THE CARRY-OVER EFFECTS OF TRIAZOLAM COMPARED WITH NITRAZEPAM AND PLACEBO IN ACUTE EMERGENCY DRIVING SITUATIONS AND IN MONOTONOUS DRIVING

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SYNOPSIS

Eighteen healthy volunteers of both sexes, aged 20 - 34 years, were tested in the morning while undertaking real car driving avoidance maneuvers and during monotonous simulated driving after 1 and 3 nights of medication with triazolam (0.25 mg), nitrazepam (5 mg), or placebo.

The study had a double-blind, randomized, cross-over design in which a minimum of 7 days washout separated the 3 treatment periods.

A trend in the behaviors, not statistically significant, favored triazolam over nitrazepam in both real car driving and simulated driving. The difference between placebo and triazolam was hardly noticeable.

INTRODUCTION

In recent years several new benzodiazepine derivatives have been developed in the search for chemical agents with effective hypnotic activity but which do not produce unwanted residual effects. This development has great social implications, especially in societies where transportation mainly relies upon private cars: a state of continual alertness is of critical importance when driving a car. However, the wide use of sleeping pills may give rise to hang-over effects that can impair driving performance.

Triazolam is a triazolobenzodiazepine differing from most others in that it is active in very low doses and has a short mean elimination half-life of 2.3 hr (Eberts et al. 1981). Thus, it could reduce the risk of residual effects. In this study, a comparison was made between triazolam, nitrazepam (mean elimination half-life of 29 hr; Kangas et al. 1979), and a placebo.

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When comparing the possible residual effects of various hypnotics on car driving performance, 2 aspects of driving stand out as particularly interesting: namely, monotonous driving and emergency avoidance situations. By employing such test situations, this study yields information that concerns performance related to driving in heavy city traffic as well as on empty highways.

**METHODS**

**Subjects**

Eighteen healthy volunteers of both sexes, between the ages of 20 -34 years possessing a current Swedish Car Driving License, were enrolled in the study.

The trial employed a double-blind, randomized, cross-over design. The study medications—triazolam (0.25 mg), nitrazepam (5 mg), and placebo—were each administered for 3 consecutive nights with a minimum of 7 days between each treatment period. Assessments were made in the morning after 1 and 3 nights of medication.

**Simulated Driving Task**

In order to detect any changes in susceptibility to driver fatigue, we created a monotonous 2.5-hr driving task in a driving simulator. The driving compartment of the simulator consisted of a real, truncated car body, complete with all controls—parts of a feed-back system of which a digital-analog computer was the brain.

A continually changing road pattern and landscape was randomly generated by the computer. A large television unit interpreted the signals and presented them visually on a wide screen in front of the driver. The program allowed for an overchanging pattern of road and landscape which included not only bends and straights but also up- and down-hill sections. Technological adaptions further mimicked real driving conditions by simulating vibrations on the road surface which, should the driver accidentally stray off the road onto the verge, increased in intensity. Activation of the controls by the driver caused the appropriate change in the visual scenario to occur (e.g., turning, braking). The driver was instructed to stay on the right side of the road and to maintain a steady 90 km/hr throughout the test. While driving the simulator the subject was exposed to a number of stimuli which, once perceived, called for a specific action to be taken. These events were pre-programmed and their presentation could not be predicted by the driver.
The computer continually monitored the driver's performance and functioning, and at the termination of a test run presented a detailed assessment of the parameters under study (brake reaction time, time off road or "across white line").

1) Visual Signals

Lights were placed both in the central visual fields and to the periphery. When they were illuminated the driver had to apply the brake. The time from stimulus appearance to application of the brake was the "Brake Reaction Time."

2) Auditory Signals

An auditory stimulus called for the same reaction as the visual stimuli already described.

Both, the visual and auditory stimuli, were presented randomly at intervals of 10 to 120 seconds.

Real Car Driving

In the real car driving situation, in contrast to the simulated monotonous task, an emergency, evasive maneuver was used (see Figure 1). The driving task was largely the same as one used in earlier studies on the effects of alcohol on driving performance (Laurell, 1977; Laurell & Törnus, 1983). On observing an avoidance signal from an apparatus mounted on the front of the vehicle, the driver had to carry out an avoidance maneuver and, doing this, try to avoid knocking over pylon cones which were placed along the avoidance path. The tolerance on either side of the car was approximately 15 cm. The number of cones knocked over was employed as a measure of driver performance. The signal could be presented at any 1 of 4 positions in the cone setting. If presented above the left headlight position, the signal appeared as an obstacle in front of and to the left of the car, thus requiring an avoidance maneuver to the right; and vice versa.

The order of presentation of positions was randomized for each subject and each treatment condition. In each session, the course was negotiated 10 times plus 2 blank runs by each subject. Two warm-up trials identical to a test trial preceded each session. The total of 14 trials lasted 30 minutes.
The road surface conditions were liable to considerable variations so the test area was sprinkled with water at regular intervals to maintain constant driving conditions. Vehicle speed was controlled by an automatic speed control system.

In order to keep motivation at a high level throughout the investigation, payment was made dependent upon performance. For each trial the driver had at his disposal a sum of 25 SEK (approximately $3.50); the sum was reduced for each cone knocked over.

Procedure

All subjects practiced the simulator task for 1 hour and the real car driving task for at least 2.5 hours or until a minimum level of performance had been reached.

The capsules of drug or placebo were taken at 2300 hours after which the subjects went to bed. After a standardized breakfast in the morning, they were brought to the simulator for testing at 0800 hours. Immediately after having completed the simulator test they took on the actual car driving task which lasted for 30 minutes. Two days later the whole procedure was repeated to examine the effects of possible accumulation.

Levels of Significance

The .05 level of significance was adopted for the whole experiment. Each of the comparisons was tested at the appropriate level of significance with respect to this basic requirement. Consequently a higher, in some cases much higher, level of significance was adopted for the individual comparisons.

RESULTS

Real Car Driving

Although the differences did not achieve statistical significance, the worst performance on both assessment Days 1 and 3 was found with nitrazepam, while triazolam and placebo appeared to have about the same effect (Figure 2).

Monotonous Simulated Driving Task

The trend noted in the real car driving was also found in the simulated conditions. Although all reaction times increased slightly as a factor of time, whether receiving
medication or placebo, the slowest reaction time appeared following taking nitrazepam on Day 1. The differences were less pronounced on Day 3. Once again, these observed trends did not achieve statistical significance (Figure 3).

**DISCUSSION**

With the small doses of the test drugs administered and the short duration of treatment, only small effects of the treatments on performance were detected. An increase in the Brake Reaction Time has been proven to reflect a decrease in the driving performance, particularly in the ability of the subject to detect obstacles along the road (Laurell & Lisper, 1978). Examination of this particular dependent variable in our study showed a tendency towards a steeper increase in the development of impaired reaction time following nitrazepam while a less step increase was noted in the triazolam and placebo conditions, which were similar. After 3 nights of medication there were few differences favoring one treatment over the other, and there was no accentuation of the performance degradation noted following nitrazepam after the first night's medication. An explanation could be that insufficient time has elapsed to permit a detectable plasma drug "build up" or, alternatively, a counteracting adaptation to the presence of the drug could have taken place.

On the Real Car Driving Task, no statistically significant differences in performance were found. Nitrazepam, however, tended to score worst while the difference between the placebo and triazolam conditions was hardly noticeable. Although small and statistically not significant with the numbers of subjects studied, the differences and trends favored triazolam over nitrazepam. Noted, however, that the carry-over performance degrading effects of the low dose of nitrazepam used were small. We feel that if we had used higher doses of the drugs this underlying trend would have been accentuated and would have led to larger and probably significant differences in favor of the drug with the short half-life (Hindmarch & Clyde, 1980).

**REFERENCES**


Figure 1. Simulated driving task: specifications of pylon arrangement, reflector positions, and relative distances.
Figure 2. Actual car driving (total means, 18 subjects) on Days 1 and 3.

The inclination of the curve shows how driving time in the simulator affects brake reaction times.

Figure 3. Regressions of brake reaction times (total means, 18 subjects) (inclination indicates change with endurance, Days 1 and 3).