

Lorazepam and the sleep EEG's microstructure: A novel approach to quantitative pharmaco-EEG investigations

Joachim Röschke, Pia Kögel, Michael Grözinger

Department of Psychiatry, University of Mainz, Germany

Corresponding author: J. Röschke, M.D., Ph.D., Dept. of Psychiatry, University of Mainz, Untere Zahlbacher Straße 8, D-55131 Mainz, Germany, roeschke@mail.uni-mainz.de

Abstract

Background: When searching for reliable and specific markers for certain psychiatric diseases, preliminary investigations of the sleep EEG's microstructure point to the view that the delta/beta correlation coefficients during NREM sleep appear increased in depressives, but not in schizophrenics. Therefore, this parameter could be hypothesized to be a marker of depression. On the other hand, subchronically, paroxetine medication in healthy subjects produces the opposite finding: a decrease in the delta/beta correlation coefficients during NREM sleep, which might be interpreted as evidence of the antidepressant action of the drug. Of course, a close connection between this effect and the antidepressant efficacy of this drug has not been demonstrated to date. **Objective:** The aim of the present paper was to illuminate the sleep EEG's microstructure under the influence of the benzodiazepine lorazepam. This drug influences the conventional sleep EEG parameters very similarly to most of the antidepressants. However, it should be assumed that benzodiazepines do not act as antidepressants. Therefore, the question arises as to whether lorazepam alters the delta/beta correlation of the sleep EEG in the same way as paroxetine. **Method:** Separately for REM and NREM sleep we calculated the correlation coefficients between different frequency bands (delta, theta, alpha, beta) from sleep EEG data of healthy subjects (n=8) from P_zC_z through the night in a double-blind placebo-controlled cross-over design (single dose of 2.5 mg lorazepam). **Results:** Despite the alterations of the conventional sleep EEG parameters, no influence of lorazepam on the sleep EEG's microstructure could be observed. **Conclusions:** Assuming the findings of the present paper can be replicated in a larger sample size, NREM alterations of the sleep EEG's delta/beta oscillations may be characteristic for depression and antidepressants (German J Psychiatry 2000;3:13-18)

Key words: sleep EEG, microstructure, lorazepam, pharmaco-EEG

Introduction

It is a well-known fact that some alterations of the conventional sleep EEG parameters according to Rechtschaffen and Kales (1968) typically appear in depressives compared to healthy controls. Depression is characterized by several sleep-related abnormalities around sleep onset, such as prolonged sleep latency, loss of stage 3-4 sleep, reduced rapid eye movement (REM)

latency and a heightened REM density. However, none of these findings are specific (Benca et al., 1992).

Despite the classical sleep EEG alterations in depression, Armitage and co-workers (1992) reported that phase and coherence between fast and slow frequency EEG measures differed significantly between depressed outpatients and healthy controls. In particular, beta and delta rhythms were less coherent in the depressed outpatient sample. A study of Röschke et al. (1997b) confirmed that the correlation of the sleep EEG's delta/beta oscillations is altered in depression. In particular, these alterations were detected during the NREM sleep cycle, where the delta/beta as well as the theta/beta correlations were

significantly more negative compared to healthy controls. These rhythms are much more out of phase during NREM sleep in depressives than in healthy controls. In another study investigating unmedicated schizophrenics we could not detect any alterations of the dynamics of different EEG rhythms (Röschke et al., 1998). This points to the view that alterations of the beta/delta activities might be specific for depression. Moreover, these results are in accordance with findings that subchronic treatment with the antidepressant drug paroxetine, a potent selective serotonin inhibitor, led to the opposite alterations of the delta/beta rhythms in healthy controls (Röschke et al., 1997a). The correlation coefficients of delta and beta rhythms were significantly lower during NREM sleep and verum condition, meaning the coupling of delta and beta oscillations during NREM sleep was much weaker under subchronically administered paroxetine medication. This opposite finding of the delta/beta correlation under paroxetine medication might be an indication of the antidepressant action of the drug. The major aim of the present paper was to illuminate the influence on the sleep EEG's microstructure of a drug which influences the conventional sleep EEG parameters similarly to most of the antidepressants, but which does not act as an antidepressant. Therefore, we administered the benzodiazepine lorazepam and investigated its influence on the sleep EEG's delta/beta correlation coefficients.

In the past thirty years, a great number of double-blind studies on the antidepressant effect of benzodiazepines have been carried out. Although it is well-known that benzodiazepines only have a symptomatic mechanism of action and symptoms usually recur immediately after drug discontinuation, different benzodiazepines have been compared with antidepressants in more than sixty controlled studies in the literature, sometimes with placebo (Schatzberg and Cole, 1978; Roth et al., 1980; Kales et al., 1986; Johnson, 1983; Jonas and Cohon, 1993; Laakman et al., 1995). In mildly to moderately depressed outpatients, a mild antidepressant effectiveness of lorazepam, alprazolam and amitriptyline and their superiority over placebo has been postulated. Compared to placebo, onset of efficacy was earlier on benzodiazepines than on amitriptyline (Laakman et al., 1995). But it is well known that there is a difference of effectiveness depending on the severity of depression, meaning that antidepressants are doubtlessly more effective in the treatment of severely depressed patients. Nevertheless, meta-analyses using intent-to-treat, as well as adequate treatment exposure studies, revealed an overall efficacy of 47-63% and a drug-placebo difference of 0-27% for benzodiazepines alprazolam, diazepam, and chlordiazepoxide (Petty et al., 1995). The aim of the present study was to contribute to the discussion as to whether lorazepam can be evaluated as a drug that influences the sleep EEG's microstructure similar to the variations seen under the potent antidepressant paroxetine. Therefore, we studied the time

course of the delta, theta, alpha and beta activity through the night and calculated the correlation coefficients of these different EEG rhythms separately for REM and NREM sleep.

Methods

Study design

The study was performed according to a double-blind, placebo-controlled cross-over design examining the sleep EEG under lorazepam medication and placebo. Eight healthy male volunteers (mean age: 26.8 years with a range from 23 to 36 years) randomly received placebo or lorazepam 2.5 mg as a single oral dose in the evening in a double-blind design. Fourteen drug-free days followed, then a single dose of placebo or lorazepam was given in a cross-over design and polysomnographies were recorded. All subjects were considered healthy according to a standardized psychiatric interview, personal or family history for psychiatric or neurological diseases, physical examination, EEG and ECG, and baseline neuroendocrine measurements. Subjects suffering from sleep disturbances were excluded. All subjects were non-smokers and were not taking drugs, which was ruled out by ratings. Consumption of alcohol was not allowed during the study period. Written informed consent to participate in the study was obtained from all subjects. The study design was submitted to the local ethics committee for approval.

Polysomnography

The recordings were performed under standardized conditions in the sleep laboratory. All investigations were performed in a sound-proofed and electrically shielded sleep laboratory. Each subject spent two successive nights - fourteen free days in-between - in the laboratory during each recording session. Following an adaptation night, a polysomnography was performed over eight hours, the EEG recordings started at 23.00 h and finished at 7.00 h when the subjects were woken. EEG signals were measured with Ag/AgCl surface electrodes, which were fixed at the positions F₂, C₂, C₃, C₄, P₂ and the mastoid according to the international 10-20 system. Interelectrode impedances were all below 5 kOhms. The sleep EEG was recorded using a Nihon Kohden EEG machine. Additionally, the EEG data from positions C₂/A₂ and P₂/A₂ were digitized by a 12 bit ADC, sampled with a frequency of 100 Hz (45 Hz low pass filter, 48 dB/octave, N=2048 data points) and stored on the disk of a Hewlett-Packard

Table 1. Mean values (\pm SD) of the spectral power densities in different frequency bands for (C_z - P_z) for both verum and placebo condition.

Power(dB)	Placebo				Lorazepam				p (group)
	Stage I	Stage II	SWS	REM	Stage I	Stage II	SWS	REM	
delta	1.48 \pm 0.24	1.76 \pm 0.20	2.25 \pm 0.22	1.20 \pm 0.14	1.70 \pm 0.25	1.65 \pm 0.27	2.01 \pm 0.43	1.44 \pm 0.29	0.659
theta	0.78 \pm 0.12	0.91 \pm 0.13	1.12 \pm 0.17	0.73 \pm 0.09	0.76 \pm 0.19	0.79 \pm 0.23	0.80 \pm 0.44	0.78 \pm 0.19	0.26
alpha	0.66 \pm 0.24	0.77 \pm 0.20	0.81 \pm 0.23	0.43 \pm 0.21	0.70 \pm 0.21	0.83 \pm 0.24	0.66 \pm 0.42	0.52 \pm 0.24	0.599
beta	0.11 \pm 0.15	0.06 \pm 0.12	-0.01 \pm 0.11	0.05 \pm 0.15	0.38 \pm 0.24	0.26 \pm 0.22	-0.04 \pm 0.34	0.33 \pm 0.25	0.029

computer. Altogether 1440 time epochs were recorded during each registration session.

Unipolar EEG derivations (versus mastoid electrode) as well as EOG and EMG of the M. mentalis were measured. The recordings of the sleep EEG were visually scored according to the criteria of Rechtschaffen and Kales (1968) based on 20s epochs. All sleep EEG recordings were scored by the same rater, who was blind for the pharmacological treatment. Subsequent spectral analysis and computation of the EEG power across the night was performed off-line for the bipolar derivation C_z - P_z . For each subject the time history of all 20s time epochs was transformed via Fast Fourier transform (FFT) algorithm to the frequency domain and all spectra unambiguously corresponding to identical sleep stages were averaged in the frequency domain (Röschke et al., 1993). Logarithmic spectral power density values (0 dB corresponding to $1 \mu V^2/Hz$) were calculated in the following frequency bands: delta (1-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-15 Hz), and beta (15-35 Hz).

Additionally we computed the correlation coefficient of the different EEG rhythms separately for REM and NREM sleep. Assuming the correlation of EEG rhythms during REM and NREM sleep cycles differs, then a different amount of REM or NREM sleep may contribute to alteration of the overall correlation of rhythms. Therefore, we calculated the correlation coefficients for the EEG rhythms under investigation separately for REM and NREM sleep. A correlation coefficient of e.g. $k_{(\alpha/\beta)} = +1.00$ means that the oscillations of the alpha and beta activity over the night is absolutely in phase. In this case the beta power increases when the alpha power increases and vice versa. A correlation coefficient of $k_{(\alpha/\beta)} = -1.00$ means that alpha power increases when beta power decreases. In this case alpha and beta power would be out of phase.

Statistical Analysis

For conventional sleep EEG parameters we performed a two-tailed Wilcoxon-test for matched pairs. The significance level was $p < 0.05$ for all sleep parameters. For analysis of the spectral power densities, we performed a two-way ANOVA with sleep stage and medication as repeated measures. In order to examine the correlation of the different EEG rhythms throughout the night, we applied a multivariate analysis of variance (MANOVA) with factors group (lorazepam/placebo) and sleep cycle (REM/NREM). In a two-way ANOVA with medication and correlation as repeated measures we tested, separately for REM and NREM sleep, whether there was any group effect or any significant interaction group by correlation. All data were z-transformed before computing the statistics.

Results

Conventional parameters

The results of the classical sleep EEG analysis under placebo and lorazepam conditions are summarized in Fig. 1. REM sleep was significantly reduced ($p < 0.01$) and the REM latency was prolonged ($p < 0.05$) when a single dose of 2.5 mg lorazepam was given.

Spectral power analysis

Table 1 summarizes the logarithmic mean values of the spectral power densities (0 dB means $1 \mu V^2/Hz$) for all

sleep stages and all frequency bands under study. For both verum and placebo conditions, the spectral power in the lower frequency bands increased with deepening of sleep, whereas the opposite effect could be observed in the higher frequency bands. An ANOVA did not detect any significant group effect except for the beta band. In the 15-30 Hz frequency range a significant ($p=0.029$) group effect and a significant interaction stage by group ($p=0.002$) could be shown. In particular, the spectral beta power increased under lorazepam medication during sleep stage I ($p = 0.01$), stage II ($p = 0.02$) and stage REM ($p = 0.01$).

Correlation coefficients during REM and NREM sleep

Tab. 2 presents the mean values of the correlation coefficients of the different EEG rhythms separated for REM and NREM sleep. Following an overall MANOVA (factors: medication and sleep stage) we could detect no effect either for the factor medication ($p=0.35$), or for the factor sleep stage ($p=0.24$), and no interaction medication by stage ($p=0.29$). However, the interaction correlation by sleep stage was significant ($p<0.001$). During NREM sleep the correlation coefficients of delta/theta were always higher than during REM sleep, regardless of medication ($p<0.01$). The most impressive changes occurred for the delta/beta activities, which change their signs between NREM (negatively correlated) and REM (positively correlated) sleep in both placebo and verum condition ($p<0.01$).

Table 2: Correlation coefficients of the EEG rhythms for REM- and NREM sleep periods through the night. No differences between groups could be detected

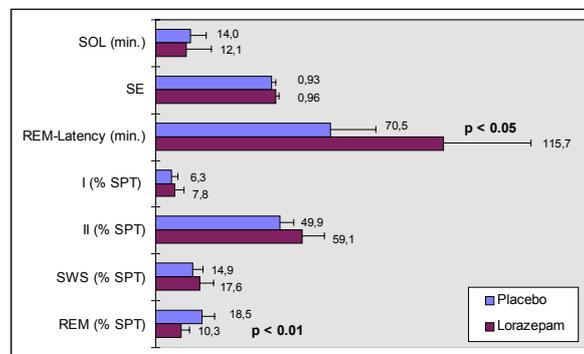
	REM		NREM	
	placebo	verum	placebo	verum
delta/theta	0.48	0.41	0.81	0.63
SD	0.20	0.22	0.14	0.17
delta/alpha	0.43	0.44	0.44	0.29
SD	0.23	0.25	0.28	0.21
delta/beta	0.43	0.48	-0.23	-0.30
SD	0.20	0.24	0.16	0.11
theta/alpha	0.62	0.76	0.56	0.53
SD	0.22	0.19	0.27	0.33
theta/beta	0.18	0.41	-0.10	0.14
SD	0.29	0.42	0.19	0.59
alpha/beta	0.47	0.58	0.23	0.27
SD	0.25	0.34	0.36	0.52

Discussion

Following conventional sleep EEG analysis according to Rechtschaffen and Kales (1968) in the present study a single dose of 2.5 mg lorazepam led to a reduction of REM sleep and a prolonged REM latency in healthy volunteers. No significant changes in EEG parameters related to sleep efficiency index, total sleep time, sleep onset latency, and number of awakenings could be detected. These results are consistent with earlier studies (Roth et al., 1980; Kales et al., 1986; Röschke et al., 1993), where it has been shown that under the influence of lorazepam the percentage of stage II increased, whereas the percentage of REM sleep was reduced to nearly half of its baseline values under drug free conditions.

However, the aim of the present paper was to investigate the sleep EEG's microstructure under the influence of the benzodiazepine lorazepam. This drug influences the conventional sleep EEG parameters very similarly to most of the antidepressants. But it should be taken assumed that benzodiazepines do not act as antidepressants. Beyond the classical sleep EEG alterations in depression, Armitage and coworkers (1992) reported that phase and coherence between fast and slow frequency EEG measures differed significantly between depressed outpatients and healthy controls. In particular, beta and delta rhythms were less coherent in the depressed outpatient sample. A study of Röschke et al. (1997b, 2000) confirmed that the correlation of the sleep EEG's delta/beta oscillations was altered in depression. In particular, these alterations were detected during the NREM sleep cycle, where the delta/beta as well as the theta/beta correlation coefficients were significantly enhanced compared to healthy controls. These rhythms are much more out of phase (higher negatively correlated) during NREM sleep

Figure 1: Conventional sleep EEG parameters under placebo conditions and lorazepam medication



in depressives than in healthy controls. In another study investigating unmedicated schizophrenics, the same group (Röschke et al., 1998) could not detect any alterations of the dynamics of different EEG rhythms and their correlations. This points to the view that the above cited alterations of the beta/delta activities might be specific for depression. Moreover, these results are in accordance with findings that subchronic treatment with the antidepressant drug paroxetine, a potent selective serotonin reuptake inhibitor, led to the opposite alterations of the delta/beta rhythms in healthy controls (Röschke et al., 1997a). Under subchronically administered paroxetine medication, the delta/beta correlation coefficients were smaller during NREM sleep, meaning the coupling of delta and beta oscillations during NREM sleep was much weaker. The authors hypothesized that this opposite effect of the delta/beta correlation under paroxetine might be an indication of the antidepressant action of the drug. Therefore, the question arises as to whether lorazepam, which alters the conventional sleep EEG parameters very similarly to most of the antidepressants, also alters the delta/beta correlation coefficients of the sleep EEG in the same way as paroxetine.

The result of the present study was that lorazepam has no influence on the sleep EEG's microstructure. We could not see any medication effect under lorazepam or any significant interaction of medication by sleep stage, so that we conclude that there is no evidence to support the view that lorazepam induces the same alterations - concerning the sleep EEG's microstructure - as paroxetine.

Assuming that the findings of the present study could be replicated in a larger sample size, NREM alterations of the sleep EEG's delta/beta oscillations may play a major role in depressive disorder and in the pharmacological treatment of depression. An increase of the delta/beta correlation coefficients might be characteristic for depression. A decrease of the coupling of delta and beta oscillations during NREM sleep cycles could be observed under subchronically administered paroxetine medication, but not under the influence of lorazepam. Paroxetine acts as an antidepressant, but lorazepam does not. From this point of view, alterations of the delta/beta correlation, when resulting in a weaker coupling of the EEG oscillations, could be hypothesized as evidence of an antidepressant action of a drug, regardless of the alterations on the conventional sleep EEG parameters.

References

- Armitage R, Roffwarg H, Rush A, Calhoun J, Purdy D, Giles D. Digital period analysis of sleep EEG in depression. *Biol Psychiatry* 1992;31:52-68
- Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry* 1992;49:651-668
- Johnson DAW. Benzodiazepines in depression. In: Trimble W (ed) *Benzodiazepines divided*. New York: Wiley, 1983;247-257
- Jonas JM, Cohon MS. A comparison of the safety and efficacy of alprazolam versus other agents in the treatment of anxiety, panic and depression: a review of the literature. *J Clin Psychiatry* 1993;54:25-45
- Kales A, Bixler EO, Soldatos CR, Jacoby JA, Kales JD. Lorazepam: Effects on sleep and withdrawal phenomena. *Pharmacology* 1986;32:121-130
- Laakman G, Faltermaier-Temizel M, Bossert-Zaudig S, Baghai T, Lorkowski G. Treatment of depressive outpatients with lorazepam, alprazolam, amitriptyline and placebo. *Psychopharmacology* 1995;120:109-115
- Petty F, Trivedi MH, Fulton M, Rush AJ. Benzodiazepines as antidepressants: does GABA play a role in depression? *Biol Psychiatry* 1995;38:578-591
- Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subj.* Public Health Services, NIH Publication No. 204, Washington, DC: US Government Printing Office, 1968
- Röschke J, Wagner P, Aldenhoff JB. The influence of lorazepam medication upon the transfer properties of the brain during sleep in man. *Eur Neuro-psychopharmacology* 1993;3:45-53
- Röschke J, Kögel P, Schloesser R, Wagner P, Mann K, Rossbach W, Benkert O. Analysis of the sleep EEG's microstructure in subchronic paroxetine treatment of healthy subjects. *Psychopharmacology* 1997a;132:44-49
- Röschke J, Sebus A, Lehment A, Wagner P, Mann K. Analysis of sleep EEG's microstructure in depressives. *Soc. Neuroscience Abstr* 1997b;23:853.

- Röschke J, Sebus A, Lehment A, Wagner P, Mann K. Analysis of sleep EEG's microstructure in schizophrenia. Soc. Neuroscience Abstr 1998;24:526
- Röschke J, Mann K. The sleep's microstructure in depression: Alterations of the phase relations between EEG rhythms during REM and NonREM sleep. submitted, 2000
- Roth T, Hartse KM, Saab PG, Piccione PM, Kramer M. The effects of flurazepam, lorazepam, and triazolam on sleep and memory. Psychopharmacology 1980;70:231-237
- Schatzberg AF, Cole JO. Benzodiazepines in depressive disorders. Arch Gen Psychiatry 1978;35:1359-1365