EFFECTS OF CHRONICALLY ADMINISTERED RITANSERIN AND LORAZEPAM ON-THE-ROAD DRIVING PERFORMANCE

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Summary. A double-blind, placebo-controlled study was conducted measuring the chronic effects of ritanserin 5 mg b.i.d. and lorazepam 1.5 mg b.i.d. upon on-the-road driving performance, daytime sleepiness and overnight sleep, in 18 healthy male volunteers. Lorazepam seriously impaired driving performance, induced daytime sleepiness and had no effect on the length of deep sleep. On the other hand, ritanserin did not impair driving performance, did not induce daytime sleepiness, and increased the length of deep sleep.

Keywords. Ritanserin, lorazepam, driving performance, daytime sleepiness, Deep Sleep.

Introduction

For more than three decennia, the therapeutic treatment of endogenous anxiety was accomplished through the use of benzodiazepines. Their clinical efficacy in reducing anxiety is widely accepted. However, besides their anxiolytic effects, benzodiazepines are commonly known to cause sedation, which is apparently linked to their fundamental mechanism of action, i.e. stimulation of GABA-receptors throughout the brain. These sedative side-effects can impair skilled performance in practical tasks such as automobile driving.

The involvement of central serotonergic mechanisms in anxiety has been suggested by Gardner (1988). With the development of new drugs, acting specifically on the serotonergic system, it has been possible to investigate the role of 5HT in anxiety. Ritanserin is a long-acting, specific and pure 5HT2 antagonist, which is ascribed thymosthenic properties (Reyntjens et al., 1986) and radically differs from the benzodiazepines in both chemical structure and pharmacology.

Colpaert et al. (1985) and Amrich and Benett (1986) reported anxiolytic-like activity of ritanserin in animal models.

Furthermore, Ceulemans et al. (1985) reported that two weeks of treatment with ritanserin 5 mg b.i.d. reduced anxiety in patients with generalized anxiety disorder. The drug appears to lack any strong sedative activity compared to conventional benzodiazepines, when administered orally in a 5 mg dose b.i.d.

The present study was carried out in healthy volunteers in order to objectively determine possible signs of sedation and driving performance impairments after 7 consecutive days of treatment with ritanserin 5 mg b.i.d., in comparison to lorazepam 1.5 mg b.i.d., a widely used benzodiazepine.
Methods

Subjects

Eighteen healthy males (mean age sd, 28.33 ± 0.79 yrs; mean weight sd, 75.95 ± 2.25 kg) were selected according to the following criteria: no prior incidence of drug, alcohol and benzodiazepine abuse, no incidence of any drug intake within two months prior to the onset of the trial, no overt cardiovascular, respiratory, hepatic or renal disorders, or any history of severe disorders of these types, no history of major psychiatric illness, no myasthenia gravis, acute glaucoma, epilepsy or diabetes. They were screened for good health by means of a pre-study medical and physical examination, including clinical chemistry.

All subjects were in possession of a valid driver's license and had driven at least 10,000 km over each of the preceding five years. Informed consent was obtained from the subjects and they were treated in accordance with the declaration of Helsinki as modified in Venice in 1983. The study's protocol was reviewed and approved by the Institute's Medical Ethics Review Committee.

Design

The three treatments (i.e. a different drug or the placebo) were administered according to a double-blind, 3-way cross-over design, with a seven-day placebo-washout period. Treatments were scheduled so that each subject received them at weekly intervals in a balanced randomized order.

Drugs and administration.

The treatments consisted of a 1-week period of administration of each of the following:

- ritanserin 5 mg b.i.d., during 7 days
- lorazepam 1.5 mg b.i.d., during 7 days
- placebo b.i.d., during 7 days

All treatments were identical in appearance. The consecutive treatment weeks were scheduled according to the scheme below:

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SCHEME

E.R. Volkerts
Before the first treatment each subject received placebo, single-blind, for seven days (placebo-baseline). The respective treatments shall be identified hereafter as RT for ritanserin, LR for lorazepam, PT for placebo and PB for placebo-baseline.

Procedure

At the start of each week, every subject received a package with the appropriate 'medication'. Drugs and placebo treatment were self-administered, orally, at exactly 10:00 hrs. am and at 16 hrs. pm (confirmed by telephone call) each day. Alcohol, drugs and medication, other than the treatments were prohibited during the entire participation in the study.

The subjects were individually familiarized with test-procedures in a preliminary "dress rehearsal". On the evening of the sixth day of the first, second, fourth and sixth week (respectively, PB and each of the three treatments), each subject was transported to the Institute. All preparations were made for continuous EEG registrations for the next 24 hours, using the Oxford Medical System (Medilog MR-90). The system consists of a portable, miniature cassette tape recorder that stores signals obtained from on-head differential preamplifiers (AD-95). The recorder bandwidth ranged from 0-40 Hz. Silver/silverchloride EEG electrodes were positioned on the scalp according to the international 10-20 system (Jasper, 1958). Recordings were taken from referential leads: left and right central and occipital, referred to the contralateral mastoid (C3-A2; C4-A1; O1-A2; O2-A1) and a F0-Cz lead. The subjects received instructions concerning the handling of the recorder. They were requested to refrain from using chewing-gum, extreme physical effort and stimulating beverages; thereafter he was driven home.

On the evening of the next (seventh) day the subjects were transported to the institute again. The electrode impedances were checked and a 20-minutes 'Multiple Sleep Latency Test' (MSLT), a standard measure of sleepiness, was performed. Then they were driven to the beginning of the highway testcircuit to undertake a 75-minutes standard over-the-road driving test. Thereafter the subjects were driven back to the institute where a second MSLT was performed. Finally a blood sample was taken, the recording apparatus were removed and they were returned home.

Driving test

The subjects performed a driving test three hours after the final drug or placebo ingestion. The test consisted of operating a specially instrumented 1987 Volvo station wagon over a 100 km circuit on a primary highway, running north-south between terminal points, 50 km apart. The subject was instructed to maintain a constant speed (90 km/hr) and a steady lateral position within the right traffic lane, except while passing slower vehicles. Speed was measured continuously from a pulse generator. Lateral position was measured continuously by an electro-optical transducer, which scanned road luminance laterally, to measure the distance separating the vehicle and left lane-line delineation. The resulting signals were analyzed, after editing for removing artifacts, to yield descriptive statistics: mean, standard deviation (SD), skew and kurtosis of speed and lateral position over the entire test.
Further statistical analyses included MANOVA (SPSS inc., 1986) for testing the main effects of treatments, including mean-pair comparisons of drug versus placebo.

Multiple Sleep Latency Test (MSLT)

Sleepiness was measured as the time the subjects took to enter at least 16 seconds of stage 1 sleep. They had to lie down on a bed and received a standard series of instructions which served to test the equipment and to establish a standard lead-in to the test. Sleep latency was measured as the elapsed time (in minutes) from lights-out to the first 16 seconds epoch scored as sleep. REM-sleep latency was measured as the time (in minutes) from the beginning of the first 64 seconds epoch of REM-sleep.

The recorded EEG data during MSLT and the preceding nights' sleep, were visually analyzed according to the standardized sleep stage classification by Rechtschaffen and Kales (1968) with 64 seconds epochs. The data were analyzed by MANOVA for testing the effects of treatments.

Results

The most revealing performance parameter was the standard deviation (SD) of lateral position. The mean (SE) of SD lateral position values for each treatment are shown in Figure 1.

It is evident that there were similar effects on SDLP in both placebo conditions. Individual SDLP values were analyzed by MANOVA. The overall effect of treatment conditions was significant ($F = 34.99; d.f = 3,15, p < .0001$). The comparison of mean SDLP in PB and PT was not significant ($F < 1$) as was that between RT and PT ($F = 1.46; df = 1,17, p < .24$). The latter can be interpreted that ritanserin 5 mg had no effect on SDLP.

In contrast, the analysis revealed significant ($F = 113; df = 1,17, p < .0001$) elevations in SDLP for LR in comparison to PT.

Figure 1: Mean (SE) of SD lateral position in treatment conditions PB, PT, RT and LR Correlations among changes (drug - placebo) in SD lateral position were calculated and tested for significance. Change scores were significantly related between RT and PB ($r = .77; Op < .001$) showing that the degrees of individual impairment or improvement were relatively consistent between these conditions. The correlation between LR and RT, and that between LR and PB were not significant ($r = -.03$, and $r = .18$, respectively).

Figure 2 shows the mean (SE) of Deep Sleep (stage 3 and 4) EEG during the night before the test day. MANOVA revealed a significant overall treatment effect ($F = 7.27; df = 1,16; p < .004$). Comparisons of mean Deep Sleep EEG in every drug condition, relative to PT, were significant for RT ($F = 18.42; df = 1,16, p < .001$) but not for LR ($F < 1$), indicating that ritanserin 5 mg b.i.d. increased the amount of Deep Sleep, in contrast to lorazepam 1.5 mg b.i.d.

Figure 2: Mean (SE) amount of Deep Sleep in treatment conditions PB, PT, RT and LR (in minutes).
Mean (SE) of sleep latency were calculated in every treatment condition, both before and after the driving test. The results are shown in Figure 3.

Figure 3: Mean (SE) Sleep Latency in treatment conditions PB, PT, RT and LR, before the driving (left) test and after the driving test (right).

Individual values were analyzed by MANOVA. The analysis revealed a significant overall effect of both times of testing. This effect was entirely due to lorazepam since the only significant difference was that between LR and PT, both before (F = 5.42; df = 1,13, p < .04) and after (F = 8.73; df 1,14, p < .01) the driving test.

Discussion

In earlier studies we demonstrated that certain benzodiazepine anxiolytics have strong impairing effects on driving performance after one day (t.i.d.) treatment. The results of this chronic study indicate that ritanserin 5 mg. b.i.d. does not cause deterioration in road tracking performance, during continuous uninterrupted highway driving. In this respect, the effect of ritanserin was about the same as that of placebo. However, driving performance was seriously impaired after treatment with lorazepam.

Mean changes in SD lateral position, attributable to the psychoactive drugs used in this study, were comparable to those shown by 24 social drinkers who were tested while their blood alcohol concentrations (BAC) were elevated to various levels in a previous calibration study (O’Hanlon et al., 1986). Mean SD lateral position increased as an exponential function of mean BAC. The mean relationship was nearly perfect (r = .99). On the strength of this relationship it is possible to reasonably define any drug effect on SD lateral position in terms of the BAC required to achieve the same effect. The results of this comparison are shown in Figure 4.

This study indicates that ritanserin 5 mg b.i.d., administered during 7 consecutive days, failed to produce a degree of impairment equivalent to any BAC-level. In contrast, 7 days treatment with lorazepam 1.5 mg b.i.d. resulted in a substantial impairment of driving performance comparable to that of 1 mg/ml BAC.

Figure 4: Mean changes in SD lateral position (from respective placebo means) in treatment conditions buspirone (BUS), clorazepate (CLOR), diazepam (DIA), oxazepam (OXA), lorazepam (LRZ) and ritanserin (RIT).

Conclusions

1. Ritanserin, when administered in a 5 mg dose b.i.d. during 7 consecutive days, had no effect on driving performance.
2. Lorazepam, when administered in a 1.5 mg dose b.i.d. during 7 consecutive days, had the potential for seriously impairing driving performance.
3. Ritanserin 5 mg b.i.d. does not seriously induce sleepiness as measured by the MSLT; lorazepam 1.5 mg b.i.d. showed the opposite effect.
4. Ritanserin 5 mg b.i.d. increased slow wave sleep (SWS); lorazepam 1.5 mg b.i.d. had no effect on this parameter.

Acknowledgement

We thank Dr. J. Arends for his support in performing this study.

References


FIGURE 1
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Conditions

SD lateral position (cm)

RT: 5 mg (b.i.d.)
LR: 1.5 mg (b.i.d.)

FIGURE 2
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Stage 3 + 4 (min.)

Conditions
FIGURE 3
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FIGURE 4
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