

Histamine blockade after astemizole in children: a single-dose, placebo-controlled study

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In children, the non-sedating, long-acting H₁-receptor antagonist astemizole is widely used for symptom relief in allergic disorders (1–8), especially in seasonal and perennial allergic rhinoconjunctivitis (1–5), and chronic urticaria (6). An astemizole dose of 0.2 mg/kg once daily is recommended for children under age 6 years and 5 mg once daily is recommended for those age 6–12 years (9). In children age 6–16 years, astemizole is well-absorbed and its active metabolite desmethylastemizole has a serum elimination half-life of 11.2 days (10). There is a paucity of published information about the effect of astemizole on skin tests in children.

We hypothesized that a single dose of astemizole would suppress the histamine-induced wheal in children. We tested this hypothesis in a randomized, placebo-controlled, double-blind, crossover study in children with allergic rhinitis.

Methods

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

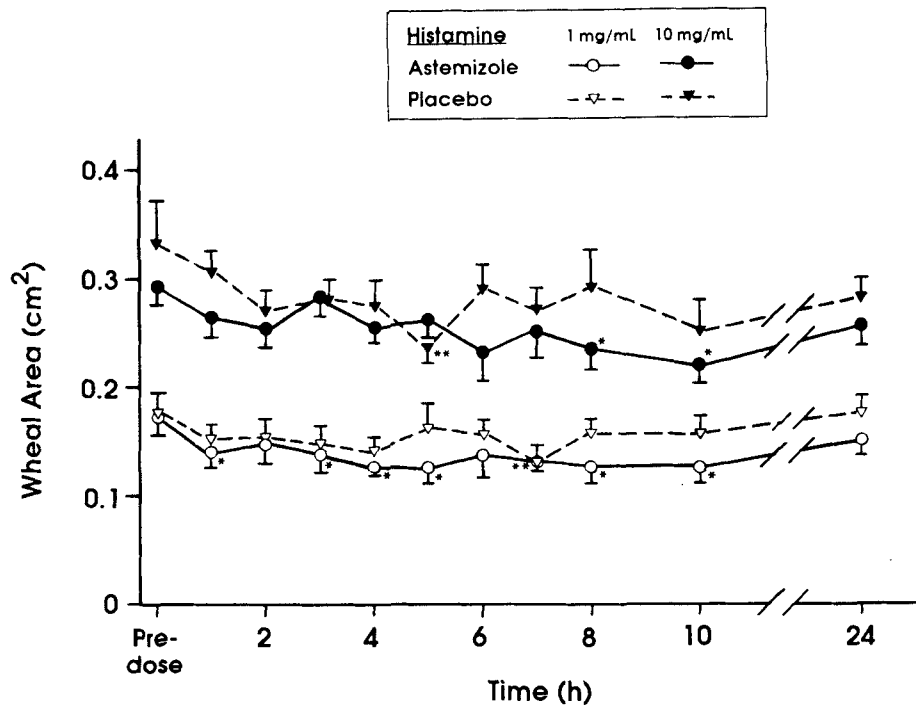
We randomly selected children age 3–8 years being treated for allergic rhinitis in the Allergy Clinic of the Children's Hospital of Winnipeg, who had not taken H₁-receptor antagonists for 7 or more days before the study and had not taken astemizole for 120 days before the study (11–13). Children weigh-

ing more than 25 kg, those with medical disorders other than allergic rhinitis and mild asthma, and those with a history of adverse reactions to H₁-receptor antagonists were excluded.

The children came to the Health Sciences Clinical Research Centre at 0800 after an 8-h fast. After a directed history and physical examination, they received a single dose of astemizole 0.2 mg/kg, maximum dose 5 mg, as astemizole (Hismanal) suspension 2.0 mg/mL, or placebo suspension, with 120 mL water. Sips of apple juice were permitted during the fast and for the first 2 h after astemizole or placebo ingestion. Two hours after astemizole or placebo ingestion, a standardized light meal was served.

Epicutaneous tests with histamine phosphate solution, 1 mg/mL and 10 mg/mL were performed in a predetermined sequence of sites on the volar surface of the forearm pre-dose, hourly from 1–8 h post-dose, and at 10 and 24 h post-dose. Ten minutes after the test was performed, the sites were examined and the wheal circumferences were traced using a felt tip marker. Wheal areas were calculated using stereometric measurement software and an IBM PC and digitizer (14, 15). The histamine-induced wheals were analyzed as absolute values and as percent reduction of control values obtained before the astemizole or placebo. The mean wheal sizes were compared to determine if there were any differences over time, using the two-way analysis of variance and Tukey and Bonferroni multiple range tests. Differences were considered significant at $p < 0.05$ (14,

Fig. 1. Mean wheal areas after epicutaneous histamine phosphate 1 mg/mL and 10 mg/mL: suppression by astemizole and placebo. * indicates significant difference, astemizole from predose wheal area ($p < 0.05$); ** indicates significant difference, placebo from predose wheal area ($p < 0.05$).



15). With 15 patients enrolled, this 2-way crossover study had a power of at least 90% to detect a 20% difference in suppression of the histamine-induced wheal by astemizole and placebo. A type 1 error of 0.05 was used on one-sided tests.

After wheal size returned to baseline, at least two weeks after the first study day, the children returned to the Health Sciences Clinical Research Centre at 0800 hours for a dose of either astemizole or placebo suspension, whichever had not been given on the initial study day, and the study was repeated as above.

At the times of skin tests, the children were questioned about mouth dryness, excitement, sedation, disorientation, dizziness, headache, sweating, nausea, vomiting, diarrhea, and difficulty urinating.

Results

Fifteen patients (12 male), mean age 5.2 ± 1.2 years (range 3.5 to 7.5 years) and mean weight 19.1 ± 2.7 kg, completed the study.

After administration of a single dose of astemizole, there was significant suppression of the wheal areas compared to predose values ($p < 0.05$), at 1, 3, 4, 5, 8, and 10 h when the test was performed with histamine 1 mg/mL, and at 8 and 10 h when the test was performed with histamine 10 mg/mL. After administration of a single dose of placebo, there was significant suppression of the wheal areas compared to pre-dose values ($p < 0.05$) at 7 h (histamine 1 mg/mL) and at 5 h (histamine 10 mg/mL). Peak suppression of histamine-induced wheal areas after

astemizole was 32–37%, higher than peak suppression of 24–26% after placebo, but the differences in wheal suppression produced by astemizole and by placebo were not statistically significant at any time (Fig. 1). No adverse effects were reported or observed.

Discussion

This study was performed using the manufacturers' recommended doses of astemizole in children with chronic allergic rhinitis who would potentially benefit from administration of an H_1 -receptor antagonist. All the children had experienced epicutaneous tests previously and could therefore give informed assent to these tests. The subjective effect of astemizole in suppression of signs and symptoms of allergic rhinitis was not studied because in single dose studies in small populations, it is a relatively insensitive measurement of the onset of action, duration of action and efficacy of an H_1 -receptor antagonist, in contrast to objective measurement of the histamine-induced wheal. In our laboratory, the wheal suppression bioassay has been found to be extremely useful for assessment of onset, duration, and extent of action of H_1 -receptor antagonists, and has a coefficient of variation of less than 5% over 6 months (14, 15).

Astemizole is an effective H_1 -receptor antagonist which has been well-studied in adults, although not in children. Peak suppression of the histamine-induced wheal of approximately 90% can be achieved promptly if a dose higher than that recommended by the manufacturer, for example, a 30 mg loading dose

is used (11, 16, 17), or if the tests are performed after one or more weeks of treatment (11, 12, 13, 17, 18). The wheal and flare suppression produced by a short course of astemizole is long-lasting; indeed, in some patients, a one or two-week course of astemizole results in wheal and flare suppression that lasts many weeks longer than the original duration of treatment. This is the reason for the requirement in this study that no patients had taken a course of astemizole within 120 days of the study.

Conflicting results have been published with regard to whether or not a single 10 mg dose of astemizole, the manufacturers' recommend dose in adults, produces significant histamine blockade (15, 19). From the pharmacokinetic point-of-view, there is no reason why it should not do so, as it is well-absorbed (10, 20). At the cellular level, however, the kinetics of astemizole binding and dissociation from H_1 -receptors are unique and it neither binds as readily nor dissociates as readily as other currently used H_1 -receptor antagonists (21).

The minimal peripheral histamine blockade produced by a single dose of astemizole in our patients may relate to a possible delay in onset of clinical efficacy after a single dose of this medication. Our data suggest that parents should be informed that astemizole may not exert its maximal antihistaminic effect in children after only one dose. Otherwise, they may erroneously conclude that it is ineffective, thus denying their child potential symptom relief in a disorder such as allergic rhinoconjunctivitis or chronic urticaria.

Although administration of a loading dose of astemizole does produce statistically and clinically significant histamine blockade (11, 17), and has been advised as a way to achieve rapid onset of the effect of this medication in adults (22), this is no longer recommended, as rarely some young patients who have taken an overdose of astemizole have experienced prolonged QTc interval and ventricular arrhythmias, including torsades de pointes (23–26).

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