Radboud Repository

Radboud University Nijmegen

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/49768

THE EFFECTS OF HALOPERIDOL, OLANZAPINE AND D-AMPHETAMINE ON EEG-COHERENCE AND SEDATION

C.A.F.J. Miller[a], E. Wezenberg[a], E.L.J.M. van Luijtelaar[b], G.S.F. Ruigt[c], W. Hulstijn[b], B.G.C. Sabbe[d], J.K. Buitelaar[a], R.J. Verkes[a]

[a]Dept of Psychiatry, Radboud University Nijmegen Medical Centre
[b]Nijmegen Institute for Cognition and Information, Radboud University Nijmegen
[c]Department of Translational Medicine, NV Organon, Oss
[d]Collaborative Antwerp Psychiatric Research Institute, University of Antwerpen

INTRODUCTION

Coherence of the electroencephelogram (EEG) is used to study the degree of synchronicity between two neural signals, obtained from two different scalp sites. High coherence between two EEG signals is interpreted as a strong functional connection between two cortical areas and a low coherence is considered as a weak cortico-cortical connection. Several lines of investigation suggest a relationship between decreased EEG-coherence in the prefrontal cortex and negative symptoms in schizophrenic patients[1,2]. Furthermore, after chronic administration of olanzapine, an increased EEG correlation in the alpha-1 frequency was found in schizophrenic patients, especially among subjects who showed an improvement towards positive and negative symptoms[2]. Olanzapine is a second generation antipsychotic drug (SGAP) and differs from classical antipsychotic drugs for having an additional $5HT_{2A}$ receptor antagonism. It is suggested that $5HT_{2A}$ receptor blockade selectively increases dopaminergic activity in the prefrontal cortex, which eventually leads to the improvement of negative symptoms[3]. Thus, increased neural synchronization, measured as an increased coherence, is thought to be induced by long term administration of olanzapine which eventually leads to an improvement of negative symptoms[2]. This opens the possibility for EEG coherence as a tool for screening drugs on their ability to improve negative symptoms. In the case where olanzapine is tested as drug that possibly improves EEG coherence due to increasing neural synchronicity, one should beware of the sedative properties of this compound. Olanzapine has, like many other SGAP, sedative properties, due to blocking of the histamine H_1 receptor, for which tolerance develops over time[4]. Since, EEG-coherence is decreased by sedation, especially in the alpha frequency band[5], a possible increase of EEG coherence, due to higher excitability of the prefrontal cortex, could be confounded by the effects of sedation when EEG-coherence is studied in the acute phase of drug administration. The objective of the present study was to explore the influence of psychoactive compounds on EEG-coherence, which on the one hand have the possibility to improve negative symptoms, but on the other hand exhibit sedative properties. Therefore, we have compared the effects of the classic antipsychotic haloperidol with the SGAP olanzapine on EEG coherence. These drugs were chosen in the knowledge that olanzapine has been shown to have greater efficacy than haloperidol in reducing negative symptoms[6]. Both antipsychotic drugs were compared with the effects of d-amphetamine, which, in experimental studies, was shown to be effective against negative symptoms[7,8].

METHODS

Subjects

Two separate studies were done, with 16 healthy volunteers each. Both studies had a placebo-controlled, double-blind, Latin-square design. In study 1 the drug conditions were Placebo, and D-amphetamine 15 mg. In study 2 the drug conditions were Placebo, Olanzapine 10 mg and Haloperidol 2.5 mg. All drugs were administered in single oral doses with a washout of one week. EEG recordings and assessment with Visual Analog Scales (VAS) were made before drug administration (T1) and 30 (T2) and 120 (T3) minutes after drug administration. Results are reported for the comparison between T1 and the time after drug administration that approximated Tmax (time to reach the maximum concentration): T2 for d-amphetamine and haloperidol and T3 for olanzapine.

EEG Recording

19 EEG electrodes (Ag/AgCl) were placed in standard positions according the international 10-20 system. Two additional EEG electrodes were placed between Fp1 and Fp2 (FPz) and between O1 and O2 (Oz) and one ground electrode was attached to the left temporal-parietal scalp. Horizontal and vertical electro-oculogram recordings were made from Ag/AgCl cup electrodes to control for eye movements and blinks. Left mastoid was used as a reference. Recordings were made while subjects were seated comfortably in a dimly lit room, awake with their eyes closed for three minutes. Bandpass filters were set between 0-70 Hz and digitized with a 204.8 Hz sample-rate. Results in this article focus on the coherence between O1 and FP1 and absolute band power values of the left frontal electrode (F7).

EEG signal analysis

The EEG and EOG signals were analyzed off-line and rereferenced using a bipolar montage, to avoid spurious coherence due the use of te same reference electrode: F7 was rereferenced with F3, O1 was rereferenced with Oz and FP1 was referenced with Pz. Frequencies for band power and coherence were defined according the guidelines of the International Pharmaco EEG Group (IPEG) [9]. The frequencies of interest were: alpha 1 (8.5-10.5 Hz), alpha 2 (10.5-12.5 Hz), beta 1 (12.5-18.5 Hz), beta 2 (18.5-21 Hz), beta 3 (21-30 Hz) and beta 4 (30-40 Hz). Additionally, gamma band frequencies (40-45 Hz) were calculated.

Visual Analog Scales (VAS)

The VAS is a self-report measure of 16 visual analogue scales. Each scale consists of a 100-mm-long horizontal line with on each end anchor words which express opposite extremes of a sensation or subjective feeling. The distance from one end of the line to the individual's mark is measured in millimetres to obtain a score ranging from 0 to 100. For the measurement of sedation the first item "sleepiness" was chosen (not at all tired vs very tired). Thus, the higher the score, the more sedated subjects felt.

Data analysis

Logarithmic transformation was applied to absolute band power values to normalize their distributions. Coherence values were transformed using the Fisher-z transformation. All data were analyzed using an univariate analysis of variance with two independent variables: drug and state, each with two levels: placebo versus compound and T1 versus Tmax. For each dependent variable a separate ANOVA was done. The dependent variables were: VAS score, absolute band power for F7 in each frequency band and coherence between O1 and FP1 in each frequency band. The possible confounding effects of sedation on coherence were investigated by an additional analysis of covariance on the coherence values. For this purpose, the VAS score "sleepiness" was used as covariate.

RESULTS

Table 1. VAS scores on the item sleepiness for d-amphetamine (n=15), haloperidol (n=12) and olanzapine (n=12).

	Placebo	*d-amp.*	*Placebo*	*halop.*	*Placebo*	*Olanz.*
T1	43,067	45,133	47,167	43,167	46,750	46,917
Tmax	41,267	28,667	46,333	42,500	42,750	75,417

As can be seen in table 1, sleepiness was largely influenced after administration of d-amphetamine and olanzapine. D-amphetamine decreased sleepiness (F = 12,467, df = 13, p = 0.003) and olanzapine increased sleepiness (F = 131,637 df = 10, p = 0.000). No significant effects were found for haloperidol.

The administration of d-amphetamine resulted in a small increase of coherence between O1and FP1, however no significant effects were found. Administration of haloperidol also resulted in a general increase of coherence between O1 and FP1. In the gamma band a significant effect was found (F = 7,06; df = 10; p = 0,02), which remained after sedation was used as covariate (F = 6,59; df = 10; p = 0,03).

Unlike d-amphetamine and haloperidol, olanzapine led to a large decrease of coherence between O1 and FP1. Univariate analysis of variance showed a difference for the following frequency bands: beta 1 (F = 20,38; df = 10; p = 0,002), beta 2 (F = 8,21; df = 10; p = 0,02), beta 3 (F = 14,7; df = 10; p = 0,003), beta 4 (F = 11,08; df = 10; p = 0,01) and gamma (F = 18,56; df = 10; p = 0,004). When sedation by means of the VAS score sleepiness was used as covariate, two frequency bands remained significant: beta 1 (F = 5,5; df = 9; p = 0,04) and gamma (F = 5,2; df = 9; p = 0,05).
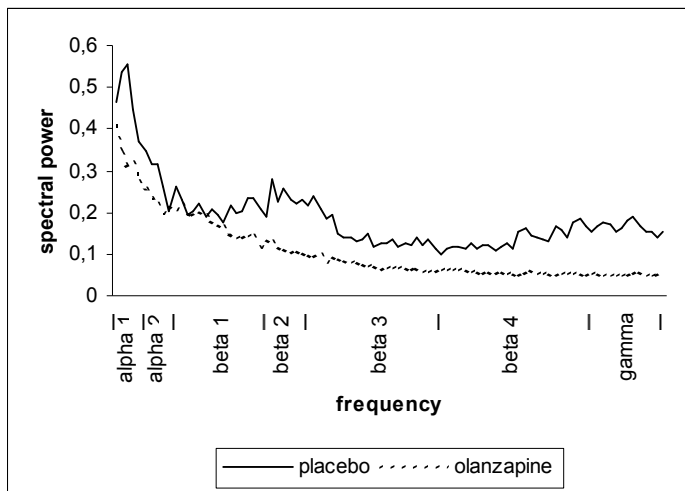

Figure 1. Spectral power of olanzapine, haloperidol and olanzapine in the left frontal electrode (F7). Absolute power values were obtained using a bipolar montage.

D-amphetamine and haloperidol had no significant effects on absolute bandpower values of the F7 electrode. However, the administration of olanzapine led to a large decrease in power, as can be seen in figure 1. A significant decrease was found in the beta 1 (F =4,903; df = 10; 0,049) and beta 3 (F =7,197; df = 10; 0,021) frequency band. For alpha 1, beta 4 and gamma there was a tendency towards a decrease of power.

DISCUSSION

D-amphetamine and haloperidol had a very small effect on coherence. Only a significant increase was found in the range between 40-45 Hz after the administration of haloperidol. Olanzapine was the most effective drug. Subjects were sedated strongly and power and coherence decreased in a large extent. Therefore it seems well established that acute administration of olanzapine decreases neural synchronization. This is the opposite of what was found after long term administration of olanzapine in schizophrenic patients[2]. In the case where sedation was used as covariate, a significant decrease remained in the beta 1 band and in the gamma band. Furthermore, no increase of coherence in the alpha-1 frequency was found, which would have resembled the effects of long term administration[2]. Thus, measuring coherence after acute administration of olanzapine seems to have no predictive value for the effects on coherence after long term treatment with olanzapine.

REFERENCES

[1] Tauscher, J. Fischer P, Neumeister A, Rappelsberger P, Kasper S. Low frontal electroencephalographic coherence in neuroleptic-free schizophrenic patients. Biol Psychiatry 1998; 44(6):438-47.

[2] Cérdan LF, Guevara MA, Sanz A, Amezcua C, Ramos-Loyo J. Brain electrical activity changes in treatment refractory schizophrenics after olanzapine treatment. Int J Psychophysiol 2005; 56(3):237-47.

[3] Ichikawa J, Meltzer HE. Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. Eur Arch Psychiatry Clin Neurosc 1999; 249: Suppl 4 IV/90-IV/98.

[4] Bourin M, Briley M. Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many psychotropic drugs. Hum Psychopharmacol Clin Exp 2004; 19: 135-139.

[5] Cantero JL, Atienza M, Salas RM, Gomez CM. Alpha EEG coherence in different brain states: an electrophysiological index of the arousal level in human subjects. Neuroscience Letters 1999; 271(3):167-70.

[6] Möller HJ. Atypical neuroleptics: a new approach in the treatment of negative symptoms. Eur Arch Psychiatry Clin Neurosci 1999; 249 Suppl 4:99-107.

[7] Angrist B, Peselow E, Rubinstein M, Corwin J, Rotrosen J. Partial improvement in negative schizophrenic symptoms after amphetamine. Psychopharmacology (Berl) 1982;78(2):128-30.

[8] Sanfilipo M, Wolkin A, Angrist B, van Kammen DP, Duncan E, Wieland S, Cooper TB, Peselow ED, Rotrosen J. Amphetamine and negative symptoms of schizophrenia. Psychopharmacology (Berl) 1996;123(2):211-4.

[9] Versavel M, Leonard JP, Herrmann WM. Standard operating procedure for the registration and computer-supported evaluation of pharmaco-EEG data. 'EEG in Phase I' of the Collegium Internationale Psychiatriae Scalarum (CIPS). Neuropsychobiology 1995; 32(3): 166-170.