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Zopiclone *versus* Diazepam effects on EEG power maps in healthy volunteers

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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.

Short communication

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Zopiclone is a hypnotic medication that belongs to the cyclopyrrolone derivatives (Blanchard et al. 1982). Chemically, the effect of cyclopyrrolones on $GABA_A$ 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 pharmaco-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 actions differ simply in magnitude, or whether they differ in more basic respects. The latter was the case: a difference of the spatial distribution of the effects showed that at least partially different neuronal populations must have been activated by the two medications.

Male subjects were selected from a subject pool for both studies. They met the requirements of right handedness, no history of head trauma, no psychiatric/neurologic disease, no drug abuse, no pathologic EEG signs, and clear presence of EEG alpha of normal frequency over occipital areas. According to the Declarations of Helsinki 1964 and Tokyo 1975, the subjects were informed verbally of their rights and of the general experimental procedure before a witness. The subjects gave written consent, and were remunerated. The two independent subject groups consisted of 12 subjects (21-23 years) in the zopiclone study (2 subjects in addition to the 10 of the earlier report, Yamadera et al. 1995), and of 10 subjects (21-25 years) in the diazepam study.

Each subject received placebo and verum (zopiclone 7.5 mg, diazepam 10 mg) as single oral doses in random sequence at intervals of one week in a cross over, double-blind procedure. Before the recording, the subjects were instructed to keep a microswitch pressed during the entire recording time (vigilance control). When this switch was released a buzzer sounded until the switch was pressed again. Thereby, the subjects were kept at a certain vigilance level.

Sixteen-channel vigilance-controlled EEG was recorded before, 1 h (used for the present comparison), 3 h and 5 h after zopiclone, and before and 2 h after diazepam. Total analysis time for each condition was three minutes in the zopiclone study, one minute in the diazepam study. A 21-channel NIHON KODEN 4317 electroencephalograph amplified the 16 channel data ("10/20 system" positions, see Fig. 1A: Fp1/2, F3/4, Fz, F7/8, C3/4, T5/6, P3/4, Pz, O1/2) using linked ears as reference (diazepam: ipsilateral ear). The differences between linked vs. ipsilateral ear references were judged to be of no consequence, as ear linking customarily is used because the potential values at the two ears tend to equipotentiality. The data were recorded on FM tape for further analysis.

Data from each subject in each of the four conditions (pre-administration and post-administration, placebo and verum) of both studies were analyzed. Off-line, the artifact-edited EEG epochs from each condition were digitized and FFT analyzed, and the power spectra were computed for each channel of each subject using a signal

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

Data:	Zopiclone Study:				Diazepam Study:			
Conditions:	before Placebo(Z)	after Placebo(Z)	before Zopiclone	after Zopiclone	before Placebo(D)	after Placebo(D)	before Diazepam	after Diazepam
Reactions:	Placebo(Z) Reaction: after minus before Placebo(Z)		Zopiclone Reaction: after minus before Zopiclone		Placebo(D) Reaction: after minus before Placebo(D)		Diazepam Reaction: after minus before Diazepam	
Effects:	Zopiclone Effect: Zopiclone Reaction minus Placebo(Z) Reaction				Diazepam Effect: Diazepam 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 μV, respectively, while the pre-administration mean values in the four conditions varied between 6.4 and 7.1 μV.

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.

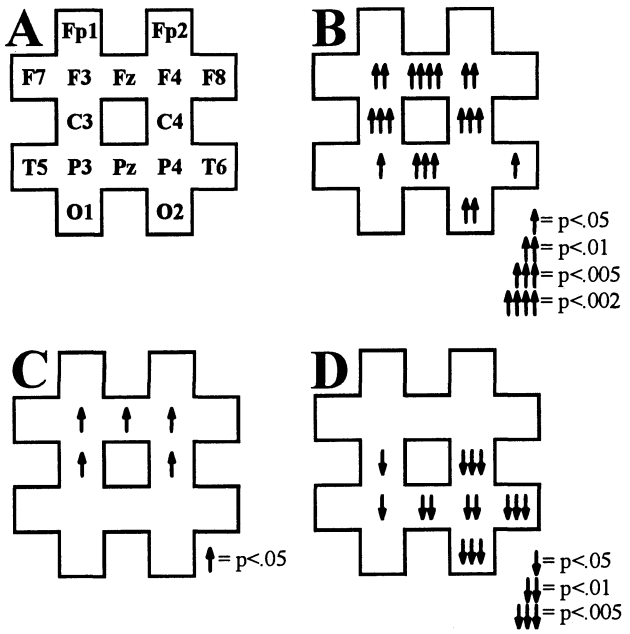

Fig. 1. A, schematic of the array of recording channels. Head seen from above, nose up, left ear left. Vertex between C3 and C4. B, comparison between the zopiclone effect and the diazepam effect on delta frequency activity (comparison of the results in Fig. 1C and D). Zopiclone increased delta activity compared to diazepam. C, map of *P*-values of the zopiclone reaction (at 1 h after zopiclone 7.5 mg administration compared to placebo). Delta frequency power after zopiclone administration increased over bilateral frontal-central regions compared to placebo. D, map of *P*-values of the diazepam reaction (at 2 h after diazepam 10 mg administration compared to placebo). Delta frequency power after diazepam decreased over central-parietal to right temporal-occipital regions compared to placebo. The arrows indicate the significances of the *P*-values.

Thus, the overall statistics showed that the delta-band effects were significantly different between zopiclone and diazepam. We observed no significant differences in the alpha band where differences between zopiclone and triazolam had been reported (Aanta et al. 1990). We note that the present zopiclone results obtained from the enlarged population as expected were very similar to those from our earlier, smaller group (Yamadera et al. 1995) where increases in the delta band absolute power over central areas were found. As to diazepam, the central-occipital decreases of delta band absolute power in our data (Yamadera et al. 1993) are in line with other reports on decrease of absolute delta power over posterior regions after diazepam (Coppola and Herrmann 1987, Saletu et al. 1987).

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.

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