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ANTIHISTAMINES FOR THE TREATMENT OF ALLERGIC RHINITIS IN CHILDREN

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It has been estimated that more than 10% of school-age children have seasonal allergic rhinitis. Although considered a relatively minor illness by many health care professionals, allergic reactions can result in missed school days, poor school performance, and impaired function on standardized tests (1). The management of allergic rhinitis consists primarily of the administration of H1-receptor antagonists (antihistamines). There is a wide array of products marketed in the United States, including both products which are available over-the-counter (OTC) and those which require a prescription(2-6). This brief review is designed to provide basic information regarding the selection and monitoring of antihistamines in children.

First-generation Antihistamines

These agents were the first H1-receptor antagonists available. They have been marketed in the United States since the 1950's. Many of the products within this group are available without a prescription. These agents are very effective, although they cause varying degrees of drowsiness which limits their usefulness. There are five major classes of first-generation antihistamines: alkylamines, ethanolamines, ethylenediamines, piperazines, and phenothiazines. Ethylenediamines (e.g. tripelennamine) and phenothiazines (e.g. promethazine) are rarely used in children with allergies due to their ability to cause gastric upset and excessive sedation. Piperazines, such as hydroxyzine, are used primarily to prevent motion sickness. Alkylamines and ethanolamines make up the largest component of the OTC antihistamine market. A small sample of the agents available is provided below. All of these agents are available in both solid (tablet or capsule) and liquid dosage forms. Many of these agents also are available in a sustained release preparation allowing twice daily dosing (6).

Oral Dosing Recommendations and Example Products

ALKYLAMINES

Brompheniramine (Dimetane®)
children < 6 yrs
0.125 mg/kg q 6-8 hrs (maximum 8 mg/day)
children 6-12 yrs
2-4 mg q 6-8 hrs (maximum 16 mg/day)
adolescents and adults
4-8 mg q 6-8 hrs (maximum 24 mg/day) or
8-12 mg q 12 hrs if using sustained release product

Chlorpheniramine (Chlor-Treimeton®)
children < 6 yrs
1 mg q 4-6 hrs (or 0.35 mg/kg/day) (maximum 8 mg/day)
children 6-12 yrs
2 mg q 4-6 hrs (maximum 12 mg/day) or
8 mg q 12 hrs if using sustained release product
adolescents and adults
4 mg q 4-6 hrs (maximum 24 mg/day) or
8-12 mg q 12 hrs if using a sustained release product

ETHANOLAMINES

Clemastine
adolescents and adults

(Tavist®) 1.24-2.68 mg q 12 hrs

Diphenhydramine children < 12 yrs
(Benadryl®) 5 mg/kg/day in divided doses every 6-8 hrs (maximum 300 mg/day)
adolescents and adults
10-50 mg every 4-8 hrs (maximum 400 mg/day)

Drug interactions are relatively infrequent with the first-generation antihistamines. The greatest potential risk is for the concomitant use of monoamine-oxidase inhibitors (phenelzine, tranylcypromine) which potentiate the anticholinergic properties of the first-generation antihistamines, resulting in hypotension and extrapyramidal effects. Patients and their families should also be aware of the additive sedative effects of alcohol and other CNS depressants with antihistamines (3).

The most frequent, and often dose-limiting, adverse effect associated with the first-generation antihistamines is sedation (3). This may affect patients in a variety of ways, ranging from impairment of learning and poor school performance (1) to adversely affecting driving performance in teen-agers (2,5). Most patients appear to become somewhat tolerant to the sedative effects after repeated dosing. Alkylamines are more likely to cause paradoxical excitation in children than other antihistamines. Other toxicities result from the anticholinergic effects of these agents and may include dry mouth, gastrointestinal upset, blurred vision, urinary retention, and tachycardia (3).

Although considered safe enough for over-the-counter use, an overdose of these agents can result in severe morbidity and mortality (5,7). Toxicity may be expressed as pronounced CNS depression or by signs of anticholinergic excess, including seizures. Approximately 5,000 to 10,000 accidental ingestions of antihistamines occur each year in children under six years of age (5). Fortunately few are fatal; however, the potential for severe consequences should be kept in mind when recommending routine use of these agents by any family member in a household with small children.

Second-generation Antihistamines

The adverse effect profile of the first-generation antihistamines led to interest in the development of newer agents. The second-generation, or "non-sedating" antihistamines, were designed to provide relief from allergy symptoms while minimizing adverse CNS effects. These agents are less likely to cross the blood-brain barrier due to the large size and ionic charge of their chemical structures. In addition, these agents lack affinity for muscarinic receptors so they possess no anticholinergic effects (3). Although currently available by prescription only, these agents have begun to eclipse the first-generation antihistamines as the treatment of choice for allergic rhinitis.

There are currently three second-generation antihistamines on the market in the United States, with several others in development or available in European countries. Terfenadine was the first non-sedating antihistamine available. It has been studied in several pediatric trials (8-12). It has been shown to be effective, compared to placebo, in controlling allergic symptoms in children (9). In addition, it has been found to be equally efficacious as first-generation agents in reducing allergy symptoms while producing significantly less sedative effect (10).

Loratadine and astemizole have also been shown to benefit children with allergic rhinitis (11-13). Comparison studies of these agents with terfenadine have shown them to be equally efficacious for allergic rhinitis in children (11,12). Of particular interest to health care professionals treating children, both loratadine and terfenadine have been found to be significantly better than placebo, chlorpheniramine, or diphenhydramine in improving performance on tests of cognitive function in children with allergic rhinitis (1,10). In contrast, a study comparing astemizole to chlorpheniramine found that neither preparation adversely affected test performance (13). Differences in testing study design and testing procedures may account for the variation in results.

At this time, however, more long-term studies are needed. None of the second-generation products marketed in the United States carry labeling for pediatric use, nor are they available in a liquid dosage form. These products are available in European countries as liquids and it is expected that they will eventually be available in the United States.

Oral Dosing Recommendations (2)

Astemizole (Hismanal®)	Children < 12 yrs 0.2 mg/kg once daily Adolescents and Adults 10 mg once daily
Loratadine (Claritin®)	Children 2-12 yrs 5 mg once daily Adolescents and Adults 10 mg once daily
Terfenadine (Seldane®)	Children 3-6 yrs 15 mg twice daily Children 6-12 yrs 30-60 mg twice daily Adolescents and Adults 60 mg twice daily

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There are several significant drug interactions with the second-generation agents. Astemizole and terfenadine are metabolized by CYP3A enzymes, part of the cytochrome P450 enzyme system. Medications which block this type of hepatic metabolism may impair the metabolism of astemizole and terfenadine. Concomitant administration of ketoconazole, itraconazole, erythromycin, clarithromycin, and diltiazem may increase serum concentrations of these antihistamines (2,3,6). Loratadine is not affected by these drug interactions.

Although the second-generation agents cause fewer adverse effects than the first-generation antihistamines, the reactions may be severe in nature. High serum concentrations of astemizole and terfenadine, whether occuring as the result of excessive doses or by inhibition of metabolism by other drugs as described above, have resulted in a prolonged QTc interval, leading to the development of torsades de pointes (14-16). The mechanism of this toxicity is not fully understood (3). Doses as small as three to four astemizole tablets have resulted in ECG abnormalities in two-year-old children (15). Activated charcoal is recommended in cases of accidental ingestion, followed by close observation until the QTc interval has returned to normal.

Lidocaine, flecainide, propranolol, and cardioversion have been used successfully to reverse the arrhythmias. Most cases reported have involved hospitalization for a period from three to five days (15,16). Patients with known cardiac conduction defects or hepatic dysfunction capable of impairing drug metabolism should not receive astemizole or terfenadine.

Cost Comparison

The following table lists average wholesale price (AWP) for several antihistamines. This represents the average cost for a pharmacy to purchase the medication. The cost to the patient will vary depending on the brand chosen, the availability of generic dosage forms, and the use of products requiring a prescription.

Antihistamine product	dosage form	quantity	cost
Brompheniramine			
-brand (Dimetane®)	2 mg/5ml elixir	120 ml	$3.12
	4 mg tablet	100	$8.64
-generic	2 mg/5ml elixir	120 ml	$1.25
	4 mg tablet	100	$2.25
Chlorpheniramine			
-brand (Chlor-Trimeton®)	2 mg/5ml syrup	120 ml	$4.26
	4 mg tablet	100	$12.23
-generic	2 mg/5ml syrup	120 ml	$2.62
	4 mg tablet	100	$3.05
Clemastine			
-brand (Tavist®)	1.34 mg tablet	16	$6.41
-generic	1.34 mg tablet	16	$5.85
Diphyhydramine			
-brand (Benadryl®)	12.5 mg/5 ml	240 ml	$7.04
	25 mg capsule	100	$11.05
-generic	12.5 mg/5 ml	240 ml	$3.15
	25 mg capsule	100	$4.33
Astemizole (Hismanal®)	10 mg tablet	30	$55.50
Loratadine (Claritin®)	10 mg tablet	30	$55.30
Terfenadine (Seldane®)	60 mg tablet	60	$73.56

Product Selection

Selection of antihistaminic therapy for children should incorporate efficacy, potential adverse effects, cost, and patient preference. The first-generation products, while being associated with a

variety of adverse effects, offer the advantage of being available in liquid dosage forms. In addition since most are available without a prescription, they are often much less expensive than the second-generation agents. Inexpensive store brands are available in most retail chain pharmacies. Although a number of products are available, it is advisable to recommend only those products which contain alkylamines or ethanolamines in order to minimize sedation. To further minimize adverse effects, avoid chronic use of combination products unless the decongestant component is considered to be absolutely necessary.

The second-generation antihistamines offer significant advantages for children with allergies, despite the lack of FDA-approved pediatric indications. The absence of sedative effects with these agents should be strongly considered when planning long-term medication use. In older children, compliance may be improved with the use of the longer-acting or sustained release products of either generation. For many patients, once or twice daily dosing will eliminate the need to take medication to school.

In summary, clinicians and families are faced with a wide variety of choices for the treatment of allergic rhinitis in children. Although further research is needed to clarify dosing recommendations for the second-generation antihistamines, there are now substantial data to document the benefits of their use in school-age children. Regardless of the agent chosen, patients and their families should be informed of potential adverse effects and drug interactions when using antihistamines.

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FDA News

The FDA has recently appointed a task force to assist vaccine manufacturers with the accelerated approval of the use of acellular pertussis vaccines (DTaP) in infants. DTaP vaccines have been associated with fewer adverse effects than vaccines with a whole-cell pertussis component. Two DTaP products are marketed in the US, Tripedia® from Connaught Labs and Acel-Imune® from Lederle-Praxis. These products are currently approved only for booster doses in children 15 months and older. The amended approval would allow use of these products during the entire immunization cycle, starting at 2 months of age.

Pharmacology Literature Review

1994 Leading Pharmaceuticals

The list of leading dollar volume pharmaceuticals has been tabulated for 1994. This index, a sample of nearly 7,000 institutions, is designed to assist pharmacies in budgetary planning. The top twenty-five products (listed in order of hospital dollars spent) are: ceftriaxone, epoetin alfa, filgrastim, alteplase, midazolam, ondansetron, intravenous immune globulin, ciprofloxacin, paclitaxel, propofol, ranitidine, urokinase, isoflurane, albumin, ceftazidime, ampicillin, ampicillin/ticarcillin with clavulanic acid, vecuronium, imipenem, fluconazole, ketorolac, etoposide, acyclovir, cefazolin, and atracurium. Alteplase, a tissue plasminogen activator used after myocardial infarction, and midazolam are the fastest growing products on the list. Ramspacher S. Leading 1994 dollar volume pharmaceuticals. **Hospital Pharmacy 1995;30:666-9, 673.**

Drug-induced Skin Reactions

The authors present a thorough review of severe skin reactions associated with medication use. Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndromes, vasculitis,

serum sickness, and angioedema are included. For those new practitioners who have yet to see a patient with one of these reactions, the article includes full color photographs. Methods for diagnosis and management of these conditions also are reviewed. Wolkenstein P, Revuz J. Drug-induced severe skin reactions: Incidence, management, and prevention. **Drug Safety 1995;13:56-68.**

Etoposide Pharmacokinetics & Pharmacodynamics

The pharmacokinetics of etoposide were studied in 18 children receiving a dosage of 25-75 mg/m2/day in three divided doses for a period of 21 days. Oral bioavailability was approximately 50%. Average clearance was 21.4 ml/min/m2, similar to values found in children after intravenous etoposide administration. The authors also found a strong correlation between neutropenia and the relative systemic etoposide exposure (time with a serum etoposide concentration > 1 microgram/ml). Sonnichsen DS, Ribeiro RC, Luo X et al. Pharmacokinetics and pharmacodynamics of 21-day continuous oral etoposide in pediatric patients with solid tumors. **Clin Pharmacol Ther 1995;58:99-107.**

Macrolide Drug Interactions

This brief review describes the established as well as suspected drug interactions involving the macrolide antibiotics. The three macrolides in current use in the United States, erythromycin, clarithromycin, and azithromycin are included as well as a number of investigational agents and compounds available in other countries. von Rosenstiel N, Adam D. Macrolide antibacterials: Drug interactions of clinical significance. **Drug Safety 1995;13:105-22.**

New Theophylline Guidelines

In 1994, concern over the potential misuse of theophylline led the FDA to appoint a panel to review the labeling of all theophylline-containing products. As a result of this panel's work, the FDA has issued revised labeling requirements for all immediate-release theophylline products. This article reviews the new labeling guidelines in addition to providing in-depth information on monitoring serum theophylline concentrations, recognizing signs and symptoms of toxicity, and identifying clinically significant drug interactions. Hendeles L, Jenkins J, Temple R. Revised FDA labeling guideline for theophylline oral dosage forms. **Pharmacotherapy 1995;15:409-27.**

Ticarcillin/Clavulanic Acid Dosing

The addition of clavulanic acid to ticarcillin effectively extends its spectrum to include beta-lactamase producing bacterial strains. The pharmacokinetic and pharmacodynamic characteristics of this combination were studied in 22 children to determine appropriate dosage recommendations. The authors used a relatively new tool, the area under the inhibitory curve (AUIC), to assess dosing. This parameter is determined by dividing the area under the serum

concentration time curve (AUC) by the minimum inhibitory concentration (MIC). The estimated dosage required to maintain adequate AUIC values was 80 mg/kg ticarcillin (with 2.7 mg/kg clavulanic acid) administered every 8 hours. Reed MD, Yamashita TS, Blumer JL. Pharmacokinetic-based ticarcillin/clavulanic acid dose recommendations for infants and children. **J Clin Pharmacol 1995;35:658-65.**

Formulary Update

The Pharmacy and Therapeutics Committee took a summer recess and did not meet during August. Monthly sessions will resume in September.

If you have comments, questions, suggestions, or would like
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