Acute and Carry-Over Effects of Brotizolam Compared to Nitrazepam and Placebo in Monotonous Simulated Driving

Jan Törnros and Hans Laurell

Reprint from Pharmacology & Toxicology 1990, 67 pp 77-80

Acute and Carry-Over Effects of Brotizolam Compared to Nitrazepam and Placebo in Monotonous Simulated Driving

Jan Törnros and Hans Laurell

National Swedish Road and Traffic Research Institute (VTI), S-581 01 Linköping, Sweden

(Received February 5, 1990; Accepted March 7, 1990)

Abstract: Eighteen healthy volunteers of both sexes, aged 20–35 years, were tested in the morning after three nights of medication with brotizolam 0.25 mg, nitrazepam 5 mg or placebo on a monotonous simulated driving task. The effect measures were subsidiary auditory reaction time and time outside road. Measurements of self-rated alertness were carried out as well. No effects were demonstrated from treatments on either measure. Nitrazepam however tended to score worst on all measures, except time outside road which could not be analysed with respect to statistical significance because of an insufficient number of subjects leaving the road. Twelve of the subjects were also tested immediately after drug intake on the first night of each medication period. Reaction time decrement was observed in both active drugs conditions with no difference between the two. The other measures, however non-significant, pointed in the same direction with the greatest decrement for nitrazepam.

Brotizolam is a thienotriazolo-substituted diazepine derivative indicated as an hypnotic for the treatment of insomnia. It has a mean elimination half-life of about 5 hrs (Langley & Clissold 1988), considerably shorter than the frequently prescribed hypnotic nitrazepam with a mean elimination half-life of 21–28 hrs (Alván & Lee 1988), although there are benzodiazepines with an even shorter half-life (midazolam, triazolam) (Cappell *et al.* 1986).

Benzodiazepines with long half-lives tend to cause greater unwanted residual effects in the morning following night-time use than benzodiazepines with short half-lives (e.g. Nicholson 1981; Roehrs 1983).

The aim of the present study was to compare brotizolam and nitrazepam with respect to effects on driving performance in the morning following late evening medication. That such effects may appear, is indicated by a car-driving simulator study where nitrazepam 5 mg was found to have some residual effects on long-term driving performance after a single dose taken at bed-time, whereas no such effects were found from triazolam 0.25 mg (Laurell & Törnros 1986).

For comparative reasons, acute effects from the drugs were studied as well.

The study was approved by the Ethical Committee of the Medical Faculty of the University of Linköping.

Materials and Methods

Eighteen healthy volunteers of both sexes, aged 20–35, were paid subjects in the study. They all had valid Swedish car driving licenses. Twelve of them participated in all conditions of the study, whereas the remaining subjects participated only in the part pertaining to residual effects.

The study employed a double-blind, randomised, repeated measurements design. The study medications were brotizolam 0.25 mg, nitrazepam 5.00 mg and placebo, orally administered in tablet form, and were each taken for 3 consecutive nights with washout periods of at least one week between treatment periods.

For the study of residual effects, assessments took place in the

morning after three nights of medication. In the acute effects part, the assessments were made immediately after intake on the first night of the medication period.

Driving task. A monotonous driving task was created in the driving simulator, with a duration of 2 hr 20 min.

The driving compartment was a real truncated car body complete with all controls. The driving controls were part of a feed-back system of which a digital-analogue computer was the brain. Control use thus affected the continually changing landscape projected on to a big screen in front of the driving compartment. Feed-back also affected e.g. steering-wheel momentum and if the wheels came off the road, the steering-wheel would give the driver a sensation about this by increased amplitude of the vertical movements.

The driver was instructed to stay on the right lane of the road projected on the screen, and to drive at a constant 90 km/hr. The computer continually monitored the driver's performance and immediately after each test drive presented a detailed presentation of the test results.

During the drive the subject was exposed to a number of auditory stimuli (steady signals) appearing at random intervals (ISI varying between 10 and 120 sec. with an average of 65 sec.). The driver was instructed to stop the signal as fast as possible by hitting the brake pedal. The time from the appearance of the signal to application of the brake force constituted the major effect measure, brake reaction time (BRT). If no response appeared within 5 sec. the signal was shut off automatically and a missed signal was registered. Time outside road was measured as well.

In order to keep motivation high during the whole experiment, the subjects were paid in relation to their performance on the driving task. Performance during the first 10 min. of the test drive was not analysed.

Procedure. All subjects practised the simulated driving task for at least one hour.

Twelve of the subjects were brought to the simulator at 8.30 p.m., where they ingested the drug. Then followed the test drive after which they were brought home for the night. On the two following nights they took the drug at 11 p.m. after which they went to bed. After having taken the drug on three consecutive nights they made the final test drive at 8.30 a.m. after having had their usual breakfast. The other 6 subjects, not participating in the acute effects part, took the drug at 11 p.m. every night at bedtime.

For compliance, the subjects were reminded on the first night of the medication period to take the drug (telephone call). They were furthermore told that some randomly selected individuals would on

Fig. 1. Acute effects: Average median brake reaction times.

one occasion or other be subjected to blood sampling, to make sure that the drugs were taken as prescribed. No actual blood sampling was, however, performed.

No other drugs (excluding coffee, tea, tobacco) or alcohol were allowed during, or three days ahead of, the medication periods.

For arousal assessments the subjects were given a Swedish version of Thayer's Activation-Deactivation Adjective Checklist (AD-ACL) (Bohlin & Kjellberg 1973) before and after each test drive in the acute effects part but only before the test drives in the residual effects part study.

Results

During cross-checking it was found that two subjects had not followed instructions properly and they were therefore excluded from the analysis.

The brake reaction time data to be analysed were: For each subject, P50 (median) values were calculated for each 10 min. period of the test drive, starting with the second period.

Acute effects.

Fig. 1 shows the brake reaction time results in the acute effects part of the study. The longest overall reaction times appeared after having taken the active drugs (drug effect significant: $F(2.18) = 3.85$; $P < 0.05$). However, a drug $\times$ time on task interaction is evident since the performance decrement over time appears greater in the active drug conditions than in the placebo condition. This effect is confirmed by a significant drug $\times$ time on task interaction ($F(24.216) = 3.86$; $P < 0.001$), and by a significant interaction

Fig. 2. Residual effects: Average median brake reaction times.

Table 1.

Acute effects: reduction in self-reported arousal as a function of time on task

Factor	Placebo	Brotizolam	Nitrazepam
Wakefulness	1.6	3.8	4.0
Energy	4.5	5.1	6.2
Stress	0.5	1.0	1.1

between treatment and linear trend of time on task ($F(2.18) = 10.84$; $P < 0.001$) (Kirk 1968). Pairwise comparisons regarding linear trends show that placebo is significantly different from both active drug conditions (nitrazepam – placebo: $F(1.18) = 13.80$; $P < 0.01$), (brotizolam – placebo: $F(1.18) = 18.40$; $P < 0.001$), whereas the difference between nitrazepam and brotizolam is not significant ($F(1.18) < 1$).

No reaction time stimuli were missed.

Six (out of ten) subjects drove off the road. The longest time outside road occurred in the nitrazepam condition (total of 155.38 sec.) compared to 27.22 sec. in the brotizolam condition and 4.02 sec. in the placebo condition. The difference between treatments is however far from significant (Friedman two-way analysis of variance by ranks: $X^2_r(2) = 2.15$; $P > 0.05$) (Kirk 1968).

As to self-reported arousal, the difference between the subjects' estimations before and after each test drive is presented in table 1 for the three factors considered relevant. No significant differences between treatments appeared for any of the factors involved (Friedman two-way analysis by ranks): wakefulness ($X^2_r(2) = 4.05$; $P > 0.05$), energy ($X^2_r(2) = 1.55$; $P > 0.05$), or stress ($X^2_r(2) = 1.15$; $P > 0.05$). The tendency, however, pointed in the same direction as the other effect measures, that is that the subjects generally were most affected in the nitrazepam condition and least in the placebo condition.

Residual effects.

Fig. 2 shows the results regarding brake reaction times from the study of residual effects. Only small differences between treatments are noticeable, and none of these differences are significant (drug: $F(2.30) = 2.07$; $P > 0.05$), (drug $\times$ time on task: $F(24.360) = 1.05$; $P > 0.05$). Nitrazepam, however, tended to score the worst and placebo the best.

No reaction time stimuli were missed.

Only three (out of 16) subjects drove off the road. Total time outside road was longest in the placebo condition (19.38 sec.) and shortest in the brotizolam condition (1.18 sec.) with nitrazepam scoring in between (7.84 sec.). It was

Table 2.

Residual effects: self-reported arousal before the test drive

Factor	Placebo	Brotizolam	Nitrazepam
Wakefulness	7.6	7.4	6.8
Energy	15.7	14.4	13.5
Stress	3.8	3.8	3.3

not considered meaningful to test these differences with regard to statistical significance.

Self-rated arousal before the test drive is presented in table 2. The differences between conditions are very small and non-significant (wakefulness: $X^2_r(2) = 1.64$; $P > 0.05$, energy: $X^2_r(2) = 3.97$; $P > 0.05$, stress: 2.38; $P > 0.05$) although pointing in the direction of lowest arousal in the nitrazepam condition and highest in the placebo condition.

Discussion

In the acute effects part of the study, the placebo condition showed the least brake reaction time prolongation as a function of time on task, with minimal difference between the two pharmacologically active drugs. Nitrazepam however tended to have the greater effect of the two. Regarding the other two effect measures, time outside road and self-rated alertness, no significant differences between treatments were found, although there was a tendency for both active drugs to have an effect, again most pronounced in the nitrazepam condition.

The acute effects on the reaction time task were expected since the onset of action of both active drugs is sufficiently rapid to have had an effect during the course of the test drive. In traditional laboratory tests, impaired performance from these two drugs, although for higher doses than those used in the present study, has been reported within the duration of the present simulator test. Nicholson (1983) thus showed impaired performance from brotizolam 0.5 hr after administration with maximal effect after 2 hrs. Grünberger *et al.* (1978) conclude: "...the psychoactivity" of brotizolam "is marked in the second hour". For nitrazepam, performance effects have been demonstrated in laboratory tests when measured one hour from administration (Griffiths *et al.* 1986).

Regarding residual effects from repeated administration for three consecutive nights, no effects from the active drugs could be demonstrated. Nitrazepam, however, scored worse than the other two conditions on the reaction time measure and on self-rated alertness, with placebo scoring best and brotizolam in between. Time outside road could not be analysed since only three subjects left the road.

The non-significant result regarding residual effects from nitrazepam (5 mg) should be compared with two studies employing the same driving simulator and similar driving tasks (Laurell & Törnros 1986 & 1989), where the same results were obtained in that no residual effects from nitrazepam (5 mg) were demonstrated after three and five consecutive nights of medication, respectively.

The 1986 study, however, shows that under some conditions, residual effects from nitrazepam (5 mg) can be demonstrated. There, a small but significant effect was found after a single dose taken at bed-time on a subsidiary reaction time task that included both auditory and visual stimulus modes including peripheral stimuli with comparatively low probability of occurrence. The 1989 study, on

the other hand, employing peripheral visual stimuli only, showed no residual effects after a single dose.

Others studying residual effects on driving performance from nitrazepam (5 mg) have similarly obtained different results. Thus Volkerts & O'Hanlon (1986) in actual car-driving failed to show an effect from treatment for two consecutive nights, whereas Betts *et al.* (1986), also in a car-driving task, but of a different kind, demonstrated performance degradation after a single dose, an effect that still persisted after eight consecutive nocturnal doses. For traditional laboratory tests, a similar picture emerges, with effects in some studies and no effects in others (Bond & Lader 1981; Hindmarch 1986).

The lack of residual effects from the short-acting brotizolam corresponds well with what has been found in laboratory tasks, where no detrimental effects have been demonstrated for similar doses (Krueger & Müller-Limmroth 1983; Nicholson *et al.* 1980).

Signs of behavioural adaptation to the residual effects from repeated nightly administration of nitrazepam, such as those found by Laurell & Törnros (1986), have also been noticed by others (Griffiths *et al.* 1986). An increased frequency of side-effects with repeated doses of nitrazepam have, however, also been reported (Godtliebsen *et al.* 1986). The issue regarding tolerance development to the degrading effects during continued use of this drug thus remains uncertain.

It seems clear, however, that whatever residual effects there might be in the morning following nocturnal intake of nitrazepam (5 mg) on simulated driving performance, these effects seem to be of small magnitude. As for the other hypnotic drugs studied in the three VTI experiments (triazolam 0.25 mg, oxazepam 25 mg, brotizolam 0.25 mg), all three with considerably shorter elimination half-lives than nitrazepam, the expected results emerged with only small or no tendencies for residual performance impairment.

Acknowledgements

This study received financial support from Boehringer Ingelheim International GmbH.

References

- Alvén, G. & D. Lee: Viewpoints on the clinical pharmacokinetics of hypnotic drugs. In: *Treatment of sleep disorders*. National Board of Health and Welfare Drug Information Committee, Sweden. 1988, 4.
- Betts, T., D. Mortiboy, J. Nimmo & R. Knight: A review of research: The effects of psychotropic drugs on actual driving performance. In: *Drugs and driving*. Eds.: J. F. O'Hanlon & J. J. de Gier. Taylor & Francis, London, 1986, 83–100.
- Bohlin, G. & A. Kjellberg: Self-reported arousal during sleep deprivation and its relation to performance and physiological variables. *Scand. J. Psychol.* 1973, **14**, 78–86.
- Bond, A. & M. Lader: Aftereffects of sleeping drugs. In: *Psychopharmacology of sleep*. Ed.: D. Wheatley. Raven Press, New York, 1981, 177–198.
- Cappell, H. D., E. M. Sellers & U. Busto: Benzodiazepines as drugs of abuse and dependence. In: *Research advances in alcohol and*

- drug problems*, Vol 9. Eds.: H. D. Cappell, F. D. Glaser, Y. Israel, H. Kalant, W. Schmidt, E. M. Sellers & R. C. Smart. Plenum Press, New York, 1986, 53–126.
- Godtliebsen, O. B., D. Jerkö, J. O. Gordeladze, J. E. Bredesen & I. Matheson: Residual effect of single and repeated doses of midazolam and nitrazepam in relation to their plasma concentrations. *Eur. J. Clin. Pharmacol.* 1986, **29**, 595–600.
- Griffiths, A. N., G. Tedeschi & A. Richens: The effects of repeated doses of temazepam and nitrazepam on several measures of human performance. *Acta psych. scand.* 1986, **332**, Suppl. 119–126.
- Grünberger, J., B. Saletu, L. Linzmayer, A. Kalk & P. Berner: Pharmacodynamic investigations with WE 941, a new triazolodiazepine, by means of psychometric analyses. *Current therapeutic research* 1978, **24**, 4, 427–440.
- Hindmarch, I.: The effects of psychoactive drugs on car handling and related psychomotor ability: A review. In: *Drugs and driving*. Eds.: J. F. O'Hanlon & J. J. de Gier. Taylor & Francis, London, 1986, 71–82.
- Kirk, R. E.: *Experimental design: Procedures for the behavioral sciences*. Brooks/Cole, Belmont, 1968.
- Krueger, H. & W. Müller-Limmroth: Residual effects of flurazepam and brotizolam on psychomotor performance. *Brit. J. Clin. Pharmacol.* 1983, **16**, 347S–351S.
- Langley, M. S. & S. P. Clissold: Brotizolam: A review of pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. *Drugs* 1988, **35**, 104–122.
- Laurell, H. & J. Törnros: The carry-over effects of triazolam compared with nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. *Acta pharmacol. et toxicol.* 1986, **58**, 182–186.
- Laurell, H. & J. Törnros: Carry-over effects of oxazepam compared to nitrazepam and placebo in acute emergency driving situations and in monotonous simulated driving. *VTI notat TF* 1989, 57–06.
- Nicholson, A. N.: The use of short- and long-acting hypnotics in clinical medicine. *Brit. J. Clin. Pharmacol.* 1981, **11**, 61S–69S.
- Nicholson, A. N.: Persistence of the effects of benzodiazepines. Pharmacodynamic studies in man. *L'Encéphale* 1983, **IX**, 81 B–86 B.
- Nicholson, A. N., B. M. Stone & P. A. Pascoe: Studies on sleep and performance with a triazolo-1, 4-thienodiazepine (brotizolam). *Brit. J. Clin. Pharmacol.* 1980, **10**, 75–81.
- Roehrs, T., F. Zorick, G. L. Koshorek, R. Wittig & T. Roth: Effects of acute administration of brotizolam in subjects with disturbed sleep. *Brit. J. Clin. Pharmacol.* 1983, **16**, 371S–376S.
- Volkerts, E. R. & J. F. O'Hanlon: Hypnotics' residual effects on driving performance. In: *Drugs and driving*. Eds.: J. F. O'Hanlon & J. J. de Gier. Taylor & Francis, London, 1986, 123–136.