Residual effects of Zoldipem 10 mg and Zopiclone 7.5 mg on driving performance and ocular saccades


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INTRODUCTION

Although quantifying the responsibility of hypnotic drugs as a cause of traffic accidents is a complex task, their consumption does indeed appear to increase involvement in traffic accidents. The impairment of alertness after taking benzodiazepines is well known. This is why the pharmaceutical companies have developed new families of hypnotics similar to benzodiazepines, such as imidazopyridines or cyclopyrrolones. However, whilst the acute and chronic effects of these compounds now appear to be firmly established, the same cannot be said for their residual effects. An open preliminary study on a driving simulator with Zolpidem 10 mg showed residual effects for a group performing the driving test at 9.00 a.m. and the absence of residual effects for the 11.00 a.m. group, the test being carried out in both cases 12 h after drug administration (Etard et al. 1995). This result could have been due to an indirect chronobiological effect resulting in increased post-hypnic inertia. The protocol followed in this study was adapted so as to bring out this effect.

The purpose of this work was to characterise the residual effects of zolpidem and zopiclone on car driving assessed using a driving simulator by comparing these effects with those of a reference hypnotic drug (flunitrazepam) and a placebo.
MATERIALS AND METHODS

Subjects:
The study was carried out on 16 healthy volunteers (9 men and 7 women) recruited from among a student population (mean age: 24.5 years).

Drugs doses:
At 11.00 p.m. the day before each session, the subject took a tablet of either zolpidem 10mg (Zd), zopiclone 7.5mg (Zc), flunitrazepam 1mg (Fln) or a placebo (C).

Design:
The study was conducted according to a balanced, double blind, cross-over design. Each subject followed four sessions held at intervals of at least two weeks. The circadian pattern of each subject was determined using the morningness-eveningness questionnaire of Horne and Östberg (1976). The subjects were divided into two groups. Subjects with the same score to the Horne and Östberg’s questionnaire were paired off with one placed in each of the two groups. One group of subjects did the test drive at 9.00 a.m., the other group at 11.00 a.m. All the subjects were required to arise at 7.30 a.m.. The medication was administered at the subject’s home under the supervision of an experimenter. The subject was required to retire to bed within half an hour. The next day, the subject was brought to the simulator site. Each subject performed an ocular saccade test immediately after the driving session. This task lasted 4 minutes.

Car driving
Simulator: the driving simulator comprises a car seat together with steering wheel and pedals, a video projector and an IBM-compatible computer. The simulation software program used was designed by the firm of ANIMATE (Cachan, France). The movements of the steering wheel and actions on the pedals are detected by means of potentiometers. The resulting signals are transformed by means of an analogue to digital card. The PC calculates the new position of the vehicle using its dynamic characteristics. The resulting image is then prepared through a database and projected onto a screen using the video projector. The entire cycle is repeated approximately 25 times a second. This apparatus has no system enabling
simulation of the movements of the car or engine noise. During each cycle, the computer records the complete set of variables characterising the movement of the car and the actions of the driver.

**The test drive**: the test involves driving for 1 ½ hours along a two-lane road in a rural environment. No other vehicle or pedestrian is represented. Driving is performed in daylight. The instructions were as follows: 1. / to ensure maximum lateral stability of the vehicle, 2. / to drive as quickly as possible whilst complying with instruction 1 /. At no time during the session did the subjects receive stimulation by actions external to the driving operation.

**Statistical analysis**: the purpose of this study was to demonstrate impaired vehicle control after ingestion of a hypnotic; the variables we adopted for analysis were lateral position variance (m2) and vehicle velocity variance (m2/sec2). The null hypothesis whereby there is no difference of variance among the 4 groups was tested with the Bartlett test (Zar, 1984). For 4 groups (DF=3), the significance threshold at 5% is $\chi^2 = 7.81$. Discovery of a significant treatment effect was followed by an F test to compare the variances 2 by 2. Then separate analysis was carried out on the 9.00 group and the 11.00 group.

**Eye movements**

**Materials and saccade test**: horizontal eye movements were recorded by an infrared light reflection eye-tracking system (Iris, Skalar, Delft, The Netherlands) or with an EOG method. For measurement of saccadic eye movements, a series of 60 targets at a 15° angle were lit up randomly to the left or right.

**Statistical analysis**: the effect of the treatments was assessed with respect to the following saccade parameters: latency (msec); duration (msec); accuracy (%). A two factor (treatment*subject) ANOVA was carried out to highlight any effect of the drugs on the saccade parameters.
RESULTS

Simulator

The overall results are given in Table 1.

Table 1: Simulator

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Variances</th>
<th>Overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fin</td>
<td>Zc</td>
</tr>
<tr>
<td>Velocity</td>
<td>11.61</td>
<td>8.24</td>
</tr>
<tr>
<td>9h00 group</td>
<td>9.53</td>
<td>7.09</td>
</tr>
<tr>
<td>11h00 group</td>
<td>13.70</td>
<td>9.39</td>
</tr>
<tr>
<td>Lateral position</td>
<td>26.27</td>
<td>4.86</td>
</tr>
<tr>
<td>9h00 group</td>
<td>52.35</td>
<td>9.50</td>
</tr>
<tr>
<td>11h00 group</td>
<td>0.18</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Variance of velocity

The treatments had no significant effect on velocity variances.

Variance of vehicle lateral position

The treatments have a significant effect on the variance of the vehicle lateral position. This effect is significant for the 9.00 a.m. group but not for the 11.00 a.m. group.

Variances with Fin and Zc are significantly different to those under placebo conditions whilst there is no effect from Zp. These effects are present in the 9.00 a.m. group only.

Ocular saccades

The overall results are given in Table 2.

Table 2: Saccades

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANOVA F</td>
</tr>
<tr>
<td>Latency (m ± se)</td>
<td>Fin</td>
</tr>
<tr>
<td>Duration (m ± se)</td>
<td>57.14</td>
</tr>
<tr>
<td>Accuracy (m ± se)</td>
<td>90.31</td>
</tr>
</tbody>
</table>
It emerges from the ANOVA that the various saccade parameters studied do not differ significantly. However there is a trend ($p = 0.089$) for the mean latencies under medication to be higher than those under placebo.

**DISCUSSION**

**Simulator**
This study demonstrates residual effects of Fln 1 mg and Zc 7.5 mg on the morning after a single dose. In the same conditions Zp 10 mg produces no residual effects.

Fln is a benzodiazepine with a long half-life (up to 30 h). The residual effects of this molecule have already been shown on the driving simulator and in actual driving conditions (Harrison and al., 1985). The results of this study confirm earlier studies and enable us to quantify the sensitivity of the simulator. Despite a short half-life (5 h) and different binding sites from those of the benzodiazepines, Zc produces impaired car driving performance as compared with the placebo. This impairment however is less than with Fln (5 times less). This result does not confirm observations made in real driving conditions by O'Hanlon et al. (1986) who with one dose of Fln 2 mg (twice that used in our study) and Zc 7.5 mg find little difference between the two molecules.

We observed that performance at 9.00 a.m. was significantly impaired with Fln 1mg and Zc 7.5 mg, but that these residual effects had worn off by 11.00 a.m.. To account for the difference in driving performances at 9.00 a.m. and 11.00 a.m., a difference in plasma concentration cannot be ruled out. However this effect is unlikely in the case of Fln which has a long half-life. In the case of Zc, the plasmatic concentration is reduced by 25% 12.00 h after medication as compared with that at 10.00 h; this drop may possibly be enough to explain the absence of any residual sedation in the 11.00 a.m. group. However, the impaired performance at 9.00 a.m. may also be due to some indirect action of the molecule through chronobiological phenomena resulting in increased post-hypnic inertia, i.e. the time between waking up and reaching optimum performance levels.

Driving performances with Zp 10 mg are not significantly different from the placebo condition. We did not get the same results as Etard et al. (1995) with this same dose. However the experimental conditions of these two studies are not identical: the study by
Etard et al. (1995) was an open study whereas this was a double-blind study; also the simulators and instructions are not the same. Controlling the velocity was more difficult on the simulator used by Etard et al. (1995), whilst controlling the vehicle's lateral position is much more difficult in our study.

Ocular saccades
Our results indicate that 12.00 and 14.00 h after the medication was administered, there is no change in the saccade parameters. These observations confirm those of Richens et al. (1993) with Zolpidem (5, 10 and 20 mg) 9.00 h after ingestion. The molecules studied no longer have any significant effect on the central oculo-motor structures thus the impaired driving performance appears to be unrelated to motor impairment (whether directly or not). We observe however for mean latency the same variations for each molecule as are observed in driving performances. This non significant result (p = 0.089) would require further experiments with a larger number of subjects or in conditions in which the method could be made more sensitive (e.g., by using a «gap» paradigm).

CONCLUSION
This study shows the residual effects of Zc 7.5 mg and Flm 1 mg on driving performances carried out at 9.00 a.m. on the morning after evening medication. Zp 10 mg produces no residual effects regardless of whether driving is performed at 9.00 or 11.00 a.m.. These results, obtained on a driving simulator after a single dose to healthy volunteers, cannot characterise the behaviour of a driver in a real driving situation where the danger is an important factor in increasing the level of alertness. Furthermore, these results cannot be extrapolated to cases of long-term treatment. However it is necessary to draw drivers' attention to the risks involved in the occasional use of hypnotics and to encourage them to take great care even if they consider their level of alertness to be sufficient, as it is often over-estimated.

RÉFÉRENCES


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