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EEG abnormalities associated with antipsychotics: a comparison of quetiapine, olanzapine, haloperidol and healthy subjects

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In this study the effects of the atypical antipsychotics quetiapine and olanzapine, and the typical antipsychotic haloperidol on EEG patterns were retrospectively investigated in 81 patients under stable monotherapy with either drug (quetiapine: $n = 22$, olanzapine: $n = 37$, haloperidol: $n = 22$). These three subgroups were compared with a control group of healthy subjects ($n = 30$) which were matched regarding sex and age. Diagnoses of patients were schizophrenia (DSM-IV 295.xx, $n = 61$), brief psychotic disorder (DSM-IV 298.8, $n = 9$), schizoaffective disorder (DSM-IV 295.70, $n = 8$) and delusional disorder (DSM-IV 297.1, $n = 3$). There were no statistically significant differences regarding demographic characteristics between the groups. Digital EEG recordings were retrieved from a database and visually assessed by two independent investigators, and one blinded regarding medication. One patient from the quetiapine group (5%), 13 olanzapine patients (35%), five of the haloperidol patients (23%) and two subjects of the control group (7%) had an abnormal EEG. Epileptiform activity was observed in four patients (11%) of the olanzapine group, and none in the others. EEG abnormalities were statistically significantly increased with dose in the olanzapine group, in contrast to patients treated with haloperidol, quetiapine or healthy subjects. In conclusion, EEG abnormalities seem to occur rarely in patients treated with quetiapine comparable to the control group, but significantly more often with haloperidol and olanzapine, possibly due to different receptor profiles of these substances. To our knowledge, this is the first electrophysiological investigation comparing the new atypical antipsychotics quetiapine, haloperidol, olanzapine with healthy subjects. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — electroencephalography; quetiapine; olanzapine; haloperidol; epileptiform activity

INTRODUCTION

A voluminous literature attests to the robustness of conventional EEG investigations and their clinical usefulness in disorders of brain function. Conventional as well as quantitative EEG studies show abnormalities in different psychiatric disorders, such as schizophrenia (e.g. Small, 1993; Primavera *et al.*, 1994). The EEG evaluation of comparatively large healthy populations usually show a certain percentage of abnormalities as well. Epileptiform activity has been hereby observed in 2%–3% of healthy volunteers (e.g. Gibbs and Gibbs, 1964; Harty *et al.*, 1942).

With regards to the pharmaco-EEG, general slowing of background activity, an increase in paroxysmal theta or delta activity and the development of epileptiform discharges are well documented with antipsychotic drugs. In quantitative EEG haloperidol shows an increase in the proportion of delta and theta as well as decreased alpha and faster beta wave activity (McClelland *et al.*, 1990; Kemali *et al.*, 1992). A study by Hubl *et al.* (2001) investigating quantitative EEGs in 10 healthy subjects on olanzapine revealed an increase in the theta band and a decrease of the beta activity. In 43 patients on olanzapine increases of both diffuse slowing (65.1%) and intermittent slowing

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(34.9%) as well as epileptiform activity in 9.3% were observed (Pillmann *et al.*, 2000). A recently published retrospective investigation (Centorrino *et al.*, 2002) showed a particular high risk of EEG abnormalities with clozapine (47.1%, $n = 17$) and olanzapine (38.5%, $n = 13$), and a moderate risk for typical antipsychotics (14.5%, $n = 214$) and another atypical antipsychotic risperidone (28%, $n = 25$). Epileptiform activity was observed for clozapine (5.9%) as well as for olanzapine (7.7%) and risperidone (4.0%), but not for haloperidol. No EEG alterations were found in five patients receiving quetiapine, which is in accordance to another investigation with 12 patients treated with quetiapine (Wetzel *et al.*, 1995).

Although quetiapine has been increasingly used as an antipsychotic there is only limited knowledge about the potential risk of EEG alterations including epileptiform activity and a lack of systematic studies with this drug. The EEG recordings were analysed retrospectively of patients treated with the new antipsychotic quetiapine and compared with those treated with olanzapine and haloperidol and a control group of 30 healthy subjects. Furthermore, the EEG alterations were correlated within the groups to possible pathophysiology with a focus on the receptor profile of the substances.

METHODS

Eighty-one patients under antipsychotic monotherapy with either quetiapine ($n = 22$), olanzapine ($n = 37$) or haloperidol ($n = 22$) were identified, who had at least one EEG recording between 04/1998 and 02/2002. Furthermore, the three different subgroups were compared with 30 healthy volunteers who were matched regarding sex and age.

No further psychotropic medication except for non-benzodiazepine hypnotics (zopiclone, zolpidem, chloral hydrate) as rescue medication were administered in the patient subgroups. The EEG data base did not allow an identification of the length of medication intake within the treatment groups prior to recordings, nor statements about the clinical outcome.

Sixty-one patients were diagnosed as schizophrenia (DSM-IV: 295.xx), nine suffered from brief psychotic episodes (DSM-IV: 298.9), eight from schizoaffective disorders (DSM-IV: 295.7) and three from delusional disorders (DSM-IV: 297.1). EEG records were taken routinely at least once from all inpatients of the Psychiatric University Hospital Munich, usually within the first week after admission.

While the patients were seated in a sound-attenuated, electrically shielded room in a reclining chair with eyes closed (resting condition) digital EEG records were obtained, using the Neuroscan Synamps system. Nineteen Zn-electrodes were placed via an electrocap according to the international 10/20 system, additional electrodes (left ocular canthis) were used to record the electrooculogram (EOG) simultanously. The impedances of all electrodes were kept below 10 kOhm throughout the session. The EEGs were recorded for at least 20 min including 5 min of hyperventilation with Cz as reference through amplifiers with a bandpass from 0.53 to 50 Hz (50 Hz notch filter), digitized at a sample rate of 250 Hz and digitally stored for further analysis and/or processing off line.

All EEGs were retrieved from the database and visually interpreted independently by two experienced raters and one experienced rater blind to medication, dosage and diagnosis of the patients. In the case of disagreement, the recordings were reassessed and discussed to achieve a consensus.

The findings were classified as normal or abnormal, with or without epileptiform activity. Abnormal results comprised diffuse slowing of background activity and increased paroxysmal theta- and/or delta activity, either generalized (theta-/delta-bursts) or focal. The appearance of any spikes, sharp waves, spike-wave- or sharp-slow-wave complexes was referred to as epileptiform activity with increased cerebrocortical excitability. The utilization and clinical significance of the term 'epileptiform activity' led to considerable disunity in the ranks of electroencephalographers since epileptic discharges may also occur in the absence of clinical seizures or in individuals without seizures, e.g. in 2%–3% of the healthy population (Gibbs and Gibbs, 1964; Harty *et al.*, 1942). However, it was decided to use this term as it was thought that it is more connected to the discharges mentioned above, provided that it is used with caution and that epileptiform activity is not necessarily related to the diagnosis of epilepsy.

The groups were statistically compared regarding sociodemographic data with an analysis of variance (ANOVA), *t*-test and χ^2-analysis. Associations of a dose related effect of medication and EEG abnormality was tested by the two-sided *t*-test for independent variables. The χ^2-analysis was further used to compare EEG abnormalities within the groups. All results are expressed as mean $\pm$ SD.

RESULTS

The following data of 81 patients (43 male, 38 female) and 30 healthy controls (16 male, 14 female) were

Table 1. Demographic characteristics of the study population according to the EEG-database and medical record, tested by the *t*-test: inpatients under monotherapy with either quetiapine, olanzapine or haloperidol in comparison with a control group with healthy subjects

	Group				
	Quetiapine	Olanzapine	Haloperidol	Control	
Patients (*n*)	22	37	22	30	
Sex (m/f)	9/13	21/16	13/9	16/14	n.s.
Age (years)					
Mean ± SD	36.4 ± 13.6	33.7 ± 13.1	42.0 ± 15.1	36.2 ± 11.0	n.s.
Range	21–66	16–82	24–80	22–61	
DSM IV-Diagnoses					
295.xx	16 (73%)	26 (70%)	19 (86%)		n.s.
298.9	2 (9%)	5 (14%)	2 (9%)		n.s.
295.7	4 (18%)	3 (8%)	1 (5%)		n.s.
297.1	0 (0%)	3 (8%)	0 (0%)		n.s.
Daily dose of medication (mg)					
Mean ± SD	563.6 ± 210.6	15.7 ± 10.5	9.1 ± 3.5		
Range	100–900	3–40	2–15		

n.s., not significant.

retrospectively analysed: The mean age (±SD) of the patients receiving quetiapine ($n = 22$) was 36.4 ± 13.6 (range = 21–66), olanzapine ($n = 37$) 33.7 ± 13.1 (range = 16–82), haloperidol ($n = 22$) 42.0 ± 15.1 (range = 24–80) and the control group ($n = 30$) 36.2 ± 11.0 (range = 22–61) years. The mean daily dosage of quetiapine was 563.6 ± 210.6 mg, of olanzapine 15.7 ± 10.5 mg and of haloperidol 9.1 ± 3.5 mg, respectively (see Table 1).

In the quetiapine group, two patients received zopiclone, two zolpidem and, in the haloperidol group, one patient chloral hydrate, one zopiclone. Patients treated with olanzapine were without sleep medication. All the EEGs of the patients with the above mentioned additional medication were normal.

Overall, there were no significant age differences between the four groups (three patient subgroups and one control group) [$F(3, 107) = 1.84$; $p = 0.14$; Scheffé: $p \geq 0.15$]. Quetiapine, olanzapine and haloperidol patients did not differ significantly in diagnoses [$\chi^2(6, n = 81) = 6.71$; $p = 0.35$]. Furthermore, no statistically significant group differences regarding sex distribution could be observed [$\chi^2(3,\ n = 111) = 1.83$; $p = 0.61$].

One of 22 patients on quetiapine (5%), five on haloperidol (23%) and two of the control group (7%) had an abnormal EEG. Furthermore, the EEGs of 13 out of 37 (35%) olanzapine patients were assessed as abnormal with four olanzapine (11%) patients showing clear epileptiform activity (see Table 2).

Within the four subgroups results regarding abnormal EEGs differed statistically significantly [$\chi^2(3,\ n = 111) = 12.45$; $p = 0.006$]. Between the quetiapine and olanzapine groups, a highly statistically significant difference [$\chi^2(1,\ n = 59) = 7.13$; $p = 0.008$] was seen in terms of EEG alterations for both slowing of background activity as well as epileptiform activity. No statistically significant difference could be observed comparing olanzapine and haloperidol [$\chi^2(1,\ n = 59) = 1.00$; $p = 0.32$] nor between quetiapine and haloperidol [$\chi^2(1,\ n = 44) = 3.09$; $p = 0.08$]. The same is true for the comparison of the control with

Table 2. Electroencephalography in patients under monotherapy with quetiapine, olanzapine or haloperidol and healthy subjects as control group; results of visual assessments of EEG recordings, classified as normal/abnormal, with/without epileptiform activity (EA)

	Group			
	Quetiapine	Olanzapine	Haloperidol	Control
n	22	37	22	30
EEG findings (visual assessment)				
Normal EEG	21 (95.4%)	24 (64.9%)	17 (77.2%)	28 (93.4%)
Abnormal EEG	1 (4.6%)	13 (35.1%)	5 (22.8%)	2 (6.6%)
Without EA	1 (4.6%)	9 (24.3%)	5 (22.8%)	2 (6.6%)
With EA	0 (0%)	4 (10.8%)	0 (0%)	0 (0%)

Table 3. Specification of EEG findings (visual assessments) under quetiapine, olanzapine or haloperidol monotherapy and in the control group according to age, sex and dosage (mean ± SD)

	Normal EEG	Abnormal EEG	
Patients under			
Quetiapine (*n*)	21	1	
Sex (m/f)	9/12	0/1	n.a.
Age (years)	36.71 ± 13.87	31	n.a.
Dose (mg)	561.90 ± 215.58	600	n.a.
Olanzapine (*n*)	24	13	
Sex (m/f)	12/12	9/4	n.s. ($\chi^2 = 1.27$; $p = 0.26$)
Age (years)	36.17 ± 13.64	29.31 ± 11.05	n.s. ($t = 1.55$; $p = 0.13$)
Dose (mg)	12.40 ± 6.74	21.7 ± 13.52	$p < 0.05$[a]
Haloperidol (*n*)	17	5	
Sex (m/f)	9/8	4/1	n.s. ($\chi^2 = 1.17$; $p = 0.28$)
Age (years)	43.06 ± 17.01	38.40 ± 3.78	n.a.
Dose (mg)	9.15 ± 3.64	9.10 ± 3.58	n.a.
Control group (*n*)	28	2	
Sex (m/f)	15/13	1/1	n.a.
Age (years)	36.32 ± 11.34	35 ± 7.01	n.a.

[a]Differences statistically significant.
n.a. was not tested by *t*-test due to limited number of patients in abnormal EEG group.
n.a., not applicable; n.s., not significant.

the haloperidol groups [$\chi^2(1, n = 52) = 2.81$; $p = 0.09$] and of the control with quetiapine groups [$\chi^2(1, n = 52) = 0.11$; $p = 0.75$]. However, a highly statistically significant result was seen between the control and the olanzapine groups [$\chi^2(1, n = 67) = 7.73$; $p = 0.005$].

The EEG results were specified according to sociodemographic characteristics (sex: χ^2-analysis; age: *t*-test) and the dose of medication per treatment group. A statistically significant dosage related effect was seen in the olanzapine group using the *t*-test [$t(1.15, 301) = 2.34$; $p = 0.03$], but not in the quetiapine and haloperidol groups (see Table 3).

DISCUSSION

In this evaluation the EEG data were reviewed from 81 patients treated either with the atypical antipsychotics quetiapine and olanzapine or the typical antipsychotic haloperidol and compared with 30 healthy subjects. The limited data of quetiapine concerning electrophysiological effects predict neither EEG abnormalities nor epileptiform activity (Centorrino *et al.*, 2002; Wetzel *et al.*, 1995). This was confirmed with our data, which showed also a low risk for EEG alterations (5%) for quetiapine and suggested a low seizure risk for quetiapine, both comparable to healthy subjects. Quetiapine differed from olanzapine which showed a dose related risk of EEG alterations of 35% and epileptiform potentials of 11%. Haloperidol with 23% of abnormal EEGs was more likely, but not statistically different to quetiapine. However, it is also important to note that numerous qualitative EEG studies indicate abnormalities in 20% to 60% of schizophrenic patients (Small, 1993; Ellingson, 1954; Small *et al.*, 1984). Furthermore, many quantitative studies have been conducted regarding background activity in schizophrenic patients: For instance, an increased delta and/or theta activity has been reported in a large number of investigations (e.g. Primavera *et al.*, 1994; Fenton *et al.*, 1980; Morihisa *et al.*, 1983). On the other hand, studies also show an increased delta activity in patients off medication for several weeks (Fenton *et al.*, 1980; Morihisa *et al.*, 1983; Coger *et al.*, 1979) and even reduction of delta and theta when medication is added again (Saletu *et al.*, 1994; Lifshitz *et al.*, 1987). This issue suggests a rather inconsistent picture. However, an EEG study by Small *et al.* (1987) in treatment resistant schizophrenic patients revealed no EEG differences between chronic drug-free schizophrenic patients and healthy volunteers, but a significant difference in terms of increased amplitudes in the delta and theta frequency bands between placebo and three antipsychotics. These findings support the impact of our data as well as other studies investigating the influence of antipsychotics treatment on EEG patterns (Westphal *et al.*, 1990; Matsuura *et al.*, 1994; Centorrino *et al.*, 2002).

Pharmacodynamic distinctions within these antipsychotics groups might lead to different effects on brain electric activity. Saletu *et al.* (1987) revealed differential effects between low and high potency antipsychotics, with increased absolute and relative delta and

theta power in the former. Substances such as chlorprothixene show, besides an affinity to dopamine-receptors, a blockade of ACh-Mus- and H1- receptors. This might be also true for clozapine with a high blockade of 5-HT2-, D4-, α1-, H1- and ACh-Mus-receptors and olanzapine, an antagonist to D1-4-, 5-HT2-, H1- and ACh-Mus-receptors (Shiloh *et al.*, 2000). Due to the similar receptor profiles of both substances, and the antagonism to H1- and ACh-Mus-receptor, a higher incidence of EEG alterations and possible seizure risk can be expected and is confirmed with the olanzapine group in our data. In contrast, quetiapine, which is a dibenzothiazepine, and has primarily 5-HT2-, D2-like and α1-receptor antagonistic properties, is without affinity to D4-, H1- and ACh-Mus-receptors (Shiloh *et al.*, 2000). This might explain the different profile of the substance regarding EEG alterations, as shown in our data.

The changes seem to be dose dependent in the case of olanzapine, since patients with abnormal EEG recordings had significantly higher dosages of the respective medication. Interestingly, abnormal EEGs were found in 23% of the haloperidol group without epileptiform activity, which is higher than in the study by Centorrino *et al.* (2002) with 7.3%. Since haloperidol mainly causes a D2-, α1-adrenergic and a decent blockade of ACh-Mus-receptors (Shiloh *et al.*, 2000), only a moderate effect on the electrophysiology might be expected.

The limitations of this study include its retrospective design with the EEG data base. There was no knowledge about the length of current medication intake, nor about psychopharmacological pretreatments. In the present study it was not possible to correlate EEG findings with clinical outcome and to specify the clinical significance of the EEG abnormalities.

Furthermore, patients in general received antipsychotic monotherapy, but six patients had a co-medication with nonbenzodiazepine hypnotics. The EEG changes following the administration of zolpidem and zopiclone show a decrease of alpha activity and an increase in delta and in beta activity with zolpidem (Patat *et al.*, 1994), and an increase of delta activity in zopiclone (Yamadera *et al.*, 1997) in healthy subjects. If at all, an increased slow activity might be expected in our sample, but all the EEGs of these patients were assessed as normal. EEG changes with chloral hydrate are not reported.

In conclusion, this study yielded some interesting findings. Olanzapine has a dose dependent seizure risk and haloperidol a modest risk of EEG alterations. Quetiapine showed a very low rate of EEG abnormalities, comparable to the control group. Due to that, the treatment option with quetiapine might be an alternative for patients with the diagnosis of epilepsy or seizures with psychosis. Nevertheless, prospective studies are required to evaluate EEG abnormalities by antipsychotics and their clinical significance.

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REFERENCES

Centorrino F, Price BH, Tuttle M, *et al*. 2002. EEG abnormalities during treatment with typical and atypical antipsychotics. *Am J Psychiatry* **159**: 109–115.

Coger RW, Dymond AM, Serafetinides EA. 1979. Electroencephalographic similarities between chronic alcoholics and chronic, nonparanoid schizophrenics. *Arch Gen Psychiatr*y **36**: 91–94.

Ellingson RJ. 1954. The incidence of EEG abnormality among patients with mental disorders of apparently nonorganic origin: a critical review. *Am J Psychiatry* **111**: 263–275.

Fenton GW, Fenwick PB, Dollimore J, Dunn TL, Hirsch SR. 1980. EEG spectral analysis in schizophrenia. *Br J Psychiatry* **136**: 445–455.

Gibbs FA, Gibbs EL. 1964. *Atlas of Electroencephalography*, Vol. 3. Addison-Wesley: Reading, MA.

Harty JE, Gibbs EG, Gibbs FA. 1942. Electroencephalic study of two hundred and seventy-five candidates for military service. *War Med (Chicago)* **2**: 923–930.

Hubl D, Kleinlogel H, Frolich L, *et al*. 2001. Multilead quantitative electroencephalogram profile and cognitive evoked potentials (P300) in healthy subjects after a single dose of olanzapine. *Psychopharmacology (Berl)* **158**: 281–288.

Kemali D, Galderisi S, Maj M, Mucci A, Di Gregorio M, Bucci P. 1992. Computerized EEG topography findings in schizophrenic patients before and after haloperidol treatment. *Int J Psychophysiol* **13**: 283–290.

Lifshitz K, Lee KL, Susswein S. 1987. Long-term replicability of EEG spectra and auditory evoked potentials in schizophrenic and normal subjects. *Neuropsychobiology* **18**: 205–211.

Matsuura M, Yoshino M, Ohta K, Onda H, Nakajima K, Kojima T. 1994. Clinical significance of diffuse delta EEG activity in chronic schizophrenia. *Clin Electroencephalogr* **25**: 115–121.

McClelland GR, Cooper SM, Pilgrim AJ. 1990. A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers. *Br J Clin Pharmacol* **30**: 795–803.

Morihisa JM, Duffy FH, Wyatt RJ. 1983. Brain electrical activity mapping (BEAM) in schizophrenic patients. *Arch Gen Psychiatry* **40**: 719–728.

Patat A, Trocherie S, Thebault JJ, *et al*. 1994. EEG profile of intravenous zolpidem in healthy volunteers. *Psychopharmacology (Berl)* **114**: 138–146.

Pillmann F, Schlote K, Broich K, Marneros A. 2000. Electroencephalogram alterations during treatment with olanzapine. *Psychopharmacology (Berl)* **150**: 216–219.

Primavera A, Fonti A, Novello P, Roccatagliata G, Cocito L. 1994. Epileptic seizures in patients with acute catatonic syndrome. *J Neurol Neurosurg Psychiatry* **57**: 1419–1422.

Saletu B, Anderer P, Kinsperger K, Grunberger J. 1987. Topographic brain mapping of EEG in neuropsychopharmacology—Part II. Clinical applications (pharmaco EEG imaging). *Methods Find Exp Clin Pharmacol* **9**: 385–408.

Saletu B, Kufferle B, Grunberger J, Foldes P, Topitz A, Anderer P. 1994. Clinical, EEG mapping and psychometric studies in negative schizophrenia: comparative trials with amisulpride and fluphenazine. *Neuropsychobiology* **29**: 125–135.

Shiloh R, Nutt D, Weizmann A. 2000. *Atlas of Psychiatric Pharmacotherapy*. Dunitz: London, 54.

Small JG, Milstein V, Sharpley PH, Klapper M, Small IF. 1984. Electroencephalographic findings in relation to diagnostic constructs in psychiatry. *Biol Psychiatry* **19**: 471–487.

Small JG, Milstein V, Small IF, Miller MJ, Kellams JJ, Corsaro CJ. 1987. Computerized EEG profiles of haloperidol, chlorpromazine, clozapine and placebo in treatment resistant schizophrenia. *Clin Electroencephalogr* **18**: 124–135.

Small JG. 1993. Psychiatric disorders and EEG. In *Encephalography: Basic Principles, Clinical Applications, and Related Fields*, Niedermeyer E, Lopez da Silva F (eds). Williams and Wilkins: Baltimore; 581–596.

Westphal KP, Grozinger B, Diekmann V, *et al*. 1990. Slower theta activity over the midfrontal cortex in schizophrenic patients. *Acta Psychiatr Scand* **81**: 132–138.

Wetzel H, Szegedi A, Hain C, Wiesner J, Schlegel S, Benkert O. 1995. Seroquel (ICI 204 636), a putative 'atypical' antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters. *Psychopharmacology (Berl)* **119**: 231–238.

Yamadera H, Kato M, Tsukahara Y, Brandeis D, Okuma T. 1997. Zopiclone versus diazepam effects on EEG power maps in healthy volunteers. *Acta Neurobiol Exp (Wars)* **57**: 151–155.

