Storage Mites in Flour Samples in Wellington, New Zealand

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Key words: Storage mites. Flour. Thyreophagus entomophagus. Tyrophagus communis.

Palabras clave: Ácaros de almacenamiento. Harina. *Thyreophagus entomophagus. Tyrophagus communis*

Stored grains and seeds have been known to be prone to contamination by mites for well over 100 years [1], but it was not until 1993 that the first documented case of anaphylaxis to mite-contaminated flour was reported [2].

To our knowledge, no studies on mite contamination of flour samples have been reported from New Zealand, although storage mites have been previously observed in a flour sample [3] and Tyroglyphid mites have been found in stored products [4]. The objective of our pilot study was to determine the incidence of mite contamination of store-bought and domestic flour-based products.

We purchased 23 flour-based products from stores and supermarkets and obtained 54 samples of flour-based products from domestic homes. We recorded brand, type of product, purchase date, time since the product had been opened, and method of storage. The flour types are shown in the Table. Ethical approval was obtained from the Central Districts Ethical Committee.

Each flour sample was transferred to a large container and thoroughly mixed. Six subsamples were then taken by spatula from different areas of the sample and examined under a dissecting microscope. Live mites were removed with a fine probe and mounted on microscope slides in Brun's medium. Mites were identified with the aid of a compound microscope using the keys of Hughes [5] and Fan and Zhang [6].

None of the store or supermarket samples had evidence of live mites. Four of the 54 domestic samples contained live mites, corresponding to an incidence of 7.4%. All 4 contaminated flour samples had been stored in kitchen cupboards for longer than 1 month. The mite species identified were

• *Thyreophagus* and *Tyrophagus* species from a wholemeal flour sample stored in a plastic container. We were unable to identify these at species level as no repeat sample could be obtained.

Table. Types of Flour Samples Collected

	Homes	Supermarkets
Wholemeal flour	6	3
Rice flour	1	1
Plain wheat flour	27	5
Buckwheat flour	0	1
Rye flour	2	2
Pancake mix	0	2
Corn flour	2	1
Custard powder	2	1
Oat bran	3	1
Bread mix	3	2
Gluten-free flour	1	0
Scone mix	1	0
Cake/muffin Mix	0	4
Indian flour[a]	5	0
Chickpea flour	1	0
Total	54	23

[a]Chapati, Bajri, Atta, Urid.

• *Thyreophagus entomophagus* from a high-grade wheat flour sample stored in its original packet.

• *Tyrophagus communis* from a wholemeal flour sample stored in a plastic container.

• *Tyrophagus communis* from a wholemeal flour sample stored in a paper bag.

This study has shown a 7.4% incidence of storage mites in flour-based products from domestic homes. The species found have previously been shown to cause allergic reactions in house dust mite–sensitized asthmatics [7].

A similar study conducted in Japan reported an incidence of 5.5% mite contamination in domestic wheat flour packages. Their study also found an incidence of 1.7% mite contamination in shop-bought samples. None of the shop-bought samples in our study were found to be contaminated.

One limitation of our study is that we did not incubate our negative samples and therefore possibly missed some larvae with the potential to grow into live mites [9]. We may also have missed some dead mite bodies as these are difficult to visualize in flour samples. Thus, the true incidence of contamination may possibly have been higher than detected.

To our knowledge, no studies in New Zealand have determined the prevalence of storage mite sensitization through either skin prick testing or specific immunoglobulin E levels. There have been undocumented incidences of anaphylaxis induced by storage mite-contaminated flour. Given the occurrence of storage mite-infested flour, such studies are warranted in New Zealand.

Storing flour for long periods of time increases the chance of mite contamination and it is advisable to store opened flour

samples in sealed containers in a refrigerator [10]. Patients with house dust mite-sensitization or aspirin sensitivity should be warned that they may be susceptible to anaphylaxis after eating food prepared with storage mite-contaminated flour products.

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An Immediate Hypersensitivity Reaction Caused by Tolperisone Hydrochloride

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Key words: Drug hypersensitivity. Tolperisone hydrochloride. Urticaria.

Palabras clave: Hipersensibilidad a fármacos. Clorhidrato de tolperisona. Urticaria.

Tolperisone is a voltage-gated sodium and calcium channel blocker and a centrally acting muscle relaxant that has been used for the symptomatic treatment of spasticity and muscle spasm and as a complex therapy of neuromuscular pain. Tolperisone-type muscle relaxants exert their spinal reflex inhibitory action predominantly via a presynaptic inhibition of the transmitter release from the primary afferent endings via a combined action on voltage-gated sodium and calcium channels. The drug has a similar chemical structure to that of lidocaine, and it also has a membrane-stabilizing effect.

Tolperisone is used worldwide and is known for its safety and good tolerability. Side effects include abdominal pain, nausea, and dizziness. However, there have been rare reports that tolperisone may induce hypersensitivity reactions [1-2].

We report the case of a 57-year-old man who presented with several episodes of pruritus, erythema, and facial edema following ingestion of several drugs to treat neuromuscular pain. Specifically, he was taking anti-inflammatory drugs such as diclofenac sodium and meloxicam, in addition to tolperisone and a combined preparation of vitamins B and lidocaine hydrochloride. The skin symptoms usually developed within 3 to 4 hours of drug intake but the patient did not know which of the drugs was responsible for the reaction. He was therefore admitted to our allergy unit with a suspect diagnosis of drug hypersensitivity to analgesics and/or muscle relaxants.

Informed consent was obtained from the patient for skin tests and challenges. The allergy work-up included a single-blind oral challenge with acetylsalicylic acid to exclude hypersensitivity to nonsteroidal anti-inflammatory drugs; a skin prick test (1:1 dilution), intradermal tests (1:100-1:10 dilutions), and an incremental subcutaneous challenge with lidocaine (combined parenteral analgesic preparations, such as a combination of diclofenac and lidocaine hydrochloride); and a skin prick test (1:1 dilution), intradermal tests (1:1000-1:10 dilutions), and an open challenge with tolperisone according to European Network for Drug Allergy recommendations [3].

The single-blind oral challenge with acetylsalicylic acid and the skin tests with lidocaine were negative, as were the skin prick and intradermal tests with the parenteral preparation of tolperisone. Nonetheless, after taking 25 mg of tolperisone, the patient developed a systemic reaction with generalized massive urticaria (Figure) and anxiety. His blood pressure and heart

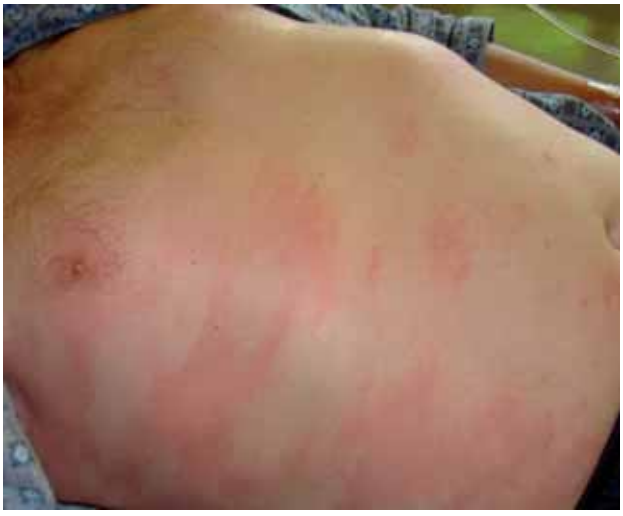

Figure. Urticaria on the abdomen following ingestion of 25 mg of tolperisone.

rate were within normal ranges and no bronchoconstriction was observed. He was successfully treated with parenteral antihistamines and corticosteroids, with complete recovery within about 4 hours.

We did not demonstrate tolperisone-specific immunoglobulin (Ig) E by skin testing, although the clinical symptoms were compatible with an immediate hypersensitivity reaction. Despite the negative skin tests, hypersensitivity to tolperisone was demonstrated by an oral challenge with 25 mg. The symptoms developed within minutes, indicating either an IgE-dependent reaction or a non-IgE dependent reaction (ie, direct histamine release from mast cells was probably involved). The case we describe confirms the notion that the sensitivity of skin tests is limited in drug hypersensitivity and that, in certain cases, hypersensitivity can only be confirmed by drug challenge tests.

There have been very few reports of hypersensitivity to tolperisone, with the first case described by Aleksandrov in 1974 [4]. There have also been 2 reports of hypersensitivity due to oral tolperisone, with symptoms ranging from urticarial rash to anaphylactic shock [5]. Kwasniewski et al [6] described a case of anaphylactic shock caused by oral tolperisone; hypersensitivity to this drug was confirmed when the patient developed anaphylactic shock following skin testing. In our opinion, thus, hypersensitivity to tolperisone is not as rare as is generally thought and the risk of such a reaction should be borne in mind by, at least, general practitioners and neurologists who prescribe this drug and allergists who diagnose drug hypersensitivity.

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Tracheomalacia: Uncommon Onset in a Patient With Severe Asthma

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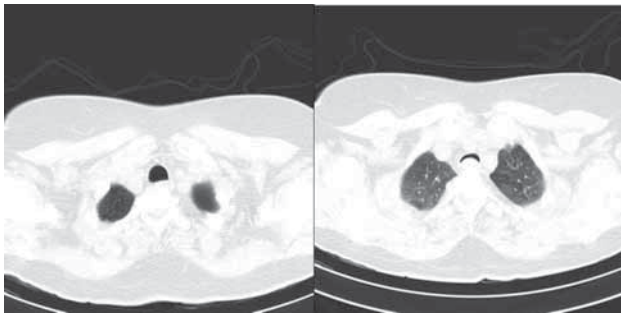
Key words: Asthma. Bronchitis. Bronchoscopy. Tracheomalacia.

Palabras clave: Asma. Bronquitis. Broncoscopia. Traqueobroncomalacia.

We report the case of a 57-year-old seamstress, ex-smoker since 2005, with a history of mild repetitive bronchitis 2 to 3 times a year in the coldest months of the year since she was 23-years-old. She was referred to our allergy unit with persistent hoarseness, a barky cough, and dyspnea on minimal exertion. In the last 6 months of 2007, she had had several episodes of bronchitis, which had required 3 emergency admissions, despite treatment with fluticasone/salmeterol 500/50 mcg twice daily, montelukast 10 mg daily, and salbutamol 200 mcg/ipratropium 40 mcg 3 times daily.

Skin prick testing (SPT) with a series of commercial aeroallergens (Laboratorios LETI SL, Barcelona, Spain) was positive for dust mites and grass and olive pollen. Total immunoglobulin (Ig) E was 172.1 U/mL. Specific IgE assays were positive for dust mites (*Dermatophagoides pteronyssinus*, 7.6; *Dermatophagoides farinae*, 10.3; *Dermatophagoides microceras*, 9.9; *Euroglyphus maynei*, 1.08 kU/L) and grass pollen (Lolium, 12.4; Cynodon, 14.9; Phragmites, 2.28 kU/L). Chest radiography showed signs compatible with chronic

A



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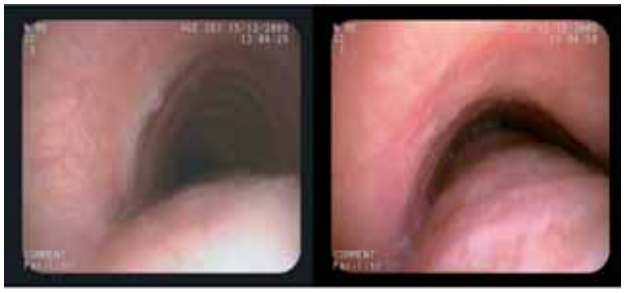

Figure. A, Computed tomography scan during inspiration and expiration. B, Bronchoscopy images during inspiration and expiration.

obstructive pulmonary disease (COPD), and a paranasal sinus X-ray showed sinusitis. The patient also had mild airway obstruction, as assessed by spirometry, and a positive bronchodilator test.

The patient was diagnosed with persistent moderate allergic asthma with sinusitis. We added to her previous treatment budesonide 800 mcg twice daily, tiotropium bromide 22.5 mcg daily, and omalizumab 300 IU/mL every 4 weeks. The progressive improvement in functional and clinical symptoms, together with the fact that no further episodes of bronchitis occurred, led to the decision to progressively withdraw budesonide, tiotropium, and montelukast. After 6 months of treatment with omalizumab, the patient only reported a barky cough, difficult expectoration, and dyspnea on minimal exertion.

The patient developed respiratory decompensation in August and October 2008, after restarting work as a seamstress (she had been off work for more than a year). Since May 2009, she has had 5 repeated episodes of bronchitis, despite treatment with systemic corticosteroids, mucolytics, and antibiotics. A computed tomography scan showed severe tracheobronchomalacia (Figure A) and a later bronchoscopy (Figure B) confirmed an 80% reduction in the cross-sectional area of the tracheobronchial lumen.

The patient started respiratory rehabilitation and treatment with fluticasone/salmeterol 500/50 mcg twice daily and oral and nebulized acetylcysteine. The options of surgery and stent placement were rejected in 2009 because of the considerable extent of the tracheobronchomalacia. The dyspnea has persisted despite treatment with continuous positive airway pressure. Novel laser treatment of the rear wall of the trachea has been scheduled for 2011. The patient currently presents 1 episode of low respiratory infection per month.

Tracheomalacia is a weakening of the lateral or anterior walls of the airway, possibly due to the destruction and/or thinning of cartilaginous rings, limiting airflow. It is characterized by a decrease of at least 50% in the cross-sectional area of the tracheobronchial lumen. Clinical manifestations include dyspnea, cough, sputum production, and hemoptysis. Bronchoscopy visualization of dynamic airway collapse remains the gold standard for the diagnosis of this condition [1].

Because of the difficulty in differentiating between COPD, asthma, and tracheomalacia, we were unable to establish which of the conditions had occurred first in our patient. Loring et al [2] sought to establish the relationship between central airway collapse and its contribution to expiratory flow limitation in patients with COPD and asthma. Of a total of 80 patients with suspected or proven tracheomalacia, 40% had COPD and 24% had asthma. Although the coexistence of tracheomalacia and COPD is well known, the implications of this coexistence are not fully understood. The pathologic progression of COPD to tracheomalacia has not yet been clearly demonstrated either [1].

Tracheomalacia is frequently recognized but infrequently diagnosed, and it is often mistaken for other obstructive ventilatory disorders [3]. We believe that before establishing a diagnosis of refractory asthma, it is important to consider and exclude other diseases such as tracheomalacia, COPD, bronchiectasis, cystic fibrosis, and vocal cord dysfunction [4].

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A Study of the Variability of the in Vitro Component-Based Microarray ISAC CDR 103 Technique

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Key words: In vitro test. Component-resolved diagnosis (CRD). Specific IgE. Microarray. Reproducibility.

Palabras clave: Test in vitro. Diagnóstico por componentes. IgE específica. Microarray. Reproducibilidad.

Specific immunoglobulin (Ig) E determination against allergens using the in vitro component-resolved diagnostic microarray technique (ImmunoCap ISAC CRD 103; Phadia, Uppsala, Sweden), has improved diagnostic accuracy [1-4], but few studies have analyzed the reproducibility of this semi-quantitative technique [5].

Reproducibility is analyzed in successive determinations carried out using the KS11 control serum provided with the test kit. This serum contains different concentrations of specific IgE against 10 allergens: rApi g 1, rBet v 2, nBos d 4, nGal d 1, nGal d 2, nGal d 3, rHev b 8, rPhl p 5, rPhl p 6, and rPhl p 7. The resulting data are then used to generate a standard curve that relates the fluorescence signal of the ISAC CRD103 microarray acquired by a laser scanner (LuxScan 10K/A, CapitalBio, Beijing, China) to known concentrations of specific IgE measured in ISAC standardized units (ISUs).

The microarray assay was performed according to the manufacturer´s instructions. The KS11 serum was analyzed for intraslide variability (4 times), intra-assay variability (8 times), and interassay variability (12 times). The reproducibility of the technique was analyzed by calculating the intraclass correlation coefficient (ICC) for overall variability using the software package SPSS 15.0 and the coefficient of variation (CV) for the variability of each of the 10 allergens using Microsoft Excel 97.

According to the classification of Fleiss [6], the ICCs were almost perfect for all 3 tests, with a score of 0.998 for intraslide variability ($P<.0001$), of 0.997 for intra-assay variability ($P<.0001$), and of 0.989 for interassay variability ($P<.0001$).

For the intraslide analysis, 7 of the 10 allergens detected by KS11 had CV values of 10% or less, and for the intra-assay analysis, 5 allergens had CV values of 15% or less. In the interassay analysis, all of the allergens had CV values of over 20%, three allergens (nBos d 4, rPhl p 5, and rPhl p 6) had values of between 20% and 30%, while 5 (rBet v 2, nGal d 1, nGal d 2, rHev b 8, and rPhl p 6) had values of under 40%. The remaining 2 allergens, rApi g 1 and nGal d 3, had values of 44% and 51%, respectively (Table).

Table. Coefficients of Variation (CV) for the 10 Allergens Detected by the Control Serum KS11 in the ISAC CRD 103 Microarray for Intraslide, Intra-Assay, and Interassay Variability Assessment

Control Serum (KS11)	Intraslide CV, %	Intra-assay CV, %	Inter-assay CV, %
rApi g 1	21	27	44
rBet v 2	7	12	32
nBos d 4	10	8	20
nGal d 1	9	39	39
nGal d 2	4	11	36
Gal d 3	117	130	51
Hev b 8	7	19	31
Phl p 5	7	10	23
Phl p 6	23	28	33
Phl p 7	3	9	26

While excellent results were observed for overall intraslide, intra-assay, and interassay variability, rApi g 1, nGal d 3, and rPhl p 6 all showed high variability in the individual analyses. Jahn-Schmid et al [5] reported similar results for rPhi p6. Moreover, in our study, nGal d3 had the highest CV. This suggests the existence of a technical problem related to the adhesion of the allergen to the slide, highlighting the need to validate each allergen individually. This requirement should be even stricter for allergens used to establish the standard curve, and to define specific IgE levels for all the allergens in the ISAC CRD 103 microarray.

Moreover, the fact that the variability of the data in the interassay analysis can be improved suggests that this technique can be used to assess sensitization profiles but is not appropriate for monitoring sensitization.

On the basis of our results, it can be concluded that, overall, the semi-quantitative ISAC CDR 103 method is a reproducible technique. However, the high variability detected for certain allergens suggests that this in vitro tool is valid for an initial study but probably not for follow-up or monitoring studies, or for establishing therapeutic decisions. In such cases, we recommend the use of quantitative tests such as specific IgE determination.

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Selective Hypersensitivity With Positive Immediate Skin Tests to Nimesulide

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Key words: Anaphylaxis. Nimesulide. Non-irritating drug-concentrations. Skin tests.

Palabras clave: Anafilaxia. Nimesulida. Concentraciones no irritativas de medicación. Pruebas cutáneas.

In a recent report of selective hypersensitivity to nimesulide with urticarial reactions [1], skin tests (skin prick testing [SPT] and intradermal testing [IDT]) with nimesulide and Sepharose-radioimmunoassay were unable to demonstrate the existence of an immunoglobulin (Ig) E–dependent mechanism.

In July 2008, a 44-year-old man with a history of mild allergic rhinitis and documented sensitivity to *Dermatophagoides* species consulted for systemic urticaria in January and urticaria with acute diarrhea in April. Both reactions had appeared within 15 minutes of taking a 100-mg tablet of nimesulide for a headache. The patient had taken these tablets at least 10 times in the previous 2 years, without adverse reactions. The symptoms disappeared spontaneously within 40 minutes, and the patient had since tolerated diclofenac and acetylsalicylic acid (ASA).

The patient and 3 healthy nonatopic individuals, who usually tolerated nimesulide, underwent parallel SPT with 1, 5, 10, and 20 mg/mL concentrations of nimesulide in distilled water. The tests were negative in the controls but induced a positive skin response with a dose-related wheal-and-flare reaction in the patient (Figure 1A).

The patient agreed to undergo a series of single-blind placebo-controlled oral provocation tests (OPTs), 1 week apart, with increasing doses of nimesulide, celecoxib, and ASA. Under controlled clinical conditions, the OPTs were performed by administering, at 90-minute intervals, 2 consecutive placebo doses (talc) followed by the drugs at a dose of l:100, 1:20, 1:10, and 1:3, and finally at the remainder of the therapeutic dose. ASA and celecoxib did not induce any adverse clinical reactions, but the nimesulide OPT was stopped after the second dose because the patient experienced diffuse urticaria, vomiting, and an associated 25% decrease in basal systolic blood pressure after 10 minutes. Intramuscular epinephrine 1 mg, intramuscular chlorpheniramine, and intravenous methylprednisolone were administered, and the symptoms resolved within 40 minutes.

In March 2009, according to Empedrad et al [2], we carried out an in vivo skin test study in 30 healthy volunteers, all regular users of nimesulide with no adverse reactions, to identify the highest concentrations of nimesulide that did not produce skin irritation. Due to the poor solubility of nimesulide in water (0.014 mg/mL), we performed the tests with a solution of nimesulide (Fingrange-Pharma, London, UK) in polyethylene-glycol 400 (PEG 400; ST-Trading- LLC, New York, USA), a semi-polar solvent with an optimal solubility of 63.120 mg/mL for nimesulide [3].

The nonirritating concentrations of nimesulide-PEG 400 solutions were identified as 20 mg/mL for SPT and 1 mg/mL for IDT. We then retested our patient with nimesulide- PEG 400 solutions at increasing concentrations and the previously effective nimesulide-water solutions. Of interest, in the case of the nimesulide-water solution, only IDT at a concentration of 20 mg/mL was positive. In the case of the PEG 400 solution, SPT was positive only at a concentration of 20 mg/mL, whereas IDT was positive from 0.2 mg/mL upwards; there was, however, no increase in the wheal-and-flare reaction with increasing concentrations of the drug up to the maximum nonirritating dose (Figure 1B).

In October 2009, skin tests performed with the nimesulide-water and nimesulide-PEG 400 solutions were negative. The spontaneous modulation of skin reactivity observed in the patient suggests that skin tests for nimesulide should be performed early because specific skin sensitivity to this drug seems to decrease quickly after the adverse drug reaction, in a similar manner to that reported for ß-lactam antibiotics [4].

The positive skin tests using nonirritating concentrations of nimesulide and the selective OPT strongly suggest a selective allergic hypersensitivity to nimesulide.

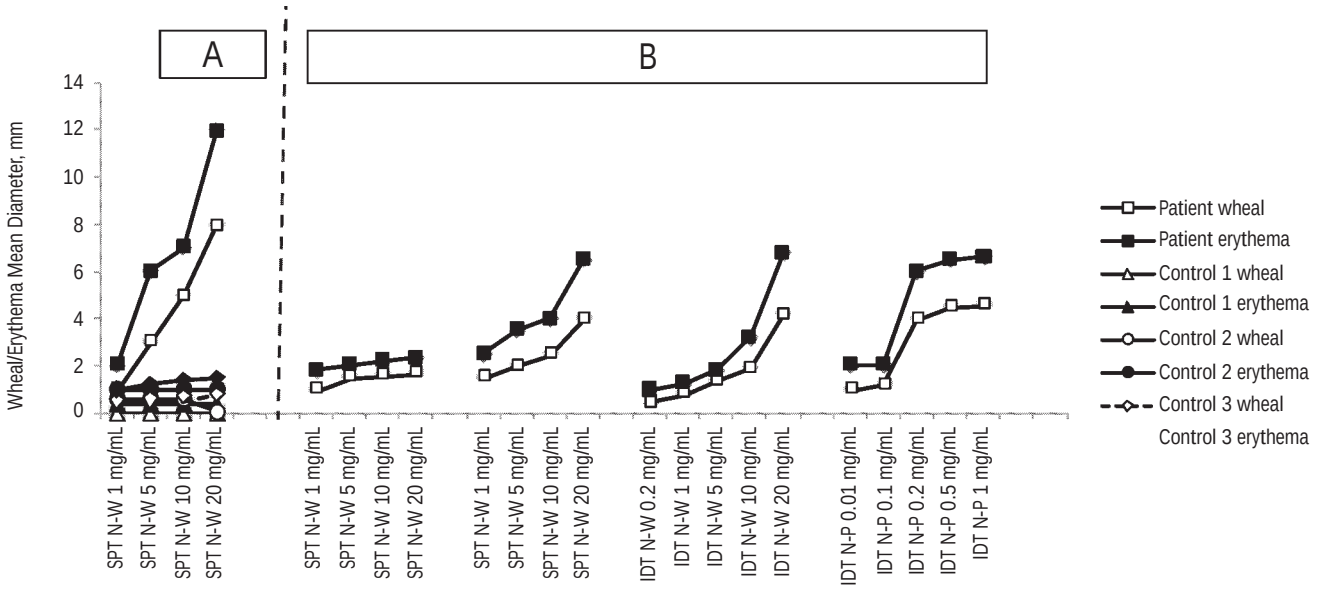

Figure. Results of skin prick tests (SPTs) and intradermal tests (IDTs) using different concentrations of nimesulide in water (N-W) in the patient and 3 healthy controls 2 months after the adverse drug-induced anaphylaxis (A), and different concentrations of N-W or nimesulide in polyethylene-glycol 400 (N-P) in the patient 1 year after the drug-induced anaphylaxis (B).

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Omalizumab (an Anti-IgE Antibody) in the Treatment of Severe Atopic Eczema

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Key words: Atopic dermatitis. Treatment. Omalizumab. SCORAD. Quality of life.

Palabras clave: Dermatitis atópica. Tratamiento. Omalizumab. SCORAD. Calidad de vida.

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease [1] that can clinically present as erythema, crusts, vesicles, and liquefaction [2]. The major symptom is pruritus, which can impair patient quality of life [1]. The SCORAD index, a severity scoring system for AD, classifies the disease as mild, moderate, or severe [3].

Conventional treatment includes emollients, antihistamine agents, corticosteroids, and calcineurin inhibitors, all of which can achieve adequate control in patients with mild to moderate AD; however, clinical manifestations and lesions are difficult to control in patients with severe AD [4].

Omalizumab, a humanized anti-immunoglobulin (Ig) E antibody that prevents the binding of IgE to its receptor, has been approved for the treatment of asthma [5]. Because

patients with AD have been found to have increased IgE levels and high-affinity receptors for IgE [1] it can be assumed that treatment with an anti-IgE antibody may decrease clinical manifestations and disease activity.

To test this hypothesis, we conducted a study in patients with a diagnosis of severe AD (SCORAD score >50 points) from the allergy service at Hospital Adolfo López Mateos in Mexico City, Mexico over a period of 10 months. A complete clinical history was taken and laboratory tests, including IgE, were requested. Omalizumab treatment was started with doses adjusted to weight and IgE levels. Patients were periodically evaluated, with physical examination and assessment of SCORAD score, use of drugs, presence of adverse effects, and quality of life using the Dermatology Life Quality Index (DLQI) [6].

The software program SPSS 15.0 for Windows was used for statistical analyses.

Eleven patients (1 male and 10 females) aged between 12 and 52 years with severe AD were enrolled.

The baseline SCORAD score ranged from 43 to 101 points, with a mean of 71.2 points. A gradual improvement was seen in all patients, with a mean of 31.54 points after 10 months ($P<.05$). Mean (SD) quality-of-life scores also improved, from 9.36 points to 3.72 (1.48) over the same period ($P<.05$)

There have been previous reports of AD treated with omalizumab. Vigo [7] reported a significant improvement in the symptoms of all 7 patients treated, and Belloni et al [8] reported a favorable response in 6 of 11 patients. Krathen and Hsu [9], however, observed no response to omalizumab in 3 patients with severe AD.

In our patients, there was a gradual improvement in SCORAD scores, accompanied by a decrease in symptoms and an improvement in quality of life, with fewer limitations in terms of attendance at school, work, etc. No adverse effects were observed.

The limitations of this study are the small sample size and the lack of comparison with a placebo group.

Omalizumab treatment progressively decreased the severity of AD, evaluated by SCORAD, with a gradual decrease in symptom intensity, which was reflected by improved quality-of-life scores.

It is necessary to conduct studies with more patients and, if similar results to the ones presented here are found, omalizumab may become a first-line therapy, capable of achieving good disease control and preventing complications in the treatment of moderate and severe AD.

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A Severe Case of Lipoatrophy Due to Human Insulin and Insulin Analogs in a Patient With Diabetes: Is an Immunological Mechanism involved?

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Key words: Diabetes. Insulins. Lipoatrophy. Type III hypersensitivity.

Palabras clave: Diabetes. Insulinas. Lipoatrofia. Hipersensibilidad tipo III.

Although there have been few reports of lipoatrophy as a cutaneous side effect of recombinant human insulin or insulin analogues, in recent years, there have been an increasing number of case reports and letters in the scientific literature indicating that lipoatrophy may also develop after treatment with these insulins [1-5]. Immunological mechanisms have been proposed, but the exact pathogenesis of lipoatrophy remains obscure [6].

Table. Specific Immunoglobulin (Ig) G and IgG4 Subclass Values and Precipitin Study Results

	Patient		Control		Patient	Control 1	Control 2
	IgG, mg/mL	IgG4, mg/mL	IgG, mg/mL	IgG4, mg/mL	Precipitins		
Apidra	2.84	0.06	0	0	(-)	ND	ND
Humalog	2.73	0.04	0	0	(-)	ND	ND
Novorapid	2.59	0.05	0	0	(-)	ND	ND
Actrapid	2.62	0.01	0	0	(+)	(-)	(-)
Insulatard	6.94	0.02	0	0	(+)	(-)	(-)
Levemir	3.38	0.08	0	0	(+)	(-)	(-)
Lantus	45.3	0.02	27.4	0	(+)	(-)	(-)
Protamine	3.44	0.05	0	0	(+)	(-)	(-)

Abbreviations: ND, not done.

A 30-year-old woman, diagnosed 2 years previously with type 1 diabetes mellitus and primary autoimmune hypothyroidism, had experienced a severe depression of the skin surface consistent with lipoatrophy over the past year; the depression affected the sites where she administered subcutaneous insulin. During this time, she had used different types of insulins, including short-acting insulin (insulin glulisine [Apidra]), insulin lispro [Humalog], insulin aspart [Novorapid]; long-acting insulin (insulin detemir [Levemir] and insulin glargine [Lantus]); and premixed insulin (insulin-aspart + isophane insulin [Novomix]). She did not relate the lipoatrophic areas with the administration of a specific insulin.

Skin biopsy of the lipoatrophic areas and immunofluorescence against immunoglobulins, complement fractions, and fibrinogen were performed. Skin prick, intradermal, and patch tests were performed with all the insulins she had been using as well as with human insulin (Actrapid), isophane insulin (Insulatard), and protamine. The results were read at 20 minutes and at 48 and 96 hours. Specific immunoglobulin (Ig) G and IgG4 subclass were measured by biotinization using ImmunoCAP (Phadia, Uppsala, Sweden) and precipitins against human insulin, protamine, and all the insulins mentioned above were determined by the Ouchterlony technique. Specific IgE against human insulin and protamine were also measured.

In vivo skin tests (prick, intradermal, and patch tests) and specific IgE against human insulin and protamine were negative (<0.35kU/L). High levels of IgG and IgG4 were observed for all the insulins tested as well as for protamine, with higher levels noted for medium- (Insulatard) and long-acting insulins (Levemir and Lantus) than for short-acting insulins (Table). As a control for the IgG and IgG4 determinations, a mixed pool of neonatal sera was used, with negative results for all the insulins tested, except for Lantus, which yielded high IgG levels. The precipitin study was positive for Actrapid, Insulatard, Levemir, Lantus, and protamine and negative for Apidra, Humalog, and Novorapid (Table). Two patients with diabetes who had used these insulins in the past served as controls and showed negative precipitins against all the insulins tested. The skin biopsy showed lipoatrophy, with some areas of inflammatory neutrophilic infiltrate but no signs of immunoglobulins, complement factors, or fibrinogen deposits in the immunofluorescence study.

The positive IgG result for 1 insulin in the control sera rendered this measurement useless, and it was therefore decided to select an alternative insulin based on the results of the precipitin study. All the long-acting insulins tested had yielded positive results in this study and therefore, after consultation with the patient, it was decided to start continuous subcutaneous insulin infusion with insulin glulisine (Apidra), for which the precipitin study had been negative. After 6 months, the lipoatrophic areas improved significantly and no new skin lesions were observed.

We have presented a case of severe lipoatrophy in a patient with diabetes. A type III hypersensitivity reaction could explain the symptoms because of the detection of precipitins to insulins used by the patient. On the other hand, the lack of an abnormal deposit of immunological components does not support this hypothesis but, as the biopsied area corresponded to an old lesion, the immunological deposits might have been eliminated over time. The excipients of all the insulins were tested and no correlation was observed with the results obtained. Although the frequency of this cutaneous complication of insulin therapy has decreased since the introduction of various short- and long-acting insulin analogues, lipoatrophy can also develop after treatment with these compounds.

The precipitin technique has been used in insulin resistance and immunity studies since the 1940s [7]. In the case described, the technique proved, once again, to be a valid method for choosing the most appropriate insulin. However, whether or not an immunological mechanism was involved in the lipoatrophic process remains uncertain, and further studies with adequate immunological assessment are necessary.

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Fixed Drug Eruption Due to Meloxicam

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Key words: Meloxicam. Fixed drug eruption. Oxicam. Cross-reaction. Patch tests.

Palabras clave: Meloxicam. Erupción fija medicamentosa. Oxicam. Reactividad cruzada. Pruebas epicutáneas.

Fixed drug eruption (FDE) is a common cutaneous adverse drug reaction involving a delayed T-cell hypersensitivity reaction [1]. The most characteristic finding of FDE is recurrence of similar lesions at the same sites and healing with residual hyperpigmentation [2]. FDE appears within minutes to several hours after intake [1]. Rechallenge is the most reliable method of identifying causative drugs, but application of patch tests, especially in the affected area, has gained the most attention to date [1]. Nonsteroidal anti-inflammatory drugs (NSAID) are one of the principal causes of FDE [3]. Although a few cases of piroxicam-induced FDE have been reported [4-7], FDE caused by oxicams is rare. We report an unusual case of FDE due to meloxicam. To the best of our knowledge, this is the first report of FDE due to meloxicam.

A 44-year-old woman with rheumatic disease was referred to our clinic for assessment of several episodes of cutaneous eruption after ingestion of analgesics. She had a history of brownish, sharply demarcated, round pruritic plaques suggestive of FDE on the right knee and forearm with concomitant vulvar pruritus 10-15 minutes after oral intake of flurbiprofen, ibuprofen, and piroxicam. The last reaction occurred 4 years ago. At presentation, the patient had no residual lesion. Because of her underlying rheumatic disease, she needed a safe NSAID. Considering the safety profile of meloxicam in patients with aspirin-exacerbated respiratory diseases (AERD) and aspirin-induced urticaria [8,9], we performed a single-blind placebo-controlled oral challenge test with increasing doses of meloxicam up to a cumulative dose of 7.5 mg. No reaction occurred with the placebo. However, 45 minutes after ingestion of meloxicam, the patient reported vulvar pruritus, and a brownish pruritic plaque appeared on the right knee (Figure). The reaction responded well to a topical corticosteroid. Four weeks later, cross-reactivity within the group was analyzed using patch tests with 0.1% piroxicam, 1% piroxicam, 1% tenoxicam, 1% meloxicam, and 10% nimesulide, all in white petrolatum, on both the previously affected area (right knee) and unaffected skin (back). Only 1% piroxicam on previously affected skin was positive at 72 hours, and the results of the remaining patch tests with oxicams and nimesulide were negative. Subsequently, oral challenge tests with nimesulide and naproxen were performed, and both were negative.

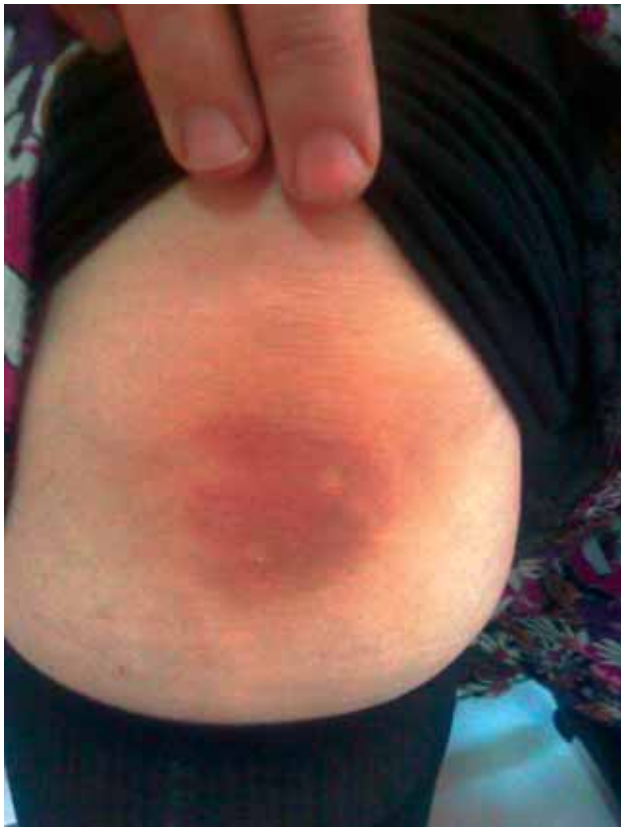

Figure. Brownish plaque that appeared on the right knee 45 minutes after ingestion of a cumulative dose of 7.5 mg of meloxicam.

Meloxicam is a cyclooxygenase (COX) 2 inhibitor that is usually safe in patients with AERD and aspirin-induced urticaria [8,9]. Therefore, we tested the tolerability of meloxicam, but our patient reacted. The finding of FDE to meloxicam could be due to different cross-reactivity patterns. Patients with AERD cross-react to all NSAIDs that inhibit COX-1 enzyme. However, in FDE, different types of cross-reactivity have been reported. The most common is cross-sensitivity between chemically related drugs [1]. Although less frequent, this event can occur as a result of multiple sensitizations to 2 or more unrelated drugs. Cross-reactivity between piroxicam, droxicam, and tenoxicam has been reported in FDE [4]. Nevertheless, no cross-reactivity was demonstrated between oxicams in other cases of piroxicam-induced FDE [5,10]. Consequently, our findings and those of other authors support possible cross-reactions in FDE caused by oxicams. The COX-1 inhibition theory of AERD seemed not to be valid in these cases. Our patient tolerated naproxen, a potent COX-1 inhibitor; however, naproxen induces bronchospasm in patients with AERD.

Patch tests are the first choice for diagnosing FDE to drugs and are based on concentrations of 1%-10% of the culprit drugs [1]. We performed patch tests with the culprit drugs at maximum concentrations of 1%, as suggested elsewhere [5-7]. Our patient had a positive patch test reaction to 1% piroxicam on the previously affected area, with a negative reaction at the unaffected site, which is compatible with previous reports [5-7]. However, patch testing with meloxicam was negative. Our patient developed exacerbation of FDE on the previously affected site after an oral provocation test with meloxicam. There may be several explanations for this finding. First, as no cases of FDE to meloxicam have been published, we applied a concentration of 1%, which was the recommended dose for testing with piroxicam in FDE. This concentration may have been too low to induce a reaction. Other reasons for negative patch test results in FDE include testing at an unaffected area only, not avoiding the refractory period, sensitization to the drug's metabolites but not to the drug itself, and limited penetration properties of the offending drug [2]. Thus, a negative skin reaction in patch tests provides limited information, and the diagnosis should not be excluded. In many cases of FDE, challenge tests are recommended to prove the diagnosis when patch test results with the culprit drug are negative, because data on the negative predictive value of these tests are insufficient. Our patient developed a positive response to meloxicam in drug challenge tests, but a negative result in the patch test.

In conclusion, possible within-group cross-reactivity should be borne in mind in patients with FDE to oxicams. If possible, meloxicam should be tested to see whether cross-reactivity is a common pattern. In any case, given the scarcity of data in the literature, concentrations of meloxicam and other oxicams used for patch tests need to be standardized.

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Drug Fever Caused by Eutectic Mixture of Local Anesthetic cream

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Key words: EMLA cream. Drug fever. Lidocaine. Prilocaine. Interleukin 6.

Palabras clave: Crema EMLA. Fiebre medicamentosa. Lidocaína. Prilocaína. Interleucina 6.

Eutectic mixture of local anesthetic (EMLA) cream is widely used to relieve pain associated with ulcers and laser treatment. EMLA and topical lidocaine cream appear to be safe [1]. We report the case of a patient who developed drug fever caused by lidocaine and/or prilocaine following the application of EMLA cream to ulcers.

A 59-year-old woman with systemic sclerosis was admitted to our hospital with ulcers measuring about 200 cm^2 on both legs. The ulcers were covered with necrotic tissue. Due to severe pain, approximately 20 g of EMLA cream was applied to the ulcers using the occlusive dressing technique (ODT) for an hour before debridement. Although the ODT produced pain relief each time, the patient consistently developed a fever of up to 39ºC about 3 hours after debridement. Apart from the recurring fever, which lasted for several hours each time, serum C-reactive protein levels also increased gradually from around 1.0 mg/dL to as high as 9.03 mg/dL. On one occasion, 2% lidocaine hydrochloride jelly was applied by ODT instead of EMLA cream before debridement. While the patient experienced less pain relief on that day, she did not develop a fever. We then applied aqueous gel alone or topical 2.5% prilocaine aqueous gel on the ulcers before debridement. No further episodes of fever were observed until EMLA cream was reapplied. At this point, since we suspected that EMLA cream might be causing the fever, we discontinued use of the cream definitively. The patient's temperature remained within normal range and the serum C-reactive protein level decreased to around 1.0 mg/dL. Patch tests performed with lidocaine, prilocaine, and EMLA cream were all negative. Since skin absorption of lidocaine is known to increase with EMLA cream application [2], we measured blood lidocaine levels 3 hours after the application of both lidocaine hydrochloride jelly and EMLA cream to the ulcers. Interestingly, while the level remained below the detection limit (<0.1 μg/mL) when lidocaine hydrochloride jelly was used, it reached 0.5 μg/mL when EMLA cream was used. An increase in the level of serum interleukin (IL) 6 was also noted when EMLA cream was used (43 pg/mL after application vs 6 pg/mL before application).

IL-6 is known to induce increases in body temperature [3], but whether the release of this cytokine was triggered directly by lidocaine or whether it was a bystander effect remains unclear. Our results suggest that lidocaine was unable to pass through the skin following the application of lidocaine cream alone, but that the application of EMLA cream increased the degree of lidocaine and/or prilocaine infiltration into the blood, causing drug fever. We were unable to measure blood prilocaine levels. Even though lidocaine and prilocaine are considered to exert an additive effect, the total plasma levels of the 2 drugs are estimated to be below 1 μg/mL [4], which is well below the toxic level of 5 to 6 μg/mL. Furthermore, while our patient developed fever, other patients with skin ulcers receiving the same amount of EMLA cream did not. It is therefore likely that our patient developed drug fever induced by EMLA cream. Our findings indicate that topical products, in addition to oral and parenteral medications, can induce systemic fever. It is important to bear in mind that EMLA cream increases the skin infiltration of lidocaine and prilocaine, and that the blood levels of these drugs are also increased, with a consequent increase in the risk of drug fever.

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