Central Nervous System Side Effects of First- and Second-Generation Antihistamines in School Children With Perennial Allergic Rhinitis: A Randomized, Double-Blind, Placebo-Controlled Comparative Study

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ABSTRACT. *Objective.* **Allergic rhinitis is common and on the rise. Antihistamines are the mainstay of treatment and are the most commonly prescribed drugs in Singapore. Treatment-related sedation and its effect on cognition are a major concern. First- and second-generation antihistamines show varying degrees of sedation, but to date, objective studies in children are lacking. The objective of this study was to assess the sedating effect of cetirizine (second-generation antihistamine) and chlorpheniramine (first-generation antihistamine) compared with placebo using an objective neurophysiological test.**

Methods. **This was a prospective, double-blind, placebo-controlled, randomized, single-dose, 3-way crossover study. Twenty-four children aged 7 to 14 years with allergic rhinitis completed the study. All children were randomly allocated to medication sequences and received 3 different drugs on 3 different days, at least 1 week apart. The P300 event-related potential was used as an objective test of sedation. Subjective assessment was by a visual analog scale.**

Results. **Chlorpheniramine and cetirizine increased P300 latency when compared with baseline. No significant increase was obtained with placebo. The significant increase in P300 latency was not accompanied by significant change in subjective somnolence as measured by the visual analog scale.**

Conclusion. **We have shown that cetirizine has sedative properties in children. The lack of correlation between P300 latency and the visual analog scale indicates that sedation induced by these drugs may not be subjectively noted.** *Pediatrics* **2004;113:e116–e121. URL: http://www.pediatrics.org/cgi/content/full/113/2/e116;** *sedation, cetirizine, chlorpheniramine, P300 event-related potential.*

ABBREVIATIONS. CNS, central nervous system; ERP, event-related potential; VAS, visual analog scale; Fz , frontal location; Cz, central location; Pz, parietal location; T_{max}, time to peak plasma drug concentration.

Allergic rhinitis is on the increase worldwide as well as in Singapore. A 1994 survey showed the prevalence of rhinitis in Singapore children to be at a staggering 44%.[1] In children with allergic rhinitis, inadequate symptom control may contribute to learning impairment; school absences; poor quality of life; and emotional, social, or behavioral disturbances.[2] Oral antihistamines are the mainstay of therapy for allergic rhinitis in children[3] and have been used effectively for managing symptoms of allergic rhinitis for >50 years. They are the most commonly prescribed drugs among outpatient doctors in the public service in Singapore.[4]

The major limitation of the use of first-generation antihistamines is sedation.[3] Being lipophilic molecules, they easily cross the blood-brain barrier and may exacerbate the decrease in cognitive function already experienced by the patient with allergic rhinitis. Sedating antihistamines have been shown to reduce learning performance in children.[5] In contrast, second-generation antihistamines are relatively lipophobic and therefore cross the blood-brain barrier less readily. Their large molecular size and greater affinity for peripheral H1 receptors also reduce their propensity to cause sedation.[6] 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.[7,8] Cetirizine, the major metabolite of hydroxyzine, is 1 of only 2 oral second-generation antihistamines that have been approved by the Food and Drug Administration for treating children younger than 5 years and 1 of 3 approved for children between 5 and 12 years of age.[9] 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.[3] The Food and Drug Administration–approved package insert for cetirizine clearly cautions about the operation of vehicles or potentially dangerous machinery while using the drug. None of the second-generation antihistamines marketed in the United States displays this precaution. Also, cetirizine overdose in children is more likely to cause sedation than overdose with the other second-generation antihistamines.[10,11]

Numerous studies in the literature have investi-

gated the sedative effects of cetirizine in adults using psychometric tests,[12–15] simulated driving,[12,15] electroencephalograms,[16,17] multiple sleep latency tests,[18,19] and P300 evoked potential.[20–22] Most conclude that cetirizine has no CNS effects. In children, such studies are limited. Our aim, therefore, was to compare the sedating effects of a second-generation antihistamine, cetirizine, and the first-generation chlorpheniramine with placebo in school-going children with allergic rhinitis using the P300 event-related potential (ERP) as an objective neurophysiological test. The visual analog scale (VAS) was used to measure subjective sleepiness or somnolence.

METHODS

Patients

Twenty-four school children, aged 7 to 14 years, who had a doctor diagnosis of allergic rhinitis for at least 1 year were recruited from the National University Hospital, Singapore. We excluded children with the following: 1) persistent or severe asthma; severe atopic dermatitis; chronic sinusitis; recurrent upper respiratory tract infections; neurologic, hearing, or cognitive impairment; behavioral disorder; or any chronic illness that, in the opinion of the investigator, precluded a child from the study; 2) long-term, regular use of oral corticosteroids or medications that may affect CNS function; and 3) history of clinically significant adverse reaction to antihistamines. This study was approved by the hospital's ethics committee.

Study Design

This was a prospective, double-blind, placebo-controlled, randomized, single-dose 3-way crossover study. The children were randomized into 1 of the 6 medication sequences, using a table of random numbers. There was a washout period of at least 1 week between each study day.

On each study day, the children would arrive at the hospital between 8:00 AM and 9:00 AM after taking breakfast. The study day would be postponed if there were: 1) hospitalization or acute illness within the last 2 weeks; 2) use of antihistamines or any other medications that may affect CNS function in the last 2 weeks; 3) presence of signs or symptoms of asthma or atopic dermatitis; or 4) consumption of dietary items that may contain methylxanthines, such as cola drinks, coffee, or chocolate in the 24 hours before the study. The number of hours of sleep the night before and rhinitis scores were recorded. The latter assessed 5 symptoms (nasal congestion/blockage, rhinorrhea, sneezing, nasal itch, and postnasal drip) on an integer scale of 0 to 3.[3,23] Zero represented absent symptoms; 1, trivial, and not bothersome; 2, bothersome but not disabling or intolerable; and 3, disabling and/or intolerable.

On each study day, the following were performed in the same sequence. First, the VAS and then the P300 ERP test were conducted. Next, they were given chlorpheniramine, cetirizine, or placebo. Thereafter, there would be a break during which there were no activity restrictions. A snack and a drink were given 1 hour after study drug administration. Two to 2.5 hours after the administration of the study drug, the children indicated their somnolence on the VAS, and then the P300 ERP test was conducted.

Medications

The children were given single oral doses of chlorpheniramine 4 mg, cetirizine 10 mg, or placebo. The doses were according to the manufacturers' recommendation for the age range. Chlorpheniramine and cetirizine tablets were crushed and placed in capsules with lactose as the vehicle. Placebo capsules had only lactose. All capsules, which appeared and tasted identical, were prepared by the pharmacist, and the investigators were blinded.

Outcome Measures

VAS

The child was shown a 10-cm line, indicating "wide awake" at 0 cm and "cannot stay awake" at 10 cm. He or she was to mark on the line the point that best described how wide awake he or she felt then.

P300 ERP test was supervised by a qualified pediatric neurologist. Each child sat upright on a couch, relaxed with eyes open, in a semidarkened sound-attenuated room. Three standard disks were fixed to the scalp according to the International 10–20 system of electrode placement. The scalp electrodes at frontal (Fz), central (Cz), and parietal (Pz) scalp locations were referred to the ears, and a ground electrode was placed on the forehead. Impedances were kept at <5 ohms. An auditory "oddball" paradigm was presented using frequent, low-pitched 1000-Hz tones and rare, high-pitched 2000-Hz tones with an interstimulus interval of 2 seconds. The overall probability of the rare tone was 0.2. The tones were presented binaurally, with 70-dB peak sound pressure. The child was to press a button when the rare tone was heard. There was automated rejection of trials with excess artifact (voltage greater than ±50 μV). Data from Fz, Cz, and Pz electrodes were determined. At least 2 testing epochs of 30 rare tones each were conducted. More trials were conducted when waveforms were poor. The P300 peak was identified by 2 independent observers as the most obvious peak between 250 and 500 milliseconds. Only the most consistent trials were considered acceptable for analysis. Waveforms without any obvious peaks were discarded. Absolute values and percentage change in P300 latency at 2 hours after dosing were compared with baseline predose values and with placebo.

Data Analysis

Baseline conditions were analyzed using Kruskal-Wallis test to detect differences among the different study days. Wilcoxon signed rank test was used to compare postdosing P300 latencies and visual analog scores with the predosing baselines for each of the 3 treatments. The statistical package for social sciences (SPSS for Windows) program was used in the analysis. Significance level for all statistical procedures was 5% (2-sided tests). For 24 subjects enrolled, the power of this crossover study to detect a significant difference ($P = .05$) in P300 latency among the 3 treatment groups was 80%.

RESULTS

All 24 children (14 boys, 10 girls) enrolled completed the study. The mean age was 9.87 ± standard deviation 1.85 years, and age range was 7 to 14 years. The mean weight was 38.12 ± standard deviation 11.44 kg with a range of 20 to 61 kg. There were 19 Chinese, 4 Malays, and 1 Indian.

The hours of sleep the night before each study day and baseline rhinitis scores did not differ significantly among the 3 groups (Table 1). Baseline P300 latencies in the 3 electrodes also did not differ significantly from each other. Using Pearson correlation, we found no significant correlation between body weight and percentage change in P300 latency in all 3 electrodes for both cetirizine and chlorpheniramine ($P > .05$).

Compared with baseline, we observed an increase in P300 latency for chlorpheniramine (Fz: $P = .01$; Cz: $P = .01$; Pz: $P = .04$) and cetirizine (Fz: $P = .02$; Cz: $P = .03$) but not for placebo (Fig 1 A–C). However, the mean percentage change in P300 latency for cetirizine and chlorpheniramine did not differ significantly from placebo.

On the basis of previous studies, an increase in the P300 latency of ≥5% after H1-receptor antagonist administration is clinically relevant.[20,24] At the Fz electrode, cetirizine and chlorpheniramine increased P300 latency by at least 5% in 8 (33%) and 11 (46%) patients, respectively, whereas for placebo, the increase in P300 latency was at least 5% in only 1 (4%)

TABLE 1. Duration of Sleep, Rhinitis Scores, and P300 Latency (Mean ± Standard Error of the Mean) Before Medication and 2 Hours After Medication ($n = 24$ for All Groups)

	Placebo			Cetirizine			Chlorpheniramine		
	Before	After	Change	Before	After	Change	Before	After	Change
Duration of sleep (h)	8.43 ± 0.16	-	-	7.99 ± 0.20	-	-	8.25 ± 0.18	-	-
Rhinitis score	1.54 ± 0.33	-	-	1.87 ± 0.44	-	-	2.13 ± 0.44	-	-
VAS	2.67 ± 0.38	2.75 ± 0.51	0.08 ± 0.37	2.48 ± 0.45	2.34 ± 0.43	-0.13 ± 0.47	2.94 ± 0.47	2.98 ± 0.53	0.05 ± 0.58
Fz (ms)	356.63 ± 6.70	361.35 ± 6.78	4.73 ± 2.22 (1.38% ± 0.66)	357.75 ± 7.86	369.18 ± 9.76	11.44 ± 4.49* (3.13% ± 1.22%)	352.45 ± 7.57	363.33 ± 8.58	10.88 ± 3.37† (3.09 ± 0.95%)
Cz (ms)	352.97 ± 6.57	359.26 ± 7.09	6.29 ± 3.98 (1.88% ± 1.19%)	355.52 ± 7.54	367.00 ± 10.07	11.48 ± 5.17* (3.12 ± 1.42%)	351.15 ± 7.76	362.29 ± 7.43	11.15 ± 3.53† (3.37 ± 1.05%)
Pz (ms)	353.76 ± 6.88	357.62 ± 7.20	3.86 ± 3.84 (1.20 ± 1.16%)	357.93 ± 7.78	366.19 ± 9.28	8.26 ± 4.14 (2.25 ± 1.16%)	351.74 ± 7.64	360.01 ± 7.33	8.27 ± 3.93* (2.54 ± 1.11%)

There were no significant differences between the groups for duration of sleep, rhinitis score, or VAS.
* $P < .05$.
† $P \leq .01$.

patient. The trend was similar at the other 2 electrodes.

There was no significant increase in VAS scores for chlorpheniramine, cetirizine, and placebo compared with baseline (Table 1) in all 3 electrodes ($P > .05$). The mean percentage change in VAS scores for cetirizine and chlorpheniramine also did not differ significantly from placebo. Using Pearson correlation, the percentage change in VAS scores for all 3 groups did not show any significant correlation with the percentage change in P300 latency for all of the electrodes.

DISCUSSION

In the present study, we have shown that both cetirizine 10 mg and chlorpheniramine 4 mg increased P300 latencies significantly compared with baseline. Only been a few studies have examined the effect of antihistamines on P300 latency in children.[24,25] None, to our knowledge, has studied the sedative effect of cetirizine in atopic children using P300 latency. Compared with many other objective tests of CNS function, it has the advantages of being relatively simple; rapid; and less affected by practice, motivation, or boredom.[20,21] It is an objective measure that is suitable for use in children and that has been used extensively to study the cognitive effects of antihistamines and other medication.[21] Prolongation of P300 latency is taken as an index of impaired cognitive function.[6]

The inclusion of chlorpheniramine as the positive control in our study was not to draw direct comparisons with cetirizine but to ensure sensitivity.[6] Chlorpheniramine 4 mg has been shown to increase P300 latency compared with baseline in children.[24] The sensitivity of this study was increased by using this dose, which is the minimal recommended dose for chlorpheniramine, so as to ensure that we could detect even mild sedative effects of cetirizine. All of these suggest that cetirizine 10 mg is at least mildly sedating in children aged 7 to 14 years.

Studies in adults are conflicting, although most objective studies show that cetirizine is not sedating within the recommended dose range. In 1 adult study, it was shown that cetirizine did not increase P300 latency significantly compared with predose baseline.[20] Other researchers have shown a small increase of P300 latency in cetirizine compared with placebo, but the results were not significant.[21,22] Cetirizine 10 mg was completely devoid of electroencephalogram changes in most studies,[14,17] although at least 1 report[26] showed otherwise. Studies using driving simulators,[12,27] multiple sleep latency,[18,19] and psychomotor tests[12–14] also showed that cetirizine had no CNS effects. Conversely, 1 study reported significantly impaired driving performance with cetirizine 10 mg.[28] Another showed significant differences in psychomotor tests between cetirizine and placebo[15]; however, there was no positive control in the latter study. With the use of subjective tests, adults generally reported a higher incidence of sleepiness than placebo controls.[29,30] This, however, must be interpreted with caution. Subjective reports of somnolence are extremely unreliable because, by its
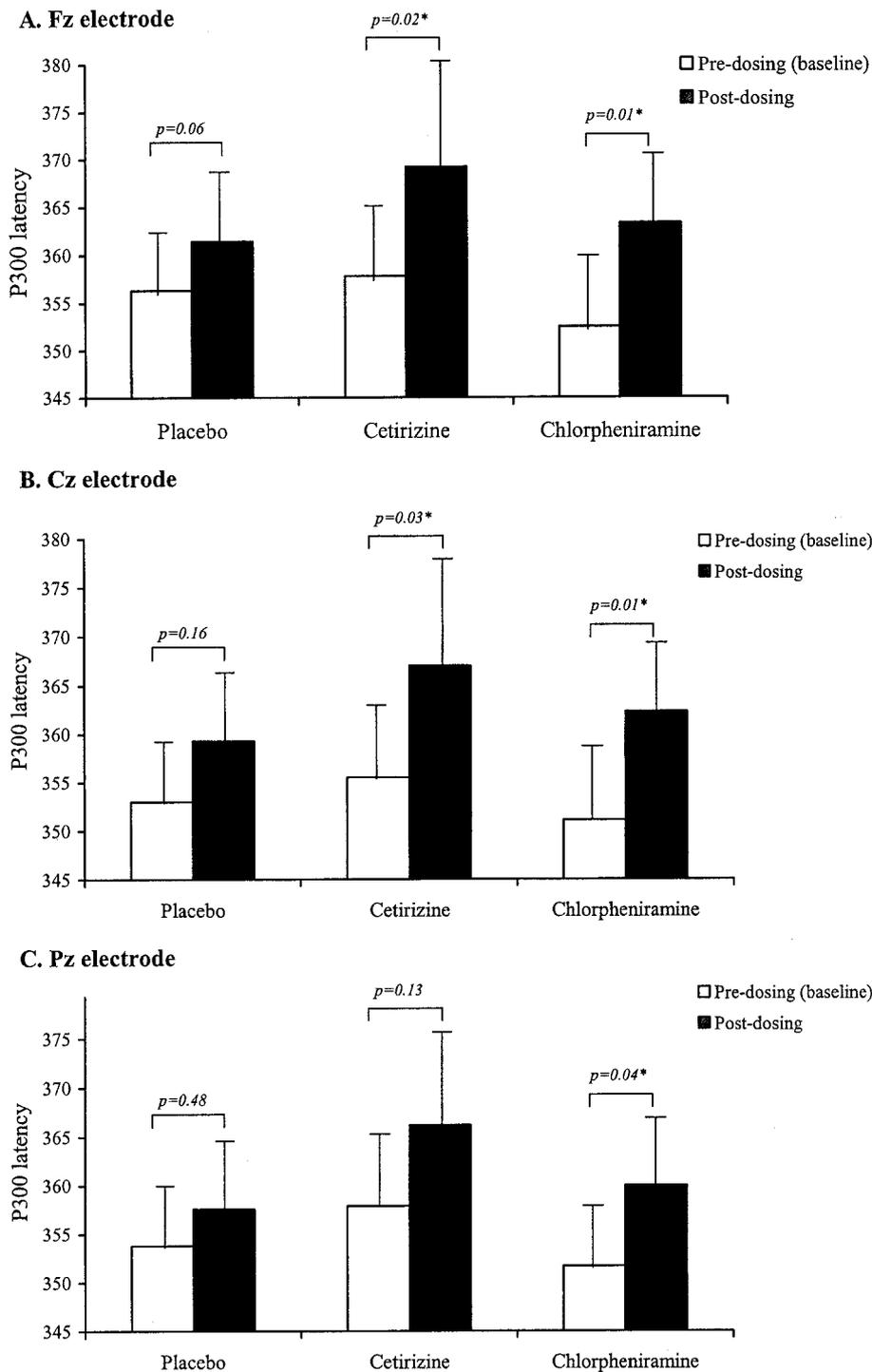
A. Fz electrode

B. Cz electrode

C. Pz electrode

Fig. 1. A–C, Mean (± standard error of the mean) pre- and postmedication P300 latencies from the Fz, Cz, and Pz electrodes, respectively. * indicates significant result

very nature, sleepiness can impair self-assessment of awareness and thus give rise to misleading results.[6]

Our finding that cetirizine is at least mildly sedating is supported by studies using position emission tomography scans. It is thought that blockade of central histamine H1-receptors is the main cause of sedation by antihistamines. Position emission tomography scans have been found to be useful in the quantitative assessment of sedation caused by first- and second-generation antihistamines. It has been reported that chlorpheniramine occupied 76.8 ±

4.2% of the available H1 receptors in the frontal cortex after a single oral dose of 2 mg,[31] whereas a single dose of cetirizine 20 mg occupied 20% to 50%.[32] However, these studies were done in adults. It is not known whether the occupancy of central histamine receptors in children is different from those in adults.

It has been suggested that cetirizine may not have significant CNS effects on children. In the Early Treatment of the Atopic Child study, subjects were given either cetirizine 0.25 mg/kg twice daily or

placebo over 18 months.[33] No significant differences were noted between the treatment and placebo groups in behavioral measures, cognitive measures (McCarthy Scales of Children's Abilities), or age of attainment of psychomotor milestones during or after the study treatment. However, these are gross measures of CNS function and may not detect subtle effects of sedation.

The effect that sedation has on learning in children is of major concern because of its implications during the school-going age. Studies in children and young adults have shown that episodes of allergic rhinitis reduce learning ability.[5] This effect is aggravated by first-generation antihistamines and partially counteracted by treatment with second-generation antihistamines. Importantly, the child may not be aware of this sedative effect. Using the VAS, which is a subjective self-rating of somnolence, we showed that the increase in P300 latency was not accompanied by a significant change in self-reported somnolence. However, it is accepted that subjective reports of sedation are not as reliable as objective tests and that discrepancy between subjective and objective assessments of sedation is common.[6] This is especially true in children, in whom up to 13% aged 5 to 14 years were unable to understand the concept of VAS and up to 39% incorrectly marked their responses on the VAS.[34]

The doses of antihistamines in this study were those recommended by the manufacturer, based on the age of the child. As the study was double-blinded, it was logistically difficult to administer the drugs according to doses calculated by weight. Nevertheless, there was no significant negative correlation between body weight and percentage change in P300 latency. This meant that in children who received a greater dose of drugs per body weight, there was no greater increase in P300 latency.

In our study, possible factors that might affect P300 latency were controlled. Baseline rhinitis scores and the number of hours of sleep the night before each study day were not significantly different among the 3 groups. We ensured that the subjects in this study did not consume dietary items or medications that might affect CNS function and that they had a snack during the break because hypoglycemia may potentially affect P300 latency.

This study had some limitations. We did not measure histamine-induced wheal and flare to evaluate blockade of peripheral H1 receptors by the treatment. However, various studies have shown that both cetirizine 10 mg[35,36] and chlorpheniramine 4 mg[24,37] are effective in suppressing histamine-induced wheal and flare in children. Another potential confounding factor was the different pharmacokinetics of both drugs. The onset of action for cetirizine is 30 minutes, and its time from oral intake to peak plasma drug concentration (T_{max}) is 60 minutes.[38] The onset of action of chlorpheniramine is 15 to 60 minutes, and T_{max} is 2 to 6 hours.[38] Although the tests were conducted after the onset of action of the drugs, it was possible that chlorpheniramine was not studied at T_{max} and hence had not yet exerted maximum sedative effect. Despite that, chlorpheniramine still caused a significant increase in P300 latency. It should be noted that maximal sedation may not correlate with peak plasma drug concentration. Central H1-receptor occupancy increased significantly with increasing plasma concentration of chlorpheniramine but not with increasing concentration of the active metabolite of ebastine[39] or terfenadine.[31] We know of no such studies with cetirizine.

In this study, we evaluated the effects of a single dose of antihistamines and not repeated doses. Although antihistamines are effective on an as-needed basis, these agents work best when they are administered in a maintenance manner.[3] Whether similar effects on P300 latency would be observed with repeated daily dosing requires additional investigation.

In conclusion, we have shown that cetirizine 10 mg is at least mildly sedating in children whoa re aged 7 to 14 years and have allergic rhinitis based on the P300 ERP. This is in contrast to many studies in adults. However, this mild sedation may not be subjectively perceived in children. More studies on cetirizine are needed to evaluate the effects of repeated dosing and also its effects on learning in children.

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