

Effect of the administration of gabaergic agonists of the GABA_A/BDZ receptor on sleep in human subjects

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Summary

The aim of the present study was to evaluate the effects of the acute administration of a single dose of a long-term benzodiazepine (10 mg diazepam), an imidazopyridine (10 mg zolpidem), a cyclopyrrolone (7.5 mg zopiclone) a complex molecular GABA_A/BDZ agonist (500 mg Gabob) and a placebo on the sleep pattern of 10 healthy subjects using a double blind incomplete block Latin square design. Night (8h duration) polysomnographic recordings of each subject were registered for six consecutive nights to evaluate polysomnographic variables related to the quantity and quality of sleep.

Results indicate no significant changes in the polysomnographic variables related to the quantity of sleep after drug administration. However, three variables related to the quantity of sleep were affected, specifically, the percentage of stage I sleep, REM sleep and stage II episodes. Zopiclone significantly improved the polysomnographic variables related to quantity of sleep when statistical comparisons were made between baseline, drug administration and washing periods. Interestingly, the placebo worsened the polysomnographic variables related to the amount of sleep, which were affected by a clear "placebo effect".

Key words: Sleep, hypnotics, diazepam, zopiclone, zolpidem, Gabob, placebo, GABA.

Resumen

El objetivo de este estudio ha sido evaluar los efectos de la administración aguda de una única dosis de una benzodiazepina de acción prolongada (diazepam, 10 mg), una imidazopiridina (zolpidem, 10 mg), una ciclopírrrolona (zopiclona, 7.5 mg), un agonista del complejo molecular GABA_A/BDZ (Gabob, 500 mg), y un placebo, sobre el sueño

en diez sujetos sanos, utilizando un diseño doble-ciego de cuadrado latino de bloques incompletos. Para ello, se hizo un registro polisomnográfico nocturno (de ocho horas de duración) de cada sujeto durante seis noches consecutivas, en donde se evaluaban variables polisomnográficas relacionadas con la cantidad y la calidad de sueño.

Nuestros resultados indicaron que no hubo ningún cambio significativo en las variables polisomnográficas relacionadas con la cantidad de sueño tras la administración de las sustancias. En cambio, los fármacos afectaron tres variables relacionadas con la calidad de sueño; en concreto, al porcentaje de la fase I de sueño, al de sueño MOR (Movimientos Oculares Rápidos) y al de los episodios de la fase II. Por otra parte, nuestros resultados pusieron de manifiesto que la zopiclona fue la sustancia que produjo una mejoría significativa en las variables polisomnográficas relacionadas con la cantidad de sueño, cuando las comparaciones estadísticas se establecieron entre la línea base, la administración del fármaco y el periodo de lavado del fármaco. No obstante, el placebo produjo un empeoramiento de las variables polisomnográficas relacionadas con la cantidad de sueño, evidenciándose un claro "efecto placebo" sobre las variables polisomnográficas.

Palabras clave: Sueño, hipnóticos, diazepam, zopiclona, zolpidem, Gabob, placebo, GABA.

Introduction

At present, the most frequent prescription in cases of sleep problems are benzodiazepines. Since their discovery, more than thirty years ago, benzodiazepines have almost totally displaced other substances such as barbiturates in the treatment of anxiety and insomnia (65,66). Recently, new compounds are being used which differ chemically from benzodiazepines, with clear advantages; among them are cyclopyrrolones and imidazopyridines, which belong to the "third generation" hypnotics.

The effects of benzodiazepine on sleep have been analyzed in various reports (3,7,10,29,53,68). In general, they improve sleep efficiency by reducing its latency and the number of awakenings. However, besides modifying "normal" sleep architecture—benzodiazepines increase phase II sleep duration, diminish delta sleep and REM sleep duration, and lengthen REM sleep

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latency– they may cause dependence and tolerance and even rebound insomnia after treatment has ended (3,10,53).

On the other hand imidazopyridines (e.g. zolpidem) and cyclopyrrolones (e.g. zopiclone) have proved to be as efficient as benzodiazepines. They induce sleep quickly, increasing the total sleep period and decrease the number of awakenings. However in contrast with benzodiazepine, they do not seem to modify sleep architecture so extensively (45,57). Specifically, no change nor an increase in delta sleep duration have been describes after zolpidem administration (61,63), while zopiclone has been found to increase (31,48) or to diminish (1,20,54) the delta phase.

Gamma-amino-b-hydroxybutiric acid (Gabob), a GABA derivative, is a natural constituent of the mammalian brain, including that of humans. This compound possesses anticonvulsant activity (5,12,50) and is considered as the physiological gabaergic agent of the body (52). However, its effects on sleep have not been studied.

The aim of the present study was to analyze the effects of acute administration of a long-term benzodiazepine (10 mg diazepam), an imidazopyridine (10 mg zolpidem), a cyclopyrrolone (7.5 mg zopiclone), a GABA_A/BDZ agonist (500 mg Gabob) and a placebo, on the sleep of 10 healthy subjects, using a double-blind incomplete block Latin square design. Night (8h duration) polysomnographic recordings of each subject were registered for 6 consecutive nights to evaluate polysomnographic variables.

Materials and method

The sample consists of 10 healthy male voluntaries, of 18 to 30 years, from the Faculty of Psychology of the National Autonomous University of Mexico (UNAM), in Mexico City. The sample was selected by interview. The questionnaire included information on age, weight, health conditions, hours of sleep and psychotropic drug consumption, including tobacco and alcohol. Once selected, the subjects were informed of the general objectives of the study and filled in a written consent form.

The design of the study was double blind. Each subject had to remain in the Sleep Laboratory of the Mexican Institute of Psychiatry (IMP) for 6 consecutive nights (habituation, base line, drug 1, washing-placebo, drug 2, washing-placebo).

Experimental procedure

Each subject went through 1 base line, as well as 2 of the 5 drugs under study and their respective washings, as corresponded to the incomplete block design (table 1). At 21:00h, electrodes were placed on the experimental subject. At 22:00h, the subjects took the drug in capsules; all capsules were physically identical. The sleep register was set from 22:30h to 6:30 h (total registration time: 8h).

The night polysomnographic recordings were performed with an 8 channel 78D Grass model

TABLE 1
Experimental desing of incomplete blocks with drugs for each subject

Subject	Drug 1	Drug 2
1	Diazepam	Zopiclone
2	Zopiclone	Placebo
3	Zolpidem	Gabob
4	Gabob	Diazepam
5	Placebo	Zolpidem
6	Diazepam	Zolpidem
7	Zopiclone	Gabob
8	Zolpidem	Zopiclone
9	Gabob	Placebo
10	Placebo	Diazepam

polygraph with a Grass electrode selector panel. The channels were distributed as follows: channel 1 was used for derivation C3-O1, channel 2 for derivation C4-O2, channel 3 for derivation C4-A1, and channel 4 for derivation O1-O2 of the EEG activity; channel 5 for derivation Fpl-A2 and channel 6 for derivation Fp2-A2, both of the EOG activity; channel 7 for derivation T3-T5 of the EMG activity, and channel 8 for derivation T4-T6 of the EKG activity. Gold electrodes of 1 cm diameter were fixed with collodion.

The polysomnographic variables evaluated were: those related to "sleep quantity" (sleep efficiency, percentage of wakefulness, percentage of awakenings and sleep latency), and those related to "sleep quality" (percentage of duration of phase I, phase II, delta and REM sleep; percentage of episodes of phase II, delta and REM sleep; phase II, delta and REM sleep latency; number of movements, phase changes and sleep cycles; and heart rate during sleep).

Results were analyzed with the BMDP-4V statistical package. The differences between effects produced by drugs and placebo on sleep on the night of administration (drug conditions) and on the following night (washing conditions) were analyzed by ANOVA. Mean values were converted as describes by Kirk (34) adjusting to the subject. Whenever statistical significance was obtained, multiple *a posteriori* comparisons were performed following the procedure describe by Duncan.

Finally, to corroborate possible statistically significant differences among the polysomnographic variables of base line, drug and washing conditions, a Friedman analysis of variance by ranks, was applied.

Statistical analysis

Table 2 shows the effects of drug and placebo administration on sleep. Statistically significant differences were found in the following variables: percentage of phase I and REM sleep duration, and percentage of phase II sleep episodes.

Regarding the percentage of phase I sleep, Gabob increased it to a greater extent than diazepam ($F = 6.73$; $p < 0.05$).

Zopiclone significantly reduced this percentage compared with zolpidem, Gabob and the placebo ($F = 6.73$; $p < 0.05$).

TABLE 2
Adjusted mean scores and standard deviations of polysomnographic variables in the total sample under drug conditions (diazepam, zopiclone, zolpidem, Gabob) and placebo

Variables (IN %)	Diazepam		Zopiclone		Zolpidem		Gabob		Placebo		F
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Sleep efficiency	99.23	0.6	98.85	0.4	98.85	0.4	98.69	0.9	98.91	0.7	ns
Wakefulness	0.76	0.6	0.95	1.1	1.13	0.4	1.98	0.9	1.08	0.8	ns
Phase I	2.98	1.2	2.10	0.6 [#]	4.00	1.4	4.80	0.9 ^{##}	4.12	2.7	p < 0.05
Phase II	48.04	6.7	56.94	11.2	39.08	8.1	49.80	3.0	41.32	7.0	ns
Delta	21.70	4.2	20.91	7.2	34.35	10.7	23.23	3.5	27.66	7.3	ns
REM	27.26	2.1 s	20.01	6.3 ss	22.53	2.8	22.12	3.6	26.86	3.3	p < 0.05
Wakefulness episodes	5.28	3.3	2.14	0.9	6.12	2.4	6.34	2.7	4.14	1.4	ns
Phase I episodes	19.90	10.8	15.70	3.4	22.40	4.4	25.50	3.3	18.00	6.7	ns
Phase II episodes	40.80	5.0	45.60	0.0 ^{###}	41.40	3.3	38.80	1.8	39.70	3.8	p < 0.05
Delta episodes	14.50	6.3	18.90	3.0	12.40	5.6	16.10	1.2	18.20	4.2	ns
REM episodes	19.40	4.4	17.40	6.3	17.30	3.4	12.90	3.0	19.80	5.9	ns
Sleep latency (min)	1.72	1.4	5.90	5.7	3.90	2.3	3.83	3.3	3.97	2.7	ns
Phase II latency (min)	4.75	1.4	4.65	0.3	5.63	2.4	4.86	1.0	3.95	0.8	ns
Delta latency (min)	15.14	1.2	13.42	0.9	12.42	2.3	13.35	2.3	9.82	2.3	ns
REM latency (min)	78.79	5.7	90.07	23.2	96.49	3.2	99.33	11.5	63.53	8.0	ns
Number movements (freq)	5.95	5.4	9.95	4.8	11.95	4.7	6.95	7.4	7.95	6.4	ns
Number phase changes (freq)	30.40	10.3	26.40	4.2	35.00	8.5	41.40	5.1	36.80	3.5	ns
Number sleep cycles (freq)	4.90	0.0	4.90	0.4	4.90	0.2	4.65	0.2	5.25	0.0	ns
Sleeping heart rate (freq)	61.38	10.7	58.20	4.1	61.45	6.6	61.22	2.5	61.78	5.2	ns

zopiclone vs. zolpidem, Gabob y placebo; ## Gabob vs. diazepam; s diazepam vs. zopiclone; ss zopiclone vs. placebo; ### zopiclone vs. Gabob and placebo
 ns: non-significant.
 min: minutes
 freq: frequencies.

With respect to REM sleep percentage, zopiclone produced the least levels, while diazepam produced the highest (F = 4.71; p = 0.05).

In the case of phase II sleep episode percentage, zopiclone increased it and Gabob produced the lowest levels of this variable (F = 8.58; p = 0.01).

Considering sleep latency, a statistically significant tendency (F = 3.71; p = 0.09) was observed: diazepam showed the lowest sleep latency and zopiclone the highest.

On the other hand, no statistically significant results were obtained in polysomnographic variables when observations under washing conditions were compared among each other.

The Friedman analysis of variance by ranks showed statistically significant differences in heart rate during sleep [X²r (2) = 6.5; (p < 0.01)] after diazepam administration and a higher heart rate was observed during sleep under base line conditions than under diazepam washing conditions (table 3).

Statistically significant differences were also found between base line conditions and drug conditions in sleep efficiency and percentage of wakefulness after zopiclone administration [X²r (2) = 6.5; (p < 0.01)]: sleep efficiency was clearly improved and a distinct decrease in percentage of wakefulness was recorded. Further significant differences were found between the drug condition and its respective washing which showed a higher percentage of phase I sleep [X²r (2) = 6.5; (p < 0.01)]. Additionally, zopiclone produced a marked increase in the percentage of phase II and delta episodes on the night of administration, compared to

washing conditions [X²r (2) = 6.5; (p < 0.01)], and in the delta phase episode percentage between base line and washing condition [X²r (2) = 6.5; (p < 0.05 and p < 0.01, respectively)].

Similarly, zolpidem produced a decrease in phase I sleep percentage compared with its respective washing [c²r (2) = 6.5; (p < 0.01)]. Regarding percentage of phase II sleep episodes and REM sleep latency, statistically significant differences were observed between base line, which showed higher values, and washing [c²r (2) = 6.5; (p < 0.01)]. Additionally, REM sleep latency was increased.

Finally, when the administered substance was a placebo, significant differences were observed between drug and washing conditions regarding sleep efficiency, with higher values in the drug condition [c²r (2) = 6.5; (p < 0.01)]. This was also true for percentage of wakefulness, but with lower values in the drug condition [c²r (2) = 6.1; (p < 0.01)]. Percentage of awakenings was also significantly different when base line and drug condition or base line and washing were compared [c²r (2) = 6; (p < 0.01)], with higher values for base line. Sleep latency was significantly lower in the drug condition compared to its washing [c²r (2) = 6.5; (p < 0.01)].

Results and discussion

No statistically significant differences were observed between treatment with diazepam, zopiclone and zolpidem in the polysomnographic variables related to

TABLE 3
Range means of total sample for base line, drug and washing by substance used
for polysomnographic study. A Friedman variance analysis by ranges was done

Variables (IN %)	Diazepam			Zopiclone			Zolpidem			Gabob			Placebo		
	BL	D	W	BL	D	W	BL	D	W	BL	D	W	BL	D	W
Sleep efficiency	1.25	2.75	2.00	1.00	2.75	2.25#	2.00	1.75	2.25	2.25	2.12	1.62	1.75	3.00	1.25#
Wakefulness	2.75	1.25	2.00	3.00	1.25	1.75#	2.00	2.25	1.75	1.75	1.87	2.37	2.37	1.00	2.62#
Phase I	2.75	1.50	1.75	2.25	1.00	2.75#	2.25	1.00	2.75#	2.50	2.00	1.50	2.25	2.00	1.75
Phase II	1.75	2.25	2.00	2.00	2.50	1.50	2.50	1.50	2.00	1.75	2.50	1.75	2.00	1.25	2.75
Delta	2.25	2.25	1.50	1.50	2.00	2.50	1.50	2.50	2.00	2.25	1.50	2.25	2.25	2.00	1.75
REM	1.25	2.00	2.75	2.00	1.50	2.50	2.25	2.00	1.75	1.50	2.00	2.50	1.50	2.50	2.00
Wakefulness episodes	2.50	1.87	1.62	2.75	1.25	2.00	2.50	1.50	2.00	2.62	2.12	1.25	3.00	1.50	1.50#
Phase I episodes	2.37	1.37	2.25	2.25	1.25	2.50	1.75	1.75	2.50	2.12	2.25	1.62	2.25	2.25	1.50
Phase II episodes	2.00	2.37	1.62	1.75	3.00	1.25#	2.75	2.25	1.00#	1.87	1.75	2.37	2.00	1.25	2.75
Delta episodes	2.00	1.87	2.12	1.50	3.00	1.50#	1.75	2.00	2.25	1.75	1.50	2.75	1.75	2.00	2.25
REM episodes	1.50	2.75	1.75	1.50	2.25	2.25	2.00	1.87	2.12	2.12	1.50	2.37	1.50	2.75	1.75
Sleep latency (min)	2.50	1.75	1.75	2.50	2.00	1.50	2.25	1.75	2.00	1.50	1.75	2.75	1.75	1.25	3.00#
Phase II latency (min)	2.25	1.75	2.00	3.00	1.25	1.75	2.50	1.50	2.00	2.50	2.50	1.00	2.75	1.50	1.75
Delta latency (min)	2.25	2.25	1.50	2.62	1.37	2.00	2.50	1.50	2.00	2.25	2.25	1.50	2.75	1.37	1.87
REM latency (min)	2.00	2.00	2.00	1.75	2.00	2.25	1.00	2.25	2.75#	1.50	2.50	2.00	2.00	1.75	2.25
Number movements (freq)	2.00	1.25	2.75	2.00	2.50	1.50	2.00	2.50	1.50	1.62	1.62	2.75	1.37	2.75	1.87
Number phase changes (freq)	2.75	1.37	1.87#	2.37	1.25	2.37	1.75	2.12	2.12	1.87	2.25	1.87	2.25	2.00	1.75
Number sleep cycles (freq)	2.13	2.13	1.75	2.00	2.25	1.75	2.25	1.87	1.87	2.38	2.00	1.63	2.13	2.13	1.75
Sleeping heart rate (freq)	3.00	1.75	1.25	2.50	1.75	1.75	2.00	1.75	2.25	2.00	2.50	1.50	2.25	2.25	1.50

p < 0.05. BL: Base line.
min: minutes D: Drug.
freq: frequencies. W: Washing.

"quantity of sleep". Similar results have been published elsewhere (4,14,17,46,60,64,70). Also, no significant differences were observed between administration of Gabob and the other drugs in these variables, which suggests a hypnotic potential of this substance. The absence of significant differences between drugs with respect to these variables is probably related to the fact that acute administration would hardly be able to improve "quantity of sleep" in healthy subjects who exhibit optimal sleep efficiency and latency, as well as percentage of vigilance. In this context, two studies by Mendelson (41,42) may be mentioned which reveal differences between healthy and insomniac subjects. Additionally, in the present study, the four substances did not show significant differences compared with the placebo in "quantity of sleep" related variables. These data agree with studies in which the hypnotic potential of these drugs was analyzed in healthy subjects (8,9,11,39,40,54) but differ from results found in insomniacs (27,46,47,49,61,63).

Regarding the polysomnographic parameters related to the "quality of sleep", and in agreement with various reports (31,44,56), first zopiclone and then diazepam produced the lowest percentage of phase I sleep (figure 1).

No significant differences were observed between the tested drugs in the percentage of phase II sleep. Although several reports describe the opposite (14,25,29,31,38,45,59,69), there are also studies with similar results as ours (8,18,56,67). Once more,

differences may be attributed to the use of healthy subjects and insomniacs.

Even though these results did not attain statistical significance, zolpidem produced a higher percentage of delta phase sleep, while zopiclone and diazepam attained a lesser percentage. Various studies have reported either an increment or no change in the delta sleep phase after zolpidem administration (14,15,25,37,51,63,67), while zopiclone administration produces either an increment, a decrease or no change in delta phase sleep (1,8,20,25,64).

Acute diazepam administration significantly increased the percentage of REM sleep (figure 1). These results differ from those of Ashton (3) and Kales et al (29, 30). However, similar results to those of our study were reported by Kanno et al (31).

In our experiments, zopiclone exhibited the lowest percentage of REM sleep, compared with diazepam and placebo (figure 1). This agrees with the results describes in some reports (33,58). However with the same drug and zolpidem, results showed no statistically significant differences in the latencies of phase II sleep and delta sleep. This does not agree with the results published by Herrmann et al (26) and Kanno et al (31), nor with those of Koshorek et al (35).

On the other hand, our results did not reveal significant differences regarding REM sleep latency between diazepam, zopiclone and zolpidem. Placebo produced the lowest latency of this phase, although statistical significance was not attained. These results are in

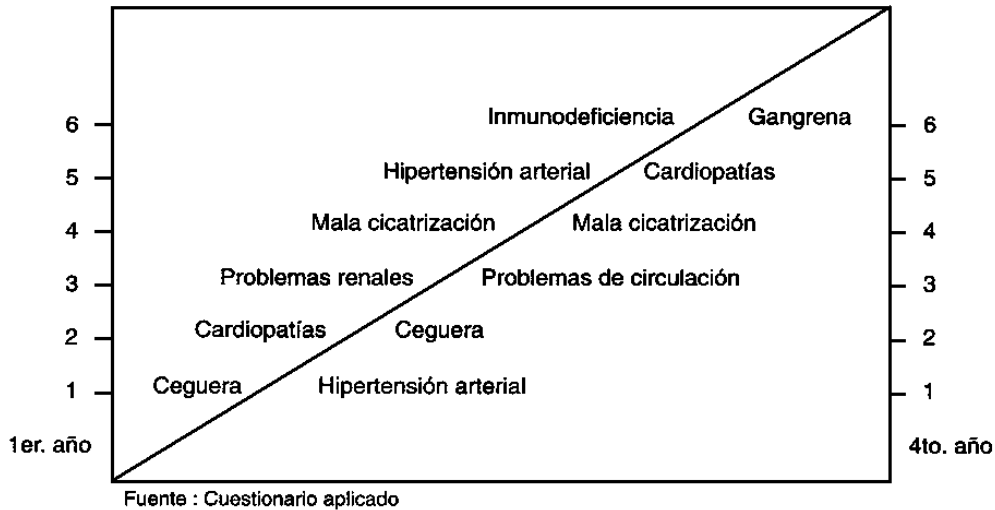


Figure 1. Polysomnographic variables significant during experimental conditions.

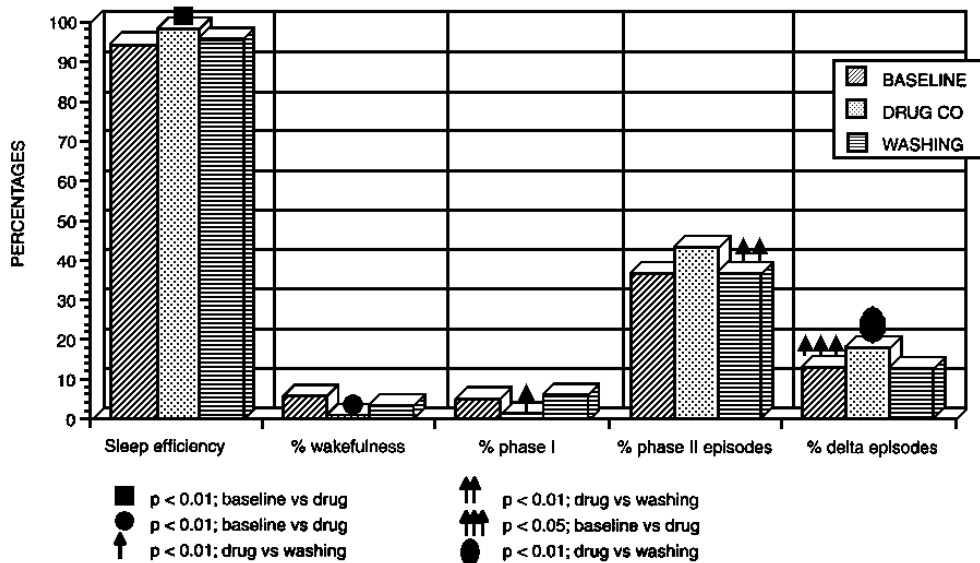


Figure 2. Polysomnographic variables significant under zopiclone treatment.

agreement with other studies (11,43,56,58,69). In contrast, García de León et al (22) found that zolpidem reduced significantly the number of movements during sleep in subjects studied during an expedition to the Himalayas.

The number of changes in phase and sleep cycles was not modified with the tested drugs. This agrees with the results of Nicholson and Pascoe (51) and of Cluydts et al (14) who used zolpidem in healthy subjects. In insomniacs, however, the number of changes seems to increase according to Jovanovic and Dreyfus (28) and Monty et al (46).

Results of drug washing agree with other reports (28, 46) on the lack of significant effects of zopiclone, zolpidem and Gabob on the polysomnographic varia-

bles related both to quantity and quality of sleep during the night following treatment. The same results were obtained for diazepam in this study, in contrast with results by other authors who have observed accumulative effects on polysomnographic variables on the night following the administration of benzodiazepines (28,62). Other studies (29) have found minimal effects of diazepam on sleep when treatment was suspended, especially if it was acute.

Zopiclone clearly improved sleep efficiency and produced a marked decrease in wakefulness percentage. Differences were statistically significant between base line and drug (figure 2) which also indicates no accumulative effects on sleep. Although zopiclone did not show a significant increase in delta sleep episodes compared to

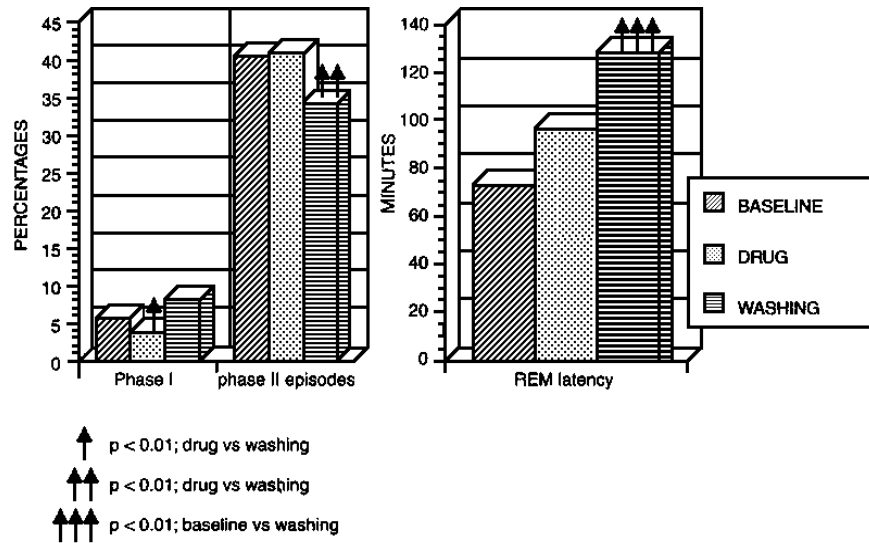


Figure 3. Polysomnographic variables significant under zolpidem treatment.

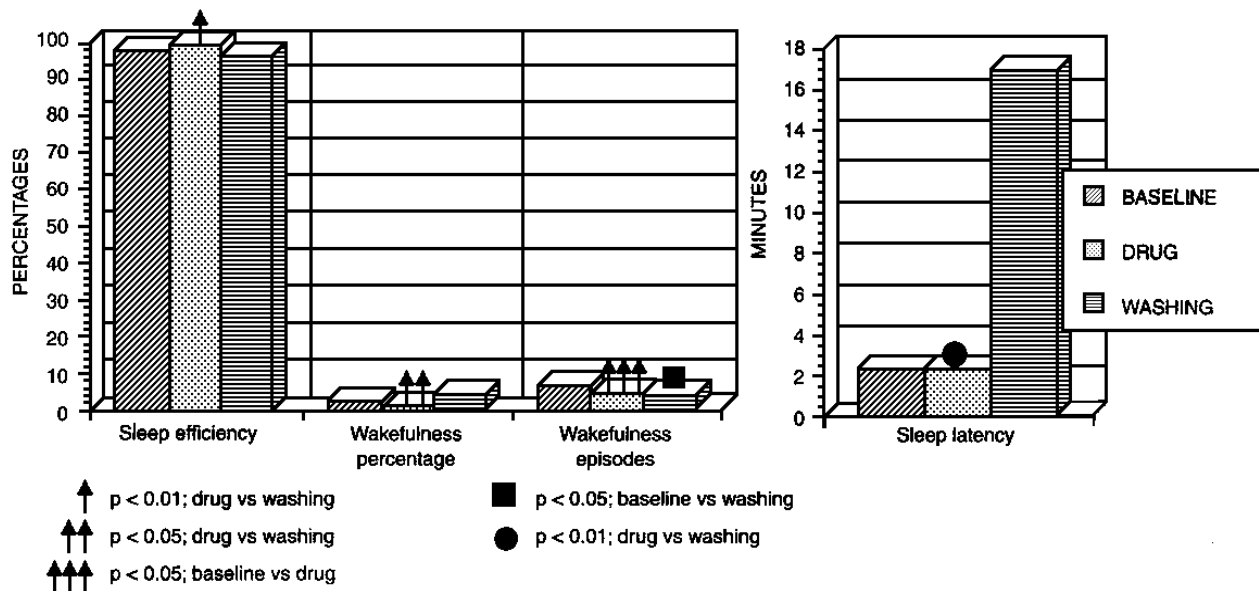


Figure 4. Polysomnographic variables significant under treatment with placebo.

the other tested drugs and placebo, it did increase this variable when treatment was compared with base line levels. This agrees with studies reported elsewhere (48).

On the night following treatment with zolpidem (washing conditions), the percentage of phase II episodes decreased; differences between base line and washing were significant (figure 3). The increase in REM sleep latency after zolpidem administration has been described (27,35,51,55), however, these studies did not find a rebound effect on REM sleep latency after treatment (36,43).

Some evidence suggests that placebo has positive effects when the subject thinks that the treatment is

efficacious and is conscious of it (19). An efficacy of approximately 35% for disorders such as anxiety and insomnia has been reported (6,13,24) (figure 4).

Finally, diazepam caused a marked decrease of heart rate during sleep compared with base line conditions (figure 5). The residual effect of diazepam only affected the heart rate variable during sleep. We have described similar results in subjects having received two doses (0.25 and 0.50 mg) of Triazolam and who have been under vigilance (21,65,66). It has thus been suggested that the decrease in heart rate would be a consequence of the reduction of the subject's activity after benzodiazepine administration (23).

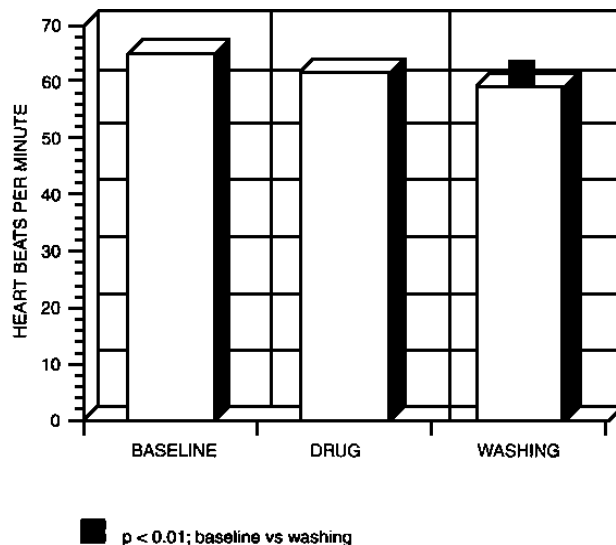


Figure 5. Mean of heart rate during sleep in subjects under diazepam treatment.

In conclusion, our results show that zopiclone significantly improves the polysomnographic variables related to "quantity of sleep" when statistical comparisons are made between base line and washing condition.

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