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ORIGINAL INVESTIGATION

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Multilead quantitative electroencephalogram profile and cognitive evoked potentials (P300) in healthy subjects after a single dose of olanzapine

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Abstract *Rationale*: Olanzapine is an atypical antipsychotic drug with a more favourable safety profile than typical antipsychotics with a hitherto unknown topographic quantitative electroencephalogram (QEEG) profile. *Objectives*: We investigated electrical brain activity (QEEG and cognitive event related potentials, ERPs) in healthy subjects who received olanzapine. *Methods*: Vigilance-controlled, 19-channel EEG and ERP in an auditory odd-ball paradigm were recorded before and 3 h, 6 h and 9 h after administration of either a single dose of placebo or olanzapine (2.5 mg and 5 mg) in ten healthy subjects. QEEG was analysed by spectral analysis and evaluated in nine frequency bands. For the P300 component in the odd-ball ERP, the amplitude and latency was analysed. Statistical effects were tested using a repeated-measurement analysis of variance. *Results*: For the interaction between time and treatment, significant effects were observed for theta, alpha-2, beta-2 and beta-4 frequency bands. The amplitude of the activity in the theta band increased most significantly 6 h after the 5-mg administration of olanzapine. A pronounced decrease of the alpha-2 activity especially 9 h after 5 mg olanzapine administration could be observed. In most beta frequency bands, and most significantly in the beta-4 band, a dose-dependent decrease of the activity beginning 6 h after drug administration was demonstrated. Topographic effects could be observed for the beta-2 band (occipital decrease) and a tendency for the alpha-2 band (frontal increase and occipital decrease), both indicating a frontal shift of brain electrical activity. There were no significant changes in P300 amplitude or latency after drug administration. *Conclusion*: QEEG alterations after olanzapine administration were similar to EEG effects gained by other atypical antipsychotic drugs, such as clozapine. The increase of theta activity is comparable to the frequency distribution observed for thymoleptics or antipsychotics for which treatment-emergent somnolence is commonly observed, whereas the decrease of beta activity observed after olanzapine administration is not characteristic for these drugs. There were no clear signs for an increased cerebral excitability after a single-dose administration of 2.5 mg and 5 mg olanzapine in healthy controls.

Keywords Atypical antipsychotics · Pharmaco EEG · Topography · Human · ERP

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Introduction

Olanzapine is an atypical antipsychotic substance of the thienobenzodiazepine class. Olanzapine binds to a number of neurotransmitter receptors. In binding studies in vitro, a high affinity for the D_1-, D_2-, D_3- and D_4-dopamine, α2- and α1-adrenergic, histaminergic H_1, muscarinergic m1-, m2-, m3- and m4- and 5-HT receptors was found for olanzapine (Bymaster et al. 1996; Schotte et al. 1996). This multi-receptor profile includes a stronger affinity for 5-HT_2, muscarinic and histaminic receptors than for dopamine D_2- receptors. It was postulated that a high affinity for 5-HT_2 receptors relative to D_2- receptors may be involved in the low potential for extrapyramidal symptoms (EPSs). Furthermore, the ratio of 5-HT_2- to D_2- receptors is discussed to be an important factor in determining the increased efficacy in atypical relative to typical antipsychotic drugs (Meltzer 1995; Kapur and Remington 1996). Also the relative affinity of a compound for the dopamine D_2- and D_4- receptors, with greater affinity for the D_4- receptor, was suggested as a differentiating feature of atypical antipsychotic substances (Van Tol et al. 1991; Seeman and Van Tol 1993). Positron emission tomography (PET) studies demonstrat-

ed that olanzapine saturates 5-HT_2 receptors and demonstrates a higher 5-HT_2 than D_2- occupancy at doses between 5 mg and 40 mg. At doses greater than 20 mg olanzapine per day, higher than 80% occupancy of dopamine receptors was observed, which was described as a potential indicator of a higher risk of EPS and prolactin elevation (Farde et al. 1992; Nordstrom and Farde 1998). Based on the experience of three patients, one report has suggested that olanzapine may lose some of its atypical clinical features in higher doses (Kapur et al. 1998). Olanzapine with a multi-receptor profile acts in several neurotransmitter systems. Consequently, complex interactions take place between the different systems. Quantitative electroencephalogram (QEEG) may reflect downstream effects of such interactions. This probably explains why QEEG changes are more related to their therapeutic effects than to the underlying mechanisms on neurotransmitter level (Fink 1969). The receptor profile of olanzapine is most similar to that of clozapine. However, it is unknown whether both substances have the same QEEG profile. Reports of quantitative EEG alterations after olanzapine administration in different frequency bands and on topographical distribution of EEG activity are still lacking. The influence of olanzapine on clinical EEG was described as diffuse and intermittent slowing without further computerised quantification (Schuld et al. 2000).

Clozapine and olanzapine differ in their safety profiles concerning increase of cerebral excitability and unspecific EEG abnormalities. Clozapine lowers the seizure threshold, and seizures occur in up to 10% and more in patients under long-term treatment (Devinsky et al. 1991; Wilson and Claussen 1995). In pre-marketing clinical trials, seizures occurred in 0.9% (22 of 2500) of olanzapine-treated patients, mainly in patients with epilepsy or Alzheimer's dementia (Eli Lilly 1996). In controlled clinical trials, seizures have rarely been observed (Beasley et al. 1997), even when the rate of unspecific EEG abnormalities increased (Pillmann et al. 2000).

EEG alterations associated with antipsychotic drugs after a single dose in healthy subjects may differ from results obtained in patients. Psychopathology or long-term treatment may lead to changes in brain function and EEG in chronic patients (Saletu et al. 1979). Therefore, investigations in healthy subjects allow a more accurate assessment of direct drug-related changes without pre-existing EEG alterations.

The event-related potential P300 was described to assess pharmacological influence on attention-dependent information processing, for example, by changing the availability of neurotransmitters at their respective receptors (Dierks et al. 1994). In patients, haloperidol and clozapine administration have different influences on P300 (Umbricht et al. 1998), indicating that the receptor profile may be an important factor of drug influences on P300.

The primary goal of the present study was to define the global and topographical QEEG changes after olanzapine administration in healthy subjects and compare them with the profile of other psychotropic substances. Furthermore, the effect of olanzapine on cognitive functions was investigated using the cognitive evoked potential P300 (Donchin and Coles 1988).

Methods

Subjects

Ten healthy men volunteered to participate in the study. The mean age was 26.7±2.6 years (range 24–31 years). Eight were right- and two were left-handed, as determined by the Edinburgh handedness scale (Oldfield 1971). All subjects were in good health and showed normal findings in a general and neurological investigation. Both electrocardiography (ECG) and laboratory investigation (clinical chemistry, thyroid-stimulating hormone, blood cell count and virology for hepatitis A, B and C) were inconspicuous. A psychiatric interview showed neither noticeable psychopathological symptoms nor a positive personal or family history for psychiatric disorders or substance abuse according to the ICD 10 criteria (Bramer 1988). All subjects were free of any psychoactive medication. Experiments were conducted in accordance with the Declaration of Helsinki (1964) and approved by the local ethics committee. All subjects gave their informed written consent to participate in the study.

Study design

The study was designed as a double-blind, placebo-controlled investigation. Each subject underwent three sessions separated by a 1-week interval. In each session, subjects received a single dose of either placebo or olanzapine (2.5 mg or 5 mg) randomly balanced, and four EEGs and P300s were recorded: the first measurement was before drug administration (baseline), the rest at 3 h, 6 h and 9 h after drug administration. A meal was served between the second (3 h) and third (6 h) EEG recordings.

EEG recordings and analysis

In each session, a vigilance-controlled EEG with eyes closed was recorded for 3 min followed by an auditory P300 measurement. Between the measurements, the electrodes were left on the scalp, and subjects were free to relax in a comfortable environment.

A 19-channel EEG according to the international 10–20 system with a sampling rate of 512 Hz was recorded (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) and stored on hard disk for off-line analysis. Cz served as recording reference. An ECG and vertical and horizontal electrooculography (EOG; 1 cm lateral to each eye) were recorded for artefact monitoring. The recording was carried out with a conventional electroencephalograph (Neuroscan Synamps) and Ag/AgCl electrodes. Impedances were kept below 5 kΩ. Before sampling, the data were bandpass filtered between 0.3 Hz and 70 Hz.

Vigilance control was warranted by presenting a 1000-Hz tone [inter-stimulus interval (ISI) 30 s ±20%] via earphones. Subjects had to press a button with the right index finger whenever they heard the tone. EEG was used for spectral analysis only in case the subjects were attending to the tone and pressed the button. When there was a correct button press, the segment (2-s duration) was selected from –4 s to –2 s before the tone was presented. For EEG data analysis, a commercial software package was used (Brain VisionAnalyser Software Version 1.01; Brain Products GmbH, Munich, Germany). Off-line the data were band-pass filtered between 1.00 Hz (12 dB/oct) and 40.00 Hz (12 dB/oct). Segments containing artefacts were rejected. Common average reference (CAR) was calculated and applied to all channels. At each electrode position, QEEG was analysed by means of spectral analysis using fast Fourier transformation, and the amplitude was calculated in nine frequency bands: delta 1.0–3.5 Hz, theta 4.0–7.5 Hz, alpha-1 8.0–9.5 Hz, alpha-2 10.0–11.5 Hz, beta-1 12.0–15.5 Hz, beta-2 16.0–19.5 Hz, beta-3: 20.0–23.5 Hz, beta-4: 24.0–27.5 Hz, beta-5: 28.0–31.5 Hz. Spectral results for all segments were averaged and a grand mean over all segments for each subject, dose

and time point was calculated followed by natural logarithmical transformation to attain a normal distribution of the data. In the following analysis, only the log-transformed data were considered.

QEEG analysis. A repeated-measurement (ANOVA) with three factors (time, dose and electrode position) was performed to investigate statistical effects. To attain a global value of EEG activity the average was calculated over all 19 electrodes for each frequency band. Post-hoc analysis was computed using a paired, two tailed *t*-test for the global value of EEG activity in every frequency band and at all different measurement time points. Results will be presented for dosage differences for all frequency bands (independent of significant ANOVA effects).

Behavioural data analysis. The analysis of the reaction time for the button press in the vigilance-controlled EEG was tested using a repeated-measurement ANOVA with two factors (time and dose). Results were regarded as significant if *P* was less than 0.05. ERPs were recorded using the same parameters as for QEEG.

ERP recordings and analysis

ERPs were recorded using the same parameters as for QEEG. To investigate the cognitive evoked potentials, an auditory odd-ball paradigm was used (Donchin and Coles 1988). Frequent 1000-Hz tones were used as non-targets and rare 2000-Hz tones as targets. Targets were presented in a random order with a probability of occurrence of 20% and an interstimulus interval of 2 s ±20%. Subjects had to response with a button press with the right index finger to indicate when they detected a target tone. EEG activity was averaged for target and non-target stimuli separately for –200 ms to 800 ms post-stimulus (1000 ms). Epochs containing amplitudes higher than 50 µV or lower than –50 µV in the EOG electrodes were not included in the average waveform. The waveforms were baseline corrected (using average EEG activity from –200 ms to 0 ms as reference). Then CAR was calculated and subsequently, segments were averaged. To determine the latency and amplitude of the P300 component, the Global Field Power (GFP) was calculated in a first step (Skrandies 1990). Then the point of time with the peak amplitude of the GFP between 260 ms and 460 ms was used to define the P300 components. P300 values and behavioural data for the correct target detection were analysed using a two-factor ANOVA for repeated measurements (time and dose).

Results were regarded as significant if *P* was less than 0.05. Variance of data is presented as standard deviations.

Results

Clinically, no severe adverse events were observed after placebo or olanzapine administration. No influence on blood pressure, heart rate and temperature was observed. Subjects reported sleepiness after olanzapine administration (10 of 10 subjects for 2.5 mg and 5 mg), maximal effect was reached at 4–6 h and ended approximately 9 h after drug intake. Dry mouth was reported by five of ten subjects after 2.5 mg and by two of ten subjects after 5 mg olanzapine. Vertigo was reported in one of ten subjects after 2.5 mg and in four of ten subjects after 5 mg olanzapine. There were no grapho-elements detected by visual inspection in the raw EEG that indicated a pathological general increase in cerebral excitability after intake of 2.5 mg or 5 mg olanzapine.

QEEG

Behavioural results

In the button-press, vigilance-monitoring task, reaction times showed a dose-dependent but not significant increase for the two-factor interaction (dose and time; $F_{6,54}$=1.46, *P*=0.21; Table 1).

Global EEG results

On average, 9.6±3.0 EEG epochs (19.2±6 s) were analysed in each subject. The three-factor ANOVA for repeated measurements for time, dose and electrode location gained significant main effects for the factor time for delta, theta, alpha-1, beta-1 and beta-2: with longer time after substance administration, the activity increased (Table 2, Fig. 1). For the factor dose, no significant main

Table 1 Mean reaction time for the button press in the vigilance-controlled electroencephalogram (EEG; *n*=10). No significant statistical interaction effects (dose and time) were observed in a two-factor analysis of variance

Vigilance-controlled EEG	Baseline	3 h	6 h	9 h
Placebo	256±72	390±75	312±77	301±81
2.5 mg Olanzapine	273±76	378±134	372±111	386±138
5 mg Olanzapine	294±112	370±156	484±150	419±122

Table 2 *F* values as a result of a three-factor analysis of variance for repeated measurements with the factors time, dose and electrode position, calculated for logarithmic transformed global electroencephalogram amplitude values (*n*=10). The results for the main factors time and dose are presented as well as the interaction of time and dose and time, dose and electrode position

	Dose $F_{2,18}$	Time $F_{3,27}$	Time vs dose $F_{6,54}$	Time vs dose vs electrode location $F_{108,972}$
Delta	0.87	3.04**	1.85	1.02
Theta	1.35	36.47***	2.28**	0.85
Alpha-1	0.42	12.86***	1.13	1.07
Alpha-2	0.06	1.11	2.47**	1.23*
Beta-1	0.11	12.72***	1.41	1.06
Beta-2	0.79	13.95***	2.59**	1.29**
Beta-3	2.72*	1.81	1.83	1.17
Beta-4	1.34	2.92*	2.62**	0.94
Beta-5	2.38	2.65	1.48	1.00

*****P<0.10, ******P<0.05, *******P<0.01

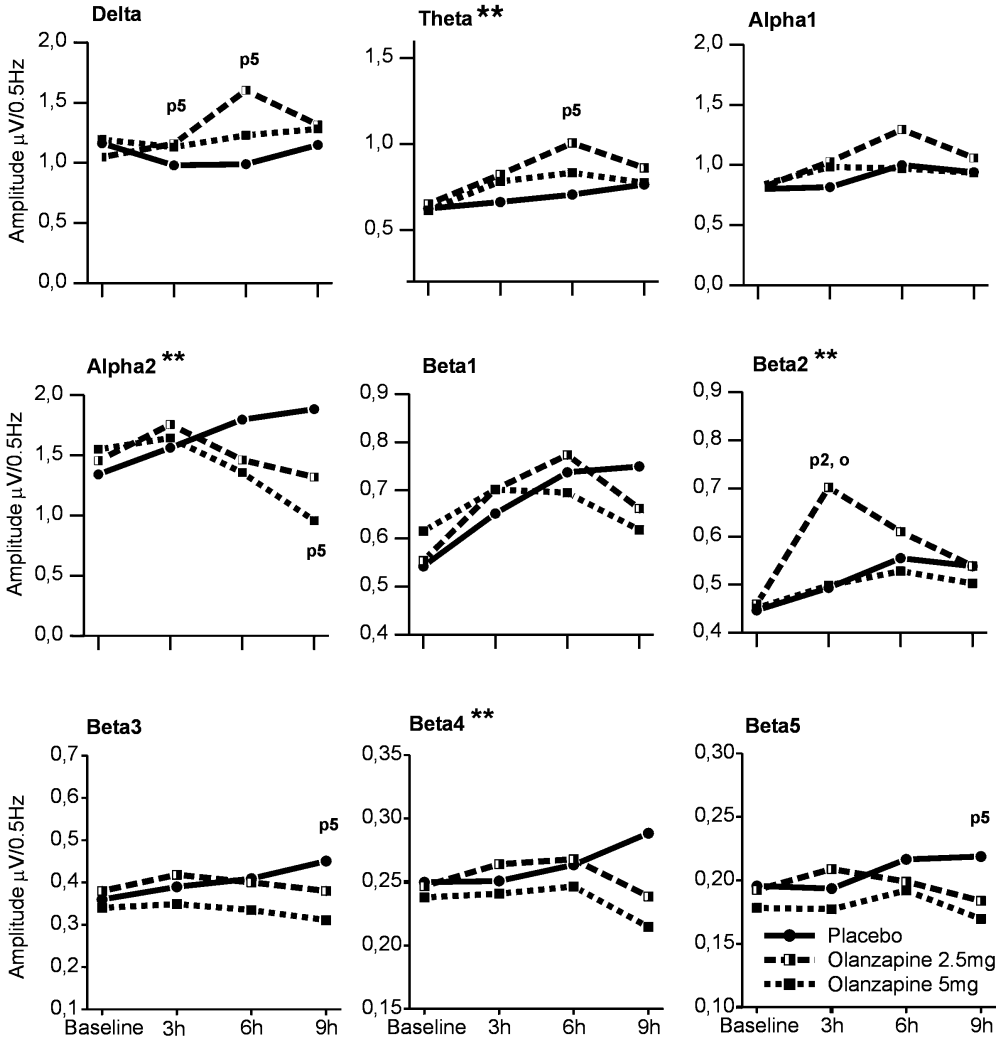

Fig. 1 Results of spectral analysis for nine frequency bands. Grand mean for ten subjects at 19 electrode positions at baseline and 3 h, 6 h and 9 h after the administration of placebo, 2.5 mg and 5 mg olanzapine. Significant interactions in the analysis of variance (ANOVA) for repeated measurements (factors time and dose) were gained for the theta, alpha-2, beta-2 and beta-4 frequency band. Significant interaction effects are indicated by ** for $P<0.05$ for all frequency bands. Significant post-hoc *t*-test results ($P<0.05$) were coded by *p2* (placebo vs 2.5 mg olanzapine), *p5* (placebo vs 5 mg olanzapine) and *o* (2.5 mg olanzapine vs 5 mg olanzapine)

effects were gained. For the interaction between time and dose, significant effects were observed for theta, alpha-2, beta-2 and beta-4 frequency bands (Table 2). Post-hoc *t*-tests were computed. Significant *t* values ($P<0.05$) are indicated in Fig. 1, independent of significant ANOVA effects for descriptive purposes.

Post-hoc *t*-tests showed significantly increased amplitudes for the delta band at 3 h and 6 h for the 5-mg dose relative to placebo. *t*-Test results for theta activity resulted in a significant amplitude increase at 6 h for the comparison of 5 mg olanzapine with placebo. In alpha-1, the amplitude pattern as a function of time and dose corresponded to that in delta and theta bands. The *t*-test values in the alpha-2 band indicated significantly lower amplitudes after 5 mg olanzapine at 9 h than after placebo. In the beta-1 band, a tendency corresponding to that in the faster beta bands with a decrease after drug administration especially at 9 h occurred. In the beta-2 band, *t*-tests revealed a significant increase at 3 h for the 2.5 mg in comparison with placebo and 5 mg olanzapine. In beta-3, 4 and 5 bands, amplitudes decreased dose dependently after the administration of the 2.5-mg and 5-mg doses, which was significant in the beta-3 and beta-5 band at the 9-h measurement. In summary, we found an increase in slow (delta, theta and alpha-1) and a decrease in fast (alpha-2 and all beta) frequency bands.

Topographical EEG analysis

Spatial alterations of brain electrical activity after olanzapine administration were represented by the interaction of dose, time and electrode position (Table 2, Fig. 2). Significant interactions were gained for the beta-2 activity with a decrease of amplitudes in occipital electrodes. With increasing time and dose, the beta-2 activity shifted towards frontal electrodes (Fig. 2a). The effect was most pronounced for the dose of 5 mg olanzapine and started 3 h after the administration; whereas, for the dose of 2.5 mg olanzapine, it started 6 h after the administration. For alpha-2 activity, a tendency of $P=0.07$ was observed (Fig. 2b). Physiological higher amplitudes over occipital electrodes decreased after the administration of olanzapine, most pronounced after the 2.5-mg dose, starting 3 h after the administration. At 9 h, this effect diminished and the occipital maximal activity was re-

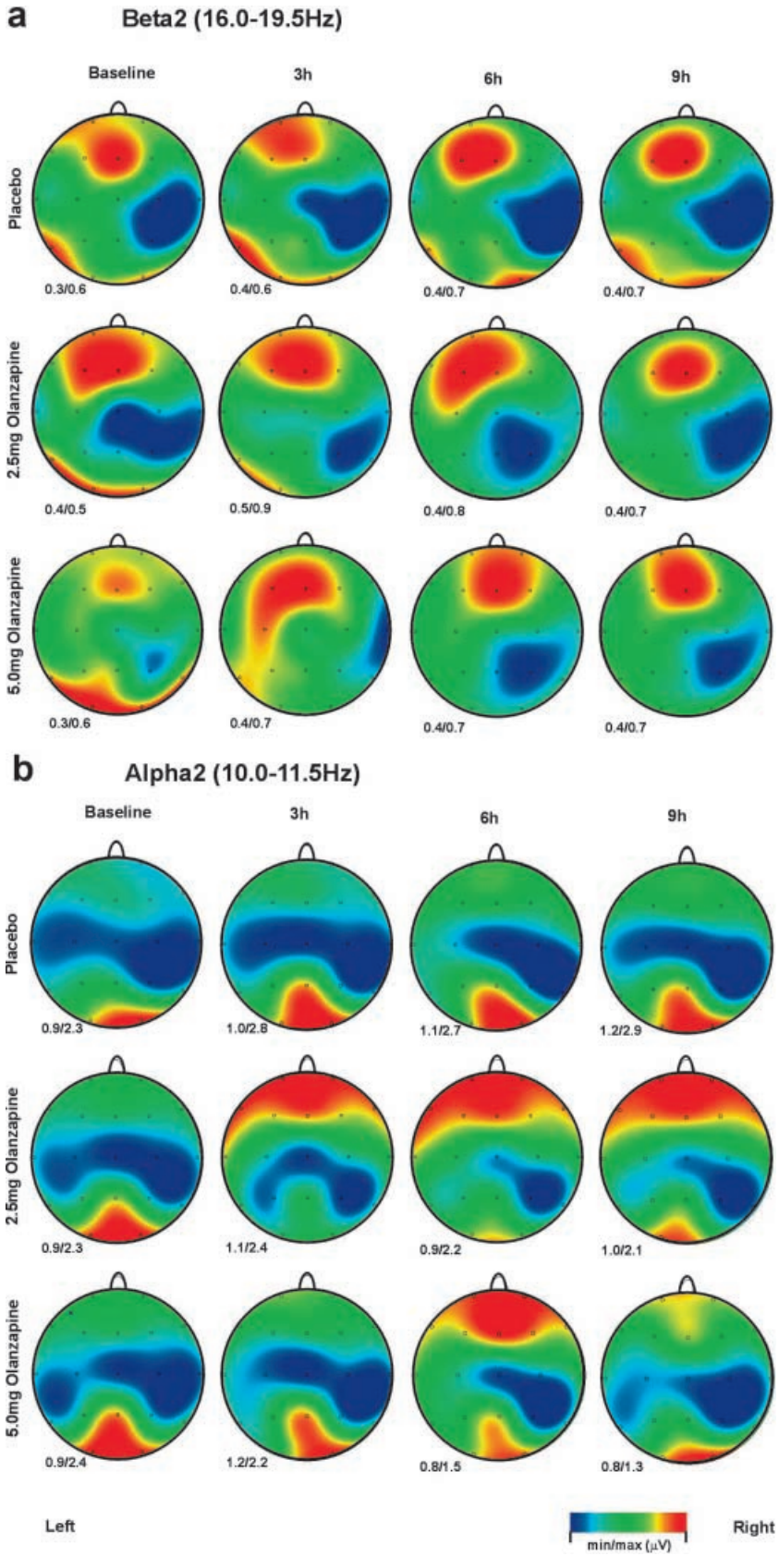

Fig. 2 Topographical distribution of vigilance-controlled quantitative electroencephalogram before (baseline) and 3 h, 6 h and 9 h after the administration of placebo, 2.5 mg and 5 mg olanzapine for the beta-2- (**a**) and alpha-2 activity (**b**). In the beta-2 band, a dose-dependent frontal shift of activity was observed. In the alpha-2 frequency band, occipital amplitudes decreased and frontal activity increased. The *topographical maps* represent the mean amplitudes measured at 19 electrode locations (*n*=10). The maps were individually scaled between maximum and minimum to focus on topographical changes

gained. For the 5-mg dose, this effect was less pronounced than for the 2.5-mg dose. Simultaneously, amplitudes increased over frontal electrodes. For a dose of 2.5 mg olanzapine, this increase started 3 h after the administration and lasted till the final measurement. For the 5-mg dose, the effect was most pronounced at 6 h. For the other frequency bands, no significant three-factor interactions (topographical alterations) were observed.

Cognitive EP

Behavioural results

The reaction time for detecting the rare target tones in the auditory odd-ball paradigm showed a dose-dependent increase after the administration of olanzapine. ANOVA showed no significant interaction between time and dose ($F_{6,54}$=0.93, P=0.48). The reaction time results verified our clinical observation of a declining vigilance 4–6 h after the administration of olanzapine which was reversed at the last measurement 9 h after the administration (Table 3).

EP results

Target epochs (18.7±6.9) were averaged for each measurement. Both latency and amplitude of P300 showed no significant differences at any time of the measurements (Fig. 3, Table 4).

There was a dose-dependent influence of reaction time which was not mirrored in the P300 GFP-amplitude or latency. Thus, we found no significant effects of olanzapine on the cognitive evoked potential component P300.

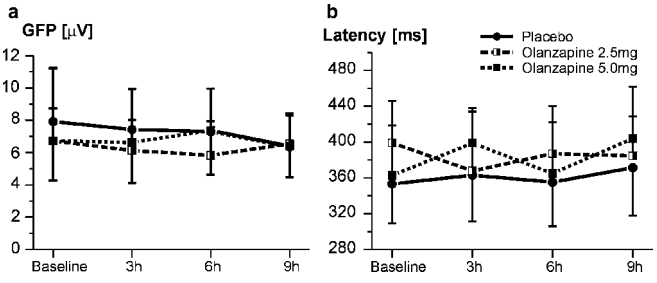

Fig. 3 Amplitude (Global Field Power, GFP) (**a**) and latency (**b**) of P300 showed no significant alterations after drug administration. Mean values over all subjects are shown at baseline and at 3 h, 6 h and 9 h after drug application

Discussion

Olanzapine is a benzodiazepine derivative and commonly associated with a treatment-emergent somnolence. In healthy subjects, clinically applied doses of olanzapine (5–20 mg) usually lead to sleep. We used one subclinical dose (2.5 mg) and one in the lower clinical dose range (5 mg) to avoid sleeping in the subjects and to ensure vigilance-controlled EEG data.

Oral administration was used since 57–100% of olanzapine is absorbed this way (Eli Lilly 1996). Plasma peaks appear 5–8 h after administration, and the last EEG measurement of the present study was carried out 9 h after the drug administration, assuring that effects occurring at maximal plasma peaks were recorded.

Findings in healthy subjects after a single dose of a psychotropic drug allow definition of the QEEG profile, independent of changes in psychopathology. The EEG profile found in normal volunteers may differ from that in psychiatric patients. This might be due to differences in brain function in patients and healthy controls or due to different sedation thresholds (Saletu et al. 1979). Various investigators have shown that clinically defined patient groups have certain electrophysiological patterns. Findings in QEEG after acute or chronic treatment in schizophrenic patients might differ from results obtained in healthy subjects (Galderisi et al. 1996).

After the administration of a single dose of 2.5 mg or 5 mg olanzapine in young healthy subjects, an increase in slow wave activity and a decrease in fast frequency bands were found. The quantitative alterations of the EEG background activity observed in this study are similar to findings described for clozapine (Galderisi et al.

Table 3 Mean reaction time for the button press in the auditory odd-ball paradigm (n=10). No significant statistical effects were observed

P300 reaction time (ms)	Baseline	3 h	6 h	9 h
Placebo	366±26	405±44	402±38	387±44
2.5 mg Olanzapine	393±38	492±87	512±75	484±75
5 mg Olanzapine	389±54	526±89	557±88	571±95

Table 4 Mean P300 amplitudes (GFP; µV) and P300 latencies (ms) are shown (n=10). No statistical effects were gained in the analysis of variance

	Baseline		3 h		6 h		9 h	
	GFP	Latency	GFP	Latency	GFP	Latency	GFP	Latency
Placebo	7.9±3.3	353.2±44.0	7.4±2.5	363.0±51.9	7.3±2.7	355.2±49.3	6.4±2.1	371.4±53.9
2.5 mg Olanzapine	6.7±2.0	399.0±47.0	6.1±1.9	367.6±70.7	5.8±2.1	386.9±53.4	6.5±1.8	384.6±44.2
5 mg Olanzapine	6.7±2.5	362.7±55.8	6.6±2.5	398.8±35.1	7.4±2.7	364.8±57.3	6.4±1.9	404.0±57.6

1996). After the administration of a single dose of olanzapine in healthy subjects, the increase was highest for delta, whereas after clozapine the increase was highest for theta activity (Galderisi et al. 1996). For a long-term treatment in schizophrenic patients with olanzapine, a general slowing of the conventional clinical EEG was reported (Pillmann et al. 2000). They differentiated a diffuse and intermittent slowing which was found in 48% and 38%, respectively, of 43 patients with various diagnoses during a treatment with 10–25 mg olanzapine plus additional medication – mainly newer antidepressants, tricyclic antidepressants and benzodiazepines. An increased slow wave EEG activity was also found in the patients with no olanzapine treatment but to a lower extent. The EEG was rated according to general categories such as light, medium and severe abnormality without quantification. Schuld et al. (2000) compared conventional EEG in schizophrenic patients who were treated with olanzapine and clozapine, and described an EEG slowing after administration of both substances. The EEG slowing after olanzapine was less pronounced and frequent than after clozapine administration. Both studies reported findings in clinical EEG recordings without quantification in the different frequency bands and without considering fast frequency bands. Our results support clinical findings of alterations during long-term olanzapine treatment. The QEEG profile corresponds to the findings described for clozapine and typical sedative antipsychotics (Galderisi et al. 1996; Saletu 2000).

In fast frequency bands, we report a decrease of activity in the alpha-2 and in all beta bands, most pronounced in the alpha-2 and beta-3, 4 and 5 range. Galderisi and colleagues (1996) found for clozapine the most pronounced decrease in the absolute amplitude in the alpha-2 band, which is according to our present findings. It has to be considered that in the two studies the chosen frequency bands were slightly different (Galderisi et al. 9.7–12.5 Hz; present study 10.0–11.5 Hz). Other studies found discrepant findings concerning EEG activity in the fast frequencies for clozapine; while Roubichek and Major (1977) reported an increase, Herrmann et al. and Itil et al. demonstrated a decrease (Herrmann et al. 1979; Itil et al. 1979).

For typical sedative antipsychotic drugs, Saletu described an increase in slow delta and theta activity with *t* values similar to those gained in the present study (Saletu 2000). They analysed the potential difference between O_z and C_z, while we compared average values gained from 19 scalp electrodes. The *t* values for the comparison of placebo with antipsychotic drug in our study lie in the same range for the slow activity, whereas the values for the alpha activity are smaller than those reported by Saletu (2000). This might be due to the fact that alpha activity is most pronounced in the occipital regions and optimally sampled between O_z and C_z. Therefore, in an average value of all 19 scalp electrodes, the alpha contributes to a lower extent than in the single recording between O_z and C_z. However, the olanzapine profile corresponds to the profile of other atypical antipsychotic drugs, such as clozapine, or to the typical substances of sedative antipsychotics, such as chlorpromazine and zotepine. The increase of slow wave activity matches the frequency distribution observed for sedative antidepressant drugs (thymoleptic substances from the amitriptyline or imipramine type; Saletu 2000). On the contrary, non-sedative antipsychotics show a decrease in alpha and an increase in beta activities without changes in delta or theta bands.

We report significant alterations of the topographical distribution of electrical brain activity after olanzapine administration for the beta-2 and a tendency for the alpha-2 band. The decrease in the beta-2 band at occipital electrodes is similar to results reported for clozapine (Galderisi et al. 1996). The changes in alpha-2 (present study 10.0–11.5 Hz) band showed an occipital decrease and frontal increase. After administration of clozapine, a general decrease in alpha-2 (9.7–12.5 Hz) with a frontal and occipital pronunciation was reported (Galderisi et al. 1996). Topography after the administration of clozapine did not show a frontal increase of activity but only an occipital decrease. Furthermore, topographical changes after the administration of benzodiazepines, to which olanzapine is structurally related, showed a frontal shift for faster frequency bands in healthy subjects (Dierks et al. 1993). Thus, the close relationship between benzodiazepines and olanzapine may explain the present result of a shift to the frontal regions observed for beta-2 and alpha-2 bands, which was found more pronounced after olanzapine than after clozapine administration. These findings could indicate that, from an electrophysiological point of view, olanzapine is more closely related to the class of benzodiazepines than clozapine.

The reaction time of the odd-ball paradigm increased slightly after the olanzapine administration, but without reaching a significant level. In the ERP analysis, amplitude and latency of the P300 component did not demonstrate any significant alterations after the olanzapine or placebo administration. These results indicate that olanzapine had no acute adverse effects on cognitive functions measured by the P300 ERP component after a single dose in healthy volunteers.

In several studies the positive effects of new-generation antipsychotic substances in comparison with typical antipsychotic drugs on disturbed cognitive functions in patients have been described (Purdon et al. 2000; Stip 2000). These effects are reflected, for example, in a normalisation of P50 suppression in schizophrenic patients under a long-term treatment with olanzapine (Light et al. 2000). However, it should be considered that in the present study normal ERP components in healthy subjects after a single dose were investigated and not the pathologically changed ERP components, which are known to occur in schizophrenic patients (Strik et al. 1994). Therefore, the finding of no significant effects on P300 amplitude, latency or reaction time can be interpreted as no acute adverse effects of olanzapine on cognitive functions measured by the P300 component without respect to eventual long-term improvements in patients with disease-related disturbed cognitive deficits.

In this first study of QEEG alterations after a single dose of olanzapine in healthy subjects, an olanzapine-related increase in slow brain electrical activity was demonstrated. This is similar to findings described for typical and other atypical antipsychotics for which treatment-emergent somnolence is common. The described topographical effects of olanzapine were more related to the EEG profile described for tranquillisers with which olanzapine is chemically related. After establishing the QEEG profile in healthy subjects, further studies may investigate and compare effects in patients.

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