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

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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-aminohydroxybutyrate (300 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 (isochronous 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 isochronous 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 isochronous) 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 (habituation, 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.
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 cyclopirolones) 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 cyclopirolone (zopiclone), and a gabaaergic 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 33 years (mean=24.4). The sample was selected by interview. Intake of psychotropic substances, tobacco 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 objectives 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-hydroxybutyrate (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) Isochronous 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 isochronous 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 comprised with the regular interval (of a total of 169 stimuli); (3) Time estimation was carried out between the isochronous RT phase and the stochastic RT phase. For a period of two minutes, the subject had to estimate the interstimuli interval of the isochronous 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.

Table 2 shows the effects of drug administration on the isochronous 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 zoplicone 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 sig-
nificantly decreased isochronus RT 9 hours after its administra-
tion, as compared with its baseline (p<0.01). Likewise, placebo
administration produced a significant increase in the time estima-
tion, as compared to its baseline (p<0.01).

Discussion

Diazepam provoked an increase in the isochronus and stochas-
tic RT after 9 and 33 hours of its administration; however, such an
increase was not statistically significant. Although benzodiazepi-
nes 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 au-
thors have communicated minimal (Ashton, 1994), or even a lack of
residual effects in a RT task after diazepam administration in he-
althy subjects (Buela-Casal et al., 1992). More recently, Sierra and
Buela-Casal (1996) did not find any residual effects with diaze-
pam, using a maintained attention task (Toulouse Péron test) and
Stanford’s somnolence scale. A possible explanation for these re-
results could be that benzodiazepine elimination half-life has not
much relation with the psychophysiological effects that they pro-
duce, 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, Koelga (1998), who carried out an extensive
review on the effects of benzodiazepines over vigilance, suggests
that there is no evidence that the deterioration in the performance
of a given task produced under normal conditions (i.e., the mon-
tony and tiredness 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 compara-
tion to its baseline, not appreciating any significant modification
in the stochastic RT. The clinical use of this substance is currently
very limited, being occasionally employed for improving cerebral
insufficiency and as antiepileptic agent (Vera and Navarro, 1999).
On the other hand, zolpidem and zopiclone did not produce signi-
ficant residual effects on the RT task, in accordance with most of
studies published (Allain, Patat and Liefury, 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
(lie in stochastic condition), it is more improbable that the sub-
ject can elaborate some type of expectancy as to when the next
stimulus will occur. This type of task is especially interesting be-
cause the wide range of stimuli which a subject must face in his
daily life does not usually keep a constant pattern. Therefore, re-
didual 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 administra-
tion of benzodiazepines (Fdez-Guardiola, Jurado and Aguilar-Jimé-
nez, 1984). Thus, it has been demonstrated that the adminis-
tration of these substances produces an increase in the time inter-
val estimate of 10 seconds between luminous stimuli which con-
stitute 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 exis-
tence of a “placebo effect” in the time estimation, producing pla-
cebo similar effects to those observed with benzodiazepines.
Such an effect might be explained by the expectancy that the sub-
ject 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 vigi-
lance level.

Finally, it was observed that zoplicone and GABOB, in com-
parrison with placebo, were the compounds that, in a very substan-

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<thead>
<tr>
<th>Table 2</th>
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</thead>
<tbody>
<tr>
<td>Mean values and standard deviations (in parentheses) in drug and washout conditions after administration of diazepam, zopiclone, zolpidem, GABOB and placebo</td>
</tr>
<tr>
<td><strong>Drug condition</strong></td>
</tr>
<tr>
<td>Isochronus RT (msec)</td>
</tr>
<tr>
<td>Stochastic RT (msec)</td>
</tr>
<tr>
<td>Time estimation (sec)</td>
</tr>
<tr>
<td>Predictive responses (percentages)</td>
</tr>
</tbody>
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<tr>
<td>Mean values and standard deviations (in parentheses) in the three experimental conditions of baseline, drug and washout</td>
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<td><strong>Isochronus RT (GABOB)</strong></td>
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<td>262.49 (66.39)</td>
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<td><strong>Time estimation (Placebo)</strong></td>
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* As compared with placebo, p<0.05

* As compared with baseline, 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 isochronous 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 isochronous) during vigilance assessment.

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References

O’Hanlon, J.F. (1995). Zopiclone’s residual effects on psychomotor and information processing skills involved in complex tasks such as car driving: a critical review. European Psychiatry, 10 (suppl 3), 137s-143s.

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