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Residual effects of benzodiazepine and non-benzodiazepine hypnotics on diurnal attention in a reaction time task

Francisca Vera, José Francisco Navarro, Mª José Blanca, Gustavo Luna* and Augusto Fernández-Guardiola*
University of Málaga and * Instituto Mexicano de Psiquiatría

The residual effects of benzodiazepines on attention and psychomotor performance have been extensively documented. However, there are very few studies comparing the action of benzodiazepines and non-benzodiazepine (imidazopiridines and cyclopirrolones) compounds on these parameters. The aim of this work was to assess the residual effects on diurnal wakefulness in healthy volunteers after nocturnal administration of a single dose of diazepam (10 mg), zolpidem (10 mg), zopiclone (7.5 mg), gamma-amino-ß-hydroxybutyrate (500 mg), or placebo. Drugs were given at 22 h (half-hour before bedtime), in a double-blind fashion according to an extended Youden Square design. Subjects slept for six consecutive nights in the sleep laboratory (habituation, baseline, drug 1, placebo, drug 2, placebo). The morning after nocturnal dosing, psychomotor performance was measured using a simple visuomotor reaction time (RT) task, with two stimulation patterns (isochronus and stochastic). The results indicated an absence of residual effects on attention after zopiclone and zolpidem intake. Likewise, administration of diazepam did not provoke a significant deterioration in the attention level. GABOB was the only drug which produced a marked decrease in the isochronus RT after 9 hours of its administration, in comparison to its baseline, not appreciating any significant modification in the stochastic RT. It is emphasized that residual impairment on RT following intake of hypnotics should be considered on the basis of the stimulation pattern used (stochastic vs isochronus) during vigilance assessment.

Efectos residuales de hipnóticos benzodiacepínicos y no-benzodiacepínicos sobre la atención diurna en una tarea de tiempo de reacción. Los efectos residuales de las benzodiacepinas sobre la atención y el rendimiento psicomotor han sido extensamente documentados. Sin embargo, existen muy pocos estudios que hayan comparado el efecto de compuestos benzodiacepínicos y no benzodiacepínicos (imidazopiridinas y ciclopirrolonas) sobre dichos parámetros. El objetivo de este trabajo fue evaluar los efectos residuales sobre la atención diurna de una dosis aguda de diazepam (10 mg), zolpidem (10 mg), zopiclona (7.5 mg), GABOB (500 mg) o placebo, administrada la noche anterior en sujetos voluntarios sanos. Los fármacos fueron administrados a las 22 h (media hora antes de acostarse), utilizando un diseño doble-ciego de cuadrado latino extendido. Los sujetos pasaron seis noches consecutivas en el laboratorio de sueño (habituación, línea-base, fármaco 1, lavado, fármaco 2, lavado). A la mañana siguiente, se examinó el rendimiento psicomotor utilizando una tarea de tiempo de reacción visomotor simple, con dos patrones de estimulación (isócrono y estocástico). Los resultados indicaron una ausencia de efectos residuales sobre la atención tras la administración de zopiclona y zolpidem. Asimismo, la administración de diazepam no provocó un deterioro significativo en el nivel de atención. GABOB fue la única sustancia que produjo un marcado descenso en el tiempo de reacción isócrono, a las 9 horas de su administración, en comparación con la línea-base, no apreciándose ningún cambio significativo en el tiempo de reacción estocástico. Se subraya que los efectos residuales sobre el tiempo de reacción tras la ingesta de hipnóticos deben ser considerados sobre la base del patrón de estimulación utilizado (estocástico vs isócrono) durante la evaluación de la vigilancia.

Benzodiazepines are usually prescribed for the treatment of anxiety and sleep disorders. However, they have frequently negative residual effects on tasks requering spatial and visual abilities and sustained attention. Moreover, benzodiazepines may provoke an impairment of motor responses, also altering the capacity to estimate the time (Bensimon et al., 1990; Bocca et al, 1999; Myzuki et al., 1987; Sierra et al., 1993). Consequently, the level of attention or vigilance of a subject is one of the variables more commonly examined in order to detect possible residual effects after administration of benzodiazepines.

Cyclopirrolones (e.g., zopiclone) and imidazopiridines (e.g., zolpidem) are a new class of hypnotics structurally unrelated to the benzodiazepines (Noble, Langtru and Lamb, 1998; Priest et al.,

Correspondencia: José Francisco Navarro
Facultad de Psicología
Universidad de Málaga
29071 Málaga (Spain)
E-mail: navahuma@uma.es

1997; Vera and Navarro, 1996a, b). Although some authors have found an apparent absence of residual effects after administration of zopiclone or zolpidem (DeClerck and Bisserbe, 1995; Tafti, Besset and Billiard, 1992), a significant impairment of attentional processes and psychomotor performance has been described in other studies after the intake of these substances (Berlin et al., 1993; Billiard et al., 1987; Mintzer and Griffith, 1999; O'Hanlon, 1995). In sum, although a few studies have evaluated the residual effects of zolpidem and zopiclone, the results obtained have been contradictory. These divergencies could be related to the tests employed, which are usually different from one laboratory to another (Bocca et al., 1999).

The residual effects of benzodiazepines on attention and psychomotor performance have been extensively documented. However, there are very few studies comparing the action of benzodiazepines and non-benzodiazepine (imidazopiridines and cyclopirrolones) compounds on these parameters. Therefore, this study was designed to assess the residual effects of an acute administration of a benzodiazepine (diazepam), an imidazopiridine (zolpidem), a cyclopirrolone (zopiclone), a gabaergic agonist (gamma-amino-ß-hydroxybutyrate), or a placebo, on diurnal wakefulness in healthy volunteers using a simple visuomotor reaction time (RT) test. Additionally, we analyze the existence of possible differences in the reaction times as a function of the stimulation pattern used (isochronic vs stochastic stimulation) during the vigilance task.

Methodology

Subjects

The sample consisted of 10 men healthy volunteer students whose ages ranged from 18 to 30 years (mean=24.4). The sample was selected by interview. Intake of psychotropic substances, tobbaco and other drugs, state of health, regularity of sleep-wake cycles, food intake and body weight were supervised. The time of drug administration was also controlled. Once selected, the subjects were informed of the general objectivs of the study and filled in a written consent for. This study was approved by the ethical Committee of the Mexican Institute of Psychiatry,where the investigation was carried out.

Drugs

Drugs were given orally at 22:00 hours (half-hour before bedtime), in a double-blind fashion according to an extended Youden Square design. Subjects sleep for 6 consecutive nights in the sleep laboratory (habituation, baseline, drug 1, placebo, drug 2, placebo) (see Table 1). The following drugs were employed: 1. Diazepam (10 mg); 2. Zolpidem (10 mg); 3. Zopiclone (7.5 mg), and 4. Gamma-amino-ß-hydroxy-butyrate (GABOB) (500 mg).

Procedure

A IBM Model 25 XT microcomputer with a Turbo Pascal program, designed for the RT task, was used. A photostimulator Grass PS22 provided the luminous flashes (by neon ignition), perceivable by the subjects with their eyes closed. A Hewlett Packard Model 5326B counter registered reaction times (time interval between stimulus and subject reaction).

The morning after nocturnal dosing (07:00 h), and the subject being still in bed, a telegraph lever was set within reach of his dominant hand in order to initiate the RT test. The subject lay supine with eyes closed on the bed in the sound-proof room. Light stimuli were supplied by a photic stimulator lamp placed 30 cm in front of the subject's face. The subject should respond as fast as possible, pressing the telegraph lever, to luminous stimuli presented. Such stimuli lasted for 10 µsec, with an intensity of 0.0015 lm/sec/cm2 that could be perceived with eyes closed. The light stimuli were supplied every 10 sec, in a 36-min period (see procedure in Vera et al., 2000).

The RT task was divided into several phases: (1) Isochronus simple RT: the subjects had to respond to the luminous stimuli with a constant interstimuli interval time (10 sec), which the subjects ignored, for a period of 10 min (total number of stimuli=61); (2) Stochastic simple RT: in this phase the isochronus stimuli were mixed with the stochastic stimuli (where the interstimuli interval corresponded to random increases of 0.5 sec, from 1 to 9.5 sec). After the appearance of a stochastic stimulus, the fixed interval of 10 sec was continued, until a new stochastic stimulus occurred, and so on. This phase had a duration of 25 min. The irregular stimuli were 36, being 133 the stochastic stimuli which complied with the regular interval (of a total of 169 stimuli); (3) Time estimation was carried out between the isochronus RT phase and the stochastic RT phase. For a period of two minutes, the subject had to estimate the interstimuli interval of the isochronus RT phase. For this purpose, no kind of stimulus was presented and the subject pressed the lever each time he considered the time between answer and answer was similar to that one occurring between stimulus and stimulus in the previous test.

Results were analyzed using the statistical package BMDP. An ANOVA test was performed to assess the possible differences between the effects produced by the drugs and the placebo on the RT, after 9 hours (drug condition) and 33 hours (drug washing condition) after their administration. The average values obtained were converted, adjusting them to the subject variable, according with the procedure used by Kirk (Kirk, 1968). In the case of obtaining any statistic significance, multiple comparisons "a posteriori" were carried out using the Duncan test. Moreover, a Friedman test was employed in order to examine possible differences among baseline, drug and washing conditions.

Results

Table 2 shows the effects of drug administration on the isochronus and stochastic RT 9 and 33 hours later. The percentage of

Table 1
Experimental design (extended Youden Square)

Subjects	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

predictive responses 9 hours after administration of zopiclone and GABOB was significantly reduced, as compared with placebo group ($p<0.05$). Moreover, although isochronus and stochastic RT were clearly increased after treatment with diazepam and zopiclone, no significant differences were reached.

As Table 3 shows, the Friedman test revealed that GABOB significantly decreased isochronus RT 9 hours after its administration, as compared with its baseline ($p<0.01$). Likewise, placebo administration produced a significant increase in the time estimation, as compared to its baseline ($p<0.01$).

Discussion

Diazepam provoked an increase in the isochronus and stochastic RT after 9 and 33 hours of its administration; however, such an increase was not statistically significant. Although benzodiazepines usually produce residual effects on attention and vigilance, markedly increasing the RT, there are several studies in which an absence of residual effects have been described. Thus, various authors have comunicated minimal (Ashton, 1994), or even a lack of residual effects in a RT task after diazepam administration in healthy subjects (Buela-Casal et al., 1992). More recently, Sierra and Buela-Casal (1996) did not find any residual effects with diazepam, using a maintained attention task (Toulose Piéron test) and Stanford´s somnolence scale. A possible explanation for these results could be that benzodiazepine elimination half-life has not much relation with the psychophysiological effects that they produce, and they may be caused by the interaction of other factors such as age, health, or simply be a consequence of its effects on sleep. In this respect, Koelega (1998), who carried out an extense review on the effects of benzodiazepines over attention, suggests that there is no evidence that the deterioration in the performance of a given task produced under normal conditions (i.e., the monotony and tireness throughout the test), may be enhanced due to the effect of benzodiazepines.

GABOB was the only drug which produced a marked decrease in the isochronus RT after 9 hours of its administration, in comparison to its baseline, not appreciating any significant modification in the stochastic RT. The clinical use of this substance is currently very limited, being ocassionally employed for improving cerebral insufficiency and as antiepileptic agent (Vera and Navarro, 1999). On the other hand, zolpidem and zopiclone did not produce significant residual effects on the RT task, in accordance with most of studies published (Allain, Patat and Lieury, 1995; Bocca et al., 1999; Luna et al., 1994).

As Table 2 shows, stochastic RT was more clearly affected by the drugs, in comparison with isochronus RT. When stimuli are presented with irregular interstimuli intervals, totally at random (like in stochastic condition), it is more improbable that the subject can elaborate some type of expectancy as to when the next stimulus will occur. This type of task is especially interesting because the wide range of stimuli which a subject must face in his daily life does not usually keep a constant pattern. Therefore, residual impairment on RT following intake of hypnotics should be considered on the basis of the stimulation pattern during vigilance assessment (Luna et al., 1994).

In comparison with the baseline, placebo produced a notable increase in the time estimation after 9 hours of its administration. Similar results have been previously described after administration of benzodiazepines (Fdez-Guardiola, Jurado and Aguilar-Jiménez, 1984). Thus, it has been demonstrated that the administration of these substances produces an increase in the time interval estimate of 10 seconds between luminous stimuli which constitute the RT test. According to these authors, the subjects tend to underestimate the time interval which occurs between stimuli due to the depressing effect of the substance, which results in an increase in the estimate time interval. Our results suggest the existence of a "placebo effect" in the time estimation, producing placebo similar effects to those observed with benzodiazepines. Such an effect might be explained by the expectancy that the subject develops when he takes a specific substance. In our study, as the subjects took every night the capsules with identical physical characteristics before going to bed, they could perhaps think that it was a substance which might had an effect on sleep and vigilance level.

Finally, it was observed that zopiclone and GABOB, in comparison with placebo, were the compounds that, in a very substan-

Table 2
Mean values and standard deviations (in parentheses) in drug and washout conditions after administration of diazepam, zopiclone, zolpidem, GABOB and placebo

	Diazepam	**Zopiclone**	**Zolpidem**	**GABOB**	**Placebo**
Drug condition					
Isochronus RT (msec)	285.02 (69.03)	289.13 (50.71)	244.99 (68.44)	209.20 (43.25)	257.04 (65.71)
Stochastic RT (msec)	340.65 (135.5)	343.57 (47.85)	319.15 (141.9)	289.06 (24.56)	291.1 (69.93)
Time estimation (sec)	10.50 (0.72)	11.22 (1.49)	10.10 (1.11)	9.48 (2.32)	9.3 (0.75)
Predictive responses (percentages)	1.63 (0.80)	0.6 * (0.33)	1.37 (0.43)	0.05 * (0.33)	1.68 (0.62)
Washout condition					
Isochronus RT (msec)	264.8 (17.61)	253.2 (12.25)	261.8 (29.57)	243.6 (31.64)	244.4 (19.61)
Stochastic RT (msec)	348.1 (32.14)	384.8 (87)	277.3 (76.28)	282.2 (25.79)	290.5 (37.07)
Time estimation (sec)	9.60 (0.5)	12.60 (2.54)	10.20 (0.63)	8.20 (0.76)	10.30 (0.46)
Predictive responses (percentages)	0.20 (0.38)	0.80 (0.49)	1.40 (0.72)	0 (0.29)	1.0 (0.73)

* As compared with placebo, $p<0.05$

Table 3
Mean values and standard deviations (in parentheses) in the three experimental conditions of baseline, drug and washout

Isochronus RT (GABOB)	Baseline 262.49 (66.39)	Drug 219.44* (43.25)	Washout 249.85 (63.28)
Time estimation (Placebo)	9.31 (0.97)	10.67* (0.75)	9.91 (0.93)

* As compared with basaline, $p<0.01$ (Friedman test)

tial way, showed a lower percentage of predictive responses. These predictive responses are related with the attention or vigilance level that the subjects show throughout the RT task. In this sense, the attention status kept in this test is characterised for presenting a number of responses given by the subject very close to the number of stimuli presented, this is to say, a low number of lack of responses and a high number of predictive responses (responses before the stimulus is given). Thus, the increase in the RT is usually associated to an increase in the number of lack of responses and a lower number of predictive responses (Fdez-Guardiola, Jurado and Aguilar-Jiménez, 1984).

Overall, our results indicate an absence of residual effects on attention of zopiclone (7.5 mg) and zolpidem (10 mg), assessed by means of a RT task in healthy subjects, in concordance with recent studies. Likewise, administration of diazepam (10 mg) did not provoke a significant deterioration in the attention level. GABOB (500 mg) was the only drug which produced a marked decrease in the isochronus RT after 9 hours of its administration, in comparison to its baseline, not appreciating any significant modification in the stochastic RT. It is concluded that residual impairment on RT following intake of hypnotics should be considered on the basis of the stimulation pattern used (stochastic vs isochronus) during vigilance assessment.

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