

The Perennial Pattern of Clinical Symptoms in Children Monosensitized to *Olea europaea* Pollen Allergens in Comparison with Subjects with *Parietaria* and *Gramineae* Pollinosis

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ABSTRACT

Because the pediatric age represents a good model to study the correlation between the exposure to allergens and development of respiratory allergy, we investigated the occurrence of a perennial type of symptomatology in children monosensitized to *Olea europaea* (*O.e.*) pollen allergens compared with subjects with monosensitization to *Parietaria* (*P*) and *Gramineae* (*G*) in order to confirm our previous observations in adults. We selected a group of 52 children with rhinitis and/or bronchial asthma and a SPT positivity only to pollens (30 to *P*, 15 to *G*, and 7 to *O.e.*). Using commercially available allergenic extracts and reagents, the following diagnostic procedures were performed: skin prick test (SPT), specific IgE assays (RAST), nonspecific bronchial provocation test (NsBPT) and specific nasal provocation test (sNPT), respectively, in patients with bronchial asthma and rhinitis. Pollen counts and a statistical analysis using Spearman's correlation test were also carried out. Six of seven children with monosensitization to *O.e.* allergens showed a perennial pattern of symptoms in

comparison to 7 of 23 and 3 of 12, respectively, in subjects with *P* and *G* pollinosis. All patients with perennial nasal symptoms of *O.e.* group exhibited a late nasal response after sNPT. Although these findings on nasal response may partially explain the occurrence of a prolonged inflammation of the nose induced by *O.e.* allergens, we think that other possibilities could be investigated. In our opinion, further studies are necessary using better purified and standardized diagnostic materials and, moreover, a greater number of *O.e.* monosensitized children living in other geographical areas need to be examined for a comparison of our results with theirs. (Allergy and Asthma Proc 18:99–105, 1997)

Olive (*Olea europaea*—*O.e.*) tree pollen is one of the most important causative agents of respiratory allergy in the mediterranean area.^{1–8} In the last few years, increasing interest has been devoted to immunological, clinical, and aerobiological aspects of this pollinosis.^{9–18}

The majority of authors suggest, with some exception,^{19,20} that *O.e.* related symptoms are prevalent during the flowering months of Olive trees.²¹

Our recent study²² demonstrated a perennial pattern of respiratory symptoms (without any particular exacerbation during the *O.e.* pollination period) in the majority of adults with monosensitization to *O.e.* pollen allergens living in our geographical area. These findings may explain our diffi-

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culty in the evaluation of the etiological significance of *O.e.* sensitization among the other nonspecific factors (especially cigarette smoke) inducing an increase of nasal and/or bronchial hyperreactivity and, moreover, in the management of symptoms (allergen avoidance, specific hyposensitization, antiinflammatory and symptomatic medications, etc.).

Pediatric age represents an ideal model to study the correlation between the exposure to pollens (other than to mites, pets, etc.) and development of allergic respiratory symptoms, as children are usually less exposed to nonspecific irritant factors (air pollution, pollutants from working activities, cigarette smoke, etc.) with the exception of viral infections. For this reason, in the pediatric age, the study of the role of allergens as agents inducing rhinitis and/or bronchial asthma is easier to carry out. Considering this background, the aim of our study was the evaluation of the occurrence of perennial symptoms in children with monosensitization to *O.e.* pollen allergens and living in the Naples area, in comparison with children with exclusive sensitization to Gramineae (G) and *Parietaria* (P) pollen allergens.

MATERIALS AND METHODS

Patients

We studied a population of 1173 children of both sexes, ranging from 3 to 13 years examined in our Allergological Centre consecutively from January 1, 1990 to December 31, 1994, for respiratory symptoms (nasal and/or bronchial) of a suspected IgE-mediated etiology. We selected a group of 52 children with immediate positive skin reaction only to pollens (P, G, *O.e.*) that were considered more frequently as causative agents of pollinosis in southern Italy and in our geographical area (Table I). Children with monosensitization to pollens not living in the Naples area and consequently not surely exposed to the same atmo-

spheric concentration of pollen grains were excluded from the research. No children of the *O.e.* group received a regular medication during olive pollination period; instead, the most with P and G sensitization and a seasonal pattern of symptoms underwent an adequate inhalation therapy with antidisreactive drugs.

We excluded the possibility of infections in upper airways and/or sinusitis by using examination/culture of nasal secretions and X rays.

At the time of our study, all patients were free from respiratory symptoms; they never received specific hyposensitization. All children (with their parents) were moreover submitted to an accurate anamnestic evaluation using an internal questionnaire in order to reduce the risk of including in the study patients in whom nonspecific factors could enhance nasal and/or bronchial hyperreactivity and, consequently, induce a nonseasonal pattern of symptoms. For this reason *O.e.* monosensitized children who were currently exposed to parents' smoke were excluded from the study.

All patients and/or their parents gave informed consent before entry into the study. The type of symptomatology referred during the visit was evaluated according to well-defined criteria (Tables I and II).

Allergenic Extracts for SPT and sNPT

All extracts used for skin testing and nasal provocation testing were glycerinated extracts, titred in PNUs (DHS Bayropharm, Milan, Italy).

Skin Prick Test (SPT)

Children were tested by the same physician by prick puncture using a standardized pricker (DHS Bayropharm, Milan, Italy). A "panel" of commercially available allergenic extracts of aeroallergens (DHS Bayropharm, Milan, Italy) (*Dermatophagoides*, *Alternaria tenuis*, *Cladosporium herbarum*, Cat and dog hair, *Parietaria*, Grass mix, *Artemisia vulgaris*, *Olea europaea*, *Betula pendula*, *Cupressus sempervirens*, *Corylus avellana*), which were considered more frequently as causative agents of respiratory allergic symptomatology in the Naples area were used.

TABLE I

Monosensitized Subjects

Patient Characteristics	<i>Parietaria</i>	Gramineae	<i>Olea europaea</i>
Number of patients	30	15	7
Age range (mean)	4-13 (9, 4)	5-13 (9, 0)	6-13 (8, 7)
Sex (M/F)	17/13	9/6	3/4
Years with clinical symptoms	2,6	3,6	3,9
Clinical symptoms			
Rhinitis only	11	5	3
Asthma only	9	3	1
Rhinitis and Asthma	10	7	3
Seasonal pattern			
Seasonal	23	12	1
Perennial	7	3	6

TABLE II

Type of Symptomatology

Perennial	Clinical symptoms lasting all the year around without any particular exacerbation during the <i>O.e.</i> pollination season.
Seasonal	Clinical symptoms experienced only during <i>O.e.</i> pollination season (from April to June).
Combined	Clinical symptoms lasting all the year around but with a clear exacerbation during <i>O.e.</i> pollination.

Antihistamines and oral corticosteroids were not used in the week preceding the tests (8 weeks when astemizole was used).

In all patients we used the volar surfaces of both forearms. Allergenic extracts were placed in the same site in order to obtain comparable SPT results.

Only reactions ≥ 3 mm diameter were considered as positive. Reactions were read after 15 minutes by using a millimeter ruler. The wheal diameters were compared to the size of a positive histamine control (10 mg/mL) and to a negative control (extraction solution without allergen). According to the Aas and Belin method,²³ a wheal of the same size as that induced by the histamine control is indicated as +++ and a reaction similar to that induced by the negative control is indicated as -. The gradings + and ++ are used for reaction sizes between the negative and the positive controls. For a reaction larger than +++, a plus is added for each doubling of the average diameter.

Serological IgE Specific Assay

A blood sample of 10 mL was obtained from each child, and serum was frozen at -20°C .

The analyses of *O.e.* serum-specific IgE were carried out using commercially available extracts and reagents (Phadebas-RAST; Pharmacia Diagnostics, Uppsala, Sweden).

All Pharmacia-Phadebas-RAST determinations were performed at the same time. The results are expressed in classes ranging from 0 to 4, according to the Phadebas-RAST specifications.^{24,25}

TABLE III

The Results of sNPT in Children with Rhinitis

Pollens	Age	sNPT (PNU)	Seasonal Pattern	Late Response (6-8 Hours)
<i>Olea europaea</i>	13	110	P	Yes
	12	220	P	Yes
	9	110	P	Yes
<i>Parietaria</i>	11	220	S	No
	10	220	S	No
	13	440	S	No
	13	110	S	No
	11	110	S	No
	9	440	S	No
	13	220	S	Yes
	11	440	S	No
Gramineae	12	110	S	No
	9	220	S	No
	11	110	S	No
	12	110	S	No

S = Seasonal; P = Perennial

TABLE IV

The Results of NsBPT in Asthmatic Children

Pollens	Age	NsBPT (mcg)	Seasonal Pattern
<i>Olea europaea</i>	11	251	S
	7	311	P
	6	370	P
	13	189	P
<i>Parietaria</i>	13	390	S
	13	422	S
	10	512	P
	7	395	S
	11	168	S
	11	156	P
	9	222	S
	12	295	P
	10	253	S
	13	288	S
	12	452	S
	9	531	P
	12	366	S
Gramineae	13	205	S
	9	195	S
	10	209	S
	6	420	S
	10	157	S
	9	188	S
	8 1/2	309	S
	13	267	S
	12	218	P
	6	351	P

S = Seasonal; P = Perennial.

Nonspecific Bronchial Provocation Test (NsBPT)

The evaluation of nonspecific bronchial hyperreactivity in children with bronchial asthma was carried out by using a methacholine inhalation challenge. Also, patients with only nasal symptoms were examined in order to verify the eventual presence of a concomitant bronchial hyperresponsiveness.

The test was performed only in children over 6 years of age using a standardized method²⁶ and a spirometer (Pubish Spiroscope Zenith data systems corporation, St. Joseph, Michigan). Inhaled B2 agonists, rapid-release theophylline, and ipratropium bromide were discontinued for at least 12 hours before the challenge. Oral B2 agonists were discontinued for at least 24 hours, disodium cromoglycate and ketotifene for at least 48 hours, antihistamines for at least 72 hours, and oral steroids for at least 1 week.

Three reproducible spiograms (with a FEV1 that did not differ $>5\%$ from the highest value) were obtained before the beginning of the challenge.²⁷

Methacholine solution (kindly supplied by Lofarma Laboratories Milan Italy) in buffered saline or buffered saline

solution alone were nebulized using a MB3 dosimeter (ME-FAR Elettromedical, Brescia, Italy).

The solution without methacholine was inhaled first, followed at variable intervals by twofold increasing concentrations of methacholine. The first dose was 20 mcg and was doubled with each inhalation until reaching a maximum cumulative dose of 1260 mcg or a fall in FEV1 of 20% or more in comparison with basic values.

Results were expressed as the provocative concentration of methacholine required to induce a 20% fall in FEV1 (PD 20 FEV1). This was calculated from the log dose-response curves by linear interpolation of the two adjacent data points.

We consider as "hyperreactive" a subject with a PD 20 FEV1 ≤ 800 mcg methacholine (≤ 200 mcg very high, ≥ 200 mcg ≤ 400 mcg moderate, and ≥ 400 mcg ≤ 800 mcg low hyperreactivity).

We did not perform bronchial provocation tests with allergen also for ethical reasons, especially the risk of severe reactions to this challenge and the lack of a standardized *O.e.* allergenic extract and procedure.

Specific Nasal Provocation Test (sNPT)

Commercially available glycerinated extracts (1500 PNU/mL) were used (Dome Hollister Stier Bayropharm, Milan, Italy). Oral and inhaled antihistamines were not used in the week preceding the challenge (8 weeks when astemizole was used). Inhaled corticosteroids were withdrawn almost 2 weeks before.

The challenge procedure, carried out only in children over 6 years of age, began with insufflation of 80 μ l (1 puff) of glycerinated solution without allergen into both nostrils. If the control stimulus did not provoke a reaction testing continued. 80 μ l (110 PNU) of allergen solution (1 puff) was sprayed into each nostril. If no symptoms occurred in 15 minutes, a double dose of solution (2 puffs = 220 PNU) was sprayed into each nostril. The challenge procedure continued, using 4 puffs (440 PNU) as a maximum dose of allergen extract. A response was defined as positive if there were at least 3 of the following: sneezing, itching, increased nasal secretions, increased nasal congestion, increased edema, or increased nasal pallor. The occurrence of a late nasal response was also recorded by us for almost 8 hours after the challenge. To avoid the deposition of allergen into the lower airways, the sprays were administered while the child was vocalizing.²⁸

We did not perform sNPT in subjects with bronchial asthma to avoid the risk of allergen inhalation. A control group of fifteen nonsensitized children was enrolled; five children were challenged respectively with *O.e.*, *P.* and *G* allergenic extracts.

Pollen Count

Aerobiological data of the geographical area in which all 52 children lived were obtained by using a Hirst-type, 7-day volumetric air sampler (VPPS-2000 Lanzoni, Milan,

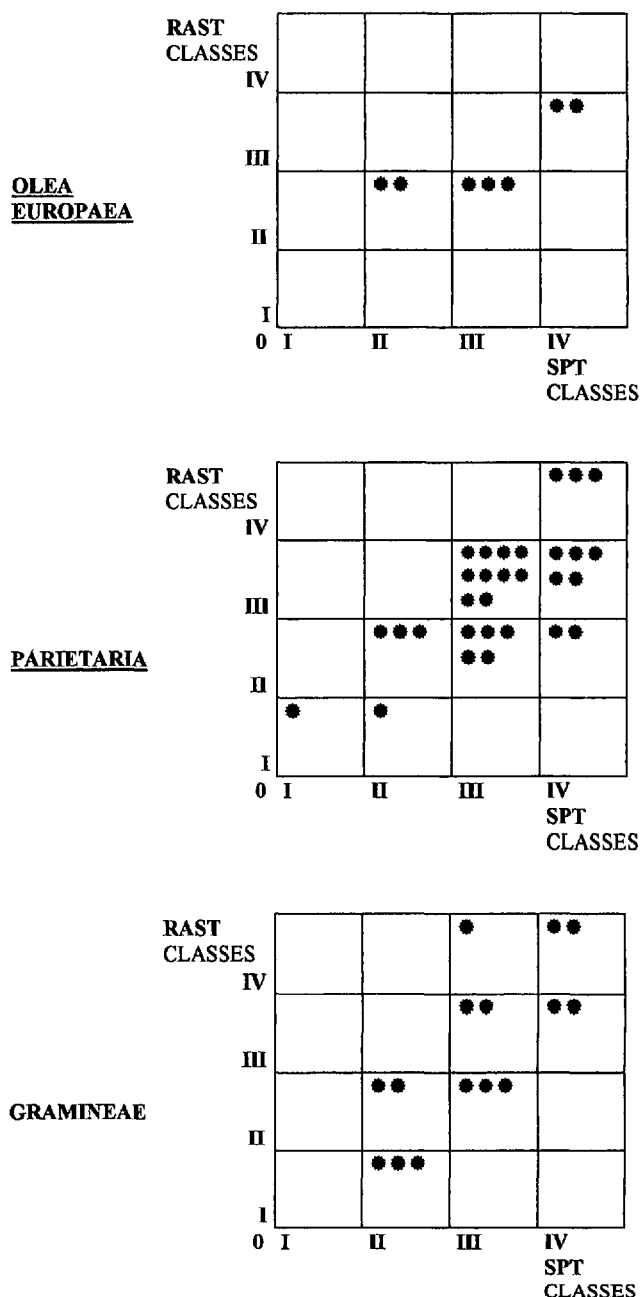


Figure 1. Comparison of positive diagnostic results: SPT and IgE serum specific determination (RAST).

Italy) placed on the A. Cardarelli Hospital, about 25 m above street level. The technical procedures have been described elsewhere.²⁹

Statistical Analysis

Nonparametric statistical analysis was used to evaluate the degree of significance between the results of SPT and specific IgE assay, and between the nasal threshold dose and IgE levels/skin test positivity for pollen allergens (Spearman's correlation test).

TABLE V

The Results of Statistical Analysis

Diagnostic Procedures	Allergen Sensitization	Number of Patients	Statistical Significance	
			rs	p
SPT vs RAST	<i>Parietaria</i>	30	0.66	$P < 0.001$
	Gramineae	15	0.89	$P < 0.001$
	<i>Olea europaea</i>	7	0.86	$P < 0.05$
sNPT vs SPT	<i>Parietaria</i>	9	0.717	$P < 0.05$
	Gramineae	4	n.a.	n.a.
	<i>Olea europaea</i>	3	n.a.	n.a.
sNPT vs RAST	<i>Parietaria</i>	9	0.75	N.S.
	Gramineae	4	n.a.	n.a.
	<i>Olea europaea</i>	3	n.a.	n.a.

n.a. = not applicable.

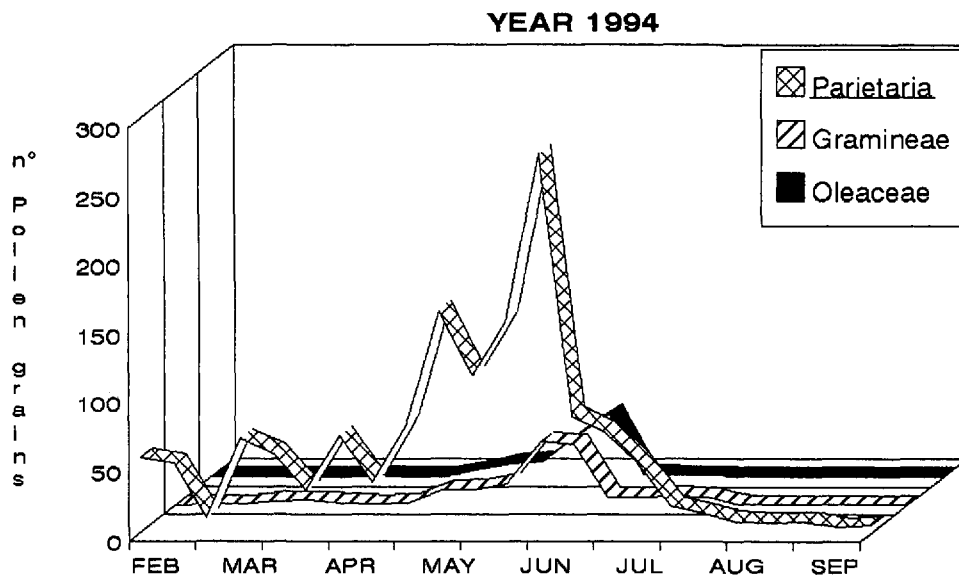


Figure 2. Results of aerobiological sampling. Airborne concentrations of Oleaceae, Urticaceae, and Graminae pollens in Naples during 1994. Results are expressed as 10-day running means based on daily observation.

RESULTS

Among 1173 children examined in our Center from 1990 to 1994, we selected a group of 52 patients with exclusive sensitization to *P*, *G* and *O.e.* (Table I).

The results of the diagnostic and provocative tests are shown in Tables III and IV, and in Figure 1. Six children of seven with monosensitization to *O.e.* allergens exhibited perennial symptoms in comparison to 3 of 12 and 7 of 23, respectively, in subjects with SPT positivity only to *G* and *P* allergens.

The results of diagnostic and provocative tests demonstrated a high degree of specific sensitization to pollen allergens in the majority of our patients. Also, the clinical symptoms (rhinitis and/or bronchial asthma) were very severe (days with respiratory symptoms, specialist's examinations, nocturnal awakenings, symptomatic drug consump-

tion, etc.) in the majority of children and required adequate preventive and symptomatic medication.

The results of sNPT showed different degrees of nasal sensitization to pollen allergens; interestingly, children with *O.e.* allergy and perennial rhinitis exhibited a late nasal response 6–8 hours after the challenge. Only one child exhibited a late response in the group of *P* monosensitized subjects, and there were none in the *G* group (Table III). No responses to sNPT were registered in the control group.

NsBPT using methacoline demonstrated a high degree of bronchial hyperreactivity in the majority of asthmatic children with pollen allergy (Table IV). Also, five patients with exclusive nasal symptoms showed a moderate (in three cases) and high (in two cases) increase of bronchial hyperresponsiveness. The results of statistical analysis are shown in Table V.

Correlations between the results of sNPT versus SPT/RAST in patients sensitized to Gramineae and *Olea europaea* are not applicable because of the low number of subjects.³⁰ The results of aerobiological sampling are indicated in Figure 2.

DISCUSSION

In the last 15 years, we have found an increasing frequency of skin positivity to pollen allergens, especially in adults but also in children with respiratory allergic symptomatology.³¹ This trend, which has been demonstrated also in other countries^{32,33} is probably related, in our geographical area, to a very high atmospheric air pollution.³⁴ In Southern Italy *P*, *G*, and *O.e.* show different patterns of pollination (Fig. 2), in particular *P* species exhibited a very long period of pollen productivity (from February to July and from September to November) which determines the occurrence, in some subjects, of multi-seasonal type of nasal and/or bronchial symptoms.³⁵

The pollination periods of *G* and *O.e.* were shorter and frequently overlap in some regions (from the end of April to June). The peculiar pattern of respiratory symptomatology, in the majority of cases, lasts only during the pollen season.

Despite the high atmospheric concentrations of some pollen grains, (such as *P*, *G*), the frequency of sensitization to these allergens in children is less compared to adults. In the pediatric age, the early exposure to mite allergens represents the most common risk factor for development of respiratory allergy.^{36,37}

These findings may contribute to explain why, from 1990 to 1994, we found only 52 children with monosensitization to *P*, *G*, and *O.e.* pollen allergens. However, the results of this study demonstrate that also the children with monosensitization to *O.e.* allergens and living in the Naples area exhibited, in six cases of seven, a nonseasonal pattern of symptomatology without any particular exacerbation during the olive pollination period. This pattern is infrequent in subjects with monosensitization to other pollens also considering the long time of flowering of *P* species.

These data concerning a group of children (even if small) show a great similarity to that obtained from a group of 24 adults living in the same geographical area with rhinitis and/or bronchial asthma and SPT positivity only for *O.e.* allergens.²²

It is very difficult to explain this peculiarity of *O.e.* pollinosis in the Naples area that has not been found in other areas with the exception of some patients reported in Spain^{19,20} in which respiratory symptoms of some lasted for several months or, in a few cases, all year around.

The occurrence of a late nasal response 6–8 hours after nasal challenge with allergen in the three *O.e.* sensitized children with rhinitis and only in one child sensitized to *P* allergens (Table III) suggests the possibility of a prolonged type of nasal inflammation, a high degree of nasal hyper-reactivity, and consequently, a perennial pattern of symptoms.

Interestingly, in the group of adults 7 of 8 patients with nonseasonal nasal symptoms showed the occurrence of a late response 6–8 hours after sNPT.²² These findings on nasal response after stimulation with allergen represent the only experimental data supporting our clinical observations regarding nasal symptoms. Although we think that, probably, bronchial symptoms may be induced by a *O.e.*-related late asthmatic response, other possibilities cannot be excluded, but they need further exploration (Table VI). However, we have demonstrated a cutaneous, serological, and, when possible, mucosal sensitization to pollen allergens trying to exclude, in subjects with perennial symptoms, the occurrence of known and well-defined conditions that could increase the airway (nasal and/or bronchial) hyperreactivity.

Moreover, we are trying to follow up all children with perennial symptoms of this study over the next few years (by using anamnestic questionnaires, SPT, symptom scores, respiratory monitoring) in order to determine the development of new sensitizations and/or other environmental conditions that could explain the nonseasonal symptoms.

In conclusion, the results of our study seem to show that different concomitant factors may be responsible for the unusual pattern of clinical symptoms in the majority of our *O.e.* monosensitized patients.

These preliminary data suggest the necessity of further studies in order to obtain better commercially purified and standardized diagnostic materials for a more appropriate diagnosis of *O.e.* allergy, and a greater number of monosensitized children living in different geographical areas need to be examined to compare our results with theirs.

TABLE VI

Other Possibilities to Explain the Perennial Pattern of *O.e.* Pollinosis in the Naples Area

- Cross-reactivity between the allergens of *O.e.* and other pollens of Oleaceae family (e.g., *Fraxinus excelsior* and *Ligustrum vulgare*, but these pollen grains are found in low concentrations in Naples area.^{38–42}
- The occurrence of a cross reactivity between *O.e.* allergens and the olive oil product (?) or other unknown foods (e.g. fruits and/or vegetables?).
- The lack of an adequate purification and standardization of the majority of *O.e.* commercially available allergenic extracts could explain the poor correlation between *in vitro* and *in vivo* tests demonstrated by Bousquet et al⁴³ and by us.⁴⁴
- As consequence of this, the possibility of nonspecific skin positivity and/or inaccurate serological diagnostic procedures.
- The possibility that allergens released by *O.e.* pollens of our area may induce different pattern of sensitization and, consequently, of clinical symptoms.⁴⁵

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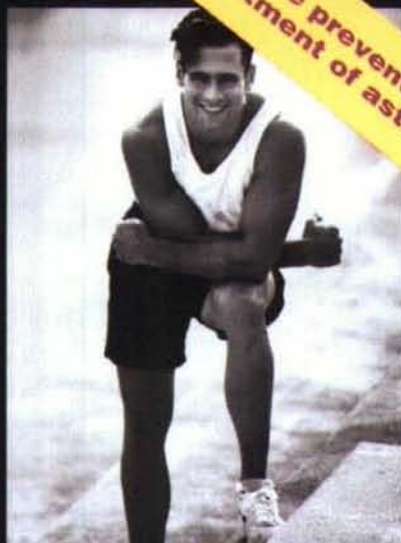
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AEROBID is indicated for use in adults and in children aged 6 and older. AEROBID may cause nausea and/or vomiting, headache, and sore throat in some patients.

References: 1. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*. NHLBI/WHO Workshop Report. Bethesda, Md: National Heart, Lung and Blood Institute; January 1995. NIH publication 95-3659. 2. Lowell FC, Spector SL, Wittig H, et al. Open trial of flunisolide aerosol in asthmatic patients. ICM study #463/520/602. Investigational new drug #10,515. September 1979. Data available on request from Forest Pharmaceuticals, Inc.

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AEROBID®/AEROBID®-M (flunisolide) Inhaler system for oral inhalation only Brief summary of prescribing information

CONTRAINDICATIONS: AEROBID (flunisolide) Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS:

Particular care is needed in patients who are transferred from systemically active corticosteroids to AEROBID Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AEROBID Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with AEROBID Inhaler. AEROBID Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AEROBID Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS: General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids (see CLINICAL PHARMACOLOGY section), patients treated with AEROBID (flunisolide) should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function. (See DOSAGE AND ADMINISTRATION for details.)

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AEROBID Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term local and systemic effects of AEROBID (flunisolide) in human subjects are still not fully known. In particular, the effects resulting from chronic use of AEROBID on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

Pulmonary infiltrates with eosinophilia may occur in patients on AEROBID Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhaled steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas in mice, but not in rats.

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids.

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low- (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 6. Oral corticoids have been shown to cause growth suppression in children and adolescents, particularly with higher doses over extended periods. If a child or adolescent on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS:

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AEROBID (flunisolide) are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater:

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%)

General: flu (10%)

Mouth and Throat: sore throat (20%)

Nervous System: headache (25%)

Respiratory: cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%)

Special Senses: unpleasant taste (10%)

Incidence 3-9%:

Cardiovascular: palpitations

Gastrointestinal: abdominal pain, heartburn

General: chest pain, decreased appetite, edema, fever

Mouth and Throat: candida infection

Nervous System: dizziness, irritability, nervousness, shakiness

Reproductive: menstrual disturbances

Respiratory: chest congestion, cough; hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing

Skin: eczema, itching (pruritus), rash

Special Senses: ear infection, loss of smell or taste

Incidence 1-3%:

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness

Cardiovascular: hypertension, tachycardia

Gastrointestinal: constipation, dyspepsia, gas

Hemic/Lymph: capillary fragility, enlarged lymph nodes

Mouth and Throat: dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation

Nervous System: anxiety, depression, lightheadedness, fatigue, hyperactivity, hypoadrenalism, insomnia, moodiness, numbness, vertigo

Respiratory: bronchitis, chest tightness; dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort

Skin: acne, hives or urticaria

Special Senses: blurred vision, earache, eye discomfort, eye infection

Incidence less than 1%, judged by investigators as possibly or probably drug related: abdominal fullness, shortness of breath.

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

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