

Adverse central nervous system effects of older antihistamines in children

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Although older, potentially sedating, “first-generation” antihistamines (H_1 -receptor antagonists) are commonly used in childhood, their central nervous system (CNS) effects have not been well-documented in young subjects. We hypothesized that diphenhydramine and hydroxyzine would affect CNS function adversely in this population. Our objective was to evaluate the effects of these medications on central and peripheral histamine H_1 -receptors in children. Fifteen subjects with allergic rhinitis were tested before and 2–2.5 h after administration of diphenhydramine, hydroxyzine, or placebo in a double-blind, single-dose, three-way crossover study. Impairment of cognitive processing was assessed objectively by the latency of the P300 event-related potential (P300). Somnolence was assessed subjectively by a visual analog scale. Peripheral H_1 -blockade was assessed by suppression of the histamine-induced wheals and flares. At the central (Cz) and frontal (Fz) electrodes, diphenhydramine and hydroxyzine increased the P300 latency significantly ($P < 0.05$) compared to baseline. Hydroxyzine increased somnolence, as recorded on the visual analog scale, significantly compared to baseline ($P < 0.05$), with a similar trend for diphenhydramine ($P = 0.07$). Both antihistamines reduced histamine-induced wheals and flares significantly compared to baseline and compared to placebo. In children, diphenhydramine and hydroxyzine are effective H_1 -receptor antagonists, but both these medications cause CNS dysfunction, as evidenced by increased P300 latency, a measure of cognitive function, and by increased subjective somnolence.

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Older, first-generation, potentially sedating H_1 -receptor antagonists are still commonly used for the treatment of symptoms of allergic disorders in children (1), as the newer, nonsedating H_1 -receptor antagonists are not available in pediatric formulations in many countries. H_1 -receptor antagonists such as diphenhydramine and hydroxyzine are generally assumed to be safe for use in children. Few objective evaluations of their adverse central nervous system (CNS) effects have been performed in young subjects (2–4), although these effects have been well studied in adults (5–8).

We hypothesized that diphenhydramine and hydroxyzine would affect CNS function significantly in children at doses commonly used in the treatment of allergic disorders (9). We tested this hypothesis in a double-blind, single-dose, placebo-controlled, three-way crossover study in 15 children. We used the latency of the P300-event-related potential as an objective measure of impairment of cognitive pro-

cessing, along with a visual analog scale as a subjective measure of somnolence, and suppression of the histamine-induced wheals and flares as a measurement of peripheral H_1 -blockade.

Methods

Patient selection

The study protocol was approved by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research. Written, informed consent was obtained from the parent of each child, and assent was obtained from the child before study entry.

Children were eligible to participate if they were aged 6–12 years, weighed 20–40 kg, and had a diagnosis of allergic rhinitis. They were excluded from the study if they had any disease other than allergic rhinitis or mild asthma; hearing, neurologic, cogni-

Table 1. Factors potentially affecting P300 latency or somnolence scores (mean $\pm$ SEM) did not differ significantly on the three study days

	Diphenhydramine		Hydroxyzine		Placebo	
Blood glucose (mmol/l) [†]	4.4±0.1	4.2±0.2	4.3±0.1	4.3±0.3	4.4±0.1	4.3±0.2
Duration of sleep (h)	10±1		10±1		10±1	
Rhinitis score* (child)	3.67±0.80		3.45±0.89		2.52±0.65	
Nasal blockage score* (child)	2.95±0.49		3.28±0.69		2.85±0.64	
Rhinitis score* (by physician)	3.23±0.54		3.70±0.64		3.24±0.61	
Nasal congestion* (by physician)	2.88±0.45		3.37±0.48		3.30±0.56	
Medications used within 48 h of study (<i>no.</i> of children)						
Inhaled glucocorticoids**	9		9		9	
None	6		6		6	

[†]Before dose and 2 h after dose.

*Before dose, maximum score = 12.

**Beclomethasone, budesonide, triamcinolone, or flunisolide.

tive, or behavioral disorder; recent acute illness; requirement for any medication which might affect CNS function (for example, a decongestant); need for an H₁-receptor antagonist regularly; or history of adverse reaction to an H₁-receptor antagonist.

Study design

During a preliminary visit, the children were assessed for their ability to meet the inclusion criteria of the study. After medical history and physical examination, they were given the opportunity to become familiar with the procedure used to measure the P300 event-related potential and with the visual analog scale for assessment of somnolence.

On 3 study days at least 1 week apart, they visited the Health Sciences Clinical Research Centre at 0800 after an adequate night's sleep and an 8-h fast. Dietary items containing methylxanthines, e.g., cola drinks or chocolate, were prohibited for 24 h before and during each study day. The child and one physician assessed allergic rhinitis symptoms on each study day and recorded scores for nasal itching, sneezing, discharge, and blockage. Procedures, as described below, were always conducted in the same sequence. Epicutaneous tests with histamine phosphate were performed, and a 5-ml blood sample was obtained for measurement of glucose, diphenhydramine, and hydroxyzine. Blood and urine samples were screened for potentially CNS-active medications other than H₁-receptor antagonists. After a standardized breakfast of 250 ml apple juice and a doughnut, P300-event-related potentials were measured and somnolence was assessed with the visual analog scale.

Children then received either diphenhydramine 10 ml (37.5 mg) (9) (prepared by adding 0.9 ml diphenhydramine injectable (Benadryl® 50 mg/ml, Warner Wellcome, Inc., Scarborough, Ontario, Canada MIL 2N3) to 11.1 ml placebo suspension, or hydroxyzine 10 ml (20 mg) (9) (prepared by adding

0.5 ml hydroxyzine (Atarax® intramuscular 50 mg/ml, Pfizer Canada, Inc., 17300 Transcanada Hwy., Kirkland, PQ, Canada H9J 2M5) to 11.5 ml placebo suspension, or the placebo suspension itself, 10 ml. These formulations appeared and tasted identical and contained no glucose or alcohol. Epicutaneous tests, blood samples for measurement of glucose and diphenhydramine or hydroxyzine, P300-event-related potentials, and assessment of somnolence by the visual analog scale were repeated 2–2.5 h after the administration of medication or placebo.

Technique of skin testing

During each visit, a different site on the volar surfaces of the forearm was used for each epicutaneous test with histamine phosphate 1 mg/ml (Glaxo Canada, Inc., Mississauga, ON, Canada) and 10 mg/ml (Sigma Chemical Co, St Louis, MO, USA) in 0.9% NaCl, sterilized by filtration (0.22 μ m, Nalge Co, Sybron Corp., Rochester, NY, USA). The sequence of test sites selected was the same in each child. The wheal and flare circumferences were traced with a pen at 10 min and transferred to paper with transparent tape. Wheal and flare areas were measured by a computerized digitizing system (10).

Serum H₁-receptor antagonist concentrations

Venipunctures were performed 1 h after EMLA® local anesthetic cream (Astra Pharma, Inc., Mississauga, ON, Canada) had been applied to the skin. Blood samples were centrifuged at 4°C. Serum was transferred into an appropriately labeled polypropylene tube, capped, frozen promptly in an upright position, and stored at –20°C until analysis. Serum diphenhydramine or hydroxyzine concentrations were measured by HPLC methods developed in our laboratory (11, 12). Blood-glucose measurements and screening tests for CNS-active chemicals in the baseline serum and urine samples were performed.

Table 2. Wheal and flare size, serum H₁-antagonist concentrations, P300 latency, and visual analog scale score before and after dose

	Diphenhydramine		Hydroxyzine		Placebo	
Wheal size, histamine 1 mg/ml (cm ²)	0.13±0.01	0.08±0.01*	0.15±0.01	0.10±0.01*	0.15±0.01	0.14±0.01
Flare size, histamine 1 mg/ml (cm ²)	1.73±0.17	1.04±0.19*	1.90±0.21	0.80±0.18*	1.83±0.23	2.15±0.25
Wheal size, histamine 10 mg/ml (cm ²)	0.23±0.01	0.14±0.1*	0.26±0.01	0.15±0.01*	0.27±0.02	0.27±0.02
Flare size, histamine 10 mg/ml (cm ²)	4.39±0.46	3.37±0.55*	4.52±0.20	2.42±0.32*	4.73±0.29	4.85±0.52
Serum concentration (ng/ml)	—	65±6	—	27±3♦	—	—
P300 latency Cz (ms)	310±6	327±7 ^{††}	308±7	330±6 ^{††}	320±7	326±10
P300 latency Fz (ms)	311±11	330±9 ^{††}	335±8	350±8 ^{††}	333±9	340±12
Visual analog somnolence score (maximum 12 cm)	4.08±0.53	5.24±0.82	3.40±0.73	5.04±1.06 ^{††}	3.14±0.56	3.66±0.57

Data expressed as mean ± SEM.

*Significantly less than baseline ($P \leq 0.05$).

[†]Significantly less than placebo ($P \leq 0.05$).

^{††}Significantly greater than baseline ($P \leq 0.05$).

♦Cetirizine arising from hydroxyzine *in vivo*: 101±14 ng/ml.

Assessment of CNS effects

The P300 event-related potential (P300) is an auditory-evoked potential that occurs approximately 300 ms after a stimulus. Its latency depends on the amount of time required for evaluation of the stimulus. It provides a direct measurement of the speed of neuronal information processing, and the impairment in information processing produced by medications.

For assessment of the P300-event-related potential, eight standard disks were fixed to the scalp with Elefix® paste (Nihon Kohden America, Inc., Irvine, CA, USA). The 10–20 system of electrode placement was utilized. An auditory “oddball” paradigm was presented using frequent, 1000-KHz (80%) and infrequent, 2000-KHz (20%) tones given at random

intervals. An eight-channel recording was made, with rejection of trials that had excess artifact, defined as voltage exceeding $\pm 250 \mu\text{V}$. During each 5-min trial, approximately 150 episodes were recorded. Four trials were done at each test time with comparison for test-retest consistency. The latencies of the P300 event-related potentials at the frontal (Fz) and central (Cz) scalp electrodes were determined for each trial. Only the two most consistent trials were used, and only latency values within 10% of each other at each test time were considered to be acceptable for analysis (4, 13–16).

The visual analog scale for somnolence, a numerically scored, subjective self-rating of drowsiness, was based on the Stanford Sleepiness Scale (17). This test was performed by showing the children a 12-cm line, indicating “wide awake” at one end, and

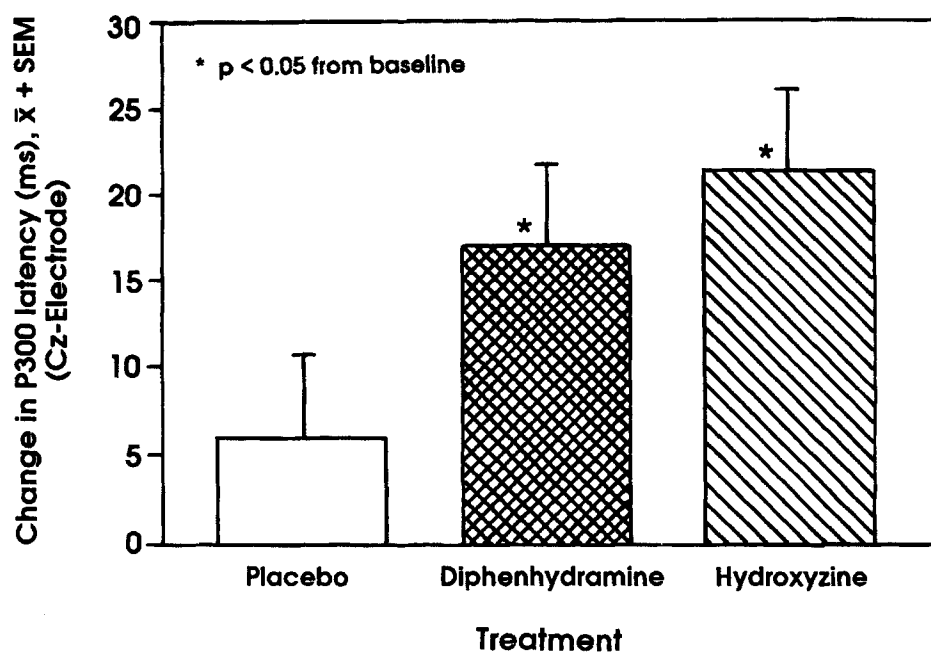


Fig. 1. Compared to baseline, diphenhydramine and hydroxyzine increased P300 latency at Cz central electrode significantly ($P \leq 0.05$), but placebo did not.

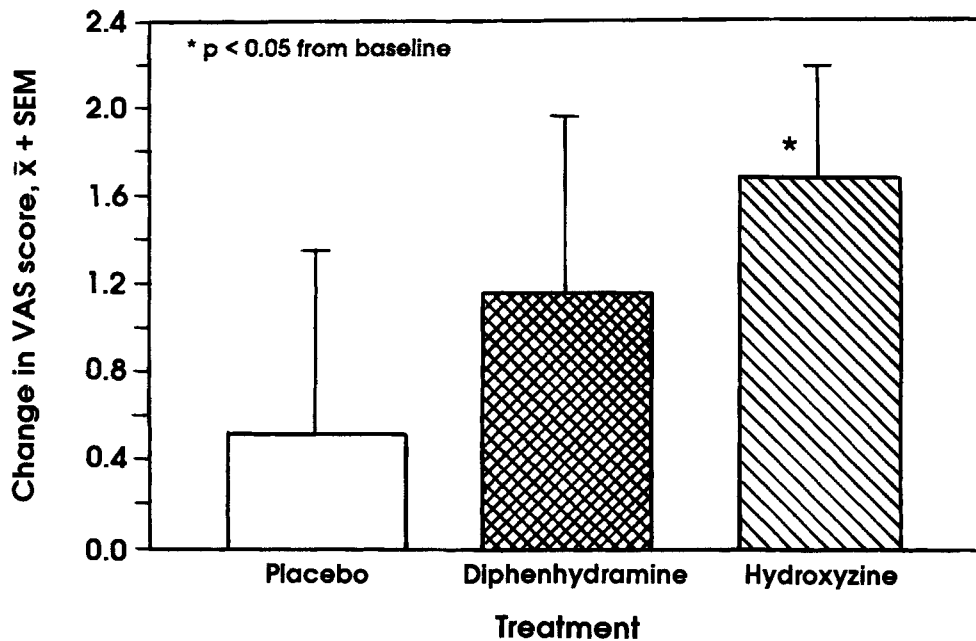


Fig. 2. Subjective somnolence increased significantly compared to baseline after hydroxyzine ($P < 0.05$), but not after diphenhydramine ($P = 0.07$) or placebo.

“can’t stay awake” at the other end, and asking them to point to the place on the line that best described how awake they felt at that moment (4).

Data analysis

Statistical analyses were performed with analysis of variance, analysis of covariance, and regression models using PCSAS. The significance level for all statistical procedures was 5% (one- and two-sided tests) (18).

Results

The mean age of the children (10 boys, five girls) was $8.9 \pm \text{SD } 1.3$ years. Their mean weight was 29.5 ± 5.5 kg. Mean blood glucose, hours of sleep the night preceding each study day, clinical score for control of allergic rhinitis symptoms, and medication use did not differ significantly on study days when diphenhydramine, hydroxyzine, or placebo were administered (Table 1).

Epicutaneous tests with histamine

Diphenhydramine and hydroxyzine significantly suppressed the mean wheal and flare areas produced by histamine phosphate 1 mg/ml and 10 mg/ml, compared to baseline and to placebo ($P < 0.05$). The effects of diphenhydramine and hydroxyzine did not differ significantly. Placebo did not significantly suppress the mean wheals and flares compared to predose baseline (Table 2). There was no correlation of peripheral H_1 -blockade with the P300 latency results or with somnolence as recorded on the visual analog scale.

Serum H_1 -receptor antagonist concentrations

Two hours after the dose, the mean serum diphenhydramine concentration was 65 ± 6 ng/ml, and the mean serum hydroxyzine concentration was 27 ± 3 ng/ml, confirming rapid absorption of the medications. The concentration of cetirizine arising from hydroxyzine *in vivo* was 101 ± 14 ng/ml (Table 2).

Measurement of CNS effects

At the central (Cz) electrode, diphenhydramine, hydroxyzine, and placebo increased the P300 latency (mean $\pm$ SEM) by 17 ± 7 , 22 ± 6 , and 6 ± 9 ms, respectively (Fig. 1, Table 2). At the frontal (Fz) electrode, diphenhydramine, hydroxyzine, and placebo increased the P300 latency by 19 ± 13 , 15 ± 4 , and 7 ± 11 ms, respectively. The increases after diphenhydramine and hydroxyzine differed significantly ($P < 0.05$) from baseline. The increase in P300 latency after both diphenhydramine and hydroxyzine was greater than the increase after placebo, but the differences did not quite reach statistical significance due to wide interindividual variation ($P = 0.07$). The increase after diphenhydramine did not differ significantly from the increase after hydroxyzine. The mean increase in P300 latency at the Cz electrode measured at 2.5 h did not correlate with the mean serum diphenhydramine concentrations measured at 2 h ($P = 0.138$, $r = 0.417$) or with serum hydroxyzine concentrations measured at 2 h ($P = 0.449$, $r = 0.314$).

The increase in subjective somnolence, as assessed by the visual analog scale, was 1.16 ± 0.83 for diphenhydramine, 1.64 ± 0.81 for hydroxyzine, and 0.52 ± 0.51 for placebo (Fig. 2, Table 2). Compared to baseline predose values, the increase after

hydroxyzine was significant ($P < 0.05$), with a similar trend for diphenhydramine ($P = 0.07$). The effects of diphenhydramine and hydroxyzine did not differ significantly. Somnolence as recorded on the visual analog scale did not correlate with the mean serum diphenhydramine concentration measured at 2 h ($P = 0.197$, $r = 0.352$) or with the mean serum hydroxyzine concentration measured at 2 h ($P = 0.919$, $r = 0.031$).

Discussion

In this single-dose study in children with well-controlled allergic rhinitis, we have documented the adverse CNS effects of diphenhydramine and hydroxyzine and related them to the ability of these H_1 -receptor antagonists to produce peripheral H_1 -blockade. The single diphenhydramine and hydroxyzine doses administered were equivalent to 10–20% of the maximum recommended daily dose of each H_1 -receptor antagonist for children aged 6–12 years (9). This is the first objective documentation of the relative CNS adverse effects and beneficial effects of these medications ever performed in a pediatric age group.

Further evidence of the adverse CNS effects of old, first-generation H_1 -receptor antagonists such as diphenhydramine and hydroxyzine in children comes from case reports of toxicity after oral overdose or even after topical application to the skin (6, 7, 19–21). Diphenhydramine has been used in the treatment of insomnia and to facilitate sleep electroencephalograms (EEGs) (22, 23), and hydroxyzine is still used occasionally as a preoperative sedative (24, 25). Diphenhydramine in a dose of 25 mg may exacerbate the learning impairment found in children with symptoms of allergic rhinitis (2).

Diphenhydramine and hydroxyzine produce CNS adverse effects because, like other, older H_1 -receptor antagonists, they cross the blood-brain barrier readily and bind to H_1 -receptors in the CNS, as well as to cholinergic, serotonergic, and α -adrenergic receptors (26–29).

In adults, the CNS dysfunction produced by diphenhydramine and hydroxyzine has been well documented in performance tests and EEG studies, in which they are frequently used as the positive controls when the potential sedative effects of newer H_1 -receptor antagonists are being investigated (5–8). In this population, tolerance to the adverse CNS effects of older H_1 -receptor antagonists during regular use has been documented in some, but not all, studies (6, 7). Whether or not tolerance to the CNS effects of diphenhydramine or hydroxyzine occurs during regular use in children is open to speculation and should be investigated in future studies in young subjects.

Physicians still recommend diphenhydramine or hydroxyzine for symptom relief of allergic disorders in children, because of their cost-effectiveness (30) and because newer, nonsedating H_1 -receptor antagonists are not available in pediatric formulations in all countries. As the beneficial effects of the older H_1 -receptor antagonists are similar to those of the newer ones (31), the potential risk of adverse CNS effects, including impaired cognitive function or somnolence, becomes an important factor to be considered when selecting an H_1 -receptor antagonist for therapeutic use (2–8). The results of this study suggest that sporadic use of diphenhydramine and hydroxyzine should probably be avoided by children participating in academic or sports activities requiring optimal cognitive functioning and alertness. Rather, their use should be reserved for situations in which some sedation is acceptable; for example, during treatment of severe pruritus caused by urticaria or atopic dermatitis.

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