Title: Carry-over effects of Oxazepam compared to Nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving

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PURPOSE

The aim was to investigate possible carry-over effects of Oxazepam into the following morning after medication as compared to Nitrazepam and placebo, in situations closely related to traffic. Comparisons were to be made on two occasions; after one night of medication and after five consecutive nights of medication.

STUDY MEDICATIONS

Oxazepam 25 mg
Nitrazepam 5.00 mg
Placebo matched

METHOD

3.1 Design

Double-blind randomized cross-over study.

3.2 Subjects

36 healthy volunteers aged 21-35.

3.3 Assessments

Two kinds of tests were used:

1. In order to detect any changes in susceptibility to the performance degrading effects of monotonous
driving, a monotonous driving task was created in a driving simulator.

The driving compartment of the simulator consisted of a real, truncated car body complete with all controls. The driving controls were parts of a feed-back system of which a digital-analog computer was the brain. Control use thus affected the landscape that was created in the computer and projected on to a big screen in front of the driving compartment. Feed-back also affected e.g. steering-wheel momentum. Road unevenness was simulated by vertical movements; if the wheels came off the road the driver was given a sensation of this by increased amplitude of the vertical movements.

The driver was instructed to stay on the right side of the road projected on the screen, and to drive at a speed of 90 km/h.

Dependent variable:
- Reaction times to flashing visual signals appearing on either of both sides of the screen.

The driver stopped the signal by hitting the brake pedal as fast as possible. Long reaction times (in relation to training results for each individual) or failure to respond to the signal (the signal lasted for 10 sec.) caused minor financial penalties. The signals were presented in random order through the session which lasted for 2 hours and 20 minutes. Interstimulus intervals varied from 10 to 120 sec.

Minor financial penalties were also associated with driving off the right driving lane.
2. In order to detect any "acute" effects of driving a situation involving an emergency evasive manoeuvre was used.

Upon a signal, the driver had to carry out an avoidance manoeuvre and, in doing this, try to avoid knocking over pylon cones which were placed along the avoidance path.

The signal could be presented at either one of four positions in the cone setting and if presented above the left headlight position, simulated an obstacle in front of and to the left of the car, and thus required an avoidance manoeuvre to the right and vice versa. In each session, the course was negotiated 10 times by each subject - one per signal alternative plus two randomized. In addition, two "blind" trials, in which no avoidance stimulus was presented, were inserted at random among the rest. Two warm-up trials preceded each session, which lasted for about 30 minutes.

The experiment vehicle was a SAAB 99. For presentation of the avoidance signal, the car had been equipped with a photocell-system, the light of which was reflected via a reflector mounted on a cone (one for each triggering point). The photocell triggered a relay, cutting the power of one of the two electromagnets and thus releasing a spring-loaded arm which served as the stimulus. A switch inside the car controlled by the experimenter decided which of the four reflectors would cause triggering to take place. Vehicle speed was controlled via an automatic speed control system. In order to maintain constant road surface conditions the test area was sprinkled with water.
Dependent variable:

earnings; the subjects were paid in relation to their performance on this task:

For each trial the driver had at his disposal a sum of 20 SEK. This sum of money was reduced for each cone, knocked over. A cone in one of the outer rows rendered a 1:50 SEK reduction and in the inner rows a 2:50 SEK reduction. Swerving into the wrong lane or performing no evasive manoeuvre at all when an avoidance manoeuvre was called for both were punished with the whole sum of 20 SEK.

3.4 Procedure

Half of the subjects participated in the simulator part of the study and the remaining 18 subjects participated on the emergency real car driving part.

Each subject in the simulator part practiced the simulator task for one hour. The evasive manoeuvre task was practiced for at least 2.5 hours or until a reasonably good and steady level of performance had been reached.

The capsules were taken at around 11 p.m. after which the subjects went to bed. After a normal breakfast (excluding coffee or tea, however) in the morning they arrived to the test site for testing at 8 a.m. Four days later the procedure was repeated.

Each test drive was followed by vein blood sampling.
A washout period of at least 7 days was applied between each of the three medications.

4 RESULTS

4.1 Evasive manoeuvres

Main results related to driver performance in the evasive manoeuvre part of the study are listed in table 1.

Table 1 Average driver performance in emergency driving task (average earnings)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 5</th>
<th>Σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>118 SEK</td>
<td>127 SEK</td>
<td>245 SEK</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>120 SEK</td>
<td>113 SEK</td>
<td>233 SEK</td>
</tr>
<tr>
<td>Placebo</td>
<td>115 SEK</td>
<td>114 SEK</td>
<td>229 SEK</td>
</tr>
</tbody>
</table>

Table 1 shows that the Oxazepam condition showed the best performance and the placebo condition the worst performance when the results from both days are added. The picture is different, however, after one night of drug intake from that after 5 consecutive nights of drug intake. The best performance on day 1 thus appeared in the Nitrazepam condition, but on day 5 in the Oxazepam condition. None of these differences were, however, significant. [Drug effect: $F(2,32)=1.95; p>.05$. Drug x day interaction: $F(2,32)=1.80; p>.05$].
4.2 Simulated monotonous driving

4.2.1 Brake reaction times

Main results related to driver performance in the monotonous simulated driving situation are illustrated in figures 1 and 2.

![Graph showing brake reaction times for Oxazepam, Nitrazepam, and Placebo after one night of drug intake.](image)

**Figure 1** Average mean brake reaction times after one night of drug intake
As figure 1 and table 2 show, after one night of drug intake the slowest reaction times appeared in the Nitrazepam condition and the fastest in the placebo condition.

After five consecutive nights of medication (see figure 2, table 2) the Nitrazepam condition scores worst, with very small difference between the other two conditions.

All differences between conditions depicted in figures 1 and 2 are, however, small and non-significant:

\[
\text{Drug effect: } F<1; \text{ n.s.} \quad \text{Drug x day interaction: } F<1; \text{ n.s.} \\
\text{Drug x time on task interaction: } F=1.28; >.05. \text{ Drug x day x time on task interaction: } F<1; \text{ n.s.}
\]
Table 2  Average mean brake reaction times

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>.91 sec</td>
<td>.90 sec</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>.92 sec</td>
<td>.92 sec</td>
</tr>
<tr>
<td>Placebo</td>
<td>.90 sec</td>
<td>.90 sec</td>
</tr>
</tbody>
</table>

4.2.2 Missed signals

No missed signals appeared on day 1. On day 5 a total of 6 signals were missed, one in the placebo condition, 2 in the Oxazepam and 3 in the Nitrazepam condition.

4.3 Other observations

After the completion of each treatment the subjects were asked to tell if the pills they had been taking the last 5 nights were a hypnotic or placebo.

It appears that the felt carry-over effects of the hypnotics studied were generally very moderate. Thus 17 (out of 36) subjects thought that they had received a hypnotic when in fact they had received placebo. 16 (out of the 36 subjects) thought they had received placebo when they had in fact received oxazepam, and 13 subjects (approximately 1/3) thought they had received placebo when they had received nitrazepam.
CONCLUSIONS

The effects found in the present study were generally small and statistically non-significant. With the small doses administered the subjects were often mistaken as to whether they had been given placebo or a hypnotic.

The results from the study of evasive manoeuvres in real car-driving did not yield very meaningful information. The driving simulator results were, although statistically non-significant, more in accordance with the hypothesis behind the present experiment. Here it can further be noted that the picture that emerges for day one is rather similar to that for day five.