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Hans Laurell and Jan Törnros

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Väg- och Trafik-Institutet

Statens väg- och trafikinstitut (VTI) • 581 01 Linköping

Swedish Road and Traffic Research Institute • S-581 01 Linköping Sweden

Interaction effects of hypnotics and alcohol on driving performance

H. LAURELL[1], J. TÖRNROS[2]

[1] Swedish Road Safety Office, S-781 86 Borlänge, Sweden.
[2] Swedish Road and Traffic Research Institute, S-581 01 Linköping, Sweden

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Twenty-four healthy volunteers, screened as moderate drinkers and not using drugs, were paid subjects in the study. The design was doubleblind, randomised, cross-over. Medications were: flunitrazepam, 2 mg; flurazepam, 30 mg; triazolam, 0.5 mg; placebo. Each drug was ingested on four consecutive nights at bedtime. Nine hours after the fourth intake, performance testing was carried out. Immediately after this, alcohol was ingested. When the blood alcohol concentration reached 0.05 %, performance testing was repeated. The driving task was to negotiate a distance of 20 km as fast as possible in a sophisticated driving simulator. In the case of a crash, the driver had to wait for 20 seconds before driving could be resumed. It was found that performance was affected by drug intake whereas no drug x alcohol interaction was evident; performance was worse after flurazepam than after any of the other two active drugs, regardless whether alcohol had been consumed or not. The subjects also rated their time to sleep onset, and their experienced tiredness the next morning.

Key words: BAC; hypnotics; driving performance; residual effects; interaction

INTRODUCTION

Complaints about sleeping problems are among the most frequent disorders in medical practice. Epidemiological evidence points to insomnia as being the most common sleep disturbance. A substantial part of the population suffers regularly or irregularly. Some 4-5 % of the adult Swedish population seems to suffer from insomnia.

For many of those who suffer from sleep disorders, an additional problem presents itself when they need to drive their cars. Of course, hypnotics or sedatives which are used to facilitate falling asleep or sustaining of it, should not be used in combination with driving, at least not after acute administration of the drug. Of more direct interest, however, are the residual effects experienced the morn-

ing after - if you have to drive after a night of medication for insomnia.

Benzodiazepines are the most commonly prescribed psychotropic substances in Sweden and accounted for 80 % of all the drugs prescribed for insomnia in 1985-1987 [1], Based on their pharmacokinetic properties, the benzodiazepines can be divided into short, intermediate and long acting substances.

Hypnotics with short half-lives tend to produce less residual effects compared to drugs with longer half-lives. The administration of any drug with a half-life longer than six hours, nightly, will result in accumulation and thus possible impairment in situations where no impairment is tolerated.

Some hypnotics have been tested for impairing properties in real car driving situations. Thus, Dutch studies have found residual impairment after administration of flurazepam, 15 and 30 mg and flunitrazepam, 2 mg when the drivers had to perform a driving task [4], involving speed maintenance and straight driving. In closed course driving tasks [5], flurazepam 15 mg has been found to cause impaired performance the next morning. Some effects were also reported for triazolam 0.25 mg, nitrazepam 5 mg, another long acting drug, however, had much greater residual effects. In simulated driving tasks, emphasizing monotonous, long-term driving [6], nitrazepam was found to have some residual effects, whereas this was not the case for triazolam 0.25 mg.

This study set out to study the residual effects of flunitrazepam, flurazepam and triazolam after late evening medication and the possible interaction effects of an additional dose of alcohol the next morning.

MATERIALS AND METHODS

Subjects: 24 healthy volunteers, aged 20-32, participated as paid subjects. All were licensed and were screened as moderate drinkers. None of the subjects was under any medication.

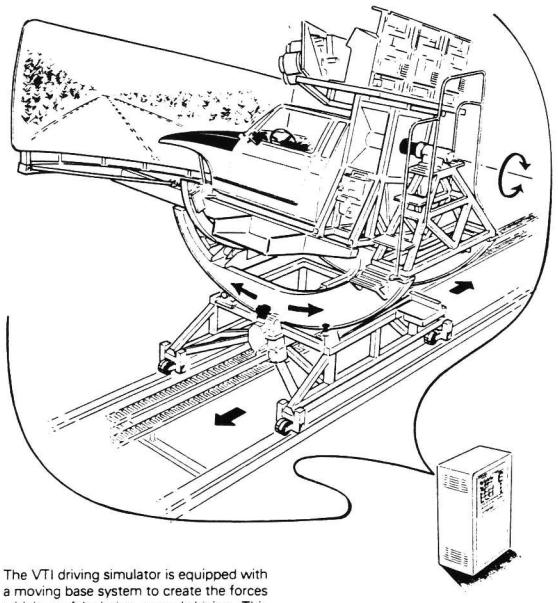
Design: Randomized, placebo controlled, doubleblind, cross-over methodology.

Medications: flunitrazepam, 2 mg; flurazepam, 30 mg; triazolam, 0.5 mg; placebo. Each drug was ingested on four consecutive nights at bedtime. Nine hours after the fourth intake, performance testing was carried out. Immediately after these tests, alcohol was ingested. The target blood alcohol concentration (BAC) was 0.05 % (the amount and time required to reach this level was determined individually for each subject prior to the performance test; the BAC was measured with a Siemens Alcomat breath testing unit at five-minute-intervals). When this level was reached, the performance testing was repeated.

Performance test: The driving test consisted of a demanding driving task in a sophisticated driving simulator (Fig. 1). The subjects were asked to drive a 20 km test distance in as short time as possible. Losing control of the car and thereby leaving the road, resulted in a "crash", which, as a penalty, stopped the stimulator for 20 seconds. The subjects were paid in relation to their average speed on the task.

In order to make the task a demanding one, the friction properties of the road surface were varied; the normally dry, high friction surface, was, at random intervals, interrupted by slippery sections. These could easily be detected by the subject since they were a whiter shade of grey than the high friction parts. Before testing, each subject was thoroughly trained to a high and stable level of driving performance. This required some three to four hours of practice driving.

On each test day, upon arrival at the institute, the subjects had a light standardized breakfast meal. No coffee was permitted during this meal. They also filled out a questionnaire concerning their sleep during the night; time to sleep onset, and subjective tiredness in the morning.



The VTI driving simulator is equipped with a moving base system to create the forces which are felt during normal driving. This is done by moving the cabin sideways and/or tilting it in different directions.

The simulator and its movements are controlled by a computer program, which also contains the equations for the vehicle dynamics. The theoretical model is quite comprehensive and includes the main factors influencing vehicle handling.

The visual system uses three TV-projector screens mounted edgewise in front of the driver giving a wide angle picture in full colour. The different roads are produced by specially developed digital electronics.

This system is very flexible and allows for varying curvature, signs, obstacles, different light conditions etc.

Fig. 1. The Driving Simulator

Upon completion of the first test run, the subject was allowed 10 minutes to consume the individualized dose of alcohol. BAC was then measured until the desired level was estimated to be reached within 10 minutes. At this point the second test drive was initiated.

The subjects were required to abstain totally from alcohol and other drugs during the medication days and for two days preceding the start of each medication period.

A wash-out period of at least three days between medications was employed.

In order to maximize compliance, the following precautions were taken:

a friend had to witness and sign a statement to the effect that the medication had been swallowed according to the plan. The subjects also signed the statement.

- dummy urine sampling.

RESULTS

The performance results were analyzed with regard to statistical significance (randomized block factorial design [7]. It was found that the drug effect was significant [$F(3,69) = 4.06$; $p < 0.05$]. The interaction between drug and alcohol, however, is not significant [$F(3,69) < 1$]. The nature of these effects are illustrated in Fig. 2.

Pairwise comparisons between drugs according to Tukey's test give the following results: the differences between effects of the drugs are significant for two comparisons: triazolam - flurazepam ($q = 4.54$; $p < 0.05$), and flunitrazepam - flurazepam ($q = 3.87$; $p < 0.05$), whereas the remaining four are not. This means that performance was worse after flurazepam than after any of the other two hypnotic drugs, regardless whether alcohol had been consumed or not. The difference was 2.9 km/h between flurazepam and triazolam and 2.4 km/h between flurazepam and flunitrazepam.

It was also shown that performance was impaired after consumption of alcohol [$F(1,23) = 11.67$; $p < .01$]. However, since the design of the study does not permit an accurate estimation of the alcohol effect (order of presentation not controlled), no safe conclusion can be drawn regarding the influence of this factor.

The average BACs in the different drug conditions were: flunitrazepam, 0.051 %; flurazepam, 0.052 %; triazolam, 0.052 % and placebo, 0.052 %.

The number of crashes was registered for each test run. Table I shows the average number in the different conditions.

An analysis of variance shows that the drug effect is significant [$F(3,69) = 3.06$; $p < 0.05$]. So is the alcohol effect [$F(1,23) = 16.31$; $p < 0.001$], whereas the drug x alcohol interaction is not [$F(3.69) < 1$]. No pairwise

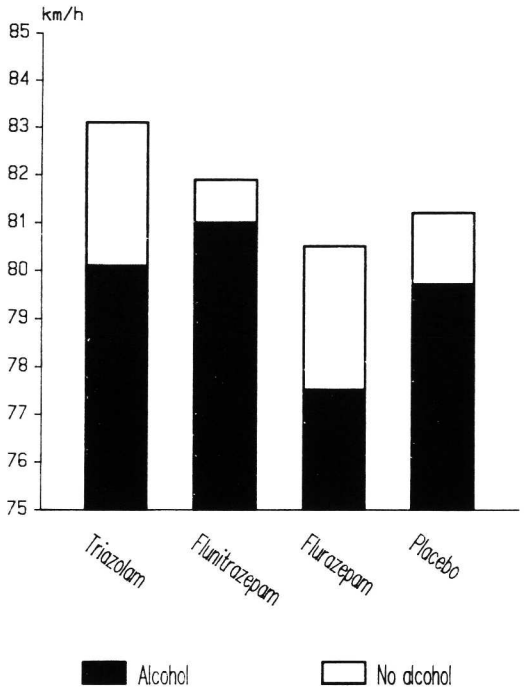


Fig. 2. Average speeds obtained in the four drug conditions, with and without alcohol involvement.

comparisons, however, turned out to be significant.

As for subjective data, after individual ranking of time to sleep onset, a Friedman's two-way analysis of variance by ranks showed that the difference between drug conditions was significant ($X^2 = 9.6; p < 0.05$). Pairwise comparisons (Wilcoxon's matched-pairs signed-ranks test) showed that only two pair wise comparisons turn out to be significant; placebo-triazolam ($T = 49$, $N = 23$; $p < 0.01$), and placebo - flunitrazepam ($T = 40$, $N = 23$; $p < 0.01$). Sleep onset, thus, was faster after triazolam and flunitrazepam than after placebo.

As for tiredness, Friedman's analysis of variance (based on individual rankings) shows that the drug effect is significant ($X^2_r = 21.3$; $p < .001$). Pairwise comparisons (Wilcoxon's signed-ranks test) reveal that three differences are significant; placebo - flunitrazepam ($T = 20$, $N = 23; p < .01$), placebo - flurazepam ($T = 45$, $N = 24; p < .01$) and triazolam - flunitrazepam ($T = 38$, $N = 23; p < .01$), whereas the remaining three are not. That is, subjects were less tired in the morning after placebo intake than after having taken flurazepam or flunitrazepam. They also felt less tired after triazolam than after flunitrazepam.

DISCUSSION

A significant effect, depending on the type of drug, on driving performance was found. Flurazepam was found to cause the worst problems and triazolam the least. Also for subjective data, triazolam showed the least carry-over effects of the three active drugs studied. These findings are in good accordance with the findings of others [4, 8]. In the study by Carskadon et al. [8] flurazepam caused more carry-over sleepiness and triazolam less. Flurazepam also affected performance in that it

Table I. Average number of crashes.

	Flunitrazepam	Flurazepam	Triazolam	Placebo	Average
No alcohol	1.1	1.8	1.0	1.7	1.4
Alcohol	1.8	2.9	2.0	2.1	2.2
Average	1.5	2.3	1.5	1.9	

produced an increase in the number of missed responses.

Borland and Nicholson [9] note that recovery of performance does not occur until around 16 hours after ingestion of flurazepam. It should be noted, however, that in this study, none of the drugs differed significantly from placebo in their influence on the driving parameters studied, thus indicating that any active drug effects were of a rather small magnitude.

No drug-alcohol interaction was found although it tended to be greatest for flurazepam.

It should be borne in mind that the subjects were young healthy volunteers, who previously never had found any need for hypnotic drugs. Thus, it is hard to generalize from the results of these subjects to more frequent users of hypnotic drugs.

As for the validity of the driving simulator, the only formal validations, so far, concern the basic characteristics of the simulator, e.g. response times in the visual presentation and the moving base system and the steering task [10, 11]. The specific driving tasks which are designed for the investigation of specific problems have not yet been validated.

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