

Clinical use of antihistamines in infants and children at risk of asthma development

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The prevalence of asthma, rhinitis, and dermatitis has increased remarkably in many countries over the past 30 years (1), and this has led to a greater awareness of the social and economic costs of allergic diseases. Moreover, bronchial asthma in children is a particular cause for concern as it has significant effects on their health, education, and quality of life. What, then, is the best approach to the treatment of children with asthma?

Bronchial challenge of an asthmatic child with, for example, an allergen extract will result in a largely IgE-mediated, immediate-type bronchoconstriction or early-phase reaction (EPR), which in a proportion of individuals will be followed by a late-phase reaction (LPR) some 8–13 h after provocation. It is thought that the LPR represents allergic inflammation in the airways in ongoing day-to-day asthma, even in very young children (2). Airway inflammation in asthma is characterized by infiltration of the bronchial mucosae by large numbers of proinflammatory cells, among which the eosinophil is prominent despite being a minority constituent of circulating leukocytes. T cells of the Th2 phenotype are present in the asthmatic airway and are thought to orchestrate eosinophilic inflammation via the release of cytokines which have profound effects on such eosinophil functions as proliferation, differentiation, accumulation, prolonged survival, and activation (3). The eosinophil has a potent armory of proinflammatory mediators, which include cytotoxic granule proteins, cytokines, and lipid mediators, with considerable potential to initiate and sustain an inflammatory response (4). Examination of endobronchial biopsies or bronchoalveolar lavage fluid from patients with mild or moderate asthma has demonstrated the presence of activated eosinophils whose

numbers correlate with disease severity (5). Moreover, eosinophil granule-derived mediators are heavily implicated in epithelial cell damage resulting in ciliary dysfunction and cell loss, both of which are thought to be central in the development of bronchial hyperresponsiveness (6). The latter can be measured in children by inhalation of histamine or methacholine (PC₂₀) followed by spirometry to assess lung function.

In children, bronchial hyperresponsiveness is not continuous and stable; for example, a child may present with very modest bronchial hyperresponsiveness, which can be greatly exacerbated by exposure to an allergen or by viral infection. In this situation, hyperresponsiveness becomes far more serious. Although we now routinely treat airway inflammation in young asthmatic children with inhaled corticosteroids, these have been widely available only for the last 20 years or so. Before this, first-generation antihistaminic drugs were widely used. Despite their side-effects, they were effective and had a modest place in the treatment of children with asthma.

For example, a group of children 12–24 months old were treated in a double-blind clinical study with ketotifen or placebo for 12 weeks. There was then a follow-up period of 4 weeks during which no treatment was given. We observed a statistically significant difference between the degree of wheeze in children taking placebo and that of children treated with ketotifen at the end of the 12-week treatment period (7). Interestingly, the effect of ketotifen was still significant compared with the placebo group 4 weeks after discontinuing treatment (Fig. 1). Similar results were seen in terms of the effect of ketotifen on nasal discharge (8). Other studies demonstrated positive effects by ketotifen in older children (9, 10). A reduction

in the subsequent prevalence of asthma was seen in infants with atopic dermatitis (11) and in infants with a history of allergy and raised serum total IgE (12).

However, the majority of studies which have examined the influence of antihistamines on asthma in young children have demonstrated only a modest therapeutic effect. This is a similar situation to that seen in the literature on adult asthma. For example, Wood-Baker & Holgate (13) compared the inhibition of bronchospasm due to inhalation of histamine or methacholine by astemizole, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyproheptadine, terfenadine, and placebo in a single group of patients with asthma. Compared with placebo, all the antihistamines provided significant protection against histamine-induced bronchoconstriction as determined by the histamine PC₂₀, cetirizine giving the greatest protection. However, none of the drugs tested had any protective effect against the effects of methacholine-induced bronchoconstriction. Furthermore, in atopic asthma patients, ebastine (14), cetirizine, and loratadine (15) effectively reduced the bronchial response to a histamine challenge. Thus, it appears that antihistamine treatment does have a favorable effect in asthma but cannot be equated with treatment with inhaled corticosteroids.

Asthma is normally treated with a combination of inhaled cromolyn, nedocromil, or corticosteroids plus β_2 -adrenergic agonists. If the condition requires further control, basic treatment can be supplemented by the use of long-acting β_2 -adrenergic agonists, theophylline, and oral corticosteroids. However, current asthma therapy is symptomatic in that discontinuation of inhaled steroids will lead to the return of asthma symptoms. To date, no intervention strategy has been shown to alter basically the natural history of the development of asthma or hay fever in children.

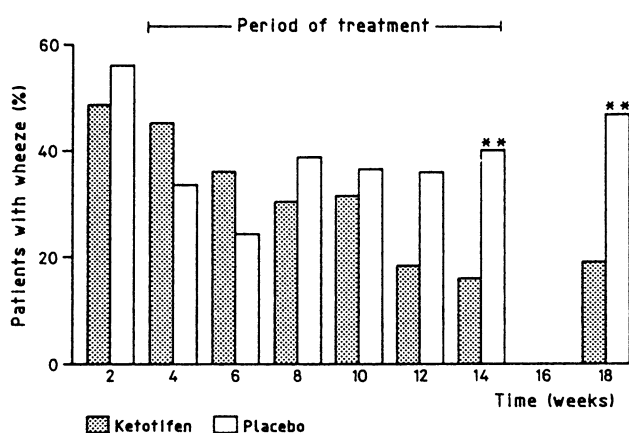


Figure 1. Number of patients with wheezing measured at 2-week intervals in course of 12-week treatment and for 4 weeks after discontinuation of treatment. Results for ketotifen and placebo groups are given in percentages of total number of patients. ** $P < 0.01$.

It is known that exposure to high levels of antigen in early life is a major trigger factor for subsequent development of asthma (16). There is therefore much interest in preventing in children the progression from atopic dermatitis to allergic asthma, a process known as the "allergic march". Cetirizine is a potent, safe, and selective second-generation antihistamine (17) with proven anti-inflammatory effects including inhibition of adhesion molecule expression, and neutrophil and monocyte accumulation. It has particular effects on eosinophil functions (reviewed in refs. 18 and 19). A recent large-scale multicenter study (ETAC [Early Treatment of the Atopic Child]) has assessed the ability of long-term treatment with cetirizine, compared with placebo, to prevent the onset of asthma in 817 children with atopic dermatitis from 12 European countries (20). Children were aged 12–24 months and selected on the basis of a diagnosis of atopic dermatitis, with no symptoms of asthma (wheezing and/or nocturnal cough), together with a parent or sibling history of atopic disease. The children were randomized into two groups and treated with cetirizine (0.25 mg/kg b.i.d.) or placebo. The number of children who developed asthma was compared between the two groups. Raised IgE levels and raised specific IgE to house-dust mite, grass pollen, or cat dander were found to predict the development of asthma. A raised blood eosinophil count just failed to reach significance as a predictor of asthma development. In children sensitized to pollen or house-dust mite, cetirizine treatment was found to halve the number of patients developing asthma. In the population which included all infants with normal or elevated specific or total IgE, there was no overall difference in the number of subjects developing asthma after receiving cetirizine or placebo. No effect by cetirizine was found in those subjects sensitive to cat-dander allergen, perhaps because most of the participating families choose to keep their pets. During the prolonged treatment period in these young children aged 1–2 years, there was no higher incidence of adverse events in the cetirizine group (2.3%) than the placebo group (2.0%) with the exception of urticaria, which was significantly less frequent in the cetirizine-treated group (5.8% vs 16.1% for the placebo group).

Cetirizine has been proven to be a safe drug. Normal human volunteers treated for 7 days with up to six times the recommended daily dosage of cetirizine did not show any lengthening of the QTc interval when compared with healthy volunteers taking placebo (21, 22). Furthermore, when cetirizine was given with the cytochrome P450 CYP3A4 inhibitors ketoconazole (23), erythromycin (24), or azithromycin (25), no electrocardiographic change could be detected, while an accidental massive overdose of cetirizine in an 18-month-old child did not cause any adverse cardiac or neurologic reaction (26).

It can be concluded that cetirizine is a safe drug suitable for the treatment of the allergic infant or child. The findings of the ETAC study provide compelling evidence that cetirizine should be considered a primary pharmacologic intervention strategy to prevent the development of asthma in high-risk groups of specifically sensitized infants.

Discussion

Sake: I have one practical question. If you follow the literature and regularly talk to pediatricians, you very often encounter discussion as to whether we should or should not use topical corticosteroids in very young infants for long periods of time. What is your opinion on this?

Knol: What do you mean by topical? In the skin and nose?

Sake: No, the nose, mostly for the airways.

Knol: I don't know. I must say that in my experience there are not many pediatricians who use inhaled corticosteroids over a long period of time. But, as far as I am aware, even if long-term treatment is given, we see no serious damage of the mucosae or skin.

Sake: I was referring to the fact that there are a lot of studies done in Denmark by Pedersen, who strongly recommends starting with high doses of corticosteroids in very young children. He also proposes to commence treating those at-risk children with corticosteroid maintenance therapy.

Knol: I am not sure that treating children with high doses of inhaled corticosteroids is necessary. We must realize that in very young children high doses of inhaled corticosteroids are not so effective because of the small tidal volume in these children, so a lot of the spray goes elsewhere and does not reach the lower airways. I certainly hope that ETAC will prove that high doses of inhaled corticosteroids are not necessary.

Timmerman: Is anything known about the blood-brain barrier in very young children? We know that develops after a period of time but is not present in neonates.

Knol: I am afraid I cannot answer that. I know of no data.

Timmerman: I ask this question because, as I said yesterday, I know of several Japanese studies where children had epileptic-like effects after using antihistamines. You have here a compound [cetirizine] which does not pass into the central nervous system so you would not expect to see any epileptic effects. Are you aware of these types of problems with the older compounds?

Knol: I'm not aware of such reports and it will be very difficult to find out because it is now 25 or 30 years since these compounds were used.

Timmerman: Does anybody have any information on this point? In Japan, it seems to be the case that young children arrive in hospital with these epileptic-like symptoms and when they looked back at the history of these children they had in many cases used antihistamines.

Tharp: This must be an extremely rare phenomenon because, for example, diphenhydramine is obtained over-the-counter and is probably the antihistamine of choice for most pediatricians in the USA, so there is no control over it and it is used very frequently. I think we would have heard more on this subject if it were responsible for epileptic-type symptoms in children.

Knol: As far as somnolence or sedation are concerned, we know that cetirizine has a very favorable safety profile, but I am not aware of any adverse effects with regard to epilepsy.

Tharp: I have just one question. I was intrigued by the fact that the initiative for the ETAC study was the observation with ketotifen. Is that right?

Knol: Yes, that's right.

Tharp: As I understand it, ketotifen is an agent that has some interesting additional properties including the ability to be a stabilizer of mast cells and perhaps also inhibit mediator release from other inflammatory cells. Was there a more conventional antihistamine that was used prior to cetirizine in this patient population that also showed these types of effects, or was this only observed with ketotifen?

Knol: I can only speak for The Netherlands, but I would say it was ketotifen and after that cetirizine. I am not aware of any other drugs.

De Vos: I can add some information. When you look at the profile of ketotifen, it's not really an antiallergic drug; in fact, it is a true H₁ antagonist which is not specific for histamine. Both ketotifen and oxatamide can interfere with serotonergic and cholinergic neurotransmission and are therefore considered to be intermediate between the first and second generations (27). So I think that the way ketotifen has been marketed does not really correspond to its true pharmacologic profile. Do you agree?

Knol: You must remember that when these studies were done the only alternatives were oral corticosteroids, and nobody wanted to use them in very small children. So, at the time, we considered the use of ketotifen as the only viable alternative. In children, ketotifen certainly had some effects in preventing asthma, and that observation led in turn to the idea of the ETAC study, in which, as we have seen, cetirizine has proved to be very effective.

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