Residual Effects of Hypnotic Drugs and Visual Information Processing Tasks in Simulated Driving

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I. Introduction

Data available on the European level show that an estimated 10% of accident victims are under the influence of a psychotropic substance at the time of the accident; nevertheless, this percentage cannot be used to establish a direct link of causality between a given product and a precise deterioration in the driving task. Scientific literature, however, provides concordant arguments which implicate the taking of benzodiazepines in the occurrence of accidents (1). Notably, benzodiazepines can lead to drowsiness related to their residual effects. To remedy these undesirable side-effects, pharmaceutical laboratories have developed new families of hypnotic drugs, such as imidazopyridines or cyclopyrrolones, which are said to have the advantage of presenting fewer residual effects due to their short half-life and their fixation sites which differ from those of traditional benzodiazepines. The choice of hypnotic molecules with the shortest half-lives and the fewest residual effects on behavioural efficiency is thus a challenge in the context of road safety.

The drugs used in the present work (zolpidem, zopiclone and flunitrazepam¹) are commonly prescribed hypnotics with different half-lives, for which we have studied the residual effects of a minimum dose after a single night-time dose. This objective is motivated by the fact that a large proportion of hypnotic drugs consumers only use them occasionally and temporarily and that the cognitive and psychomotor deterioration which follows their use can be especially strong at the start of treatment and tends to decrease after a few days.

A review of the literature shows that the residual effects of these hypnotic drugs on driving behaviour are more or less marked depending on the experimental conditions (2).

The half-life of flunitrazepam is between 19 and 30 hours. It has residual effects on memory and on information processing time in healthy subjects after a single dose of 1 mg (3). After more than one hour of simulated driving, 1 mg of flunitrazepam affected the lateral position of the vehicle (4). During driving tests on subjects suffering from sleep disturbances, Vermeeren et al. (5) did not demonstrate any residual effects from 2 mg of flunitrazepam on the vehicle lateral position but Volkerts et al. (6) showed that it had residual effects on driving performances.

Zolpidem (10 mg) is a molecule belonging to the imidazopyridine family. It has a very short half-life of between 1.4 and 2 hours. In simulated driving, in an open procedure, the daytime effects of a single night-time dose of 10 mg of zolpidem modify driving performances of healthy subjects: difficulty in maintaining a constant speed and an

¹ Flunitrazepam, less prescribed these past years, has been included in the study as a positive control to evaluate the sensitivity of the procedure.
increase in the variability of the vehicle's lateral position (7). But under a double blind procedure (4), no residual effects of zolpidem (10 mg) were observed.

Zopiclone (7.5 mg) is a hypnotic drug of the cyclopyrrolone group; its half-life varies from 4 to 5 hours. In an actual over-the-road driving test, 7.5 mg of zopiclone causes residual effects among insomniac subjects after two nights of treatment (6), increasing variability in the vehicle's lateral position. The day after a single dose taken by a small sample of healthy subjects, this molecule does not lead to any modification in response time for braking (3), whereas with a larger sample, in early morning, the average variance in the lateral position of the vehicle increases (4, 8).

We can note a lack of studies concerning the modifications these hypnotics may cause on processing visual information during the driving task. The driving task is principally performed on the basis of visual information and the processing of this information must be considered not only as a manifestation of hypotheses made by the driver but also as an explanation of his actions (9). Insofar as this processing is not done passively, we postulated that if the visual processing is modified by the use of hypnotic drugs, it will be expressed through behavioural modifications.

In previous work, we tested this hypothesis with a task of visual anticipation of collision when arriving at an intersection (10). Average response time and error rates were not found to be deteriorated by the residual effects of flunitrazepam, zopiclone or zolpidem. Only flunitrazepam appeared to cause subjects to focus their attention on an element which, while relevant for the task (a road sign playing the role of a spatial reference), was not used correctly. But our sample was very small (10 subjects). In a more systematic approach, the present work therefore proposes to identify the residual effects related to a single night-time dose of the same hypnotics on the capacity to visually estimate his/her own self-speed and to visually anticipate a situation of collision with another vehicle parked along his/her trajectory. We thus performed two experiments with an identical procedure.

II. Methodology

II.1. Subjects
Sixteen subjects, all experienced drivers, participated in the experiments. They underwent a medical examination to confirm their good physical condition and the absence of any treatment at the time of their inclusion and during the previous 15 days. They were informed that the study was to test the effects of certain sleeping capsules, with no more information about the drugs used. They provided written informed consent and were paid for their participation. The experimental protocol was submitted for approval to the Ethics Committee.

II.2. General procedure
The experiments were based on traditional laboratory techniques concerning perception psychology: the subjects were submitted to repetitive visual situations for which they had to give a perceptive judgement.

The pictures were generated on a Silicon Graphics station with a resolution of 1280*1024 pixels and an image refresh rate of 60 Hz. The visual scenes simulated the rectilinear movement of a driver and were projected on a large screen (60° horizontally by 49° vertically) using a video projector. The subjects were sitting facing the projection screen on the seat of a simplified driving unit.
Each subject participated in five sessions of each experiment. The duration of each session was around half an hour. The first session, or training session, without taking any medication, was performed the day of the medical examination preceding the study. The four other sessions were conducted according to a double-blind, balanced and crossed design. Each session was separated from the following by a washout period of at least 15 days, and the sessions for a given subject were carried out on the same day of the week. Flunitrazepam (1 mg), zolpidem (10 mg), zopiclone (7.5 mg) and a placebo were given in an identical capsule. Subjects received one capsule at 11.00 PM the day before each session. The medication was administrated at the subject's home under the supervision of an experimenter. The subject's session began at 9 AM the next morning, i.e. 10 hours after taking the capsule. The subjects' night-time activity was recorded by actigraphy from 11 PM to 7.30 AM to verify bedtime and waking time.

II.3. First experiment: perception of his/her self-speed
The subject was presented visual sequences simulating rectilinear displacement. The visual sequences had a duration of 8 sec.

II.3.1. Design
- 4 treatments;
- 5 simulated speeds: 50, 60, 70, 80 and 90 km/h;
- 5 environments: carriageway with uniform road surface and road markings, carriageway with low-texture density with or without road markings and carriageway with high-texture density with or without road markings;
- 3 conditions: road was rectilinear with or without an intersection at the end. In the case with an intersection, visual sequences were interrupted at a constant distance from the intersection (50 metres) or at a constant time duration from the intersection (2 seconds);
- 2 repetitions.

II.3.2. Task
Participants had to estimate their own self-speed and to note it on a result form.

II.3.3. Results
Estimated speeds were submitted to a four-factor analysis of variance (MANOVA) performed using Statistica software (4 treatments * 5 simulated speeds * 5 environments * 3 conditions). Only the main preliminary results will be presented here.

![Graph](image)

**Figure 1.** Estimated speeds as a function of simulated speeds.
Simulated speeds (SIs) were relatively well evaluated by the subjects (F[4,60]=82.84, p<.001) and the correlation between SIs and estimated speeds (ESs) was 0.997 (figure 1).

The treatment had no significant effect on ESs (F[3,45]=0.27, NS). The average ES values were 69, 69.5, 66.4 and 65.8 km/h, respectively, for placebo, flunitrazepam, zopiclone and zolpidem.

The effect of the carriageway (F[4,60]=42.7, p<.001) showed that the uniform road surface with markings gave ESs lower than the other carriageways (figure 2). This means that a textured road surface increases the sensation of self-speed.

![Figure 2. Average estimated speeds as a function of the type of carriageway.](image)

### II.4. Second experiment: anticipation of collision with a stationary vehicle

The subject rectilinearly approaches a vehicle stopped in his/her lane. Visual sequences had duration of 8 sec and were interrupted before the potential collision.

#### II.4.1. Design
- 4 treatments;
- 3 time to collision: sequences were interrupted 1, 2 or 3 seconds before the potential collision;
- 5 environments: carriageway with uniform surface and road markings, carriageway with low-texture density with or without road markings and high-texture density with or without road markings;
- 5 simulated speeds: 50, 60, 70, 80 and 90 km/h;
- 2 repetitions.

#### II.4.2. Task
Participants had to estimate the moment they expected the collision to take place by pressing on a button.

#### II.4.3. Results
Estimated times to collision (estimated TTCs) were transformed in percentage of actual time to collision, then submitted to a four-factor analysis of variance (MANOVA) performed using Statistica software (4 treatments * 3 TTCs * 5 environments * 5 simulated speeds). Only main preliminary results will be presented here.
Treatment did not influence estimated TTCs (F[3,45]=0.31, NS). Average estimated TTC values were 118.6, 118, 119.5 and 119%, respectively, for placebo, flunitrazepam, zopiclone and zolpidem.

Simulated speeds had an effect on estimated TTCs (F[4,60]=12.2, p<.001) which were higher with high simulated speeds than with low ones. Thus, high simulated speeds involved a higher sensation of imminent collision than low simulated speeds (figure 3).

![Figure 3. Estimated time to collision as a function of simulated speeds.](image)

The environment influence estimated TTCs (F[4,60]=11.38, p<.001), which were higher for a uniform carriageway with markings than with other environments (figure 4). Thus the presence of texture on the road surface seems to increase the sensation of imminent collision.

![Figure 4. Average estimated time to collision as a function of the type of texture.](image)

III. Discussion, conclusion and perspectives

Active molecules had no residual effects on visual performance parameters, be it flunitrazepam, zopiclone or zolpidem. Thus, although the results of these two experiments are consistent with results of past studies using identical procedures without any treatment, they failed to show residual effects of drugs contrary to tests using tasks that were analogue or close to the driving tasks, in particular when they measure variations in the lateral position of the vehicle. Thus, flunitrazepam and zopiclone were often shown to
have residual effects compared to a placebo, although the lack of methodological standards from one study to the other can sometimes produce unclear or contradictory results (2, 11). As our test only made use of motor responses concerning perceptual judgements, it only used a small portion of the driving task and probably should be adapted to more realistic and interactive situations to be effective. It also involves a certain concentration of the participants and was neither as automatic, nor as monotonous, as driving tasks used in other studies.

The experiments also may not be sensitive enough, however, to show the residual effects of hypnotics but, on the other hand, the molecules studied may be devoid of residual effects concerning the processing of visual information. Thus, other studies using more sensitive and realistic simulation techniques are doubtless needed to improve this initial approach.

References
2. O'Hanlon JF (1995) Zopiclone's residual effects on psychomotor and information processing skills involved in complex tasks such as car driving: a critical review. Eur Psychiatry 10 (suppl 3): 137s-143s