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The H_1-Receptor Antagonist *dextro*-Chlorpheniramine Impairs Selective Auditory Attention in the Absence of Subjective Awareness of This Impairment

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Although previous studies have shown that the human attention system is partially affected by chlorpheniramine, the effects of chlorpheniramine on human auditory selective attention have not yet been explored. This study examines the effects of a single dose of 4 mg of *dextro*-chlorpheniramine on human auditory selective attention by means of the evaluation of the event-related brain potential (ERP) processing negativity (PN). The study sample consisted of 20 healthy male humans, who received either a single 4-mg dose of *dextro*-chlorpheniramine or a placebo in a double-blind design. The subjects were given a dichotic listening task, in which they were instructed to press a response button upon detecting deviant tones (target) while their ERPs were recorded. In parallel, subjective tests evaluated the daytime sleepiness, overall vigor, and affect of the subjects. Results showed that the auditory selective attention is impaired under the effects of chlorpheniramine, as reflected by an attenuation of PN amplitude and by a decrease of performance in the group of subjects who took a single 4-mg dose of *dextro*-chlorpheniramine. No subjective change in the daytime sleepiness, overall vigor, or affect of the subjects was observed. This lack of conscious awareness of the side effects may lead to situations of risk in tasks for which auditory information is important, because no subjective indicators of attention impairment are available to the subjects.

CHLORPHENIRAMINE IS ONE of the antihistamines currently used to treat symptoms of allergies and colds.[1] In addition to its expected therapeutic effects, it has been reported to cause side effects in the central nervous system, including daytime sleepiness, as indicated by both subjective[2–7] and objective[6,8] measurements; however, in some studies, subjective tests have shown no effects.[8–10] It has also been reported that chlorpheniramine impairs human performance,[2,11] although some studies failed to support these findings.[3,10] Finally, it has been shown that chlorpheniramine affects the auditory attentional system, increasing the latency of the auditory P300,[5,7] an event-related brain potential (ERP) regarded as a sign of stimulus processing within working memory,[12] and decreasing mismatch negativity amplitude,[13] an ERP related to a preattentive sensory mechanism automatically detecting changes in the acoustic environment.[14]

Although the appropriate functioning of auditory selective attention is essential in daily human activity,[15] knowledge concerning the effects of chlorpheniramine on human auditory attention is presently limited. This knowledge would be very useful for the prescription of medicines containing such antihistaminic substances and could be used to reduce the risk of accidents in people under its effects in potentially dangerous situations (e.g., driving).

This study explored the effects of a single dose of 4 mg of *dextro*-chlorpheniramine (*d*-chlorpheniramine) on human auditory selective attention by means of processing negativity (PN), an ERP that reflects the voluntary selection mechanism of attended information from the total information received[16] and that has been used to evaluate the effects of psychopharmacologic manipulations on selective attention.[17,18] In parallel to the ERP recording, the subjective effects of chlorpheniramine were also evaluated.

Methods

Subjects and procedure

Twenty healthy paid male subjects (mean age, 21.1 ± 1.7 years) took part in the study. Half the subjects

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received a capsule containing 4 mg of *d*-chlorpheniramine, and the other half received a capsule containing a placebo, in a double-blind design. The experimental procedure was approved by the ethical committee of the Spanish Ministry of Health, and subjects gave informed consent to their participation. The session started at 10:00 a.m. with the drug ingestion, and the ERP recording began 150 min later, when the plasma level of the *d*-chlorpheniramine reached its peak.[19] In addition, every 2 hours, the subjects subjectively evaluated their sleepiness with the Stanford Sleepiness Scale (SSS)[20] and their overall vigor and affect with visual analog scales (VAS).

Pure tones of 60 msec duration were presented monoaurally at an intensity of 85 dB through headphones to either the subjects' right or left ear, in random order, at a stimulus-onset asynchrony (SOA) ranging randomly from 580 to 680 msec. Four blocks of 500 stimuli, containing 90% standard (1,000 Hz) and 10% deviant (1,100 Hz) tones, were used. Subjects were instructed to listen selectively to the tones in one ear (attended) and to press a response button each time they heard a deviant tone (target), ignoring all contralateral tones. The ERPs were recorded from F3, Fz, F4, C3, Cz, and C4 electrodes. Electroencephalogram epochs (not exceeding ± 75 μV) of 390 msec, including 40 msec of baseline period, were averaged per stimulus class.

Data reduction and analysis

The exogenous ERP components to the unattended standard stimulus were identified according to the following latency windows: P1 at 30 to 65 msec, N1 at 70 to 130 msec, and P2 at 120 to 200 msec. The PN was assessed in the negative difference (Nd)[21] wave, which was obtained separately for the right and left ears by subtracting the ERP to the standard tones in the unattended ear from the ERP to the standard tones in the attended ear. The Nd was analyzed as the mean amplitude in the 50- to 200-msec interval (early PN) and in the 200- to 350-msec interval (late PN). Because of excessive eye movements, one subject from the control group was excluded from the analysis for both attention conditions; two additional control subjects were excluded for attention to the right ear condition.

Analyses of variance (ANOVAs) for repeated measures, with treatment (control vs. chlorpheniramine), ear stimulated (left vs. right), and electrode position (frontal vs. central) as factors, were applied to P1, N1, and P2 amplitudes and latencies and to Nd amplitude at the defined intervals.

For target stimuli, a correct button press within the SOA interval was regarded as a hit. An incorrect button press during this period was classified as an error, and a trial with no response was classified as a miss. Analysis of performance, SSS, and VAS was made through ANOVA of repeated measures.

Results

ERPs

The unattended standard stimuli elicited, in the chlorpheniramine and control groups, respectively, a P1 peak amplitude (μV) and latency (msec) at Fz (mean [SE]) of 0.4 (0.2), 37 (3.2), and 0.2 (0.1), 44 (5.1); an N1 peak at Fz of −2.0 (1.3), 104 (6.6), and −2.3 (1.4), 117 (9.0); and a P2 peak at Cz of 1.9 (1.3), 182 (19.4), and 1.1 (1.5), 191 (17.4). Analysis of N1, P1, and P2 amplitude and latencies did not show differences between control and chlorpheniramine groups, except for the N1 peak latency, which showed that the chlorpheniramine group had shorter latency than the control group ($F[15,1] = 11.80$, $p = 0.004$). Analysis of interactions showed no differences for P1 and P2 peaks. For N1 peak amplitude, electrode position × treatment was significant ($F[15,1] = 7.64$, $p = 0.01$).

In the PN analysis (Fig. 1), the mean average amplitude of the Nd wave at Cz in the chlorpheniramine and

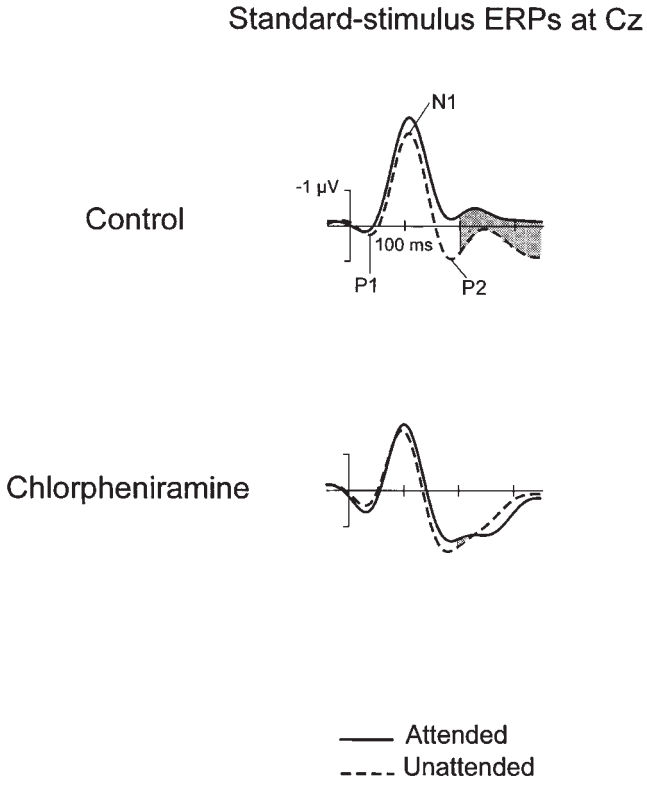

FIG. 1. ERPs for the attended and unattended standard stimuli in the control and chlorpheniramine groups at the Cz electrode. Note that PN in the chlorpheniramine group was significantly smaller than in the control group.

control groups, respectively, was −0.1 μV (±0.1 μV) and −0.4 μV (±0.2 μV) in the 50- to 200-msec interval, and it was −0.5 μV (±0.2 μV) and 0.1 μV (±0.2 μV) in the 200- to 300-msec interval. The analysis of the Nd mean amplitude showed no differences for treatment factor at 50 to 200 msec. However, Nd mean amplitude at 200 to 350 msec was smaller in the chlorpheniramine group than in the control group ($F[15,1] = 4.58$, $p = 0.04$). Interaction analysis was significant only for electrode position × treatment interaction at the late interval ($F[15,1] = 3.82$, $p = 0.03$).

Performance and subjective side effects

Subjects in the chlorpheniramine group made significantly fewer hits than those in the control group (56% and 64%, respectively) ($F[15,1] = 4.89$, $p = 0.03$) and more errors (39% and 32%) ($F[15,1] = 4.75$, $p = 0.03$). They had a mean longer reaction time (0.429 and 0.402 seconds) ($F[15,1] = 5.76$, $p = 0.02$), and there were no differences in the misses (5% and 4%). Finally, the scores on the SSS and VAS scales of the control group subjects were not statistically different from those of the chlorpheniramine group subjects.

Discussion

Chlorpheniramine effects on auditory selective attention showed that subjects who took *d*-chlorpheniramine had a small but significant reduction in the late phase of PN amplitude. In accordance with previous studies,[16] the PN amplitude reduction suggests that under the effects of chlorpheniramine there are difficulties in generating and maintaining the attentional trace of the characteristics of the relevant stimuli. These difficulties may lead to errors in the filtering out of irrelevant auditory information from the surroundings[22, 23] and could explain the decrease in performance observed in the subjects who took *d*-chlorpheniramine. To determine whether the reduction in PN was caused by increased processing of unattended stimuli or to reduced processing of attended stimuli, a posterior analysis of a 200- to 350-msec mean amplitude interval for both types of stimuli was performed. However, the failure of this comparison to reach significance precludes a clear explanation of why the attentional alteration occurred. However, the fact that we did not find differences between groups in exogenous ERPs, similar to Serra and colleagues,[13] suggests that chlorpheniramine can selectively alter cognitive processes related to human auditory attention without worsening subject's sensory processing.

Moreover, the results of this experiment showed that the impairment of selective attention is not associated with a subjective increase in sleepiness or with a subjective deterioration in overall vigor and affect. Although a similar discrepancy between objective and subjective side effects has been observed recently with diphenhydramine,[24] our results differ from those of previous chlorpheniramine studies[2, 3, 6, 7] and indicate that individuals under the effects of chlorpheniramine could be deprived of subjective indicators of the reduction of their attention, increasing the risk of accidents (e.g., while driving).[15] Furthermore, we believe that it would be useful for those medicines containing chlorpheniramine to carry a warning about the possibility that this substance may cause attentional alterations without provoking subjective side effects, given that presently a large number of medicines containing chlorpheniramine can be acquired without a prescription.[25]

Finally, we emphasize that two limitations of this study were the small sample size and the failure to control the interindividual differences in response to the medication. To confirm our results, studies with larger samples and different measure times are required.

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