

Small bowel enteropathy associated with olmesartan medoxomil treatment

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Abstract

Sprue-like enteropathy associated with treatment with olmesartan medoxomil, an angiotensin II receptor blocker, has been described recently. Herein, we report two patients who developed chronic severe non-bloody diarrhea, weight loss, and muscle wasting after prolonged use of olmesartan. Histologic and immunohistochemical examination of multiple duodenal biopsies revealed severe villous atrophy. Clinical signs ceased upon drug discontinuation. Physicians should be aware of this enteropathy even if olmesartan has been taken for months or years. Whether this adverse event is specific for olmesartan or is a class effect of angiotensin II receptor blockers is currently unknown. To the best of our knowledge, these case reports are the first reported in Greece.

Keywords Sprue-like enteropathy, olmesartan, villous atrophy

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Introduction

Treatment of hypertension with olmesartan medoxomil, an angiotensin II receptor blocker (ARB), is associated with very few adverse events, commonly dizziness and headache [1]. However, a sprue-like enteropathy in association with olmesartan was described 4 years ago and was manifested as chronic diarrhea, weight loss, and various degrees of nausea, vomiting, abdominal pain, bloating, and fatigue associated with anemia, hypoalbuminemia, and electrolyte disturbances in view of negative serology for celiac disease [2]. Small intestinal biopsies demonstrated variable degrees of villous atrophy and mucosal inflammation but non aberrant or clonal expansion of intra-epithelial lymphocytes (IEL). Interestingly, some patients had histologic evidence of collagenous sprue, lymphocytic gastritis, or microscopic colitis but the pathogenetic mechanism remains unknown [3]. Malabsorption resolves after olmesartan

discontinuation. Herein, we present two additional cases of olmesartan-associated enteropathy (OAE) diagnosed in our department with a brief review of literature.

Case reports

Case 1

A 75-year-old male treated for hypertension with olmesartan (40 mg q.d.) for one year, was admitted for abdominal bloating, 8-10 watery non-bloody stools daily and loss of 20 kg of body weight in the last month. He denied recent travels, sick contacts, dietary changes, other medications or additional systemic symptoms. He had failed empiric treatment with opioid-receptor agonists, rifaximin, metronidazole and gluten-free diet. A screening colonoscopy performed prior to development of diarrhea was unremarkable. On admission, he was emaciated but active. The hemoglobin was 9.0 g/dL, albumin 2.6 g/dL (3.4-5.4 g/dL) but serum levels of IgA, C-reactive protein (CRP), TSH, gastrin, VIP, and chromogranin A, and urine 5-hydroxyindoleacetic acid were normal. Stool culture, parasitology, and *Clostridium difficile* toxins A and B were negative. IgA antibodies to tissue transglutaminase (TTG) and endomysium (EMA), and HLA-DQ2 and DQ8 were negative. An abdominal CT scan was unremarkable. Ileocolonoscopy with random terminal ileum and colonic biopsies showed no evidence of inflammation. However, at gastroduodenoscopy scalloping of the duodenal mucosal folds was observed and biopsies revealed moderate villous blunting, normal numbers of IEL, and absence of subepithelial collagen deposition (Fig. 1). Olmesartan was replaced by alternative hypertensive.

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Conflict of Interest: None

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Two months later, he reported 1-2 formed stools daily without abdominal symptoms and had regained 10 kg of body weight. He has been well since then.

Case 2

A 69-year-old male with diabetes mellitus type 2 and hypertension treated with olmesartan for three years presented with a 2-year history of watery, non-bloody diarrhea, pre-defecatory abdominal pain, and 15-kg weight loss. An abdominal CT had revealed an edematous proximal small bowel. On admission, he had profound muscle wasting. Hemoglobin was 10.6 g/dL, albumin 2.9 g/dL, and he had deficiencies in vitamin D and zinc. Serum CRP, TSH, and IgA, liver function tests, and stool cultures, parasitology and *Clostridium difficile* toxins A and B were normal or negative. At esophagogastroduodenoscopy mosaic pattern appearance of the duodenum was seen; duodenal biopsies confirmed villous atrophy. Serum IgA antibodies to deaminated gliadin, EMA, and TTG on unrestricted diet were negative. Discontinuation of olmesartan resulted in immediate resolution of abdominal symptoms and diarrhea within one month. Five months later, laboratory tests and duodenal biopsies demonstrated restoration of anemia, hypoalbuminemia and macronutrient deficiencies, normal villi architecture, IEL numbers and absence of lamina propria inflammation.

Discussion

Non-celiac enteropathies may cause severe malabsorption [4]. Olmesartan treatment has been associated with very few alarm signals and in the pivotal trial ROADMAP in 4447 patients with diabetes mellitus, the rates of diarrhea and abdominal discomfort were similar in olmesartan- and

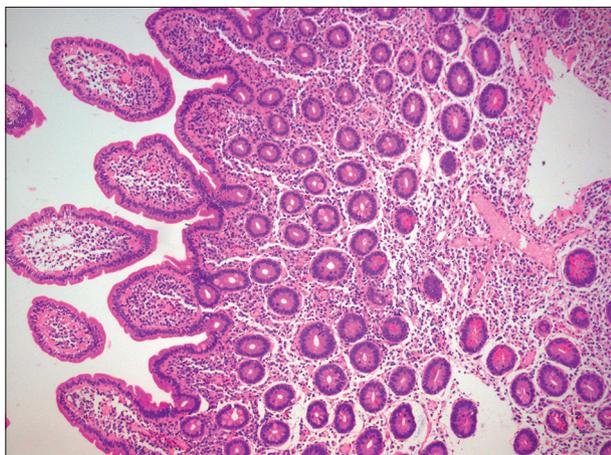


Figure 1 Histopathology section of duodenal mucosa demonstrating moderate degree of villous atrophy and chronic inflammatory infiltrate in the lamina propria (Hematoxylin & Eosin staining x 200 magnification)

placebo-treated patients. In a retrospective analysis the adjusted hazard for gastrointestinal disease-related hospitalization in 10,370 olmesartan users was 1.09 (0.98-1.20) compared with 24,815 patients treated with other ARBs [5]. However, evidence is accumulating in the last 4 years that olmesartan may be associated with severe enteropathy and malabsorption. Rubio-Tapia *et al* were the first to describe 22 patients with severe, non-celiac enteropathy who improved after discontinuation of olmesartan [2]. In 72 adult patients with non-celiac enteropathy, De Gaetani *et al* reported 16 patients with OAE and 15/16 patients improved after olmesartan withdrawal [6]. Additional cases have been reported from other countries [7,8]. As in our patients, in all these cases, OAE manifestations necessitating often hospitalization and parenteral nutrition resolved soon after olmesartan discontinuation. These reports have led the USA Food and Drug Administration to publish in July 2013 a “Drug Safety Communication” and approve changes to the USA label to address concern on OAE noting that no other ARBs had been involved in the occurrence of such cases [9].

Cessation of treatment with olmesartan leads to rapid resolution of symptoms and histological abnormalities, which argues against a chance relation between olmesartan treatment and enteropathy [2]. However, the mechanisms underlying OAE are unknown. Activation of cell-mediated immune mechanisms and inhibition of transforming growth factor resulting in deregulation of gut immune homeostasis have been proposed [2]. Interestingly, the prevalence of HLA-DQ2 in OAE (68%) is higher than in the general population (25-30%) but serology is atypical for celiac disease indicating that although HLA-DQ2 may increase the risk of immune-mediated damage, olmesartan does not act as a triggering factor for overt clinical expression of silent celiac disease. In addition, OAE neither exhibits any association with other autoimmune conditions nor resolves on a gluten-free diet OAE. May also result from a pro-apoptotic effect of angiotensin II on intestinal epithelial cells. The renin-angiotensin system regulates fluid and electrolyte absorption in the human gut. Angiotensin II binds to AT1 receptor expressed throughout the entire alimentary tract which activates growth-promoting factors and mediates major effects of angiotensin II, and to AT2 receptor expressed particularly in the duodenum and jejunum which induces opposite effects [10]. Angiotensin II promotes apoptosis of enterocytes. In addition, drug-induced AT1 receptor blocking exerts translocation of AT2 receptors which may favor binding of angiotensin II to AT2 receptors. Olmesartan shows high affinity for AT1 receptors. In case of AT1 receptor saturation by olmesartan, circulating angiotensin II could bind only AT2 receptor, with consequent pro-apoptotic effect which may ultimately lead to villous atrophy without inflammatory reaction and increase in IEL numbers. Why only olmesartan has been associated with sprue-like enteropathy is probably due to the fact that olmesartan differs from most other ARB drugs. So far, no association between azilsartan, another ARB with medoxomil, and enteropathy has been reported.

OAE is rare in individuals who routinely use the medication; however, physicians should be aware of this potential side effect because suspension of the drug leads to resolution of symptoms

avoiding unnecessary testing for celiac disease diagnosis and initiation of a trial of gluten-free diet [4].

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