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A 54-year-old man, with a previous history of myocardial ischemia in treatment with acetylsalicylic acid 200 mg, ticlopidine and atenolol 50 mg for the previous 4 years, was referred to our department after suffering, 3 years ago, an erythematous and itching eruption in the hands and arms and later in the abdomen and groins, that was started 20 min after administration a tablet of acetylsalicylic acid and a tablet of chlorazepate. The episode resolved within 60 min, with no specific treatment. Acetylsalicylic acid was straight afterwards removed. Later he noticed a similar episode of erythematous and itching eruption on his hands, 15 min after the administration a new tablet of chlorazepate.

We performed intradermal tests with acetylsalicylate of lysine up to a concentration of 18 mg/ml, and with diazepam, midazolam and chlorazepate according to the pharmaceutical concentration commercialized; all these tests were negative both in immediate and in the late readings. We also performed patch testing with chlorazepate, the results of which were also negative.

An oral challenge with 100 mg of acetylsalicylic acid was negative, but

10 min after the oral administration of 2.5 mg of chlorazepate intense pruritus and erythema was noted, which resolved with the administration of 10 mg of cetirizine. One week later, 60 min after the oral challenge with 5 mg of diazepam, a similar episode to the previous one was observed, which also resolved after the administration of 10 mg of cetirizine. Finally, the oral provocation with 25 mg of bentazepam was negative.

Chlorazepate is a long-acting benzodiazepine used for preoperative anxiolysis and sedation. It is metabolized in the microsome oxidases of the liver, across the N-desalkylation and hydroxylation pathways, via the cytochrome p450 (CYP450) (CYP3A4) complex (3). The resulting product is an active metabolite called N-desmethyldiazepam or nordiazepam, common to other benzodiazepines such as chlordiazepoxide, diazepam, ketazolam, medazepam, pinazepam and prazepam. N-desmethyldiazepam mediates all the pharmacological effects.

In the literature we have reviewed we have only found a case of delayed hypersensitivity to the chlorazepate dipotassium (3), which described a

Hypersensitivity to chlorazepate dipotassium

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Key words: chlorazepate dipotassium; drug allergy; immediate hypersensitivity.

The benzodiazepines can produce several types of adverse reactions inclusive hypersensitivity reactions. Until now hypersensitivity reactions have been described following the use of the following benzodiazepines: diazepam (1), tetrazepam (2, 4), clobazam, oxazepam, alprazolam, etizolam (5), nitrazepam, midazolam, temazepam and chlorazepate (3).

Immediate hypersensitivity to chlorazepate dipotassium.

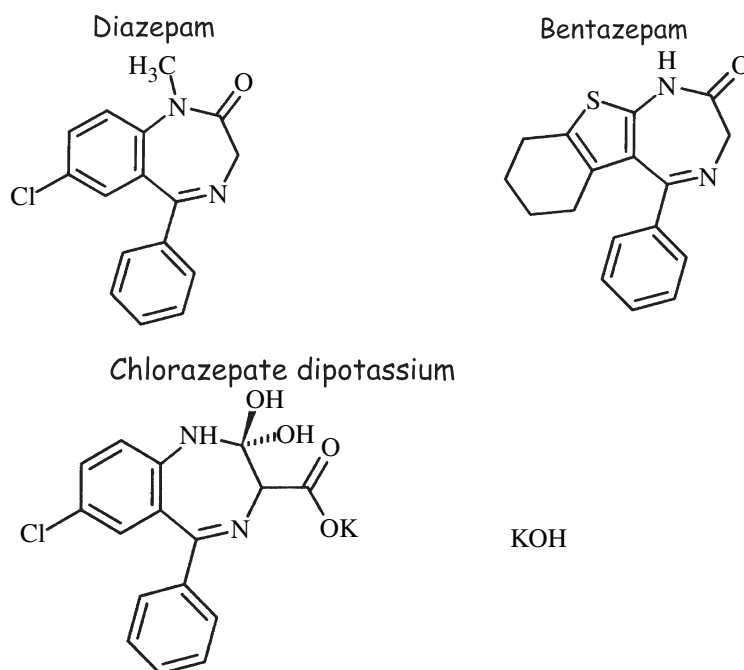


Figure 1. Diazepam, bentazepam and chlorazepate dipotassium.

34-year-old woman who developed a generalized maculopapular exanthem beginning on the hands, one day after the administration of chlorazepate. The patch test with chlorazepate was positive. The prick test and intradermal test with chlorazepate were negative; the lymphocyte transformation test showed proliferative lymphocyte reactivity to chlorazepate in the culture supernatants of peripheral blood mononuclear cells, coincubated with human liver microsomes, whereas in the culture cells without the addition of microsomes no significant proliferation was observed.

We expose a case of probable immediate hypersensitivity to the chlorazepate dipotassium. Although the speed of the appearance of the symptomatology and the clinical characteristics of the episode would seem to point towards an IgE-mediated reaction, the negativity of the cutaneous tests prevents us establishing the pathogenic mechanism with total certainty. It seems clear that it is not a delayed hypersensitivity reaction, because of the quickness of the symptomatology and negative patch test result.

Our patient presented the same symptomatology after the administration of diazepam, although he tolerated the provocation with bentazepam. It is not surprising the existence of cross-reactivity between chlorazepate and diazepam, because of the similar chemical structure of both molecules (Fig. 1), composed by a benzodiazepinic ring with another benzene ring adhered to 5 carbon. In addition both molecules are metabolized in the liver giving rise to the same intermediate active metabolite, the nordiazepam, which probably also accounts for the immunological adverse effects (3, 6). On the contrary, bentazepam belongs to a different drug subgroup called tienodiazepines, which differ in their chemical structure, by the substitution of the benzene ring by a tiofene ring adhered to the diazepinic ring, maintaining the other benzene ring in the 5' carbon extreme. Brotizolam, clotiazepam and etizolam also belong to this group.

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IgE-dependent nephrotic syndrome due to inhalation of chironomid larvae

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Key words: *Chironomus thummi*; immunoglobulin E; nephrotic syndrome.

A 54-year-old man, without any specific past history, ground lyophilized chironomid larvae (*Chironomus thummi*) to feed exotic fish in November 2003. He had prepared this type of powder 5 months before, and had noticed a mild rhinitis. On this occasion, he presented an extensive facial angioedema and dyspnea

in < 15 minutes.

The symptoms subsided within the next hours without any treatment. Within 2 days a generalized edema and a weight increase occurred.

A week later, proteinuria was 3.8 g/24 h, the level of seric proteins was lowered at 44 g/l, total cholesterol had raised to 3.99 g/l (previously controlled at 2.17 g/l). Creatinine was 10 mg/l. A renal biopsy was carried out showing minimal changes with sparse mesangial immunoglobulin (Ig)M deposits, parietal vascular deposits of C3, and intracytoplasmic droplets of albumin in tubulae. A nephrotic syndrome was diagnosed. Simvastatin was prescribed. A prick test with the larvae composed powder gave an impressive reaction, the diameter of the wheal reaching more than 4 cm. After 2 months, a persistent proteinuria was noticed: 1.68 g/l. Seric protides were 62 g/l, total cholesterol 2.5 g/l. Three months later, proteinuria had disappeared. Spirography was normal, test to methacholin (1600 gamma) was negative. The immunologic screen was normal: anti-nuclear antibodies (ACAN), blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total complement, C3 and C4, levels of IgM, IgA, subgroups of IgG, IgE, lymphocyte counts (CD3, CD4, CD8, CD57, B cells). Prick tests to 12 common inhalants were negative. Cap Rast to *C. thummi* was > 100 KU/l. The search for IgEs to *Artemisia salina*, mosquito, shrimp, mites, was negative.

These data support the diagnosis of IgE-dependent nephrotic syndrome because of the inhalation of chironomid larvae.

Red larvae of *C. thummi* are used to feed exotic fish. Their hemoglobin is a potent allergen: Chi t 1 (1). Respiratory allergies, urticaria and angioedema are observed (2, 3). Sensitization might not be so rare: 4% of patients with respiratory allergy have positive prick test to these larvae, with associated sensitivity to mosquito, shrimp, mites. However,

Immediate facial angioedema and nephrotic syndrome induced by *Chironomus thummi*. An impressive sensitization was demonstrated.