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Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation?

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Few studies have addressed the modifications in visual information processing brought about by taking hypnotic substances. The present experiment with healthy subjects investigated the residual effects of taking a single night-time dose of hypnotics on collision anticipation capacities the next morning. Visual sequences simulated the movement of a driver approaching an intersection where another vehicle was arriving. Ten participants had to estimate, as quickly as possible, whether the other vehicle would arrive before or after them at the intersection. They were tested after having taken a capsule of zolpidem (10 mg), zopiclone (7.5 mg), flunitrazepam (1 mg) or a placebo. The results show no residual effects of the molecules. Only flunitrazepam, a benzodiazepine with a long half-life, appears 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), is not used correctly.

Key words: anticipation of collision, driving, flunitrazepam, residual effect, zopiclone, zolpidem

Introduction

Driving a vehicle requires the use of sensorial, cognitive and motor functions which lead to a behaviour that must be adapted to the various situations encountered in the road system. Psychotropic drugs (alcohol, narcotics, medication) act on the central nervous system and alter its functions. This alteration causes behavioural modifications which can lead to an increase in driving risks (Brookhuis, 1998; Riedel *et al*., 1998; Maes *et al*., 1999; Menzin *et al*., 2001).

Thus, 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 (De Gier, 1995; Sherwood, 1998). This percentage is very near that of the consumers in the general population and cannot be used to establish a direct link of causality between a given product and a precise deterioration in the driving task (Girre *et al*., 1988). However, the scientific literature provides a group of concordant arguments which implicate the taking of benzodiazepines in the occurrence of accidents, with an excess number of drivers involved in accidents having taken these medicines (Barbone *et al*., 1998; Arditti *et al*., 1993). Moreover, it has been observed that drivers who were at fault may more often be under the influence of medication than drivers who were not at fault (Benzodiazepines/Driving Collaborative Group, 1993).

Benzodiazepines belong to the psycholeptic family, depress mental activity and deteriorate vigilance. Furthermore, cumulative (Willumeit *et al*., 1991) or residual effects may persist among healthy subjects the day after a bedtime dose. Benzodiazepines act both on psychomotor performances, on spontaneous motor activity and on sleep (Mattmann *et al*., 1982). However, these symptoms depend on the duration of action of the molecule, which is lower for benzodiazepines with short half-lives than for those with long half-lives (Volkerts and O'Hanlon, 1986; Laurell and Tornros, 1991).

Within this context, the study of the effect of psychotropic drugs on driving performance is a highly interesting challenge for road safety, and debate is focusing on the choice of hypnotic molecules with the shortest possible half-lives and on those with fewer residual effects on behavioural efficiency (Volkerts, 1986; Mercier-Guyon, 1994; O'Hanlon and Allain *et al*., 1995).

The present study aimed to identify the residual effects related to a single night-time dose of hypnotics with variable half-lives on the ability to anticipate a collision the next morning. This objective was motivated by the fact that a large proportion of hypnotic drug 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 (Hindmarch and Kern, 1992), tending to decrease after a few days (Allen *et al*., 1991).

The hypnotic drugs studied: effects on driving behaviour

Zolpidem, zopiclone and flunitrazepam are commonly prescribed hypnotics with different half-lives, for which we have studied the residual effects of a minimum dose. Maes *et al*. (1999) noted that

zolpidem and zopiclone had moderate effects on driving ability whereas flunitrazepam had severe effects.

Flunitrazepam is a reference benzodiazepine hypnotic whose residual effects have been evaluated in many tests (Bond and Lader, 1975; Lader *et al*., 1982; Harrison *et al*., 1985). It was included in the study as a positive control to evaluate the sensitivity of the procedure. Its half-life is between 19 h and 30 h and it has a wide range of activity on all sleep parameters (Blois, 1997). Flunitrazepam was shown to have residual effects on memory and on information processing time in healthy subjects after a single dose of 1 mg (Harrison *et al*., 1985). No residual effects were found on visual reaction times (Lader *et al*., 1982). After more than 1 h of simulated driving, 1 mg of flunitrazepam affected the lateral position of the vehicle (Bocca *et al*., 1999). During driving tests on subjects suffering from sleep disturbances, Vermeeren *et al*. (1995) did not demonstrate any residual effects from flunitrazepam 2 mg on the vehicle lateral position, although the subjects felt drowsier and less active than with a placebo. Conversely, Volkerts *et al*. (1983, 1984) showed that flunitrazepam, 2 mg, had residual effects on driving performances.

Zolpidem (10 mg) is a molecule belonging to the imidazopyridine family and differs from benzodiazepine in its chemical structure and its pharmacological and clinical profiles (Undén and Schechter, 1996). It has a very short half-life of between 1.4 h and 2 h on average (Salva and Costa, 1995). Cognitive, vigilance and performance tests do not show any residual effects, and reaction times are not modified by zolpidem (Nicholson and Pascoe, 1986; Fairweather *et al*., 1992; Lavoisy *et al*., 1992). However, in simulated driving, the daytime effects of a single night-time dose of 10 mg of zolpidem modify driving performances of healthy subjects (Etard *et al*., 1995). In an open procedure, these authors observed a decrease in their ability to maintain a constant speed and an increase in the variability of their vehicle's lateral position on the carriageway. On the other hand, under a double-blind procedure (Bocca *et al*., 1999), or with a real driving test on insomniac women (Vermeeren *et al*., 1995), no residual effects of zolpidem (10 mg) were observed.

Zopiclone (7.5 mg) is a hypnotic drug of the cyclopyrrolone group, whose effects on sleep are mainly visible at the start of the treatment. Its half-life varies between 4 h and 5 h (Fernandez *et al*., 1995). Subjectively, zopiclone is well tolerated, improves sleep and does not cause morning drowsiness (Hajak *et al*., 1994). Choice reaction time and errors of choice reaction time were not modified by zopiclone in young subjects (Seppala *et al*., 1982; Billiard *et al*., 1987; Tafty *et al*., 1992). In a test of complex reaction time using healthy subjects the morning after a single dose, only a 10-mg dose significantly modified average reaction times, but doses of 10 mg and 7.5 mg significantly modified subjective sensations of alertness, performance levels and drowsiness (Broadhurst and Cushnaghan, 1987). On the other hand, in an actual over-the-road driving test, 7.5 mg of zopiclone caused residual effects among insomniac subjects after two nights of treatment (Volkerts *et al*., 1984), increasing variability of vehicle's lateral position. The day after a single dose taken by a small sample of healthy subjects (n = 9), this molecule did not lead to any modification in response time for braking (Harrison *et al*., 1985), whereas with a larger sample, in early morning, the average variance in the lateral position of the vehicle increased (Vermeeren *et al*., 1998; Bocca *et al*., 1999; Vermeeren *et al*., 2002).

Thus, the residual effects of these hypnotic drugs on driving behaviour are more or less marked depending on the experimental conditions (O'Hanlon, 1995), with very few studies to date concerning the modifications they may cause on processing visual information during the driving task.

Perceptual activities at the origin of driving behaviour

The driving task consists of undertaking travel that is orientated towards a goal within a spatial field, and involves avoiding potential or real obstacles which may block travel, thus entailing control and mastery of the vehicle. It involves constant adjustments of the trajectory in relation to the environment (Van der Hulst *et al*., 1999). Thus, the driver must interpret all the information currently at his disposal. He can foresee the evolution of the present situation in case he does not act or, in contrast, if he undertakes any form of action, and he can then estimate what consequences this evolution will have for him. The driver must therefore process the gathered information to infer the evolution of the situation and take decisions which he feels are suitable given the current and foreseen status of the system, using his own previous experience (Wetherell, 1986; Cavallo *et al*., 1997; Blouin *et al*., 1999).

In this context, the processing of visual information is not only a manifestation of hypotheses made by the driver, but also an explanation of his actions (Berthelon *et al*., 1995). In so far as this processing is not performed passively, we can postulate that it is modified by the use of hypnotic drugs (Wetherell, 1986) which will be expressed through behavioural modifications.

Using a task of collision anticipation and a technique of forced choice under a time constraint, we postulated that any modification of behavioural variables may demonstrate a decrease in the level of awareness as well as residual effects from the molecules tested (O'Hanlon *et al*., 1982). Subjects were presented with visual simulations of a rectilinear arrival to an intersection. Another vehicle was arriving at the intersection and they had to decide, as rapidly as possible, whether the other vehicle would arrive before or after themselves at the intersection. We recorded the quality of the subjects' responses, as well as their reaction times, which are regarded as a sensitive laboratory measure analogous to real-life performances such as car driving (Hindmarch and Clyde, 1980), presupposing that a decrease in responses quality and/or an increase of reaction time will reflect a decrease in driving performances.

Materials and methods

Subjects

Ten subjects, all experienced drivers (having driven 100 000 km), participated in the experiment. There were four men (mean age 29 years, range 24–42 years; mean weight 75 kg) and six women (mean age 27 years, range 23–29 years; mean weight 59 kg) and all had normal eyesight or normally corrected eyesight. All practised sport regularly.

Before the experiment, the subjects underwent a medical examination to confirm their good physical condition and the absence of any treatment at the time of their inclusion or during the previous 15 days. The criteria for exclusion were sleep, alertness, neurological, cardiovascular, respiratory, hepatic, renal and metabolic pathologies.

They were informed that the aim of the study was to test the effects of certain sleeping capsules, with no more information about the drugs used. The experiment was explained to them and they provided their written informed consent. The experimental protocol was submitted for approval to the Ethics Committee, Caen, France.

Procedure

The experiment was 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 under a time constraint.

The pictures used were generated on a Silicon Graphics station with a resolution of 1280 × 1024 pixels and an image refresh rate of 60 Hz. The real-time image obtained was recorded on a Umatic videocassette recorder and was time-coded for computer control during the experiment. The visual scenes were projected for subjects on a large screen (60° by 49°) using a video projector. The subjects were sitting facing the projection screen on the seat of a simplified driving unit. The steering wheel was equipped with two buttons, one on the right and the other on the left, designed to record their responses.

The visual sequences simulated the rectilinear movement of a driver approaching an intersection at 70 km/h. Another vehicle arrived straight from the right of the intersection at 10 km/h. This vehicle could arrive at the intersection 1000 ms, 500 ms or 200 ms before or after the subject, with this factor being defined as the vehicle crossing interval. Each sequence had a maximum duration of 5 s and was interrupted at least 1 s before the driver arrived at the intersection.

The road environment varied and could be: a carriageway with a uniform surface (Fig. 1A), a carriageway with a textured surface and road markings (Fig. 1B) or a carriageway with a textured surface, road markings and trees in the background of the visual scene (Fig. 1C). In half of the visual scenes, a road sign without specific meaning was placed near the intersection. This road sign was not informative, it was just a spatial reference in the driver's field of view (e.g. Fig. 1C).

The three types of scenes and the presence or absence of a road sign defined six experimental sets. In each set, the six intersection crossing intervals were presented six times in random order. Each subject thus saw 216 visual sequences. The order of presentation of the sets was counterbalanced from one subject to another.

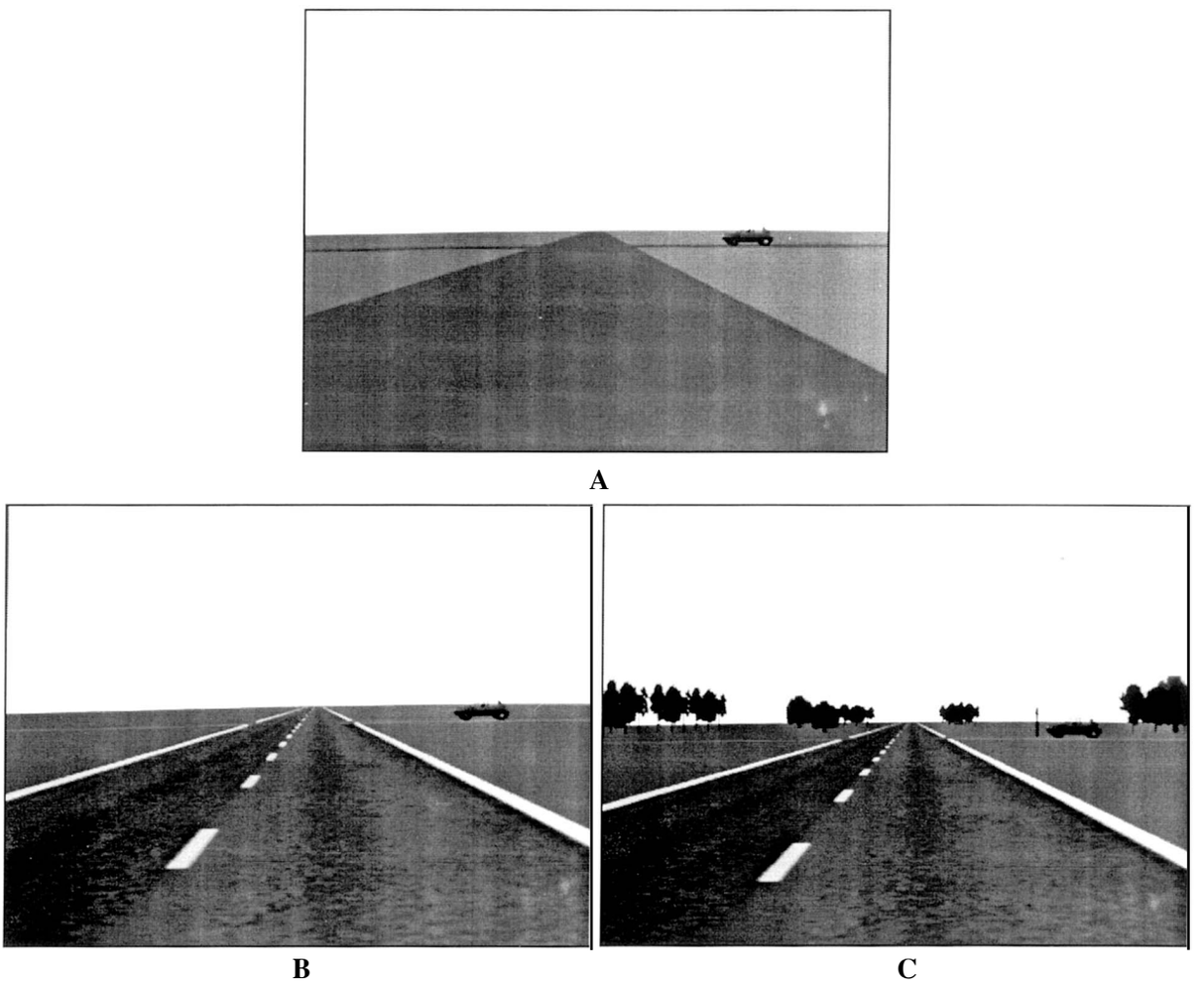

Figure 1 Examples of images used in the experiment. The road environment had (A) a uniform carriageway, (B) a textured carriageway with road markings and (C) a textured carriageway with road markings, trees in the background and a road sign near the intersection

Task

For each visual sequence, the subjects had to estimate whether the other vehicle would arrive at the intersection before or after them. They were informed that they must not take in account any right of way. The responses were gathered by pressing on one of the two buttons on the steering wheel of the driving unit which was connected to the computer operating the system. Pressing interrupted the visual sequence. The next sequence began a few seconds later.

Design

Each subject participated in five experimental sessions. The duration of each session was 1 h and 15 min. 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. A complete experimental design would have require 24 subjects. Thus, a combination of medication was associated to its inverse, and we tried to balance the location of medications as far as possible.

Each session was separated from the following by a washout period of at least 15 days (O'Hanlon and Volkerts, 1986; Bocca *et al*., 1999), 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 23.00 h on the day before each session. The medication was administrated at the subject's home under the supervision of an experimenter. The next morning the subject was brought to the experimentation room. The session began at 09.00 h (i.e. 10 h after taking the capsule).

The subjects were required to abstain from alcohol and intensive physical exercise for 24 h before each experimental session and their night-time activity was recorded by actigraphy from 23.00 h to 07.30 h (Gaëhwiler Electronic, CH-8634 Hombrechtikon, Stäfa, Switzerland). By pinpointing the periods of night-time inactivity corresponding to sleep phases, these records were only used to verify that the rest recommendations laid down in the experimental protocol had been applied (bedtime and waking time). In other studies, this type of recording has demonstrated that flunitrazepam decreased nocturnal motor activity (Mattman *et al*., 1982; Borbely, 1984) as do zopiclone and zolpidem, the latter in the first part of the night only (Bocca, 2000).

Dependant variables

Error rates (ERs, percentage of errors), response times (RTs) and points of subjective equalization (PESs) were analysed. Response times corresponded to the time interval between the start of the visual stimulation and pressing on the button on the steering wheel.

To calculate the PESs, we first counted the percentage of cases for which subjects gave 'the other vehicle arrives before me at the intersection' responses as a function of the crossing interval of the vehicles at the intersection. Individual data were fitted by a logistic function. The value of the crossing interval, for which the percentage of 'before responses' was equal to 50%, was interpolated from this function, and defined as the PES (Fig. 2) (Bonnet, 1986)

This PES corresponded to a crossing interval for which the subject could not decide whether the vehicle would arrive at the intersection before him or after him, and therefore corresponded to a crossing interval estimation for which the subject had the impression of colliding with the vehicle. If the PES had a negative value, the subject had a tendency to perceive the vehicle as systematically arriving at the intersection earlier than it is really the case. As the task was to analyse if the other vehicle arrived before or after oneself without taking in account the right of way, this can be interpreted as an overestimation of the vehicle speed or as a underestimation of his own speed. Conversely, if the PES had a positive value, it signified that the subject had a tendency to perceive the vehicle as systematically arriving at the intersection later.

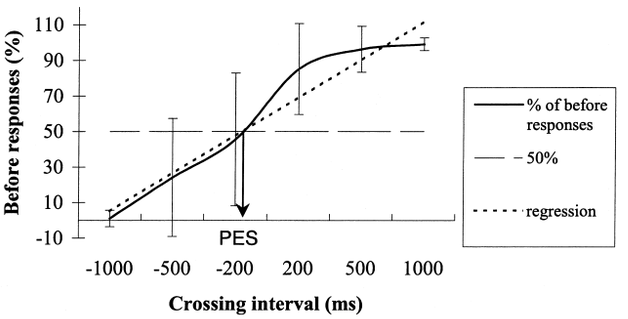

Figure 2 Mean percentage of 'the other vehicle arrives before me at the intersection' responses as a function of the crossing interval. The percentage varies between 0% and 20% when the other vehicle arrives less than 500 ms after the subject at the intersection (negative crossing intervals), corresponding to a false response. The percentage varies between 90% and 100% when the vehicle arrived more than 500 ms before the subject at the intersection (positive crossing interval), and in this case it corresponds to a correct response. Vertical bars represent SDs

The PES was therefore a good approximation of subjective bias.

Statistical analysis

Error rate and response time were submitted to a four-factor analysis of variance (MANOVA) performed using Statistica software (StatSoft, Tulsa, OK, USA) (four treatments × three environments × presence or absence of road sign × six crossing intervals). Where main effects or interactions were significant, exhaustive comparisons were made using the C-contrast test routine. $p < 0.05$ was considered statistically significant.

The method used to calculate PESs made the crossing interval factor disappear; thus, PESs were submitted to a three-factor analysis of variance.

Results

Treatment effects

The treatment had no significant effect on RTs [$F(3,27) = 0.14$, NS], nor on ERs [$F(3,27) = 0.38$, NS] (Table 1).

However, an interaction between treatment and sign factors [$F(3,27) = 3.62$, $p < 0.025$] indicated that flunitrazepam with a sign led to greater negative biases than flunitrazepam without a sign [$F(1,9) = 18.68$, $p < 0.002$] (Fig. 3).

Effect of the crossing interval

The intersection crossing interval affected RTs [$F(5,45) = 15.83$,

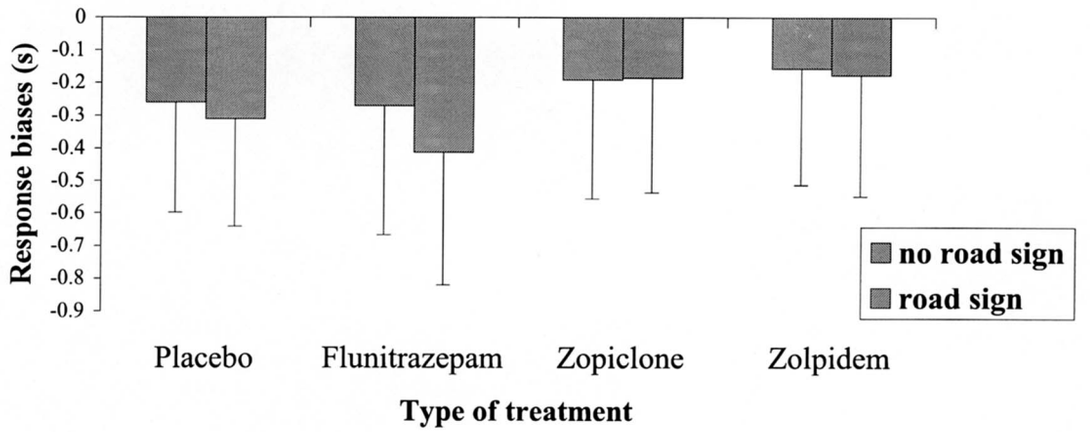

Figure 3 Mean points of subjective equalization as a function of the treatment and of the presence of a sign near the intersection. Vertical bars represent SDs

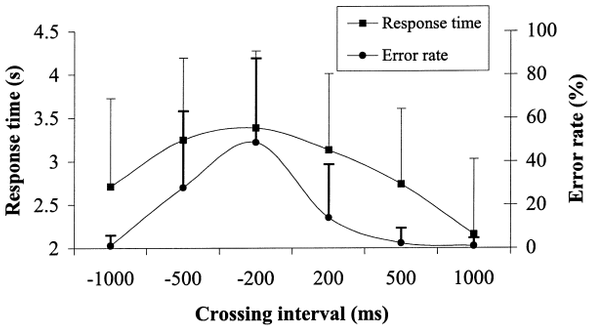

Figure 4 Mean response time and error rate as a function of the crossing interval. A negative crossing interval means that the vehicle will arrive at the intersection after the subject and, inversely, a positive crossing interval means that it will arrive at the intersection before the subject. Vertical bars represent SDs

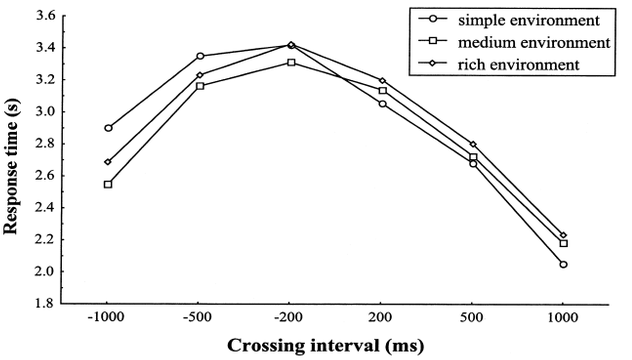

Figure 5 Mean response times as a function of the type of environment and of the vehicles' crossing interval

Table 1 Mean response time, error rates and points of subjective equalization (PESs) as a function of the treatment

	RTs (s)	ERs (%)	PES (s)
Placebo	2.91 (1.01)	16.02 (19.6)	–0.28 (0.33)
Flunitrazepam	2.89 (0.98)	18.05 (33)	–0.34 (0.4)
Zopiclone	2.94 (1.05)	14.86 (27.4)	–0.19 (0.33)
Zolpidem	2.85 (0.95)	14.39 (28.3)	–0.17 (0.36)

SDs given in parenthesis.

Table 2 Mean response time, error rates and points of subjective equalization as a function of the type of environment

Type of environment	RTs (s)	ERs (%)	PES (s)
Sign	2.93 (0.99)	16.27 (30.33)	–0.27 (0.37)
No sign	2.85 (1.01)	15.39 (29.05)	–0.22 (0.36)
Simple	2.91 (1.02)	16.63 (30.6)	–0.26 (0.37)
Medium	2.84 (0.98)	16 (29.1)	–0.23 (0.37)
Rich	2.93 (0.99)	14.86 (29.32)	–0.25 (0.36)

SDs given in parenthesis.

$p < 0.001$] and ERs [$F(5,45) = 9.36, p < 0.001$] and there was a positive correlation between RTs and ERs ($r = 0.82$) (Fig. 4). Thus, the greater the crossing interval, the lower the ERs and the RTs. Conversely, the smaller the crossing interval, higher the ERs and the RTs. We noted an ease in analysing the condition where the vehicle arrived 1000 ms before the subject at the intersection and a difficulty in analysing the condition where it arrived 200 ms after the subject (Fig. 4).

Effect of the sign and of the road environment

Although PESs were smaller without the sign than with the sign, the difference was not significant [$F(1,9) = 3.46$, $p < 0.09$] (Table 2). The RTs were shorter without the sign than with the sign [$F(1,9) = 6.26$, $p < 0.03$], but ERs did not significantly vary in relation to the road sign (Table 2).

ERs and RTs and PESs did not significantly vary from one environment to another (Table 2).

Environment and crossing interval factors interacted [$F(10,90) = 4.9, p < 0.001$]: the simplest environment produced longer RTs than the two other environments when the vehicle arrived 1000 ms and 500 ms after the subjects at the intersection [$F(1,9) = 10.81$, $p < 0.009$] (Fig. 5).

Discussion and conclusions

In the present work, we tested the residual effects of a single dose of psychotropic drugs on a task of visual anticipation of collision. We analysed ERs, RTs and PESs in function of the treatments and in function of the anticipation of motion *per se*.

Concerning treatments, the results were not in line with results from previous studies: an active molecule had no residual effects on performance parameters, be it flunitrazepam, zopiclone or zolpidem. Thus, our test was perhaps not sensitive enough to underline these effects, although it had been efficient in past experiments with a curvilinear approach of an intersection showing that field-independent drivers were better than field-dependent ones (Berthelon *et al*., 1998) [the field dependence/independence dimension distinguishes people in terms of their ability to perceive something separate from its context, and to adopt an analytic attitude during spatial problem solving (Shoptaugh and Whitaker, 1984)], as were experienced drivers compared to non-drivers (Berthelon *et al*., 1995), at picking up relevant dynamic information in complex road environments (versus abstract environments). Moreover, experienced drivers tended to analyse the intersection situations more rapidly than non-drivers (Berthelon *et al*., 1995). In the present study, the approach of the intersection was rectilinear, which simplified the task and probably decreased the sensitivity of the test. Moreover, the sample used was very small, which probably decreased its power. A more systematic approach with a larger sample could probably help to resolve these questions.

Whatever the case, the test failed to show any residual effects of drugs contrary to tests using tasks analogue, or close to, the driving tasks, in particular when they measure the variations in the lateral position of the vehicle. Thus, flunitrazepam and zopiclone were often shown to have residual effects compared to placebo (Etard *et al*., 1995; Bocca *et al*., 1999), although the lack of methodological standards from one study to the other can sometimes produce unclear or contradictory results (O'Hanlon, 1995; Vermeeren *et al*., 1995; Undén and Schechter, 1996). Because 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 efficient (O'Hanlon, 1988). The test involves a certain concentration of the participants and was neither as automatic, nor as monotonous, as driving tasks used in other studies, which may also explain its lack of sensitivity.

Otherwise, subjects were informed that they were going to be taking sleeping capsules for three of the four sessions (placebo) and it might be argued that this information created the feeling that they were not in a normal state. For example, taking fictitious doses of alcohol leads to a deterioration in performances in simulated driving situations (Breckenridge and Dodd, 1991), and subjects expecting the greatest deterioration were those that displayed the greatest deterioration, whether they had ingested alcohol or a placebo (Fillmore and Vogel-Sprott, 1995). However, the present experiment, performed in crossover and double-blind set-up, eliminated this hypothesis.

Nevertheless, flunitrazepam used as a positive control gave higher negative PESs in situations with a sign than in situations without a sign. Because, in the driver's field of view, the vehicle gets visually closer to the sign before reaching the intersection, subjects could have assimilated the sign as a reference point, which would explain their tendency to see the other vehicle as arriving before themselves at the intersection. In a previous study, performed without treatment, the road sign had the opposite effect and reduced PESs, providing a better analyse of the other vehicle's motion (Berthelon *et al*., 1999). Flunitrazepam may thus have caused the subjects' visual attention to be focused on an environmental cue (the road sign used as a spatial reference) and may amplify the difficulty they have in pinpointing the singular movement of the other vehicle independently of spatial references located near the intersection (Berthelon *et al*., 1995, 1998).

Concerning the anticipation of motion, the test confirms our previous work. First, we found that subjects managed to estimate relatively well when the other vehicle arrived at the intersection (the overall average percentage of error was approximately 15.8%). However, they had specific difficulties in analysing the condition where the vehicle arrived 200 ms after them at the intersection (high ERs and long RTs); they fused it with the conditions where the vehicle arrived before them (negative bias). This phenomenon, which was constant from one environment to another, could be due to the subjects' underestimation of their own speed or to the subjects' overestimation of the other vehicle's speed (Berthelon *et al*., 1999). Second, speed and accuracy of the responses varied with the crossing interval of the vehicles at the intersection. The greater this interval, the lower the RTs and ERs. Inversely, the shorter the interval, the more difficult it is to determine whether the other vehicle will arrive before or after oneself, and thus the greater the RTs and ERs. These results could be the manifestation of uncertainty related to the difficulty of the task: more uncertainty involves taking more time to analyse the situation (Welfort, 1980; Owen and Warren, 1987; Berthelon *et al*., 1998).

In addition to these general effects, there appeared to be more local visual determinants of perceptual judgements which are expressed by a modification of the executive function. Thus, RTs were higher with the simple environment than with the two others in the situations where the vehicle arrived after the subject at the intersection. In this case, the environment only consisted of a linear perspective and the intersection lines; the subjects had no information about their own speed and may have waited until the distance between the intersection and the other vehicle was short enough to make their perceptual judgements (Cavallo *et al*., 1997). The presence of a sign also increased RTs, which confirms the use of relative movements between some environmental elements (sign or intersection lines) and the other vehicle in the estimations. Such an analysis of relative movement requires a longer information processing time, which could explain the increase in response time (Berthelon *et al*., 1995; Berthelon *et al*., 1998). Because the test involves a spatio-temporal estimation linked to work memory, it would be interesting to investigate whether the modification of perception time can be evaluated, as is the case with psychostimulant drugs and cannabis.

In short, this test demonstrates that only flunitrazepam, a reference benzodiazepine with a long half-life, appears to be different from the other molecules and leads to subjects' focusing their attention on a road sign that plays the role of a spatial reference. However, the test may not be sensitive enough to show the residual effects of hypnotics but, on the other hand, the molecules studied may be devoid of any residual effects concerning the visual anticipation of collision. The results also confirm the basic idea that it is difficult to assess the deleterious effects of drugs on a task, such as driving a car. Indeed, driving is a

learned task which is subjected to conditions caused by variable external circumstances and to conditions related to constant or transitory personal features (Irving and Jones, 1992). This is one of the reasons why laboratory tests must be validated by more realistic driving tests (O'Hanlon, 1988). Thus, other studies using more sensitive and realistic simulation techniques are doubtless needed to improve this initial approach. Finally, it should be noted that, while work on a single dose of these drugs taken by healthy subjects cannot give a precise prediction of the effects after several days of treatment, it nonetheless provides substantial results and can be considered as a preliminary to more specific studies on patients (Vermeeren *et al*., 1995).

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