Zopiclone versus Diazepam effects on EEG power maps in healthy volunteers

Hiroshi Yamadera¹,², Masaaki Kato², Yasuji Tsukahara²,³, Daniel Brandeis⁴ and Teruo Okuma²

¹Department of Neuropsychiatry, Nippon Medical School, Tokyo 113, Japan; ²National Center of Neurology and Psychiatry, Kodaira 187, Japan; ³Department of Psychiatry, Saitama Medical College, Moro, Saitama 350-04, Japan; ⁴Department of Child and Adolescent Psychiatry, University of Zurich, CH-8028 Zurich, Switzerland

Abstract. EEG effects of zopiclone (7.5 mg), a cyclopyrrolone derivative with hypnotic action, were compared with effects of diazepam (10 mg). Multichannel EEG recordings, double-blind crossover trials with placebo, and oral single doses were used in healthy volunteers. Vigilance-controlled EEG before and after zopiclone (and placebo), and before and after diazepam (and placebo) were analyzed into FFT power spectra. Effects were assessed as placebo-referred pre-post-medication power differences in four frequency bands. Overall statistics showed significant (P<0.007) global differences between medication effects in the delta frequency band (0.5-3.5 Hz). After zopiclone, fronto-central delta increased bilaterally, whereas after diazepam delta decreased over centro-parietal to right temporo-occipital regions. These spatially different brain electric effects show that different neuronal populations must have become active in response to zopiclone and diazepam.

Key words: zopiclone, hypnotic medication, diazepam, single dose, healthy volunteer, quantitative EEG, EEG power mapping
Zopiclone is a hypnotic medication that belongs to the cyclopyrrole derivatives (Blanchard et al. 1982). Chemically, the effect of cyclopyrrole derivatives on GABA<sub>A</sub> receptor functions is different from that of benzodiazepines (Concas et al. 1994). There are several different reports about zopiclone-induced changes of slow wave sleep (SWS) in polysomnography in healthy volunteers, i.e., increase, no change, and decrease (Nicholson and Stone 1982, 1987, Kanno et al. 1983, Kim et al. 1986, Billiard et al. 1987, Hayashida et al. 1993, Aeschbach et al. 1994) were reported. We found that zopiclone increased SWS in the early phase of total night recordings (Kato et al. 1991). Diazepam is one of the traditional benzodiazepines and is known to decrease SWS (e.g., Coppola and Herrmann 1987, Saletu et al. 1987). It was argued that zopiclone might induce natural sleep in comparison with benzodiazepines (Kanno et al. 1983). In sum, the sleep studies showed some disagreement. The underlying question is whether the mode of action of the two medications is basically different.

Earlier we reported results of quantitative pharmacoelectroencephalograph (EEG) studies on zopiclone (Yamadera et al. 1995) and diazepam (Yamadera et al. 1993). In the zopiclone study, power in the delta (0.5-3.5 Hz) EEG frequency band was found to increase compared with placebo at 1 h after medication administration over bilateral fronto-central regions. This difference diminished at 3 and 5 hours. On the other hand, diazepam decreased delta power compared with placebo at 2 h after administration over the central and right parieto-temporo-occipital regions. In the theta (4-7.5 Hz) and alpha (8-12.5 Hz) frequency bands, both medications caused decreases of power, and both caused increases of power in the beta band (13-40 Hz).

The present comparison study was done to clarify the differences in EEG effects after zopiclone and diazepam. We compared the earlier diazepam results (Yamadera et al. 1993) with zopiclone results obtained in an extension of our previous study that was published in Japanese (Yamadera et al. 1995); this extension involved additional subjects but expectedly produced very similar results. It was judged most reasonable to compare the one-hour-post zopiclone data with two-hours-post diazepam data as zopiclone was reported to reach maximal effects earlier than bezodiazepines, at about 60 vs. 90 min (Aanta et al. 1990). On the other hand, oral diazepam showed maximum plasma concentration at 2 h after administration (Friedman et al. 1992).

An important issue in this comparison between the two medications is whether the electrophysiological ac-

...
TABLE I
Structure and terminology of the data analysis applied to the data from each channel and subject. In the two independent studies, data were obtained from each subject in all four conditions.

<table>
<thead>
<tr>
<th>Data:</th>
<th>Zopiclone Study:</th>
<th>Diazepam Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions: before</td>
<td>after</td>
<td>before</td>
</tr>
<tr>
<td>Placebo(Z)</td>
<td>Placebo(Z)</td>
<td>Zopiclone</td>
</tr>
<tr>
<td>after</td>
<td>Placebo(Z)</td>
<td>Placebo(D)</td>
</tr>
<tr>
<td>minus</td>
<td>before</td>
<td>before</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Placebo(D)</td>
<td>Diazepam</td>
</tr>
</tbody>
</table>

Reactions:
- Placebo(Z) Reaction: after minus before
- Zopiclone Reaction: after minus before
- Placebo(D) Reaction: after minus before
- Diazepam Reaction: after minus before

Effects:
- Zopiclone Effect: Placebo(Z) Reaction minus Placebo(Z) Reaction
- Diazepam Effect: Placebo(D) Reaction minus Placebo(D) Reaction

Processor (NEC SAN-EI 7T18). The absolute power values were averaged over spectral frequency points in four frequency bands: delta (0.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz) and beta (13-30 Hz).

Channel-wise, the values in the four frequency bands were treated as specified in Table I: (1) the reactions to the placebo and medication administrations were computed as power differences between "after" minus "before" administration; (2) the medication effects were computed by referring the reactions to the medications to the associated placebo reactions, computed as differences between verum reaction minus placebo reaction; (3) the differences between the two medication effects were computed and tested for significance.

T-statistics were used, paired within and unpaired between medications. Double-sided P-values are reported.

In order to assess the overall significance of the difference between medication effects, global medication effects were computed as means of the effects (absolute power differences verum minus placebo) across all channels, separately for the four frequency bands. In the delta frequency band, compared with placebo, zopiclone caused a global power increase, but diazepam caused a decrease across subjects. This global difference between the medication effects for zopiclone and diazepam was significant at $P<0.007$ ($df=20$). The mean zopiclone and diazepam effects (square root of power values) were $+0.5$ and $-0.9 \mu V$, respectively, while the pre-administration mean values in the four conditions varied between 6.4 and 7.1 $\mu V$.

The post-hoc, channel-wise tests of the differences of the two medication effects in the delta band showed that the effects differed significantly over anterior, central and parietal areas. This is illustrated in Fig. 1B which shows that the tests yielded significant differences of the medication effects in 9 of the 16 channels. As indicated by the global results, the different effects of the two medications were not differences in magnitude but in direction of the effects, increase versus decrease; moreover, the effects occurred in different brain areas: after zopiclone, there were significant increases over anterior and central areas (Fig. 1C), while diazepam caused decreases over central-parietal and right temporo-occipital areas (Fig. 1D).

In the theta as well as in the alpha frequency band, both medications caused global decreases as compared with placebo, while in the beta band, both medications caused global increases of power. In these three frequency bands, the global differences of the medication effects did not reach significance, although there were significant differences in the described direction in various individual channels.
The significant effects of diazepam and zopiclone on delta EEG band activity in this study were opposite to each other, i.e., diazepam decreased delta activity over posterior areas while zopiclone increased delta over anterior areas. Thus, there was not a different magnitude of the effect, but different directions and, still more important, different spatial distributions. The anterior-posterior differences of the two medication effects cannot have been influenced by the references since combining or splitting the ear references could, in the worst case, only affect lateralizations.

In sum, the present study found different spatial distributions of the brain electric fields after zopiclone and diazepam administration. Different spatial distributions (maps) of EEG potential or power values must have been caused by the activity of at least partially different neuronal populations in the brain (see Lehmann and Skrandies 1984, Lehmann 1987). Thus, the brain electric results indicate that different brain systems became active after the two medications, in agreement with results of receptor studies (Concas et al. 1994). The specific mechanisms responsible for these different effects obviously are of continued interest for future investigations.

The authors thank Drs. Thomas Koenig and Dietrich Lehmann for critical comments on an earlier version of this paper.


Received 15 December 1996, accepted 8 April 1997