Hydrochlorotiazide-induced acute non-cardiogenic pulmonary edema

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Summary. We report the case of a 64 year-old male with non cardiogenic pulmonary edema episodes after oral administration of 12.5 mg of hydrochlorotiazide.
In vitro immunologic study with basophil activation test and late cellular activation study (CD69 and production of interferon gamma) with chlorotiazide were performed, and no activation was observed.
As a consequence, like in previous cases published, the pathogenic mechanism remains unknown, and it probably is an idiosyncratic reaction.

Key words: Hydrochlorothiazide, Lung edema, Side effects.

Introduction

Hydrochlorothiazide is a thiazidic diuretic drug very frequently used in the treatment of high blood pressure and in edemas of cardiac, hepatic or renal origin. Several side effects have been described unrelated to its pharmacological activity, such as photosensitivity, skin exanthema and sexual dysfunction [1]. Most of these processes are not severe. The literature describes few side effects implying vital risk related to this diuretic drug; one of them is acute pulmonary edema. This entity, first described by Steinberg [2] in 1968, had been described in approximately 34 occasions by 1996 [3], and in 13 more cases up to now.

We describe the case of a male who suffered two episodes of acute pulmonary edema after oral administration of 12.5 mg of hydrochlorothiazide.

Case report

A 64-year-old male with previous diagnosis of hypercholesterolemia, high blood pressure and atrial fibrillation. The patient is under continuous treatment with Atacand® (Candersartan 8 mg), Apocard® (Flecainide 100 mg) and Prevencor® (Atorvastatine 10 mg).

First episode:

On October 12th 2002, the patient received Atacand plus® (Candesartan 16 mg, hydrochlorothiazide 12.5 mg) from his chemists, and one hour after administration of the first dose he presented with severe dyspnea that required his admission in the Hospital Emergency Unit. The following clinical data were obtained: blood pressure 100/60, temperature 36.5ºC, 26 breaths/minute. Pulse 100 beats/minute. Lung auscultation: decreased lung sound. Heart auscultation: normal. Laboratory parameters: blood count: H 5,200,000/mm^3; Hg 17.9 g/dl, Hto 51.7%. Leukocytes 11500 (94% neutrophils, 3% lymphocytes, 3% monocytes), Sat O_2 85%, pH 7.42, pO_2 60 mm Hg, pCO_2 34 mm Hg. Electrocardiogram: normal. Chest X-ray: diffuse interstitial lung infiltration. Blurred hilum. Helicoidal CT: negative for lung thromboembolism. Minimum bilateral pleural effusion.

The patient received treatment with furosemide i.v., amoxicillin + clavulanic acid and salbutamol, and was discharged after 18 hours.

The patient continued this treatment with Atacand®, Apocard® and Prevencor® with a good tolerance until February 12th 2003.

Second episode:

On February 12th 2003, one hour after administration of the first dose of Atacand plus®, the patient presented with severe dyspnea, vomiting, face flushing and profuse sweating, which required his admission in the Hospital Emergency Unit.

The following results were obtained: blood pressure 80/40. Lung auscultation: normal. Pulse 90 beats/minute. Blood count: RBC 5,360,000/mm^3, Hb 18.2 g/dl, Hto 52.8%. Leukocytes 1100/mm^3 (63s, 291, 7 m). Blood gases: Pa O_2 51 mm Hg, Pa CO_2 34 mm Hg, Sat O_2 85%, pH 7.37. Chest x-ray: normal. Helicoidal TC: Not suggestive of lung thromboembolism. Electrocardiogram: normal. The patient recovered under treatment with s.c. adrenaline, i.v. corticosteroids and i.v. dopamine, with good evolution, and was discharged after 24 hours. Heart echography after discharge was normal.

Immunological study:

Basophil activation test [4] at two concentrations of chlorothiazide (0.025 and 1 mg/ml) was negative. In the lymphocytic proliferation study after cellular culture for 72 hours and in CD69 expression and intracellular cytokines (IFN gamma) after culture at two chlorthiazide concentrations (0.025 and 1 mg/ml), no differences were found with the controls [5,6].

Mononuclear cells were obtained with Ficoll-Paque standard procedure. The cells were adjusted at 1 x 10^6/ml in RPMI 1640 supplemented with 10% FCS previously uncomplemented, L-Glutamine 2mM and Gentamicine at 40 mg/ml concentration. One hundred µl of cell suspension were placed in each well, with 100 µl of complete medium, in flat-bottomed 96-well plates. Different concentrations of chlorothiazide were added (0.025-1 mg/ml) and incubated for 72 hours at 37ºC, in the presence of 5% of CO_2. Sixteen hours before finalising the culture, 1 µCi of tritriated thymidine was added to in each well. DNA was taken from the cells on paper using a Skatron cellular harvester and the counts per minute were quantified in a beta counter. The lymphocyte proliferation in response to chlorothiazide was compared with the basal situation with no drug.

Study of intracellular cytokines after short culture with chlorothiazide

Whole blood was adjusted at 1 x 10^6 CMN/ml with PBS and incubated in a tube for six hours at 37ºC and 5% of CO_2 at different chlorotiazide concentrations (0.025-1 mg/ml) with 10 mg/ml of brefeldin A. Subsequently, it was washed with PBS and marked with the following monoclonal antibodies (Becton-Dickinson) using Fix and Perm (Caltag) for permeabilization: $IFN\gamma_{FITC}/CD69_{PE}/CD45_{PerCP}/CD3_{APC}$. The sample was acquired in a FACSCalibur flow cytometer (Becton-Dickinson). The T lymphocyte population (CD3+) was analysed, and its IFNγ production and its CD69 expression in presence of chlorothiazide were compared with the culture in baseline conditions.

Discussion

We present the case of a patient with two episodes of acute lung edema induced by diuretic drugs (hydrochlorothiazide).

This case has similarities and differences with the ones previously published. As for the differences, this is a male whereas the relation of predominant women is usually 9:1 [7]. In none of the episodes the usual hemoconcentration found in this kind of reaction was observed.

Concerning the similarities, the age of the patient is close to the previous cases: 56 years [8], and the reaction started in all the cases within the first 60 minutes after administration of the drug. In the second episode, leukopenia is found, which is characteristic of these processes. This was not observed in the first episode, maybe due to the corticosteroid treatment before going to the hospital.

The mechanisms that induce these clinical processes are unknown. In previous articles different immunological parameters have been studied in order to try to explain them [9]. At the moment of the reaction, a decrease in the IgG levels and normality in the rest of isotypes was observed, as well as normal complement values [9]. An autoimmune etiopathogenesis has been suggested due to possible formation of anti-hydrochlorothiazide IgG and its deposition in alveolar membranes inducing acute lung edema [9]. Based on the peripheral leukopenia found in several of these patients, the lung edema has been attributed to its intrapulmonar sequestration [9].

In vivo, only one case of positive patch test with hydrochlorothiazide has been registered although the concentration used or the inclusion of controls were not mentioned in the article [10]. Nevertheless this immune mechanism seems unlikely because this reaction seems exclusive to hydrochlorothiazide and not to other thiazidic diuretic drugs [11]. In fact, several of these patients tolerate other thiazidic drugs such as furosemide, with which a cross-reaction could be expected [11]. In our patient, a lymphocytic immunological activity could not be shown, nor an immediate immunological reactivity by basophil activation test, which has proven its usefulness not only in IgE-mediated reactions [4] but also in NSAID-

induced idiosyncratic reactions [12]. Another reason to find this immediate activation way unlikely is that none of the cases described have associated skin symptoms which are characteristic of these reactions or have presented *in vitro* basophil activation.

Therefore, today we can only presume that this is an idiosyncratic reaction exclusive to this thiazidic diuretic drug.

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