

Nonsteroidal anti-inflammatory drugs enhance allergic reactions in a patient with wheat-induced anaphylaxis

T. Shirai*, T. Matsui, T. Uto, K. Chida, H. Nakamura

Key words: gluten; histamine release; nonsteroidal anti-inflammatory drug; oral challenge; wheat-induced anaphylaxis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to enhance the symptoms of food-dependent exercise-induced anaphylaxis (1, 2). We report a rare case of wheat-induced anaphylaxis not related to exercise in which oral challenges with wheat and gluten-induced whole blood histamine release were enhanced by NSAIDs.

A 59-year-old man was admitted to our hospital for investigation of recurrent food-induced anaphylaxis. He first developed urticaria after eating noodles at age 58. Since then he frequently had urticaria and occasionally experienced anaphylaxis, including dyspnoea, wheezing, angioedema, and loss of consciousness after ingesting wheat, including noodles, bread, breaded cutlets, and tempura (Japanese deep-fried foods). It was determined that he had these episodes of anaphylaxis without exercise. Total IgE was 160 IU/ml. Skin-prick testing and specific IgE were positive for wheat and gluten, the major allergen in wheat-induced allergy. To determine an elimination diet and to instruct the patient, open oral challenges were performed. Oral challenges with

bread, noodles, cutlets, and tempura were all negative. However, when 30 mg of diclofenac sodium, an NSAID, was taken just before the challenge, he developed urticaria 1 h after eating noodles or tempura. He developed no symptoms after taking diclofenac sodium only.

To clarify the effect of NSAIDs on wheat-induced anaphylaxis, we measured histamine release after *in vitro* exposure to gluten with or without tolmetin sodium, an NSAID, in this patient and a normal control subject. Heparinized whole blood samples were taken and incubated with gluten at concentrations ranging from 2.5 to 2500 µg/ml and with tolmetin sodium at concentrations ranging from 0.125 to 12.5 mg/ml for 30 min at 37°C. After centrifugation, histamine was measured in the cell-free supernatants by radioimmunoassay. Histamine release was found to be positive with gluten at the concentration of 2500 µg/ml in the patient. With tolmetin sodium at concentrations of 0.125 and 1.25 mg/ml, gluten-induced histamine release was not affected. However, tolmetin sodium at the concentration of 12.5 mg/ml enhanced the gluten-induced histamine release at all concentrations of gluten. Interestingly, tolmetin sodium enhanced histamine release even in the absence of gluten in the control subject as well as in the patient. Histamine release was not found in other conditions in the control subject. At follow-up 1 year after the discharge, he remained asymptomatic after strict elimination of wheat.

The results of our *in vitro* study indicate that the induction of positive oral challenges with wheat after pretreatment with an NSAID is, at least partly, because of enhancement of histamine release. To our knowledge, this is the first report of wheat-induced anaphylaxis not related to exercise confirming that NSAIDs enhance type I allergic reactions. Previous studies demonstrated that NSAIDs enhance *in vitro* histamine release induced by IgE- or non-IgE-mediated mechanisms (3). In our

study, histamine release was induced by tolmetin sodium even in the absence of allergen. In this regard, we speculate that the extent of enhancement of histamine release may depend on the type and dose of the NSAIDs as our patient developed no symptoms after taking diclofenac sodium only. We found that enhancement of the allergic symptoms induced by NSAIDs is not a specific phenomenon in food-dependent exercise-induced anaphylaxis, but can occur in other type I allergic diseases. Furthermore, pretreatment with NSAIDs under controlled conditions is useful for confirming the diagnosis of food-induced allergy when food challenge tests fail to induce positive reactions.

*Department of Internal Medicine
Fujinomiya City General Hospital
3-1, Nishiki-cho, Fujinomiya, 418-0076
Japan
Tel: 81-544-27-3151
Fax: 81-544-23-7232
E-mail: fmyhsp@lilac.ocn.ne.jp

Accepted for publication 30 January 2003
Allergy 2003; 58:1071
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ISSN 0105-4538

References

1. HARADA S, HORIKAWA T, ASHIDA M, KAMO T, NISHIOKA E, ICHIHASHI M. Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. *Br J Dermatol* 2001;**145**:336-339.
2. AIHARA M, MIYAZAWA M, OSUNA H, TSUBAKI K, IKEBE T, AIHARA Y et al. Food-dependent exercise-induced anaphylaxis: influence of concurrent aspirin administration on skin testing and provocation. *Br J Dermatol* 2002;**146**:466-472.
3. WOJNAR RJ, HEARN T, STARKWEATHER S. Augmentation of allergic histamine release from human leukocytes by nonsteroidal anti-inflammatory-analgesic agents. *J Allergy Clin Immunol* 1980;**66**:37-45.

Anaphylactic drug reaction to celecoxib and sulfamethoxazole: cross reactivity or coincidence?

C. Schuster*, B. Wüthrich

Key words: anaphylactic reaction; celecoxib; cotrimoxazole; cross reaction; sulfamethoxazole; sulfonamides.

We have previously reported on anaphylactic reactions to celecoxib (Celebrex[®]) which was confirmed by a controlled oral provocation test

with 50 mg of the particular drug. The allergological investigation revealed a positive lymphocyte stimulation test

A case of possible cross-sensitization between celecoxib and sulfonamides.

(LTT) with Celebrex[®] (1). Here we report a patient (female, 47 years) who experienced vomiting, flushing, shivering and loss of consciousness 30 min after ingestion of a 200-mg tablet, celecoxib. She was admitted to the emergency where hypotension (50/35 mmHg) was documented. One year previously she had regularly been taking celecoxib for the treatment of whiplash trauma.

The patient was referred for diagnostic work-up to the Allergy Unit of the University Hospital of Zurich, Switzerland. Her drug history revealed an episode of vomiting and vertigo after taking Bactrim[®] (sulfamethoxazole and trimethoprim). Although scratch and patch tests were negative to all substances, the lymphocyte proliferation tests (LTT, performed by W. Pichler, Division of Allergology, Bern, Switzerland), however, were clearly positive for sulfamethoxazole [stimulation index (SI): 5.9] and for celecoxib (SI: 10.2). The patient refused further oral provocation tests.

Only very few anaphylactic reactions to celecoxib have been reported in the literature. Our previous patient experienced an anaphylactic reaction after an oral provocation with 50 mg Celebrex[®] and his LTT was found to be positive (1). In another patient with anaphylactic reaction to

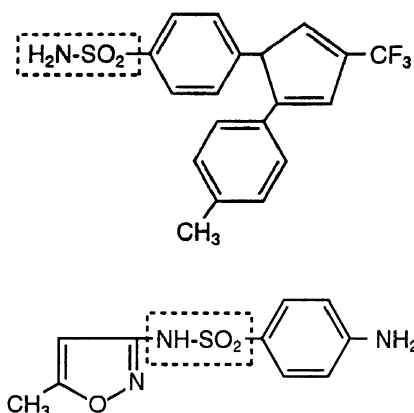


Figure 1. Structural formulas. Celecoxib (upper panel): non aromatic amine, Sulfamethoxazole (lower panel): aromatic amine.

Celebrex[®], oral provocation was positive but LTT and skin tests were negative (2). In the third report, laboratory analysis using an enzyme-linked immunosorbent assay failed to demonstrate IgE (3). More reports exist about patients with delayed-type hypersensitivity reactions, documented by positive skin patch test and LTT (4).

Cross reactions between sulfonamides and the sulfur moiety of a celecoxib is discussed controversially. The product labelling of Celebrex[®] contains a warning that patients with 'sulfa'-allergies should avoid using this drug. To date, no clinically relevant cross reactions have been reported. The Canadian pharmacovigilance centre has received 220 unconfirmed reports of probable and 562 reports of possible adverse events to celecoxib. Seventy-four of these reports included cutaneous symptoms, of which 16 reported an allergy to sulfonamides (5).

Due to the great structural differences amongst the various sulfonamides, cross reactivity has been disputed (6). Celecoxib contains a nonaromatic amine (Fig. 1). In sulfamethoxazole the sulfonamide is bound to a methylated heterocyclic ring and a benzole ring. The adverse side-effects are attributed either to the aromatic amine group or the heterocyclic ring (6). Both of these chemical structures are not found in celecoxib.

The exact mechanism that ultimately caused sensitization in our patient remains unresolved: either an independent (coincidental) sensitization to the two drugs or a real cross reactivity might have been responsible for this

unusual observation. Until further investigations are available, patients with a known sulfonamide allergy should avoid using celecoxib.

*Department of Dermatology, Allergy Unit University Hospital of Zürich, Gloriastrasse 31, CH-8091 Zürich, Switzerland
Tel: +41(1) 255-3079
Fax: +41(1) 255-4431
E-mail: wuetric@derm.unizh.ch

Accepted for publication 17 January 2003
Allergy 2003; 58:1072
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ISSN 0105-4538

References

- GROB M, PICHLER WJ, WÜTHRICH B. Anaphylaxis to celecoxib. *Allergy* 2002;**57**: 264–265.
- WEBER-MANI U, REIMERS A, PICHLER WJ, MÜLLER U. Celecoxib-induzierte Anaphylaxie.
- LEVY MB, FINK NJ. Anaphylaxis to celecoxib. *Ann Allerg Asthma Immunol* 2001;**87**:72–73.
- GROB M, SCHEIDEGGER P, WÜTHRICH B. Allergic skin reaction to celecoxib. *Dermatol* 2000;**201**:383.
- McMORRAN M, MORAWIECKA I. Celecoxib (Celebrex): 1 year later. *CMAJ* 2000;**162**:1048–1050.
- KNOWELS S, SHAPIRO L, SHEAR NH. Should celecoxib be contraindicated in patients who are allergic to sulfonamides? *Drug Saf* 2001;**24**:239–247 and 2002;**25**: 297–300.

Safety of rofecoxib in nonsteroidal anti-inflammatory drugs intolerance

F. J. Muñoz-Bellido*, M. Terrón, A. León

Key words: anaphylactoid reaction; angioedema; asthma; cyclooxygenase-2; nonsteroidal anti-inflammatory drugs; nonsteroidal anti-inflammatory drugs intolerance; rofecoxib; urticaria.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the

management of pain and inflammatory disorders. Adverse effects of NSAIDs are mainly related to gastrointestinal bleeding and renal damage. Cutaneous, respiratory and anaphylactoid reactions are also often observed in general practice.

Rofecoxib can be taken safely by most patients with NSAIDs intolerance.

The enzyme that appears to be central to the mechanism of adverse reactions exists in at least two isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), encoded by distinct genes. Many studies have argued that inhibition of COX-1 is the likely mechanism of such adverse effects (1–3). Hence, it is hoped that selective inhibition of COX-2 would be equally efficacious but better tolerated than nonselective inhibition.

The coxibs are selective inhibitors of COX-2. Several trials have been designed to detect the equivalence of efficacy between NSAIDs and coxibs and the associated risk of gastrointestinal, renal or cardiovascular adverse effects (4–14). In the same way, several studies (15–18) have evaluated the safety of coxibs in asthmatic patients with ASA intolerance. Nevertheless, there are few studies about the safety of coxibs in patients with cutaneous and/or anaphylactoid reactions with NSAIDs (19–21).

The aim of this study was to investigate the tolerance of rofecoxib, a COX-2 selective inhibitor, in patients suffering cutaneous, respiratory and/or anaphylactoid reactions with NSAIDs.

Individuals who have a history of bronchial asthma, rhinitis, conjunctivitis, urticaria, angioedema or anaphylactoid reactions with two or more unrelated NSAIDs were included.

After written informed consent, patients were submitted to single-blind, placebo-controlled, per oral challenge test with rofecoxib. In the same way, the challenge test with the suspected drugs was previously performed if necessary for diagnosis.

Exclusion criteria were pregnancy or lactation, symptomatic bronchial asthma, rhinitis, urticaria or angioedema, and contraindication to epinephrine. Patients under treatment with antihista-

mines or oral corticoids were also excluded.

Single-blind, placebo-controlled per oral challenge tests were performed with opaque capsules administered one per hour.

Heart rate and arterial pressure were measured. Peak flow was monitored in patients who had suffered respiratory reactions (rhinitis or bronchial asthma).

On challenge day 1, three placebo capsules (empty capsules) were administered. On the subsequent challenge days, increasing doses of the drug tested were used from 1/8 up to total therapeutic dose (rofecoxib, from 3 up to 25 mg; 47 mg cumulative dose).

If more than one drug was tested, they were administered with at least a 1-week interval.

The tests were considered positive if cutaneous or mucosal manifestations,

rhinitis, conjunctivitis or bronchial asthma appeared, or when hypotension or a decrease of at least 20% in the peak-flow was detected.

The study group comprised 61 patients: 21 males (mean age 49.47 years; range from 16 to 70 years) and 40 females (mean age 44.47 years; range from 21 to 78 years).

Clinical findings in our patients include cutaneous, respiratory and anaphylactoid reactions with NSAIDs (Table 1). The NSAIDs involved in adverse reactions in our patients are shown in Table 2.

Of the 61 patients who underwent the challenge test with rofecoxib, only one (1.64%) experienced adverse reaction. The patient presented angioedema of her lips and eyelids, and oedema of her hands approximately 5 h after finishing the challenge test. She had previously experienced urticaria/angioedema with

Table 1. Drugs implicated in adverse reactions to NSAIDs

Drug	Number of patients	Percentage of drugs	Percentage of patients
Salicylic acid derivatives			
ASA	41	28.67	67.21
Lisine-acetylsalicylate	1	0.70	1.61
Arylacetic acid derivatives			
Diclofenac sodium	18	12.59	29.51
Aceclofenac	2	1.40	3.28
Indomethacin	3	2.10	4.92
Arylpropionic acid derivatives			
Ibuprofen	6	4.19	9.84
Naproxen	8	5.59	13.11
Ketoprofen	7	4.89	11.47
Dexketoprofen	1	0.70	1.64
Arylcarboxylic acids			
Ketorolac	3	2.10	4.92
Amino aryl carboxylic acid derivatives			
Mefenamic acid	1	0.70	1.64
Isonixin	2	1.40	3.28
Lisine-clonixinate	1	0.70	1.64
Pyrazolones			
Phenylbutazone	1	0.70	1.64
Propyphenazone	8	5.59	13.11
Metamizol	31	21.68	50.82
Thiazine carboxamides			
Piroxicam	1	0.70	1.64
Meloxicam	1	0.70	1.64
Others			
Nimesulide	2	1.40	3.28
Acetaminophen	5	3.50	8.20

Table 2. Clinical findings in adverse reactions to NSAIDs

Clinical findings	Number of patients	Percentage of patients
Conjunctivitis	5	8.20
Rhinitis	5	8.20
Bronchial asthma	14	22.95
Urticaria/angioedema	55	90.16
Anaphylactoid reaction	4	6.56

other NSAIDs. This patient tolerated acetaminophen without adverse reaction.

Another patient suffered dyspepsia, nausea and diarrhoea several hours after the challenge test. This patient had a history of lactose intolerance, but symptoms appeared in two different challenge tests despite using rofecoxib solution (without lactose).

All of the five patients who experienced adverse reactions with acetaminophen tolerated the whole dose of rofecoxib.

None of the 61 patients experienced symptoms of renal damage.

Development of the coxibs, a new group of anti-inflammatory drugs, represents a response to the unsatisfactory therapeutic profile of NSAIDs. Although the pathogenetic mechanism of NSAIDs intolerance is still unclear, there are several studies supporting the theory that the enzyme cyclooxygenase and leukotrienes may play a crucial role (1–3). Hence, an increasing number of studies provide evidence that selective COX-2 inhibitors may be a useful alternative in the anti-inflammatory treatment for patients with NSAIDs intolerance (15–21).

Dahlen et al. (16) reported that celecoxib did not induce bronchospasm in 27 aspirin-intolerant asthmatic patients. García-Rodríguez et al. (20) observed that celecoxib seems to be a safe drug for patients suffering from NSAIDs intolerance with urticaria/angioedema.

Regarding rofecoxib, Hinrichs et al. (17) provide evidence that the said drug is well tolerated in a patient with aspirin intolerance and mainly extrapulmonary symptoms (urticaria, rhinitis and conjunctivitis). Stevenson et al. (18) conclude that cross-reactivity between aspirin and rofecoxib does not occur in patients with aspirin-sensitive respiratory

disease. Schellenberg et al. (21) describe an anaphylactoid reaction to rofecoxib in a patient with a previous adverse reaction to a COX-1 inhibitor. Sánchez-Borges et al. (19) investigated the clinical tolerance of a large number of cutaneous reactors to four different COX-2 inhibitors (nimesulide, meloxicam, rofecoxib and celecoxib), and the reaction rates varied between 3.0% for rofecoxib and 33.3% for celecoxib. Such differences would be related to the degree of COX-1 inhibition *in vitro*, as reported by Warner et al. (3). Hence, the lesser the inhibition of COX-1, the lesser is the reaction rate.

Our results confirm the tolerance of rofecoxib in NSAIDs-intolerant patients, both with asthma and with cutaneous or anaphylactoid reactions. These results also seem to confirm the cyclooxygenase theory.

Furthermore, we wish to remark that in our study all of the patients with previous adverse reactions to acetaminophen tolerated the oral challenge test with rofecoxib. Presently, acetaminophen is usually the most recommended alternative in aspirin intolerance. When this drug is not tolerated, choosing an alternative anti-inflammatory drug is a great, even unresolved problem.

Finally, we think that the existence of gastrointestinal symptoms in one patient in our study is not conclusive because of her history of lactose intolerance. However, the lack of cross-reactivity between rofecoxib and other NSAIDs in patients with NSAIDs intolerance does not exclude rofecoxib from participating in other types of reactions (22).

In summary, the results presented in this study suggest that rofecoxib can be taken safely by most patients with NSAIDs intolerance. Nevertheless,

given that a small percentage of patients presented adverse reactions, we think that the oral challenge test is mandatory to allow administration of rofecoxib in patients with NSAIDs intolerance.

We thank the nurses of the Unit of Allergy, Hospital Martínez Anido, Salamanca, Spain, without whose dedicated efforts this study could not have been conducted.

*Unidad de Alergia
Hospital Martínez Anido
Los Montalvos
s/n. 37192-Salamanca
Spain

Accepted for publication 18 February 2003
Allergy 2003; 58:1072–1075
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ISSN 0105-4538

References

1. SZCZEKLAK A. The cyclooxygenase theory of aspirin-induced asthma. *Eur Respir J* 1990;**3**:588–593.
2. SZCZEKLAK A, STEVENSON DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol* 1999;**104**:5–13.
3. WARNER TD, GIULIANO F, VOJNOVIC I, BUKASA A, MITCHELL JA, VANE JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci USA* 1999;**96**:7563–7568.
4. FITZGERALD GA, PATRONO C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Eng J Med* 2001;**345**:433–442.
5. WEAVER AL. Rofecoxib: clinical pharmacology and clinical experience. *Clin Ther* 2001;**23**:1323–1338.
6. SILVERSTEIN FE, FAICH G, GOLDSTEIN JL, SIMON LS, PINCUS T, WHELTON A et al. Gastrointestinal celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomised controlled trial. *JAMA* 2000;**284**:1247–1255.
7. BOMBARDIER C, LAINE L, REICIN A, SHAPIRO D, BURGOS-VARGAS R, DAVIS B et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Eng J Med* 2000;**343**:1520–1528.

8. ZHAO SZ, REYNOLDS MW, LEJKOWITH J, WHELTON A, ARELLANO FM. A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib based on the World Health Organization/Uppsala Monitoring Centre safety database. *Clin Ther* 2001;**23**:1478–1491.
9. WOYWODT A, SCHWARZ A, MENGEL M, HALLER H, ZEIDLER H, KOHLER L. Nephrotoxicity of selective COX-2 inhibitors. *J Rheumatol* 2001;**28**:2133–2135.
10. Cardiovascular safety of COX-2 inhibitors. *Med Lett Drugs Ther* 2001;**43**: 99–100.
11. Adverse effects of rofecoxib (continued). *Prescribe Int* 2001;**10**:82–83.
12. KONSTAM MA, WEIR MR, REICIN A, SHAPIRO D, SPERLING RS, BARR E et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;**104**:2280–2288.
13. FLEMING M. Cardiovascular events and COX-2 inhibitors. *JAMA* 2001;**286**:2808.
14. MUKHERJEE D, NISSEN SE, TOPOL EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;**286**:2809.
15. SZCZEKLIK A, NIZANKOWSKA E, BOCHENEK G, NAGRABA K, MEJZA F, SWIERCZYNSKA M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;**31**:219–225.
16. DAHLEN B, SZCZEKLIK A, MURRA JJ. Celecoxib in patients with asthma and aspirin intolerance. *N Eng J Med* 2001;**344**:142–143.
17. HINRICH S, RITZKOWSKY A, HUNZELMANN N, KRIEG T, SCHARFFETTER-KCHANEK K. Rofecoxib as an alternative in aspirin hypersensitivity. *Allergy* 2001;**56**:789.
18. 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.
19. SÁNCHEZ BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F, RAMÓN PÉREZ C. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;**87**:201–204.
20. GARCÍA-RODRÍGUEZ RM, HINOJOSA M, CAMACHO-GARRIDO E, BERGES GIMENO P, MARTÍN GARCÍA C. Celecoxib, safe in NSAID intolerance. *Allergy* 2002;**57**: 1085–1086.
21. SCHELLENBERG RR, ISSEROW SH. Anaphylactoid reaction to a cyclooxygenase-2 inhibitor in a patient who had a reaction to a cyclooxygenase-1 inhibitor. *N Eng J Med* 2001;**345**:1856.
22. KAUR C, SARKAR R, KANWAR AJ. Fixed drug eruption to rofecoxib with cross-reactivity to sulphonamides. *Dermatology* 2001;**203**:351.

Effects of rofecoxib, celecoxib, and parecoxib on anti-IgE-induced histamine release from human skin mast cells and basophils

B. F. Gibbs, W.-H. Boehncke*

Key words: basophil; celecoxib; cyclooxygenase; mast cell; parecoxib; rofecoxib; urticaria.

Although the symptoms of urticaria are primarily due to histamine release from mast cells, treatment with H1 antihistamines is often insufficient. One

explanation is that the actions of other mast cell mediators, such as prostaglandins and thromboxanes, have been overlooked. These mediators are formed from arachidonic acid by cyclooxygenases (COXs), of which there are two isoforms, with the inducible COX-2 being responsible for pseudoallergic responses. In line with this notion is the beneficial effect of the selective COX-2-inhibitor rofecoxib in the treatment of some patients with chronic idiopathic urticaria reported recently (1).

It has previously been shown that some nonsteroidal anti-inflammatory drugs may interfere directly with histamine release (2). We therefore investigated the effect of the selective COX-2-inhibitors rofecoxib, celecoxib, and parecoxib on anti-IgE-induced histamine release from human basophils ($n = 5$) as well as human skin mast cells from five donors undergoing minor skin surgery. However, the drugs failed to inhibit histamine

Selective cyclooxygenase-2-inhibitors do not inhibit histamine release *in-vitro*.

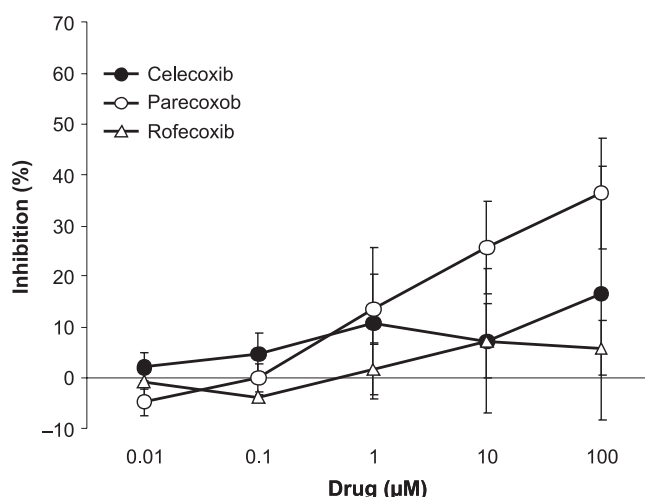


Figure 1. Inhibition of anti-IgE-induced histamine release from human skin mast cells by the selective COX-2-inhibitors rofecoxib, celecoxib, and parecoxib. Human skin mast cells, isolated by enzymatic dispersion, were incubated with the drugs for 15 min before stimulation with anti-IgE for 30 min (with appropriate controls). Histamine contents in both lysed cell pellets and supernatants were determined spectrofluorometrically. Results were first calculated as percentage histamine release of total and corrected for spontaneous release as well as solvent effects. Results are expressed as mean percentage inhibitions of anti-IgE-induced histamine release in the absence of the compounds ($24.5 \pm 6.4\%$, corrected for spontaneous secretions) $\pm$ SEM. Similar results were observed following simultaneous addition of the drugs with the stimulus (not shown).

release except for parecoxib which produced 40% inhibition in skin mast cells at 100 μ M (Fig. 1), although this was not statistically significant. Thus, COX-2-inhibitors do not appear to directly affect histamine release to a clinically meaningful degree.

This interpretation was further supported by *in-vivo* data: in five volunteers, wheal formation induced by prick tests with the histamine-secretagogue, compound 48/80 (3), was not significantly altered following 1 week of treatment with rofecoxib (Vioxx[®], MSD, Haar, Germany; 25 mg/day) (35 ± 16 vs. 41 ± 18 mm²); this was also found in three volunteers after 3 days of treatment with parecoxib (Dynastat[®], Pharmacia, Erlangen, Germany; 2×40 mg i.m./day) (30 ± 15 vs. 25 ± 18 mm²).

We conclude that the clinical improvement seen in CIU patients under treatment with rofecoxib is not associated with direct blockade of histaminergic action. Moreover, prostaglandins and thromoxanes may well not be involved to a large extent in causing immediate symptoms. Whether these drugs may have some delayed action resulting in feedback inhibition of histamine release *in vivo* remains to be resolved.

*Department of Dermatology
Johann Wolfgang Goethe-University
Theodor-Stern-Kai 7
D-60590 Frankfurt
Germany
Tel: (+49) 69 6301 5743
Fax: (+49) 69 6301 5117
E-mail: boehncke@em.uni-frankfurt.de

Accepted for publication 14 April 2003
Allergy 2003; 58:1075–1076
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ISSN 0105-4538

References

- BOEHNCKE W-H, LUDWIG RL, ZOLLNER TM, OCHSENDORF FR, KAUFMANN R, GIBBS BF. The selective cyclooxygenase-2 inhibitor rofecoxib may improve the treatment of chronic idiopathic urticaria. *Br J Dermatol* 2003;148:1–2.

- FARNAM J, GRANT JA, LETT-BROWN MA, HUNT C, THUESON DO, GILLAS PC. Complement- and IgE-mediated release of histamine from basophils *in vitro*. V. Differential effects of drugs modulating arachidonic acid metabolism. *J Immunol* 1985;134:541–547.
- FADEL R, RAMBOER I, CHATTERJEE N, RIHOUX J-P, DERDE M-P. Cetirizine inhibits bradykinin-induced cutaneous wheal and flare in atopic and healthy subjects. *Allergy* 2000;55:382–385.

Delayed hypersensitivity reactions to diclofenac

R. D. Klingenberg*, I. D. Bassukas, N. Homann, E. F. Stange, D. Ludwig

Key words: diclofenac; fever; hypersensitivity reaction; multiforme exanthema; Raynaud's phenomenon; toxic hepatitis.

A 72-year-old woman presented with high rising temperatures (40°C), chills, a bright red and confluent exanthema sparing the extremities and Raynaud's phenomenon since 7 days. The patient used

A hypersensitivity reaction to diclofenac with recurrent fever, exanthema, toxic hepatitis and Raynauds phenomenon was confirmed by cutaneous patch test.

diclofenac sodium (75 mg) intermittently since 2 years for pain control, and she presented with similar symptoms already in the past.

C-reactive protein (53 mg/l), white blood cell count (12.8 mg/l) and liver enzymes were slightly elevated (AST: 51U/l; ALT: 75U/l; γ GT: 178U/l; AP: 178U/l). There was a moderate normocytic anemia (Hb 124 g/l), lymphocytopenia (1.16/nl) and eosinophilia (0.70/nl). Immunoglobulin E (IgE) (2489 mg/dl) and IgG (2440 mg/dl) were elevated; IgM and soluble IgA, immunogenic markers and bone marrow aspiration cytology were normal. Skin biopsy showed a lymphocyte-predominated dermatitis with histomorphological signs of vasculitis, consistent with multiforme exanthema.

Antibiotic therapy was unsuccessful, but symptoms improved within 12 h after initiation of steroid therapy (prednisone 100 mg daily).

Epicutaneous patch testing with diclofenac (pure in petrolatum and commercial solution), carried out 4 weeks later, showed a characteristic type IV hypersensitivity reaction (palpable, warm, reddish induration) after 48 h (Fig. 1).

Diclofenac is a worldwide used, generally well tolerated, anti-inflammatory drug. Mild adverse reactions are frequent, but severe side effects such as hepatitis, renal toxicity, rhabdomyolysis, anaphylactic shock or eosinophilic pneumonitis account for <1% (1). A hypersensitivity reaction to diclofenac in the presented case is strongly suggested by



Figure 1. Epicutaneous patch test with commercial diclofenac and pure diclofenac substance in petrolatum (72 h after application).

(i) clinical symptoms and recurrence after reexposition (ii) laboratory work-up (elevated IgE, blood and tissue eosinophilia in absence of atopy, parasitic infections or myeloproliferative disease), (iii) positive epicutaneous patch test and (iv) prompt relief of symptoms following steroid therapy.

Mechanism of side effects to diclofenac has already been discussed in the context of hepatitis (2) and cutaneous manifestations (i.e. multiforme erythema) (3), but never for recurrent fever or Raynauds phenomenon. The underlying mechanism is thought to rely on amplification of mast-cell degranulation and enhanced biosynthesis of lipooxygenase products of arachidonic acid, causing vasodilatation and edema (4). Cell-mediated hypersensitivity with inhibition of cyclooxygenase, leading via inhibition of the prostaglandin- E_2 production to an increase in Th-2-response (overproduction of interleukin-4), might be another promoter of allergic reaction (5). As in the present case, epicutaneous patch test is a valid and simple measure to confirm drug-induced hypersensitivity reaction *a posteriori* (6). In case of doubt – after exclusion of infectious causes – a probatory and successful treatment with glucocorticosteroids may be helpful.

*Division of Gastroenterology
Department of Internal Medicine I
University of Lübeck
Ratzeburger Allee 160
23538 Lübeck
Germany

Accepted for publication 10 March 2003

Allergy 2003; 58:1076–1077

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ISSN 0105-4538

References

- CARSON JL, WILLETT LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. *Drugs* 1993;**46**:243–248.
- MANOUKIAN AV, CARSON JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. Incidence and prevention. *Drug Saf* 1996;**15**:64–71.
- DELRIO FG, PARK Y, HERZLICH B, GROB D. Diclofenac induced rhabdomyolysis. *Am J Med Sci* 1996;**312**:95–97.
- SAMPSON AP. The leukotrienes: mediators of chronic inflammation in asthma. *Clin Exp Allergy* 1996;**26**:995–1004.
- IBANEZ MD, ALONSO E, MUNOZ MC, MARTINEZ E, LASO MT. Delayed hypersensitivity to paracetamol (acetaminophen). *Allergy* 1996;**51**:121–123.
- ROMANO A, PIETRANTONIO F, DI FONSO M, GARCovich A, CHIARELLI C, VENUTI A et al. Positivity of patch tests in cutaneous reaction to diclofenac. Two case reports. *Allergy* 1994;**49**:57–59.

Not all adverse drug reactions originate from active component: coloring agent-induced skin eruption in a patient treated with rifampicin

Z. Çalişkaner*, S. Öztürk, M. Karaayvaz

Key words: drug reaction; patent blue; rifampicin; tuberculosis.

Colorants are commonly used excipients in many prescription and nonprescription drugs. As these agents are capable of various reactions, it may be postulated that at least a

part of drug reactions are not attributed to the active drug.

There may be unknown addi-

tives in drugs that cause in reactions. In this report, the case of a 22-year-old male patient who developed an unusual skin reaction to a specific additive of a rifampicin preparation has been described.

Adverse drug reaction is a commonly encountered problem in daily medical practice. Some frequent drug reactions occur with certain drugs and are well known. However, there is always a possibility of experiencing extraordinary or unreported reactions with commonly used drugs. In rare occasions, some drug-related reactions can be attributed to drug additives only. In this report, the case of a 22-year-old male patient who developed an unusual skin reaction to a

An unusual skin reaction to a specific additive.

specific rifampicin formulation has been described. The steps leading to the diagnosis of an adverse drug reaction and the role of pharmacologically inert substances of formulations are also discussed.

A 22-year-old man was admitted to a physician with painless swellings at the right-side of his neck for 4 weeks. Initial physical examination revealed multiple, nontender, soft, rubbery and movable lymph node enlargements at the right cervical region. Ultrasonographic examination showed multiple lymph node enlargements at the right cervical region. The largest lymph node was 63 × 37 mm in diameter, and of centric hypoechoic nature. An excisional biopsy of this lymph node was performed. Histopathologic findings were compatible with tuberculosis lymphadenitis (caseous necrosis in the central part of the node). Tuberculosis bacillus was not identified by cultures, polymerase chain reaction (PCR) assay and other known methods. On the basis of strong pathological evidences, antituberculous therapy was started with isoniazid, rifampicin, ethambutol and morphazinamide (1).

On the 11th month of treatment, cervical lesion re-enlarged, became tender and warm because of superinfection and abscess formation. The patient was hospitalized and wound debridement, dressing and topical treatment with rifamycin SV were performed in addition to antituberculous therapy. Response to treatment was achieved and superinfection controlled. However, the patient developed recurring skin eruptions during this treatment. At this stage, the patient consulted our Allergy Department to evaluate the skin eruptions.

The clinical findings were daily recurring, self limited, macular, itchy rashes, symmetrically placed on the face, ears, buttocks, elbows and knees. The lesions appeared at the same time every day and lasted about 45 min, then disappeared spontaneously without any treatment. These findings were considered as an unusual drug reaction. The patient was taking isoniazid, rifampicin, ethambutol and topical rifamycin SV when referred to our department. So, there are four different drugs that may cause this reaction.

As the elimination and re-administration procedure is the keystone in evaluating a possible drug reaction, rifamycin SV application was discontinued in the first step. It was the strongest possibility because reactions caused by topical rifamycin SV application have been reported several times (2–5). Skin testing with rifamycin SV was performed as well, as the IgE-mediated hypersensitivity reactions to rifamycin SV have been described repeatedly (3–5). Epidermal skin testing (prick test) was carried out with undiluted rifamycin SV. Skin response was negative. Then intradermal testing with 1/1000 and 1/100 dilutions of the drug was performed. Intradermal testing was also negative in each dilution. Furthermore, the skin lesions did not disappear even before the discontinuation of rifamycin SV. Depending on these results it was concluded that rifamycin SV was not the causative drug.

At the second step, other three drugs were evaluated. All drugs were discontinued and re-administered one by one. The skin eruptions recurred only after rifampicin re-administration. In addition, a close relationship between the daily onset time of the reaction and rifampicin intake was established when reviewed retrospectively. In fact, the symptoms were recurring regularly about half an hour after rifampicin administration.

But another clinical observation conflicted this finding: some days the patient did not experience skin eruptions after rifampicin dose. This inconsistency was examined in detail. The drugs given to inpatients were provided by the hospital pharmacy. Two different brands of rifampicin preparation were available in stock and the patients were having either brand randomly.

Diagnostic procedures were revised in accordance with the recent finding. Challenges with different rifampicin formulations (named as 'Brand-A-rifampicin' and 'Brand-B-rifampicin') were performed on different days. Skin eruptions appeared only with Brand-A-rifampicin. Additional challenges with Brand-A-rifampicin were repeated two more times on different days (re-challenge). The same results were obtained in each challenge. Brand-A-rifampicin

was found to be responsible for the allergic reactions.

Why Brand-A-rifampicin causes skin eruption while the Brand-B-rifampicin did not? As active components in each preparation are the same, any pharmacologically inert substance like drug capsule material, might have been responsible. To find out the responsible factor within Brand-A-rifampicin preparation, the patient was challenged with empty capsule and with active drug powder on separate days. No reaction was observed with active drug challenge, but the skin rashes recurred after the administration of an empty capsule which implies that the patient was sensitive to one of the capsule shell excipients of Brand-A-rifampicin.

Rifampicin is one of the major drugs used for the treatment of mycobacterial infections, and has been prescribed throughout the world for over 20 years. It is usually well tolerated, however, many reports have shown that rifampicin could induce a variety of adverse effects including flu-like syndrome, thrombocytopenia, hemolytic anemia, renal failure, various cutaneous reactions and life-threatening anaphylactic reactions. Many of these reactions have been considered allergic in origin (6, 7).

Several types of cutaneous reactions, from urticaria to toxic epidermal necrolysis, associated with rifampicin treatment have been described (8–12). However, daily recurring, symmetric and self-limited itchy macular eruptions have not been reported. Furthermore, all the previously described skin reactions were linked directly to rifampicin. But, in our case, the eruptions were related to a specific rifampicin preparation, most probably arising from a specific excipient of that preparation.

Two available rifampicin preparations contain the same active drug and drug capsule shell excipients titanium-dioxide and erythrosine, except patent blue V (PBV) in Brand-A-rifampicin and indigotin (indigo blue) in Brand-B-rifampicin. So, it may be postulated that PBV might be causative agent for the skin reaction.

Drug capsule shell materials contain pharmaceutically acceptable coloring agents such as PBV (E131). This dark bluish-violet synthetic coal tar dye is also

used as a food color additive and diagnostic aid in lymphatic mapping. As in other coloring agents, PBV may also cause allergic or pseudo-allergic reactions (either by direct histamine release, or by alternate activation of the complement system) such as rashes similar to nettle rash, itching, nausea, low blood pressure, tremors and breathing problems (13, 14). For this reason, using PBV as a food additive is banned in some countries (15, 16). Most of the reported reactions were related to PBV injections for radiologic imaging (17–19). However, PBV may also cause adverse events when used as a drug additive. Chadwick et al. reported an urticarial reaction in a 5-year-old girl after the use of tablets containing PBV (20). In addition, there are some reports about allergic and pseudo-allergic reactions arising from different drug coloring agents (21–26).

Colorants are commonly used excipients in many prescription and nonprescription drugs. As these agents are capable of various reactions, it may be postulated that at least a part of drug reactions are not attributed to the active drug. There may be unknown additives in drugs, that cause in reactions. Therefore, many drugs might be excluded from the treatment schemes and patients erroneously labeled as allergic to questionable drugs.

In this case, had rifampicin been wrongly implicated to cause the allergic reaction, this patient would have been deprived of an important drug. However, careful clinical observation and through investigations have shown that the patient could tolerate another rifampicin formulation without any complication.

This case also reveals an important detail: when an adverse reaction attributed to a drug is reported, the additives of suspected drug should also be mentioned. These kinds of reports may provide an opportunity to recognize drug additive-related adverse events. Furthermore, as many colorants associated with a wide range of health problems have been banned in some countries, their continued use within drug formulations is controversial. The safer formulations may offer safer treatment courses.

As a result, when a drug-related adverse event was investigated, active components and excipients should be evaluated together, as all reactions may not be attributable directly to the active component. So, using the names of the inert substances associated with proprietary name or approved name of the drug may be vital in our opinion.

*GATA Allerjik Hastaliklar BD
Etlik, Ankara, 06018
Turkey

Accepted for publication 18 February 2003
Allergy 2003; 58:1077–1079
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ISSN 0105-4538

References

- KANLIKAMA M, MUMBUC S, BAYAZIT Y, SIRIKCI A. Management strategy of mycobacterial cervical lymphadenitis. *J Laryngol Otol* 2000;**114**:274–278.
- MANCUSO G, MASARA N. Contact urticaria and severe anaphylaxis from rifamycin SV. *Contact Dermatitis* 1992;**27**:124–125.
- CARDOT E, TILLIE LEBLOND I, JEANNIN P, FACON A, BREUIL K, PATTE F, TONNEL AB. Anaphylactic reaction to local administration of rifamycin SV. *J Allergy Clin Immunol* 1995;**95**:1–7.
- EREL F, KARAAVVAZ M, DEVECİ M, OZANGUC N. Severe anaphylaxis from rifamycin SV. *Ann Allergy Asthma Immunol* 1998;**81**:257–260.
- MAGNAN A, VENEMALM L, PORRI F, VERVOLET D. Anaphylactic reaction to rifamycin SV: presence of specific IgE antibodies. *J Allergy Clin Immunol* 1999;**103**:954–956.
- MARTINEZ E, COLLAZOS J, MAYO J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine (Baltimore)* 1999;**78**:361–369.
- GROSSET J, LEVENTIS S. Adverse effects of rifampin. *Rev Infect Dis* 1983;**3**:440–450.
- GOEL A, BALACHANDRAN C. Bullous necrotizing fixed drug eruption with hepatitis due to rifampicin. *Indian J Lepr* 2001;**73**:159–156.
- IREDALE JP, SANKARAN R, WATHEN CG. Cutaneous vasculitis associated with rifampin therapy. *Chest* 1989;**96**:215–216.
- GOLDIN HM, SCHWEITZER WJ, BRONSON DM. Rifampin and exfoliative dermatitis. *Ann Intern Med* 1987;**107**:789.
- GUPTA CM, BHATE RD. Shortness of breath with urticaria due to once monthly rifampicin. *Lepr Rev* 1987;**58**:308–309.
- OKANO M, KITANO Y, IGARASHI T. Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol* 1987;**17**:303–304.
- DUBOST JL, CHEVALLIER H. Allergic reactions to patent blue violet: mechanisms, frequency and treatment. *Phlebologie* 1982;**35**:739–746.
- Diagnostic agents. In: REYNOLDS EFJ, ed. Martindale. The extra pharmacopoeia. London: The Pharmaceutical Press, 1993, 777 pp.
- SMOLINSKE SC. Handbook of food, drug, and cosmetic excipients. Boca Raton, FL: CRC Press, 1992.
- GOLDSMITH E, HILLYARD N. Battle for the Earth: today's key environmental issues. Child & Associates, Brookvale, UK, NSW, 1988.
- MOSTAFA A, CARPENTER R. Anaphylaxis to patent blue dye during sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2001;**27**:610.
- MULLAN MH, DEACOCK SJ, QUINEY NF, KISSIN MW. Anaphylaxis to patent blue dye during sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol* 2001;**27**:218–219.
- BARBER CJ. Serious adverse reaction to patent blue violet at lymphography. *Clin Radiol* 1989;**40**:631.
- CHADWICK BL, HUNTER ML, EVANS MT, HUNTER B. Allergic reaction to the food dye patent blue. *Br Dent J* 1990;**168**:386–387.
- BELL T. Colourants and drug reactions. *Lancet* 1991;**338**:55–56.
- LEVESQUE H, MOORE N, COURTOIS H. Reporting adverse reactions by proprietary name. *Lancet* 1991;**338**:393.
- MAGNER J, GERBER P. Urticaria due to blue dye in thyroid tablets. *Thyroid* 1994;**4**:341.
- GROSS PA, LANCE K, WHITLOCK RJ, BLUME RS. Additive allergy: allergic gastroenteritis due to yellow dye #6. *Ann Intern Med* 1989;**111**:87–88.
- FRAZIER CA. Allergic reaction to yellow dye no. 5. *South Med J* 1990;**83**:1234.
- MATHEU V, ZAPATERO L, ALCAZAR M, MARTINEZ-MOLERO MI, BAEZA ML. IgE-mediated reaction to a banana-flavored drug additive. *J Allergy Clin Immunol* 2000;**106**:1202–1203.

The influence of atopic constitution, the severity and exacerbation of the disease on the serum eosinophil cationic protein (ECP) concentration in patients with bronchial asthma

S. Kovacevic*, M. Bogic, A. Peric-Popadic, Z. Jovicic, S. Raskovic, Lj. Stefanovic

Key words: allergic rhinitis; asthma; atopy; eosinophil cationic protein; exacerbation of asthma.

Activated eosinophil leukocytes in asthma, secrete numerous mediators, among which is eosinophil cationic protein (ECP) (1). The secreted form of ECP is considered to be the marker of eosinophil activity (2). Serum

The most consistent correlation of serum ECP concentration is with the status of disease activity.

ECP concentration is the earliest indicator of allergen-induced bronchial inflammation, before the onset of symptoms and prior to change of bronchial reactivity (3).

The objective of this study was to explore the influence of severity, exacerbation and type of the disease as well as association of chronic allergic rhinitis with serum ECP concentration in asthmatic patients.

Serum ECP concentration was measured by UniCAP 100 apparatus (Pharmacia CAP system ECP FEIA, Uppsala, Sweden), in 46 asthmatic patients and 15 healthy subjects.

The results are reported as geometric mean (Gecp). Correlation coefficients were calculated by Spearman's rank correlation test.

Geometric mean of ECP in serum (Gecp) in this group of patients was 7.5 µg/l, while it was 3.05 µg/l in the 15 healthy subjects (controls). In patients with asthma there is significant correlation of serum ECP concentrations in relation to state of disease activation (exacerbating/stable) ($R = 0.897$), the severity of clinical picture (mild/moderate/severe) ($R = 0.79$) and types of

Table 1. Geometric mean of serum ECP in asthmatic patients in relation to the severity and state of activity of the disease

State of asthma	Severity of asthma	No. of subjects	Geometric mean ($\mu\text{g/l}$)
Exacerbated	Mild	5	8.6
Exacerbated	Moderate	9	6.6
Exacerbated	Severe	15	10.4
Total		29	8.7
Stable	Mild	7	6.6
Stable	Moderate	6	5.9
Stable	Severe	4	4.8
Total		17	5.9
Total		46	7.5

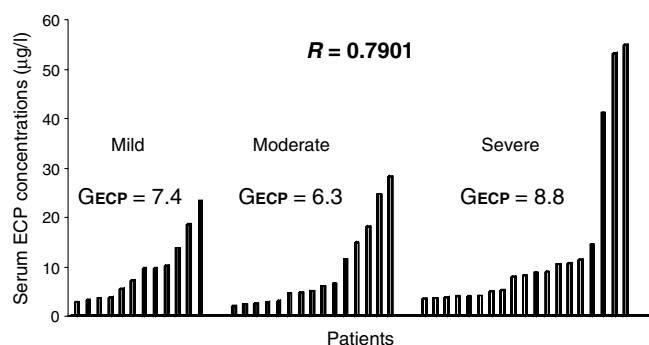


Figure 1. Distribution of serum ECP concentrations ($\mu\text{g/l}$) in patients with various severity of asthma and geometric mean of serum ECP (GeCP) in patients with mild ($n = 12$), moderate ($n = 15$) and severe ($n = 19$) asthma. R = correlation coefficient of serum ECP concentrations in patients with various severity of asthma (Spearman's rank correlation coefficient). n = number of patients in specific groups.

Table 2. Correlation of serum ECP concentrations in patients with exacerbating severe asthma, $n = 15$, in relation to the type of asthma and the degree of exacerbation

	Type/ECP	Degree of exacerbation/ECP
R	-0.5804	-0.8125

R , Spearman's rank correlation coefficient.
Severity (mild/moderate/severe).
Type (atopic/nonatopic).
Degree of exacerbation (mild/moderate/severe).
 n , number of patients.

Table 3. Geometric mean of serum ECP concentrations in patients with atopic and nonatopic exacerbating and stable asthma

Type of asthma	State of asthma	Number of patients	Geometric mean ($\mu\text{g/l}$)
Atopic	Exacerbated	13	9.5
	Stable	12	6.8
	Total	25	8.1
Nonatopic	Exacerbated	16	8.1
	Stable	5	4.1
	Total	21	6.9
Total		46	7.5

asthma (atopic/nonatopic) ($R = 0.88$) (Table 1, Fig. 1). Serum ECP concentration in patients with exacerbating asthma significantly correlated with the degree of exacerbation ($R = 0.9$) (Table 2). The patients with asthma and chronic allergic rhinitis have significantly higher ECP concentrations in serum compared with the patients with asthma but without rhinitis ($R = 0.87$). All these data were consistent with the findings of other authors (4). The findings of higher correlation of serum ECP concentrations in patients with atopic asthma in a stable form in relation to patients with nonatopic stable asthma ($R = 0.831, 0.794$, respectively) were in concordance with the increased activity of eosinophil leukocytes in subjects with atopy (Table 3). The poorest but still significant correlation of serum ECP was with the severity of the disease.

Further investigations on the role of ECP in inflammation of asthma are required.

*Zike Popovica 45
15000 Sabac
Yugoslavia

Accepted for publication 31 January 2003
Allergy 2003; 58:1079–1081
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ISSN 0105-4538

References

1. DJUKANOVIC R. Asthma: bolest inflamacije i remodelisanja disajnih puteva. BIBLID; 0370-8179, 1997;125:319–324.
2. HAMANN JK. Eosinophil mediators. In: BUSSE W, HOLGATE S, editors. *Asthma and rhinitis*. London: Blackwell Science; 1995: 298–316.

3. VATRELLA A, PONTICIELLO A, PARRELLA R, ROMANO L, ZOFRA S, DI LEVA A et al. Serum eosinophil cationic protein (ECP) as a marker of disease activity and treatment efficacy in seasonal asthma. *Allergy* 1996;**51**:547–555.
4. ZIMMERMAN B. Eosinophil cationic protein as a marker of inflammation in childhood asthma. *Allergy Proc* 1994;**15**:134–135.

Two cases of anaphylaxis after dwarf hamster bites

T. Niitsuma*, A. Tsuji, M. Nukaga, A. Izawa, M. Okita, N. Maruoka, S. Morita, M. Tsuyuguchi

Key words: anaphylaxis; hamster; pet allergy.

Case 1. A 23-year-old woman with symptoms of anaphylaxis was admitted in September 1999. From October 1998, she had three dwarf hamsters as pets. The hand with which she usually handled the hamster became itchy, as did her face. On the day of admission, a hamster had bitten the third finger. After 5 min, the bitten finger became warm, red, and swollen. The swelling and redness spread to the arm, and she felt sick. After several minutes, she began to feel dizzy, and the redness spread over the entire body. On admission she required emergency treatment with intravenous aminophylline and hydrocortisone. Symptoms gradually resolved after several hours.

The reaction to common hamster epithelium was class 2 on testing with CAP-RAST (Pharmacia, Uppsala, Sweden) in December 1999.

Anaphylaxis after dwarf hamster bites.

Case 2. A 45-year-old woman was admitted because of symptoms of anaphylaxis in September 2000. Atopic bronchial asthma had been diagnosed at the age of 16 years. For the last 3 years she had two dwarf hamsters as pets. The patient had been bitten on the hands 3 times. She noticed that cough and dyspnea worsened when she cleaned the hamster cage. On the day of admission, one of the hamsters bit the thumb. After several minutes, the bitten thumb became warm, red, and swollen. Moreover, palpitations and malaise occurred. After 20 min, the patient had an asthmatic attack and took inhaled salbutamol. A few minutes later, she fainted at home. On admission, the conscience level was somnolence. She required emergency treatment with inhaled salbutamol sulfate solution and intravenous hydrocortisone. After about 1 h, anaphylactic symptoms gradually resolved.

The reaction to common hamster epithelium was negative on testing by CAP-RAST in October 2000. She stopped keeping hamsters as pets in December 2001. The reaction to specific IgE antibody against dwarf Dzungarian hamsters (*Phodopus sungorus*) epithelium, examined by CAP-RAST in February 2003, was class 4 (24.1 UA/ml).

Several case reports have documented the occurrence of anaphylaxis after rodent bites (1, 2), but reports on anaphylactic reactions to hamster bites are rare (3). A literature search revealed 15 case reports of hamster bites, all of which were from Japan, reflecting the increased popularity of having hamsters as pets. One case was life-threatening. Nine of 13 patients for which the presence or absence of allergic disease was stated had allergic conditions. Serum samples from 10 of 15 patients were examined for specific Immunoglobulin E (IgE) antibody to common hamster epithelium. The test results were

positive in three patients (30.0%), including one of ours. Some patients show an immediate hypersensitivity reaction to hamster saliva on prick or scratch tests (3). Our cases of anaphylaxis secondary to hamster bites should alert emergency-room physicians that serious, potentially life-threatening complications such as anaphylaxis may be caused by hamster bites. Recently, some patients had evidence of the lack of sensitization to common hamster (*Cricetus cricetus* and *Mesocricetus auratus*), which is usually tested when allergy to hamsters is suspected (4). The reaction to specific IgE antibody against dwarf hamster epithelium, as done in patient 2, should therefore also be tested.

*Third Department of Internal Medicine
Tokyo Medical University
6-7-1, Nishi-shinjuku,
Shinjuku-ku Tokyo 160-0023,
Japan

Accepted for publication 7 April 2003
Allergy 2003; **58**:1081
Copyright © Blackwell Munksgaard 2003
ISSN 0105-4538

References

1. TEASDALE EL, DAVIES GE, SLOVAK A. Anaphylaxis after bites by rodents. *Br Med J (Clin Res Edn)* 1983;**286**:1480.
2. HESFORD JD, PLATTS-MILLES TAE, EDLICH RF. Anaphylaxis after laboratory rat bite: an occupational hazard. *J Emerg Med* 1995;**13**:765–768.
3. TOMITAKA A, SUZUKI K, AKAMATSU H, MATSUNAGA K. Anaphylaxis after hamster bites: a rare case? *Contact Dermatitis* 2002;**46**:113.
4. BERTO JM, PELAEZ A, FERNANDEZ E, LOMBARDERO M, FERRER M. Siberian hamster: a new indoor source of allergic sensitization and respiratory disease. *Allergy* 2002;**57**:155–159.