CLINICAL CASE

OLMESARTAN AS AN UNCOMMON CAUSE OF ENTEROPATHY

Mendoza Rodríguez R, Fernández Cano MC, Carrero Castaño A, Redondo Cerezo E

VIRGEN DE LAS NIEVES HOSPITAL. GRANADA.

Abstract

Diarrhoea is the cardinal symptom of multiple pathologies in the digestive system, with multiple aetiopathogenesis. Chronic causes include pathologies such as coeliac disease, the main cause of villous atrophy in the small intestine. However, diarrhoea can also appear as an adverse reaction to drugs, sometimes with a pathophysiological basis in non-celiac enteropathy, causing malabsorptive syndromes. Angiotensin II receptor antagonist antihypertensives, such as Olmesartan, used to treat hypertension, diabetic nephropathy and heart failure, can cause enteropathy. Although rare, this condition should be considered in patients with severe diarrhoea and weight loss. The exact pathophysiology is unknown, but a type I immune response and inhibition of TGF-β, a key molecule in intestinal homeostasis, are suspected.

Olmesartan enteropathy occurs in both sexes, mainly in the elderly, and is characterised by chronic diarrhoea, weight loss and steatorrhoea. Laboratory abnormalities are variable, histological findings are non-specific and there is no response to a gluten-free diet. Clinical improvement after discontinuation of the drug confirms the diagnosis.

Treatment consists of discontinuation of Olmesartan, which usually results in complete resolution of symptoms. The prognosis is excellent, and follow-up endoscopy is not required if symptoms improve after withdrawal of the drug and there is no diagnostic uncertainty with another entity.

Keywords: olmesartan, enteropathy, diarrhoea.

Raúl Mendoza Rodríguez
Virgen de las Nieves Hospital. Granada.
rmendozar770@gmail.com

Mendoza Rodríguez R, Fernández Cano MC, Carrero Castaño A, Redondo Cerezo E. Olmesartan as an uncommon cause of enteropathy. RAPD 2024;47(4):156-159. DOI: 10.37352/2024474.3

Introduction

Diarrhoea is one of the most common adverse drug reactions. One of the main causes of chronic diarrhoea is coeliac disease, which is also the main cause of villous atrophy of the small intestine. However, much less frequently, there are other non-coeliac enteropathies that form a heterogeneous, extensive group characterised by diarrhoea and malabsorption.[1,2]. The drug origin of diarrhoea is a not insignificant cause of diarrhoea that must be considered in the differential diagnosis.

Angiotensin II receptor antagonists are a group of drugs widely used in the treatment of arterial hypertension, diabetic nephropathy and heart failure. Olmesartan (as one of its main representative) is a rare cause of enteropathy and should be considered in the evaluation of a patient with severe diarrhoea and weight loss.

A clinical case illustrating this association is presented below.

Clinical case

A 62-year-old woman with arterial hypertension, dyslipidaemia and grade 3A chronic kidney disease who had been on chronic treatment with Olmesartan 40 mg for five years together with Pantoprazole 20 mg and Diltiazem 120 mg. She started with diarrhoea of 15-20 bowel movements per day for three months, together with a weight loss of 12 Kg and colicky pain in the right iliac fossa, which was relieved by defecation. Her family history included a daughter with coeliac disease. Laboratory tests showed mild iron deficiency anaemia (with normal anti-transglutaminase antibodies) as well as a stool culture and Clostridioides difficile toxin test, which were negative. Upper gastrointestinal endoscopy was also requested, where macroscopically only signs of chronic gastritis were observed with duodenum with mild punctate erythema (Figure 1), and colonoscopy where three superficial ulcers were visualised in the cecum. Duodenal biopsies showed marked villous atrophy with pan-mucosal lymphocytic infiltrate and prominent intraepithelial lymphocytosis (Figures 2 & 3), and a non-specific chronic inflammatory infiltrate was found in biopsies of the cecum. It was decided to withdraw Olmesartan, after which the patient experienced a significant clinical improvement, decreasing the number of bowel movements to normal and recovering the lost weight. After two months of evolution, and taking into account the patient's family history, it was decided to perform a new ADD (Figure 4) with biopsies in which normalisation of the histological findings at the duodenal level was observed (Figure 5).

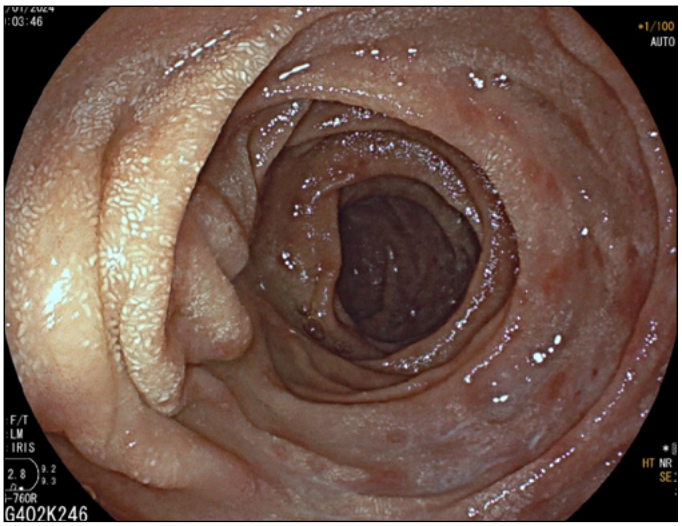

Figure 1. Second duodenal portion with mild punctate erythema, at diagnosis.

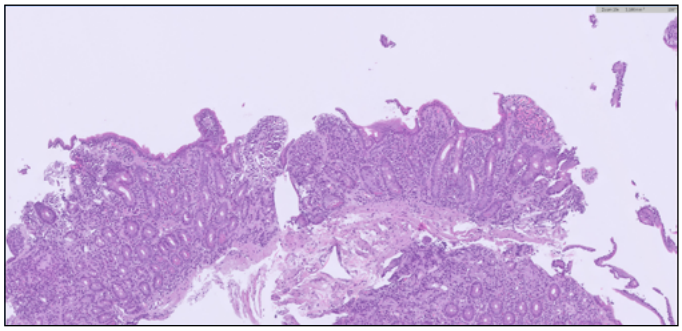

Figure 2. Endoscopic incisional biopsies of the second duodenal portion, at diagnosis. Marked villous atrophy and villous shortening with chronic panmucosal lymphocytic infiltrate.

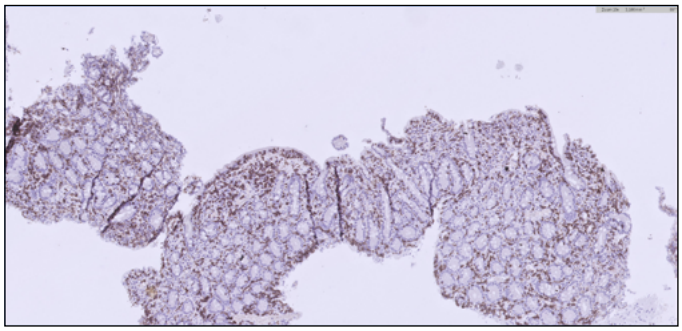

Figure 3. Endoscopic incisional biopsies of the second duodenal portion. Significant intraepithelial lymphocytosis quantified by CD3 immunohistochemistry.

Discussion

Duodenal villous atrophy with seronegative inflammatory infiltrate for celiac disease is a diagnostic challenge. Within the differential diagnosis we must consider autoimmune enteropathy, Crohn's disease, eosinophilic enteritis, giardiasis, tropical sprue, Whipple's disease, graft-versus-host disease, common variable immunodeficiency, bacterial overgrowth, neoplastic pathology (lymphomas) and drug origin (azathioprine, methotrexate, mycophenolate mofetil, etc.)[3-6].

DOI: 10.37352/2024474.3

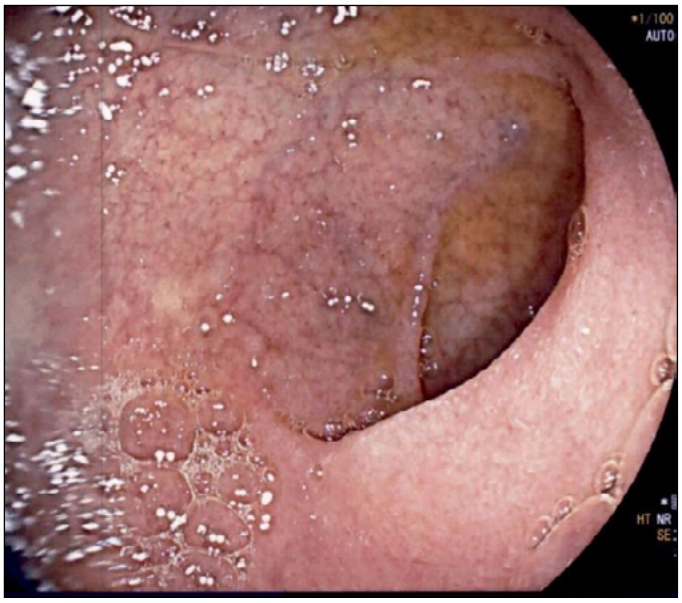

Figure 4. Second duodenal portion without notable alterations, after 2 months of Olmesartan withdrawal.

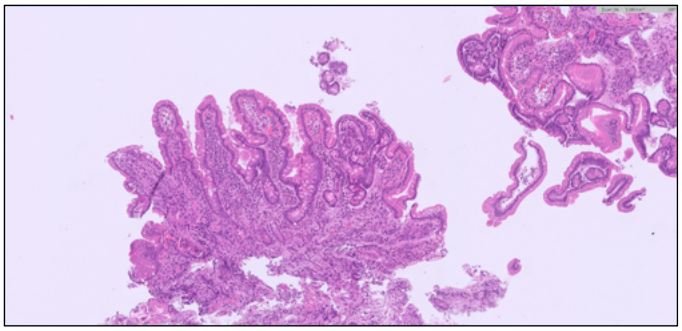

Figure 5. Endoscopic incisional biopsies of the second duodenal portion, after two months of Olmesartan withdrawal. Duodenal mucosa with preserved villous architecture, mild chronic panmucosal inflammation in the absence of intraepithelial lymphocytosis.

Since the study by Rubio-tapia J *et al* in 2012[1] in which the association between Olmesartan and enteropathy was described for the first time, and despite the fact that some studies have cast doubt on it[7], there have been numerous studies in the literature that have described this relationship[2,3,5,6,8-18].

The pathophysiological mechanisms underlying this association remain unknown. Due to the prolonged latency period between the introduction of Olmesartan and the onset of diarrhoea, it seems that the immune response involved is primarily type I. On the other hand, it appears that ARB inhibits TGF-β, a molecule involved in the maintenance of intestinal homeostasis. Furthermore, Olmesartan-associated enteropathy shares many immunological features with untreated coeliac disease, such as increased CD8+ T lymphocytes, overexpression of IL-15 or disruption of zonulin-1 protein[2,15]. Another theory postulates that majority inhibition of angiotensin type 1 (AT-1) receptors due to Olmesartan's high specificity for them, causes angiotensin to bind to the AT-2 receptor, which has a widely known pro-apoptotic function in enterocytes[6].

On the other hand, some studies suggest that Olmesartan-associated enteropathy may exhibit another endoscopic and histological phenotype related to a type I hypersensitivity reaction, with the appearance of ileal nodules with normal duodenum, as well as a monocytic and eosinophilic histological infiltrate without evidence of villous atrophy[10].

Olmesartan-associated enteropathy affects both sexes equally and occurs mainly in the seventh and eighth decades of life[4]. It is characterised by the presence of chronic diarrhoea, weight loss and steatorrhoea ,other digestive symptoms such as nausea, vomiting, bloating and asthenia may be present, the absence of coeliac-associated antibodies and no response to a gluten-free diet; in addition, histological findings of enteropathy (intraepithelial lymphocytosis, villous atrophy and subepithelial collagen deposition)[4] should be observed, which not only appear in the duodenum but can occur throughout the entire gastrointestinal tract; however, it seems that it is mainly the histological alterations in the duodenum that determine the clinical phenotype of this entity, with gastric and colonic pathological changes being of lesser importance[2]. Other causes of enteropathy must also be excluded and clinical improvement after withdrawal of Olmesartan must be demonstrated[1]. Analytical alterations are non-specific, the most frequent being the appearance of normocytic normochromic anemia and hypoalbuminaemia[4].

The mean time of enteropathy onset is 3.1 years (range 6-120 months), so it is necessary to consider this entity regardless of the time the patient has been on Olmesartan treatment[9].

The role of genetics in the pathogenesis of this entity is unknown. The presence of HLA-DQ2 and HLA-DQ8 occurs in up to 70% of patients, without this being necessary for the onset of enteropathy. Most patients are seronegative for anti-enterocyte antibodies[1,5,6].

In relation to endoscopic diagnosis, it is only necessary to perform upper gastrointestinal endoscopy in a first approach. If no endoscopic or histological alterations are found in the duodenum, colonoscopy may be considered to identify possible mucosal and histological alterations in the colon - compatible or not with this entity.

Olmesartan-associated enteropathy is not a unique adverse effect of this ARB, but has also been described in the case of Telmisartan, Valsartan and Irbesartan[2].

DOI: 10.37352/2024474.3

Treatment of Olmesartan-associated enteropathy consists of immediate discontinuation of the drug, with all patients responding, provided that the initial diagnosis and causal association were correct, with normalisation of stools, analytical alterations and weight gain. In those rare cases where the patient shows slow improvement, some studies point to the possible usefulness of Budesonide[19].

The short and long-term prognosis of the patients is excellent, with complete cessation of symptoms when the drug is discontinued. Because of this, and in the case of an adequate response to drug cessation, it is not necessary to perform a control endoscopy to observe the resolution of the initial histological alterations, this being a cost-effective strategy.

Bibliography

1. *Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc. 2012;87(8):732–8.*

2. *Schiepatti A, Minerba P, Puricelli M, Maimaris S, Arpa G, Biagi F, et al. Systematic review: Clinical phenotypes, histopathological features and prognosis of enteropathy due to angiotensin II receptor blockers. Vol. 59, Alimentary Pharmacology and Therapeutics. John Wiley and Sons Inc; 2024. p. 432–44.*

3. *Onteddu NK, Pulivarthi VSKK, Ginnavaram M, Kedika R. Olmesartan-induced enteropathy. BMJ Case Rep. 2018;2018.*

4. *Choi EYK, McKenna BJ. Olmesartan-associated enteropathy a review of clinical and histologic findings. Arch Pathol Lab Med. 2015 Oct 1;139(10):1242–7.*

5. *Ebrahim VS, Martin J, Murthy S, Odstrcil E, Huang H, Polter D. Olmesartan-Associated Enteropathy. Baylor University Medical Center Proceedings. 2017 Jul 1;30(3):348–50.*

6. *Ianiro G, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: Sprue-like enteropathy associated with olmesartan. Vol. 40, Alimentary Pharmacology and Therapeutics. Blackwell Publishing Ltd; 2014. p. 16–23.*

7. *Menne J, Haller H. Olmesartan and intestinal adverse effects in the ROADMAP study. Vol. 87, Mayo Clinic Proceedings. Elsevier Ltd; 2012. p. 1230–1.*

8. *Shahzad MA, Harding D, Ruszkiewicz A, Tran E, England G, Philpott H. Gastrointestinal: Olmesartan-induced enteropathy. Vol. 33, Journal of Gastroenterology and Hepatology (Australia). Blackwell Publishing; 2018. p. 1691.*

9. *Adike A, Corral J, Rybnicek D, Sussman D, Shah S, Quigley E. 230 houstonmethodist.org/debakey-journal. 2016.*

10. *Famularo G, Aglitti A, Magrini L. Olmesartan-induced enteropathy: More than one entity? Eur J Intern Med. 2022 Nov;105:113.*

11. *Kajihara Y. An unusual cause of severe watery diarrhea. Eur J Intern Med. 2022 Aug 1;102:110–1.*

12. *Socorro Briongos-Figuero L, Cuevas-González J. Clinical Picture Olmesartan-associated sprue-like enteropathy [Internet]. Vol. 402, www.thelancet.com. 2023. Available from: www.thelancet.com*

13. *Jadvani D, Jha P, Singh M. Olmesartan-Induced Enteropathy: A Case Report. Cureus. 2023 Jun 13.*

14. *Matos ARF, Coelho E, Caridade S. Olmesartan-induced enteropathy: A case of recurrent diarrhoea. Eur J Case Rep Intern Med. 2020;7(8).*

15. *Marietta E V., Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, et al. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec 1;42(11–12):1303–14.*

16. *Sasaki S, Hashimoto S, Yamamoto K, Sakaida I. Olmesartan-associated enteropathy mimics endoscopic findings of celiac disease. Vol. 59, Internal Medicine. Japanese Society of Internal Medicine; 2020. p. 1777–8.*

17. *Marthey L, Cadiot G, Seksik P, Pouderoux P, Lacroute J, Skinazi F, et al. Olmesartan-associated enteropathy: Results of a national survey. Aliment Pharmacol Ther. 2014;40(9):1103–9.*

18. *Dong YH, Jin Y, Tsacogianis TN, He M, Hsieh PH, Gagne JJ. Use of olmesartan and enteropathy outcomes: a multi-database study. Aliment Pharmacol Ther. 2018 Mar 1;47(6):792–800.*

19. *Kempenaers S, Bogaert J, De Maeyer M, Hauthem P Van, Ramael M, Schoeters P. Olmesartan-induced enteropathy treated with budesonide [Internet]. Available from: www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-286_Benicar.cfm.*

DOI: 10.37352/2024474.3