

Hypersensitivity to diazepam

R. Asero*

Key words: anaphylaxis; diazepam; drug allergy; skin tests.

A 28-YEAR-OLD NURSE experienced collapse and generalized urticaria while she was undergoing a gastroscopy for suspected *Helicobacter pylori* infection. Before the start of the procedure, lidocaine (lignocaine) oral spray and 10 mg intravenous diazepam was administered; in addition, 1 mg flumazenil was given intravenously at the end of gastroscopy. The physicians reported that symptoms appeared "some minutes" after administration of the drugs. Rescue therapy with intravenous antihistamines and steroids was given by the personnel who performed the gastroscopy; the patient gradually recovered over the following 2 h. The woman had no history of respiratory allergy or drug intolerance, and was otherwise well.

Skin prick tests (SPT) and intradermal tests (ID) were carried out using the suspected drugs (diazepam 5 mg/ml; flumazenil 0.1 mg/ml; lidocaine 2%). Readings were taken at 15 min and skin reactions were graded by comparison with the wheal induced by negative control (saline) and by positive control (histamine 10 mg/ml). The patient gave informed written consent before the start of the procedure. In view of the severity of the adverse reaction, and because two of the three suspect compounds were for injection, the patient was not re-challenged with them.

On the SPT, no reactivity to lidocaine or flumazenil was observed; diazepam

Generalized urticaria and shock after i.v. infusion.

induced a moderate wheal-and-flare reaction (mean diameter about 50% of that induced by histamine 10 mg/ml). On the ID, diazepam induced a clearcut wheal-and-flare reaction but, again, the other drugs induced no reactions. Both SPT and ID with diazepam 5 mg/ml did not induce any skin reaction in three normal controls. Diazepam hypersensitivity was diagnosed (1).

Diazepam sensitivity is probably very rare: a search carried out on MEDLINE revealed that no case of allergy to this drug has been reported during the last 20 years. Although, for safety reasons, we did not perform confirmatory challenges, this woman showed immediate skin reactivity to diazepam both on SPT and ID. This seems to suggest an IgE-mediated pathogenesis, but a mechanism based on nonspecific histamine release from mast cells could be responsible for the anaphylactic episode as well. Immediate (IgE-mediated) allergic reactions have been described only for a limited number of drugs. Heteroantiseria, chymopapain, insulin, clotting factors, and other therapeutic macromolecules (2), as well as muscle relaxants (3), act as complete antigens whereas most low-molecular-weight drugs, including β -lactams and sulfonamides, need haptenation to become immunogenic (2). Whatever the pathogenic mechanism involved, this study suggests that diazepam should be included on the list of drugs that are able to induce hypersensitivity reactions.

*Ambulatorio di Allergologia
Ospedale Caduti Bollatesi
via Pieve 20
20021 Bollate (MI)
Italy
Fax: + 39 02 3504288
E-mail: r.asero@libero.it

Accepted for publication 20 June 2002
Allergy 2002; 57:1209
Copyright © Blackwell Munksgaard 2002
ISSN 0105-4538

References

1. JOHANSSON SGO, HOURIHANE J O'B, BOUSQUET J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
2. SULLIVAN TJ. Drug allergy. In MIDDLETON E, REED CE, ELLIS EF, ADKINSON NF, YUNGINGER JW, BUSSE WW, editors. *Allergy: Principles and Practice*, 4th edn. St Louis: Mosby, 1993, 1726–1746.
3. DIDIER A, CADOR D, BONGRAND P, et al. Role of quaternary ammonium ion determinants in allergy to muscle relaxants. *J Allergy Clin Immunol* 1987;**79**:578–581.

Zinc-regulation of immunodominant *Aspergillus* antigens

A. N. Chandrakala, B. Venkatappa*

Key words: *Aspergillus fumigatus*; ASPFM1; ASPFM2; zinc.

ALLERGIC BRONCHOPULMONARY aspergillosis (ABPA) is a complication of allergic asthma, caused by *Aspergillus fumigatus*.

Allergy is a hypersensitivity reaction initiated by immunologic mechanisms that

produces IgE antibodies in response to low doses of protein allergens, to develop typical symptoms of asthma. Johansson et al. (1) confirmed that actinomycetes and molds can induce IgG antibodies in allergic alveolitic patients. Both IgE and IgG antibodies are found in ABPA (2).

Nutritional and biochemical factors may influence the expression and regulation of these antigens in ABPA patients. In the case of *A. fumigatus* it has been postulated that iron and zinc deprivation stimulate the synthesis of products

An effect on variability of immunodominant antigens from ASPFM1 or ASPFM2.

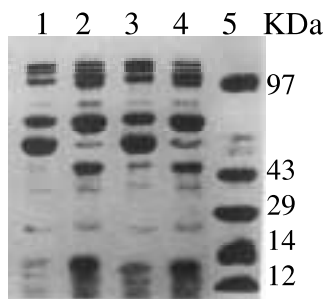


Figure 1. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). Pattern of proteins of *A. fumigatus* BV 7468 clinical isolate from patient, BV 588 isolate from peanut kernels. Lane 1: Clinical isolate grown on CD medium. Lane 2: Clinical isolate grown on SAM. Lane 3: Environmental isolate grown on CD medium. Lane 4: Environmental isolate grown on SAM. Lane 5: Molecular weight markers.

involved in the survival of the invading fungus (3). We report here that zinc starvation could be considered as a new biosignal for *A. fumigatus* from the host environment.

Two strains of *A. fumigatus* (BV 7468 and BV 588) were used in this study. The fungus was grown on solid Sabourauds' agar medium (SAM) containing traces of zinc sulfate (ZnSO_4) and 1% agar (pH 6.5). Mycelia were harvested from Sabourauds' and Czapek-Dox (CD) broth mixed with Tris-HCl lysate buffer (pH 7.5) containing 1 mM EDTA. Mycelia were homogenized with a French press at a pressure of 12 000 lb/in² and lysate was prepared with 1% SDS and incubated for 20 min at 60°C. Final extracts (15 000 g for 10 min) were aliquoted and stored at -30°C. Electrophoresis was performed on (12%) acrylamide slab gels (3).

Protein extracts from *A. fumigatus* were analyzed by PAGE for the presence of immunodominant antigens (Fig. 1). The characteristic double antigenic band in the 45 kDa region of ASPFM1 was present at high levels only when *A. fumigatus* was grown in CD medium. In this study we investigated the influence of culture medium on the biosynthesis of immunodominant antigens.

Addition of zinc inhibits ASPFM1 production; 50 μM completely abolishes it, but stimulates mycelial growth (Fig. 2A). Zinc concentrations of 5 μM or more almost double the amount of mycelia with respect to the control with-

out added zinc, demonstrating that zinc is a limiting factor for growth in SAM (Fig. 2B). We show here that ASPFM1 synthesis is strongly inhibited by micromolar concentrations of zinc.

Two strains of *A. fumigatus* were grown for 72 h in CD medium with or without 50 μM zinc. A double band corresponding to a 37 kDa component of ASPFM2 was detected in zinc-starved growth medium from both strains (Fig. 3). Absence of zinc dramatically modified the protein patterns for ASPFM1 and related antigens (Fig. 2).

ASPFM1 and ASPFM2 may be zinc-responsive proteins, expressed *in vitro* under conditions of zinc-starvation. They are readily synthesized *in vivo*, as shown by the high levels of circulating antibodies that are directed specifically against them in several forms of aspergillosis (ABPA and aspergilloma) (4).

Antigens of *A. fumigatus* strains may contain T- and B-cell epitopes and favor

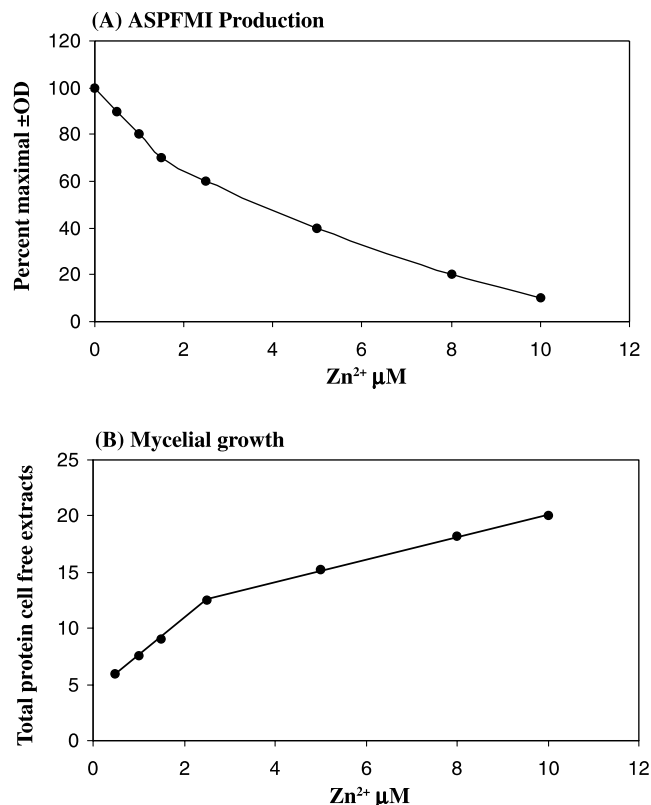


Figure 2. Effect of the addition of increasing concentrations of Zn^{2+} on ASPFM1 production. Cultures were supplemented with ZnSO_4 to obtain final concentrations of 0, 5, 10, 15, 20 μM present in total mycelial extracts obtained after 48 hr of growth. Results in panel A are expressed as the percentage of the maximal OD measured for ASPFM1. The amount of total protein in cell extracts in panel B was determined as indicated in material and methods.

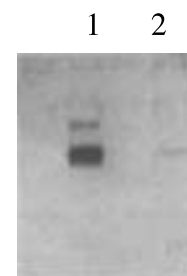


Figure 3. Presence of zinc regulated proteins in BV 7468 clinical isolate. Total mycelial extracts (20 μg of protein/lane) from the indicated *Aspergillus fumigatus* strain, cultured for 48 hr at 28°C in CD medium with or without 50 μM Zn^{2+} , separated on an SDS-14% polyacrylamide gel. Lane 1 = ASPFM1 production in absence of 50 μM Zn^{2+} . Lane 2 = ASPFM1 inhibition in presence of 50 μM Zn^{2+} .

the possibility of developing immunotherapy protocols using specific synthetic peptide epitopes.

*Department of Microbiology
Immunology Division
Sri Krishnadevaraya University
Anantapur-515 003
Andhra Pradesh
India

Accepted for publication 11 June 2002
Allergy 2002; 57:1209–1211
Copyright © Blackwell Munksgaard 2002
ISSN 0105-4538

References

- JOHANSSON SGO, HOURIHANE J O'B, BOUSQUET J et al. A revised nomenclature for Allergy. An EAACI position statement. *Allergy* 2001;**56**:813–824.
- PATTERSON R, GREENBERGER PA, HALWIG JM, LIOTA JL, ROBERT M. ABPA natural history and classification of early disease by serologic and roentgenographic studies. *Arch Intern Med* 1986;**146**:916–921.
- LAEMMLI UK. SDS-polyacrylamide gel electrophoresis. *Nature* 1979;**227**:680–685.
- COULOT P, BOUCHARA JP, RENIER G, et al. Specific interaction of *Aspergillus fumigatus* with fibrinogen and its role in cell adhesion. *Infect Immun* 1994;**62**:2169–2177.
- BOUCHARA JP, TRONCHIN G, LARCHER G, CHABASSE D. The search for virulence determinants in *Aspergillus fumigatus*. *Trends Microbiol* 1995;**3**:327–330.

Histamine release in idiopathic cold urticaria

R. Asero*, A. Tedeschi, M. Lorini

Key words: cold urticaria; histamine releasing factors; urticaria.

IDIOPATHIC COLD urticaria (ICU) is characterized by the rapid onset of pruritus, erythema, and swelling after a cold stimulus in the absence of any abnormal circulating protein (1). Pathogenesis is still unclear.

Autoantibodies to FcεR1 or IgE are not always associated with disease.

ICU can be passively transferred to normal individuals (2), and cold-depend-

ent histamine release can be obtained from skin biopsies (3). Serum from patients with ICU may cause a wheal-and-flare reaction on intradermal injection and may contain anti-IgE autoantibodies (4). Altogether, several immunological features of ICU resemble those of chronic idiopathic urticaria (5). We studied five patients (4 men and 1 woman, aged 13–57 years (mean 32 years)) seen with ICU in 1997–1999. At the baseline visit, intradermal tests with fresh autologous serum (ASST) were carried out (6) and blood samples were taken for in-vitro basophil histamine release assays (HRA) (6). Three patients accepted a follow-up visit in June 2001, when an ice-cube test, ASST, and HRA were carried out. On HRA a 5% release cutoff value was used. Sera were tested with basophils from six normal donors. As a control, basophils were stimulated with an optimal dose (10 µg/ml) of goat polyclonal antihuman IgE. Serum from one patient that showed significant histamine releasing activity was filtered through an Amicon anisotropic, hydrophilic YM membrane with a 10 kDa cutoff. Both fractions > and < 100 kDa were tested on HRA.

At the baseline visit, all five patients scored strongly positive on ASST. Sera from five, one, none, and five patients induced histamine release from basophils of donor numbers 1, 2, 3, and 4,

respectively (Table 1). The responses of basophils to anti-IgE and to patients' sera did not show any correlation (Table 1). At the follow-up visit patients 1 and 3 had recovered from their disease and were negative on the ice-cube test and on ASST. By contrast, patient 2 still had active disease and was positive on both tests. On HRA, serum from patient 3 (in clinical remission) still induced histamine release, whereas sera from patients 1 (in remission) and 2 (clinically active) were negative (Table 1). Only the fraction > 100 kDa of serum from patient 3 induced histamine release from basophils.

At the baseline evaluation, all five patients were positive on ASST, and their sera (variably) induced histamine release from basophils of two out of four donors. Notably, the releasing activity of sera in no way paralleled that of anti-IgE, suggesting that a mechanism other than anti-IgE was responsible for basophil activation.

Altogether these findings show the presence of circulating histamine releasing factors that are already active at body temperature in these patients. Occasionally cold urticaria resolves spontaneously (1), as in two out of three of our participants. We could, therefore, evaluate the histamine releasing activity of sera from two ICU patients during two distinct clinical phases both *in vivo* and

Table 1. *In vivo* and *in vitro* findings

Patient information	1	2	3	4	5	Anti-IgE (10 µg/ml)
Sex/age	M 28	M 57	M 13	M 29	F 34	
Duration (months)	250	72	2	2	8	
Baseline findings						
Ice-cube test	Pos	Pos	Pos	Pos	Pos	
ASST	Pos	Pos	Pos	Pos	Pos	
HRA (%) Donor 1	28.9	34.2	26.3	47.4	36.8	9
HRA (%) Donor 2	0	2.1	9.1	3.6	2.9	0
HRA (%) Donor 3	0	0	2	0	0	23.6
HRA (%) Donor 4	5.7	10.1	20.3	7.4	10	67.3
Follow-up findings						
ICT	Neg	Pos	Neg			
ASST	Neg	Pos	Neg			
HRA (%) Donor 5	3	3	13			20.6
HRA (%) Donor 6	0	0	24.3			20
Fraction > 100 kDa Donor 6			20			
Fraction < 100 kDa Donor 6			0			

ASST: autologous serum skin test; HRA: histamine release assay; ICT: ice cube test.

in vitro. Both the ice-cube test and ASST were found to parallel disease activity, which was not the case for HRA (negative in a patient with an ongoing disease but still positive in a patient in clinical remission). As previously observed (6), *in-vitro* histamine releasing activity of serum was associated with the > 100 kDa fraction containing immunoglobulins. Our findings suggest that the presence of functionally active autoantibodies, directed against *FcεRI* or against IgE, is not necessarily associated with disease activity in ICU, and that histamine release from basophils (*in vitro*) and mast cells (ASST) might not be mediated by the same factor.

In effect, IgG-depleted sera from patients with chronic idiopathic urticaria maintain their ability to induce histamine release on ASST (7). The reasons why patients with ICU experience their clinical symptoms only after a cold stimulus remain unclear. Notably, symptoms are often at a maximum after the area exposed to cold is warmed (1), suggesting that reactive vasodilation may facilitate the activity of circulating histamine releasing factors on mast cells, maybe causing an increase in the concentration of these factors in the skin.

*Ambulatorio di Allergologia
Ospedale Caduti Bollatesi
via Piave 20
20021 Bollate (MI)
Italy
Tel: + 39 02 35006309
Fax: + 39 02 3504288
E-mail: r.asero@libero.it

Accepted for publication 21 June 2002
Allergy 2002; 57:1211–1212
Copyright © Blackwell Munksgaard 2002
ISSN 0105-4538

References

1. KAPLAN AP. Urticaria and angioedema. In ELLIS EF, ADKINSON NF, YUNGINGER JW, BUSSE WW, editors. *Allergy. Principles and Practice*, 4th edn. Mosby Year Book 1993, 1553–1580.
2. WANDERER AA, MASELLI R, ELLIS R, ISHIZAKA K. Immunologic characterization of serum factors responsible for cold urticaria. *J Allergy Clin Immunol* 1971;**48**: 13–22.

3. KAPLAN AP, GAROFALO J, SIGLER R, HAUBER T. Idiopathic cold urticaria: in vitro demonstration of histamine release upon challenge of skin biopsies. *N Eng J Med* 1981;**305**:1074–1077.
4. GRUBER BL, BAEZA ML, MARCHESE MJ, AGNELLO V, KAPLAN AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;**90**:213–217.
5. GREAVES MW. Chronic urticaria. *N Eng J Med* 1995;**332**:1767–1772.
6. ASERO R, TEDESCHI A, LORINI M, SALIMBENI R, ZANOLETTI T, MIADONNA A. Chronic urticaria: novel clinical and serological aspects. *Clin Exp Allergy* 2001; **31**:1105–1110.
7. FAGIOLO U, KRICEK F, RUF C, PESERICO A, AMADORI A, CANCIAN M. Effects of complement inactivation and IgG depletion on skin reactivity to autologous serum in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2000;**106**:567–572.

Allergy to carboxymethylcellulose

N. Muroi, S. Mori, S. Ono, H. K. Takahashi, T. Fujii, S. Hosoi, K. Henmi, M. Nishibori*

Key words: anaphylaxis; carboxymethylcellulose; ELISA; IgE; sensitization.

UPPER AND LOWER gastrointestinal examinations using barium sulfate suspension are routine in the clinic. Various ingredients are added to the suspension, such as carboxymethylcellulose sodium (CMC), which improves the coating and flow of the suspension. In a previous study (1), we reported a patient who had an anaphylactic reaction after upper gastrointestinal examination using a barium meal containing CMC. We identified CMC as an antigen in nine additives to the suspension, using skin scratch tests and *in-vitro* histamine release from a peripheral leukocyte preparation (1,2). CMC is thought to be inert, and not

absorbed, so this result was surprising. Although the incidence of anaphylactic reactions from barium examinations is estimated at only one in several thousand (3,4), the absolute number of cases may be higher because of the total number of examinations performed. Anaphylactic shock is the most severe side effect of drug treatment and it is often fatal. Therefore it is important to know of the presence and the titer of antigen-specific IgE.

We developed an enzyme-linked immunoassay (ELISA) for detecting CMC-specific IgE using CMC covalently fixed to the plate, biotinylated secondary antibody (antihuman IgE goat IgG) and streptavidin peroxidase. We obtained written informed consent from the patient who experienced the anaphylactic reaction to CMC (1) to use her serum as a positive control. We screened a total of 387 subjects attending Ako Municipal Hospital for their annual health check from February to June 2000.

The reaction intensities were evaluated and put into six categories: *negative* (ELISA OD at 1 : 2 dilution of serum < 1.5 × [ELISA OD at 1 : 16 dilution of serum]); *suspected positive* (ELISA OD at 1 : 8 dilution of serum < the mean of ELISA OD of negatives at 1 : 8 dilution + 3 SD = 0.150); and *positive* (ELISA OD at 1 : 8 dilution of serum ≥ the mean of ELISA OD of negatives at 1 : 8 dilution + 3 SD). There were four *positive* classifications depending on the intensity of ELISA at a 1 : 8 dilution of serum: 1 + (0.15 ≤ OD < 0.200); 2 + (0.200 ≤ OD < 0.250); 3 + (0.250 ≤ OD < 3.00); 4 + (0.30 ≤ OD). Among the 387 subjects, we found 36 positive individuals (9%), 6 of whom had a high CMC-specific IgE (4 +) comparable to the patient.

To date, it has been suggested that M-class immunoglobulins are produced as a major subclass for exogenous polysaccharide antigens in a T-cell independent manner (5). However, it was apparent that an IgE-class antibody against a carboxymethylated form of natural polysaccharide was raised in our patient. Furthermore, mass surveillance using the ELISA method of sensitization by CMC, in healthy people at their annual health check, revealed that IgE

Unexpected high incidence of sensitization by carboxymethylcellulose.

production against CMC was not a rare event. Indeed, it is surprising that the incidence of sensitization by CMC (9%) was about half of that by common allergens in Japan (such as *Dermatophagoides pteronyssinus*, orchard grass, and ragweed).

Physicians currently face the dangerous possibility of administering CMC-containing injections to people with high levels of CMC-specific IgE. There are intraarticular corticosteroid injections (6) that contain several mg of CMC. Using such medicine containing a large quantity of CMC may induce an anaphylactic reaction in people with high CMC-specific IgE, especially when there is direct injection of the drug into body fluid. Attention must be given to sensitization by CMC and the medicinal use of CMC.

The authors thank Kurozumi Medical Foundation, Suzuken Memorial Foundation, and Mishimakaiun Memorial Foundation for financial support.

*Department of Pharmacology
Okayama University Graduate School of
Medicine and Dentistry
2-5-1 Shikata-cho
Okayama 700-8558
Japan
Tel/fax: + 81 86 2357140
E-mail: mbori@md.okayama-u.ac.jp

Accepted for publication 6 August 2002
Allergy 2002; 57:1212-1213
Copyright © Blackwell Munksgaard 2002
ISSN 0105-4538

References

- MUROI N, NISHIBORI M, FUJII T, et al. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. *N Engl J Med* 1997;**337**: 1275-1277.
- NISHIBORI M, MUROI N, FUJII T. Correspondence: Anaphylaxis from carboxymethylcellulose component of barium sulfate suspension. *N Engl J Med* 1998;**338**:623.
- GELFAND DW, SOWERS JC, DEPONTE K, et al. Anaphylactic and allergic reactions during double contrast studies. *Am J Roentgenol* 1985;**144**:405-406.
- JANOWER ML. Hypersensitivity reactions after barium studies of upper and lower gastrointestinal tract. *Radiology* 1986;**161**:139-140.
- FELDMAN M. Interaction between immune cells in antibody production. In: ROITT IM, BROSTOFF J, MALE DK, editors. *Immunology*, 3rd edn. London: Mosby 1993, 93-108.
- MACE S, VADAS P, PRUZANSKI W. Anaphylactic shock induced by intraarticular injection of methylprednisolone acetate. *J Rheumatol* 1997;**24**:1191-1194.

An epidemic form of AEP

N. Tomac*, N. Kuyucu, T. Tezic, F. Duru,
S. Karademir, Y. Gurer

Key words: acute eosinophilic pneumonia; epidemic sudden deaths; environmental moulds.

A NEW FORM of eosinophilic pneumonia as a cause of sudden death related to environmental factors has been reported over the past 10 years (1,2). It is a distinct form of eosinophilic pneumonia associated with the development of acute respiratory failure.

This report aims to describe the possible cause of sudden deaths of eight previously healthy children in one village over a period of 6 months by using the necropsy of the last child, revealing acute eosinophilic pneumonia. Because of this unusually high death rate, the Ministry of Health started regional investigations of the area and examined another 13 healthy children belonging to the families of the deceased.

Eight children (four girls, four boys) between the ages of 4-6 years (mean 5 ± 0.9) died suddenly in a small village in the southeast region of Turkey between July 1996 and January 1997. These children belonged to six families living in four houses near to each other. Five of the families were related, the other family was neighboring them. The eight children who died were all of preschool age and used to play in a damp stable. They had all played in the stable a few hours before the onset of their symptoms and died within 1-2 h before reaching a health center. Before death, all

suffered from dyspnea, spasmodic large tremors of the extremities—like generalized tonic and clonic seizures—cyanosis, and urine incontinence.

The 13 healthy children were hospitalized for examination and laboratory tests were all normal except for peripheral blood eosinophilia in 3 of 13 ($> 600/\text{mm}^3$, range 856-1284); 4 of 7 had eosinophilia in sputum (6%, 10%, 12%, and generalized, respectively); IgE was elevated in 9 of 13 (69%) and 4 had more than 1000 IU/ml. *Aspergillus fumigatus* and *Alternaria tenuis* specific IgE were mildly positive for 5 of 7 children examined. Serum precipitant antibodies to *A. fumigatus* were positive in 4 of 11 (36%) children. Skin prick tests with 40 common allergens (Alk, Denmark) were applied to 13 children and revealed positive reactions to moulds in 13/13 (100%) children, to DP and DF in 6/13 (46%), to pollens in 10/13 (77%), to feathers in 8/13 (61%), and to foods in 11/13 (85%).

Their houses, especially the stable, were damper and mouldier than the other houses of the village. There were unusually high numbers of fast growths of *Alternaria*, *Aspergillus*, *Penicillium* and *Rhizopus* in the cultures from these places.

The cause of acute eosinophilic pneumonia and its pathophysiologic mechanisms are unknown, but it may be a hypersensitivity phenomenon as suggested by Badesch et al. (2). Although environmental factors have been suggested, most patients do not have an identifiable cause for parenchymal lung disease. A mechanism has been proposed that relates to inhaled allergens such as trichloroethane, and *Trichosporon* moulds (3).

The high prevalence of hyper-IgE, blood and sputum eosinophilia, precipitant antibody elevation, and skin prick test reactivity to common moulds in the study group, suggest that all of the children had developed hypersensitivity reaction to environmental moulds. Although the surviving 13 children were all allergic to moulds, they were either too small to play outside or were old enough to go school during the daytime; therefore, they were not severely exposed to moulds in the stable.

According to our investigation, the reason for acute eosinophilic pneumonia (AEP) in the last child who died, and those who died previously, may have

Acute eosinophilic pneumonia caused by moulds might explain epidemic deaths.

been high exposure to toxicogenic moulds. Our hypothesis has also been supported by the fact that no more deaths have occurred since renovations were made to their environment.

In conclusion, this report may be the first to point out a possible link between epidemic sudden deaths from AEP and environmental moulds.

*Zonguldak Karaelmas Universitesi

Tip Fakültesi Dekanlığı

Incivez67100

Zonguldak

Turkey

Tel: + 372 257 4010

Fax: + 372 261 0155

E-mail: nazantomac@yahoo.com

Accepted for publication 11 June 2002

Allergy 2002; 57:1213–1214

Copyright © Blackwell Munksgaard 2002

ISSN 0105-4538

References

1. ALLEN JN, PACTH ER, GADEK JE, DAVIS WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med* 1989;**321**:569–574.
2. BADESCH DB, KING TE, SCHWARZ MI. Acute eosinophilic pneumonia: a hypersensitivity phenomenon? *Am Rev Respir Dis* 1989;**139**:249–252.
3. POPE-HARMAN AL, DAVIS WB, ALLEN ED, CHRISTOFORIDIS AJ, ALLEN JN. Acute eosinophilic pneumonia: a summary of 15 cases and review of the literature. *Medicine* 1996;**75**:334–342.

NSAID-sensitive patients tolerate rofecoxib

A. Valero, M. Baltasar, E. Enrique, L. Pau, M. T. Dordal, A. Cisteró, E. Martí, C. Picado*

Key words: angiedema; asthma; nonsteroidal anti-inflammatory drug; NSAID; rofecoxib; urticaria.

DRUGS THAT ARE usually tolerated well, such as paracetamol, may induce asthma attacks when higher than recommended doses are given to people who are intolerant to nonsteroidal antiinflammatory drugs (NSAIDs) (1). Rofecoxib is usually recommended at doses of 12.5 or 25 mg,

but higher doses can be prescribed. Because the safety of high doses has not been explored, this study aimed to assess the tolerability of 50 mg of rofecoxib (Vioxx, MSD) in NSAID-intolerant people.

Ninety-three

people were included in the study: 66 women and 27 men with a mean age of

43 ± 15 (SD) years (range 18–78). Fifty-eight patients had experienced nonallergic cutaneous reactions (urticaria and/or angioedema) and 43 asthma attacks after taking therapeutic doses of various NSAIDs (2).

After written consent had been given, a single-blind placebo-controlled challenge with rofecoxib was carried out on two study days, separated by 7–14 days. On day 1 the challenge consisted of placebo, rofecoxib 6.125 mg, rofecoxib 12.5 mg; and on day 2, placebo, rofecoxib 25 mg, rofecoxib 25 mg. The maximal cumulative dose was 50 mg.

Forced spirometry was monitored at baseline, during the administration of the doses, and within 3 h after the last dose had been given.

A questionnaire and a peak expiratory flow (PEF) meter were given to each patient to record any delayed adverse reactions within the 24 h after the tolerance test.

The oral tolerance test was positive when any of the following criteria were met: urticaria and/or angioedema; a decrease of 20% or more from the baseline value in forced expiratory volume in 1 s (FEV₁); the occurrence of a delayed asthmatic reaction, defined as a decrease of 30% or more in the PEF from baseline.

The NSAIDs involved in adverse reactions are shown in Table 1.

One person with previous history of NSAID-induced urticaria developed urticaria 24 h after rofecoxib challenge. The remaining 92 patients tolerated 50 mg of rofecoxib without any immediate or late-phase reaction.

Rofecoxib has proved to be very well tolerated by NSAID-sensitive asthma patients. In two separate studies Szczeklik et al. (3) and Stevenson et al. (4) challenged 12 and 60 acetylsalicylic acid (ASA)-intolerant asthmatics, respectively, with rofecoxib; none of them experienced any symptoms or decline in FEV₁ values.

Table 1. Drugs involved in adverse reactions

ASA	77 (82%)
Pirazolones	51 (55%)
Diclofenac	36 (39%)
Paracetamol	13 (14%)
Ibuprofen	12 (12%)
Naproxen	5 (5%)
Piroxicam	3 (3%)
Meloxicam	2 (2%)
Indometacin	2 (2%)
Acetofenac	1 (1%)
Nimesulide	1 (1%)
Tenoxicam	1 (1%)
Niflumic acid	1 (1%)
Salsalato	1 (1%)

Similarly, we report 43 NSAID-sensitive asthmatic people who tolerated rofecoxib. In contrast to previous studies, we challenged our patients with 50 mg of rofecoxib. This dose may be needed when potent analgesia or antiinflammatory effects are required. Our results add to the evidence that rofecoxib is a well-tolerated antiinflammatory drug that can be prescribed safely to patients who have NSAID-induced asthma.

Adverse cutaneous and systemic reactions precipitated by rofecoxib have been reported (5–7). However, we observed a delayed urticarial reaction in only one of the 58 people tested, and this was with a higher dose of rofecoxib than used in studies by Asero (5), Sanchez-Borges et al. (6) and Nettis et al. (7). The reasons are unclear for the high prevalence of adverse reactions in some studies.

In summary, rofecoxib—even at a high dose—can be prescribed safely to patients with NSAID-induced asthma. According to our results, most people with adverse cutaneous reactions from NSAIDs can tolerate a high dose of rofecoxib.

*Servei de Pneumologia i Allergia Respiratoria
Hospital Clinic
Villarroel
17008036 Barcelona
Spain
Fax: + 34 93 4510993
E-mail: cpicado@medicina.ub.es

Accepted for publication 13 August 2002

Allergy 2002; 57:1214–1215

Copyright © Blackwell Munksgaard 2002

ISSN 0105-4538

References

1. SETTIPANE RA, SCHRANK PJ, SIMON RA, MATHINSON DA, CHRISTIANSEN SC, STEVENSON DD. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995;**96**:480–485.
2. JOHANSSON SGO, HOURIHANE JO'B, BOUSQUET J, et al. A revised nomenclature for allergy. Am EAACI position statement from EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
3. SZCZELIK A, NIZANKOWSKA E, BOCHENEK G, NAGRABA K, MEJZA F, SWIERCZYNSKA M. Safety of specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;**31**:219–225.
4. STEVENSON DD, SIMON RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;**108**:47–51.
5. ASERO R. Tolerability of rofecoxib. *Allergy* 2001;**56**:916–917.
6. SÁNCHEZ-BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F. NSAID hypersensitivity in the COX-2 inhibitor era. *ACI Int* 2001;**13**:211–218.
7. NETTIS E, DI PAOLA R, FERRANNINI A, TURSÌ A. Tolerability of rofecoxib in patients with cutaneous adverse reaction to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2002;**88**:331–334.

Allergic contact urticaria to oatmeal

S. de Paz Arranz*, A. Pérez Montero,
L. Zapatero Remón, M. I. Martínez Molero

Key words: allergic contact urticaria; atopic dermatitis syndrome; oatmeal.

ONE ALTERNATIVE hygienic measure in the treatment of atopic dermatitis syndrome is the use of emollient substances. As well as having emollient properties, colloidal suspensions containing oat extract also have anti-itching and anti-inflammatory effects (1,2). In recent years, several cases of sensitization to oat preparations have been reported, chiefly in the form of allergic contact dermatitis (3,4).

Local challenge of an AEDS lesion.

This case involves a 7-year-old girl with history of IgE-mediated allergic rhinoconjunctivitis, allergic asthma, and atopic dermatitis syndrome from the age of 3 years, under suitable clinical control. After bathing, oat cream was applied to her arms and trunk; after 15 min she presented swollen lesions where the cream had been applied. These lesions did not spread to other locations, nor were there any systemic symptoms. The symptoms disappeared in less than 1 hour without treatment. Subsequently, this child has not used creams or lotions containing oats, and has tolerated several moisturizing products without any problems. She presents no problems when she eats foods containing oats or other cereals, although she has been advised to avoid eating oats.

The girl was subjected to skin tests using common pneumoallergens and foods (CBF Leti, Madrid, Spain), including cereals and the standard European battery of contact agents. This study included an open patch test according to von Krogh and Maibach (5) using the cream discussed above; 10 checks were performed, 5 topical and 5 nontopical. Specific IgE (Pharmacia Diagnostics, Uppsala, Sweden) was detected for oats and other cereals.

The results of the skin tests were positive for grass, rice and oat pollens, and were negative for the other pneumoallergens and foods. The open patch test was positive, and swollen lesions appeared on the right forearm 10 min after the cream was applied. These symptoms disappeared 30 min after administration of oral cetirizine. The checks were negative. The result for oat-specific IgE was positive, at 0.76 kU/l, and negative for the other cereals.

We present a case of allergic contact urticaria (6) due to a colloidal suspension of oats that was probably IgE-mediated in origin, diagnosed using the open patch test, a positive skin test, and the demonstration of oat-specific IgE. Allergic contact urticaria and/or dermatitis caused by oat extract are not reported as frequently as might be expected. Nevertheless, Pigatto et al. (3) carried out a study on children with atopic dermatitis syndrome and healthy control individuals with the aim of evaluating the frequency of sensitization to colloidal suspensions of oats and rice. They found no cases of contact sensitization, and showed the existence of

irritation reactions in tests performed on the skin with readings after 48 h. This study did not show a higher number of cases of sensitization to oat preparations, and therefore supports their safety.

Riboldi et al. (4) reported three cases of atopic eczema syndrome in children, aggravated by sensitization to oat extract. This was shown by a positive skin contact test and positive specific IgE using RAST. None of the three patients presented contact urticaria as a symptom of this aggravation.

Sensitization to oats, in the form of allergic contact dermatitis or urticaria, must be ruled out – particularly when patients mention cutaneous symptoms, or the aggravation of existing ones after application of products that contain oats (7). Although sensitization to oat preparations does occur, they may be considered safe to use, and they represent another therapeutic option for atopic dermatitis syndrome.

*C/Luis Cabrera 92 1°7
28002 Madrid
Spain

Accepted for publication 8 August 2002
Allergy 2002; **57**:1215
Copyright © Blackwell Munksgaard 2002
ISSN 0105-4538

References

1. NEVOT S, LLEONART R, CARAS R. Atopic dermatitis today. *Allergol Immunopathol* 1997;**25**:203–208.
2. HANIFIN J. Atopic dermatitis: New therapeutic considerations. *J Am Acad Dermatol* 1991;**10**:97–101.
3. PIGATTO P, BIGARDI A, CAPUTO R, et al. An evaluation of the allergic contact dermatitis potential of colloidal grain suspensions. *Am J Contact Dermatitis* 1997;**8**:207–209.
4. RIBOLDI A, PIGATO P, ALTOMARE G, GIBELLI E. Contact allergic dermatitis from oatmeal. *Contact Dermatitis* 1988;**18**:316.
5. VON KROGH G, MAIBACH HI. The contact urticaria syndrome, an update review. *J Am Acad Dermatol* 1981;**5**:328–342.
6. JOHANSSON SGO, HOURIHANE JO'B, BOUSQUET J, et al. A revised nomenclature for allergy. An EAACI position statement from EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
7. ROTHE M, GRANT-KELS JM. Atopic dermatitis: An update. *J Am Acad Dermatol* 1996;**35**:1–13.