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CETRIZINE INDUCED DROWSINESS: ELECTROENCEPHALOGRAPHIC CONCOMITANTS

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ABSTRACT

Background: Cetirizine, 2nd generation antihistamine, has less central adverse effects compared with the first generation but is not completely devoid of sedative effect. Electroencephalography (EEG) is one of the tests to assess sedation**. Aims:** The aim of this study was to find and compare the EEG changes in drowsy and non-drowsy subjects after cetirizine administration. **Methods and Material:** A crossover, placebo-control, double-blind study was conducted on consenting 30 healthy male volunteers. We subjected three (baseline, placebo, cetirizine) 5-min EEG recordings in eye closed condition to fast Fourier transformation and divided EEG frequencies into slow (0.5-6.5 Hz), extended alpha (6.5-14 Hz), alpha1 (6.5-8 Hz), alpha2 (8.5-10 Hz), alpha3 (10.5-12 Hz), alpha4 (12.5-14 Hz) and beta (14.5-32 Hz). **Statistical analysis used:** The statistical analysis was done using Friedman followed by multiple comparisons. **Results:** Nine out of thirty subjects developed symptoms of drowsiness after cetirizine administration. In drowsy subjects EEG beta, extended alpha and its sub-segment alpha 2 and alpha 3 activities significantly decreased in cetirizine treated condition as compared to baseline. In non-drowsy subjects, there was significant increase in EEG slow and alpha1 activity in cetirizine treated condition as compared to baseline. There was significant decrease in EEG alpha3 activity at most of the sites when EEG activities between non-drowsy and drowsy subjects were compared. **Conclusion:** Our study suggested that cetirizine most likely decreases EEG power of alpha2, alpha3 and beta activities (i.e. above 8.5 Hz) in subjects experiencing drowsiness and increases EEG slow and alpha1 activities (i.e. below 8.5 Hz) despite no symptoms of drowsiness. On comparison, EEG alpha3 activity decreased in symptomatic as compared to asymptomatic subjects.

INTRODUCTION

Despite subjective variations in experiencing the drowsiness as an adverse effect of histamine H_1 antagonists can have potential serious implications.[1] Sedative effects of drugs impair the superior cognitive functions which can severely impair daytime activities in which concentration and a high degree of alertness and skill are required. Under laboratory conditions, recommended doses of 2nd generation antihistamines do not produce drowsiness; however sedation at therapeutic doses have been reported.[2] Cetirizine is more sedating than loratadine and terfenadine in some clinical trials.[3,4] Experiments revealed electroencephalogram (EEG) power in alpha and theta-band is highly correlated with drowsiness.[5] The spectral parameters in EEG recordings is useful in assessing the central side-effects of drugs.[6]

Aim of the study: The aim of our study was to find and compare EEG changes in drowsy and non-drowsy subjects after cetirizine administration.

MATERIALS & METHODS

Study design: This was cross-over, placebo-controlled, double blind experimental study.

Study place: The study was conducted for one year in the EEG laboratory of B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal

Ethics approval: Prior ethical clearance was obtained from the institute.

Inclusion criteria: Thirty informed consented right handed healthy male volunteers (mean age 27.7± 2.9 years; BMI 22.65±1.8 kg/m^2) participated in the study.

Exclusion criteria: The persons suffering from or having any history of neurological, hepatic, cardiac, respiratory or renal disorders were not included in the study. Similarly the persons under any medication or abuser of any substance having effect on central nervous system were also excluded from the study. Females were excluded to avoid EEG variation due to hormonal fluctuation during their reproductive cycles.

Sample size: Thirty

Materials

The drug (cetirizine 10 mg) used in the study was selected from the pharmacy which was available under the brand name of *Cetzine.* The tablet of *Cetzine* was crushed and packaged into capsule. The placebo used in the study was glucose which was also packaged identical to the drug capsule. Digital EEG machine (Nihon Kohden-Neurofax: optiplex GXMT5120) with sampling rate 250 was used for acquisition of EEG signals.EEG waveforms were reduced and analyzed using “Focus” software (version 1.1). [7]

Grouping: 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.

Methods

All subjects were instructed to have normal (minimum 6-8 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. After 10 minutes of supine rest, EEG recording for 5 minutes in eye closed condition of all the subjects was performed at room temperature of 26±2ºC between 8-10 am to avoid the effect of temperature and of diurnal variation in EEG. 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 cut-off and high cut-off frequency was maintained at 0.5 Hz and 70Hz respectively.

Baseline recording of all 30 subjects i.e. first recording of EEG was taken after randomization of subjects into two groups- cetirizine and placebo. Cetirizine/placebo was administered to the respective group of subjects immediately after the first recording and then subjects were allowed to relax in laboratory for two hours. The subjects were asked to report drowsiness if they experienced during that period. The second EEG recording was done after two hours of first recording on the same day. After 7±2 days of second recording and cross-over of subjects (i.e. the initial placebo group became the cetirizine group and initial cetirizine group became the placebo group), cetirizine and placebo were given to the subjects accordingly. Again subjects were asked to report drowsiness if they experienced after taking cetirizine/placebo and third EEG recording was done after two hours of cetirizine/placebo administration.

After visual inspection of EEG waves, 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. 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).[8] 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.

Statistical analysis: 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. Data were presented in the form of median (inter-quartile range) and analyzed with statistical software SPSS 11.5. A p value of <0.05 was considered statistically significant.

RESULTS

Among 30 subjects nine experienced drowsiness after cetirizine administration, whereas others twenty one showed no any symptoms of drowsiness.

In symptomatic subjects (who reported drowsiness), the extended EEG alpha activity overall decreased but the reduction was significant only at sites Cz, Pz, F8, C4, P4, P3 and O1 (shown in Table 1).

Table 1: Comparison of power of EEG extended alpha (6.5-14 Hz), alpha2 (8.5-10 Hz) and alpha 3 (12.5-14 Hz) activity among baseline, placebo and cetirizine treated symptomatic subjects (n=9)

Electrode sites	Baseline (n=9) μV^2	Placebo (n=9) μV^2	Cetirizine (n=9) μV^2	p	p_1	p_2
	Extended alpha (6.5-14 Hz) activity					
Cz	126.4(97.72 - 198.96)	129.34(36.02- 150.96)	60.02(32.32 - 82.06)	**0.032**	NS	NS
Pz	190.48(122.52 -202.48)	164.6(41.4 - 241.38)	57.72(31.34- 115.52)	**0.045**	NS	**0.015**
F8	34(22.44 - 53.46)	29.64(10.74 - 56.1)	16.04(8.86 - 21.22)	**0.045**	NS	NS
C4	114.56(91.42 - 135.18)	96.32(21.04 - 121.62)	44.06(21.66 - 54.4)	**0.032**	NS	**0.021**
P4	177.6(114.84 - 191.72)	116.62(28.84- 191.16)	54.58(24.54 - 99.16)	**0.045**	NS	**0.021**
P3	115.24(92.52 - 135.08)	103.46(23.18- 150.18)	48.86(17.92- 101.64)	**0.045**	NS	**0.028**
O1	128.02(79.4 - 199.62)	115.64(24.86- 234.72)	38.88(21.36- 105.26)	**0.045**	NS	NS
	alpha2 (8.5-10 Hz) activity					
Pz	67.76(21.84 - 105.62)	25.9(12.24 - 76.1)	11.24(11 - 51.22)	**0.045**	NS	**0.028**
C4	29.48(16.34 - 66.18)	19.2(9.52 - 29.14)	8.8(7.32 - 21.72)	**0.045**	NS	**0.021**
O2	51.38(25.08 - 80.26)	30.52(10.06 - 59.36)	11.98(5.24 - 49.62)	**0.045**	NS	NS
T5	18.32(11.74 - 26.98)	27.2(5.02 - 33.66)	6.76(3.14 - 20.16)	**0.045**	NS	NS
	alpha 3 (12.5-14 Hz) activity					
Fp2	3.68(3.08 - 6.72)	5.1(3.38 - 9.74)	2.5(1.96 - 3.58)	**0.032**	NS	NS
F4	4.58(3.7 - 7.74)	10.22(3.28 - 15.94)	3.54(2.8 - 5.86)	**0.018**	NS	NS
Fp1	3.9(2.84 - 7.38)	5.04(2.06 - 13.76)	3.3(1.98 - 4.46)	**0.016**	NS	**0.028**
O1	13.34(2.82 - 34.54)	11.08(3.94 - 40.38)	4.56(4.04 - 9.1)	**0.045**	NS	**0.021**

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. Fp1-Left prefrontal,Fp2-Right prefrontal, F4-Right frontal, F8-Right anterior temporal, T5-Left posterior temporal, C4-Right central,P3-Left parietal,P4-Right parietal,O1-Left occipital,O2-Right occipital,Cz-Midline central, Pz- midline parietal.

On multiple comparisons, we found significant decline in extended alpha activity in cetirizine treated compared to baseline at some sites in those subjects. EEG alpha 2 activity also found to be overall decreased after cetirizine intake however the significant reduction was only at sites Pz, C4, O2 and T5 (Table 1). Similar changes were found in alpha 3 activity in drowsy subjects which were significant at sites Fp2, F4, Fp1 and O1. EEG beta activities followed the same pattern with significant change at sites Pz, F4 and O1 (shown in Table 2).

However there was no significant difference in power spectra of EEG slow, alpha 1 and alpha 4 activities at any sites in drowsy subjects among baseline, placebo and cetirizine. In asymptomatic subjects (who did not report any sign of drowsiness after cetirizine administration), there was significant increase in EEG slow and alpha1 activities in cetirizine treated condition as compared to baseline (Table 3). There was no any significant difference in EEG activity when baseline and placebo was compared.

On comparison of EEG activities between symptomatic and asymptomatic subjects, there was no significant change in power of EEG slow, extended alpha, alpha 1, alpha 2 and beta activities except alpha 3 which significantly decreased in symptomatic subjects at all the recordings sites excluding C4, T6 and F7 (Table 4).

Table 2: Comparison of power of EEG beta (14.5-32) activity among baseline, placebo and cetirizine conditions of cetirizine treated symptomatic subjects(n=9)

Electrode sites	Baseline (n=9) μV^2	Placebo (n=9) μV^2	Cetirizine(n=9) μV^2	p	p_1	p_2
Pz	20.44(12.64 - 31.02)	21.24(15.44 - 29.14)	18.44(12.52 - 23.34)	**0.032**	NS	NS
F4	19.34(15.92 - 23.76)	24.94(14.3 - 31.58)	18.52(13.74 - 21.02)	**0.045**	NS	NS
O1	15.56(9.72 - 29.78)	15.9(10.82 - 16.96)	9.74(5.92 - 12.04)	**0.018**	NS	**0.028**

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. Pz- midline parietal, F4-Right frontal,O1-Left occipital.

Table 3: Comparison of power of EEG slow (0.5-6.5 Hz) activity among baseline, placebo and cetirizine conditions of cetirizine treated asymptomatic subjects (n=21)

Electrode sites	Baseline (n=21) μV^2	Placebo (n=21) μV^2	Cetirizine (n=21) μV^2	p	p_1	p_2
Slow (0.5-6.5 Hz) activity						
Cz	89.94(79.66 - 128.74)	95.18(80.18 - 129.22)	110.58(87.24- 145.5)	**0.009**	NS	**0.008**
Pz	82.2(64.38 - 98.1)	74.84(63.42 - 94.26)	87.88(71.82 - 110.3)	**0.001**	NS	**0.004**
T6	33.5(22.34 - 47.34)	31.62(27.64 - 51.96)	36.06(28.96 - 51.42)	**0.010**	NS	**0.007**
C3	58.68(48.86 - 70.44)	59.1(50.88 - 85)	63.9(53.52 - 90.48)	**0.013**	NS	**0.009**
	Alpha 1 (6.5-8 Hz) activity					
F3	6.8(5.52-10.64)	6.24(5.34-13.28)	9.26(7.7-11.7)	**0.012**	NS	**0.006**
C3	6.9(5.42-8.84)	6.64(4.78-13.44)	9.16(7-11.7)	**0.016**	NS	**0.003**

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. Cz-Midline central, Pz- midline parietal, T6-Right posterior temporal, C3-Left central, F3-Left frontal.

Table 4: Comparison of power of EEG alpha 3 (10.5-12 Hz) activity between symptomatic and asymptomatic subjects in cetirizine treated condition

Electrode sites	Asymptomatic subjects (n=21) μV^2	Symptomatic subjects (n=9) μV^2	p
Fz	10.92(6.8 - 17)	4(3.84 - 7.08)	0.015
Cz	13.46(7.96- 21.2)	4.96(4.58 - 7.28)	0.005
Pz	13.76(9.98- 29.9)	7.34(5.54 - 13.4)	0.032
Fp2	5.56(3.16 - 8.52)	2.5(1.96 - 3.58)	0.003
F8	3.78(1.94 - 5.96)	1.58(1.1 - 2.28)	0.012
F4	8.42(4.16- 12.84)	3.54(2.8 - 5.86)	0.009
C4	10.02(7.08- 15.1)	3.88(3.1 - 6.7)	NS
T4	2.24(1.38 - 4.28)	1.2(0.8 - 1.42)	0.009
T6	9.4(4.68 - 18.84)	3.44(2.94 - 8.44)	NS
P4	12.62(8.6- 26.82)	7.8(3.9 - 9.7)	0.044
O2	18.24(8.04- 35.3)	5.66(3.62- 14.54)	0.028
Fp1	5.28(3.56 - 7.78)	3.3(1.98 - 4.46)	0.022
F7	2.64(1.94 - 4.4)	1.74(1.6 - 2.04)	NS
F3	6.6(4.68 - 11.78)	3.5(2.5 - 4.3)	0.011
C3	8.8(6.44 - 13.52)	3.66(2.84 - 4.88)	0.003
T3	2.52(1.4 - 3.68)	1.16(0.98 - 1.8)	0.014
T5	7.02(3.4 - 19.9)	2.92(2.32 - 4.76)	0.039
P3	10.12(7.58- 24.5)	4.48(3.26 - 8.92)	0.014
O1	19.26(5.98- 31.6)	4.56(4.04 - 9.1)	0.012

p<0.05, considered statistical significant; NS=no statistical significant difference. Fp1-Left prefrontal, Fp2-Right prefrontal, F3-Left frontal, F4-Right frontal, F7-Left anterior temporal, F8-Right anterior temporal, T3-Left mid temporal,T4-Right mid temporal,T5-Left posterior temporal, T6-Right posterior temporal,C3-Left central,C4-Right central,P3-Left parietal,P4-Right parietal,O1-Left occipital,O2-Right occipital, Fz-Midline frontal,Cz-Midline central, Pz- midline parietal.

DISCUSSION

In our study, one third of subjects (nine out of thirty) developed symptoms of drowsiness after cetirizine administration which contradicts the report that second generation antihistamines have equivalent therapeutic effect as classical antihistamines without their undesired side effects.[9]

In symptomatic subjects, the EEG extended alpha and beta activities significantly decreased in cetirizine treated condition as compared to baseline. Among the extended alpha activities, the alpha 2 and alpha 3 activities were found significantly reduced. The decrease in power of EEG extended alpha activity in our study supported the findings of previous study that revealed decline in power of EEG

alpha activity in the range of 8-13 Hz with neuroleptics (sedative/non-sedative), anxiolytics and hypnotics.[10] The antihistamine with sedative properties like Ketotifen, promethazine were associated with decreased EEG alpha activity.[11,12] Thus, decrease in power of extended alpha, alpha 2 and alpha 3 activity in symptomatic subjects in our study might be suggestive of sedative properties of cetirizine. We also found reduced power of EEG beta activity in symptomatic subjects after cetirizine administration which supported the previous result that revealed sedative drugs decrease the power of beta 1 in the range of 13-20 Hz. [10]

In asymptomatic subjects, there was significant increase in power of EEG slow and alpha 1 activities in cetirizine treated condition as compared to baseline. Sedative and hypnotic drugs strongly increases EEG delta/theta ratio.[10] Sedation has been described as either an annoying subjective sensation of drowsiness or an actual objective impairment of cognitive function and psychomotor performance and even both.[13-15] Increased low-voltage slow-wave activity and decreased alpha activity was reported with many sedative drugs, and these changes are explained as the development of drowsiness.[16] Gilbert et al found reduced power of EEG slow activity (delta and theta wave) in subjects after smoking nicotine-containing cigarettes which was correlated with decreased drowsiness. [17] Thus, increase in power of EEG slow activity in our study can be correlated with the sedative effects of cetirizine despite of no symptoms of drowsiness reported by the subjects. The reasons for impediments of symptoms despite of positive changes in electrical activities of central neurons need further exploration. However, higher threshold for experiencing the drowsiness in these asymptomatic subjects cannot be ruled out. Our finding of rise in power of EEG alpha 1 activity in asymptomatic subjects was supported by the result of Sannita et al who found notably increase in power of EEG extended alpha (6.5-14 Hz) and its sub segment alpha 1 (6.5-8 Hz) after administration of cetirizine 20 mg to the subjects. [8]

When EEG power of frequency bands between symptomatic and asymptomatic subjects were compared, there was significant decrease in EEG alpha 3 activities in symptomatic subjects at most of the sites like mid-central (Fz, Cz, &Pz,), left central (C3), prefrontal (Fp1 & Fp2), frontal (F3 & F4), anterior temporal (F8), middle temporal (T3 & T4), posterior temporal (T5), parietal (P3 & P4) and occipital (O1 and O2). The reduction in power of alpha 3 activities in symptomatic subjects can be correlated with the degree of drowsiness experienced by the subjects. However, some subjects are particularly susceptible to the CNS effects of antihistamine, whereas others appear to be more resistant.[1] Therefore, the threshold for subjective feeling of drowsiness might show individual variation.

Sedative side-effect of a drug is dose dependent.[18] 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.[19] The large molecular size and relatively lipophobic nature reduce the potential of second generation antihistamines to cross the blood-brain barrier readily. In addition their greater affinity for peripheral H_1 receptor also reduce their propensity to cause sedation.[20] 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 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 of placebo.[23] Nevertheless development of drowsiness in one third of subjects with 10 mg cetirizine in our study appears to be substantial, especially while prescribing cetirizine.

CONCLUSION

Our study suggests that EEG power of extended alpha, alpha 2, alpha 3 and beta activities (i.e. above 8.5 Hz) reduces in subjects who experience drowsiness after cetirizine administration. Cetirizine in therapeutic dose also increases EEG slow and alpha 1 activities (i.e. below 8.5 Hz) despite lack of feeling of drowsiness. Hence our study concluded that there is change in EEG activity of subjects after cetirizine intake irrespective of presence or absence of symptoms of drowsiness. On comparison between symptomatic and asymptomatic subjects, only EEG alpha3 activity significantly declined in symptomatic subjects and this finding can be correlated with degree of drowsiness regardless of subjective threshold. Hence a physician/pharmacist must consider the sedative effect of cetirizine and counsel patients before delivery of this drug.

Limitations of the study: The limitation of this study was that the plasma concentration of drug at the time of EEG recording could not be measured because of feasibility reason. Comparison of sedative effect of cetirizine between healthy subjects and patient on cetirizine can be one of the future directions of study.

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REFERENCES

1. Rihoux JP, Donnelly F. CNS effects of histamine H_1 antagonists. Clin Exp Allergy. 1999; 29(3):143–146.
2. Mattila MJ, Paakkari I. Variations among non-sedating antihistamines: are there real differences? Eur J Clin Pharmacol. 1999; 55(2):85-93.
3. Katzung BG (ed).Basic & Clinical Pharmacology. 11th ed**.** USA: The McGraw-Hill Companies 2004. p. 276.
4. Spencer CM, Faulds D, Peters DH. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs. 1993; 46(6):1055-80.
5. Pal NR, Chuang CY, Ko LW, Chao CF, Jung TP, Liang SF, et al. EEG-based subject- and session-independent drowsiness detection: an unsupervised approach. EURASIP Journal on Advances in Signal Processing. New York: Hindawi Publishing Corporation 2008; id:519480.

6. Rajna P, Veres J. Assessing the sedative (adverse) effects of antiallergic drugs by quantitative electroencephalography: effects of setastine a non-sedating antihistaminic drug. Ther Hung.1994; 42(1):14-20.
7. Ghimire N, Paudel BH, Khadka R, Singh PN, Das A. Electroencephalographic changes during selective attention. Asian J Med Sci. 2015; 6(2):52-67.
8. Sannita WG, Crimi E, Riela S, Rosadini G, Brusasco V. Cutaneous antihistaminic action of cetirizine and dose-related EEG concomitants of sedation in man. Eur J Pharmacol. 1996; 300(1-2):33-41.
9. Woodward JK. Pharmacology of antihistamines. J Allergy Clin Immunol. 1990; 86(4 Pt 2):606-12.
10. Niedermeyer E, Silva FH. EEG and Neuropharmacology, In: Electroencephalography: basic principles, clinical applications, and related fields. 5th ed. Pennsylvania: Lippincott Williams & Wilkins publisher.2004; p.695-697.
11. Vollmer R, Matejcek M, Greenwood C, Grisold W, Jellinger K. Correlation between EEG Changes Indicative of Sedation and Subjective Responses. Neuropsychobiol. 1983; 10:249-253.
12. Itil TM (ed.). Psychotropic Drugs and the Human EEG. Switzerland:Karger; I974. p.377.
13. Gengo FD. Antihistamine selection: Use vs. Side effects. J S Pharmacist. 1990; 92:59–68.
14. Falliers CJ, Brandon ML, Buchman E, Connell JT, Dockhorn R, Leese PT, et al.

Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. Ann Allergy. 1991; 66:257–62.

15. Meltzer E, Welch MJ. Adverse effects of H_1-receptor antagonists in the central nervous system. In: F. E. R. Simons. (ed.) Histamine and H_1-receptor antagonists in allergic disease. New York: Marcel Dekker Inc. 1996; 357–81.
16. FII~'K M. EEG and Human Psychopharmacology. Annu. Rev. Pharmacol. 1969; 9:241-258.
17. Gilbert DG, Meliska CJ, Welser R, Estes SL. Depression, personality, and gender influence EEG, cortisol, beta-endorphin, heart rate, and subjective responses to smoking multiple cigarettes.Personality and individual differences. 1994; 16(2):247-264.
18. Timmerman M. Why are non-sedating antihistamines non-sedating?Clin Exp Allergy.1999; 29(3):13–18.
19. Snowman AM, Snyder SH. Cetirizine: actions on neurotransmitter receptors. J Allergy Clin Immunol. 1990; 86(6 Pt 2):1025-8.
20. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. Clin Exp Allergy. 1999; 29(3):133–142.
21. Chishty M, Reichel A, Siva J, Abbott NJ, Begley DJ. Affinity for the P-glycoprotein efflux pump at the blood-brain barrier may explain the lack of CNS side-effects of modern antihistamines. J Drug Target. 2001; 9:223–228.
22. Chen C, Hanson E, Watson JW, Lee JS. P-glycoprotein limits the brain penetration of nonsedating but not sedating H_1-antagonists. Drug MetabDispos. 2003; 31:312–318.
23. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol. 1998; 81:478.