EEG POWER SPECTRA OF NON-REM SLEEP INDUCED BY THE NORADRENALINE REUPTAKE INHIBITOR ORG 4428 IN HEALTHY SUBJECTS

A.L. van Bemmel, M.T.G. Vermeeren, G. Ruigt (*) and C. Sennef (**)
Academic Mood Disorders Clinic and Sleep Laboratory, Dept. of Psychiatry and Neuropsychology, Univ. of Limburg. P.O. Box 616, 6200 MD Maastricht, The Netherlands. (*) Dept. of Neuropharmacology, NV Organon, (**)
Medical Research & Development unit, P.O. Box 20, 5340 BH Oss, The Netherlands.

Studies with antidepressant drugs (ADs) on EEG sleep in humans suggest that ADs do not all produce similar EEG spectral response patterns (Van Bemmel, 1996). This might be due to differences in pharmacological actions among the various ADs. To support this notion, further research to identify and to interpret EEG response patterns induced by the various ADs is needed.

In the present study this issue is further explored in healthy subjects with two different daily dosages of ORG 4428. This is a novel tetracyclic compound with antidepressant like properties on animal sleep (Ruigt and Van Proosdij, 1993). It is a potent noradrenaline reuptake inhibitor without significant interaction with any other known neurotransmitter system (Ruigt et al., in preparation).

Table 1 shows the main aspects of the dosage schedule.

Table 1

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2 F/ n=2 M</td>
<td>25 mg</td>
<td>100 mg</td>
<td>placebo</td>
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<tr>
<td>n=2 F/ n=2 M</td>
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<td>25 mg</td>
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F = female; M = male
The subjects were randomly assigned to 3 test-periods in a double-blind 3-way cross-over study design. Placebo or ORG 4428 (25 or 100 mg) was administered twice in each test-period: once at 10:30 p.m. and once the next morning at 8:00 a.m.. During each test-period sleep EEG was recorded in the sleep laboratory between 11:00 p.m. and 7:00 a.m. after the first administration. The first sleep recording was preceded by an adaptation night. Prior to the sleep recordings the subjects were encouraged to sleep at regular bedtimes for at least two nights and to refrain from alcohol consumption and beverages containing caffeine. There was a 6-16 days interval between the test-periods.

Twelve healthy subjects participated in the study (6 females and 6 males, mean age = 21.8 years, SD = 1.4, range 20-24). The data from one subject were omitted (female, 100 mg/placebo/25 mg) in the analysis because of technical problems during the sleep recordings.

In each subject one EEG signal [obtained from the same lead (C3-A2 or C4-A1)] was used in the analysis. It was low-pass filtered for spectral analysis at 25 Hz (24 dB/oct) and subsequently digitized at 64 samples/s. Digitized data were processed by a fast Fourier transform routine. Power spectra were calculated over 4-s intervals from 0.75-15 Hz in 0.25 Hz bins, by applying a rectangular window. The 0.25 bins were condensed into 1 Hz-wide frequency bins. Bins will be referred to by mentioning their upper limit. So power density in the 1 Hz bin is the sum of the power density of 0.75 and 1 Hz; power density in the 2 Hz bin is the sum of the power density of 1.25, 1.50, 1.75 and 2 Hz etc. To obtain a resolution of 30-s, power values of 7.5 adjacent 4-s epochs were summed for each frequency bin thus calculated. Visual scores of the same 30-s epochs were synchronized with the series of power spectral epochs. The influence of ORG 4428 on non-REM sleep power was analyzed on the basis of the longest common amount of non-REM sleep stages 2, 3 & 4, accumulated from sleep onset onwards (which turned out to be 289.5 minutes). This approach offers the possibility to compare the EEG power production in the same amount of non-REM sleep in all nights (Beersma and Achermann, 1995; Van Bemmel et al., 1995).

Since the absolute values of the power densities of the higher frequencies are several orders of magnitude lower than those of the lower frequencies and since the interindividual variation is considerable, absolute values are not very suitable for a visualization of changes in power spectra (Dijk et al., 1989). Therefore, power values are expressed relative to power values in baseline, which latter values were taken as 100%. Figure 1 shows the means of the power spectra of the entire group.
Figure 1.
Power spectra of 289.5 min non-REM sleep, following two different dosages of ORG 4428, relative to power spectra of baseline (=100%). Means of the entire group (n=11). Power densities are plotted at the upper boundaries of the frequency bins. The absolute power values were analyzed using a general linear model of SPSS Advanced Statistics 7.0. No significant dose- or sequence-effects were found.

The statistical analysis revealed no significant changes.

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