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ELECTROENCEPHALOGRAM CHANGES DUE TO CETIRIZINE

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ABSTRACT

Introduction: Cetirizine, second generation antihistamine, has appeared to reduce the incidence of sedation present with first generation antihistamine. The objective of the study was to find out the electroencephalogram changes after 15 mg single dose of cetirizine administration. **Methods:** A cross-over, placebo-controlled, double-blind study was carried on 30 healthy male volunteers (age 22- 33 years). The 5 min electroencephalographic recordings were done at baseline and with placebo and cetirizine. The electroencephalogram was decomposed into its constituent frequency bands: slow, alpha1, alpha2, alpha3, alpha4 and beta by Fast Fourier Transformation (FFT) and three sets of data were compared by Friedman followed by multiple comparisons. **Results:** With cetirizine, power of EEG slow activity significantly increased at C_z[111 (88.1-149.4) vs.92.4 (79.7-130.4) μV^2, p=0.021], P_z [88.6 (72.5-130.7) vs. 83.3 (65.1-101) μV^2, p=0.008] and C3 [69.3 (57.5-91.7) vs. 58.7 (49.4-71.1) μV^2, p= 0.004] sites whereas power of EEG beta activity significantly decreased at T5 [8 (6.1 - 11.3) vs. 9.4 (6.8 - 13.5) μV^2, p= 0.020] and O1 [13.1 (9.0 - 19.1) vs.15.9 (10.3 - 22.0) μV^2, p= 0.043] sites, and alpha2 activity at O2 [34 (10.0 - 67.2) vs. 41.3 (16.8 - 84.6) μV^2, p= 0.041] site**. Conclusion:** The study showed that single dose of 15 mg cetirizine causes changes in electrical activity of different areas of cerebral cortex which are reflected in electroencephalogram.

KEYWORDS: alpha activity, beta activity, slow activity.

INTRODUCTION

The second generation antihistamine like cetirizine has minimal sedative effects. Sedation usually reflects measurable impairment of superior cognitive functions.[1] Second generation antihistamines have been reported to cause varying degrees of dose related sedation.[2, 3]

Cetirizine (20mg) substantially increased power in 6.5-8.0Hz frequency sub-segment of electroencephalogram (EEG), however no changes observed with 10mg cetirizine.[4] EEG power in alpha and theta-band is highly correlated with changes in subject's cognitive state.[5] Increased low-voltage slow-wave and decreased alpha activity suggest drowsiness after drug intake.[6] Decreased EEG slow activity is correlated with decreased drowsiness.[7] The spectral parameters in "pharmaco" EEG recordings seem to be useful in objective definition of the psychotropic side-effects of drugs.[8]

Since the literature on central effect of cetirizine is not conclusive, further research is needed in this regard, which may be reflected in EEG. Therefore, we designed a study with an objective to find out EEG changes due to cetirizine.

METHODS

The cross-over, placebo-controlled, double blind experimental study was conducted on thirty right handed healthy male volunteers of age between 18-40 years having body mass index (BMI) 18.5-25 kg/m^2 with written consent of all participants after approval from medical ethical committee of B. P. Koirala Institute of Health Sciences, Dharan, Nepal. Persons with history or presence of any neurological, hepatic, cardiac, respiratory or renal disorders and on any medication were excluded.

Cetirizine used in the study was product of GSK pharmaceutical company, India available as brand name of *CETZINE* and the placebo was glucose (100 mg- which does not produce any significant changes in EEG) packaged in capsules identical in appearance and weight.

Procedure

The health status of all 30 subjects was assessed by taking medical history and physical examination. The subjects were randomized into two groups- placebo and cetirizine.

All subjects were instructed to have normal (minimum 6 hours) night sleep and provided breakfast (fruit cake-150gm) two hours before the recordings. The EEG disc electrodes were placed according to International 10-20 system of electrode placement. The EEG recordings for 5 minutes of all the subjects were performed in EEG laboratory at room temperature of 26±2ºC in supine eye closed position after 10 minutes of supine rest between 8-10 am. The morning time and short duration of only 5 min of EEG recordings were scheduled to avoid the effects of normal sleep in subjects having shorter sleep latency in comfortable laboratory environmental conditions. The referential montage was used to record EEG. Electrodes impedance was kept less than 5 kilo-ohms. Time constant was maintained at 0.3Hz. Low cutoff and high cutoff frequency was maintained at 0.5 Hz and 70Hz respectively. The sampling rate, 240 Hz was used for acquisition of EEG signals. Digital EEG machine (Nihon Kohden-Neurofax: optiplex GXMT5120) was used.

Baseline recording i.e. first recording of EEG was taken after randomization of subjects into two groups. Cetirizine/placebo was administered to the respective group of subjects immediately after the first recording and after two hours, when the drug reaches its maximum plasma concentration, second EEG recording was done. Cetirizine reaches its peak plasma level in 1 hour after drug administration regardless of dose and its plasma half-life varies from 6.5-10 hours.[4] Third EEG recording was done after 7±2 days of second recording i.e. after wash out period of study drug which is maximum of 100 hours and cross-over of subjects (i.e. the initial placebo group became the cetirizine group and initial cetirizine group became the placebo group) after administration of cetirizine and placebo to the subjects of respective groups two hours prior to third EEG recording.

EEG waveforms were reduced and analyzed using "Focus" software (version 1.1). After visual inspection, five artifact-free-5 sec epochs of EEG were selected from just before the end of 1st, 2nd, 3rd, 4th and 5th minute of recordings during eye closed condition in supine position. Thereafter Fast Fourier Transformation (FFT) was performed to segregate EEG waveform into different frequencies bands as similar to the study done by Sannita et al (1996) - slow (0.5-6.5 Hz), extended alpha (6.5-14 Hz) and beta (14.5-32 Hz) bands. The extended alpha (6.5-14 Hz) band was further divided into four sub segments alpha 1 (6.5-8 Hz), alpha 2 (8.5-10 Hz), alpha 3 (10.5-12 Hz) and alpha 4 (12.5-14 Hz).[4] The spectral power for each band thus obtained was exported to Microsoft Excel worksheet files for further analysis. The powers from five epochs were averaged for each subject.

Friedman test was used for overall comparison of EEG parameters among baseline, placebo and cetirizine treated conditions followed by multiple comparisons (baseline vs. placebo; baseline vs. cetirizine; placebo vs. cetirizine) using Wilcoxon's Sign Rank test.

A p value of <0.05 was considered statistically significant. Data were analyzed with statistical software SPSS 11.5.

RESULTS

Changes in EEG activity

On overall comparison by Friedman and multiple comparisons by Wilcoxon's sign Rank test, in cetirizine treated condition; there was significant increase in EEG slow activity at midline central, midline frontal and left central (CZ, PZ and C3 sites respectively) cerebral regions (Table 1) whereas EEG beta activity significantly decreased at left postero-temporal and left occipital cerebral cortex (T5, O1 sites respectively) (Table 2) as compared to baseline. Similarly, EEG alpha2 activity also decreased at right occipital cortical region (O2 site) (Table 3) in comparison to baseline. The changes in relative power of other frequency segment of spectrum- extended alpha (or other sub-segments of extended alpha activity- alpha 1, alpha 3 and alpha 4) were not significant after placebo and cetirizine administration and therefore not shown in tabular form. The changes in power of EEG slow activity, beta activity and alpha 2 activity are shown in Table 1, Table 2 and Table 3 respectively.

Table: 1. Comparison of power of EEG slow (0.5-6.5 Hz) activity (μV^2) among Baseline, Placebo and Cetirizine treated

Electrode sites	Baseline (n=30)	Placebo (n=30)	Cetirizine (n=30)	p	p_1	p_2	p_3
	Median (inter-quartile range)						
Fz	94.36(82.08-129.25)	116.52(97.74-150.72)	107.31(88.2-133.13)	NS	NS	NS	NS
Cz	92.4(79.75-130.40)	110.16(84.43-151.80)	111.09(88.13-149.45)	**0.016**	NS	**0.021**	NS
Pz	83.37(65.17-101)	77.04(70.38-119.3)	88.66(72.55-130.73)	**0.007**	NS	**0.008**	NS
Fp2	94.44(66.14-133.11)	100.95(71.97-126.81)	105.97(72.15-134.52)	NS	NS	NS	NS
F8	60.54(42.64-84.32)	49.23(41.51-92.46)	65.45(52.23-80.67)	NS	NS	NS	NS
F4	81.34(60.81-99.13)	90.12(73.06-112.17)	81.76(66.94-106.69)	NS	NS	NS	NS
C4	63.01(53.12-87.38)	76.8(56.91-101.17)	65.9(55.88-102.74)	NS	NS	NS	NS
T4	22.06(16.89-28.89)	20.54(17.46-30.64)	25.79(20.56-32.58)	NS	NS	NS	NS
T6	38.53(24.23-46.92)	32.25(27.77-51.06)	39.47(29.74-50.52)	NS	NS	NS	NS
P4	68.54(50.95-85.82)	66.14(56.56-102.77)	65.68(52.72-92.39)	NS	NS	NS	NS
O2	59.19(48.15-73.16)	67.12(50.58-90.79)	66.78(49.81-78.97)	NS	NS	NS	NS
Fp1	90.09(71.57-140.79)	111.32(84.8-140.73)	86.97(65.80-126.73)	NS	NS	NS	NS

F7	58.42(47.81-92.18)	61.25(45.45-94.84)	56.6(40.09-77.19)	NS	NS	NS	NS
F3	72.09(57.02-89.71)	80.69(68.47-102.16)	77.43(62.14-100.33)	NS	NS	NS	NS
C3	58.72(49.49-71.14)	62.67(54.61-88.45)	69.39(57.56-91.75)	**0.002**	NS	**0.004**	NS
T3	23.74(20.32-26.35)	24.56(19.63-36.70)	25.26(21.89-30.36)	NS	NS	NS	NS
T5	33.45(26.71-42.53)	34.08(22.91-41.38)	34.93(24.61-46.76)	NS	NS	NS	NS
P3	60.11(46.59-75.58)	64.31(51.17-89.76)	67.01(47.16-81.90)	NS	NS	NS	NS
O1	53.6(42.06-77.25)	66.94(41.29-88.61)	57.25(46.45-85.53)	NS	NS	NS	NS

$p<0.05$, considered statistical significant; NS=no statistical significant difference. p=Overall p value by Friedman's test; p_1= baseline vs. placebo; p_2= baseline vs. cetirizine; p_3= placebo vs. cetirizine

Table: 2. Comparison of power of EEG beta (14.5-32 Hz) activity (μV^2) among Baseline, Placebo and Cetirizine treated

Electrode sites	Baseline (n=30)	Placebo (n=30)	Cetirizine (n=30)	p	p_1	p_2	p_3
	Median (interquartile range)						
Fz	19.78(16.42 - 29.68)	21.85(14.85 - 28.93)	19.88(15.16 - 33.27)	NS	NS	NS	NS
Cz	22.18(16.92 - 30.87)	25(15.46 - 31.4)	24.43(16.18 - 38.41)	NS	NS	NS	NS
Pz	20.26(16.08 - 27.12)	20.6(13.59 - 25.50)	19.26(14.21 - 26.37)	NS	NS	NS	NS
Fp2	15.15(11.59 - 18.31)	13.87(10.45 - 21.36)	13.69(11.11 - 18.14)	NS	NS	NS	NS
F8	9.43(7.37 - 12.78)	9.49(6.99 - 12.77)	8.75(6.99 - 11.03)	NS	NS	NS	NS
F4	18.68(13.5 - 25.21)	18.92(12.27 - 29.54)	16.21(13.06 - 26.07)	NS	NS	NS	NS
C4	15.7(13.56 - 22.62)	18.06(11.76 - 23.28)	16.57(11.6 - 22.47)	NS	NS	NS	NS
T4	6.52(4.65 - 9.53)	5.93(4.72 - 9.17)	5.78(4.49 - 7.33)	NS	NS	NS	NS
T6	11.23(6.97 - 13.69)	9.57(7.63 - 13.70)	9.39(7.28 - 13.25)	NS	NS	NS	NS
P4	16.83(12.63 - 24.00)	17.68(11.31 - 21.93)	15.8(11.19 - 21.14)	NS	NS	NS	NS
O2	19.74(15.49 - 24.54)	18.18(11.75 - 23.20)	18.85(12.65 - 23.11)	NS	NS	NS	NS
Fp1	14.74(10.92 - 19.12)	14.35(11.68 - 19.57)	15.79(12.5 - 19.45)	NS	NS	NS	NS
F7	9.14(6.71 - 11.96)	8.92(6.89 - 13.18)	9.39(6.91 - 14.03)	NS	NS	NS	NS
F3	16.05(12.96 - 21.82)	16.98(12.06 - 22.86)	18.39(13.30 - 24.47)	NS	NS	NS	NS
C3	16.74(10.96 - 18.32)	15.53(10.23 - 21.20)	15.62(11.15 - 20.93)	NS	NS	NS	NS
T3	6.79(4.40 - 8.68)	5.7(4.31 - 7.70)	6.51(4.49 - 7.69)	NS	NS	NS	NS
T5	9.44(6.80 - 13.58)	8.89(5.42 - 11.19)	8.03(6.12 - 11.36)	**0.029**	NS	**0.020**	NS
P3	15.79(10.36 - 18.1)	13.92(10.64 - 16.81)	13.56(11.5 - 19.37)	NS	NS	NS	NS
O1	15.9(10.39 - 22.05)	13.76(9.59 - 21.84)	13.12(9.06 - 19.14)	**0.032**	NS	**0.043**	NS

$p<0.05$, considered statistical significant; NS=no statistical significant difference. p=Overall p value by Friedman's test; p_1= baseline vs. placebo; p_2= baseline vs. cetirizine; p_3= placebo vs. cetirizine

Table: 3. Comparison of power of EEG alpha 2 (8.5-10 Hz) activity (μV^2) among Baseline, Placebo and Cetirizine treated

Electrode sites	Baseline (n=30)	Placebo (n=30)	Cetirizine (n=30)	p	p_1	p_2	p_3
	Median (inter-quartile range)						
Fz	26.3(16.77 - 62.97)	19.39(8.08 - 44.72)	28.1(11.41 - 47.96)	NS	NS	NS	NS
Cz	33.56(17.48 - 73.20)	21.22(7.88 - 47.30)	32.37(13.19 -55.43)	NS	NS	NS	NS
Pz	52.35(16.11 - 109.92)	23.29(8.37 - 66.73)	36.73(11.7 - 68.67)	NS	NS	NS	NS
Fp2	15.13(7.81 - 37.79)	11.64(4.24 - 23.93)	16.37(5.79 - 25.78)	NS	NS	NS	NS
F8	9.22(4.63 - 29.96)	5.87(2.49 - 16.34)	7.4(3.51 - 15.32)	NS	NS	NS	NS
F4	19.78(11.79 - 54.91)	15.58(5.98 - 30.77)	18.75(9.53 - 41.42)	NS	NS	NS	NS
C4	24.4(14.73 - 54.94)	15.11(5.54 - 34.04)	19.45(9.27 - 31.82)	NS	NS	NS	NS
T4	5.64(2.20 - 13.43)	3.52(1.84 - 6.66)	3.89(2.12 - 7.01)	NS	NS	NS	NS
T6	22.92(11.22 - 61.7)	11.2(4.52 - 47.54)	15.83(6.39 - 48.68)	NS	NS	NS	NS
P4	45.43(13.11 - 84.76)	17.44(6.43 - 60.66)	32.81(7.96 - 45.82)	NS	NS	NS	NS
O2	41.34(16.82 - 84.64)	16.74(9.31 - 96.78)	34.04(10.06 -67.26)	**0.046**	**0.045**	**0.041**	NS
Fp1	15.63(7.03 - 35.86)	10.05(4.19 - 26.95)	14.3(6.39 - 27.17)	NS	NS	NS	NS
F7	7.35(4.15 - 22.46)	6.53(2.64 - 16.4)	8.43(3.36 - 15.16)	NS	NS	NS	NS
F3	16.57(10.13 - 41.47)	12.99(6.01 - 33.65)	20.69(8.30 - 28.48)	NS	NS	NS	NS
C3	19.74(10.93 - 40.90)	16.57(6.34 - 28.93)	18.65(7.70 - 30.88)	NS	NS	NS	NS
T3	5.21(2.14 - 10.56)	4.35(1.83 - 10.33)	4.34(2.26 - 9.93)	NS	NS	NS	NS
T5	24.14(7.86 - 47.26)	7.35(4.18 - 48.27)	18.35(5.98 - 37.88)	NS	NS	NS	NS
P3	39.44(8.69 - 70.70)	16.71(6.28 - 54.47)	31.98(6.92 - 60.16)	NS	NS	NS	NS

O1	43.52(18.24 - 99.33)	14.69(8.12 - 155.22)	31.83(10.8 - 69.33)	NS	NS	NS	NS

$p<0.05$, considered statistical significant; NS=no statistical significant difference. p=Overall p value by Friedman's test; p_1= baseline vs. placebo; p_2= baseline vs. cetirizine; p_3= placebo vs. cetirizine

DISCUSSION

Our study showed enhanced power of EEG slow activity at mid-central-parietal and left central cortical regions in cetirizine treated condition as compared to baseline similar to the result of Kaneko et al (2000) who found that H_1 receptor antagonists (cyprohepatadine, diphenhydramine, promethazine and pyrilamine) increased the EEG power spectra of the delta and theta bands in rats.[9] Tokunaga et al (2007) also found that cyproheptadine caused a significant increase in EEG delta activity.[10] Our result was also similar to the result of Vollmer et al (1983) who found that H_1 receptor blocking agent, Ketotifen, one mg twice daily for three weeks increased the relative power of the EEG theta rhythm.[11] Kakiuchi et al (1997) also found that cyproheptadine and ketotifen (30 mg/kg) enhanced EEG power spectra at low frequency bands such as delta and theta in rabbits.[12] Hence our study suggests that CNS effect of cetirizine is similar to that of other H_1 receptor antagonists. Pechadre et al (1988) found that at six hours terfenadine (an antihistamine) increased EEG slow waves.[13] But they did not show any variation in EEG spectral parameters at any time after cetirizine (10 mg) administration. However, in our study we found increase in power of EEG slow activity after two hours of cetirizine (15 mg) administration similar to the result obtained by Pecharde et al with terfenadine. Our finding was similar to result of EEG mapping done by Salute et al (1987) which revealed low potency neuroleptics (chlorprothixene) increased absolute and relative delta and theta power.[14] This finding confirms that cetirizine has also sedative effects like chlorprothixene. In the adult, at the onset of drowsiness the alpha waves were replaced by low voltage slow activity, mainly in the range of 2-7 Hz.[15] In our study, we found increase in slow activity in cetirizine treated that indicates the appearance of drowsiness after cetirizine administration.

We found decrease in power of EEG beta activity at left postero-temporal and left occipital cerebral cortical regions in cetirizine treated condition. This result was similar to the effect of sedative drugs on EEG which showed decrease in power of EEG beta1 activity in range of 13-20 Hz.[15] Rajna et al (1994) found that setastine, a non-sedating antihistaminic drug, increased the beta frequency range in the median areas of both hemispheres.[8] However, cetirizine in our study found the opposite results suggesting that it has sedating effects.

The decrease in power of EEG alpha2 activity at right occipital cortical areas in cetirizine treated condition in our study is similar to the result of Vollmer et al (1983) who found that H_1 receptor blocking agent, Ketotifen, decreased the relative power of EEG fast alpha activity.[11] Sannita et al (1996) found increase in alpha1 activity (6.5-8 Hz) and suggested the existence of some histaminergic (H_1) specificity of the mechanisms modulating vigilance and of a threshold dose of cetirizine for sedative action.[4] However, we did not find any change in power of alpha1 activity in cetirizine treated instead there was decrease in power of alpha2 activity (8.5-10 Hz). The sedative properties of promethazine, first generation antihistamine, were associated with decreased EEG alpha activity.[16] The onset of drowsiness is characterized by alpha dropout in the adults.[15] Therefore, decrease in power of alpha2 activity in our study indicated that cetirizine had the effect of drowsiness.

Increased low-voltage slow-wave activity and decreased alpha activity was reported with many drugs, and these changes are explained as the development of drowsiness.[6] Gilbert et al (1994) found that decreased EEG slow activity (delta and theta wave) in subjects after smoking nicotine-containing cigarettes and the finding was correlated with decreased drowsiness.[7] We found increased slow activity in cetirizine treated subjects which may have relationship with increased drowsiness due to cetirizine administration. Our finding that cetirizine causes sedation is supported by other studies using positron emission tomography (PET) scans. It is thought that blockade of central histamine H_1-receptors is the main cause of sedation by antihistamines. Positron emission tomography scans have reported that chlorpheniramine occupied 76.8 ± 4.2% of the available H_1 receptors in the frontal cortex after a single oral dose of 2 mg, whereas a single dose of 20 mg cetirizine occupied 20% to 50% which may be the potential cause of sedation.[17,18]

In our study we also compared the EEG changes between placebo and cetirizine treated. In such comparisons we did not find any significant differences in EEG activity between placebo and cetirizine treated. However, there was significant difference in EEG activity between baseline and cetirizine treated at many sites. The significant difference in EEG activity between baseline and placebo treated was only at one site which may be due to an expectancy effect of placebo whereby an inert substance which is believed to be a drug. These findings suggest that the psychological expectancy effects of placebo on EEG were somewhere between baseline and cetirizine. This might have caused no overall significant difference in EEG activity between placebo and cetirizine treated condition but significant difference in EEG activity between baseline and cetirizine treated condition. Dykewiczet al (1998) also found that the incidence of sedation associated with cetirizine at the recommended adult dose of 10 mg is less than that seen with first-generation antihistamines but greater than that seen with placebo.[19]

Sedative side-effect of a drug on the CNS is dose related.[3] This might result from a patient's individual sensitivity, disease-induced sedation, or drug dosages that are for various reasons relatively or absolutely larger (patient's weight, poor response, reduced drug clearance, interactions etc.). Low incidence of sedative effects of cetirizine is most likely caused by its diminished potential to cross the blood-brain barrier and also may be partly the result of its greater selectivity for H_1 receptors, compared with its effect at other receptors that may be involved in sedation.[20] Second-generation antihistamines are relatively lipophobic and therefore cross the blood-brain barrier less readily. Their large molecular size and greater affinity for peripheral H_1 receptors also reduce their propensity to cause sedation.[2] Recent studies have shown that the poorer affinity of these newer antihistamines for the P-glycoprotein efflux pump at the blood-brain barrier may also explain their relative lack of central nervous system (CNS) side effects.[21,22]

The plasma concentration of drug could not be measured because of feasibility reason which is the limitation of our study.

CONCLUSION

It is concluded that 15 mg of single dose of cetirizine increases power of EEG slow activity at mid-central-parietal and left central cortical regions whereas it decreases the power of EEG beta activity at left postero-temporal and left occipital cortex along with decrease in alpha2 activity at right occipital cortex. Comparison of sedative effect of cetirizine between healthy subjects and patient on cetirizine can be one of the future directions of this study.

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