, we looked for the effects of these two drugs in single doses on healthy volunteers. The second aim of this study was to determine changes in night-time motor activity during the 2 post-drug nights.

2. Experimental

2.1. Subjects

The study was carried out on 33 healthy volunteers (21 men and 12 women, mean age 27.5 years; range 20–67) who reported no disorders of sleeping, alertness, neurological, cardiovascular, respiratory, hepatic, renal or metabolism; no chronic or transitory use of medication, except contraceptives, during the 2 years prior to the experiment; no cigarette consumption>10 cigarettes per day or alcohol consumption >28 units per week.

2.2. Designs

The study was conducted according to a balanced, double-blind, crossover design. Each subject followed four sessions held at intervals of 2 weeks. Zolpidem 10 mg, zopiclone 7.5 mg, flunitrazepam 1 mg or placebo in identical capsules were administered at the subject's home under the supervision of an investigator between 10.30 p.m. and 11.30 p.m. All hypnotics were administered at the lowest therapeutic dose. Flunitrazepam was introduced into this study as a positive control since night motor activity was already determined with this drug (Mattmann et al., 1982).

The subjects placed the activity monitor on the non-dominant wrist at the time of taking the capsule and removed it at the end of the first night for 16 subjects and at the end of the 3rd night for the 17 others. The subjects were instructed to retire to bed within 30 min of taking the medication and to rise between 7.30 a.m. and 8.30 a.m. The start and duration of the night being imposed by the protocol, these parameters were not studied.

The experiments took place from Monday evening to Saturday morning. To avoid any possible interference with changes in chronobiological rhythms from one day of the week to the other, for one subject, the medication was delivered on the same day of the week for all four sessions.

2.3. Actigraphy

The actigraph (Gaehwiler Electronic, CH-8634 Hombrechtikon, Switzerland) counts, over 1-min epochs, the occurrence of supra-threshold movements (acceleration greater than 0.1 g). To determine the start and the end of the sleep period, actigraphic data were temporarily smoothed by a moving window averaging with a 30-min width. The start of the sleep period was determined as being the first period of total inactivity, and the end of the sleep period as being the last period of total inactivity. Over the sleep period thus determined, three parameters defined by Middelkoop et al. (1993) were then calculated with raw unsmoothed actigraphic data:

- The activity level (AL) is the mean activity count/1-min epoch.
- The movement index (MI) is the percentage of epochs with an activity count greater than zero.
- The mean duration of uninterrupted immobility periods (DIP). An uninterrupted immobility period is made up of consecutive epochs with an activity count=0.

2.4. Statistical analysis

The effects of the medication on each of the actigraphic parameters were assessed using an ANOVA with two factors (medication×subject) followed by a multiple mean comparison test with the placebo condition (Dunnett's *t* test). $P<0.05$ was considered as statistically significant. Statistical analysis was performed using SAS 6.10.

3. Results

During the night under treatment, flunitrazepam, zopiclone and zolpidem significantly reduced the AL [$F(3.32)=13.2$; $P<0.001$] and the MI [$F(3.32)=9.2$; $P<0.0001$] and increased the DIP [$F(3.32)=12.5$; $P<0.0001$] (Fig. 1). The most important effects were observed following ingestion of flunitrazepam and the smallest one after ingestion of zolpidem.

As early as the first post-drug night, the effect of treatment on the DIP and the MI disappeared ([$F(3.16)=1.26$; $P=0.29$ for DIP]; [$F(3.16)=1.58$; $P=0.2$ for MI]). On the other hand, the treatment still had an effect on the

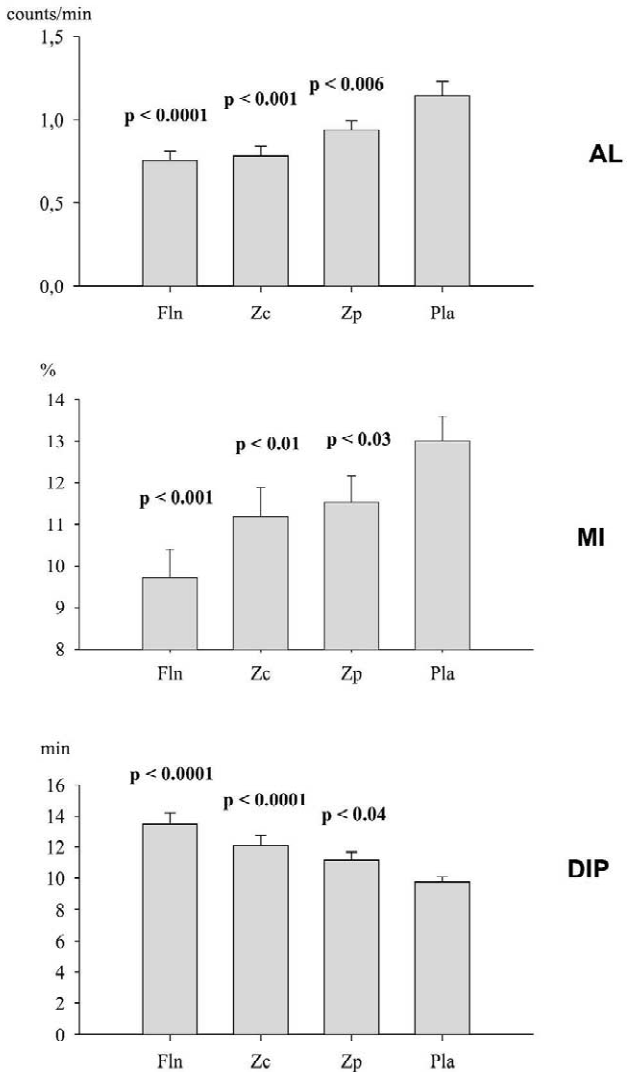

Fig. 1. Effects of treatments on activity level (AL), movement index (MI) and duration of uninterrupted immobility periods (DIP). Results are expressed as means+S.E. Significant comparisons to placebo using Dunnett's test are depicted. Fln, flunitrazepam 1 mg; Zc, zopiclone; Zp, zolpidem 10 mg; Pla, placebo.

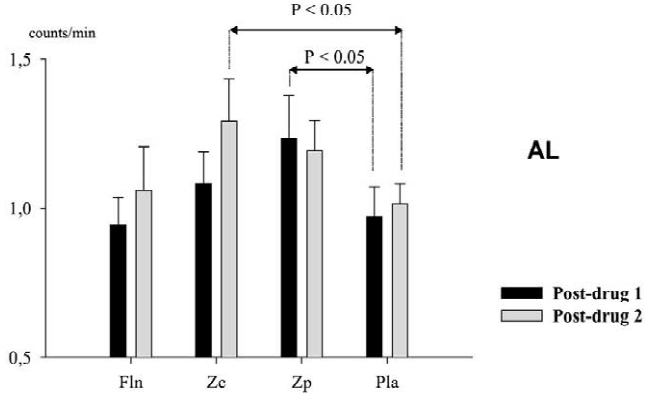

Fig. 2. Effects of treatments on activity level (AL) of post-drugs nights. Mean+S.E. and Dunnett's test statistical significant results are represented.

AL [$F(3.16)=3.19$; $P=0.02$] but it was only significant for zolpidem (Fig. 2). However, what we see here is an increase in the AL (by 26%) compared with placebo and hence an inversion of the effect observed during the night under medication.

During the second post-drug night, the effect of zolpidem had worn off whereas zopiclone increased the AL by 17% [$F(3.16)=2.25$; $P=0.08$].

4. Discussion

4.1. Nights under treatment

In the healthy young subjects of the present study, flunitrazepam, zolpidem and zopiclone reduced night-time motor activity. Only flunitrazepam had been previously studied using actigraphy: the drop in the MI that we observed at a 1-mg dose (25%) is similar to that found by Mattmann et al. (1982) with a 2-mg dose. Thus, our study extends this finding to zolpidem and zopiclone.

The marked changes in night-time motor activity found here with zolpidem and zopiclone contrast with the moderate changes in sleep structure observed by the polysomnographic studies. Despite this apparent disagreement, we nevertheless tried to determine whether these changes in night-time motor activity might result from altered sleep structure.

In order to verify this hypothesis, we took as a basis a study of Middelkoop et al. (1993) that quantified the level of night-time motor activity in function of PSG sleep stages. These data enable a theoretical value of actigraphic parameters to be calculated for any hypnogram. We performed this theoretical calculation from the various studies that quantified, stage by stage in healthy subjects, alterations to sleep structure induced by flunitrazepam, zopiclone and zolpidem administered at comparable doses to that of our study (except for flunitrazepam, where the studies only involved doses of 0.5 mg or 2 mg). For each parameter and each molecule, we then calculated the percentage variation as compared with the theoretical values of the night under placebo. The result of this theoretical calculation is compared with the actual values of our study in Table 1.

For the AL and the MI, there are good agreements between the observed values and theoretical values, except for the study by Nicholson and Stone (1982), where, although leading in the same direction, predicted variations in AL and MI are substantially smaller than in our study. On the other hand, for variations in DIP, the theoretical values are systematically lower than the observed values.

According to Middelkoop et al. (1993), the MI and the AL mainly depend on the quantity of stage 1 and WASO whilst the DIP depends primarily on the slow wave sleep and, to a lesser extent, on stage 2 sleep. Thus, we may

Table 1
Actual and theoretical variations in actigraphic parameters during the night after intake of 7.5 mg zopiclone (Zc), 10 mg Zolpidem (Zp) and 1 mg flunitrazepam (Fln)

			MI	AL	DIP
Zc	Actual effect		−15	−31	+23
	Estimated effect	Nicholson and Stone, 1982	−5	−3	+7
		Billiard et al., 1987	−16	−23	+15
		Billiard et al., 1989	−22	−34	+12
Zp	Actual effect		−12	−17	+14
	Estimated effect	Nicholson and Pascoe, 1986	−13	−23	+5
		Brunner et al., 1991	−8	−11	+5
Fln	Actual effect		−25	−34	+37
	Estimated effect	Nicholson and Stone, 1980 (0.5 mg)	−13	−21	+12
		Borbély et al., 1985 (2 mg)	−40	−51	+4
		Gaillard and Blois, 1989 (2 mg)	−35	−51	+2

All values are expressed in percentage of the night under placebo. See text for explanations.

conclude that actigraphy, through measurement of MI and AL, is a fairly reliable technique for assessing stage 1 and WASO changes due to the intake of hypnotics while it does not afford access to changes in slow wave sleep.

4.2. Post-drug nights

During the first post-drug night, the AL was higher for zolpidem than for placebo. This is therefore the opposite effect from that observed during the night under treatment when the AL was lower for zolpidem than for placebo. For zopiclone, we also observed an inversion, but it was delayed, appearing only during the second post-drug night. These effects in the opposite direction to that observed during the night under medication may be likened to a rebound effect. The timing of this rebound effect could depend on the hypnotic half-life, which is longer for zopiclone than for zolpidem. This increase in motor activity cannot be interpreted as being secondary to a change in WASO. Indeed, Brunner et al. (1991) have shown that WASO is lower during the post-zolpidem night than during the post-placebo night and this decreasing ought therefore to be accompanied by a decrease in the AL. In the present study flunitrazepam did not alter motor activity during the 2 post-drug nights. This result confirms observations of Mattmann et al. (1982). Owing to flunitrazepam long half-life, one may suppose that the rebound effects come later and that an increased AL would be noticeable several nights after discontinuation.

For the first post-flunitrazepam night, the theoretical AL calculated on the basis of sleep stages obtained by Borbély et al. (1985) and Gaillard and Blois (1983) is decreased by 11 and 17%, respectively, as compared with the post-placebo night, whereas the value observed in our study was only 3%. Thus, for post-flunitrazepam nights as well as for post-zolpidem nights, actigraphy systematically gives higher values than those that would be expected from an alteration of the structure of sleep alone.

4.3. Disagreement between actigraphy and PSG; limitation of the study

Contrary to other changes in actigraphic parameters observed in the present study, variations in DIP during the night under medication and in AL during the post-drug nights cannot be interpreted as sleep structure modifications. Although polysomnography and actigraphy reach an acceptable level of agreement in normal subjects (Sadeh et al., 1994), there are systematic differences in patients suffering from sleep or psychiatric disorders (Sadeh et al., 1995; Jean-Louis et al., 2000; Pilsworth et al., 2001). In other words, control mechanisms of sleep and control mechanisms of motor activity during sleep can be differently affected by pathologic conditions. The same probably holds true for subjects treated with hypnotic drugs. This result once again underlines our inadequate understanding of the underlying mechanisms of motor activity during sleep.

Moreover, even though we could conclude from the present study that variations in AL and MI after taking hypnotics reflect a decrease in light sleep and WASO, this conclusion is valid only with healthy subjects but is not necessarily true with insomniac patients. The first reason is that relationship between actigraphy and PSG is not the same for insomniac and normal subjects (see review in Verbeek et al., 2001). The second reason is that the effects of hypnotics on sleep structure—and thus on sleep dependant actigraphic parameters—are not quantitatively the same in good and insomniac sleepers. In the present experiment, as homogeneous samples of insomniacs are difficult to recruit for pharmacotherapy studies, we choose to study normal sleepers; that choice is justifiable because

a large segment of the population use hypnotics only occasionally for a single night.

5. Conclusion

Actigraphy highlights major modifications to night-time motor activity following ingestion of zopiclone and, to a lesser degree, zolpidem. Changes to AL and MI after taking hypnotics may be interpreted as modifications of sleep structure. More specifically, they probably chiefly reflect decreases in light sleep and WASO. These are also the two sleep stages that hypnotics are particularly aimed at. Actigraphy thus seems particularly well-suited to assessing the therapeutic effects of hypnotics.

This study demonstrates the value of actigraphy when assessing short-term use of hypnotics. Such value stems in particular from the possibility of studying a large population. In addition, being easy to use, inexpensive and ambulatory, it is a suitable means for studying rebound and long-term effects of hypnotics, which cannot be done with PSG.

References

Billiard, M., Besset, A., de Lustrac, C., Brissaud, L., 1987. Dose–response effects of zopiclone on night sleep and on night-time and daytime functioning. Sleep 10 (Suppl. 1), 27–34.

Billiard, M., Besset, A., De Lustrac, C., Brissaud, L., Cadilhac, J., 1989. Effects of zopiclone on sleep, daytime somnolence and nocturnal and daytime performance in healthy volunteers. Neurophysiol. Clin. 19, 131–143.

Borbély, A.A., 1984. Ambulatory motor activity monitoring to study the timecourse of hypnotic action. Br. J. Clin. Pharmacol. 18 (Suppl 1), 83S–86S.

Borbély, A.A., 1986. New techniques for the analysis of the human sleep–wake cycle. Brain Dev. 8, 482–488.

Borbély, A.A., Loepfe, M., Mattmann, P., Tobler, I., 1983. Midazolam and triazolam: hypnotic action and residual effects after a single bedtime dose. Arzneimittelforschung 33, 1500–1502.

Borbély, A.A., Mattmann, P., Loepfe, M., 1984. Hypnotic action and residual effects of a single bedtime dose of temazepam. Arzneimittelforschung 34, 101–103.

Borbély, A.A., Mattmann, P., Loepfe, M., Strauch, I., Lehmann, D., 1985. Effect of benzodiazepine hypnotics on all-night sleep EEG spectra. Hum. Neurobiol. 4, 189–194.

Brunner, D.P., Dijk, D.J., Münch, M., Borbély, A.A., 1991. Effects of zolpidem on sleep and sleep EEG spectra in healthy young men. Psychopharmacology 104, 1–5.

Crowley, T.J., Hydinger-Macdonald, M., 1979. Bedtime flurazepam and the human circadian rhythm of spontaneous motility. Psychopharmacology 62, 157–161.

Gaillard, J.M., Blois, R., 1983. Effect of the benzodiazepine antagonist Ro 15-1788 on flunitrazepam-induced sleep changes. Br. J. Clin. Pharmacol. 15, 529–536.

Gaillard, J.M., Blois, R., 1989. Differential effects of flunitrazepam on human sleep in combination with flumazenil. Sleep 12, 120–132.

Gillin, J.C., Spinweber, C.L., Johnson, L.C., 1989. Rebound insomnia: a critical review. J. Clin. Psychopharm. 9, 161–172.

Gimeno, V., Sagales, T., Miguel, L., Ballarin, M., 1998. The statistical distribution of wrist movements during sleep. Neuropsychobiology 38, 108–112.

Jean-Louis, G., Mendlowicz, M.V., Gillin, J.C., Rapaport, M.H., Kelsoe, J.R., Zizi, F., Landolt, H., von Gizycki, H., 2000. Sleep estimation from wrist activity in patients with major depression. Physiol. Behav. 70, 49–53.

Mattmann, P., Loepfe, M., Scheitlin, T., Schmidlin, D., Gerne, M., Strauch, I., Lehmann, D., Borbély, A.A., 1982. Day-time residual effects and motor activity after three benzodiazepine hypnotics. Arzneimittelforschung 32, 461–465.

Middelkoop, H., Van Hilten, B., Kramer, C., Kamphuisen, H., 1993. Actigraphically recorded motor activity and immobility across sleep cycles and stages in healthy male subjects. J. Sleep Res. 2, 28–33.

Nicholson, A.N., Stone, B.M., 1980. Activity of the hypnotics, flunitrazepam and triazolam, in man. Br. J. Clin. Pharmac. 9, 187–194.

Nicholson, A.N., Stone, B.M., 1982. Zopiclone: sleep and performance studies in healthy man. Int. Pharmacopsychiatry 27 (Suppl 2), 92–97.

Nicholson, A.N., Pascoe, P.A., 1986. Hypnotic activity of an imidazopyridine (zolpidem). Br. J. Clin. Pharmacol. 21, 205–211.

Parrino, L., Terzano, M.G., 1996. Polysomnographic effects of hypnotic drugs. A review. Psychopharmacology 126, 1–16.

Pilsworth, S., King, M., Shneerson, J., Smith, I., 2001. A comparison between measurements of sleep efficiency and sleep latency measured by polysomnography and wrist actigraphy. Sleep 24, A106.

Sadeh, A., Hauri, P.J., Kripke, D.F., Lavie, P., 1995. The role of actigraphy in the evaluation of sleep disorders. Sleep 18, 288–302.

Sadeh, A., Sharkey, K.M., Carskadon, M.A., 1994. Activity-based sleep–wake identification: an empirical test of methodological issues. Sleep 17, 201–207.

Verbeek, I., Klip, E.C., Declerck, A.C., 2001. The use of actigraphy revised: the value for clinical practice in insomnia. Percept Mot. Skills 92, 852–856.