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Original article

Monosodium benzoate hypersensitivity in subjects with persistent rhinitis

Background: Very few data are available from the literature on whether nonatopic subjects affected by persistent rhinitis may show the appearance of objective symptoms of rhinitis after the ingestion of food additives such as tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), p-hydroxybenzoate (E218), sodium metabisulphite (E223), and monosodium glutamate (E620). It is still unclear whether the ingestion of food additive may cause, as well, a consensual reduction of nasal peak inspiratory flow (NPIFR). Therefore, we used a double-blind placebo-controlled (DBPC) study to evaluate this hypothesis.
Patients and methods: Two hundred and twenty-six consecutive patients (76 males and 150 females) aged 12–60 years (mean age 40.2 ± 16.3 years). After 1 month of an additive-free diet regimen, an open challenge was carried out (food additive-rich diet for 2 weeks). After this period, challenges were administered in a DBPC manner using the above-mentioned substances under investigation.
Results: Twenty of 226 subjects (8.8%) reported an improvement of the symptoms of rhinitis after additive-free diet. More precisely, six of 226 (2.6%) were symptom-free and 14 of 226 (6.2%) showed an improvement in their symptoms after an additive-free diet. As far as the results for DBPC are concerned, 20 challenges with monosodium benzoate induced both objective (i.e. sneezing and rhinorrhoea) and subjective symptoms (nasal blockage and nasal itching) of rhinitis with reduction of NPIFR ≥20%, 45 challenges induced subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching), without reduction of NPIFR ≥20% of the basal value, two with tartrazine, seven with erythrosine, 19 with monosodium benzoate, three with p-hydroxybenzoate, six with sodium metabisulphite, and eight with monosodium glutamate, respectively.
Conclusions: The observation that nonatopic persistent rhinitis may be caused by the frequent, probably daily, ingestion of small doses of a nontolerated substance is intriguing and suggests that at least some patients with 'chronic vasomotor rhinitis' may be intolerant to a particular food additive. Therefore, food additives can be considered triggers or aggravating factors, rather than aetiological factors.

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Key words: double-blind placebo-controlled; food additives; nasal peak inspiratory flow; persistent rhinitis.

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It is estimated that 2–4% of the general population suffers from chronic nasal disease with daily symptoms and need for medication (1). Around 30–70% of these subjects show a so-called 'idiopathic' rhinitis (1, 2), for it is defined as rhinitis with no proven immunological, microbiological, pharmacological, hormonal, or occupational causes (1, 3–5). Among the possible causes of these 'idiopathic' cases of rhinitis, drugs and food additives have been frequently acknowledged (6, 7). A range of allergic-like symptoms can follow the ingestion of sulphite, tartrazine, monosodium glutamate, monosodium benzoate, p-hydroxybenzoate, and erythrosine (8–11). Reactions to these compounds cannot be distinguished, clinically, from an IgE-mediated rhinitis. More commonly, the daily consumption of food additives leads to continuous and protracted symptoms that mimic allergic phenomena (11).

Abbreviations: SD, standard deviation; NPIFR, nasal peak inspiratory flow; DBPC, double-blind placebo-controlled; E218, *p*-hydroxybenzoate; E102, tartrazine; E127, erythrosine; E 211, monosodium benzoate; E218, *p*-hydroxybenzoate; E223, sodium metabisulphite; E620, monosodium glutamate.

While these symptoms occur by activating biochemical pathways that mediate inflammation (12), IgE specific for the triggering agents are not involved. These unusual reactions to chemical additives can be attributed to hypersensitivity (13). Previously, these reactions were called idiosyncratic or pseudo-allergic reactions (11–13). The symptoms that characterize nonallergic rhinitis are usually similar to those occurring in persistent allergic rhinitis, with the exception of eye symptoms that are less frequent whereas nasal blockage is more prominent. Such symptoms are often precipitated by nonspecific stimuli, such as cigarette smoking, strong odours, perfumes, alcoholic beverages, cold air, and hot spicy food (1).

From a chemical and functional perspective, food additives are a heterogeneous group of substances including preservatives, such as antimicrobials and antioxidants, dyes, emulsifiers, stabilizers, and sweeteners. Their consumption is a matter of public concern and debate, particularly because they may cause a number of illnesses. However, there is a great discrepancy between the subjective perception of hypersensitivity to food additives and the results of objective diagnostic tests (1, 14–16). If hypersensitivity to food additives is suspected, the only method to prove this hypothesis is to test it by a double-blind placebo controlled (DBPC) challenge test (14, 15).

The objective of this study was to evaluate the prevalence of hypersensitivity to additives in a group of subjects affected by persistent rhinitis. We examined the results obtained after a period of diet, without and with food additives, on daily symptoms and we also evaluated the results of DBPC with six food additives in the same subjects.

Patients and methods

Patients

Two hundred twenty-six patients (76 males and 150 females) aged between 12 and 60 years (mean age 40.2 ± 16.3 years), who referred to the Outpatients Allergy Unit of the Policlinico GB Rossi of Verona Italy, were enrolled in the study. All patients were affected by persistent rhinitis. Written informed consent was obtained from each participant, and the Institutional Review Board of the Department of Internal Medicine, University of Verona, Italy, approved the study, that was conducted according to the Declaration of Helsinki of 1975.

Subjects were evaluated by an allergist physician and by a dietician previous to admission to the study. None of the subjects suffered from other clinically significant diseases besides persistent rhinitis. Rhinitis was classified as persistent and moderate–severe, based on the clinical history and symptoms (present for more than 4 days a week and more than 4 weeks) (1, 17).

All subjects filled in a respiratory questionnaire based on the standardized Clinical European Community Respiratory Health Survey, which is a structured questionnaire aimed at evaluating the presence of asthma symptoms (18). No subject had history, or symptoms, of asthma.

None of the subjects was taking oral steroids during the study; neither had they been taking them during the 2 months previous to enrolment in the study. Patients underwent therapy for the symptoms of rhinitis with different antihistamines and/or with vasoconstrictors, with partial improvement. None of the women participating in the study was pregnant nor breastfeeding the child during the study. Only patients fulfilling all the criteria reported in Table 1 were considered eligible for the study.

Study design

All patients visited the clinic four times (at time 0, 7, 30, and 45 days) before undergoing the DBPC. At visit 1 patients were given a daily diary card of symptoms and were informed of the purpose of the study. All patients were asked to fill in a daily clinical diary (see *Assessment of the symptoms of rhinitis*). At visit 2, 7 days later, the daily diary cards were checked carefully and then the patients started the additive-free diet. At visit 3, 30 days later, the daily diary cards were checked again and patients with an improvement in rhinitis symptoms during the food additive-free diet started an open challenge with a food additive-rich diet. At visit 4, 15 days later, the daily diary cards were checked for the last time. Finally, all patients underwent the DBPCs (Fig. 1).

Assessment of the symptoms of rhinitis

Before and during the periods of diet, each patient recorded symptom scores in a daily diary card. Patients reported nasal blockage, sneezing, rhinorrhoea, and nasal itching that were rated on an arbitrary four-point rating scale, from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, and 3 = severe). Therefore, the scores of total symptoms ranged from 0 to 12 and represented the sum of the scores referring to the presence of nasal blockage, nasal itching, sneezing, and rhinorrhoea.

Elimination diet (without food additives) and open challenges

An elimination additive-free diet was started (14–16) by all patients. After 1 month of additive-free diet, during which 20 patients showed an improvement in their rhinitis symptoms, an open chal-

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Long-lasting (>6 months) rhinitis including nasal blockage, watery rhinorrhoea, itching of the nasal mucosa, and episodes of sneezing paroxysm	Positive skin prick test results with the common airborne allergens, including pollen (grass, mugwort, ragweed, olive, birch, cypress, parietaria, and plantain), mites, moulds (*Alternaria, Aspergillus*, and *Cladosporium*) and dander of cat and dog and foods
Diagnosis of rhinitis in the absence of both structural deformities and nasal polyps on ear, nose, and throat investigation	Smoker or exsmoker subjects
Normal plain radiograph film and/or computed tomography scan	Patients who had used intranasal corticosteroids, antihistamines, and vasoconstrictors in the preceding 2 weeks

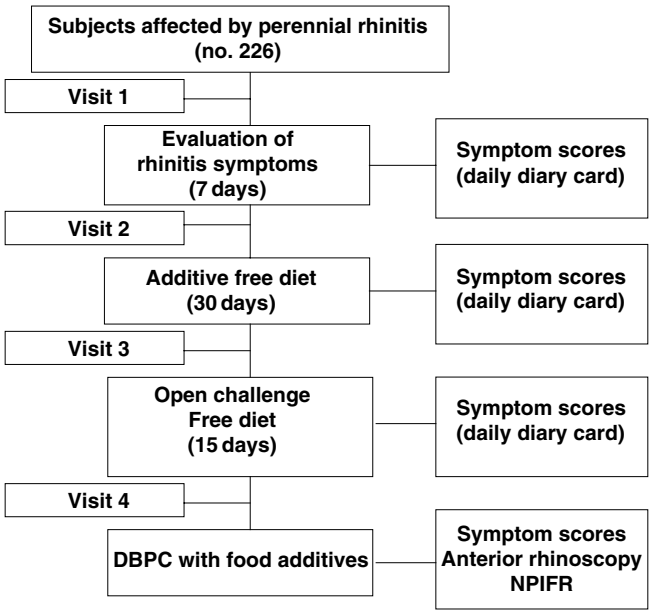

Figure 1. Study design.

lenge with a food additive-rich diet was carried out. After 3 days, nasal symptoms relapsed and/or worsened progressively in these patients, lasting throughout the whole open-challenge period. Table 2 reports the food excluded and included during the food additive-free diet and food additive-rich diet, respectively.

Table 2. Food additive-rich*

Breakfast
Muesli, dried apricots (containing sulphites), yoghurt, margarine (containing preservatives), honey, and jam (containing preservatives)

Lunch and dinner
Instant broth (containing glutamate), spaghetti with tomato in box (containing preservatives); potato salad (containing benzoic acid), fish salad (containing benzoic acid), matured cheese (containing preservatives) ham (containing preservatives), burger; olives (containing colouring), seasoning: paprika, thyme, oregano, pepper, nutmeg, oil, vinegar, garlic, onion; fruit jelly (containing colouring agents), apple, blueberries/strawberries (fresh or frozen) (containing benzoic acid)

Drink
Coffee, tea, chocolate bar, fizzy drinks (containing benzoic acid and colouring agents)

* The diet was explained and personalized to the patients by a dietician.

Table 3. Doses (mg) used for double-blind placebo-controlled challenges

Substances under investigation	First dose	Second dose	Third dose	Low dose	High dose
Tartrazine (E102)	10	10	20	10	40
Erythrosine (E127)	50	50	100	50	200
Monosodium benzoate (E211)	50	50	100	50	200
p-Hydroxybenzoate (E218)	50	50	100	50	200
Sodium metabisulphite (E223)	5	5	10	5	20
Monosodium glutamate (E620)	100	100	200	100	400

Food additive challenges

The chemicals which have been tested and the doses are reported in Table 3. A food additive oral challenge was performed. The food additives and placebo were in gelatine capsules. For each of the six chemicals, pharmacists, who ensured that placebo and substances were all similar, prepared a specific set with different doses. The subjects, the doctor, and the ambulatory assistants were all blinded to the contents of the challenge. The food chemical challenge was performed under the supervision of the doctor. Bronchodilators, adrenaline and resuscitation equipment were available all the time for the treatment of any acute effect caused by the challenges from additives. A food additive at a time was used for the challenge. Each substance under investigation was tested at an interval of at least 1 week. Challenges were administered in a DBPC fashion during the morning hours. Before each DBPC, patients received a sham challenge with placebo (talc). When no symptoms had been noted after the sham challenge, DBPC was performed 1 h later using either placebo or the substance under investigation. The substances and the placebo were given in a randomized sequence. Three placebo capsules and three doses of the substance under investigation were given at the dosages reported in Table 3. Each dose was given at intervals of 3 h, if no symptoms had developed during the previous administration. Both objective and subjective symptoms were carefully recorded after each dose (see *Evaluation of DBPC*).

Nasal peak inspiratory flow measurement

Nasal peak inspiratory flow (NPIFR) of all patients was measured before, during and after the oral additive food challenge, using a portable inspiratory flow meter (Clement Clarke International Ltd, Edinburgh, UK), with a proper face mask. Before testing, patients were advised to blow their noses to expel secretions. All measurements were made in a sit down position, with a good seal round the face mask, and patients were forced to inspire from the residual volume to total lung capacity through their nose, with their mouth closed (19).

Evaluation of DBPC

The results of the test for each substance were evaluated and correlated with the available case history information. The results of the challenge test were considered 'positive' when the patients developed rhinitis symptoms (i.e. nasal blockage, sneezing, and rhinorrhoea) with a fall of NPIFR by at least 20% from the postsham challenge. The provocation results were designated as 'probably negative' if subjective symptoms (i.e. nasal blockage without other symptoms of rhinitis) were present, without significant reductions of NPIFR; as 'negative' when the patients had neither objective nor subjective changes.

Statistical analysis

Age of patients has been presented as mean ± SD. Symptom scores were evaluated as total symptom score (TSS), (the sum of individual symptoms). The TSS during the run-in period, additive-free diet and open challenge were expressed as median (the range minimum and maximum). Nonparametric statistics was used for analysis. We used a Kruskal–Wallis test, as first analysis. If significant changes were detected, a posthoc analysis was performed by use of the Wilcoxon signed rank test. $P \leq 0.05$ was considered statistically significant.

Results

All the enrolled patients completed the study. Twenty of 226 patients showed an improvement in their symptoms while on diet, whereas 206 patients did not. Particularly, six of 226 (2.6%) were symptom-free and 14 of 226 (6.2%) showed an improvement in their symptoms.

Daily score of symptoms of rhinitis during pre-DBPC periods

In the group with amelioration (20 subjects), the median of the rhinitis symptom score before the additive-free diet was 8.5 (range 2–12) and decrease significantly after diet to 2.5 (range 0–4) ($P < 0.05$). In the nonresponder group (206 subjects) no significant change of rhinitis symptom score nor even a worsening of symptoms was observed: the median value before the diet was 8.0 (range 2–12) and after diet 8.5 (range 3–12) ($P = \text{NS}$). In the group in which the subjects improved their symptoms to additive-free diet, during the open challenge with additive-rich diet, the median of the rhinitis symptom score 7.5 (range 5–12) was higher compared with the median of the period of the additive-free diet 2.5 (range 0–4) ($P < 0.05$), whereas we found no differences between the period before the additive-free diet and the open challenge period ($P = \text{NS}$).

Challenge

Double-blind placebo-controlled trials were performed in all patients, improved and unimproved to additive-free diet. The group without amelioration was used as the control group to DBPC. We performed a total of 9452 challenges. This number is the sum of all the following tests: 1356 [226 of patients tested and six of placebo used for the sham challenge (basal values of NPIFR), plus 4048 (number of capsules of placebo used for DBPC), plus 4048 (number of capsules of food additives used for DBPC].

All data reported below have been calculated with reference to the total number of capsules of food additive used for DBPC (4048). With respect to DBPC-induced rhinitis, 20 challenges (0.5%) were considered as 'positive', because the patients presented objective and subjective symptoms of rhinitis with a reduction of NPIFR ≥20% from the basal value. Forty-five challenges (1.1%) were considered as 'probably negative', because the patients referred only nasal blockage but without fall of NPIFR ≥20% of the basal value and without other objective symptoms of rhinitis. Finally, 3983 challenges (98.4%) were considered as 'negative' because neither objective nor subjective symptoms of rhinitis were observed (Table 4).

As regards dose-inducing rhinitis, the DBPCs with monosodium benzoate at a dose of 100 mg gave a positive reaction in 20 patients. The other reactions, induced to DBPCs, were considered as 'probably negative': tartrazine in two patients at the dose of 40 mg, erythrosine in seven patients at the dose of 200 mg, monosodium benzoate in 19 patients at the dose of 200 mg, p-hydroxybenzoate in three patients at the dose of 200 mg, sodium metabisulphite in six patients at the dose of 20 mg, and finally monosodium glutamate in eight patients at the dose of 400 mg.

Repeated challenge tests were performed in all patients with reactions considered 'positive', and 'probably negative', but no changes occurred.

Discussion

In this study 20 of 226 patients (8.8%) suffering from persistent rhinitis reacted to monosodium benzoate, with typical symptoms of rhinitis, proved by a DBPC additive challenge, with a reduction in NPIFR by at least 20%, after sham challenge. The same patients showed an amelioration of their rhinitis symptoms with an additive-free diet. More precisely, six of 226 (2.6%) were symptom-free and 14 of 226 (6.2%) showed an improvement in

Table 4. Results of DBPC with regard to symptoms of rhinitis

Substance	Symptoms of rhinitis with reduction of NPIFR ≥20% of basal value (P) *n* (%)	Subjective symptoms of rhinitis without reduction of NPIFR ≥20% of basal value (PN) *n* (%)	No symptoms of rhinitis (N) *n* (%)	No. of total tests
Placebo	0 (0)	0 (0)	5404 (100)	5404*
E102	0 (0)	2 (0.3)	676 (99.7)	678
E127	0 (0)	7 (1.0)	671 (99.0)	678
E211	20 (3.0)	19 (2.9)	619 (94.1)	658
E218	0 (0)	3 (0.5)	675 (99.5)	678
E223	0 (0)	6 (0.9)	672 (99.1)	678
E620	0 (0)	8 (1.2)	670 (98.8)	678
Total additives	20 (0.5)	45 (1.1)	3983 (98.4)	4048

P, positive response for rhinitis; PN, probably negative response for rhinitis; N, negative response for rhinitis.
* Total number of placebo capsules used for challenges.

their symptoms. This is the first controlled clinical trial that demonstrates the possible role of food additives in persistent rhinitis.

Rhinitis is a symptomatic disorder characterized by rhinorrhoea, nasal blockage, sneezing, and nasal itching (1, 2, 4). After the exclusion of common cold, rhinitis can be classified either as allergic or nonallergic, noninfectious (1). The last category of rhinitis usually includes rhinitis of both known and unknown origins (1, 20).

A number of studies claiming that food additives are responsible for an array of clinical conditions, including urticaria, angio-oedema, anaphylaxis, asthma, chronic fatigue syndrome, irritable bowel syndrome, headache, collagen and vascular diseases, and even behavioural disturbances, have appeared in the medical literature (6, 7, 9, 13, 14, 21–27).

The prevalence of adverse reactions to food additives is reported in two population-based studies. In a Danish study in schoolchildren, 6.6% perceived adverse reaction to food additives and 2% developed adverse reactions to a mixture of food colourings, preservatives, and flavours. The main symptoms were aggravation of atopic dermatitis or urticaria. One per cent reacted to DBPC challenge, with a mixture of colourings or preservatives in capsules (26). In a UK population study including children and adults, 7.4% of subjects reported adverse reactions caused by food additives. In that study three subjects had a positive challenge to groups of food additives, i.e. colourings, preservatives, and antioxidants. The symptoms were headache, upper abdominal pain, eczema, and mood swings. The prevalence of food additive intolerance was 0.026% (27). The great variation in prevalence estimates of the two studies reflects the difficulty of studying adverse reactions to a large group of substances, such as food additives. It also reflects the heterogeneity of the populations included in such studies. On the contrary, the subjects in our study were affected only by persistent rhinitis and none was atopic or allergic.

Therefore, few data are presented in the literature about the relationship between rhinitis and food additives. To address the relationship between rhinitis and food additive, we performed a comprehensive literature search from 1965 to December 2002 using MEDLINE database and a manual research on Allergy, ENT, and pulmonary-specialized journals. We found only three case reports on the relationship between rhinitis and food additive, and 13 reviews, mostly anecdotal reports, heavily biased by the lack of appropriate diagnostic procedures. Asero described three case reports (28–30). The first case is of chronic rhinitis caused by intolerance to sodium benzoate diagnosed by rigorously controlled methods (28). The second case is of multiple intolerance to food additives causing both persistent rhinitis and worsening of chronic urticaria (29). The third case is of nonatopic persistent rhinitis caused by intolerance to benzoate (30).

A reaction of intolerance means that the ingestion of additives with foods is the cause of the disease and that the elimination of these additives from ingested foods should lead to complete clearance of symptoms. Relapses may occur after the re-introduction of the additives. In our study, only six of 226 patients, after the additive-free diet, demonstrated a complete remission and 14 of 226 an improvement of the rhinitis symptoms. The data of additive-free diet and additive-rich diet demonstrate that food additives could be triggers or aggravating factors, rather than aetiological factors. These results could explain why food additives provoke an exacerbation of an existing chronic disease, such as persistent rhinitis.

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References

1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001;**108**(Suppl.):S147–334.
2. Togias AK. Non-allergic rhinitis. In: Mygind N, Naclerio RM, editors. Allergic and non-allergic rhinitis: clinical aspects. Copenhagen: Munksgaard, 1993:159–166.
3. Jones NS, Carney AS, Davis A. The prevalence of allergic rhinosinusitis: a review. J Laryngol Otol 1998;**112**:1019–1030.
4. Lund VJ. International Rhinitis Management Working Group. International consensus report on the diagnosis and management of rhinitis. Allergy 1994;**49**(Suppl. 19):1–34.
5. Carney AS, Jones NS. Idiopathic rhinitis: idiopathic or not? Clin Otol 1996;**21**:198–202.
6. Ortolani C, Bruijnzeel-Koomen C, Bengtsson U, Bindslev-Jensen C, Bjorksten B, Host A et al. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee. Allergy 1999;**54**:27–45.
7. Wuthrich B. Food-induced cutaneous adverse reactions. Allergy 1998; **53**(Suppl. 46):131–135.

8. Petrus M, Bonaz S, Causse E, Rhabbour M, Moulie N, Netter JC et al. Asthma and hypersensitivity to benzoates. Arch Pediatr 1996;**3**:984–987.
9. Reus KE, Houben GF, Stam M, Dubois AE. Food additives as a cause of medical symptoms: relationship shown between sulfites and asthma and anaphylaxis; results of a literature review. Ned Tijdschr Geneeskd 2000;**144**:1836–1839.
10. Stevenson DD. Monosodium glutamate and asthma. J Nutr 2000; **130**(Suppl. 4S):1067S–1073S.
11. Corder EH, Buckley CE III. Aspirin, salicylate, sulfite and tartrazine induced bronchoconstriction. Safe doses and case definition in epidemiological studies. J Clin Epidemiol 1995;**48**:1269–1275.
12. Kowalski ML, Sliwinska-Kowalska M, Igarashi Y, White MV, Wojciechowska B, Brayton P et al. Nasal secretions in response to acetylsalicylic acid. J Allergy Clin Immunol 1993;**91**:580–598.
13. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;**56**:813–824.
14. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double blind placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with hypersensitivity to food and additive and/or ASA. Clin Exp Allergy 2001;**31**:1607–1614.
15. Sampson HA. Adverse reactions to foods. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice, 5th edn. St Louis: Mosby-Year Book, 1998: 1162–1182.
16. Di Lorenzo G, Pacor ML, Vignola AM, Profita M, Esposito-Pellitteri M, Biasi D et al. Urinary metabolites of histamine and leukotrienes before and after placebo-controlled challenge with ASA and food additives in chronic urticaria patients. Allergy 2002;**57**:1180–1186.
17. Demoly P, Allaert FA, Lecasble M, Bousquet J, PRAGMA. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy 2003;**58**:672–675.
18. Burney PGJ, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994;**7**:954–960.
19. Wilson A, Dempsey OJ, Sims EJ, Coutie WJR, Paterson MC, Lipworth BJ. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 2000;**30**:833–838.
20. Jessen M, Malm L. Definition, prevalence and development of nasal obstruction. Allergy 1997;**52**(Suppl. 40):3–6.
21. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;**121**:953–959.
22. Jones VA, McLaughlan P, Shorthouse M, Workman E, Hunter JO. Food intolerance: a major factor in the pathogenesis of irritable bowel syndrome. Lancet 1982;**2**:1115–1117.
23. Warner JO. Food and behaviour. Allergy, intolerance or aversion. Pediatr Allergy Immunol 1993;**4**:112–116.
24. Lunardi C, Bambara LM, Biasi D, Zagni P, Caramaschi P, Pacor ML. Elimination diet in the treatment of selected patients with hypersensitivity vasculitis. Clin Exp Rheumatol 1992;**10**:131–135.
25. Wuthrich B. Adverse reactions to food additives. Ann Allergy 1993;**71**:379–384.
26. Fuglsang G, Madsen G, Halken S, Jorgensen S, Ostergaard PA, Osterballe O. Adverse reactions to food additives in children with atopic symptoms. Allergy 1994;**49**:31–37.
27. Young E, Patel S, Stoneham M, Rona R, Wilkinson JD. The prevalence of reaction to food additives in a survey population. J R Coll Physicians Lond 1987;**21**:241–247.
28. Asero R. Food additives intolerance: a possible cause of persistent rhinitis. J Allergy Clin Immunol 2002;**110**: 937–938.
29. Asero R. Multiple intolerance to food additives. J Allergy Clin Immunol 2002;**110**:531–532.
30. Asero R. Persistent rhinitis induced by benzoate intolerance. J Allergy Clin Immunol 2001;**107**:197.