

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

Kar Hui Ng, MBBS*; Daniel Chong, MBBS*; Chin Khoo Wong, MBBS, MMed‡; Hian Tat Ong, MBBS, MMed‡; Chien Yee Lee, MBBS, MRCP‡; Bee Wah Lee, MD, FRCP, FAAAAI*; and Lynette Pei-Chi Shek, MBBS, MRCP*

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.

From the *Department of Paediatrics, National University of Singapore, Singapore; and ‡Department of Paediatrics, National University Hospital, Singapore.

Received for publication May 28, 2003; accepted Oct 6, 2003.

Reprint requests to (L.P.-C.S.) Department of Paediatrics, National University of Singapore, 5 Lower Kent Ridge Rd, Singapore 119074. E-mail: paeshekl@nus.edu.sg

PEDIATRICS (ISSN 0031 4005). Copyright © 2004 by the American Academy of Pediatrics.

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 children³ 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 $\pm 50 \mu\text{V}$). 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 $9.87 \pm$ standard deviation 1.85 years, and age range was 7 to 14 years. The mean weight was $38.12 \pm$ 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 $\geq 5\%$ 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 \pm 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 \pm 0.16	-	-	7.99 \pm 0.20	-	-	8.25 \pm 0.18	-	-
Rhinitis score	1.54 \pm 0.33	-	-	1.87 \pm 0.44	-	-	2.13 \pm 0.44	-	-
VAS	2.67 \pm 0.38	2.75 \pm 0.51	0.08 \pm 0.37	2.48 \pm 0.45	2.34 \pm 0.43	-0.13 \pm 0.47	2.94 \pm 0.47	2.98 \pm 0.53	0.05 \pm 0.58
Fz (ms)	356.63 \pm 6.70	361.35 \pm 6.78	4.73 \pm 2.22 (1.38% \pm 0.66)	357.75 \pm 7.86	369.18 \pm 9.76	11.44 \pm 4.49* (3.13 \pm 1.22%)	352.45 \pm 7.57	363.33 \pm 8.58	10.88 \pm 3.37+ (3.09 \pm 0.95%)
Cz (ms)	352.97 \pm 6.57	359.26 \pm 7.09	6.29 \pm 3.98 (1.88 \pm 1.19%)	355.52 \pm 7.54	367.00 \pm 10.07	11.48 \pm 5.17* (3.12 \pm 1.42%)	351.15 \pm 7.76	362.29 \pm 7.43	11.15 \pm 3.53+ (3.37 \pm 1.05%)
Pz (ms)	353.76 \pm 6.88	357.62 \pm 7.20	3.86 \pm 3.84 (1.20 \pm 1.16%)	357.93 \pm 7.78	366.19 \pm 9.28	8.26 \pm 4.14 (2.25 \pm 1.16%)	351.74 \pm 7.64	360.01 \pm 7.33	8.27 \pm 3.93* (2.54 \pm 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 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 report²⁶ showed otherwise. Studies using driving simulators,^{12,27} multiple sleep latency,^{18,19} and psychomotor tests¹²⁻¹⁴ 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 placebo¹⁵; 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

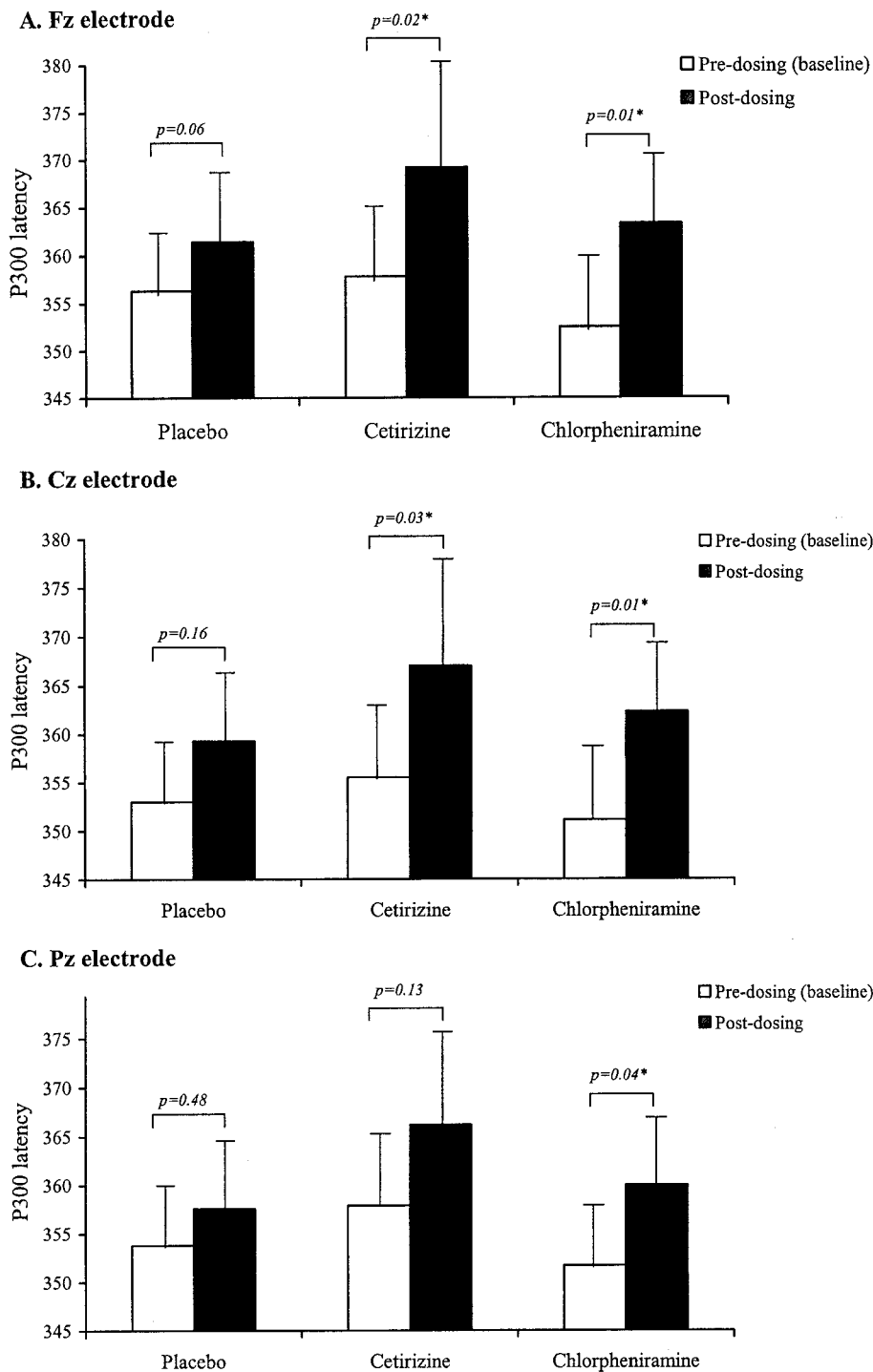


Fig. 1. A–C, Mean (\pm standard error of the mean) pre- and postmedication P300 latencies from the Fz, Cz, and Pz electrodes, respectively. * indicates significant result

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 \pm

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 ebastine³⁹ 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 who are 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.

ACKNOWLEDGMENTS

This study was supported by a National University Hospital, Singapore, Research Training Grant (RP#EF2000/035/ROC-008).

We thank Dr D. Goh and Dr E. Khor for help in recruiting patients; clinical psychologist Lydia Hoalim for assistance with neuropsychometric tests; Karen, Yvonne, and other staff at The Neuroscience Center for technical expertise; Siew Ping for preparing the medications; and Jina Loh, Magase, and Peck Choo for administrative support.

REFERENCES

1. Goh DYT, Chew FT, Quek SC, Lee BW. Prevalence and severity of asthma, rhinitis, and eczema in Singapore schoolchildren. *Arch Dis Child.* 1996;74:131-135
2. Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol.* 2001;108:S45-S53
3. Dykewicz MS, Fineman S, Skoner DP, 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;81:478-518
4. Lim KH, Yap KB. The prescribing pattern of outpatient polyclinic doctors. *Singapore Med J.* 1999;40:416-419
5. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann Allergy.* 1993;71:121-126
6. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy.* 1999;29(suppl 3):133-142
7. 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
8. Chen C, Hanson E, Watson JW, Lee JS. P-glycoprotein limits the brain penetration of nonsedating but not sedating H1-antagonists. *Drug Metab Dispos.* 2003;31:312-318
9. Galant SP, Wilkinson R. Clinical prescribing of allergic rhinitis medication in the preschool and young school-age child: what are the options? *BioDrugs.* 2001;15:453-463
10. Hansen JJ, Feilberg Jorgensen NH. [Accidental cetirizine poisoning in a four-year-old boy]. *Ugeskr Laeger.* 1998;160:5946-5947
11. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. *Drug Saf.* 2001;24:119-147
12. Gengo FM, Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. *Ann Allergy.* 1987;59:53-57

13. Shamsi Z, Kimber S, Hindmarch I. An investigation into the effects of cetirizine on cognitive function and psychomotor performance in healthy volunteers. *Eur J Clin Pharmacol*. 2001;56:865–871
14. Sannita WG, Crimi E, Riel S, Rosadini G, Brusasco V. Cutaneous antihistaminic action of cetirizine and dose-related EEG concomitants of sedation in man. *Eur J Pharmacol*. 1996;300:33–41
15. Ramaekers JG, Uiterwijk MM, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur J Clin Pharmacol*. 1992;42:363–369
16. Alford C. A comparison of antihistamines using EEG and questionnaire-based assessments. *Med Sci Res*. 1989;17:421–423
17. Pechadre JC, Beudin P, Eschaliere A, Trolese JF, Rihoux JP. A comparison of central and peripheral effects of cetirizine and loratadine. *J Int Med Res*. 1991;19:289–295
18. Seidel WF, Cohen S, Bliwise NG, Dement WC. Cetirizine effects on objective measures of daytime sleepiness and performance. *Ann Allergy*. 1987;59:58–62
19. Schweitzer PK, Muehlbach MJ, Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. *J Allergy Clin Immunol*. 1994;94:716–724
20. Simons FE, Fraser TG, Reggin JD, Simons KJ. Individual differences in central nervous system response to antihistamines (H1-receptor antagonists). *Ann Allergy Asthma Immunol*. 1995;75:507–514
21. Simons FE, Fraser TG, Reggin JD, Simons KJ. Comparison of the central nervous system effects produced by six H1-receptor antagonists. *Clin Exp Allergy*. 1996;26:1092–1097
22. Simons FE, Fraser TG, Maher J, Pillay N, Simons KJ. Central nervous system effects of H1-receptor antagonists in the elderly. *Ann Allergy Asthma Immunol*. 1999;82:157–160
23. Gross G, Jacobs RL, Woodworth TH, Georges GC, Lim JC. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2002;89:56–62
24. Simons FE, Reggin JD, Roberts JR, Simons KJ. Benefit/risk ratio of the antihistamines (H1-receptor antagonists) terfenadine and chlorpheniramine in children. *J Pediatr*. 1994;124:979–983
25. Simons FE, Fraser TG, Reggin JD, Roberts JR, Simons KJ. Adverse central nervous system effects of older antihistamines in children. *Pediatr Allergy Immunol*. 1996;7:22–27
26. Bonifazi F, Provinciali L, Antonicelli L, et al. Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects. *J Invest Allergol Clin Immunol*. 1995;5:40–46
27. Gengo FM, Gabos C, Mechtler L. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Ann Allergy*. 1990;64:520–526
28. Vermeeren A, Ramaekers JG, O'Hanlon JF. Effects of emedastine and cetirizine, alone and with alcohol, on actual driving of males and females. *J Psychopharmacol*. 2002;16:57–64
29. Zyrtec. In: *Physicians' Desk Reference*. 53rd ed. Montvale, NJ: Medical Economics Co; 1999:2447–2450
30. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1999;104:927–933
31. Yanai K, Ryu JH, Watanabe T, et al. Histamine H1 receptor occupancy in human brains after single oral doses of histamine H1 antagonists measured by positron emission tomography. *Br J Pharmacol*. 1995;116:1649–1655
32. Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci*. 2002;72:409–414
33. Stevenson J, Cornah D, Evrard P, et al. Long-term evaluation of the impact of the h1-receptor antagonist cetirizine on the behavioral, cognitive, and psychomotor development of very young children with atopic dermatitis. *Pediatr Res*. 2002;52:251–257
34. Shields BJ, Cohen DM, Harbeck-Weber C, Powers JD, Smith GA. Pediatric pain measurement using a visual analogue scale: a comparison of two teaching methods. *Clin Pediatr (Phila)*. 2003;42:227–234
35. Simons FE, Johnston L, Simons KJ. Clinical pharmacology of the H1-receptor antagonists cetirizine and loratadine in children. *Pediatr Allergy Immunol*. 2000;11:116–119
36. Watson WT, Simons KJ, Chen XY, Simons FE. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J Allergy Clin Immunol*. 1989;84:457–464
37. Simons FE, Luciw GH, Simons KJ. Pharmacokinetics and efficacy of chlorpheniramine in children. *J Allergy Clin Immunol*. 1982;69:376–381
38. Antihistamines (systemic). In: *Drug Information for the Health Care Professional, USP DI*. 20th ed. Microdex, Inc; 2000:343–353
39. Tagawa M, Kano M, Okamura N, et al. Neuroimaging of histamine H1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. *Br J Clin Pharmacol*. 2001;52:501–509

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
Kar Hui Ng, Daniel Chong, Chin Khoon Wong, Hian Tat Ong, Chien Yee Lee, Bee Wah Lee and Lynette Pei-Chi Shek
Pediatrics 2004;113;e116
DOI: 10.1542/peds.113.2.e116

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/113/2/e116
References	This article cites 37 articles, 2 of which you can access for free at: http://pediatrics.aappublications.org/content/113/2/e116#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Pharmacology http://www.aappublications.org/cgi/collection/pharmacology_sub Therapeutics http://www.aappublications.org/cgi/collection/therapeutics_sub Allergy/Immunology http://www.aappublications.org/cgi/collection/allergy:immunology_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Kar Hui Ng, Daniel Chong, Chin Khoon Wong, Hian Tat Ong, Chien Yee Lee, Bee Wah Lee and Lynette Pei-Chi Shek

Pediatrics 2004;113:e116

DOI: 10.1542/peds.113.2.e116

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/113/2/e116>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2004 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

