

pruritus, dyspnoea, chest pain, diarrhoea. Blood pressure was 120/60 mmHg, while the pulse was arrhythmic as well as the heart beat. Electrocardiogram (ECG) showed atrial fibrillation (average ventricular frequency 120 beats/min). He was treated with 1 g of hydrocortisone i.v. and 10 mg clorpheniramine maleate i.m.; after 10 min, as he did not improve, 250 ml of saline solution with 1 g of methylprednisolone and 50 mg ranitidine i.v. were administered.

The patient after 5 min improved and presented only a mild erythema of the face and chest. Another ECG was carried out and showed sinus rhythm (78 beats/min.) so that no antiarrhythmic drugs had to be administered.

Echocardiography showed no ventricular kinetic disorder, normal cardiac size, normal valvular flow, ejection fraction 60%.

Blood tests were normal except for erythrocytation rate (ESR) (25 mm), C reactive protein (CRP) (19.50 mg/l), gammaglobulins (22.5%), glycemia (171 mg/dl), uric acid (9.40 mg/dl), alkaline phosphatase (353 U/l), neutrophilia (76%), monocytes (3%).

The patient reported that he had been under treatment for over 25 years with histamine antagonists (H1 and H2) associated, more recently, with anti-leucotrienes because of a systemic mastocytosis diagnosed elsewhere after skin, bone and bone marrow biopsy. He reported frequent episodes of flushing with intense pruritus, dyspnoea, diarrhoea and severe hypotension; during the last two attacks, about 1 year and 6 months before, treated elsewhere, atrial fibrillation had been registered.

In literature, it has been reported that cardiac involvement may occur during systemic anaphylaxis (3); in fact it has been shown that mastocytes are present in human heart (4), that during anaphylaxis there is a release of mediators from cardiac mastocytes (5) and that histamine causes an increased frequency and ejection fraction (6). This may explain the cardiac involvement in the case of systemic mastocytosis above reported as the patient had a negative history of cardiac disease and there were no predisposing factors for arrhythmia (alcohol, coffee, cocaine, hyperthyroidism, drugs).

We considered it of interest to report this case as it suggests that cardiac

anaphylaxis may occur during a systemic mastocytosis attack even if further studies on the cardiac involvement in systemic mastocytosis are needed.

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References

1. Golker L, Bernhard JD. Mastocytosis. The Lancet 1997;**349**:1379–1385.
2. Thomas D, Dragodanne C, Frank R, Prier A, Chomette G, Grosgeat Y. Systemic mastocytosis with myo-pericardial localization and atrioventricular block. Arch Mal Coeur Vaiss 1981;**74**:215–221.
3. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol 2002;**110**:314–318.
4. Patella V, Marinò I, Lamparter B, Arbustini E, Adt M, Marone G. Human heart mast cells. Isolation, purification, ultrastructure and immunologic characterization. J Immunol 1995;**106**:386–393.
5. del Balzo UH, Levi R, Polley MJ. Cardiac dysfunction caused by purified human C3a anaphylatoxin. Proc Natl Acad Sci USA 1985;**82**:886–890.
6. Vigorito C, Russo P, Ricotti JB, Chiariello M, Poto S, Marone G. Cardiovascular effects of histamine infusion in man. J Cardiovasc Pharmacol 1983;**5**:531–537.

Isolated urticaria to ondansetron and successful treatment with granisetron

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Key words: drug allergy; ondansetron; urticaria.

The 5-Hydroxytryptamine₃ (5-HT₃) receptor antagonists (ondansetron, granisetron, dolasetron and tropisetron) are

powerful, well tolerated antiemetic drugs for which very few hypersensitivity reactions have been described (1–6).

In October and November 2003, a 42-year-old man presented two episodes of isolated and generalized urticaria a few hours after chemotherapy for pancreatic adenocarcinoma, consisting of gemcitabine, oxaliplatin, ondansetron, alizapride chlorhydrate and methylprednisolone. The first episode appeared 12 h after the first course and the second 30 min after the second ondansetron injection (other drugs had not yet been given). For the third course of chemotherapy, ondansetron was replaced by metopimazine and a high dose of methylprednisolone. Hypersensitivity reaction did not occur following this replacement, although nausea and vomiting were severe. Before these episodes, the patient had never been given ondansetron. The patient had no other medical history, in particular other drug allergy, apart from an intermittent allergic rhinitis (because of plane tree and birch) for about 8 years. Since Levine demonstrated for penicillins that IgE-dependant reactions could occur up to the 72th hour after drug administration (7), an IgE-dependant mechanism is always suspected when a typical clinical pictures of drug hypersensitivity occurs within the first 24 h after drug intake.

To confirm the presence of IgE antibodies specific for ondansetron, skin test was performed with this drug and two other 5-HT₃ receptor antagonists. Prick tests to ondansetron (pure concentration: 2 mg/ml), dolasetron (20 mg/ml) and granisetron (1 mg/ml) were all negative. Intradermal tests (IDT) to ondansetron proved positive at 0.2 mg/ml, with a wheal at 30 min of 2.5 times that of the initial papule. The IDTs tested negative to dolasetron and granisetron at 1/10 and at full concentrations. As these drugs are injected in short infusion, we choose to test up to pure concentration. Seven normal controls were tested and proved negative for IDTs to ondansetron at 0.2 mg/ml (wheals under 1.1 times that of the initial wheal); one emerged as positive

We describe a unique case of urticaria due to a selective allergy to ondansetron.

at 2 mg/ml (wheal of 1.5 times). Because the patient required 5-HT₃ receptor antagonists, we challenged him the same day with granisetron. He received intravenously at 30-min intervals and under strict hospital surveillance increasing doses of granisetron, starting with 1 mg up to the therapeutic dose of 100 mg. He consequently failed to experience any hypersensitivity reaction and could thereafter complete his chemotherapy trial.

The 5HT₃-induced anaphylaxis has been described several times (1–6) and considered as a class effect (6) until a recent report (5) where the authors described an IgE-mediated allergy to granisetron and safe use of ondansetron. Both ondansetron and tropisetron share an indole heterocycle, however ondansetron and granisetron do not and this may possibly explain the absence of cross-reactivity between the latter two drugs. Considering the positive skin tests in our patient, the negative skin tests in seven controls and negative histamine release test in one case report (5), ondansetron does not appear to be a nonspecific histamine-releaser. Our case report underlines the importance of a thorough drug allergy work up.

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References

1. Ross AK, Ferrero-Conover D. Anaphylactoid reaction due to the administration of ondansetron in a pediatric neurosurgical patient. *Anesth Analg* 1998;**87**:779–780.
2. Kossey JL, Kwok KK. Anaphylactoid reactions associated with ondansetron. *Ann Pharmacother* 1994;**28**:1029–1030.
3. Weiss KS. Anaphylactic reaction to ondansetron. *Arch Intern Med* 2001;**161**:2263.
4. Chen M, Tanner A, Gallo-Torres H. Anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993;**119**:862.
5. Kanny G, Beaudouin E, Moneret-Vautrin DA. IgE-mediated allergy to granisetron and safe use of ondansetron. *J Allergy Clin Immunol* 2001;**108**:1059–1060.
6. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine(3) receptor antagonists: a class effect? *Lancet* 1996;**347**:584–585.
7. Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med* 1966;**275**:1115–1125.

Allergy to pholcodine: first case documented by oral challenge

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Key words: intradermal test; oral challenge; pholcodine.

Pholcodine (morpholinyl-ethyl-3 morphine) is an anti-tussive opiate indicated for the symptomatic treatment of cough. This substance is a component of many medicinal products. We report the first documented case of allergy to pholcodine proved by positive oral challenge.

In 1992, a female, 33 years old, presented with facial angio-edema 8 h after taking Respilène® (Coopération Pharmaceutique Française, Melun, France), syrup containing pholcodine associated with domperidone, tixocortol and bacitracine, for a sore throat. Symptoms resolved after i.v. administration of corticosteroids.

She had a history of facial angio-edema related to a β -lactam for 8 years.

Prick tests to routine airborne allergens were negative. Intradermal test (IDT) to

5 μ g/ml pholcodine (Coopération Pharmaceutique Française) was positive: the diameter of the papula was 3 mm after injection and the diameter of the wheal at 15 min was 7 mm, surrounded by erythema. The patch test (20% in vaseline) was negative at 48 h. Skin tests with domperidone, tixocortol, bacitracine and β -lactams were negative (1, 2).

The basophil activation test and leukotriene release test were negative to pholcodine and to amoxicillin.

Open oral challenge with pholcodine was performed with 5 and 15 mg, 1 h apart. Results were positive with the total 20-mg dose: laryngeal angio-edema occurred 9 h after the second dose, disappearing a few hours after corticosteroid i.v. injection. An oral challenge to amoxicillin, 500 mg, was negative.

No case of allergy to pholcodine was found either in the literature or in the French pharmacovigilance database. One case of recurring eosinophilic cellulitis (Wells' syndrome) has been reported, involving other drugs including pholcodine (3). The diagnosis was confirmed by histology. Circulating immune complexes and a peri-vascular deposit of IgG and C3 were detected by direct immunofluorescence. An immunological mechanism mediated by drug-induced immune complexes was postulated. Pholcodine was not formally involved.

This case report documents allergy to pholcodine demonstrated by clinical history, positive skin test and oral challenge at a total 20-mg dose. This reactogenic dose is compatible with the presumed intake: two spoonfuls of Respilène® contain 12 mg of pholcodine. The allergic mechanism involved in this reaction was not formally established: the positive intradermal test indicates an IgE-mediated allergy, but the delay before the reaction is unusual. During the interview, the patient mentioned history of suspected allergy to β -lactams. However, this incident reported might be related to a concomitant intake of pholcodine.

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