Enteropathy associated with chronic use of olmesartan

Dear Editor,

In July 2013, the US Food and Drug Administration approved the inclusion of intestinal disorders (sprue-like enteropathy) as an adverse drug reaction (ADR) in the instruction leaflet for olmesartan, an antihypertensive drug of the angiotensin II inhibitor family. To date, a total of 46 ADR cases have been reported but we have found no related article in the Spanish bibliography (bibliographic search on PubMed using keywords: olmesartan, sprue, enteropathy, villous atrophy and sprue-like enteropathy, for the last 10 years). Below, we present the case of a patient who developed an enteropathy secondary to the chronic intake of this drug.

The patient was a 73-year-old male who attended to the Emergency Department with chronic diarrhea, asthenia, and weight loss of 15 kg. In his pathological history the following stood out: high blood pressure of more than 10 years evolution, treated with olmesartan (20 mg/day) for the last 8 years, and prostate adenocarcinoma, currently healed after undergoing a prostatectomy in 2006. It is worth mentioning that 10 months before visiting our centre, the patient was diagnosed with coeliac disease by means of a duodenal biopsy (duodenal mucous membrane with flattened villi, glandular crypts hyperplasia and marked intraepithelial lymphocytosis); since then, he had been following a strict gluten-free diet. Since the patient was not responding to treatment, he underwent a breath test, ruling out bacterial overgrowth, but was diagnosed with lactose and fructose intolerance. In spite of being on a diet that restricted foods containing these components, his clinical state worsened progressively, so he decided to consult us.

A physical examination showed that he had high blood pressure (BP 90/60 mmHg) and, therefore, the administration of olmesartan was suspended, with no other relevant finding observed. The laboratory tests indicated Na+ 141 mEq/l, K+ 1.5 mEq/l, Ca2+ 5.2 mg/dl, Mg2+ 0.5 mg/dl, total proteins 6.3 g/dl; the haemogram and the other baseline biochemical analyses were normal.

The immunological and genetic study (HLA-DQ2 and HLA-DQ8) ruled out coeliac disease (anti-tissue transglutaminase antibodies 0.8 U/ml [< 4.0 U/ml], DQB1*05:02:01, DQB1*05:03:01). The immunoglobulin dosage was normal. The microbiological faeces exam and HIV serology were both negative. The thoracic and abdominal CT scan did not reveal relevant disorders, and the barium swallow exam showed a progressive ileum contrast dilution, with a radiological pattern indicating intestinal malabsorption. Examination was completed by a fibergastroscopy and fibercolonoscopy, neither of which identified macroscopic changes. The histology and immunohistochemical studies showed flattened villi, crypts hyperplasia and marked intraepithelial lymphocytary infiltration (positive CD3 and CD5). There were no signs of microscopic colitis, lymphoproliferative disorder or PAS-positive markers.

During hospitalisation, while receiving no specific medical treatment, the number of depositions decreased progressively until the clinical condition resolved after 3 weeks. Based on the suspicion of enteropathy secondary to olmesartan, the patient was instructed to follow a regular, unrestricted diet, which he tolerated correctly.

Once the patient improved clinically, he was discharged from the hospital. In subsequent outpatient follow-up visits (2 months later), we found that the patient had regained 10 kg, with no new episodes of diarrhea.

The most frequent aetiology seen within chronic diarrhea syndrome associated with villi atrophy is coeliac disease. Some of the less frequent causes are: variable common immunodeficiency, autoimmune enteropathy, bacterial overgrowth, infections (e.g. giardiasis, Whipple’s disease, and tuberculosis), intestinal lymphoma, collagenous sprue, Crohn’s disease, tropical sprue, and drugs.

Our review of the cases reported to date revealed that most patients had been previously diagnosed with coeliac disease.
non-responsive to a gluten-free diet, or refractory coeliac disease. No relation between the length of exposure to olmesartan and enteropathy has been described. The intestinal epithelium damage could be related to the immune-mediated cellular response secondary to an imbalance between anti-inflammatory and pro-inflammatory factors. The most frequent symptoms are diarrhoea and weight-loss; other possible symptoms are: fatigue, nausea and abdominal pain. Although the histopathological findings are not specific, it is worth mentioning that most patients present the symptoms described in the anatomopathological study undergone by our patient (villi atrophy with variable inflammation). The gluten-free diet and treatments for other types of enteropathy (glucocorticoids, anti-diarrhoea, pancreatic enzymes, antibiotics, etc.) tend to be ineffective. It has been observed that once olmesartan is suspended, there is a remission of symptoms and histological disorders. Intestinal biopsy has not been repeated for this patient.

In view of the abovementioned, we conclude that the clinical condition presented by our patient was secondary to the intake of olmesartan. According to the Naranjo algorithm, causality is considered probable (7 points). This adverse reaction has been notified to the Spanish Agency of Medicines and Medical Devices.

References


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Enteropathy by olmesartan

Dear Editor,

Olmesartan medoxomil is a drug belonging to the angiotensin II type 1 receptor antagonist, which was approved in 2002 as a treatment for arterial hypertension. Although diarrhoea is a very frequent adverse effect in patients undergoing chronic drug treatment, the mechanisms by which it develops are mostly unknown. Enteropathy with villous atrophy has been previously associated with certain drugs, such as some immunosuppressants. In June 2012, Rubio-Tapia et al. reported 22 cases of enteropathy with villous atrophy in patients who were being treated with olmesartan medoxomil and later, in May 2013, DeGaetani et al. described the case of a series of patients with intestinal villous atrophy with absence of coeliac disease, in which some of the patients, with no defined aetiology, either had been or were being treated with olmesartan. To date, there are few documented cases in the medical literature associating this drug with the onset of severe diarrhoea with significant weight loss, and most of these have histological analyses of the duodenum showing villous atrophy. As a result, in July 2013, the U.S. Food and Drug Administration issued an alert listing enteropathy as a severe side effect caused by olmesartan. In the following paragraphs, we describe a case diagnosed at our centre that presented severe diarrhoea with associated malnutrition.

The patient was a 78-year old male who, in March 2013, consulted about diarrhoea of about one month evolution. His pathological history included longstanding, essential arterial hypertension that had been treated, for 8 years with 40 mg olmesartan administered on a daily basis. The patient had diarrhoea with 4 to 5 daily depositions, which were abundant and watery, but did not present blood, pus or mucous. Diarrhoea episodes intensified after meals and did not subside during night sleep. He had lost 10 kg over the previous 2 months and presented incapacitating asthenia. He had not travelled abroad or been in contact with people presenting similar symptoms. Physical examination indicated that his weight was 53.8 kg, with a BMI of 21. No lesions were detected on his skin or oral cavity. His blood test levels indicated: creatinine 4.2 mg/dl (0.5-1.1 mg/dl), potassium 2.7 mEq/l (3.5-4.5 mEq/l), pH 7.2 (7.35-7.45) and bicarbonate 13.8 mEq/ml. Laboratory tests also indicated total proteins of 4.4 g/dl (6.4-8.3), retinol binding protein 2.95 mg/dl (3.0-6.0), albumin 2.57 g/dl (3.3-5.2), prealbumin 13.3 mg/dl (20.0-40.0), phosphorus 1.6 mg/dl (2.7-4.5), calcium 7.4 mg/dl (8.7-10.3), iron 23 ug/dl (65-175), with magnesium, folic acid and vitamin B12, all within normal ranges. The haemogram showed anaemia, with Hb 9.8 g/dl (12-18). We ordered a complete microbiological study including the following: a total of 3 stool cultures, which showed regular flora for the sample, toxin and culture for Clostridium difficile, which were negative; no parasites were detected in the faeces. The serology for rotavirus and HIV, as well the serum DNA test for cytomegalovirus (CMV) were all negative; IgG through indirect immunofluorescence for Leishmania, negative; 3 determinations through immunochromatography for Giardia Lamblia, negative. Elastase and faecal calprotectin determination were within normal ranges. Alfa-1-antitrypsin clearance was 15.6 mg/g (<24), which, in the presence of diarrhoea, was