Olmesartan induced enteropathy affecting the entire gastrointestinal tract: a case report

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Abstract

Olmesartan, a well-known and powerful antihypertensive drug, was first described to cause enteropathy in 2012. A possible mechanism may be inhibition of the intestinal immune suppressive effect of transforming growth factor-beta (TGF-β), with a consequential increase of intestinal T-cell inflammation.

We present the case of a 60-year-old woman who developed large volume, watery diarrhoea with 8kg weight loss only two weeks after starting olmesartan 20mg daily with a secondary mild acute kidney insufficiency and hypokalaemia. Coeliac serology was negative. Endoscopy revealed no macroscopic lesions. Histology showed increased gastric, duodenal, ileal and colonic intraepithelial lymphocytes with partial duodenal villous atrophy, hence affecting the entire gastrointestinal tract.

After cessation of olmesartan, symptoms improved within a week; therefore a diagnosis of olmesartan induced enteropathy was made. Extra immunohistochemical stains to further investigate the underlying pathophysiology were inconclusive. (Acta gastroenterol. belg., **2023,** 86, **95-97**).

Key words: Olmesartan, chronic diarrhoea, enteropathy, adverse drug event**.**

Introduction

Arterial hypertension affects 20.0% of the adult Belgian population, increasing to 40.4% of adults aged 65 years and older (1). On top of lifestyle measures, five major drug classes are recommended for routine treatment: ACE-inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics. First choice is a combination treatment with an ACE-inhibitor or ARB plus CCB or diuretic (2).

In 2020, 22.68% of the adult Belgian population was prescribed antihypertensive treatment, of which 23.51% took an ARB and 10.31% olmesartan (data provided by Farmanet).

Olmesartan is a powerful antihypertensive drug that blocks the angiotensin II receptor type 1 (AT1), antagonizing all effects of angiotensin II mediated by the AT1-receptor (3). Olmesartan induced enteropathy (OIE) was first described in a case series of 22 patients in 2012 (4). Since then, over a hundred cases of olmesartan and few cases of other ARB (irbesartan, valsartan, telmisartan) induced enteropathy have been described (5,6).

We present a patient with OIE that affects the entire gastrointestinal tract while taking olmesartan 20mg. Symptoms developed remarkably quickly after introduction of olmesartan and improved a few days after stopping olmesartan, as expected. We performed multiple immunohistochemical stains in an effort to gain more insight in the possible pathophysiological mechanism.

Case history

A 60-year-old Caucasian female presented with anorexia and diarrhoea for two weeks. She had progressively worsening, large volume, non-bloody, non-mucoid watery diarrhoea up to twelve times daily and three times overnight. There were associated epigastric cramps, nausea and vomiting for three days. She reported non-intentional weight loss of around 8kg in the past month. She denied having a fever.

Her medical history included arterial hypertension, hypercholesterolemia, atrial flutter, lymphocytic colitis and goiter. Her daily drug therapy consisted of spironolactone 25mg, bisoprolol 2.5mg, atorvastatine 10mg and olmesartan 20mg.

Physical examination showed normal vital signs, bradyphrenia and a diffuse tender abdomen. Lab results were remarkable for minimal inflammation (CRP 14mg/L; upper limit of normal (ULN) 5mg/L; WBC 7.9x10³/µL, ULN 10.3x10³/µL), mild hypokalaemia (3.36mmol/L, lower limit of normal (LLN) 3.5mmol/L), decreased renal function (CKD-EPI 51mL/min opposed to normal baseline, LLN 60mL/min) and elevated liver enzymes (AST 111U/L, ULN 32U/L; ALT 222U/L, ULN 52 U/L; γ-GT 115U/L, ULN 36U/L; Alk P 161U/L, ULN 105U/L), tissue transglutaminase IgA and total IgA were normal, viral hepatitis serology was negative. Stool examination was unremarkable.

Abdominal ultrasound visualised a normal liver, bile ducts and gallbladder, and limited hyperperistalsis in the small intestine. Esophagogastroduodenoscopy and ileocolonoscopy showed no macroscopic lesions.

Histologic examination revealed a similar picture in all samples (Figure 1).

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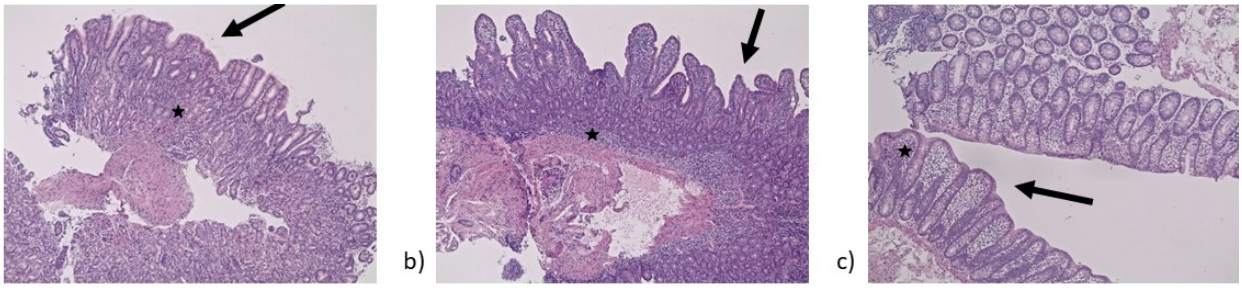

Figure 1. — Histology samples taken one month after introduction of olmesartan. Arrows indicate villous atrophy, stars are placed in regions with increased number of lymphocytes. a) lymphocytic gastritis without gastric intestinal metaplasia or crypt atrophy, b) chronic duodenitis: increase of intraepithelial lymphocytes with partial villous atrophy, c) lymphocytic colitis: increase of surface intraepithelial lymphocytes without thickening of the basal membrane.

All gastric biopsies showed a picture of lymphocytic gastritis without atrophy, but with increased number of lymphocytes (CD3+, CD8+) between the foveolar epithelial cells. Helicobacter pylori immunohistochemistry was negative.

In the duodenum there was a significant (>40 per 100 enterocytes) increase of intraepithelial lymphocytes (CD3+, CD8+) with mild villous atrophy, but without crypt proliferation as in celiac disease Marsh type 3a.

The colonic biopsies revealed a picture similar to lymphocytic type of microscopic colitis with an increased number of surface intraepithelial lymphocytes (>20 CD3+, CD8+ intraepithelial lymphocytes per 100 enterocytes) without thickening of the basal membrane or indications of acute or chronic colitis.

Furthermore, in the terminal ileum a high number of intraepithelial lymphocytes was observed between enterocytes with preserved villi and crypts, which may be physiologic at this place (Peyer's patches).

FOXP3 and a CD25 immunochemical stains were performed but were not contributing to the diagnosis. These stains were respectively overstained (not assessable) and understained (false negative).

On admission, IV fluids and potassium substitution were started and olmesartan was paused. This led to a 50% decrease in diarrhoeal frequency and normalisation of renal function after one week.

Given her elevated liver enzymes, hepatic viral and autoimmune serology was determined and proved positive for ANF 1/80 and anti-smooth muscle cell (SMC) antibodies. Although ANF titres were low, based on the elevated liver enzymes and combination with positive anti-SMC antibodies, a liver biopsy was performed to investigate possible autoimmune hepatitis (AIH). While awaiting the results, budesonide 9mg once daily was started considering the beneficial effect for both enteropathy and possible AIH. Liver biopsy showed primarily centrilobular macrovesicular steatosis with mononuclear inflammation and without fibrosis, compatible with non-alcoholic steatohepatitis. Thus budesonide was slowly tapered. Diarrhoea and abdominal complaints continued to improve. Three months after hospitalisation she remained asymptomatic.

On further questioning, her general practitioner had prescribed olmesartan 40mg in March 2017 as well. Two months later she developed similar complaints (anorexia, watery diarrhoea without blood or mucus and 10kg weight loss). In July 2017 she was admitted to hospital with severe diarrhoea and secondary acute kidney insufficiency (AKIN stage 3), hypokalaemia and uremic stupor. She developed torsade de pointes secondary to hypokalaemia and sotalol (then prescribed for her atrial flutter) which reached higher plasma levels due to decreased renal clearance. Biopsies taken during sigmoidoscopy showed an increased number of intraepithelial lymphocytes, suggestive of lymphocytic colitis (however, no proximal biopsies were taken). Olmesartan was stopped during hospitalisation and restarted only one month before current hospitalisation.

Discussion

Diarrhoea is accountable for 7% of adverse drug reactions through multiple mechanisms (7). In literature, OIE has an estimated incidence of <0.05% of olmesartan users (8). Overall OIE is observed to start months/years after introduction of olmesartan. Our patient developed diarrhoea after only a few weeks, which seems exceptionally early.

Rubio-Tapia *et al.* describe six clinical features to help decide whether gastrointestinal complaints can be contributed to olmesartan (4). These are: [1] gastrointestinal symptoms, [2] negative IgA tissue transglutaminase antibodies, [3] evidence of enteropathy with or without collagen deposition or intraepithelial lymphocytosis, [4] lack of clinical response to gluten exclusion, [5] exclusion of other causes of enteropathy, [6] evidence of clinical and histological improvement after suspension of olmesartan. Applying these criteria to our patient, all but one (criterion 4) are fulfilled. We did not start a gluten free diet, considering clinical improvement was already reached.

The mechanism of OIE remains unclear. A role for transforming growth factor beta (TGF-β) has been proposed considering the important role in immune homeostasis as a T cell regulator, interactor with the

microbiota and keeper of self tolerance. Angiotensin II stimulates the TGF-β signalling cascade; thus, blocking the AT1 receptor could inhibit this effect (similarly, TGF-β is known to play an important role in the pathophysiology of inflammatory bowel disease through insufficient immune tolerance (9)). Olmesartan is a very potent AT1 receptor blocker, possibly explaining why it results in enteropathy more frequently than other ARBs. Extra immunohistochemical staining for the presence of T cells was performed. We hypothesized that if TGF-β signalling cascade is diminished, less CD4+/CD25+ regulatory T cells (and more specifically the FOXP3 subset seems important) and more effector T cells will be found (9,10). Presence of more CD3+ and CD8+ effector T cells was confirmed; stains for regulatory T cells were unfortunately inconclusive.

A second remarkable histologic finding is the extent of the inflammation: all biopsied levels were involved. In literature, involvement of multiple gastrointestinal areas (e.g. duodenal villous atrophy and lymphocytic colitis or gastritis) is common; inflammation affecting the entire gastrointestinal tract is however not often seen. In 2017, only colonic biopsies were taken, so the full extent of lesions was not determined. Whether the extent of the involved gastrointestinal areas is related to the severity of symptoms, is unknown.

OIE is most often seen with olmesartan 40mg, suggestive of a dose-dependent effect with less severe complaints staying under the radar. Our patient developed more serious complications while taking olmesartan 40mg compared to 20mg. She presented earlier since she recognized the symptoms, however, no relationship between duration of olmesartan administration and severity of duodenal damage has been found (8). For an individual patient presenting with diarrhoeal complaints while taking olmesartan and an initial negative investigation, it seems safe to reassess the indication of olmesartan and where appropriate, to change to a different antihypertensive medication.

After termination of olmesartan, quick clinical (within a week) and histological (within a year) improvement is expected (4,5,11). Follow-up endoscopy was not undertaken since there would be no therapeutic implications given the already established clinical improvement.

In literature, glucocorticoids are frequently administered, often before a definite diagnosis is made, in combination with supportive therapy (IV fluids, electrolyte correction, total parenteral nutrition,...). Budesonide 9mg orally in withdrawal scheme is frequently used because of its topical efficacy and few systemic adverse events. A standard recommendation regarding the use of glucocorticoids has not been made. In less severe cases, cessation of olmesartan may be sufficient. Two systematic reviews mention 143 different cases of OIE (5,12). Glucocorticoids were administered (intravenously or orally) in 59 patients before a definite diagnosis was made, with improvement but no complete resolution of complaints. After cessation of olmesartan, glucocorticoids could be tapered in all patients. This means 58% of OIE patients did not require glucocorticoids. Further investigation is needed to determine which patients benefit most from administration of glucocorticoids.

In conclusion, OIE is rare but can present with severe manifestations and a thorough medication review can be crucial in finding the culprit. A case of unexplained diarrhoea while taking olmesartan warrants cessation of the drug in addition to providing supportive therapy.

Conflict of interest

Nele Van Horebeek, Romaric Croes, An Vonck and Erwin Colpaert declare that they have no conflict of interest.

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