

Delayed skin reactions to metamizol

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Key words: delayed drug allergy; metamizol; nonsteroidal antiinflammatory drugs; patch tests; pyrazolones; skin tests.

PYRAZOLONE DERIVATIVES, especially metamizol, are some of the most prescribed analgesics throughout the world. They are frequently implicated in severe and unpredictable reactions. According to the etiologic mechanism, the following classification is proposed (1, 2):

Three cases of delayed drug allergy.

1. Allergic reactions, usually anaphylaxis and urticaria/angioedema, probably due to an IgE-mediated mechanism. In these cases, patients tolerate different nonsteroidal antiinflammatory drugs (NSAIDs).
2. Nonallergic NSAID hypersensitivity (3) (NSAID intolerance), probably via cyclooxygenase inhibition, leading to an overproduction of leukotrienes. NSAIDs can precipitate asthma attacks and/or urticaria or angioedema.
3. Severe skin and/or mucosal reactions, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, and contact dermatitis. Probably a cell-mediated mechanism is implicated.
4. Other clinical syndromes, such as agranulocytosis, thrombocytopenia, and vasculitis whose mechanism is unknown.

Here we present three cases of adverse skin reactions to systemic administration of metamizol (Nolotil).

Patient 1: An 18-year-old man began treatment for pharyngoamygdalitis with amoxicillin (500 mg/8 h), metamizol (500 mg/8 h) and acetaminophen (650 mg/8 h) orally. After 48 h he developed a generalized maculopapular exanthema without pruritus. The clinical picture was spontaneously resolved in 15 days with mild desquamation.

Patient 2: A 61-year-old woman who received metamizol 2 g and clarithromycin 500 mg intravenously. After 12 h she developed a maculopapular exanthema with pruritus. This reaction was resolved in 15 days after antihistamine treatment.

Patient 3: An 80-year-old woman received metamizol 500 mg/8 h orally for 4 days. Two days after withdrawal, she developed a generalized exanthema with progressive vesiculation and exudation. The diagnosis was eczematous dermatitis.

Allergic tests: We performed skin prick tests (SPT) with metamizol at 400 mg/ml, intradermal tests (ID) with dilutions from 1 : 1000 to 1 : 10 and patch tests (PT) with Leukotest on each patient's back with metamizol 10% in water. Readings of SPT and ID were done at 20 min, 6 h, 12 h, 24 h and 48 h. Patch tests were read at 48 h and 96 h. SPT, ID and PT were also performed in 10 control patients. In patients 1 and 2, we also carried out skin tests and single-blind placebo-controlled challenge tests (SBPCCT) with the other implicated drugs. Challenge with acetylsalicylic acid was performed in order to confirm (or not confirm) nonallergic NSAID hypersensitivity. Challenges with metamizol were not carried out for ethical reasons and skin tests results.

The results of the study are shown in Table 1. Most allergic reactions to pyrazolone derivatives are those whose suspected mechanism is IgE-mediated

Table 1. Results from skin tests and placebo-controlled challenge with analgesics

Patient	Drug	SPT	ID	PT	SBPCCT
1*	Met	–	–	++/++	NT
	Amo	–	–	–	–
	Ace	–	NT	NT	–
	Cla				
	ASA				–
2†	Met	–	+	NT	NT
	Amo				
	Cla	–	NT	NT	–
	ASA				–
3‡	Met	+	+	++/++	NT
	Amo				
	Cla				
	ASA				–

SPT, ID and PT were negative in 10 control patients.

ASA, acetylsalicylic acid; Ace, acetaminophen; Amo, amoxicillin; Cla, clarithromycin; ID, intradermal tests; Met, metamizol; NT, not tested; PT, patch tests; SBPCCT, single-blind placebo-controlled challenge; SPT, skin patch tests.

* ID positive at 12 h; negative at 20 min and 6 h.

† SPT positive at 24 h and 48 h; negative at 20 min, 6 h and 12 h.

‡ ID positive at 24 h and 48 h; negative at 20 min, 6 h and 12 h.

(e.g. anaphylaxis or urticaria) or cell mediated (contact dermatitis and fixed drug eruption) (4–6). In our country (probably due to high a prescription rate, usually of metamizol) pyrazolones cause approximately 47% of all adverse reactions to NSAIDs and 10% of adverse reactions to all drugs (7). SPT and ID tests, read at 12, 24 and 48 h, and patch tests prove useful in the diagnosis of delayed allergy to metamizol, and they avoid the need to perform challenges. Considering these skin and patch tests results, these adverse reactions to metamizol are probably due to an immunological mechanism that is cell mediated.

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Occupational asthma to grain pests

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Key words: *Anisakis simplex*, baker's asthma; cereal pests; *Ephestia*; *Eurygaster*.

WORKERS WHO ARE occupationally exposed to cereal dust have a high prevalence of asthma (1). We have found an important prevalence of sensitization to

Crossreactivity with *Anisakis simplex*.

Anisakis simplex in patients who suffered from baker's asthma without problems after ingesting raw fish. We describe here a cereal worker who suffered from IgE-mediated occupational asthma because of two highly prevalent cereal pests in our area: *Eurygaster austriaca* (family Pentatomidae, order Heteroptera) and

Ephestia kuehniella (family Phycitidae, order Lepidoptera). The patient was not sensitized to cereal flour or mites but presented skin tests positive to *A. simplex* without problems after eating fish.

The skin prick tests (SPT) and serum IgE levels (Pharmacia Diagnostics CAP-FEIA or in-house RAST ELISA) were used to evaluate the patient's sensitivity to these pests and to *A. simplex*. Clinical sensitivity to *Eurygaster* and *Ephestia* was measured by bronchial challenge test according to previous publications (2). Allergen cross-reactivity with *A. simplex* was evaluated by RAST inhibition. The controls were a pool of 40 asthma patients with different etiologies.

SPT were positive to *Eurygaster*, *Ephestia* and *A. simplex*. A high level of IgE antibodies was measured against the three parasites. RAST inhibition showed cross-reactivity between *Eurygaster* and *A. simplex* (Fig. 1).

The pathogenesis of the respiratory symptoms of cereal workers remains obscure when sensitization to cereal or mite allergens cannot be proved.

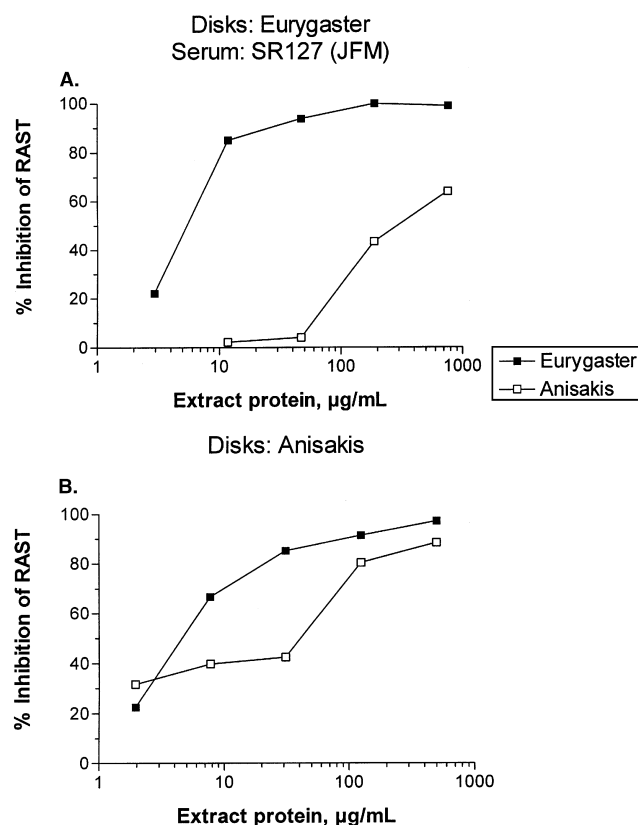


Figure 1. RAST inhibition of (A) *Eurygaster* disks and (B) *Anisakis simplex* disks, using serum SR 127 (JFM).

Although sensitization to *Ephestia* as a cause of occupational asthma has been described (3) we have not found any report about *Eurygaster* as a cause of asthma. The clinical importance of pests in causing baker's asthma should not be underestimated (4). The results showed allergenic cross-reactivity between *A. simplex*, *Eurygaster* and *Ephestia*. This may be a cause of sensitization to *A. simplex* in cereal workers, not related to fish ingestion.

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Vascular rings can give cough

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Key words: asthma; cough; vascular rings.

VASCULAR RINGS result from abnormalities of the aortic arch; symptoms are often

manifest early in life (the first year). Some forms, like an aberrant right subclavian artery, became symptomatic later in life and often cause no signs. Symptoms may be due to tracheal or esophageal compression, the main signs being stridor, dyspnea, recurrent respiratory infections, and dysphagia (1, 2).

We present the case of a vascular ring with atypical manifestation. An 18-year-old woman referred episodes of paroxysmal cough in springtime for two years (asymptomatic for the rest of the year). We performed skin prick tests, which were positive to several pollens and negative to mites, fungi, and danders. Total serum IgE level (CAP Pharmacia, Uppsala, Sweden) was 94 KU/l and specific IgE to pollens and mites was < 0.35. Haemogram, biochemistry and ionotest were normal. A Mantoux test was negative. Pulmonary function tests showed a forced expiratory volume in 1 s (FEV₁) of 2900 (90%), and a forced vital capacity (FVC) 3800 (105%). A methacholine challenge test performed in springtime was negative. Chest and sinus X-rays did not reveal any abnormality. The diagnosis was cough with pollen sensitization, indicating antihistaminic and bronchodilator treatment. The woman had a poor evolution, with monthly catarrh, and a persistent nonseasonal cough with nocturnal predominance.

We performed other explorations: plethysmography and thoracic CT scans were normal. In view of the nocturnal cough we suspected gastroesophageal reflux and therefore performed a barium esophagram. This revealed a posterior–anterior indentation of the esophagus, compatible with aberrant subclavian artery without evidence of gastroesophageal reflux (Fig. 1). The presence of a left aortic arch with aberrant right subclavian artery travelling behind the esophagus and compressing it, was confirmed by arteriography (Fig. 2). Invasive treatment was ruled out by vascular surgery, and with codeine therapy she remains partially asymptomatic.

This case supports previous evidence suggesting later manifestation of aberrant

Symptomatic vascular rings are a rare cause of isolated cough.



Figure 1. A barium esophagram revealed posterior–anterior indentation of the esophagus (arrows), compatible with aberrant subclavian artery without evidence of gastroesophageal reflux.

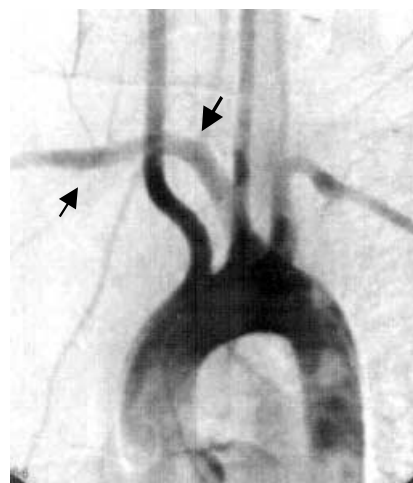


Figure 2. Arteriography shows left aortic arch with aberrant right subclavian artery travelling behind the esophagus (arrows).

subclavian artery symptoms. However, in contrast to the cases described previously in the clinical form, she presented cough as the main symptom in the absence of an esophageal clinic (1–4). Although isolated cough is a rare manifestation of vascular ring, such a diagnosis should be considered in patients with this sign, when there is worsening or an unsuccessful response to antiasthmatic treatment.

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Skin reactions to pine processionary caterpillar

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Key words: caterpillar; children; cutaneous lesions; IgE; *Thaumetopoea pityocampa*.

THAUMETOPOEA PITYOCAMPA (TP) is one of the most relevant species of Lepidop-

tera causing damage to population in Europe (1, 2).

We describe five cases of different cutaneous reactions to TP in children in which the role of an IgE-mediated mechanism was researched.

The cutaneous lesions were diagnosed as reactions to TP, considering the clear relationship between the clinical features and the typical distribution of lesions and contact or exposure to TP. Skin prick tests (SPT) with extract of whole caterpillar (L5) were performed in all children. It was prepared at a dilution of 1 : 10 w/v in accordance with previous studies (2) and it was tested on 10 nonexposed children as a control. Estimation of delayed immunity to TP was not performed due to the age of the patients and the lack of reliable proof.

Data obtained from the patients are shown in Table 1. Positive SPT to TP were found only in the fifth case (8 × 5 mm). This child had a total IgE of 690 kU/l and blood eosinophils were normal; IgE immunoblotting detected several bands on caterpillar extract with apparent molecular weights between 45 and 4 kDa. He was diagnosed with IgE-mediated contact urticaria in accordance with the EAACI revised nomenclature (4).

TP is capable of producing skin lesions. Although a toxic-irritative mechanism has been implicated in these reactions (1), an IgE-mediated hypersensitivity mechanism has been found in some cases (2). We present five cases of different cutaneous reactions to TP in

Five children with cutaneous reactions to *Thaumetopoea pityocampa*.

children. One of these types, the pustular contact dermatitis, has not yet been described. Pustular contact reactions to patch tests have been found more frequently in atopic patients, and are considered irritant phenomena; this might explain our case in which direct contact with caterpillar hairs occurred. Maculopapular dermatitis is the typical delayed cutaneous reaction to TP (1). Bullous dermatitis caused by processionary caterpillars is more unusual, although it has been described (3). An IgE-mediated mechanism has only been found in one child with contact urticaria in this study.

We think the type of reaction provoked by TP depends on several factors, mainly previous exposure to and degree of contact with caterpillars. The natural evolution after repeated contact seems similar to that with bites from other insects, although wider research should be performed to confirm these hypotheses.

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Table 1. Comparison of five children with different cutaneous reactions to pine processionary caterpillar *Thaumetopoea pityocampa*

Case	Sex/age (years)	Episodes	Clinical features		
			Cutaneous lesions	Latency/duration	IgE mechanism
1	m/4	2	Sterile pustules in palms of both hands	24 h/5–6 days	No
2	f/8	1	Bullous and pruritic eruption in legs	2–3 h/6–7 days	No
3	m/2	1	Papuloerythematous eruption	3–4 h/3–4 days	No
4	f/3	Several	Very pruritic in neck and high extremities		No
			Papuloerythematous eruption	3–4 h/3–4 days (first episodes)	
5	m/9	Several	Very pruritic in high extremities	Immediately/3–4 days (last episodes)	Yes
			Papuloerythematous eruption	3–4 h/3–4 days (first episodes)	
			Very pruritic in neck and high extremities	Immediately/ < 1 day (last episodes)	

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Gentamicin-induced anaphylaxis

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FOR DECADES gentamicin has been used successfully as an antibiotic. Adverse effects are mainly toxic, like nausea, diminution of hearing, and irritant contact dermatitis (1, 2). The major causes of allergic contact dermatitis are gentamicin-containing eye- or ear-drops (1-3). Provocation of allergic contact dermatitis by systemic application has been observed (4,5). Reported systemic allergy, including drug-induced cytopenia (6) and exanthema (7), is very rare.

We report a case of systemic anaphylaxis after intravenous gentamicin. A 70-year-old woman was referred for dermatosurgery because of large, malodorous venous leg ulcers with a history of contact sensitization (lanolin, cetylstearyl alcohol, adeps lanae, amerchol, geraniol). Some years ago she had a total hip endoprosthesis for coxarthrosis.

She had perioperative antibiotics with intravenous cefotiam followed by intravenous gentamicin, according to bacterial resistance. During the first injection of gentamicin she developed anaphylaxis and was treated in intensive care for 5 days. A few weeks after full recovery,

After intravenous injection.

Table 1. Patch test results

Drug preparation	24 h	48 h	72 h	96 h
Framycetin sulfate 10% in pet.	neg	(+)	+	+
Gentamicin sulfate 20% in pet.	neg	+	+	++
Kanamycin sulfate 10% in pet.	neg	+	+	++
Neomycin sulfate 20% in pet.	neg	+	+	++
Nebacetin solution (neomycin)	neg	neg	neg	+
Neomycin powder	neg	(+)	+	+
Cefotiam i.v. solution (Spizef)	neg	neg	neg	neg

Pet., petrolatum

we performed open patch testing that showed type IV sensitization to gentamicin sulfate and cross-reacting antibiotics (Table 1). A rubbing test with gentamicin caused a pruritic reaction after 20 min and erythema after 5 days. Positive prick and scratch test reactions were found for gentamicin. The patient noted a mild systemic reaction (tachycardia, vertigo, nausea). Therefore we did no i.c. testing. Sulfite intolerance must be considered in cases of suspected gentamicin allergy (8) although it had no role in this case because we used a sulfite-free preparation.

Anaphylaxis to gentamicin is a rare event (9). Sensitization from pretreatment with other aminoglycoside antibiotics can be responsible. We observed a combined type IV/type I sensitization. We suspect sensitization to gentamicin due to previous treatments with neomycin solution, framycetin cones, and gentamicin ointment.

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Severe hypoproteinemia in infant with AD

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Key words: atopic dermatitis; elimination diet; hypoproteinemia.

ATOPIC DERMATITIS (AD) is a recurrent chronic disease (1). Frequent relapses

induce the parents of children with AD to self-impose dietary restrictions and seek help from alternative medicine (2, 3).

During inappropriate elimination diet.

We report a case of an exclusively breast-fed girl infant, who developed eczema at 15 days old. The mother was dissatisfied by the outcome of a pediatrician-suggested diet, so she consulted a naturopathic doctor who prescribed a "cytotoxic" test—a fraudulent alternative diagnostic procedure (4, 5). Based on the results of this test, at 5 months the child's daily diet consisted of three 220 ml-meals of rice-milk, three spoons of rice-cream, a pap of rice-cream in vegetable soup with sunflower oil, and one apple. After about 20 days of this diet, acrocyanosis and edema appeared on her feet and legs, followed by a reduction of diuresis.

When hospitalized, she was in a poor clinical condition with generalized edema (Fig. 1) and low diuresis. She weighed 7480 g. Blood and urine findings were normal except for the following: total proteins 2.85 g/dl; albumin 1.48 g/dl (52%); total serum IgE 273 kU/l; specific serum IgE (Pharmacia CAP system) for cow's milk class 3 (12.4 kU/l), for soy bean class 2 (3.35 kU/l), egg white class 5 (63.1 kU/l), wheat class 3 (5.86 kU/l), peanuts class 2 (3.39 kU/l), peas class 3 (12.8 kU/l). Proteins were not found in the urine. After examination we introduced an extensively hydrolyzed formula (Nutramigen; MediJohnson, Milan). After 7 days of this diet diuresis increased (from 930 to 1240 ml) and weight decreased to 6780 g (resulting in a total weight loss of 700 g). Eczema improved and scratching was less evident.

Hematic examinations performed on day 7 showed total proteins of 5.11 g/dl, and albumin 3.27 g/dL (63.9%).

The infant girl described in the present report had AD during exclusive breastfeeding (6). This condition requires the intervention by an expert because it may involve interruption of breastfeeding, giving a diet based on



Figure 1. Generalized edema more evident (A) in the face and (B) in the legs (fovea sign) in an infant with atopic dermatitis and hypoproteinemia.

highly hydrolyzed milk—even an aminoacid mixture (7).

In our case, the mother—discouraged by the pediatrician's interventions—imposed a diet without medical supervision. It was very low in protein (4.2 g/day), lipids (7.4 g/day), and calories (650 kcal/day), but was high in sugars (132.2 g/day) (daily requirements protein 13.5 g, lipids 37.5 g, 718 kcal, sugar 74.5 g), resulting in hypoproteinemia, edema and low diuresis. Hospitalization and a diet based on extensively hydrolyzed milk brought about a rapid recovery.

This case highlights the potential danger of inappropriate elimination diets in

infants with AD, who are at risk of developing hypoproteinemia because of the albumin-rich exudate that may be lost through lesions (8).

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