

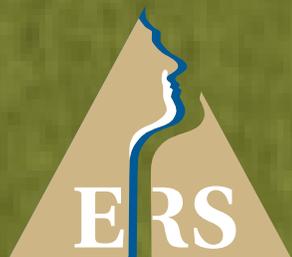


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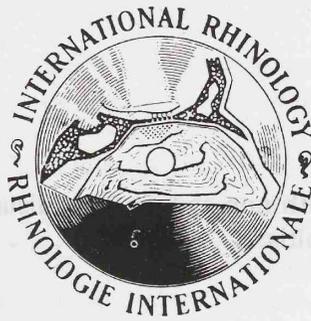
Abstract Book

*Symposium held at the Vth
International Congress of
Paediatric
Otorhinolaryngology*

**MODERN ANTIHISTAMINE
TREATMENT IN
PAEDIATRIC
RHINOCONJUNCTIVITIS**

*Ghent, Belgium
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Symposium held at the Vth International Congress of Paediatric
Otorhinolaryngology in Ghent (Belgium), 7th June 1991

Chairmen: Dr. N. Mygind, Copenhagen (Denmark)
Dr. I. Dab (Belgium)

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Preface

This supplement to RHINOLOGY deals with allergic rhinitis in childhood and its treatment with H₁-antihistamines, especially astemizole for oral use, and levocabastine for direct application in the nose and the eyes. Although allergic rhinitis is not the most serious of the allergic diseases, it is definitely the most frequent. Evidence is presented in this volume suggesting that its prevalence has increased over the last decades, and air pollution is incriminated as a likely cause. Astemizole is a potent H₁-antihistamine with unique pharmacokinetics, in that the plasma half-life of the drug plus its active metabolite is about 10 days. Data are presented showing equal drug kinetics in children and adults. Sedation has not been reported more frequently in children treated with astemizole, even in a high dose, than in those receiving a placebo.

A review of the literature on astemizole in childhood allergic rhinitis showed convincing efficacy. Apparently, astemizole is more potent than other antihistamines, and some efficacy has been reported also in atopic dermatitis and bronchial asthma. However, most of the studies cited are still unpublished or have only been presented as abstracts. Definite conclusions on these points should therefore await the publication of double-blind studies performed in well-defined populations, and presented in international journals having a good referee system. Astemizole-induced increase in appetite and weight gain does not seem to be a major problem in children, but simple measurements of body weight has not been used systematically in the studies quoted.

A considerable number of studies in adults have shown efficacy of levocabastine both as eye drops and as a nasal spray. Levocabastine is effective when used every 12 hours, showing prolonged receptor binding of this molecule. Short-term side effects are limited to the irritancy from the preservative. The effect of twice-daily administration of levocabastine was at least as good or better than that of cromoglycate, given four times each day. Efficacy on sneezing seemingly equals that of a steroid spray, demonstrating the importance of histamine as the major biochemical mediator of itching and sneezing. These studies showed a high degree of placebo response in the nose, and especially in the eyes, emphasizing the importance of a placebo group. Limited evidence indicates that levocabastine also is of value in children.

In conclusion, astemizole is a valuable long-acting, non-sedating antihistamine, second to none of the other antihistamines in efficacy, and well suited for continuous use in adults and children. Levocabastine seems to be a promising drug

for topical use, well suited for on-demand use in the nose and, especially, in the eyes. Its place in therapy is well documented in adults, and preliminary results suggest that it will also be helpful in older children. Small children may not fancy having anything dropped into their eyes or sprayed into the nose.

Copenhagen, June 1992

Niels Mygind,
Guest Editor

Epidemiology of allergic diseases in children

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SUMMARY

The one-year-prevalence rate of bronchial asthma in children varies from 1-3%, when investigated in general practice, to 5-7% in population studies. The prevalence rate is highest in young boys. Eighty percent of the asthmatic children are allergic, house dust-mite allergy being the most common allergy. The one-year-prevalence rate of rhinitis is 5-10% in general practice, and 10-12% in population studies. Again, the prevalence rate is highest in young boys. About 90% of children with rhinitis symptoms are allergic, with pollen allergy as the most common allergy. Risk/factors for developing allergic diseases are many. The predisposition is probably the most prevailing risk factor. Period of birth, sex, race, diet, the presence of other allergic diseases, tobacco smoking, pollution, and allergens in the environment, all these factors alone or in combination almost double the risk. There is no doubt that both asthma and hay-fever prevalences have steadily increased within the last 50 years. Also, admissions to hospitals/or childhood asthma have continued to increase, while the mortality of asthma in children has not risen statistically. This increase is in contrast to the effective medication available/or both asthma and allergic rhinitis, and to the number of preventive/factors known to us today. The time has come to try to change it at all costs. The outcome of allergic rhinitis and asthma shows that only 10% are cured, 50% ameliorate, 30% remain unchanged, and 10% deteriorate. Factors determining the outcome are age, immunotherapy, sex, mother's age at childbirth, infections, other allergic diseases, and signs and symptoms of food allergy. In the future, we must find new ways of treating these diseases. We should perhaps start the treatment before the symptoms have appeared, with drugs without side effects, i.e. antihistamines, bronchodilators, and corticosteroids as inhalation therapy. Also, we must by all means try to decrease the growing pollution, because this is one of the factors which are known to increase both the allergic and the non-allergic hyper-reactivity in the bronchi and the nose.

INTRODUCTION

During recent years better and more specific medication for asthma and rhinitis has become available. Furthermore, we know much better how to prevent these diseases in children. Despite these facts, the number and severity of hay fever and asthma is increasing: The figures are roughly twice as high as 20 years ago. Today's medication is very effective, including non-sedating antihistamines, corticosteroids, and bronchodilators; the latter two medications are usually given as inhalation therapy. This kind of treatment has practically no side effects and can effectively prevent release of mediators and the inflammatory response. The freons in locally applied bronchodilators and corticosteroids seem to provoke bronchospasm in 25% of patients with hyperreactive airways, but within the last 2-3 years these types of medication have been changed into non-freon-containing powders, during which period the prevalence of the diseases has increased. Prevention includes advice to highly predisposed parents about avoidance of animal dander and house dust mites in the environment, and avoidance of smoking and infections.

What is the explanation of the substantial and statistically significant increase in atopic diseases over recent decades, despite the effective medication and well-known preventive measures? Does the medicine in some way or another harm the organism? Are we focussing on the wrong things when trying to prevent the diseases from starting, or are there other explanations? A genetic predisposition must be present, if atopy is to develop. Thirty to forty percent of the population have the capacity to spontaneously produce IgE specific to environmental allergens. We are beginning to understand more about the genes bearing the IgE-diseases. Several different genes seem to be involved. One is the gene on chromosome No. 6, another could be located on the Y-chromosome, because the allergic diseases are more common in males than in females. It is well known, however, that not all individuals with allergen-specific IgE have an atopic disease. Factors in the environment that lead to manifest reactions of the allergic diseases are infections, toxic agents, psychological factors, and exposure to specific allergens.

There are two more important co-factors that may lead to an increase in atopic disorders. Heavier air pollution (outdoors and indoors) and increased exposure to house dust mites due to altered living conditions. The period in which the prevalence of allergic diseases has increased, is characterized by increasing concentrations of atmospheric pollutants (oxides of nitrogen, ozone, sulphuric dioxide, aerosol particles, and vehicle exhaust fumes).

Pollution

Indoor and outdoor pollutants damage the epithelium of the respiratory tract, especially in young children, which may cause an increase in permeability to

inhalant allergens and decreased activity of the ciliated epithelium. The damage to the epithelium may enhance the IgE-mediated immune response, if it facilitates the penetration of allergens. Furthermore, by binding to the allergens, the pollutants may enhance the production of specific IgE molecules against the allergen. Allergic pollen diseases have a higher prevalence in heavily industrialized towns than in rural environments (Muranaka et al., 1986; Takafuji et al., 1987).

Tobacco smoking and, in children, passive smoking elevates IgE serum levels, even in neonatal cord blood, if the mother has been smoking during the pregnancy, and increases the incidence of allergic airway diseases.

House dust mites

The importance of house dust mites in the induction of allergic asthma was clearly demonstrated in Papua New Guinea, where formerly asthma was practically unknown. In a few years, the prevalence of house-dust-mite-induced asthma rose to 7% in parallel with an increasing number of mite-containing blankets and mattresses (Dowse et al., 1985).

The improved insulation in modern houses built after the 'oil crisis' results in poorer ventilation and higher humidity, thereby increasing the number of house dust mites and moulds. The prevalence of mite allergy is directly correlated to the mite-allergen content in the house (Platts-Mills et al., 1989).

The great popularity of pets, kept in about 50-60% of European households, increases the sensitization to animals, particularly cat dander. Cat seems to be the pet most difficult to avoid, presumably because the cats, licking themselves, spread the allergens in the whole house via aerosolized sputum. Cat allergens have been shown to be present in mattresses in houses where the cat was actually removed years ago (Wentz et al., 1990).

The purpose of this report is to present figures for prevalence of asthma and rhinitis in children, risk factors, evolution, and outcome of these diseases.

EPIDEMIOLOGICAL METHODS

Epidemiologic research in the fields of asthma and allergic rhinitis can be carried out at three different levels: (1) in the general population; (2) in general and family practice; and (3) in the hospital. The incidence rate is defined as the number of new cases per year in the population. The one-year-prevalence rate is defined as the number of persons reporting the disease within one year prior to the interview. The cumulative prevalence rate is defined as the number of persons reporting ever having had symptoms of the diseases prior to the interview. As in many other diseases, it is difficult to define in population studies bronchial asthma and rhinitis. The figures for incidence and prevalence of these diseases are therefore much more comparable when based on the medical

diagnosis as compared to questionnaires, even when made by good interviewers. Furthermore, most patients with asthma consult their general practitioner. The general practitioner may, however, underdiagnose asthmatic patients because of the similarity of asthma to 'wheezing bronchitis' in children. Concerning rhinitis, the problem is quite different. About half of the patients with rhinitis symptoms do not consult their general practitioner, and they are hardly ever hospitalized. Therefore, the occurrence of bronchial asthma is optimally evaluated in general practice and in hospitals, and the occurrence of rhinitis optimally in the population and by the general practitioner.

Bronchial asthma

The one-year-prevalence rate of bronchial asthma in children varies from 1-3% in general practice to 5-7% in population studies (Fleming and Crombie, 1987; Gergen et al., 1988; Holmgren et al., 1989; Hurry et al., 1988; Pedersen and Weeke, 1987; Usherwood, 1987). The average asthma patient consults his or her general practitioner five times per year. The one-year-period prevalence rate of asthma in general practice is twice as high in boys as in girls. The peak occurs at the age of 8-15 years. The prevalence of asthma is higher in black than in white populations. Eighty percent of asthmatic children are allergic, and 50% of the allergic children have only one allergy, 15% have more than four allergies. House-dust-mite allergy is the most common allergy in asthmatic children followed by allergies to pets, pollen, and fungi. In children younger than 2 years of age, cow's milk allergy is the most common allergy followed by allergy to eggs (Osterballe et al., 1981). Among the initially non-allergic asthmatic children, one of ten developed allergy within the following two years, for which reason it is recommended to repeat skin prick testing in non-allergic asthmatic children. The severity of asthma is moderate in about 50% of the children, very severe in about 10%, and mild in the remaining 40%. About 80% of children with food allergy develop inhalant allergy at a later stage, and it is still to be studied whether prevention can change this rate.

Rhinitis

The one-year-prevalence rate of rhinitis is 10-20% in the population studies and 5-10% in general practice (Fleming and Crombie, 1987; Weeke, 1987). The simple question in a questionnaire: "Are you allergic to pollen?" seems to correlate very well with the diagnosis of allergic pollen rhinitis made by the physician (Pedersen, unpublished data). The highest prevalence rate is in boys aged 8-12 years. About 90% of children with rhinitis symptoms have one or more allergies, allergy to pollen is found in about two-thirds of them, to mites in about one-third, and to pets in one-third. There is a significantly higher prevalence in urban than in rural areas, except for Israel, where the opposite seems to be the

case (Geller-Bernstein and Levin, 1987). The age of onset of hay fever is between 2-4 years of age for half of the children, so this disease has an early onset in children.

If one looks at the seasonal variation of the one-year-consultation rate in general practice because of rhinitis, there is a marked peak in the period of the pollen season, caused by patients with acute symptoms. This is in contrast to the seasonal variation of consultations because of asthma during the year, for which the consultation pattern is equally distributed except for children between 0-4 years of age, who have a peak at the end of the year. In other studies different patterns are reported with a small peak in the asthma consultations in the autumn, well correlated to the increase in mite allergens during this season.

Risk factors

There is a high genetic risk of developing atopic diseases. Without parental predisposition, about 5-15% of children develop allergic diseases. With a single parental predisposition the risk is about 35%, with double parental allergy the risk is about 50%, and if both parents have the same disease the risk is 60% (Kjellman et al., 1988). The incidence of atopic disease before 7 years of age is correlated with the cord-blood IgE concentration and moderately influenced by the month of birth, so the risk is twice as high in children born in May than in children with similar cord-blood IgE and born in November (Croner and Kjellman, 1986). The maternal diet does not seem to influence the development of allergy in a child. After birth, a reduction in the prevalence of food allergy, especially cow's milk allergy, can be obtained, if the child is breast-fed or fed by hypo-allergenic hydrolysates of casein or whey proteins until 6 months of age (H0st, 1989). It is well known that food allergy in the first 1-2 years of age is followed by inhalant allergy in about 80% of the children (Bock, 1982).

Tobacco smoking in the house is another well-known factor increasing the risk of developing allergy, presumably by the same factor as pollutants. Tobacco smoke contains irritants and pollutants that are known to damage the epithelium of the airways. Boys develop allergy more frequently than girls. The reason for the sex differences, which have been demonstrated in many different studies, is not known. The allergy predispositions for boys start in the neonatal period, and the cord-blood IgE is higher in boys than in girls.

Day care can be another risk factor. Infections in children in day-care institutions occur more often than in children looked after at home, although it is not in all the different studies that this factor influences the risk.

The period of birth is another important risk factor, particularly in hay-fever patients. In Scandinavia, this increased risk is especially pronounced in patients developing birch-pollen and grass-pollen allergy (Weeke, 1987). In Southern Europe, the same increase in hay fever in patients born before or during the

pollen season of *Parietaria*, has not been found (Troise et al., 1989). A peak in pollen with short-term heavy load is perhaps necessary; furthermore, a combination of this peak in pollen and pollutants may increase the risk. In a Swedish investigation it was clearly shown that this risk factor could not be demonstrated before 1965, indicating that factors other than pollen may influence the occurrence of hay fever (Aberg, 1989). In most investigations the period of birth of asthmatic patients does not influence the development of allergic diseases.

Increased prevalence

There is no doubt that both asthma and hay-fever prevalences have steadily increased within the last 50 years. Within the last 20 years a doubling of the prevalence rate in adult hay-fever patients in general practice has been shown in many studies (Geller-Bernstein and Levin, 1987, Gergen et al., 1988). Investigations in children are few. Studies from Sweden indicate that the increase in prevalence rate of asthma and rhinitis appears in both the allergic and non-allergic group (Eriksson, 1990, Gerritsen et al., 1990). An inverse relation between number of siblings and prevalence of allergic disease has been found (Strachan, 1989).

Admissions to hospital for childhood asthma have continued to increase, indicating an increase in the number of asthmatic children experiencing severe attacks (Anderson et al., 1986). The mortality of asthma in children has not increased, at least not in Denmark (Sears, 1990; Pedersen and Weeke, 1987). As mentioned in the beginning, this increase is in contrast to the effective medication available for both asthma and allergic rhinitis, and to the number of preventive factors we know about today. Instead of just looking at the increasing figures the time has come to try to change it at all costs.

Prognosis

Many years ago, we believed that children would be growing out of their asthma. It was said that: "They were allergic to their parents, especially the mother"; by moving away from home the asthma symptoms would disappear. This is not today's truth. The outcome of asthma and allergic rhinitis is as follows: Only 10% are cured, but 50% ameliorate, 30% remain unchanged, and 10% deteriorate. Factors determining the outcome are age, immunotherapy, sex, mother's age at childbirth, infections, other allergic diseases, and signs and symptoms of food allergy (Anderson, 1989). New ways of treating these diseases are needed and, perhaps, we should start the treatment earlier in an attempt to inhibit inflammation and development of chronic diseases in the lungs or in the nose.

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Central nervous system side-effects of antihistamines in schoolchildren

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SUMMARY

There are no studies available in the literature on the effects of classical antihistamines on the central nervous system (CNS) in children. Clinical studies indicate that somnolence occurs more often with classical antihistamines than with placebo. There is no difference in inducing somnolence in children between placebo and astemizole or teifenadine, two new antihistamines that have thoroughly been shown to have no sedative effect greater than placebo in adults. A double-blind, cross-over trial investigating the CNS-effects of astemizole and chlorpheniramine in schoolchildren failed to show a negative effect of either of these drugs on pe,jormance.

INTRODUCTION

The classical antihistamines have been widely used for years, for both adults and children with allergic conditions (Simons, 1989). They are effective, but their use has been somewhat limited, especially in schoolchildren, because of concerns regarding their sedative effects. One of the most important aspects of learning in the classroom is attentiveness; the ability to spend an appropriate amount of time concentrating on the material to be learned. Impairment of attention has long been felt to be a significant problem with the classical antihistamines. Young children may also suffer from stimulatory effects on the central nervous system (CNS) such as excitation, irritability, hyperactivity or insomnia.

In order to get around some of these problems, clinicians have for years switched from one class of antihistamines to another. The major classes of the classical antihistamines are the ethanalamines (e.g. diphenhydramine), the ethylenediamines (e.g. pyribenzamine), the alkylamines (e.g. cl)lorpheniramine), and others including the phenothiazines (Rimmer and Church, 1990). Some children become quite sedated or inattentive while taking one type of antihistamine, but react less severely to another class.

The sedative properties of traditional antihistamines can be quite beneficial in some situations regarding infants and young children with atopic eczema (Krause

and Shuster, 1983). These infants scratch their skin and the itch-and-scratch cycle causes further inflammation. The inflammation and itch may prevent sleep at night, so the use of a sedative antihistamine is advantageous under these circumstances.

In this paper, we review the literature on CNS-effects of antihistamines in schoolchildren. In addition, we summarize the results of a comparative study with a traditional antihistamine, chlorpheniramine, and a non-sedating antihistamine, astemizole, with regard to their CNS-effects in schoolchildren. The results of this study will be published elsewhere in more detail.

LITERATURE REVIEW

Allergic diseases are common in children and adolescents (Weeke, 1987). Although there are now many years of experience with the use of traditional antihistamines in childhood, and considerable clinical experience with the varying sedative effects of the different classes of traditional antihistamines, there have been no prospective, scientifically valid studies of the CNS-effects of these drugs on schoolchildren. Sedation is commonly reported as a side effect of traditional antihistamines in children, although a comparison of different studies is difficult. Its incidence appears to be lower than in adults. In a post-marketing surveillance of ketotifen in Great Britain, sedation occurred in 6% of children and 14.2% of adults (Maclay and Crowder, 1982).

The occurrence of sedation in children has more extensively been evaluated in recent studies comparing non-sedating antihistamines with placebo or reference drugs. Terfenadine and, particularly, astemizole have been studied in a paediatric population (see Wood, this supplement). Although incidences in different studies cannot be compared, the overall figures show a comparable incidence of sedation in the astemizole- or terfenadine-treated children and placebo. No significant differences were found in any of the individual studies (Table 1). In line with these findings, incidences of sedation were comparably low in comparative studies with astemizole and terfenadine (Table 2). Sedation is more common in children treated with traditional antihistamines than in those treated with non-sedating antihistamines (Table 3). In view of the low number of patients, incidences vary considerably. In one study only, a significantly higher incidence of sedation was reported with clemastine when compared with astemizole (Moller and Johansson, 1984).

STUDY ON CNS-EFFECTS OF ASTEMIZOLE AND CHLORPHENIRAMINE IN SCHOOLCHILDREN

Although clinical studies indicate that the newer antihistamines such as astemizole are non-sedating in children as well, the CNS-effects of these drugs have not been systematically studied in children. This is in contrast to the many

Table 1 Incidence of sedation in placebo-controlled trials with non-sedating antihistamines in children.

reference (astemizole vs placebo)	type of patient	number of patients		age (mean and range)		sedation	
		ast.	plac.	ast.	plac.	ast.	plac.
(Hedley et al., 1984)	hay fever	47	50	9.7 (6-12)	9.5 (6-12)	0	0
(Perez Martin et al., 1985)	allergic rhinitis	18	18	9.1 (4-16)	11.1 (4-16)	6	5
(Sobocki, 1985)	hay fever	17	19	12 (8-15)	12 (8-16)	0	0
(Villa Aseni et al., 1988)	hay fever	15	16	8.97 (3-16)		1	1
(De Loore, 1982)	respiratory allergies	12	11	3.5 (2-8)	8 (3-11)	1	0
(Hugenin et al., 1988)	common cold	23	27	6.2 (2-15)	5.7 (2-15)	0	0
total	n	132	141			8	6
	%					Ø%	4.3%
(terfenadine vs placebo)							
		terf.	plac.	terf.	plac.	terf.	plac.
(Lockhardt and Maneksha, 1983)	allergic diseases	58	55	9.25 (3-12)	9.4 (3-12)	9	5
(Guill et al., 1986)	hay fever	77	40	9.3 (6-12)	8.7 (6-12)	3	1
(Molkou and Beaumont, 1985)	allergic rhinitis	40	40	9.5 (5-12)	9.7 (5-12)	0	0
(Villa Aseni et al., 1988)	hay fever	17	16	8.97 (3-16)		2	1
total	n	192	151			14	7
	%					7.3%	4.6%

psycho-performance and other tests that have been used to show an absence of CNS-effects with these drugs in adults.

Thus, we set out to study one of the supposedly less sedating traditional antihistamines, chlorpheniramine, as well as one of the newer antihistamines, astemizole, with regard to their CNS-effects on schoolchildren. Both cognitive performance and subjective side effects were evaluated in 92 children of 8-16 years. Both drugs were used in the recommended dose. The trial was double-blind and cross-over with an intermediate wash-out period of six weeks.

Details on the study design and results will be reported elsewhere. We can conclude that astemizole and chlorpheniramine are safe for use in children. No significant difference was noted in subjective symptoms of sedation or other side

Table 2 Incidence of sedation in comparative trials: Astemizole vs terfenadine in children.

reference	type of patient	number of patients		age (mean and range)		sedation	
		ast.	terf.	ast.	terf.	ast.	terf.
(Villa Aseni et al., 1988)	hay fever	15	17	8.97 (3-16)		1	2
(Grillage et al., 1986)	allergic rhinitis	28	34	9.3 (6-12)	9.5 (6-12)	1	1
(Passali et al., 1988)	allergic rhinitis	18	13	-		0	0
(Tkachyck, 1988)	hay fever	22	22	(4-13)		0	0
total	n %	88	86			2 2.4%	3 3.5%

Table 3 Incidence of sedation in children in comparative studies: Non-sedating antihistamines vs classical antihistamines.

reference	type of patient	type of drug (number of patients)		age (mean and range)		sedation	
		non-sedative	classical	non-sedative	classical	non-sedative	classical
(Villa Aseni et al., 1988)	hay fever	astemizole (n= 15)	chlorpheniramine (n = 17)	8.97 (3-16)		1	1
(Moller and Johansson, 1984)	hay fever	astemizole (n=40)	clemastine (n=20)	13 (6-16)	13 (8-16)	7 (/40)	7 (/20)*
(Villa Aseni et al., 1988)	hay fever	terfenadine (n= 17)	chlorpheniramine (n = 17)	8.97 (3-16)		2	1
(Varonier and Dieterich, 1984)	hay fever	terfenadine (n= 15)	clemastine (n= 15)	6.7 (3-11)		0	2
(Gi.itlich et al., 1986)	atopic dermatitis	terfenadine (n=28)	ketotifen (n=28)	(3-13)		0	1
(Baver et al., 1988)	hay fever	loratadine (n=21)	chlorpheniramine (n=19)	7.6 (4-12)	7.8 (4-12)	0	4

* Significantly more sedation in Clemastine group.

effects during the two active treatments. There was also no difference between any of the medication periods and baseline. The performance of the children was not adversely affected by any of the two drugs. Although neither drug affected attention span, short-term memory or co-ordination in a deleterious manner, children did better on tests for short-term memory while on astemizole than while on chlorpheniramine. The improvement noted in subtests of some of the performance tests was not clinically significant. The changes were substantially influenced by learning effects and were not systematic.

DISCUSSION

There is a striking lack of data on CNS-effects of traditional antihistamines in schoolchildren. In clinical studies, traditional antihistamines do induce sedation in children. Its incidence, however, appears to be lower than in adults. Whether this difference is due to a lower susceptibility of children to the sedating effects of antihistamines or to a lower attentiveness to recognize mild sedative effects can not be concluded from these studies. The fact that particularly young children are more sensitive to stimulatory effects of centrally acting antihistamines than adults is in line with the former hypothesis.

In line with the clinical experience in adults, the incidence of sedation during an astemizole or terfenadine treatment is comparable to placebo. In comparative trials versus traditional antihistamines, the incidence of sedation with the newer drugs is lower. Significant differences, however, were rarely reached, although the small sample-size may be responsible for this observation. We have not been able to find significant differences in the incidence of sedation in astemizole- or chlorpheniramine-treated children in a cross-over trial involving 92 children. Moreover, neither of the two drugs significantly induced sedation when compared to the drug-free base-line situation. A learning effect may have reduced somewhat the sensitivity of our trial. Relevant performance impairments can, nevertheless, be excluded in our trial. It must be admitted that, also in adults, not all tests show significant effects with classical antihistamines (Hindmarch and Easton, 1986). Other tests may be more sensitive to detect CNS-effects with classical antihistamines in children. We feel, however, that our performance tests adequately assess attentiveness, the most important aspect of learning in the classroom.

In conclusion, the newer antihistamines, astemizole and terfenadine, give no more sedation than placebo in clinical trials in children. Astemizole does not adversely affect the performance of schoolchildren. Although somnolence is not a rare side effect with classical antihistamines in paediatric clinical studies, we did not observe a negative effect of chlorpheniramine on performance. Further confirmation of this finding is needed before definite conclusions on this aspect can be made.

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Pharmacokinetics of astemizole in children

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SUMMARY

Astemizole is often administered to children in the treatment of rhinconjunctivitis and urticaria with good efficacy and few side effects. Both astemizole and its major metabolite desmethylastemizole (DMA) are clinically effective without annoying side effects such as sedation. The pharmacokinetics in adults is well known. In three different studies we have investigated the pharmacokinetic properties of the drug in children. Study I (absorption): Thirty-eight children 8-16 years old (mean 12.6 years) and weighing 25-80 kg (mean 45 kg), with rhinconjunctivitis due to birch pollen, were pretreated with either astemizole 5 mg daily or placebo for two weeks. Then, all children were treated with astemizole in doses increasing every week, i.e. 5, 10, 20 and 40 mg per day. There was a good correlation between the given dose per kg body weight and the plasma concentration of astemizole plus hydroxylated metabolites, indicating that astemizole is completely absorbed. Study II (time to reach steady state): A group of 21 children 7-18 years old (mean 13.9 years), plus 2 younger children, 2 and 5 years old, with allergy against birch- or grass pollen were treated with astemizole 10 mg daily for 12 weeks. Astemizole had reached steady-state plasma levels when the first sample was taken after 1 week, DMA reached steady state within 4 weeks. Study III (elimination half-life [$t_{1/2}$]): In 10 of the children from study II, $t_{1/2}$ for astemizole plus DMA could be calculated (two samples) and was 10.8 days. In another study, 19 children 6-16 years old (mean 11.6 years) were treated with astemizole 10 mg daily for 10 weeks and followed with blood samples after the treatment had stopped. Astemizole was only found in the first sample taken after 24 hours. DMA had a $t_{1/2}$ of 11.2 days and was found in the last sample 85 days after treatment in two children. Elimination was monophasic in 17 and biphasic in 2 children. We conclude that astemizole in children is well absorbed, has a very long plasma half-life, and the pharmacokinetic properties are similar to what is found in adults.

INTRODUCTION

Astemizole, a potent H₁-histamine receptor antagonist, is widely used in the treatment of rhinoconjunctivitis and urticaria. The pharmacokinetics in adults is well known (Heykants et al., 1986). Orally, it is almost completely absorbed with peak plasma concentrations of astemizole and its metabolites within 4 hours. The first-pass metabolism is extensive and there is a quick distribution to well-perfused tissues. Both astemizole and its major metabolite desmethylastemizole (DMA) are clinically effective without annoying side effects such as sedation. The parent compound astemizole has an elimination half-life of approximately 1 day, while DMA has an elimination half-life of approximately 10 days. Thus the drug is extremely long-acting. Furthermore, the metabolites cannot be eliminated by dialysis due to a high degree of binding to plasma proteins.

Astemizole is often administered to children with good efficacy and few side effects. In three different studies we have investigated the pharmacokinetic properties of the drug in children. Study I was primarily designed to evaluate the prophylactic effect of pre-seasonal treatment of astemizole, and to investigate if higher doses of the drug would increase the efficacy without increasing the risk of sedation and other side effects in children with allergic rhinoconjunctivitis. This study is described in detail elsewhere (Andlin-Sobocki and Moller, 1991).

The children and their parents were given verbal and written information about the aims and the methods of the studies, and the parents gave their informed consent. The studies were approved by the Human Ethics Committee of Umeå (studies I and III) and Uppsala (study II).

I. ABSORPTION

Thirty-eight children, 8-16 years old (mean 12.6 years) and weighing 25-80 kg (mean 45 kg), with rhinoconjunctivitis due to birch pollinosis were given either astemizole 5 mg daily or placebo for two weeks. Then, all children were treated with astemizole in doses increasing every week, i.e. 5, 10, 20, and 40 mg per day. Blood was taken before the start of medication and after each of the last four weeks. There was little difference in the plasma level of astemizole plus hydroxylated metabolites (APHM) in the two groups of children, i.e. pretreated or not pretreated. The correlation between the given dose of astemizole and APMH levels after each treatment week is shown in Figure 1.

Due to the long half-life of astemizole it is fairly correct to assume that levels of APMH increased linearly between measurements. Thus, it was possible to estimate for each child the plasma level of APMH on every day of treatment. The daily symptoms of rhinoconjunctivitis were correlated to pollen counts and levels of APMH with the aid of a dynamic statistical model (Brostrom and Moller, 1989; Andlin-Sobocki and Moller, 1991). Increasing daily doses of astemizole up to 0.25 mg/kg, corresponding to a plasma concentration of

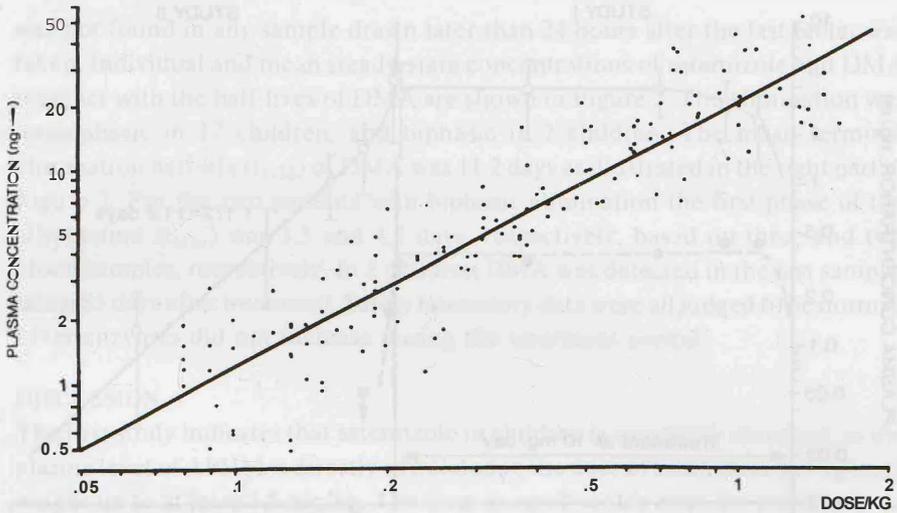


Figure 1. Correlation between plasma level of astemizole plus hydroxylated metabolites and given dose of astemizole (reproduced with permission of Paediatric Allergy and Immunology, Munksgaard).

4 ng/ml, gave less hay-fever symptoms. Still higher doses, up to 40 mg/day and corresponding to 0.5-1.6 mg/kg, gave little improvement. Sedation and other side effects did not increase with higher doses. Various laboratory tests did not reveal any abnormalities that were judged to be a result of the medication. However, liver enzymes increased during the treatment period, although all values were within normal limits.

II. TIME TO REACH STEADY STATE

A group of 23 children with allergy against birch- or grass pollen were treated with astemizole 10 mg daily for 12 weeks. The children are further described in Table 1. Two young children, a boy 2.5 years old (weight 19 kg) and a girl 6 years old (weight 20 kg), were included in the study, but not in the statistical analysis. Blood was taken before the medication and 1, 2, 4, 12 and 16 weeks after the start of treatment. Plasma from each sample was analyzed for levels of astemizole and

Table 1. Demographics of the two groups of children in the studies primarily designed to evaluate loading and elimination, respectively.

	loading	elimination
Number of children	21	19
Male/female	14/7	13/6
Age: mean \pm SD	13.9 \pm 2.8	11.6 \pm 3.1
Weight: mean \pm SD	52.9 \pm 13.2	39.5 \pm 13.0

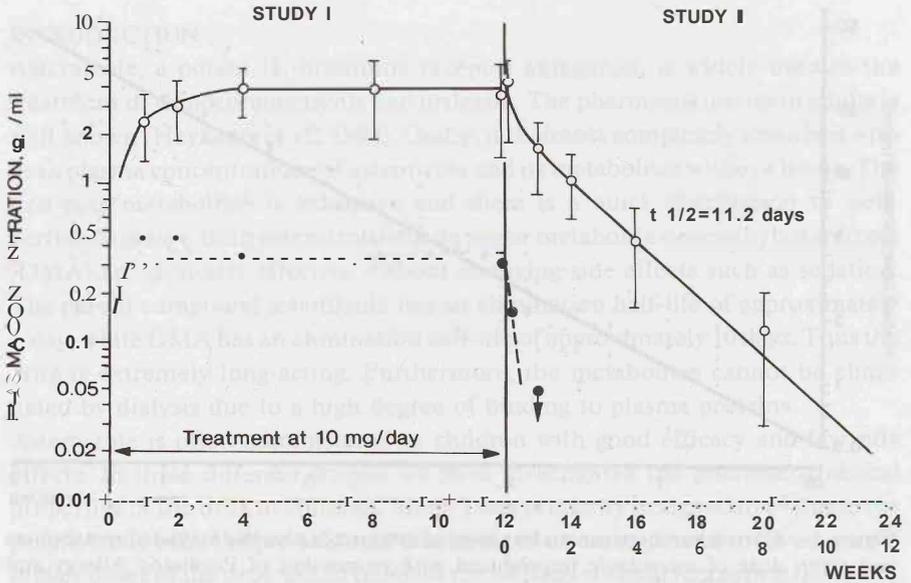


Figure 2 Loading and steady-state concentrations (left part of the figure) and elimination (right part of the figure) of astemizole (closed circles) and desmethylastemizole (open circles) in two separate groups of children.

DMA using a method described by Woestenborghs et al. (1986). The time for astemizole and DMA to reach steady state is shown in the left part of Figure 2. Safety laboratory data were all judged to be normal. Liver enzymes did not increase during the treatment period.

III. ELIMINATION HALF-LIFE

For ten of the children in the previous group, the blood sample 12 weeks after the start of treatment was taken 1 to 5 days after the last treatment day. Thus, two blood samples were obtained after the stop of medication and the elimination half-life of DMA could be calculated to 10.8 days. It was not possible to estimate the elimination half-life of astemizole.

In a study primarily designed to investigate the elimination, 20 children with rhinoconjunctivitis due to grass-pollen allergy were included. One girl left the study already after one week of treatment at her own will for reasons considered not to be related to the treatment and was not included in the analysis. The demographic data of the remaining 19 children are presented in Table 1. They were treated with 10-mg tablets astemizole once daily for 10 weeks. Blood was taken immediately before the start of medication and after the cessation of therapy 24 hours, 1, 2, 4, 8, and 12 weeks after the last tablet was taken. Astemizole

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The first study indicates that astemizole in children is completely absorbed, as the plasma level of APM is directly correlated to the dose of astemizole per kg body weight up to at least 1.6 mg/kg. The time to reach steady state for children 6-17 years old, is for astemizole less than 1 week and for DMA approximately 4 weeks, which is similar to adults. The findings in two younger children suggest that the pharmacokinetics of astemizole is similar also in lower-age groups. The comparatively high doses used by these children without side effects further emphasizes the safety of astemizole. The elimination half-life DMA was 11.8 days which is similar to adults. In the study designed to evaluate the elimination half-life, the $t_{1/2\beta}$ of DMA was 11.2 days calculated on the basis of more blood samples during the elimination phase. This is again similar to adults. As in adults, the elimination half-life of the parent compound astemizole was too short to be established due to the study design.

Together these three studies shows that the pharmacokinetics of astemizole in children and adults are similar. In addition, the studies further emphasize that astemizole given in high doses to children, is free of serious side effects.

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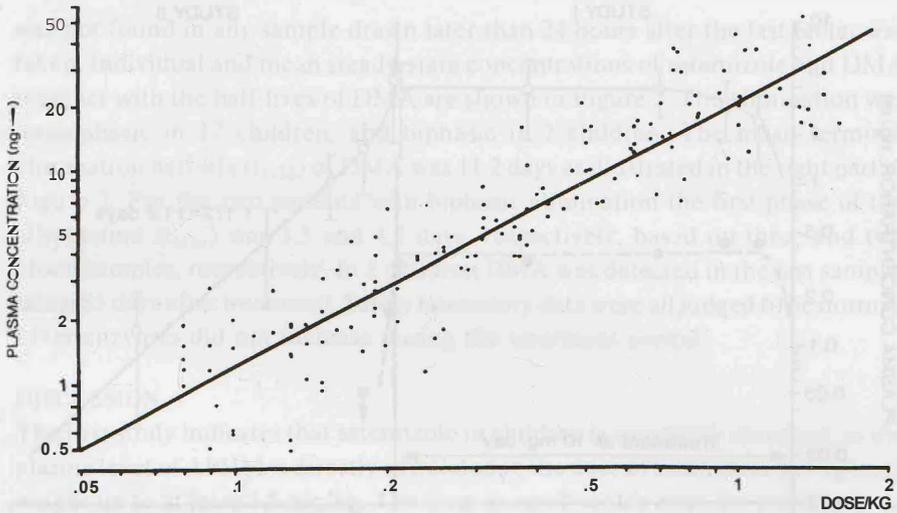


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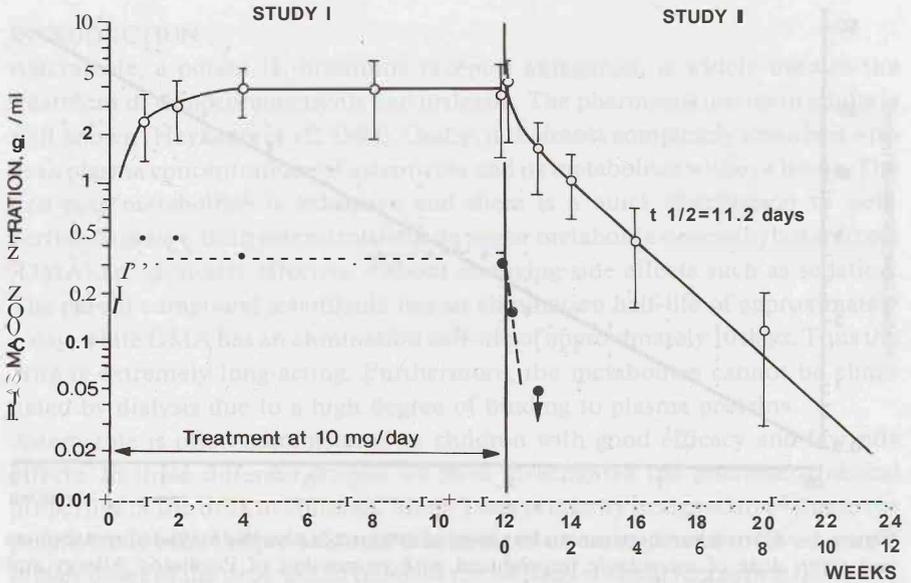


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Clinical experience with non-sedating antihistamines in paediatric allergic rhinitis

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SUMMARY

This paper reviews all clinical studies involving the use of astemizole in children. The indications of seasonal allergic rhinitis, perennial rhinitis and various allergic disorders were considered in a total of 21 studies (1,008 patients). Reference compounds were placebo and other antihistamines, such as chlorpheniramine and terfenadine. Astemizole and other antihistamines were effective in the treatment of these disorders with a more favourable result for those treated with astemizole. Astemizole appeared very satisfactory as regards laboratory data and absence of side effects.

INTRODUCTION

Allergic rhinoconjunctivitis, including the seasonal type (hay fever) as well as the perennial one, is a commonly occurring problem in children. The development of non-sedating antihistamines in recent years has led to an improved range of treatment options available for these children. This paper reviews the data from all studies carried out with astemizole in children aged 6 months to 18 years with allergic rhinoconjunctivitis.

CLINICAL STUDIES: SEASONAL ALLERGIC RHINITIS (HAY FEVER)

Ten studies are described for the indication of hay fever (Table 1). These involved 586 children treated with astemizole, placebo, clemastine, chlorpheniramine or terfenadine. The age range in these studies was 1-18 years and the doses ranged from 5 mg/day to 40 mg/day or 0.2 mg/kg/day. The duration of treatment ranged from 18 weeks.

Guinnepain (1987) performed an open study in 59 children, aged 2-15 years. They received 0.2 mg/kg/day of astemizole suspension for 4 weeks. Good to excellent results were obtained in 86% of patients. All symptoms improved to a similar extent. Tolerance was judged to be good or very good in 98% of cases.

Table 1 Studies with astemizole in children with seasonal allergic rhinitis.

authors	no. of patients	age range years	reference compound	duration weeks	dose
Guinépain (1987)	59	2-15	no	4	0.2 mg/kg
Martin Du Pan and Huguenin (1985)	43	1-18	no	4	0.2-0.4 mg/kg
Sobocki (1985)	36	8-16	placebo	4	5, 10, 20, 40 mg
Hedley et al. (1984)	97	6-12	placebo	8	5 mg
Villa Asensi et al. (1988)	65	6-16	placebo terfenadine chlorpheniramine	1	0.2 mg/kg
Moller and Johansson (1984)	60	6-16	clemastine	4	5 mg
Grillage et al (1986)	65	6-12	terfenadine	8	5 mg
Tkachyk (1988)	44	4-13	terfenadine	8	?
Novembre et al. (1989)	51	6-13	terfenadine	4	0.2 mg/kg
Janssen Research Group (1986)	66	6-12	terfenadine	8	5 mg
total	586	1-18		1-8	

Twenty-one children (aged 1-18 years), in whom the normal dose of astemizole was doubled to 0.4 mg/kg/day, were studied by Martin Du Pan and Huguenin (1985). Treatment was effective with no side effects. Twenty-two further children were studied for 4 weeks on either 0.2 mg/kg/day or 0.4 mg/kg/day. Results were slightly in favour of the higher dose although not significant. No side effects were noted.

Sobocki (1985) treated 36 patients aged 8 to 16 years. Seventeen patients received astemizole, 5 mg daily and 19 patients received placebo as prophylactic treatment. In a second phase all 36 patients received astemizole in increasing doses: 5 mg/day initially for 1 week with the dose being doubled at weekly intervals ending with 40 mg/day for 1 week. At 0.25 mg/kg/day hay-fever symptoms were improved more than at lower doses, but the difference was slight. Higher doses resulted in little further improvement.

Hedley et al. (1984) studied 97 children aged 6-12 years, treated with either astemizole 5-mg suspension per day or placebo. Symptom severity was recorded on daily visual analogue scales, and astemizole was found to be significantly more effective than placebo. Significantly more chlorpheniramine syrup was used as rescue medication in the placebo group (Figure 1). Both treatments were well tolerated and there were no reports of sedation or dry mouth.

Villa-Asensi et al. (1988) compared astemizole, terfenadine and chlorpheniramine to placebo and to each other in a 1-week study involving 65 children (Figure 2). Only astemizole was found to be significantly superior to placebo overall and regarding improvement of "red eyes". Astemizole was also significantly superior to the other antihistamines in the relief of ocular symptoms.

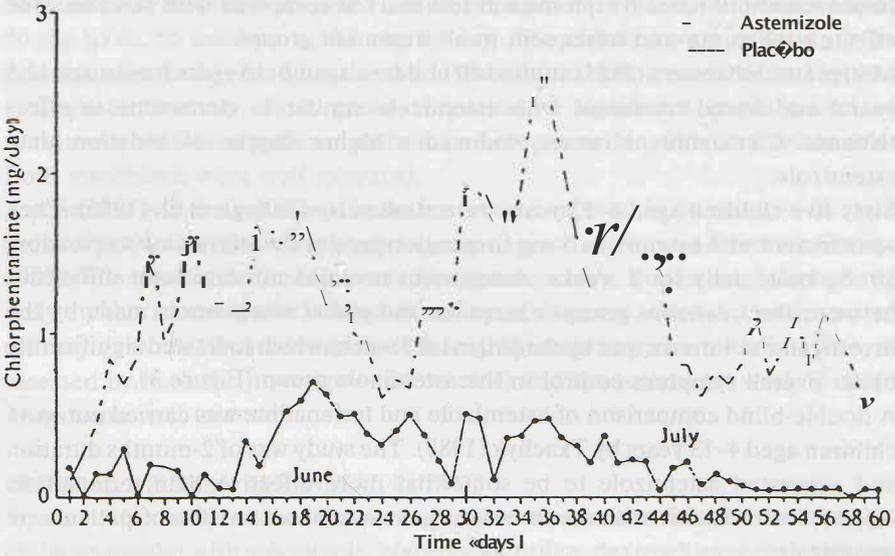


Figure 1. Mean daily use of rescue medication (chlorpheniramine) in an 8-week study (June 1 to July 30, 1983) comparing astemizole and placebo in children (N=97) with seasonal allergic rhinitis (Hedley et al., 1984).

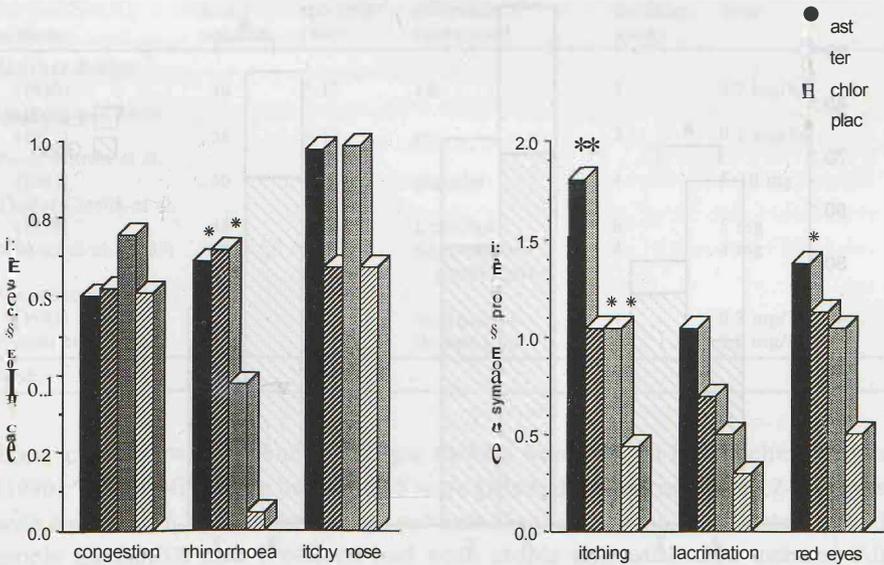


Figure 2. Mean symptom improvement in children with seasonal allergic rhinoconjunctivitis (N=65) with astemizole, terfenadine, chlorpheniramine and placebo for nasal (left) and ocular (right) symptoms (Villa Aseni et al., 1988).

Improvement of nasal symptoms was less marked compared with placebo. Side effects were minor and infrequent in all treatment groups.

Moller and Johansson (1984) studied 60 children aged 6-16 years (mean age 12.5 years) and found treatment with astemizole similar to clemastine in effectiveness. Clemastine, however, induced a higher degree of sedation than astemizole.

Sixty-five children aged 6-12 years were studied by Grillage et al. (1986). They were treated with astemizole 5-mg suspension per day or terfenadine suspension, 30 mg twice daily for 8 weeks. Assessment revealed no significant difference between the treatment groups except for the global assessments made by the investigator at 4 weeks, and by the patient at 8 weeks which indicated significantly better overall symptom control in the astemizole group (Figure 3).

A double-blind comparison of astemizole and terfenadine was carried out in 44 children aged 4-13 years by Tkachyk (1988). The study was of 2-months duration and suggested astemizole to be somewhat more effective than terfenadine. Appetite stimulation with some weight gain was noted in 50% of patients on astemizole.

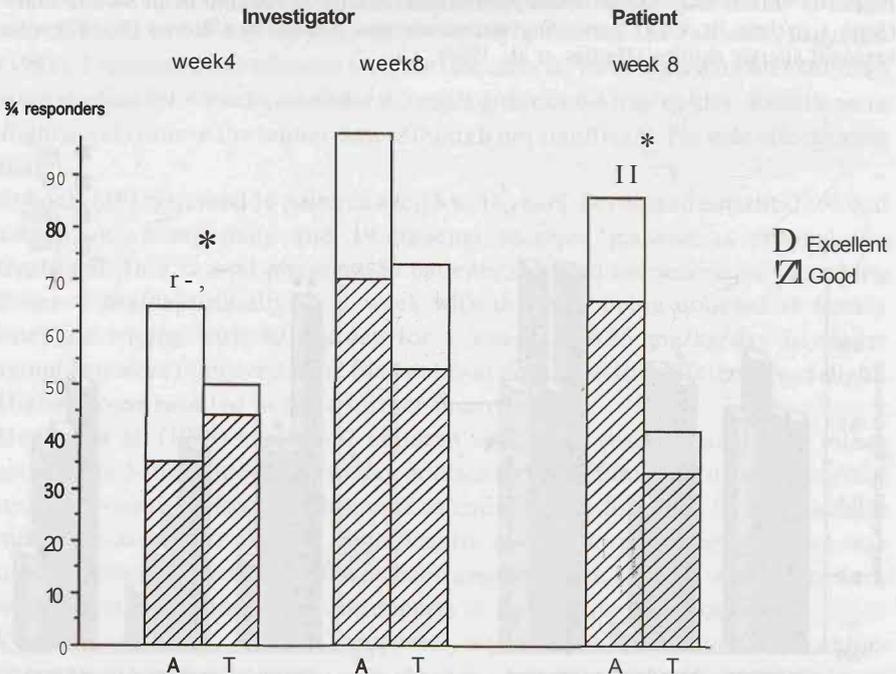


Figure 3. Global assessments of treatment efficacy by investigator (week 4 and 8) and patient (week 8) in children with seasonal allergic rhinitis (N = 65). Percentage of responders (good to excellent results) are indicated for astemizole (A) and terfenadine (T); * $p < 0.05$ (Grillage et al., 1986).

Novembre et al. (1989) treated 51 children, aged 6-13 years, with terfenadine, 30 mg b.i.d., or astemizole, 0.2 mg/kg/day. The children were suffering from seasonal allergic rhinoconjunctivitis and the study duration was 32 days. This was a single-blind study. Both groups experienced significant improvement of symptoms, with no significant difference between terfenadine and astemizole. Both treatments were well tolerated.

Astemizole and terfenadine suspension were compared in 66 children (6 to 12 years of age) in a single-blind study in general practice (Janssen Research Group, 1986). The dose of terfenadine was 30 mg twice daily, that of astemizole 5 mg daily in the morning, for a total duration of 8 weeks. Global assessment of efficacy demonstrated astemizole to be significantly superior to terfenadine, as assessed by both the investigator (at week 4) and the patient (at week 8). Both drugs were well tolerated.

CLINICAL STUDIES: PERENNIAL RHINITIS

Seven studies are described for the indication of perennial rhinitis involving 284 children treated with astemizole, placebo, ketotifen, dextrochlorpheniramine or terfenadine. The age range in these studies was 2-16 years. The duration of treatment ranged from 2-6 weeks (Table 2).

Table 2 Studies with astemizole in children with perennial allergic rhinitis.

authors	no. of patients	age range years	reference compound	duration weeks	dose
Sanchez-Borges (1990)	40	2-12	no	2	0.2 mg/kg
Da Silva and Mori (1987)	38	3-12	no	2	0.2 mg/kg
Perez Martin et al. (1985)	40	4-16	placebo	4	5-10 mg
Tiszler-Cieslik et al. (1989)	48	6-12	ketotifen	6	5 mg
Naspitz et al. (1987)	58	6-12	dextrochlorpheniramine	4	4 mg
Monteleone et al. (1988)	29	2-15	terfenadine	4	0.2 mg/kg
Passi.li et al. (1988)	31	?	terfenadine	4	0.2 mg/kg
total	284	2-16		2-6	

Forty children with perennial allergic rhinitis were treated by Sanchez-Borges (1990). Twenty-five were boys and 15 were girls and the age range was 2-12 years with a mean of 6.7 years. Seventeen patients also had asthma, 3 patients also had atopic dermatitis and 1 patient had both atopic dermatitis and asthma. All children were treated with astemizole, 0.2 mg/kg/day for 14 days. There was a significant improvement in symptom scores in 37 patients (93%). Two children experienced appetite increase. One child had documented weight increase.

An open study with astemizole suspension (0.2 mg/kg) was also performed by Da Silva and Mori (1987) in 38 patients, aged 3-12 years. The study lasted 2 weeks. Patients' diary data showed significant improvement of sneezing, runny nose and nasal obstruction from the first day of treatment, while itchy nose and eyes, and lacrimation improved somewhat later on. Treatment was judged to be good or excellent by 79% of patients.

Perez Martin et al. (1985) treated 40 children with perennial allergic rhinitis with either astemizole or placebo. The age range was 4-16 years. For children weighing more than 25 kg the dose was 10 mg t.i.d. for 3 days, 10 mg b.i.d. for 2 days, then 10 mg daily for the remainder of 4 weeks. The doses were halved for children weighing less than 25 kg. Astemizole was reported to be effective with no difference in side effects from placebo.

Forty-eight children with perennial allergic rhinitis were treated by Tiszler-Cieslik et al. (1989) with astemizole (5 mg/day) or ketotifen (2 mg/day) for 6 weeks. The age range of the children was 6-12 years. Overall results were good or excellent in 79% of the astemizole group compared with 37% of the ketotifen group.

Astemizole (4 mg daily) was compared to dextrochlorpheniramine (2.5 mg t.i.d.) in a 4-week study in 58 children aged 6-12 years (Naspitz et al., 1987). Improvement in runny nose and itchy nose and eyes was similar in the two groups, while astemizole was significantly better in relieving sneezing, lacrimation and nasal congestion. The reduction in symptoms was similar for astemizole and dextrochlorpheniramine during the first week, whereafter there was a further reduction with astemizole and not with dextrochlorpheniramine (Figure 4). Significantly more drowsiness was seen with dextrochlorpheniramine.

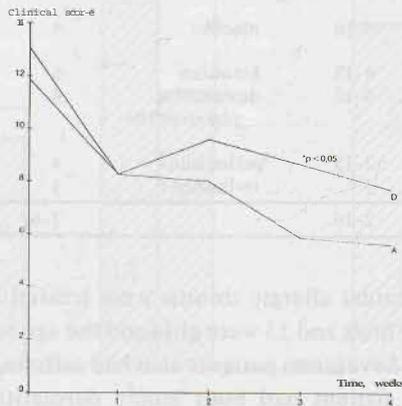


Figure 4. Overall clinical assessment by the investigator in a study comparing astemizole with dextrochlorpheniramine in children (N=58) with perennial allergic rhinitis (Naspitz et al., 1987).

A single-blind comparison of astemizole (0.2 mg/kg/day) or terfenadine (30 mg b.i.d. if over 6 years of age, 15 mg b.i.d. if less than 6) was carried out in 29 children with chronic allergic rhinitis by Monteleone et al. (1988). The study duration was at least 4 weeks. Clinical improvement was noted in more patients on astemizole than on terfenadine, this difference being just not statistically significant ($p = 0.05$). Increased appetite with weight gain was noted in 4 patients on astemizole and 6 patients on terfenadine. Passali et al. (1988) carried out a very similar study on 31 children and found that 94% improved while on astemizole and 69% improved on terfenadine. Astemizole was reported to have a more favourable effect in allaying symptoms although the difference was not significant. No side effects were reported.

CLINICAL STUDIES: VARIOUS ALLERGIC DISORDERS

Four further studies are described where the indications included various allergic disorders, but generally the majority of the patients were hay-fever sufferers (Table 3). These included a further 138 patients ranging in age from 6 months to 12 years. The duration of treatment in these studies ranged from 2 to 6 weeks. Richarz-Barthauer (1987) evaluated 44 children, 2 to 12 years of age, in an open setting. The dose of astemizole was 0.2 mg/kg/day and treatment lasted 2 to 4 weeks. Significant improvement in symptoms was observed in the various indications, i.e. allergic rhinitis and conjunctivitis, urticaria and atopic dermatitis. Compared to previous treatment, the onset of action of astemizole was judged to be similar. Only one patient complained of mild appetite and weight increase.

Serembe and Durigato (1984) studied 20 children of whom 2 had allergic oculorhinitis, 11 had allergic asthma, and 7 had both of these. The age range was 3-12 years and the dosage 5 mg/day for up to 5 weeks (mean duration 3.6 weeks). There was a similar reduction with astemizole in ocular, nasal and pulmonary symptoms (Figure 5). Results were "good to excellent" in 14 patients (70%). No adverse reactions were reported.

Table 3. Studies with astemizole in children with various allergic disorders.

authors	no. of patients	age range years	reference compound	duration weeks	dose
Richarz-Barthauer (1987)	44	2-12	no	2-4	0.2 mg/kg
Serembe and Durigato (1984)	20	3-12	no	5	5 mg
Molkhou et al. (1989)	51	0.5-2	no	6	0.2 mg/kg
De Loore (1982)	23	2-11	placebo	4	0.2 mg/kg
total	138	0.5-12		2-6	

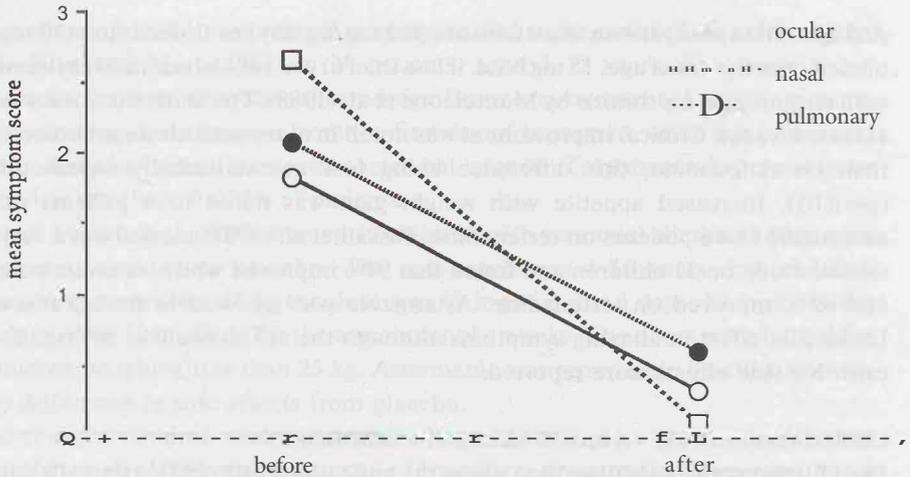


Figure 5. Mean score for ocular, nasal and pulmonary symptoms before and after treatment with astemizole in children (N=20) with various allergic disorders (Serembe and Durigato, 1984).

Fifty-one children under 2 years of age were evaluated by Molckhou et al. (1989) in an open study. They were treated with astemizole (0.2 mg/kg/day) for an average period of 6 weeks. Clinical tolerance was "good or excellent" in 98% of cases. There were 2 cases of drowsiness reported, 1 case of agitation with increased appetite, and 1 case of nausea. Nine children (18%) had a moderate corrected weight increase (lying between 0.5 and 0.95 SD).

A placebo-controlled study was performed in Belgium by De Loore (1982). He treated 23 children (2-11 years) with either astemizole (0.2 mg/kg/day) or placebo. All children suffered from cough or difficult breathing, symptoms which were significantly more improved in the astemizole- than in the placebo group. Also, nasal and ocular symptoms were improved. In global evaluations by both patients and investigators, astemizole was considered significantly better than placebo.

LABORATORY DATA: HAEMATOLOGY AND BIOCHEMISTRY

For the evaluation of the haematological and biochemical data all clinical studies with astemizole in children were considered, including 4 studies in asthmatic children (De Bode, 1983, Samanek, 1981 and 1982, Prinsen, 1983).

In total, laboratory data are available from 9 studies (Table 4) for 313 children. The age range of the astemizole-treated patients was 6 months to 16 years, and the dosage range 0.2 mg/kg/day or 5-40 mg/day. Duration of treatment ranged from 3 to 12 weeks. No consistent changes were observed in blood values; there was no evidence of toxicity for bone marrow, peripheral blood, liver and kidney function, or electrolytes balance.

Table 4. Studies with astemizole in children for which haematological and biochemical data are available.

authors	indication	no. of age patients		reference range	duration compound	dose weeks
Sobocki (1984)	seasonal	38	8-16	placebo	4	5, 10, 20, 40 mg
Perez Martin et al. (1985)	perennial	40	4-16	placebo	4	5-10 mg
Naspitz et al. (1987)	perennial	58	6-12	dextrochlorpheniramine	4	4 mg
Serembe and Durigato (1984)	various	20	3-12	∅	5	5 mg
Molkhou et al. (1989)	various	51	0.5-2	no	6	0.2 mg/kg
De Bode (1983)	asthma	10	11-16	∅	4	10 mg
Samaneck (1981)	asthma	30	6-14	placebo	3	10-20 mg
Samaneck (1982)	asthma	30	8-15	placebo	5	5-10 mg
Prinsen (1983)	asthma	36	5-15	ketotifen	12	10 mg
total		313	0.5-16		3-12	

CONCLUSION

The efficacy of astemizole in children with seasonal or perennial allergic rhinitis or a variety of allergic disorders was evaluated in 21 clinical studies involving a total of 1,008 children treated with astemizole, placebo, chlorpheniramine, dextrochlorpheniramine, clemastine, ketotifen or terfenadine (Table 5). Duration of treatment ranged from 1 to 8 weeks. Dosage of astemizole ranged from 0.2 mg/kg/day to 40 mg/day, the actually recommended dose now being 0.2 mg/kg/day. Astemizole was shown to have beneficial effects in the various indications, the results obtained with astemizole generally being more favourable than those of the reference compounds. The incidence of side effects with astemizole was low. Sedation was clearly lower with astemizole than with sedating antihistamines and similar to that reported with terfenadine.

Table 5. Summary of studies with astemizole.

indication	no. of studies	no. of patients	age range years	duration weeks
seasonal allergic rhinitis	10	586	1-18	1-8
perennial allergic rhinitis	7	284	2-16	2-6
various allergic disorders	4	138	0.5-12	2-6
total	21	1,008	0.5-18	1-8

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Levocabastine: a new topical approach for the treatment of paediatric allergic rhinoconjunctivitis

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SUMMARY

Levocabastine is a novel H₁-receptor antagonist for topical use, which is being investigated in allergic rhinitis (nasal spray) and conjunctivitis (eye drops). Its anti-allergic effects have been demonstrated in nasal and ocular provocation tests. Clinical studies have been performed in 1,363 patients with allergic rhinitis and 1,218 patients with allergic conjunctivitis, comparing levocabastine mainly to placebo and cromoglycate. Levocabastine was effective when used at a dose of 2 sprays per nostril or 1 drop per eye twice daily, which if necessary can be increased up to four times daily. Levocabastine was superior to placebo in alleviating symptoms such as sneezing, itchy nose, runny nose, itchy eyes, red eyes and lacrimation. In global evaluations some 60% of patients had good to excellent results with the nasal spray and some 75% with the eye drops. Levocabastine was shown to be as good or even slightly better than cromoglycate. Onset of action was fast, with 73% of patients reporting symptom relief within 30 min after administration of levocabastine nasal spray. Adverse experiences were similar in type and incidence with levocabastine, cromoglycate and placebo, for nasal spray as well as eye drops. The most frequent complaints were nasal and ocular irritation, respectively, with a similar incidence for the three drugs. Limited data are available in children so far, but they indicate response rate and adverse-experience profile to be similar to what was observed in adults.

Levocabastine, thus, is an interesting new antihistamine available for topical use in allergic rhinoconjunctivitis. It has been extensively evaluated in adults, and preliminary data indicate that it can also be useful in allergic children.

INTRODUCTION

When the possibility exists of administering a drug topically, i.e. when the target tissues are accessible, the topical route of administration offers several advan-

tages over systemic treatment, especially in children. The first one is that a topically administered drug avoids the general circulation, reducing the risk for toxicity and systemic side-effects. Secondly, since topical application results in high local concentrations, the amount of drug to be administered can be reduced, further reducing possible risks for side effects. In allergic rhinitis and conjunctivitis most symptoms are known to be histamine-mediated, histamine being released locally in the superficial layers of the nasal and ocular mucosa. There seems to be, therefore, a good medical rationale for a topically administered antihistamine. At present, no antihistamine is available in monotherapy for both nasal and ocular use.

The new H₁-blocking antihistamine levocabastine, a cyclohexylpiperidine molecule, has been developed both as nasal spray and eye drops. In this paper the available data with levocabastine will be reviewed, with particular attention to the use in children.

ANIMAL PHARMACOLOGY

Animal studies have shown levocabastine to be an extremely potent histamine H₁-receptor antagonist (Van Wauwe, 1989). In the compound 48/80 test in rats,

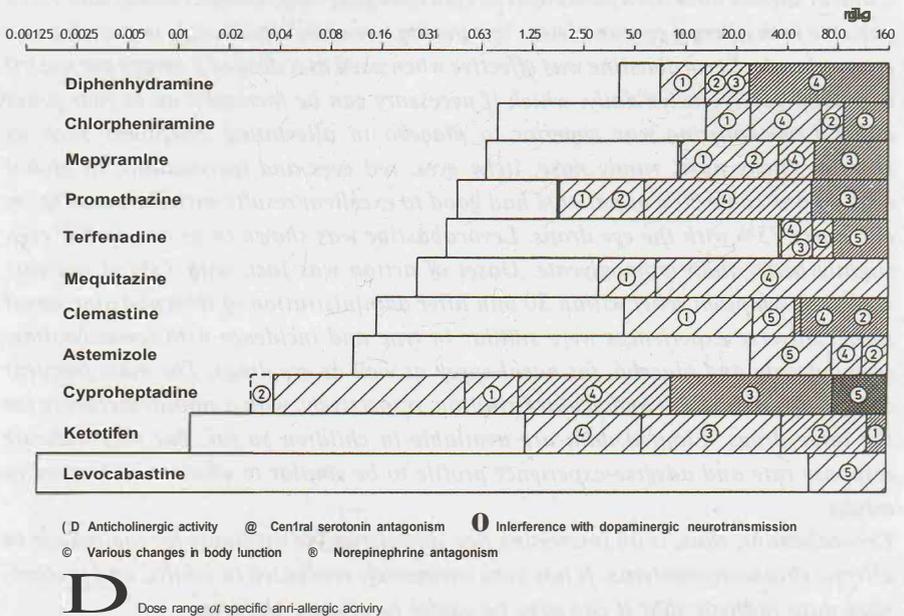


Figure 1. Specificity of levocabastine: Pharmacological activity profiles in rats of various antihistamines and levocabastine. Effective doses for different activities are compared with the primary anti-allergic activity (protection from compound 48/80-induced lethality) (Van Wauwe, 1989).

oral levocabastine counteracted the lethal effect of intravenous compound 48/80 with an ED_{50} of 0.002 mg/kg, which is several times lower than that for any other presently available antihistamine. Furthermore, treatment with levocabastine resulted in an immediate but also persistent effect over at least 16 hours. The effect readily declined after 24 hours.

Levocabastine is also a very specific antihistamine (Figure 1; see also Van Wauwe, 1989). In rats, levocabastine dosed orally up to 160 mg/kg, i.e. 106,000 times the effective antihistamine dose, was devoid of anti-serotonin, anticholinergic and anti-dopamine activity. Only at 43,400 times the effective antihistamine dose some α -adrenergic antagonism was noted.

CLINICAL PHARMACOLOGY

Nasal provocation tests

Nasal provocation tests performed in three double-blind, placebo-controlled studies showed levocabastine nasal spray (2 sprays per nostril) to prevent the symptoms induced by the allergen challenge. Figure 2 shows one of these studies (Pecoud et al., 1987) in which 12 atopic patients underwent nasal provocation tests with allergen, each time 5 to 15 min after a single administration of either placebo, cromoglycate or levocabastine. The effect on rhinorrhoea and the number of sneezes was significantly better after treatment with levocabastine than after placebo and also better than after cromoglycate. Nasal allergic reaction threshold was clearly increased after levocabastine, the difference being significant versus cromoglycate and placebo.

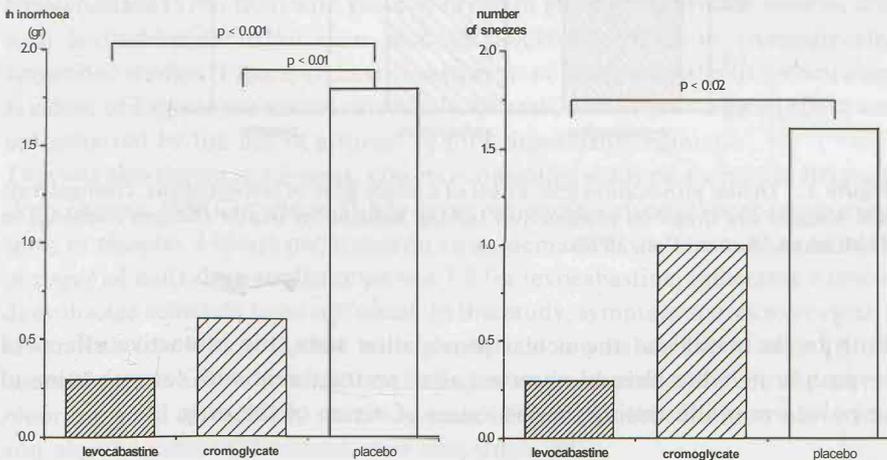


Figure 2. Nasal provocation test: Effect of a single dose of levocabastine, cromoglycate and placebo nasal spray on rhinorrhoea and sneezing induced by nasal allergen challenge (N = 12) (Pecoud et al., 1987).

Ocular provocation tests

Ocular provocation tests showed similar protective effects of levocabastine eye drops in five studies. One study (Rimas et al., 1990) was performed in children (9-17 years, N=25), comparing a single dose of levocabastine, placebo and cromoglycate administered 15 min before ocular allergen challenge. The allergic reaction threshold was increased significantly with levocabastine as compared to placebo and cromoglycate. Conjunctival itching was significantly less with levocabastine than with placebo or cromoglycate (Figure 3).

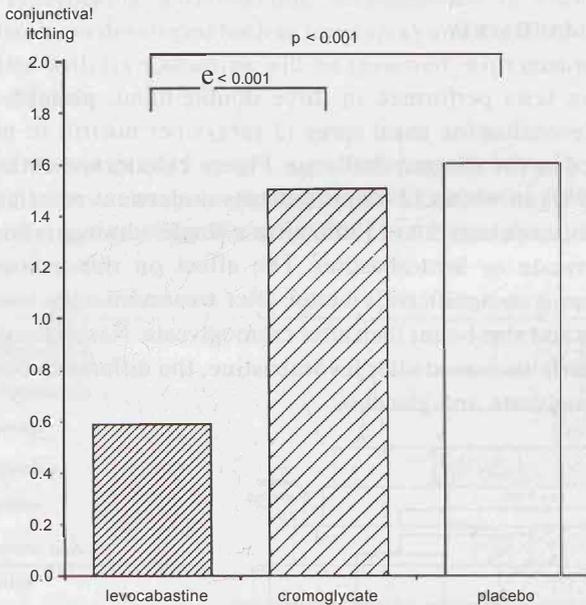


Figure 3 Ocular provocation test: Effect of a single dose of levocabastine, cromoglycate and placebo eye drops on conjunctival itching induced by ocular allergen challenge in 25 children (Rimas et al., 1990).

Both in the nasal and the ocular provocation tests, the protective effects of levocabastine were already observed after pretreatment with levocabastine of only 5-15 min, illustrating the fast onset of action of the drug.

THERAPEUTIC STUDIES

Several clinical trials have been performed with levocabastine nasal spray and eye drops in patients with allergic rhinitis and conjunctivitis. All trials were done

with parallel study groups, most were double-blind. Study durations were generally 2 to 4 weeks. In most trials levocabastine was compared with placebo or cromoglycate; some trials with the nasal spray used nasal steroids as reference drug, while levocabastine eye drops were also compared with antazoline/naphazoline eye drops. The dose of levocabastine varied from 1 spray per nostril o.d. to 2 sprays per nostril q.i.d. for the nasal spray and from 1 drop per eye o.d. to 1 drop per eye q.i.d. for the eye drops; the reference drugs were used in the usually recommended doses (cromoglycate at a q.i.d. dose).

Symptoms were scored as either absent, mild, moderate or severe, using a visual analogue scale. Evaluations were done daily by the patient in a patient's diary and by the investigator at regular follow-up visits. The following symptoms were assessed in most trials:

- 1) in allergic rhinitis: sneezing, runny nose, itchy nose, blocked nose;
- 2) in allergic conjunctivitis: ocular irritation, redness, eye itching, lacrimation, swollen eyelids.

At the end of treatment, the patient and/or the investigator gave a global evaluation of the study medication as either excellent, good, moderate or poor.

Levocabastine nasal spray

Data were available from 23 clinical trials including a total of 1,363 allergic rhinitis patients (Vanden Bussche et al., 1988).

Global evaluations at the end of treatment were significantly in favour of levocabastine. Significantly more patients had good to excellent results with levocabastine (57%) than with placebo (37%) in placebo-controlled studies, and with levocabastine (63%) than with cromoglycate (47%) in cromoglycate-controlled studies (Figure 4). Levocabastine nasal spray was effective when used at a dose of 2 sprays per nostril twice daily. Overall, a more pronounced effect was not achieved by the use of a three- or four-times daily regimen.

This was also shown in a 2-week, placebo-controlled study performed in Belgium (Van Durme, 1988), in which 31 hay-fever patients received levocabastine nasal spray or placebo, 2 sprays per nostril on an on-demand basis. The median number of required daily drug applications was 1.8 for levocabastine, indicating a twice-daily dosage schedule to be sufficient. In this study, symptom scores were clearly lower with levocabastine than with placebo, at low as well as at high pollen concentrations. Global evaluations favoured levocabastine with 69% of patients reporting good or excellent results, versus 42% for placebo. Both levocabastine and placebo nasal applications were well tolerated.

Figure 5 is an illustration of a 2-week study on 77 patients (Schata et al., 1989) comparing levocabastine to both placebo and cromoglycate (2 sprays per nostril q.i.d.). Global evaluations by the investigator showed a significant superiority of

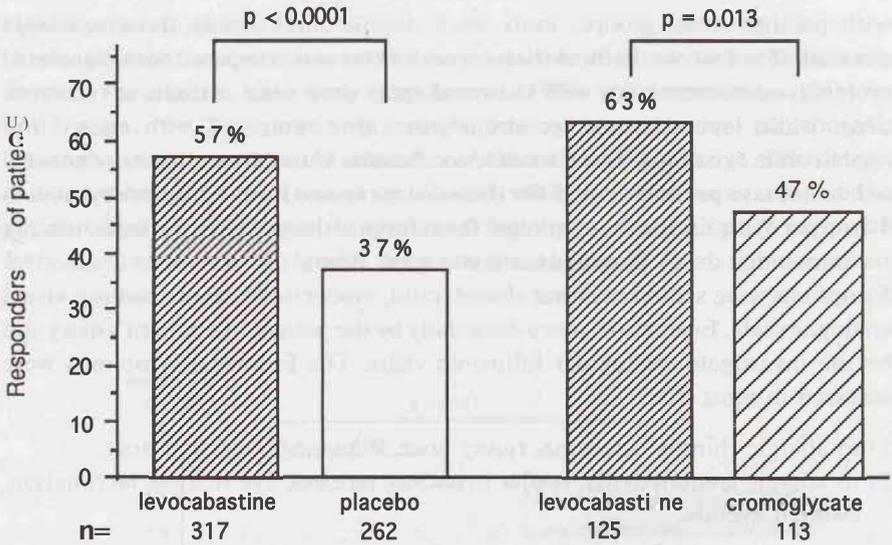


Figure 4 Nasal spray, global evaluation: Response rate (percentage of good to excellent results) at the end of treatment in placebo-controlled and cromoglycate-controlled studies (Vanden Bussche et al., 1988).

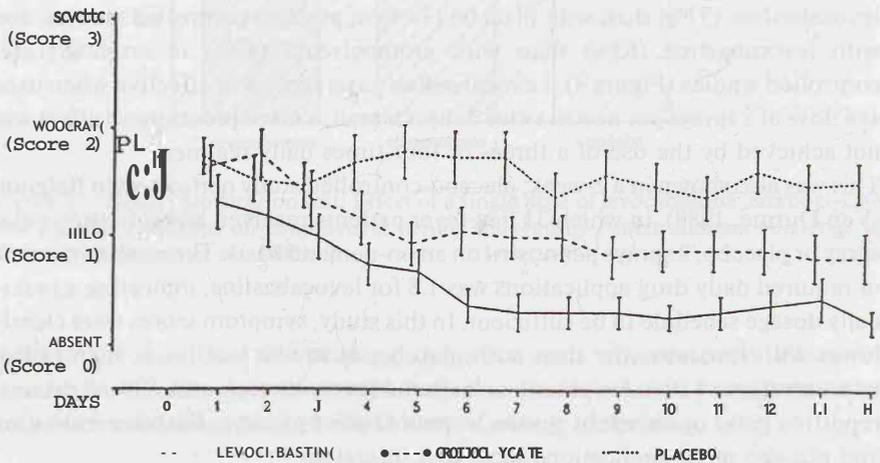


Figure 5 Nasal spray, comparison with cromoglycate and placebo: Patients' diary scores for itchy nose on levocabastine, cromoglycate and placebo (2 sprays per nostril q.i.d.) in a 2-week study (N=77) (Schata et al., 1989; with permission from the author).

levocabastine over cromoglycate and placebo: In 78% of patients good to excellent results were obtained with levocabastine versus 42% with cromoglycate and 35% with placebo. Daily symptom-scores were always lowest in the levocabastine group, as shown for itchy nose in Figure 5. All medications were well tolerated. In one study (Van de Heyning et al., 1988), patients treated for 2 weeks with levocabastine nasal spray, were subsequently treated with beclomethasone for another 2 weeks. The effects already produced by levocabastine on nasal discharge and sneezing could not be further improved by the steroid treatment. In a recent study (Belgian GP-study, 1989), onset of action of levocabastine was evaluated by the patients after the first application of levocabastine nasal spray. Symptom relief within 30 min was reported in 73% of levocabastine-treated patients.

Adverse experiences were similar in type and incidence with levocabastine (23% of patients), placebo (21% of patients) and cromoglycate (19% of patients; see also Vanden Bussche et al., 1988). Nasal irritation was the most frequently reported complaint, with a similar incidence in the three groups (5-6%).

Levocabastine eye drops

Twenty-one clinical trials were performed assessing the efficacy of levocabastine eye drops, including a total of 1,218 patients with allergic conjunctivitis (Vanden Bussche et al., 1988).

Global evaluations at the end of treatment showed response rates to be highest with levocabastine (Figure 6). Good to excellent results were seen in significantly more patients with levocabastine (71%) than with placebo (55%). Compared to cromoglycate, response rates were 80 and 76% for levocabastine and cromoglycate, respectively. Overall, levocabastine eye drops proved to be highly effective in relieving the typical symptoms of allergic conjunctivitis. Levocabastine administered b.i.d. was shown to be at least as effective as cromoglycate administered q.i.d., in a 2-week study in 33 patients (Zawodnik et al., 1989). Good to excellent results were reported in 67% of patients on levocabastine and 54% on cromoglycate. Symptom scores for itchy eyes, burning sensation and swollen eyelids were lower with levocabastine than with cromoglycate.

A comparison with antazoline/naphazoline eye drops, performed in 66 patients (Bende and Pipkorn, 1987) showed somewhat better *control* of eye symptoms with levocabastine. Sixteen patients (44%) complained of ocular irritation in the antazoline/naphazoline group versus none in the levocabastine group.

The overall incidence of adverse experiences reported was similar with levocabastine (29%), placebo (31%) and cromoglycate (31%), as was the type of adverse experiences (Vanden Bussche et al., 1988). Eye irritation was the most frequent complaint in all three groups (16% in all three groups).

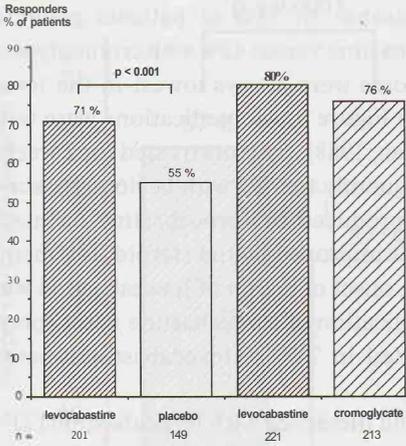


Figure 6 Eye drops, global evaluation: Response rate (percentage of good to excellent results) at the end of treatment in placebo-controlled and cromoglycate-controlled studies (Vanden Bussche et al., 1988).

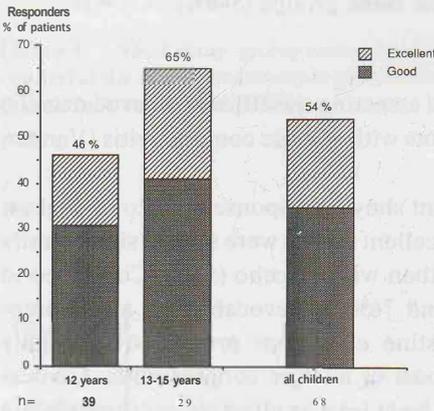


Figure 7 Children, nasal spray: Response rate (percentage of good to excellent results) in children aged < 12 years, aged 13-15 years, and combined (Janssen Research Foundation, 1990).

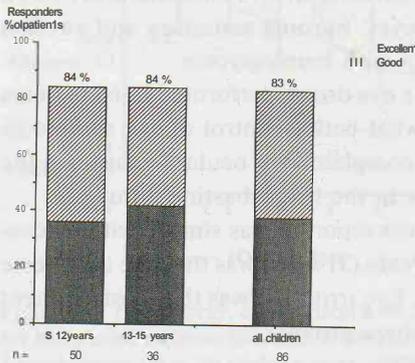


Figure 8 Children, eye drops: Response rate (percentage of good to excellent results) in children aged < 12 years, aged 13-15 years, and combined (Janssen Research Foundation, 1990).

DATA IN CHILDREN

So far, only a few studies were performed specifically in children. Yet, some children participated in most of the studies available. Therefore, a small analysis of the data in children was performed (Janssen Research Foundation, 1990). For this purpose 15 years was defined as the upper age. Most children were between 6 and 15 years, only 14 were younger than 6 years. Only global evaluations and adverse experiences were analyzed, as the data were too heterogeneous to allow other analyses.

Levocabastine nasal spray

In total, 152 children with allergic rhinitis participated in clinical trials, more than half of them treated with levocabastine in comparison with placebo or cromoglycate. Global evaluations showed the percentage of children with good to excellent results to be about 54%, which is similar to the response rate that was observed in adult patients (Figure 7). Incidence and type of adverse experiences were almost identical to what was reported for adult patients.

Levocabastine eye drops

The eye drops were studied in 184 children, most of them receiving levocabastine versus placebo and cromoglycate. Good to excellent results were seen in about 83% of children on levocabastine, which is a similar response rate as that seen in adults (Figure 8). The same is true for adverse experiences.

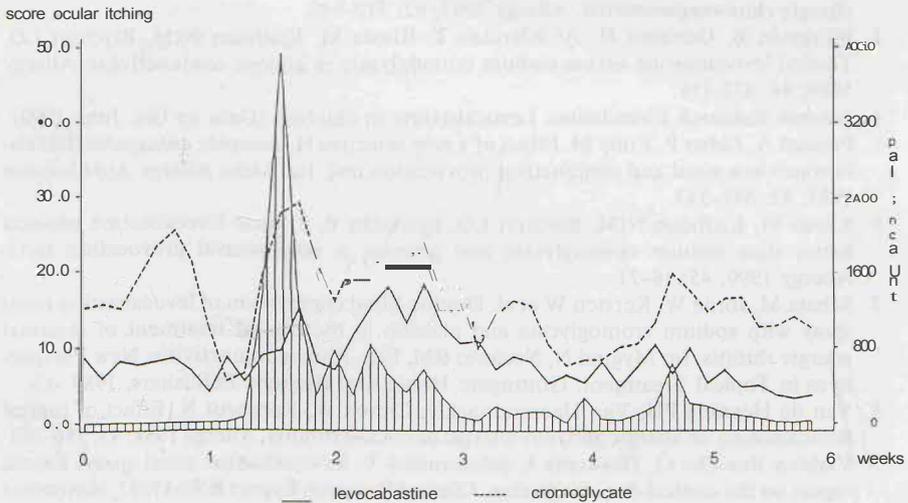


Figure 9. Children, eye drops vs cromoglycate: Patients' diary scores for ocular itching on levocabastine and cromoglycate in a 6-week study in children (N = 37). Pollen count is also indicated (Bjorksten et al., 1999; with permission from author).

Two studies with levocabastine eye drops were performed specifically in children. Figure 9 shows the effects of levocabastine (1 drop per eye b.i.d.) and cromoglycate (1 drop per eye q.i.d.) in 37 patients (Bjorksten et al., 1989). Mean daily symptom-scores were lower for levocabastine than for cromoglycate for itching, tearing and erythema at low as well as at high pollen concentrations. The global evaluation by the patients was significantly in favour of levocabastine with 85% good to excellent results with levocabastine versus 57% with cromoglycate.

CONCLUSION

Levocabastine nasal spray and eye drops were shown to be effective treatment for, respectively, allergic rhinitis and conjunctivitis. The drug provides fast symptom relief. Sustained symptom control is possible with a twice daily dose regimen. The incidence of adverse experiences is low and hardly differs from placebo. Preliminary data indicate the drug also to be valid therapy for children with allergic rhinoconjunctivitis.

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New strategies for the prevention and treatment of allergic rhinitis in children

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SUMMARY

Allergic rhinitis (AR) is a very common disease in children, often underdiagnosed and with underestimated complications. Its prevalence has increased during the last years, due to changes in environmental factors. The therapeutic strategy will include prevention by identification and eviction of the main allergens, associated to pharmacological therapy. Among antirhinitic drugs, the new generation of non-sedative specific antihistamines represent the main choice. We report our own experience with astemizole, one of these new antihistamines which confirms that astemizole is an effective and safe drug for the management of AR in children.

EPIDEMIOLOGY

Allergic rhinitis (AR) is a very common disease occurring in approximately 10% of children and up to 20% of adolescents (Smith, 1984). It is often underdiagnosed, especially in asthmatic children. It has been estimated that 75% of asthmatic children suffer from AR (Viner and Jackson, 1976).

Its importance as a cause of morbidity is also underestimated. AR may be a cause of serious discomfort for the child as well as for the family. In older children loss of smell, a frequently unrecognized complication, may lead to poor eating habits and decreased appetite, which increases family tension at meal-times. Repeated throat-clearing and coughing, especially at night, may also be present. The noisy breathing, irritating sniffing, coughing and throat-clearing often lead to social isolation at school and discord at home.

In addition, AR may cause several complications including abnormal facial development with orthodontic problems, Eustachian tube dysfunction, serous otitis media and sinusitis. The frequent association of paranasal sinusitis in children with asthma has been observed and sinusitis has been considered a contributing factor in bronchial asthma.

Eighty children between 4 and 14 years of age suffering from asthma were investigated by us in order to evaluate the prevalence of sinusitis, to establish the relationship between these two diseases, and to evaluate whether sinusitis therapy improves the symptoms of asthma (Businco et al., 1981). Fifty-five out of 80 children showed clinical and radiological findings of sinusitis. After appropriate therapy 34 out of 55 children showed improvement in sinus X-rays and 20 children had significant decrease in severity of asthma ($p < 0.001$).

Many surveys, carried out in different countries, have shown a rise in AR prevalence during the last years, particularly among children (Anderson, 1989; Burr et al., 1974; Fleming and Crombie, 1987). A recent survey by Burr et al. (1989), on 12-year-old children, has confirmed a striking increase in asthma and hay-fever prevalence (by about 50%) during the last 15 years. Since the same group of investigators conducted two more surveys - the former in 1973 and the latter in 1988 - using the same methodology in 12-year-old children at the same school, the reported rise in allergic diseases prevalence seems to be real, and not related to a greater readiness to diagnose the disease.

ENVIRONMENTAL FACTORS AND PREVENTION

It is not established which factors could have caused the rise of allergic disease prevalence. It is known that the house dust mite and other indoor-allergens are the main cause of perennial AR in children. Modern housing may be part of the explanation why allergy seems to be increasing in developed countries (Lau et al., 1989; Strachan, 1989). Indeed, changes in modern houses might have created a more suitable environment for mites and for other indoor-allergens. New discoveries on mite biology have shown that mites breed when humidity is more than 70%, temperature is more than 23 °C, and that they are capable of surviving at temperatures up to 60 °C (Korsgaard, 1983). In the last few decades, especially after the "oil crisis", every effort was made to save on household heating. Doors and windows were sealed off, thus reducing ventilation and increasing humidity. Energy-saving measures have led to insufficient ventilation of rooms and the use of synthetic insulating materials which emit various chemical substances, resulting in an increased concentration of household pollutants. Well-insulated buildings with poor ventilation may thus represent a risk factor for allergic sensitization not only to house dust mite but also to a number of thermophilic *Actinomycetes*. Allergic diseases of the upper and lower respiratory tract occur by inhalation of allergens in poorly ventilated buildings where the cold-water spray

humidifiers have become contaminated by micro-organisms. In addition, central heating, fitted carpets and upholstered furniture may have dramatically augmented the number of mites in indoor environments. The vacuum cleaner, which has generally been considered to be an efficient and hygienic house-cleaning tool, especially recommended for people allergic to house dust, has been recently shown unable to detach and remove the mites and their faeces from carpet-pile and upholstery. Also the use of cold-water detergents, as opposed to the traditional method of boiling bedding and linen, may represent another contributing factor to the proliferation of mites in modern houses.

The negative influence of these environmental conditions seems to be more important for children with a family history of allergic diseases, thus stressing that environmental factors mainly play an important role in subjects with a genetic propensity for allergic disease (Tables 1 and 2).

Table 1. Sequence of events conducting to allergic disease.

Initial exposure to inhalant allergens
↓
Development of IgE antibodies
+
Continued exposure to the relevant allergen
↓
IgE-mediated allergic disease

Table 2. Risk factors for acute attacks of asthma.

- IgE antibodies to inhalant allergens
- Continued exposure to the relevant allergen

THERAPY

As for asthma, there is no drug that can cure AR. However, an adequate therapeutic strategy will lead to a disappearance of the symptoms in the majority of the cases. This strategy includes:

- Identification and elimination of the main offending allergens (Table 3);
- Antihistamine drugs;
- Sodium cromoglycate;
- Topical corticosteroids (severe cases);
- Immunotherapy.

There is no doubt that antihistamines have been the main step in the treatment of AR. Indeed, they still remain one of the most effective drugs for AR. The new generation of non-sedative, specific H₁-receptor antagonists with reduced or no side effects has catapulted antihistamines to the forefront among antirhinitic drugs. Astemizole is a specific antagonist of H₁-histamine receptors with

Table 3. Preventive measures against house dust mite.

-
- Temperature < 20 °C
 - Humidity = 40-50%
 - Washing sheets, linen and curtains at > 60 °C
 - Dry-heating of woolen clothes and plush at > 60 °C
 - Vacuum cleaner with microfilter
-

prolonged action (Awouters et al., 1983; Laduron et al., 1982; Niemegeers and Awouters, 1984). It displays no chemical relationship with any known drug, and can be classified as a new group, i.e. piperidinic. In vitro studies have shown that the drug has a high potential for inhibiting the contractions induced by histamine in guinea-pig ileum preparations (Awouters et al., 1983). In various animal models, astemizole demonstrated to have a considerably longer-lasting anti-histamine effect, and a higher potency than those of any other antihistamine tested (Awouters et al., 1983; Niemegeers and Awouters, 1984).

Studies in humans, undertaken to demonstrate its anti-allergic activity, have already shown that in atopic patients a 10-mg daily dosage significantly inhibits skin and nasal reactions after intradermal or intranasal testing with histamine, house dust mite and pollen (Howarth et al., 1988; Van Cauwenberge, 1984).

The activity of astemizole has also been evaluated in numerous studies performed on patients suffering from different allergic disorders, both adults and children (Holgate, 1988; Vanden Bussche et al., 1987). In the majority of these, its overall effect in alleviating symptoms was reported as excellent and good in 50 to 100% of the cases.

Up to now more than 1,200 allergic children below 12 years have been treated with astemizole in numerous studies performed in different countries [Backer et al., 1989; Blockhuys et al., 1987; Bollag et al., 1987; Da Silva and Mori, 1987; Garibay, 1985; Grillage et al., 1986; Guinnepain, 1987a, b; Hedley et al., 1984; Huguenin et al., 1986; Janssen Pharmaceutica, 1984; Moller and Johansson, 1984; Perez Martin et al., 1985; Richarz-Barthauer, 1987; Serembe and Durigato, 1984]. The drug appears to be safe and its potent antihistamine action is associated with a degree of sedation comparable to that of placebo (Hedley et al., 1984; Janssen Pharmaceutica, 1984; Vanden Bussche et al., 1984a, b). Thanks to its long half-life, a once-daily dosage is sufficient for a 24-hour protection from the first to the last day of treatment.

PERSONAL EXPERIENCE WITH ASTEMIZOLE IN THE TREATMENT OF AR IN CHILDREN

We have a large personal experience with allergic children which have been treated with astemizole, which we consider efficacious and safe to use in paediatrics. We have recently reported (Monteleone et al., 1991) on our experi-

ences in 30 pre-school children aged 2-6 years, and suffering from rhinitic or cutaneous allergic symptoms. However, these patients only represented the Italian contribution to a multicentre, international study. Our patients, as well as those from several investigators in Austria, Belgium and Portugal following the same protocol, were pooled (Janssen Pharmaceutica, 1990) to obtain a population of 135 children, aged 2-6 years (71 male and 43 female). We present here the data of 83 patients with AR symptoms which were included in this international, multicentre study.

Patients were included in the study on the following criteria; children below 6 years of age presenting typical allergic symptoms affecting the nose as confirmed by positive skin and/or RAST test.

Patients were treated, in an open design, with 0.1 ml/kg body weight of an astemizole suspension (2 mg/ml) during 3 weeks. Other anti-allergic concomitant medications were not allowed. All patients were visited at the beginning and at the end of the study, after a 3-week therapy. Symptom severity was assessed on a 0-3 scale for sneezing, rhinorrhoea, blocked nose, itchy nose, difficult breathing, lacrimation, red eyes, itchy eyes and swollen eyelids. The parents were asked to record daily the symptom severity on the same 0-3 scale (Figure 1). At the end of the study, investigators and patients separately gave an overall evaluation on the treatment effects/patient conditions on the following scale: (1) cured; (2) excellent; (3) good; (4) moderate; (5) poor; or (6) inefficient. Possible adverse experiences were recorded.

Results

The occurrence of rhinitis symptoms was seasonal for 53% of the patients and non-seasonal for 47% of them. The mean duration of the disease was 18.8 ± 3 months (mean \pm SD) for seasonal rhinitis, and 16.8 ± 2.5 months for non-seasonal rhinitis. All evaluated symptoms were statistically significantly improved at the end of the trial: sneezing ($p < 0.0001$), runny nose ($p < 0.0001$), blocked nose ($p < 0.0001$), itching nose ($p < 0.0001$), difficult breathing ($p < 0.0001$), lacrimation ($p < 0.0001$), red eyes ($p < 0.0001$), itching eyes ($p < 0.0001$), swollen eyelids ($p < 0.0001$). Global scores as mean nose symptoms and mean eye symptoms were also significantly improved ($p < 0.0001$; Figures 2 and 3). Patients' diaries gave the same information: The development of the mean nose symptoms is shown in Figure 4.

The global evaluation by the investigators showed 7.3% of symptom free patients, 71.9% of good or excellent results and 20.8% of poor or moderate results. The same evaluation done by the patients showed 12.1% of symptom-free patients, 69.7% of good or excellent results and 18.2% of poor or moderate results (Figure 5).

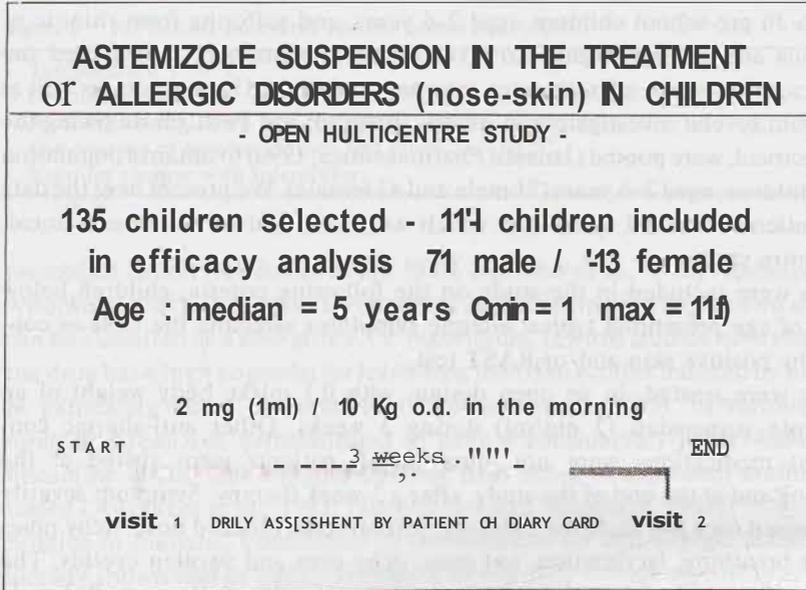


Figure 1. Open multicentre study: Study design.

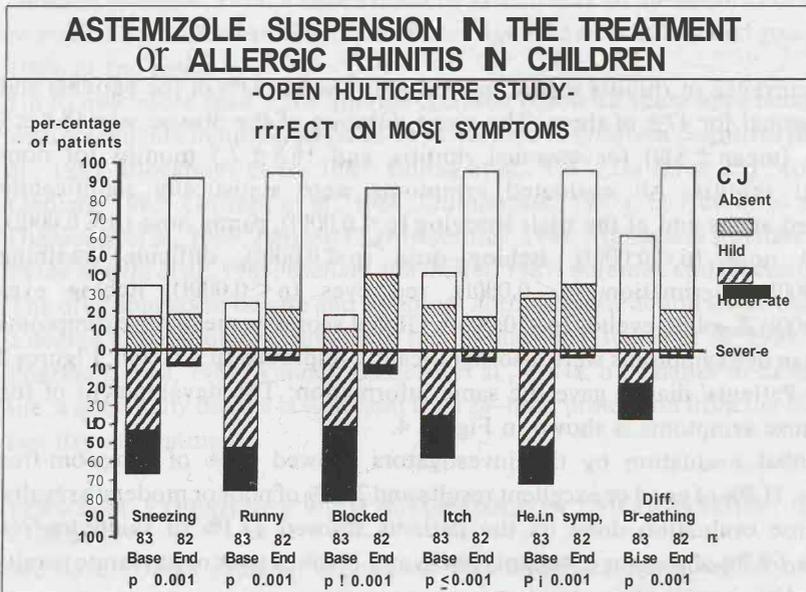


Figure 2. Open multicentre study: Effect on nose symptoms.

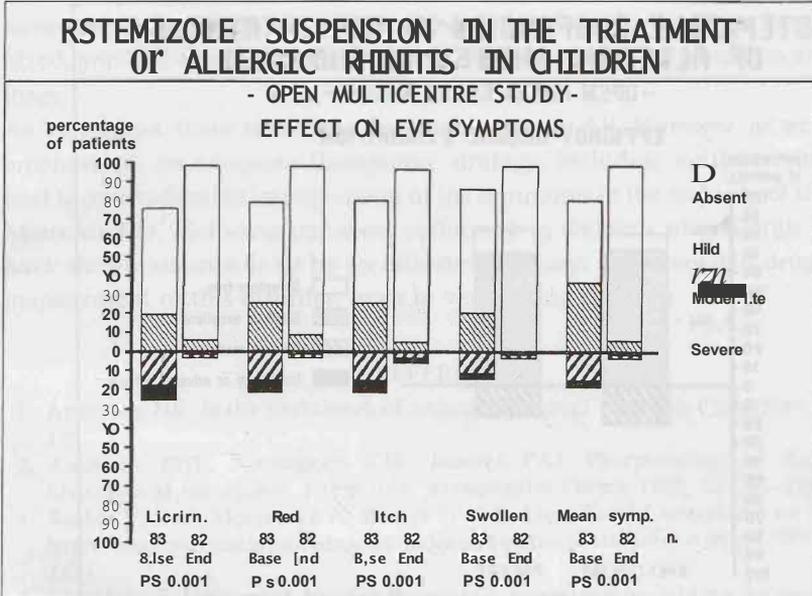


Figure 3 Open multicentre study: Effect on eye symptoms.

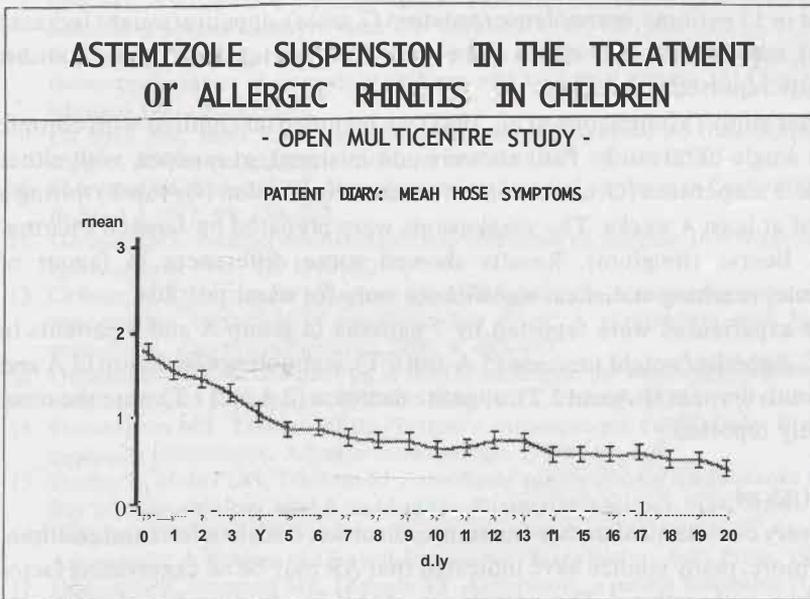


Figure 4 Open multicentre study: Patients' diaries, mean nose symptoms.

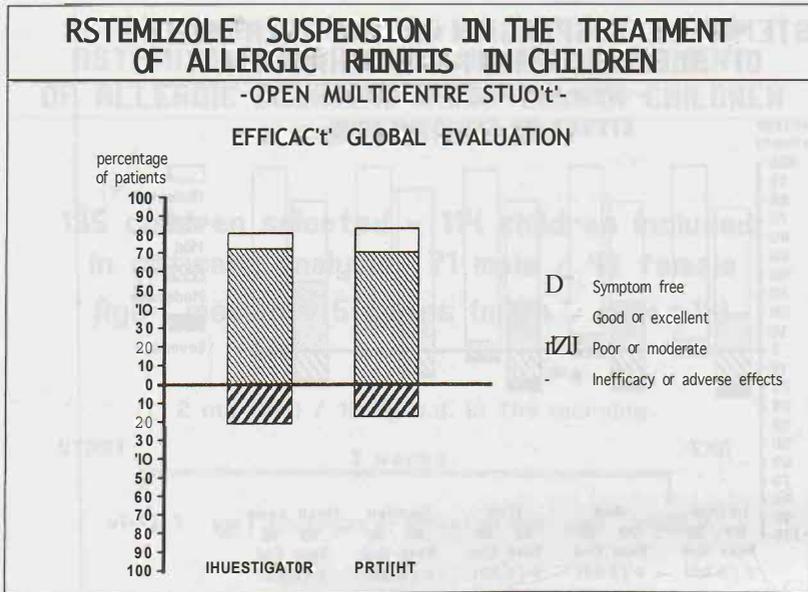


Figure 5. Open multicentre study: Efficacy global evaluation.

A total of 134 patients were included in the safety analysis. Side effects were reported in 17 patients: somnolence/sedation (7 cases), appetite/weight increase (5 cases), mouth dryness (3 cases) and decreased appetite (1 case) were the most frequently reported side effects.

In another study (Monteleone et al., 1988) we included 40 children with chronic AR in a single-blind study. Patients were administered, at random, with either astemizole suspension (Group A) or terfenadine suspension (Group T) during a period of at least 4 weeks. The suspensions were prepared by Janssen Pharmaceutica, Beerse (Belgium). Results showed some differences in favour of astemizole, reaching statistical significance only for nasal pruritus.

Adverse experiences were reported by 7 patients in group A and 9 patients in group T. Appetite/weight increase (5 A and 6 T), somnolence/sedation (3 A and 2 T), mouth dryness (1 A and 3 T), appetite decrease (2 A and 1 T) were the most frequently reported.

CONCLUSION

AR is a very common and rather frustrating disorder, both in adults and children. Furthermore, many studies have indicated that AR may be an aggravating factor in children with asthma. The prevalence of AR in children has significantly increased over the last years. Different environmental factors in modern housing

have contributed to this prevalence rise. Once these factors have been recognized, preventive environmental measures should be taken in order to eliminate them.

As for asthma, there is no drug that is able to cure AR. However, as we already emphasized, an adequate therapeutic strategy, including antihistamines, will lead to a considerable improvement of the symptoms in the majority of the cases. Many studies, including our own, performed in children with allergic rhinitis, have shown astemizole to be an effective, safe and well-tolerated drug for the management of this disorder, even in very young children.

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