

Auriculotemporal syndrome: differential diagnostic of food allergy

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Key words: auriculotemporal nerve; children; erythema; Frey's syndrome.

Three children suffering from cutaneous symptoms related to food were referred to our department.

A 7-year-old girl had a history of facial flushing extending from the left corner of the mouth to the left temporal area when she ate apple, orange and candies. The flushing began at 4 months of age when solid foods were introduced. The clinical symptoms appeared immediately on mastication and disappeared within a few minutes after eating. Checking her antecedents, it was found that forceps had been used in the delivery. Skin tests by prick–prick were negative for the foods mentioned above.

A 4-year-old boy presented with facial erythema in the right cheek some time after eating olives, York ham or fried tomato sauce since he was 2 years of age. Cutaneous erythema spontaneously disappeared in half an hour. Skin prick tests (SPT) with a battery of common inhalants and food were negative. In his personal history, forceps had been used for the delivery.

An 18-month-old boy had a history of facial erythema that began at 5 months of age when solid foods, particularly apple, orange and melon were introduced. Five minutes after ingestion, an erythema appeared in the left cheek and

disappeared spontaneously in 1 h. This child had been delivered with the aid of low forceps. SPT with a commercial battery of food and with fruits were all negative. Specific IgE measured with the Pharmacia CAP system IgE FEIA (Uppsala, Sweden) to apple, orange and melon were negative. Open oral challenge test with apple reproduced the symptoms, that subsided approximately 15 min after the food was taken. No sweating was noted.

These three cases correspond to the auriculotemporal syndrome (ATS), also known as gustatory flushing syndrome or Frey's syndrome, described for the first time by Duphœnix in 1757 and published by Frey in 1923 (1).

The condition is uncommon in children. It has been related to facial trauma produced by the use of forceps in the delivery and our cases had this antecedent. However, it has been described even in some cases without instrumental delivery (2, 3). The symptoms start immediately on mastication and disappear spontaneously several minutes after stopping. It is triggered by those foods that increase salivation like fruits, candies, spices and hard food which need more mastication.

The pathophysiology of the syndrome is not completely understood. The most accepted theory is that after the injury of the nerve, regenerating parasympathetic fibrils may become misdirected, joining with distal sympathetic nerves. Consequently, mastication leads to sweating and erythema on the auriculotemporal nerve distribution area, instead of salivation. In children without a trauma antecedent, congenital aberrant innervation might be the cause.

Diagnosis may be suggested by clinical symptoms and confirmed by negative allergologic studies and a positive oral provocation with the implied food.

In children it appears to be a benign condition and no specific therapy is recommended. Spontaneous remissions have been described after 2–5 years of

follow up (2, 4). However, in most of the publications the follow-up is not reported. In our cases no remission was observed even after 6 years, 2 years and 13 months.

In conclusion, although rare, ATS must be included in the differential diagnosis of adverse food reactions but mainly of food allergy. The knowledge of this syndrome is necessary to prevent complicated diagnostic techniques, and avoiding wrong diets of elimination.

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Allergy to dogfish

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Key words: anaphylaxis; dogfish; fish allergy; parvalbumins.

Fish is a common cause of immediate food allergy (1–3) and parvalbumins

represent the main described allergens (Gad c 1, Gad m 1, Sal s 1) (4–6).

Parvalbumins are calcium binding proteins from fish muscle which showed a

Sensitization to dogfish and related species.

molecular mass of around 12 kDa. All of them have similar biologic properties, although the aminoacid sequence is particular to each species, which clearly separated parvalbumins of bony fishes from those of cartilaginous fishes (7, 8).

Dogfish is a big fish member of the Carcharhinidae family related to Squalidae and Rajidae families.

A 56-year-old man, with allergic rhinitis developed anaphylaxis (perioral itching, generalized redness, tongue and laryngeal edema and dyspnea) immediately after eating cooked dogfish. Epinephrine and other parenteral drugs were required at the Emergency room. Two years ago he presented one episode of contact urticaria while cleaning dogfish at his wife's fish shop. No previous dogfish or shark-like fishes intake was referred. Posterior ingestion of hake, horse mackerel, swordfish anglerfish and molluscs, as well as small pieces of ray (Rajidae family), were tolerated without adverse reactions.

Skin Prick tests (SPT), performed with commercial extracts, were positive to mites and negative to others common inhalants, codfish, herring, clam, squid, prawn, and *Anisakis simplex*. SPT with

raw and cooked dogfish extract were strongly positive in the patient. Four atopic and one exposed nonatopic subjects were used as controls, with negative results. Prick-prick tests with raw pieces of dogfish, *Squalus acanthias* and ray were positive (wheal diameter of 15, 30, and 20 mm, respectively). Serum specific immunoglobulin E (IgE) by means of enzyme allergosorbent test (EAST) (HY-TEC-EIA Hycor Biomedical Ltd, Penicuik, UK) against the same allergens were 1.4, 3.47 and 0.8 kU/l, respectively.

Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) in 12.5% acrylamide gel, was performed and showed similar protein bands in the three fishes, with molecular masses between 13 and 107 kDa and a more prominent band at approximately 13 kDa in ray extract. The SDS-PAGE immunoblotting revealed one IgE-binding protein band of < 14 kDa in *Squalus*, whereas no band can be seen in ray and dogfish extract. The SDS-PAGE immunoblotting using a rabbit polyclonal serum anti-herring parvalbumin showed, in the three extracts, bands with similar molecular mass to that appeared in the *Squalus* extract. High molecular weight bands seem to be parvalbumin aggregates (Fig. 1).

The EAST-inhibition assays demonstrated inhibition of IgE binding to *Squalus* proteins by different dilutions of

dogfish and ray extracts, up to 54 and 86% respectively, when inhibitor allergen concentration was 1 mg/ml. Homologous inhibition was observed (> 90%) whereas sunflower pollen extract did not affect EAST values to *Squalus* (< 10%).

In conclusion, this case illustrates sensitization to dogfish and related species. A thermostable allergen with an apparent molecular mass of 14 kDa, probably a parvalbumin, is implicated.

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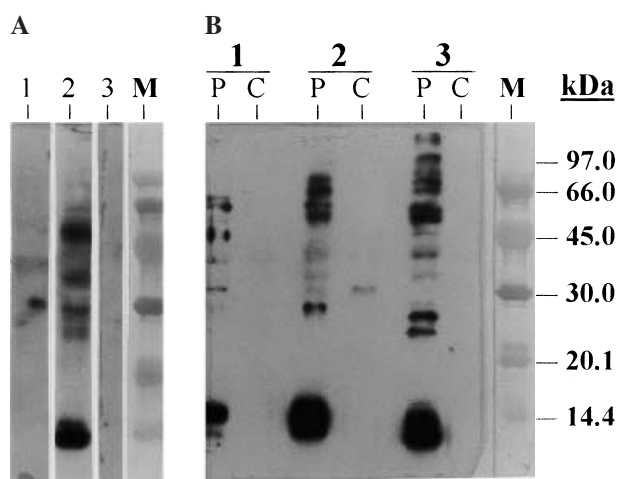


Figure 1. (A) sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting-IgE: Lane (1) dogfish; (2) *Squalus*; (3) ray; (M) marker. (B) The SDS-PAGE immunoblotting polyclonal serum anti-herring parvalbumin. P, patient; C, control serum. Lane (1) dogfish; (2) *Squalus*; (3) ray; (M) marker.

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Allergy to human insulin

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Key words: diabetes mellitus; human recombinant insulin; insulin lispro; systemic reaction.

Adverse reactions to insulin were not uncommon in the past, with porcine and bovine preparations (1). The introduction of human

recombinant insulin has lowered, but not eliminated, allergic reactions, now reported in <1% of diabetic patients treated with insulin (2).

Insulin allergy may be manifested as an immediate-type IgE-mediated local

or systemic reaction, delayed type hypersensitivity or as serum sickness, varying in severity from mild discomfort to life-threatening events.

We describe a case of anaphylactic reaction due to allergy to human recombinant insulin.

A 60-year-old man with no history of allergy was diagnosed as having non-insulin-dependent diabetes mellitus in 1999. In June 2002, treatment began with human recombinant insulin (Humulin NPH®, Lilly, Indianapolis, IN). Shortly after initiating treatment he developed local hives at the injection sites, 25–30 min after each injection, which subsided within 1–2 h without treatment.

In October 2002, 5 min after the insulin injection, he presented palmo-plantar pruritus, generalized urticaria, facial angioedema, oedema of the tongue, shortness of breath with dyspnoea and wheezing. He was treated with adrenaline and systemic corticoids.

We report a case of severe systemic reaction to human recombinant insulin in a patient with diabetes mellitus. Tests performed demonstrated immediate type 1 hypersensitivity to human insulin.

The patient was admitted to our hospital in December 2002 to evaluate a possible insulin allergy. Physical examination was normal. Total serum IgE was within the normal limits. Specific IgE to human recombinant insulin and insulin lispro were 2.6 and 1.5 kU/l (class 2), respectively (EAST, Bial-Aristegui, Bilbao, Spain). Specific IgE to latex was negative. Cutaneous tests were performed with human recombinant insulin, porcine insulin, the human insulin analogue lispro and additives of insulin preparations (protamine, *paraben*, metacresol, phenol, zinc, isophane) using the Novo Insulin Allergy kit (NovoNordisk A/S, Bagsvaerd, Denmark). Prick and intradermal tests were negative for all the additives. Intracutaneous tests (1/100) were positive for human and porcine insulin and for human insulin lispro as well. Tests performed in 10 controls were negative.

Severe systemic reactions to insulin are rare in clinical practice today. Näf et al. (2) describe a patient suffering from general urticaria following human insulin injection. Moriyama et al. (3) report the case of a 45-year-old type 1 diabetic man with itching skin rash and facial oedema after injection of porcine insulin.

In our case, results of clinical signs, cutaneous and *in vitro* tests showed that immediate-type IgE-mediated hypersensitivity caused the reaction. This patient had a positive reaction with porcine insulin. As he had never been treated with it in the past, there may be cross-reactivity between both insulins.

In most patients with allergy to human insulin, insulin lispro (a genetically engineered insulin analogue) (Humalog®, Lilly, Indianapolis, IN) has been well tolerated due to its rapid dissociation in monomers (4). However, our patient showed positive results in the tests to this type of insulin.

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Urticaria and angioedema due to itraconazole

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Key words: angioedema; candidiasis; itraconazole; oral challenge test; triazole antifungal agent; urticaria.

New antifungals for topical and systemic treatment of mycotic infections of the skin and nails

have been developed in the last decade. Itraconazole is a new triazole agent used for treat-

ment of histoplasmosis, coccidioidomycosis, sporotrichosis, candidiasis and selected cases of cryptococcosis and aspergillosis. This analogue of ketoconazole has a broader antifungal spectrum with a higher safety profile. Itraconazole is metabolized in the liver by a greater specificity for the fungal cytochrome P-450 14- α -demethylase (1).

Allergic reactions caused by antifungal drugs are not frequent in the everyday clinical practise. The immediate hypersensitivity to itraconazole is extremely rare and there are no well-documented

Cutaneous reaction to an antifungal drug with positive challenge test.

reports demonstrating an allergic reaction. This drug has been associated with photosensitivity rash (2), drug eruption (3) and acute generalized exanthematous pustulosis (4). Cross-reactivity with other azole derivatives is possible, but it has not been demonstrated. Until now, the pathogenic mechanism of adverse reactions from itraconazole and other azole derivatives is unknown. There are two reports of desensitization to itraconazole (5–6).

A 65-year-old man began oral treatment with itraconazole (Sporanox®; Janssen-Cilag, Madrid, Spain), 100 mg twice a day for prophylaxis of candidiasis. Three days after, he developed angioedema of the face and generalized urticaria. The symptoms responded promptly to parenteral steroids. He had no allergic personal or familiar background. He had previously been tolerating this drug 2 years ago without any problem. There were no previous episodes of urticaria or angioedema and no sunlight exposure was referred.

Skin prick test with common airborne, latex, anisakis, alimentary allergens, and itraconazole with a concentration of 10 mg/ml were all negative. A double-blind oral challenge test with commercial itraconazole was performed showing an immediate response with symptoms of eruption maculopapular and angioedema within 2 h from the initiation of the test. Parenteral 6-methyl-prednisolone 80 mg and dexchlorpheniramine 5 mg were administered, after which the clinical picture abated. No late response was observed.

In order to find an alternative treatment, we performed a double-blind oral challenge test with other triazole antifungals agents, with a normal tolerance of fluconazole 100 mg and ketoconazole 200 mg. As no other cause could be identified, itraconazole was probably the cause of the angioedema. There were no further episodes of urticaria in the patient after the withdrawal of the involved drug.

To our knowledge, we report the first case of acute urticaria and angioedema due to itraconazole where the immediate response in the challenge test strongly suggest that itraconazole was the drug responsible of the clinical reaction

produced by an IgE-mediated hypersensitivity mechanism.

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Tolerance to the synthetic pentasaccharide fondaparinux in heparin sensitization

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Key words: adverse drug reaction; anticoagulation; heparin intolerance; high and low molecular heparins; synthetic pentasaccharide; therapeutic alternatives.

Case 1: A 68-year-old female patient was referred to our department with a history of repeated

localized skin reactions at the injection sites after the administration of

Fondaparinux is an alternative in heparin intolerance.

nadroparin, certoparin and heparin sodium. The lesions were itchy and eczematous in nature, developed shortly after starting the respective anticoagulant medication, and persisted for several days. Patch testing was performed with multiple heparin preparations (heparin-Na, heparin-Ca as well as certoparin, dalteparin, nadroparin, the xylanopolyhydrogensulfate pentosanpolysulfate, and the synthetic heparin pentasaccharide fondaparinux) and showed a type-IV sensitization to certoparin. Prick testing was negative, yet intracutaneous (i.c.) testing revealed a positive reaction to nadroparin, dalteparin, heparin-Ca and heparin-Na. The subcutaneous (s.c.) administration of pentosanpolysulfate and fondaparinux was tolerated without skin changes.

Case 2: A 62-year-old female patient presented with a history of localized skin reactions at the injection sites after nadroparin and one other heparin that could not be named. Patch tests with the above mentioned panel showed a type-4 reaction to nadroparin and dalteparin. Prick tests revealed no sensitization. I.c. testing, however, resulted in a delayed-type reaction after 6 days to heparin-Na and heparin-Ca. Subsequently, s.c. challenge with pentosanpolysulfate and fondaparinux was performed. Fondaparinux was well tolerated, yet pentosanpolysulfate yielded a positive reaction after a few days.

Adverse reactions to various kinds of heparins (high and low molecular-weight) are a well known problem in daily clinical practice (1). Whereas immediate-type reactions to heparins are rare, delayed-type reactions have been increasingly reported in recent years (1). Lesions usually develop 2–4 days after injection and are erythematous, infiltrated and sometimes eczematous in nature. Lesions may become generalized, if treatment is continued. The structural similarities of high and low molecular-weight heparins entail a high likelihood of cross reactions between different kinds of heparin prep-

arations. The heparinoid danaparoid-Na and the related pentosanpolysulfate have frequently been used as alternatives, yet we and others have reported on skin reaction to the latter as well (1, 2) and a cross-reactivity between heparins and the former has also been described (3, 4). Hirudin which has been used as alternative drug for patients with heparin induced thrombocytopenia (5) has also been shown to cause delayed-type hypersensitivity reactions (6, 7) and its repeated application has even led to fatal outcomes. This emphasizes the necessity for an alternative, structurally different drug.

Fondaparinux, a synthetic pentasaccharide, is the first in a new class of antithrombotic agents that selectively inhibit coagulation factor Xa. In several clinical trials, fondaparinux turned out to be more effective than enoxaparin in preventing venous thromboembolism after major surgery (8, 9). The drug has also been shown to be effective in the therapy of acute venous thromboembolism and acute coronary syndrome. Antibody-induced thrombocytopenia in association with fondaparinux has so far not been described (9).

Similar to one of our cases previously described (2), our second case stresses the fact that delayed-type, localized skin reaction to pentosanpolysulfate can occur without prior exposure to that particular drug, if sensitization has taken place with structurally related heparins. Fondaparinux, as a novel drug, appears to be a valuable alternative agent in these circumstances and in cases, in which one wants or needs to avoid hirudin.

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Skin delayed-type hypersensitivity to josamycin

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Key words: delayed-type hypersensitivity; josamycin; macrolides; skin tests; toxicoderma.

Although intolerance reactions to macrolides are common, allergic reactions mediated by effectors of specific immunity seem to be exceptional. We report on a patient who presented with a

delayed-type hypersensitivity to josamycin in the form of a maculo-papular exanthema.

Allergic reactions caused by drugs are hypersensitivity reactions mediated by effectors of specific immunity, i.e. antibodies or T lymphocytes (1, 2). Allergies to macrolides are rare (3, 4). We report on a patient who presented with a proven delayed-type hypersensitivity (DTH) reaction to josamycin.

A young woman aged 32 years, with no particular medical history, was referred to this service for investigation of a toxicoderma to josamycin (Josacine®, Bayer Pharma, Puteaux, France). Two years previously, on the second day of treatment with josamycin, prescribed for rhino-pharyngitis, the patient presented with a generalized erythema, leading to stoppage of the treatment. The signs disappeared within a few days.

Skin tests with josamycin (using the drug in its commercialized form, diluted 10% in water), undertaken 2 years after the drug reaction, were negative at the 72-h readings. The prick tests and the intradermal reactions were also negative on immediate and delayed readings. Josamycin was reintroduced during hospitalization, at progressive doses, under medical supervision. Four hours after taking a full dose of josamycin (one tablet of 500 mg), the patient presented with a generalized maculo-papular exanthema, which increased in intensity during 24 h and regressed over a week's time.

A new series of skin patch tests was performed 2 months later. Tests were positive at the 72-h readings with a typical aspect of contact dermatitis (Fig. 1). A biopsy confirmed the diagnosis of skin DTH reaction and revealed a prominent infiltration of mononuclear cells. Immunostaining demonstrated a majority of CD3+ lymphocytes, about two-thirds of these cells being CD8+ T cells.

Reactions to macrolides are rare, and principally concern erythromycin and spiramycin (3, 5). The series published in the literature do not exceed 10 cases. The mechanisms of the reactions observed have rarely been evaluated by skin tests capable of confirming the allergic origin of the accident, in order to distinguish it from intolerance (pseudo-allergic) reactions. Certain authors confirm the existence of an immuno-allergic reaction if the drug

A case of delayed-type hypersensitivity to josamycin in the form of a maculo-papular exanthema.

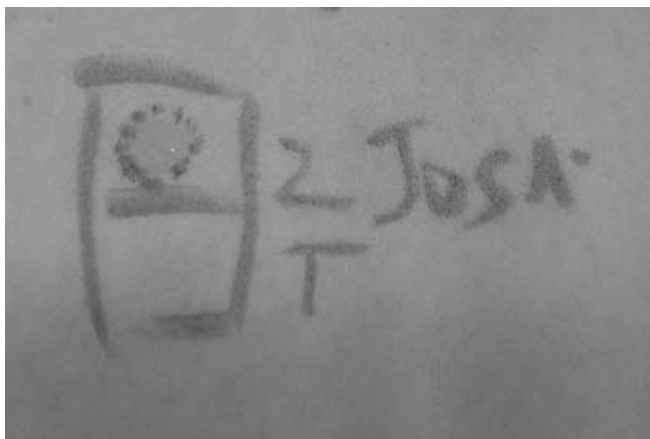


Figure 1. Patch test for josamycin (reading at 72 h).

reintroduction test is positive (6), whereas such observations only prove that the drug is responsible for causing the reaction observed in the patient, but seems insufficient to define the mechanisms (allergic or pseudo-allergic) of the reaction.

If intolerance reactions when taking josamycin are not uncommon, reactions of a proven allergic origin seem to be exceptional and we have not found another case in the literature. Our patient presented a skin DTH reaction to josamycin. The first series of tests with josamycin were negative, probably because of the long time (2 years) between the last intake of josamycin and the commencement of tests. Reintroduction of josamycin was followed by a skin DTH reaction. This was associated with reactivation of specific T cells as patch tests were positive 2 months later. Skin tests to other macrolides have not shown evidence of cross-reactions, which is a common finding in immediate (type I) hypersensitivity to macrolides. Further, skin tests on control subjects using josamycin have shown no delayed inflammatory reaction at the site of drug skin contacts.

Diagnosing patients who present a skin eruption typical of toxicoderma caused by macrolides must be carried out with particular care and should start with precise, detailed questioning. The dermatological investigation must be undertaken at some distance from the accident, 6 weeks to 6 months later, and should consist at first of patch tests. If the patch tests are positive, the drug that was implicated is considered contraindicated, after having looked for an allergic cross-

reaction with other macrolides, a hypothesis which seems rare (3, 6). If the patch tests are negative, the investigation must be completed with prick tests, then with tests for intradermal reactions, if the prick tests are negative (7). Any positive results lead to the same contraindication of the molecule. If these tests are negative, the drug may be reintroduced, under surveillance. A negative provocation test allows the drug to be taken again. If the provocation test is positive, it would appear necessary to redo the dermatological tests at a later date. Although the first series of tests (carried out 2 years after the allergic reaction) were negative, the second series of tests (carried out 2 months after reintroduction) were positive, which enabled the diagnosis of DTH.

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Successful docetaxel tolerance induction

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A 35-year-old man with stage T₄N₃M₀ nonsmall cell lung carcinoma was admitted to hospital for docetaxel infusion.

In July 2001, the appearance of a superior cava syndrome lead to the diagnosis of undifferentiated lung carcinoma at stage T₄N₃M₀. This patient was treated by thoracic radiotherapy (40 Gy) together with cisplatin 100 mg/m² and vinorelbine 25 mg/m² resulting in a dramatic regression of the cava syndrome.

After three cycles of first-line chemotherapy, a right cerebral occipital

We describe the case of an anaphylactic reaction 5 min after an i.v. injection of docetaxel and a successful tolerance induction 12 weeks later.

Table 1. One-day protocol of tolerance induction to docetaxel (13 doses were prepared by the pharmacy of the university hospital and injected intravenously at 30-min intervals)

docetaxel (% of therapeutic dose of 75 mg/m ²)
1/10 ⁶
3/10 ⁶
1/10 ⁵
3/10 ⁵
1/10 ⁴
3/10 ⁴
1/10 ³
3/10 ³
1/10 ²
3/10 ²
1/10
3/10
1/2

metastasis and a left inguinal metastasis appeared. They were treated by local radiotherapy (10 Gy), and chemotherapy was changed. In November 2001, he received docetaxel (Taxotere^R) 75 mg/m² which resulted in the appearance of an immediate (< 5 min) and generalized urticaria associated with bronchospasm, without any drop of the blood pressure. This severe anaphylactic reaction was successfully treated by intravenous dexchlorpheniramine and dexamethasone. Chest X-rays failed to show any sign of pneumonitis. The administering of docetaxel was halted and anticancer treatment ensued with localized radiotherapy and gemcitabine. This treatment did not prevent the progression of the disease and the development of further metastases (hepatic and suprarenals).

Because the patient was young and no other treatment was available for his metastatic lung cancer, a tolerance induction of docetaxel was administered in February 2002 without any premedication and according to the protocol detailed in Table 1. Thirteen increasing

doses were injected every 30 min under hospital supervision. All doses were prepared by the pharmacy of our University Hospital. Preceding every injection, the appearance of any signs of hypersensitivity was checked. This protocol lasted 6 h and 30 min. The patient remained under medical observation for 24 h.

No sign of immediate or delayed hypersensitivity reaction was observed. A second therapeutic course was planned 3 weeks after the first induction of the Docetaxel. Regrettably the patient died the day before the second course because of the progression of the cancer.

Paclitaxel and its related compound docetaxel are highly active drugs in the treatment of breast, ovarian, lung and other cancers (1).

Hypersensitivity reactions occur in 2–5% of patients treated with paclitaxel and 25–50% of patients treated with docetaxel (1, 2). Docetaxel is recommended as an alternative for patients who have experienced hypersensitivity reactions to paclitaxel (2, 3). In some cases, this alternative is complicated by hypersensitivity to docetaxel (4), and tolerance induction to paclitaxel has been proposed (5). We have applied this alternative to other drugs with success (6, 7) and have now applied it to docetaxel. In this particular patient, we have not referred to the mechanism of docetaxel hypersensitivity, although we did perform skin prick (10 mg/ml) and intradermal (1 mg/ml) tests which were proved to be negative (not shown). The immunological mechanism of taxoid hypersensitivity is unknown, although for paclitaxel a direct mast cell activation is postulated (2) as well as an hypersensitivity to some excipients (i.e. cremophor EL for paclitaxel, polysorbate 80 for docetaxel) has been suggested but never demonstrated (3). Prophylactic treatment with oral glucocorticosteroids, H1-antihistamines and in some cases tolerance induction are all likely to be effective in most patients. Exten-

sive basic studies are required in order to better understand taxoid hypersensitivity considering the great potential of these drugs in many cancer cases.

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