

Occupational asthma caused by carnation (*Dianthus caryophyllus*) with simultaneous IgE-mediated sensitization to *Tetranychus urticae*

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Key words: allergens; *Dianthus caryophyllus*; occupational asthma; *Tetranychus urticae*.

Tetranychus urticae (TU) is a known occupational allergen which frequently parasitizes carnations (*Dianthus caryophyllus*) (1).

Therefore, the investigation of occupational allergy caused by carnation implies nonconsideration of TU as a causative agent.

A case of occupational respiratory allergy to carnation, with simultaneous sensitization to TU in the same patient, is described.

A 29-year-old woman, smoking 15 cigarettes per day, with neither personal history of atopia nor other antecedents of interest, having been employed at a flower supplier during the previous 2 years, was studied at our allergy unit. She had sneezing, rhinorrhea, coughing, wheezing and dyspnea while cleaning carnations at the flower shop. She also showed no respiratory symptoms in relation with other flowers. During holidays the patient was totally asymptomatic.

Two carnation extracts, from petals and stems, were prepared (ALK-Abelló, Madrid, Spain). Only fresh flowers not infested by TU were used. Additionally,

two TU extracts, from TU scratched from infested carnation leaves (TU-S) and from isolated bodies of TU (TU-B) were obtained (BIAL-ARISTEGUI, Bilbao, Spain) as previously described (1). Skin prick tests (SPT) with carnation stem (at 5% w/v), petal (at 2.5% w/v) and the two TU (at 1 mg/ml) extracts were positive. Simultaneously, negative response was obtained with a battery of frequent inhalants. SPT with carnation and TU extracts were negative in 10 atopic and 10 nonatopic patients who were used as control subjects.

Total IgE was 203 kU/l. Serum-specific IgE [radioallergosorbent test (RAST)] to both petals and stem extracts was RAST class 3. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting showed two IgE-binding bands of 25 and 28 kDa present both in carnation petal and stem extract. In both TU extracts, four protein IgE-binding bands of 67.1, 48.8, 33.7, and 18.8 kDa were visible. Thirteen additional bands, ranging from 16.9 to 83.0 kDa, were detected in the TU-S extract which may be due to a contamination with carnation allergenic proteins.

Metacholine challenge test showed bronchial hyperreactivity (5 mg/ml). Specific bronchial provocation test with a dilution of 1/64 of carnation stem extract (10% w/v) was positive, eliciting a dual response. Occupational asthma caused by carnation was diagnosed. As bronchial challenge test with TU-B extract was negative, being administered the maximum concentration of 1 mg/ml, asthma from TU could not be confirmed. In this case, a subclinical sensitization to TU or rhinitis caused by TU is possible. Additionally, it cannot be ruled out that administering higher TU doses during bronchial challenge test might have triggered an asthmatic reaction.

Respiratory allergy to carnation has been described before (2–4) and, in this latest paper, a simultaneous sensitization to TU in the same patient is proved.

Nevertheless, in the two latest articles there is no mention of the use of extracts from flowers in which parasitization by TU had been ruled out. However, it is important to keep this in mind in order to reach the right etiology, given that carnation industry workers may be doubly sensitized, as described above, or even to be sensitized to TU, but not to carnation proteins as proved by Delgado et al. in 16 workers who handled carnations at a greenhouse (1). Vidal et al. (2) proved type-I hypersensitivity to proteins from carnation and other flowers in a patient, without considering allergy to TU. However, bronchial provocation test was not performed because the patient showed rhinitis but not asthma.

This case proves that in carnation workers showing respiratory symptoms, it is essential to investigate the flowers and their parasite TU separately, given that, either one of them, or both simultaneously, could act as an occupational allergen.

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References

1. DELGADO J, ORTA JC, NAVARRO AM, CONDE J, MARTÍNEZ A, MARTÍNEZ J et al. Occupational allergy in greenhouse workers: sensitization to *Tetranychus urticae*. Clin Exp Allergy 1997;27:640–645.

2. VIDAL C, POLO F. Occupational allergy caused by *Dianthus caryophyllus*, *Gypsophila paniculata*, and *Lilium longiflorum*. *Allergy* 1998;**53**:995–998.
3. SÁNCHEZ-GUERRERO IM, ESCUDERO AI, BARTOLOMÉ B, PALACIOS R. Occupational allergy caused by carnation (*Dianthus caryophyllus*). *J Allergy Clin Immunol* 1999;**104**:181–185.
4. CISTERÓ-BAHIMA A, ENRIQUE E, ALONSO R, SAN MIGUEL M, BARTOLOMÉ B. Simultaneous occupational allergy to a carnation and its parasite in a greenhouse worker (Letter). *J Allergy Clin Immunol* 2000;**106**:780.

Persistent asthma following accidental exposure to formaldehyde

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Key words: asthma; formaldehyde; occupational disease.

Occupational asthma caused by formaldehyde has occasionally been documented in subjects who demonstrated clinical features consistent with allergic airway hypersensitivity to this low-molecular-weight chemical (1–4), although the nature of the underlying immunological mechanism remains unknown. In these cases, specific immunoglobulin (Ig)E antibodies against formaldehyde were either not assessed (1–3) or not detected (4).

We evaluated a 31-year-old male who had been accidentally exposed for about 2 h to formaldehyde that leaked from a malfunctioning reactor gasket while working in a chemical plant producing urea-formaldehyde resins. Over the following hours, he developed asthma symptoms and was admitted to a local emergency room. He had smoked one pack of cigarettes a day for 13 years and

Table 1. Results of functional and immunological assessments after acute inhalation exposure to formaldehyde

Time since inhalation accident	FVC L (% pred)	FEV ₁ L (% pred)	Histamine PC ₂₀ (mg/ml)	Specific immunoglobulin E against formaldehyde (IU/ml)
1 day	4.35 (93)	2.40 (60) + 38% after BDT	NA	NA
8 days	4.29 (91)	3.19 (81)	0.07	3.4
26 days	4.74 (101)	4.17 (106)	0.03	NA
3 months	4.57 (98)	3.83 (97)	<0.01	<0.35
6 months	4.29 (91)	3.65 (92)	0.019	<0.35
13 months	4.25 (91)	3.29 (83)	0.018	NA

FVC, forced vital capacity; FEV₁: forced expiratory volume in 1 s; PC₂₀, concentration of histamine causing a 20% fall in FEV₁; BDT, inhaled bronchodilator; NA, not assessed.

reported no history of pre-existing respiratory disease. Physical examination revealed diffuse expiratory wheezing. Arterial blood gas analysis showed mild hypoxaemia (Pa,O₂ 7.45 kPa). A chest radiograph was normal. On the next day, spirometry showed marked airflow limitation (Table 1). The subject improved rapidly on treatment with methylprednisolone for 4 days and inhaled corticosteroids.

Eight days later, immunological assessment showed an increased level of specific IgE antibodies against formaldehyde (CAP system, Uppsala, Sweden) at 3.4 IU/ml, which was no longer detectable on subsequent assessments (Table 1). Skin-prick tests with common allergens gave a positive response to house-dust mite. One month after the inhalation accident, specific inhalation challenges with formaldehyde for 30-min periods at concentrations of 0.5, 1 and 3 ppm did not elicit significant changes in FEV₁. Over the following 13 months, the subject continued to experience asthma symptoms and serial lung function tests revealed normal spirometric values with persistent bronchial hyperresponsiveness to histamine (Table 1) despite avoidance of exposure to formaldehyde and treatment with inhaled budesonide (400 µg twice a day).

In this subject, the strong temporal relationship between accidental high-level exposure to formaldehyde and the rapid onset of asthma symptoms is consistent with a nonimmunological form of asthma, most often referred to as 'reactive airways dysfunction syndrome' (RADS) or 'irritant-induced asthma' (5). The

relevance of specific IgE antibodies against formaldehyde in our subject remains unknown. Airway sensitization to formaldehyde could be reasonably excluded, as inhalation challenge with formaldehyde failed to provoke a bronchial response. A similar observation has been reported in a subject who developed asthma after intense exposure to isocyanates (6). Specific IgE antibodies against toluene diisocyanate were found in the subject's serum while specific inhalation challenges were negative. Our findings suggest that airway sensitization to formaldehyde should be properly assessed through specific inhalation challenge, as the presence of specific IgE antibodies may reflect exposure rather than immunologically-mediated OA.

This report indicates that high-level exposure to formaldehyde can cause the development of persistent asthma through a presumably nonimmunological mechanism. This possibility should be considered when evaluating the work-relatedness of asthma among subjects exposed to intermittently high levels of formaldehyde.

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References

- HENDRICK DJ, LANE DJ. Occupational formalin asthma. *Br J Ind Med* 1977;**34**: 11–18.
- NORDMAN H, KESKINEN H, TUPPURAINEN M. Formaldehyde asthma – rare or overlooked? *J Allergy Clin Immunol* 1985; **75**(1 Pt 1):91–99.
- BURGE PS, HARRIES MG, LAM WK, O'BRIEN IM, PATCHETT PA. Occupational asthma due to formaldehyde. *Thorax* 1985;**40**:255–260.
- KIM CW, SONG JS, AHN YS, PARK SH, PARK JW, NOH JH et al. Occupational asthma due to formaldehyde. *Yonsei Med J* 2001;**42**:440–445.
- VANDENPLAS O, MALO JL. Definitions and types of work-related asthma: a nosological approach. *Eur Respir J* 2003;**21**:706–712.
- PALCZYNSKI C, GORSKI P, JAKUBOWSKI J. The case of TDI-induced reactive airway dysfunction syndrome with the presence of specific IgE antibodies. *Allergol Immunopathol (Madr)* 1994;**22**:80–82.

Glottis oedema due to loratadine

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Key words: antihistamine; glottis oedema; loratadine; side effects.

Loratadine is a long-acting antihistamine agent showing a partial selectivity for peripheral H1 receptors (1), commonly used as symptomatic treatment in patients suffering from seasonal or perennial allergic rhinitis as well as urticaria and allergic dermatitis in both adults and children.

The side effects reported in literature are rare and include headache, somnolence, mild gastrointestinal complaints and cutaneous rash (1–3), whereas no case of potentially life-threatening adverse event has been so far reported.

Glottis oedema due to loratadine.

We present here a case of glottis oedema associated to the ingestion of loratadine used as antiallergic symptomatic drug.

A 27-year-old woman had 7 years before a diagnosis of allergic rhinitis because of grass pollen. She was prescribed to take every evening from April to September each year a tablet of loratadine (10 mg). In the last 5 years she has also been taking on a regular basis an oral contraceptive (estroprogestinic). In April 2002 she began the usual daily intake of loratadine without any problem. The 4th of July she suffered a moderate dyspnoea associated to glottis oedema requiring admission to the ER and treatment with e.v. cortisone. Four days later, she was admitted again to the ER because of a new severe dyspnoea associated to glottis oedema, requiring the administration of adrenaline. After having been referred to an Allergy Department, she was prescribed prednisone *per os* (50 mg) on need and was advised to take with her an adrenaline preparation ready for self-administration. She experienced on July 11 and 15 two new episodes of dyspnoea and glottis oedema, slowly controlled by the administration of prednisone. On July 15 she was examined at our Allergy Service, where the immediate interruption of the assumption of loratadine was suggested. After the interruption of the drug intake, no new episodes of dyspnoea and/or glottis oedema was reported by the patient in the following 6 months. At the end of this observation period and after having obtained informed consent, the patient was submitted to skin prick test on the volar surface of the forearm with a 1.3 mg/ml solution of loratadine, prepared with two water-soluble tablets of loratadine (10 mg of drug each) in 15 ml of sterile saline. The drug solution evoked a wheal 2 mm and an erythema 5 mm in diameter in 25 min, whereas no reaction at all was seen with saline and a 5-mm wheal plus a 15-mm erythema was observed for histamine hydrochloride 10 mg/ml. The allergological assessment performed at the same time with a standard panel of inhalant allergens (ALK-Abellò, Milan, Italy), confirmed the former diagnosis of allergy to grass and a sensitization to cat not diagnosed before (wheal 5 mm and erythema

15 mm in diameter for both inhalant allergens in 15 min). Clinically relevant sensitization to Hymenoptera venom was excluded by means of intradermal tests with serial dilutions of venom extracts (Pharmalgen, ALK-Abellò, Milan, Italy).

Hypersensitivity to antiallergic drugs is a rare phenomenon, but its relevance should not be nonetheless ignored. Reactions because of corticosteroids range from minor rashes to more serious cardiovascular collapse (4), whereas exacerbations of the underlying recurrent chronic urticaria have been reported after treatment with cetirizine (5). Some first-generation antihistamines have been associated to potentially life-threatening dysrhythmias because of their effects on ion channels, but loratadine has been shown safe from this point of view (6). However, it should be remarked that the identification of uncommon adverse reactions to antihistamines is obviously difficult because they may mimic the underlying disease that led to the intake of such a drug.

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References

- HARIA M, FITTON A, PETERS DH. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs* 1994;**48**:617–637.
- VAN CAUWENBERGE P, JUNIPER EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy* 2000;**30**:891–899.
- SALMUN LM, HERRON JM, BANFIELD C, PADHI D, LORBER R, AFFRIME MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years *Clin Ther* 2000;**22**:613–621.

4. BUTANI L. Corticosteroid-induced hypersensitivity reactions. *Ann Allergy Asthma Immunol* 2002;**89**:439–445.
5. TELLA R, GAIG P, BARTRA J, GARCIA-ORTEGA P. Urticaria to cetirizine. *J Investig Allergol Clin Immunol* 2002;**12**:136–137.
6. TEN EICK AP, BLUMER JL, REED MD. Safety of antihistamines in children. *Drug Saf* 2001;**24**:119–147.

Fixed drug eruption caused by articain

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Key words: amide; articain; fixed drug eruption; local anesthetic.

Local anaesthetics are usually well tolerated. However, immediate- and delayed-type hypersensitivity reactions do occur occasionally (1). In contrast, we are aware of only two case reports on fixed drug eruptions (FDE) (2, 3). Here, the case of FDE triggered by the amide articain is documented; this drug has not previously been reported to cause FDE.

Over the last 8 years, a 45-year-old woman had observed seven episodes of dark red plaques developing shortly after dental treatments with the application of articain (Ultracain®) as local anesthetic. The symptoms began 8–12 h after the treatment, and resolved spontaneously within 14 days. No other drugs were taken.

Skin tests (prick and patch tests) with local anesthetics from the ester- and the amide-type including articain and relevant preservatives remained negative. Subsequently, subcutaneous provocation tests were performed with increasing doses of articain (maximum dose: 2 ml; cumulative dose: 3.8 ml). Forty-eight hours later, the patient presented with dark bluish macules and plaques on both hands (Fig. 1A). A skin biopsy documented a lichenoid infiltrate along the epidermo-dermal border,

The local anesthetic articain of the amide subgroup is capable of inducing fixed drug eruptions.

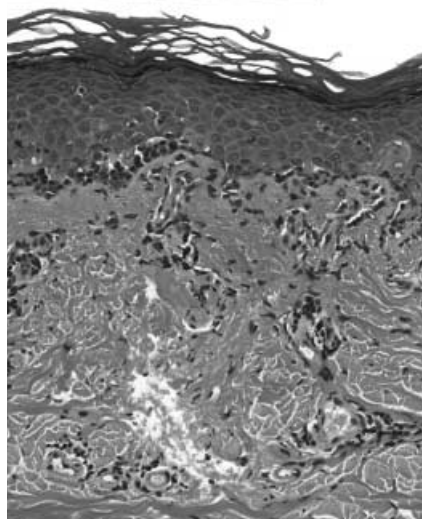


Figure 1. Clinical (A) and histological (B) appearance of fixed drug eruption on both hands. Forty-eight hours after rechallenge with articain, dark bluish macules and plaques are visible. Histologically, a lichenoid infiltrate along the epidermo-dermal border and necrotic keratinocytes are seen (original magnification: $\times 200$).

consisting of mainly lymphocytes with some eosinophils and neutrophils. Within the epidermis, necrotic keratinocytes were readily detectable (Fig. 1B). This finding was consistent with the clinical diagnosis of a fixed drug eruption.

Although episodes of adverse reactions to local anesthetics are not uncommon,

true allergic reactions are seemingly rare. The clinical picture of contact dermatitis is usually caused by compounds of the ester type, whereas the rare cases of anaphylactic reactions are triggered by amides. We are aware of only two reports on FDE to local anesthetics, namely mepivacaine (2) and lidocaine (3), both of them belong to the amide subgroup. Our observation adds articain to the list of amide anesthetics capable of inducing FDE. So far, there has been no report on a FDE triggered by an ester anesthetic. Diagnosis of FDE can be tried by topical provocation on previously affected sites (4), but re-challenge with the drug in question seems to be a more reliable method.

In summary, we here report on a patient with FDE caused by articain as documented by provocation and histology. So far, only two other cases of FDE to local anesthetics have been published, both also triggered by amides. The FDE might possibly be a clinical manifestation observed with local anesthetics of the amide but not the ester type.

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References

1. SCHATZ M, FUNG DL. Anaphylactic and anaphylactoid reactions due to anesthetic agents. *Clin Rev Allergy* 1986;**4**: 215–227.
2. TORRES MJ, GARCIA JJ, CANO MORATINOS AM, RONDON C, BLANCA M. Fixed drug eruption induced by mepivacaine. *J Allergy Clin Immunol* 1995;**96**:130–131.
3. GARCIA JJ, TORRE F, SANCHEZ M, MARTIN JA, CANTO G. Fixed drug eruption induced by lidocaine and patch testing. *J Investig Allergol Clin Immunol* 1997;**7**: 127–128.
4. ALANKO K. Topical provocation of fixed drug eruption. A study of 30 patients. *Contact Dermatitis* 1994;**31**:25–27.

Stevens–Johnson syndrome associated with azithromycin followed by transient reactivation of herpes simplex virus infection

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Key words: azithromycin; cytokine; herpes simplex virus; reactivation; Stevens–Johnson syndrome.

Stevens–Johnson syndrome (SJS) is an acute and life-threatening disease, which involves skin and visceral organs. The pathophysiology of the disease has not been well established.

A 5-year-old boy, previously in good health, had a fever on October 7, 2000. He was treated with azithromycin (AZM) for 3 days since October 10. On October 13 he showed oral pain and skin eruptions with bullae. On October 15 he presented many oral aphthae. He was treated with aciclovir and cefazolin. However, his condition deteriorated. On October 18, he was transferred to our hospital.

On admission he showed skin eruptions with bullae and erythema on his face and extremities, bilateral conjunctivitis, and oral ulcers. Nikolsky's sign was easily demonstrated. His temperature was 37.7°C. He presented erosions at the penis. Laboratory investigation revealed normal complete blood count, differential, erythrocyte sedimentation rate, urinalysis, liver and renal function tests, electrolytes, coagulation study, antinuclear antibody, serum immunoglobulin and CH50 except CRP (6.9 mg/dl). His antibodies against herpes simplex virus (HSV), VZV and *Mycoplasma pneumoniae* did not increase. Skin tests using scratch-patch test (1) with AZM induced a positive reaction.

We diagnosed him as having SJS, therefore, betamethasone, panipenem/betamipron and ulinastatin were administered. Also topical treatments were started. His condition gradually improved, the steroid was withdrawn on

A pediatric case of SJS associated with AZM and reactivation of HSV infection.

Table 1. Laboratory data, serum cytokines and ECP levels and HSV antibodies in the patient

	Day 8	Day 16	Day 20	Day 28	Day 35	Day 56
WBC (/μl)	9320	10 110	14 190	10 190	3920	7550
AST/ALT (IU/l)	20/11	20/13	21/26	49/74	83/197	25/21
HSV IgG/IgM (U/ml)	81.9/ <0.80	ND	ND	46.1/2.01	49.4/1.18	64.6/ <0.80
IFN-γ (pg/ml)	62.8	51.2	83.4	67.9	38.7	61.7
TNF-α (pg/ml)	8.7	6.5	9.5	9.7	5.1	8.4
IL-2 (pg/ml)	2.7	1.9	3.1	2.7	2.0	2.8
IL-4 (pg/ml)	10.7	7.8	11.7	9.8	4.9	7.4
IL-5 (pg/ml)	5.5	4.3	5.8	4.6	3.0	4.2
IL-6 (pg/ml)	160.6	88.0	38.2	22.0	22.3	14.0
IL-10 (pg/ml)	7.9	7.4	8.4	12.8	7.4	7.1
ECP (μg/l)	4.8	3.0	<2.0	<2.0	3.3	ND

Day 1 represents the first day of his treatment with AZM. On Day 8 he was admitted to our hospital. Normal ranges of all seven cytokines in serum are <0.1 pg/ml. And that of ECP in serum is <2.0 μg/l. ECP, eosinophilic cationic protein; HSV, herpes simplex virus; WBC, white blood cell; IFN, interferon; AST/ALT, aspartate aminotransferase/alanine aminotransferase; TNF, tumor necrosis factor; IL, interleukin; ND, not determined.

November 7. However, on November 14 (day 35) he had slight fever with mild liver dysfunction. We found a significant increase of HSV specific immunoglobulin M antibody. Thereafter, his laboratory findings improved.

We measured the serum cytokines and ECP levels. Interleukin-6 and ECP levels were increased on day 8 and decreased dramatically on day 28 (Table 1).

This is the first report of SJS associated with AZM. Azithromycin has a longer half-life, which might relate to the high risk of adverse effects (2). However, he had acute pharyngitis, which would prompt the development of SJS. We demonstrated the slight increase of ECP, which would suggest that activated eosinophils might play a certain role in SJS.

The reactivation of HSV was observed after his recovery from SJS. This reactivation could be induced mainly by the immunosuppression because of steroid therapy.

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References

1. YAWALKAR N, REIMERS A, HARI Y, HUNZIKER T, GERBER H, MULLER U et al. Drug-induced linear IgA bullous dermatosis associated with ceftriaxone- and metronidazole-specific T cells. *Dermatol* 1999;**199**:25–30.
2. GARCIA-DOVAL I, LECLEACH L, BOCQUET H, OTERO XL, ROUJEAU JC. Toxic epidermal necrolysis and Stevens–Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000;**136**:323–327.

Delayed-type hypersensitivity to heparins

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Keywords: adverse effect; cross-reaction; Delayed-Type Hypersensitivity; drug allergy; fondaparinux; heparin; intradermal test; patch-test; pregnancy; skin prick test; subcutaneous challenge.

Tromboprophylaxis in pregnancy is usually carried out with low molecular weight heparins (LMWH). Sensitization to LMWH is problematic as cross-reactivity is common and hirudins and oral anticoagulants are contra-indicated in pregnancy.

A 33-year-old woman with anti-phospholipid syndrome and severe

trombo-embolic episodes in the past was referred for investigation for heparin hypersensitivity. On referral she was pregnant in week 28. Until pregnancy was recognized she was treated with coumarin. Then treatment with commercialized preparations of unfractionated and fractionated heparins was instituted, but generalized pruritus and eczema at the injection sites occurred.

The patient was investigated for allergy towards commercialized UFH, LMWH and Fondaparinux. Basophile Histamine Release, patch tests and skin prick test were negative. Intradermal tests (IDT) with the LMWHs were negative on immediate readings, but positive on day 2 with pruritic eczematous lesions at the sites of injection. The IDT with heparin sodium was positive on concentration 1 : 1. Subcutaneous challenge (SCC) was not performed. Intradermal tests and SCC for Fondaparinux were negative.

In week 37 a caesarean was performed. Fondaparinux was used without complications (Table 1).

Delayed-Type Hypersensitivity (DTH) is a frequently reported cutaneous side-effect of heparins and heparinoids (1–3).

Cross-reactions between UHF, LMWH and heparinoids are common in DTH (1, 2, 4). Danaparoid reacts with heparin-associated antibodies in up to 73% of patients with DTH (1). Whether DTH predisposes to Heparin-Associated Thrombocytopenia (HAT) is discussed, as heparin-platelet factor 4 antibodies have been described in this condition (5).

Fondaparinux is a synthetic coagulation factor Xa-inhibitor which does not cross-react *ex vivo* with the anti-platelet antibodies responsible for HAT (6). This might explain the lack of cross-reactivity described here.

The procedures of investigation are similar to those described by other investigators (3, 7) and appears reliable and safe. No other adverse reaction

Use of the synthetic heparin Fondaparinux in a pregnant woman with Delayed-Type Hypersensitivity to heparins.

Table 1. Investigation of Delayed-Type Hypersensitivity for heparins (Patch-, skin prick- & intradermal tests)

	D0	D3	D7
Patch test			
Heparin sodium (Leo® Pharma) 25 000 IU/ml 30% aq. & p.p.	–	–	–
Dalteparin (Pharmacia®) 10 000 IU/ml, 30% aq. & p.p. ³	–	–	–
Enoxaparin (Aventis Pharma®) 10 000 IU/ml, 30% aq. & p.p. ³	–	–	–
Tinzaparin (Leo® Pharma) 3500 IU/ml, 30% aq. & p.p.	–	–	–
Skin prick test			
Heparin sodium (Leo® Pharma) 5000 IU/ml, 1 : 100–1 : 1 ³	–		
Dalteparin (Pharmacia®) 10 000 IU/ml, 1 : 100–1 : 1 ³	–		
Enoxaparin (Aventis Pharma®) 10 000 IU/ml, 1 : 100–1 : 1 ³	–		
Tinzaparin (Leo® Pharma) 4000 IU/ml, 1 : 100–1 : 1	–		
Fondaparinux (Sanofi Synthelabo®) 5 mg/ml, 1 : 100–1 : 1	–		
Intradermal test			
	D0	D2	
Heparin sodium (Leo® Pharma) 5000 IU/ml, 1 : 10 000–1 : 1 ³	+	+	(1 : 1)
Dalteparin (Pharmacia®) 10 000 IU/ml, 1 : 10 000–1 : 1 ³	–	+	(1 : 1)
Enoxaparin (Aventis Pharma®) 10 000 IU/ml, 1 : 10 000–1 : 1 ³	–	+	(1 : 1)
Tinzaparin (Leo® Pharma) 4000 IU/ml, 1 : 10 000–1 : 1	–	+	(1 : 1)
(20 neg. controls)			
Fondaparinux (Sanofi Synthelabo®) 5 mg/ml, 1 : 10 000–1 : 1	–	–	
(two neg. controls)			
Subcutaneous challenge			
Fondaparinux (Sanofi Synthelabo®) 5 mg/ml, 0.5 ml	–	–	

–, Negative; +, positive.

occurred and a safe alternative was found.

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References

- GRASSEGGER A, FRITSCH P, REIDER N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001;**27**:47–52.
- KOCH P, REINHOLD S, BUSCH C. Delayed allergic skin reactions to subcutaneous heparins. Tolerance of 2 recombinant hirudins. *Contact Dermatitis* 2000;**42**: 278–279.
- FIGARELLA I, BARBAUD A, LECOMPTE T, DE MAISTRE E, REICHERT-PENETRAT S, SCHMUTZ JL. Réaction cutanée d'hypersensibilité retardée avec polysensibilisation aux héparins et héparinoïdes [Cutaneous delayed hypersensitivity reactions to heparins and heparinoids]. *Ann Dermatol Vénereol* 2001;**128**:25–30.
- MOREAU A, DOMPMARTIN A, ESNAULT P, MICHEL M, LEROY D. Delayed hypersensitivity at the injection sites of a low-molecular-weight heparin. *Contact Dermatitis* 1996;**34**:31–34.
- HARENBERG J, HUHLE G, WANG L, HOFFMANN U, BAYERL C, KEROWGAN M. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy* 1999;**54**:473–477.
- GIANGRANDE PL. Fondaparinux (Arixtra): a new anticoagulant. *Int J Clin Pract* 2002;**56**:615–617.
- MORA A, BELCHI J, CONTRERAS L, RUBIO G. Delayed-type hypersensitivity skin reactions to low molecular weight heparins in a pregnant woman. *Contact Dermatitis* 2002;**47**:177–178.