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The second-generation (peripherally-selective) antihistamines in children

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A number of changes have occurred since 1995, when the first review of antihistamines was published in *Pediatric Pharmacotherapy*. While several new antihistamines have been introduced onto the market during the past six years, others have been withdrawn. During this period, the proarrhythmic effect of some antihistamines became known, leading to the voluntary removal of terfenadine and astemizole by their manufacturers. In addition to our general increase in knowledge about adverse effects, much more information is available on the safety and efficacy of these drugs in atopic children. In this review, we will focus on the three second generation antihistamines currently available, cetirizine, fexofenadine (the active metabolite of terfenadine), and loratadine, and their use in the pediatric population.

Mechanism of action

All antihistamines are reversible, competitive antagonists at histaminic (H_1) receptors. They act by inhibiting binding of circulating histamine to its receptor site, but do not prevent histamine release. Administration of an antihistamine results in inhibition of respiratory, vascular, and gastrointestinal smooth muscle constriction, a decrease in histamine-activated secretions from salivary and lacrimal glands, and anti-inflammatory effects. Antihistamines also decrease capillary permeability, which reduces the wheal and flare response to an allergen, as well as diminishes itching.[1]

The second generation antihistamines are selective for peripheral H_1 receptors. These agents are associated with less sedation and anticholinergic effects than the non-selective first generation antihistamines. The current agents also lack the cardiotoxic effects of the first peripherally-selective agents, terfenadine and astemizole.[2,3]

Recent Clinical Trials

The safety and efficacy of the second generation antihistamines are well established in adolescents and adults.[2,4] Although there are differences in potency as measured by their ability to suppress a histamine-induced wheal and flare response (cetirizine > fexofenadine > loratadine), there appears to be relatively little difference in patient response at equivalent doses.[5,6]

Several studies have become available in recent years that describe the efficacy of the second generation antihistamines in younger children. In 1999, Sienra-Monge and colleagues published the results of a trial comparing cetirizine and loratadine in children ages 2-6 years.[7] Eighty children with known allergies were randomized in this prospective, double-blind, longitudinal study. The children received a dose of 0.2 mg/kg of either drug for a period of 28 days. As anticipated, cetirizine produced a significantly greater inhibition of the wheal response compared with loratadine. Eosinophil counts and global evaluations by the investigators were not different between the groups. Both drugs produced significant improvement in symptoms, according to the parents' diaries, but cetirizine appeared to cause a greater reduction in rhinorrhea, sneezing, nasal obstruction, and nasal pruritis. The authors concluded that both drugs were well tolerated and effective, with a greater response seen from cetirizine.

Over the past several years, results from the Early Treatment of the Atopic Child (ETAC) program have provided clinicians with a great deal of information about antihistamines in

toddlers.[8,9] These investigators hypothesized that early intervention with an antihistamine would be safe in atopic young children and would prevent or delay the onset of asthma. A total of 817 European children with atopic dermatitis at 1 to 2 years of age were randomized to receive 0.25 mg/kg cetirizine twice daily or placebo. While the overall analysis failed to reach statistical significance, in the subset of children sensitized to pollen or dust mites, there was a 50% reduction in the development of asthma symptoms compared to the placebo group.[8]

The safety evaluation conducted during the ETAC trial was published separately.[9] A total of 399 children receiving cetirizine and 396 receiving placebo were evaluated over a period of 18 months. Compared with placebo, the cetirizine-treated toddlers had no clinically relevant differences in neurologic or cardiovascular symptoms, growth, behavior, developmental assessments, or laboratory tests. The overall rate of adverse effects was 2.3% in the cetirizine group versus 2.0% for placebo.

Pharmacokinetics

The pharmacokinetic profiles of the second generation antihistamines have been well studied in adults. All three agents have a rapid onset of action, with a time to maximum concentration averaging 1 to 2 hours. Administration with food causes a delay in absorption that is not believed to be clinically significant. Cetirizine and fexofenadine are primarily excreted as unchanged drug, with average elimination half-lives in adults of 8 and 14 hours, respectively. Loratadine undergoes hepatic metabolism through the cytochrome P450 enzyme system, with an average half-life of 8 to 28 hours for the parent drug and active metabolites.[1]

Children appear to have a more rapid elimination of cetirizine than adults. In a study of 15 infants and toddlers (age range 6 to 23 months) given a single cetirizine dose of 0.25 mg/kg, Spicak and colleagues found an average elimination half-life of 3.1$\pm$1.8 hours, with an apparent oral clearance of 2.13$\pm$1.15 ml/min/kg and an apparent volume of distribution of 0.44$\pm$019 L/kg.[10] Approximately 67% of the dose was excreted unchanged. In a study of 2-6 year old children given a 5 mg oral dose, elimination half-life was 5.55$\pm$0.98 hours, with an apparent clearance of 1.27$\pm$0.80 ml/min/kg and an apparent volume of distribution of 0.60$\pm$0.38 L/kg.[11] Despite this more rapid elimination, duration of effect was similar to that of adults, so that no change in dose appears to be needed.

Pharmacokinetic studies of both fexofenadine and loratadine in children have provided results similar to those in adults. Fexofenadine pharmacokinetic parameters were evaluated in a study of 14 children (mean age 9.8+1.8 years). The patients were given a single 30 or 60 mg oral dose. Average elimination half-lives were 18.3$\pm$2.0 and 17.6$\pm$1.0 hours, for the 30 and 60 mg doses, respectively, and were comparable to adult values.[12] The pharmacokinetics of loratadine were studied in 18 children (ages 2-5 years).[13] Each patient was given a single 5 mg oral dose. Time to maximum concentration averaged 1.17$\pm$0.38 hours with an area under the curve for the desloratadine metabolite of 61.4$\pm$25.4 ng · hr/ml, similar to values for adults.

Drug Interactions

Because of its metabolism by cytochrome P450 3A4 and 2D6 isozymes, loratadine clearance is affected by drugs altering these pathways. Azole antifungals (fluconazole, itraconazole, ketoconazole, and miconazole), cimetidine, and macrolide antibiotics (azithromycin, clarithromycin, and erythromycin) can inhibit loratadine metabolism, resulting in increased plasma levels.[1] While toxic drug accumulation has not been reported in patients taking these drugs with loratadine[2], it is advisable to switch patients to an alternative second generation antihistamine to avoid a potential interaction.

Adverse Effects

In general, the second generation antihistamines are well tolerated. Despite their relative selectivity for peripheral receptors, some patients may still experience drowsiness and fatigue. Sedation appears to occur most frequently with cetirizine (14%), occasionally with loratadine (8%), and rarely with fexofenadine (1%). Other adverse effects reported with this class include: headache (1-12%), dry mouth (3-5%), sore throat (1-2%), and nausea, vomiting, or stomach pain (1-2%).[1,2]

Overdoses have been reported with the second generation antihistamines in both adults and children. Symptoms of overdose commonly include central nervous system (CNS) depression, arrhythmias, and cardiovascular collapse. In children, paradoxical CNS stimulation may be present, with hallucinations, psychosis, delirium, ataxia, and seizures.[1,14] Management of an overdose should begin with gut decontamination, followed by supportive care. Hemoperfusion may be used in extreme cases; none of the second generation antihistamines are removed by dialysis.[1]

Effects on Learning

The negative effects of allergies on learning are well known. While the first generation antihistamines have been beneficial in relieving allergy symptoms, they often impaired learning by producing sedation.[2] The second generation agents appear to offer a significant benefit in this area; although to date, only the effects of loratadine on school performance have been evaluated. In a 1993 study by Vuurman and colleagues, 52 children with allergic rhinitis (ages 10 to 12 years) were randomized to receive either loratadine at a dose of 10 mg per day, diphenhydramine at a dose of 25 mg twice daily, or a placebo for two weeks.[15] Their results were compared to a control group of 21 children without allergies who were receiving no medication. The atopic children in the placebo and diphenhydramine groups scored significantly lower than the control group on the standardized computer simulation. The subjects in the loratadine group achieved better scores than the other treatment groups, but were still inferior to the controls. The authors concluded that allergic reactions reduce learning ability, but that this impairment may be partially offset by the use of loratadine.

Similar results have been found in a number of trials comparing the first and second generation agents in adults during tests of cognitive and psychomotor performance.[16,17] The second generation antihistamines have significantly less effect on performance than the first generation agents or placebo. Among the second generation antihistamines, cetirizine appears to have a greater potential to adversely affect performance, likely as a result of its sedating effects.[18]

Dosing Recommendations

Cetirizine dosing for children 2-5 years of age is 2.5 mg given once daily. For adults and children 6 years of age and older, dosing should begin at 5 mg given once daily. Dosing may be increased to 10 mg once daily depending on symptom severity. In patients with decreased renal or hepatic function, the lower 5 mg dose is recommended.

Therapy with fexofenadine should begin at 30 mg given twice daily in children 6-11 years of age and at 60 mg twice daily or 180 mg once daily for adults and children 12 years of age and older. In patients with renal impairment, it is recommended that 60 mg be given once daily.

Loratadine may be given to children 2-5 years of age at a dose of 5 mg once daily. In children 6 years of age and older and adults, a 10 mg dose may be given once daily. Patients with renal or hepatic dysfunction should be given the standard dose only every other day. All of the second generation antihistamines may be given without regard to meals.

Availability

Cetirizine hydrochloride is marketed as Zyrtec® by Pfizer. It is available in 5 and 10 mg tablets, as well as a 5 mg/5 ml banana-grape flavor syrup. Fexofenadine, Allegra® by Aventis, is available in 30, 60, and 180 mg tablets and 60 mg capsules. Loratadine is marketed by Schering-Plough under the brand name Claritin®. It comes as regular 10 mg tablets, a rapidly-disintegrating mint flavored 10 mg tablet, and a 1 mg/ml fruit flavored syrup. Both Zyrtec® and Claritin® syrups contain sugar, but are alcohol and dye-free.

None of the second generation antihistamines are currently available as generic products. Patent life for several of these products is nearing its end; it is expected that generics will be available in the future. It is anticipated that Schering-Plough's desloratadine (Clarinex®), the active metabolite of loratadine, will be released later this year.[19] In the future, single isomer preparations of some of these products can also be expected.

Cost

Average wholesale prices (AWP) for a month supply of the second generation antihistamines are listed below. While similar in price, it should be remembered that these agents, because of their prescription-only status, are significantly more expensive than the first generation (nonselective) antihistamines.

Cetirizine	
5 or 10 mg tablets (#30)	$57.53[a]
120 ml syrup (for a child)	28.03
Fexofenadine	
60 mg tablets (#60)	59.66
Loratadine	
10 mg regular tablets (#30)	67.30
10 mg disintegrating tablets (#30)	77.60
120 ml syrup (for a child)	28.02

[a] Cost for approximately 1 month of therapy based on AWP listings in Drug Topics Red Book 2000.

Summary

The second generation antihistamines offer significant advantages with less sedation and anticholinergic effects than the first generation agents, resulting in less disruption of daily activities and interference with school performance. Selection of an antihistamine from

within this group should be based on the individual child's needs. Cetirizine provides the greatest antihistaminic effect, but causes the greatest degree of sedation. In young children, loratadine may be a better, since it has been shown to have little impact on cognitive function and is available in an oral liquid dosage form. Fexofenadine, the least sedating of the group, may be the best choice for older children now that it can be dosed once daily. With continued research in this area, it appears that the second generation antihistamines will become a mainstay in the treatment of atopic children.

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Pharmacology Literature Review

Nitric oxide review

This review describes the research conducted to date with inhaled nitric oxide in the treatment of pulmonary hypertension in premature and term neonates. The authors focus on the eight clinical trials that have been conducted in neonates, but include some smaller reports and animal research as background. Hoehn T, Krause MF. Response to inhaled nitric oxide in premature and term neonates. **Drugs 2001;61:27-39.**

Sotalol pharmacokinetics/dynamics

The relationship between dose, concentration, and antiarrhythmic effects of sotalol were evaluated in 25 children. The subjects were divided by age (neonates, infants, and children 2-12 years) and given oral sotalol doses of 10, 30, and 70 mg/m^2. Clearance was linearly correlated with body surface area and creatinine clearance. As anticipated, increases in QT_c and R-R intervals were dose related. There was also a linear relationship between serum concentration and antiarrhythmic response. Saul JP, Ross B, Schaffer MS, et al. Pharmacokinetics and pharmacodynamics of sotalol in a pediatric population with supraventricular and ventricular tachyarrhythmia. **Clin Pharmacol Ther 2001;69:14-57.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/23/01:

1. The restriction on eptifibatide (Integrilin®) was amended to include patients with acute coronary syndrome.
3. The restriction on olanzapine (Zyprexa®) was amended to include use by Neurology.
2. Botulinum toxin type B injection (Myobloc®) was added to the Formulary for patients with cervical dystonia unresponsive to botulinum toxin type A. Use of this drug is restricted to the Neurology division.

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