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THE EFFECTS OF CETIRIZINE ON PSYCHOMOTOR PERFORMANCE IN HEALTHY VOLUNTEERS

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SUMMARY

In this study, the effects of cetirizine, a second generation H_1-receptor antagonist, on psychomotor functions were assessed by using subjective and objective psychometric tests and the results were compared to those obtained with placebo and the positive control pheniramine. 10 healthy volunteers orally received placebo, cetirizine (10 mg) and pheniramine (25 mg) in single doses according to a double blind, Latin square design. Subjective effects and performance were evaluated by means of visual analog scales, digit symbol substitution test, number connection test, letter cancellation test, Stroop test and pursuit rotor test. According to the results, the subjects felt themselves more lethargic and muzzy after placebo and pheniramine whereas cetirizine caused excitement. Objective tests revealed that compared to baseline cetirizine significantly impaired performance in Stroop test-2 and the pursuit rotor test, whereas pheniramine led to decrements in all objective tests. When the impairments in psychomotor performance observed after cetirizine were compared to placebo no distinction could be made between cetirizine and placebo. In summary, we concluded that cetirizine, a second generation antihistaminic agent, has no demonstrable effect on psychomotor performance at recommended therapeutic dose in young subjects.

ÖZET

Çalışmamızda 2.kuşak bir antihistaminik olan setirizinin psikomotor fonksiyonlar üzerine olan etkileri subjektif ve objektif psikometrik testlerle araştırılmış, sonuçlar plasebo ve feniraminin oluşturduğu etkiler ile karşılaştırılmıştır. Bu amaçla 10 sağlıklı gönüllüye çift-kör ve Latin karesi düzenine göre plasebo, setirizin (10 mg) ve feniramin (25 mg) ağız yolundan ve tek doz halinde uygulanmış, uygulamayı izleyen 0.5, 1, 2, 4 ve 6. saatlerde vizüel analog skalalar ile subjektif etkiler; sayı-sembol testi, sayı birleştirme testi, harf iptal testi, Stroop testi ve pursuit rotor testi ile psikomotor performans değerlendirilmiştir. Çalışmadan elde edilen sonuçlara göre plasebo ve feniramin uygulamasını takip eden saatlerde denekler kendilerini daha yorgun ve

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J. Fac. Pharm. Istanbul
38(1) (2005-2006)

dalgın, setirizin uygulanmasından sonra ise heyecanlı hissetmişlerdir. Objektif testler değerlendirildiğinde, setirizinin sadece Stroop test-2 ve pursuit rotor testlerinde bazal değerlere kıyasla anlamlı bir performans düşüşüne yol açtığı, feniraminin tüm objektif testlerde performans azalması yaptığı görülmüştür. Setirizin ve feniraminin bu etkileri plasebo ile kıyaslandığında, feniraminin Stroop testi 1-3 ile pursuit rotor testiyle ölçülen performansı plaseboya göre istatistiki bakımdan anlamlı bir şekilde düşürdüğü görülmüş, setirizin ile plasebo arasında bir fark saptanmamıştır. Bu sonuçlar, setirizinin genç deneklerde önerilen tedavi dozlarında psikomotor fonksiyonları belirgin bir şekilde etkilemediğini göstermektedir.

Keywords: Cetirizine, antihistaminics, psychomotor performance, pheniramin

INTRODUCTION

Cetirizine is a long-acting, selective H_1- receptor antagonist and it has been used in therapy since 1987 (1). Cetirizine is a metabolite of hydroxyzine, a classical antihistaminic agent. It is well known that classical antihistaminics e.g., chlorpheniramine, diphenhydramine, inhibit H_1-receptors in the brain and cause sedation (2). It is claimed that the second generation antihistaminic agents do not penetrate the central nervous system, therefore they do not have central side effects such as sedation and antimuscarinic effects. Nevertheless, it is asserted that cetirizine may penetrate the brain and cause advers effects (3-6). Controversial results were also reported for other new generation antihistaminic agents (7). The aim of this study was to investigate the effects of a single oral dose of cetirizine (10 mg) on psychomotor functions in healthy young volunteers. Additionally, the results were compared to those obtained with placebo and a classical antihistaminic drug pheniramine, the positive control.

RESULTS AND DISCUSSION

According to the results obtained, the subjects felt themselves more lethargic and muzzy after placebo and pheniramine, whereas cetirizine caused excitement. Objective tests revealed that compared to baseline cetirizine significantly impaired performance in Stroop test-2 and the pursuit rotor test, whereas pheniremine led to decrements in all objective tests. Placebo also produced impairment in Stroop tests 1-2-3 and pursuit rotor tests when compared with baseline results. When the impairments in psychomotor performance observed after cetirizine and pheniramine were compared to placebo, pheniramine was found to be significantly different from placebo in the Stroop tests 1 and 3 and the pursuit rotor test, whereas no distinction could be made between cetirizine and placebo (Table 1 and Table 2).

Table 1. Effects of cetirizine on performance

Task	Unit	Baseline (mean±SD)	Maximal Change* (mean±SD)	P value#
VAS/ Excited-Calm	mm	79.8±16.6	72.3±21.0	NS
VAS/ Energetic-Lethargic	mm	35.3±20.7	43.2±17.8	NS
VAS/ Muzzy-Clearheaded	mm	64.9±21.5	68.2±20.9	NS
VAS/ Relaxed-Tense	mm	31.0±22.6	28.0±25.2	NS
DSST	sec	76.5±10.4	78.4±10.3	NS
Trail Making Test	sec	12.9±3.3	13.9±3.1	NS
Letter Canc. Test	No. of letters	633.1±39.2	637.5±25.7	NS
Stroop Test-1	sec	20.5±1.8	20.9±1.9	NS
Stroop Test-2	sec	22.4±2.0	23.5±3.0	NS
Stroop Test-3	sec	34.2±4.2	34.9±4.0	NS
Pursuit Rotor Test	sec	27.0±1.1	27.1±1.1	NS

VAS: vusual analog scale
* Maximal change within 6 hr of experiment
# When compared to placebo

Table 2. Effects of pheniramine on performance

Task	Unit	Baseline (mean±SD)	Maximal Change* (mean±SD)	P value#
VAS/ Excited-Calm	mm	73.7±19.3	78.4±15.5	NS
VAS/ Energetic-Lethargic	mm	29.6±19.3	48.9±19.5	NS
VAS/ Muzzy-Clearheaded	mm	72.8±16.7	53.0±18.4	P<0.05
VAS/ Relaxed-Tense	mm	21.7±19.7	26.8±24.9	NS
DSST	sec	76.1±8.5	79.5±7.7	NS
Trail Making Test	sec	12.3±2.5	14.6±3.1	NS
Letter Canc. Test	No. of letters	636.2±36.3	634.8±21.5	NS
Stroop Test-1	sec	20.2±1.8	21.8±2.6	P<0.05
Stroop Test-2	sec	21.8±1.9	23.8±3.4	NS
Stroop Test-3	sec	33.2±4.2	36.4±3.5	P<0.01
Pursuit Rotor Test	sec	26.4±1.7	24.9±2.1	P<0.01

VAS: vusual analog scale
* Maximal change within 6 hr of experiment
# When compared to placebo

In accordance to the majority of studies found in the literature (5,8,9), these results, indicate that cetirizine has no marked effect on subjective and objective measures of central nervous system function at recommended therapeutic doses in healthy volunteers.

J. Fac. Pharm. Istanbul
38(1) (2005-2006)

EXPERIMENTAL

Subjects: 4 Male and 6 female subjets between 22-33 years of age were included in the study. None had used any sedatives or other drugs or alcohol for one week preceding the experiments. All were in good mental and physical health at medical examination. Each subject was thoroughly familiarized with the experimental procedure in a training session the day before the experiments and all of them gave oral consent to the study. Before commencing the experiment, the study was approved by the related local Ethic Committee located in University of Istanbul, Cerrahpasa Medical Faculty. The subjects were required to fast overnight. The first series of psychometric tests were given at 8 a.m., the results of which served as baseline. At 8:30 a.m. the subjects took a tablet of cetirizine (10 mg), pheniramine (25 mg) or placebo (lactose) in a double blind manner. Cetirizine and pheniramine tablets were purchased from the market. Tests were repeated 0.5, 1, 2, 4 and 6 hours after administration of drugs or placebo. A breakfast consisting of toast and orange juice were offered 1 hour after drug intake. Sandwiches and caffeine-free beverages were offered for lunch.

Subjective Test: For the subjective assessment of drug influence on mood, four 10 cm analog scales, visual analog scales (VAS) (10) were employed. Their labels were energetic-lethargic, muzzy-clearheaded, calm-excited and relaxed-tense. Scores were measured in millimeters from the beginning of the line to the point the subject marked according to his/her momentary mood.

Objective Tests: The objective psychometric tests used were a digit symbol substitution test (DSST), a letter-cancellation test, trail making test, Stroop test and pursuit rotor test. DSST is designed to evaluate recognition and recoding of visual information. To minimize learning effects 8 equivalent versions were applied, one of them being part of Wechsler Adult Intelligence Scale (11). The different versions had been constructed by rear-ranging the symbol-number relationship according to random numbers. The subjects were instructed to complete the test as quickly and as accurately as possible. The time needed to substitute 75 symbols was recorded. The letter cancellation test (10,12,13) consisted of 14 lines with 658 letters (d and p) marked with one, two or three dots above or below the letter. To complete each line 15 seconds were allowed. The measure of performance consisted of the number of letters correctly marked with a total period of 210 seconds. The trail making test consisted of 25 circles distributed over a DIN A4 sheet of paper. The circles contained numbers from 1 to 25. The subjects were instructed to connect the circles with a pencil in numerical order from 1 to 25 as quickly as possible. The start was pointed out and the time measured in seconds with stopwatch. Stroop test consisted of three sections (14). In Stroop test-1, volunteers had to read the name of the colors (yellow, red, blue, green). In Stroop test-2, subjects read the color lines. Finally in Stroop test-3, subjects had to read the colors which were given wrong names e.g., 'yellow' was written blue. The subjects should read as 'blue'.

The time was determined in seconds with stopwatch. Pursuit rotor test is used for determining motor function impairment (15,16). The subjects were instructed to follow a 1cm spot light that rotates 33 times per minute by using a photosensitive pen. The subjects should pursue the light in 30 second of period and pursuing time was determined by means of recorder in second.

Statistical Analysis: For data analysis, nonparametrical tests were used (17). Changes from baseline values were analyzed by Wilcoxon matched pairs signed rank test. Comparison between groups were made with Kruskal Wallis and Mann-Whitney-U tests.

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J. Fac. Pharm. Istanbul
38(1) (2005-2006)

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