Olmesartan-induced Enteropathy Manifesting as Wernicke-Korsakoff Syndrome

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Abstract

Cases of sprue-like enteropathy associated with olmesartan have sporadically been encountered since it was first reported in 2012, and their most characteristic manifestation is severe diarrhea. We herein report the first case of sprue-like enteropathy manifesting as Wernicke-Korsakoff syndrome due to vitamin B1 malabsorption with only minimally increased bowel movements. When patients are receiving olmesartan and they complain of nonspecific chronic gastrointestinal symptoms, it is important to consider changing the drugs before any serious malabsorption syndrome develops.

Key words: olmesartan-induced enteropathy, celiac disease, Wernicke-Korsakoff syndrome, malabsorption syndrome, urine anion gap, intestinal pseudo-obstruction

Introduction

Olmesartan is an angiotensin II receptor blocker (ARB) that was approved as an antihypertensive agent in 2002 in the United States and in 2004 in Japan. Olmesartan-induced enteropathy was first reported by Rubio-Tapia et al. in 2012 (1). It is a condition in which the patient presents with the chief complaints of severe chronic diarrhea and weight loss, and duodenal biopsy specimens show villous atrophy with inflammation on histopathological examination. Although olmesartan-induced enteropathy shares a similar pathology with celiac disease, the serology of celiac disease was negative and a gluten-free diet was found to be ineffective (1). Enteropathy as an adverse effect of olmesartan and other ARBs such as irbesartan (2 cases) (2, 3), valsartan (4), telmisartan (3), and eprosartan (5), have sporadically been reported since then, and their most prominent and characteristic manifestation is severe diarrhea. We herein report the first case of olmesartan-induced enteropathy causing Wernicke encephalopathy with only minimally increased bowel movements, in which the diagnosis was therefore challenging.

Case Report

A 76-year-old Japanese man had experienced a decreased appetite, nausea, and abdominal distension since late February 2011. The patient passed loose, soft stools that were not watery once daily. The results of blood tests performed by the primary care physician (PCP) between April and June were all normal, but upper and lower gastrointestinal endoscopy showed atrophic gastritis. Therefore, we assessed the patient for Helicobacter pylori antibodies and performed the rapid urease test and a histopathological evaluation, all of which were negative. In June, the patient received medication from a mental health clinic, but because the symptoms did not improve and his body weight further decreased by 23 kg, he stopped the medication; he was referred to our department in November. The patient had been suffering from hypertension since his 30s. Amlodipine (5 mg/day) administration was initiated in 2005, and olmesartan from May 2008; the patient is currently receiving 30 mg/day of olmesartan. He denied the use of any other new medications or nonsteroidal anti-inflammatory drugs. He had no history of smoking or alcohol consumption. Physical examination showed that the patient had a height of 165 cm, a body
Nystagmus was ameliorated on physical examination, but bance disappeared, and his body weight increased by 3 kg. B1, the patient's loss of appetite, nausea, and gait distur-
tand 10 days after the intravenous administration of vitamin
potension were noted, no clear symptoms of heart failure or
Moreover, as sinus tachycardia and a tendency towards hy-
Moreover it was uncommon that the patient had only mimi-
Duodenal biopsy findings after discontinuing olmesartan
manifesting as Wernicke-Korsakoff syndrome with recurrent
usually an adverse drug effect tends to have an acute onset. However, in cases of olmesartan-induced enteropathy, the symptom onset was months to years after the initiation of olmesartan, and therefore the diagnosis in this case was challenging. Moreover it was uncommon that the patient had only minimally increased bowel movements, not severe diarrhea as previously reported. Nonetheless the measurement of the urine anion gap indicated malabsorption syndrome, which was thought to have been caused by intestinal pseudo-obstruction without producing severe diarrhea. Intestinal pseudo-obstruction has also been reported in celiac disease (7), and in addition to malnutrition and anorexia due to enteropathy in this case, intestinal pseudo-obstruction led to bacterial overgrowth thus causing the vitamin B1 deficiency (8). Additionally, the ferritin levels were observed to have increased in our patient and this may be a difference in

weight of 47 kg, and body mass index of 17 kg/m². His body temperature was 36.3°C; pulse rate, 101/min; blood pressure, 101/81 mmHg; respiratory rate, 12 breaths/min; and saturation from pulse oximetry (SpO₂) was 98%. The patient had no heart murmur, third heart sound or jugular venous distension. The patient had bilateral pitting edema on his lower legs and presented with unilateral gaze-evoked

Figure 1. Cranial fluid-attenuated inversion recovery-magnetic resonance imaging shows periaqueductal hyperintensi-
ses. The antihypertensive agents were discontinued, since the gastrointestinal symptoms were ameliorated and his blood pressure increased to 160/90 mmHg, the PCP resumed the administration of olmesartan on late December, 2011. One week later, the patient complained of recurrent decreased appetite and nausea. After experiencing diarrhea (five bowel movements during a 2-day period), he passed soft stools once daily, and his body weight decreased to 47 kg so he came to our hospital again 3 weeks after the re-
sumption of olmesartan for treatment. His vital signs were as follows: body temperature, 35.1°C; pulse rate, 93/min; and blood pressure, 132/75 mmHg. The neurologic findings showed no worsening of his symptoms. The laboratory find-
ings were as follows: sodium level, 139 mEq/L; potassium level, 2.9 mEq/L; and chloride level, 116 mEq/L. Hyper-

Discussion

This was the first case of olmesartan-induced enteropathy manifesting as Wernicke-Korsakoff syndrome with recurrent nonspecific chronic gastrointestinal symptoms. Usually an adverse drug effect tends to have an acute onset. However, in cases of olmesartan-induced enteropathy, the symptom onset was months to years after the initiation of olmesartan, and therefore the diagnosis in this case was challenging. Moreover it was uncommon that the patient had only minimally increased bowel movements, not severe diarrhea as previously reported. Nonetheless the measurement of the urine anion gap indicated malabsorption syndrome, which was thought to have been caused by intestinal pseudo-obstruction without producing severe diarrhea. Intestinal pseudo-obstruction has also been reported in celiac disease (7), and in addition to malnutrition and anorexia due to enteropathy in this case, intestinal pseudo-obstruction led to bacterial overgrowth thus causing the vitamin B1 deficiency (8). Additionally, the ferritin levels were observed to have increased in our patient and this may be a difference in

Figure 1. Cranial fluid-attenuated inversion recovery-magnetic resonance imaging shows periaqueductal hyperintensities.
comparison to celiac disease in which the ferritin levels decrease (9).

From the point of view of drug-induced enteropathy, the crude incidence rate for intestinal malabsorption associated with angiotensin-converting enzyme (ACE) inhibitors (ACEIs), olmesartan, and other ARBs has been reported to be 2.4 per 100,000 person years (PY), 5.6 per 100,000 PY and 1.8 per 100,000 PY, respectively. Olmesartan was associated with an adjusted rate ratio of 2.49 (95% confidence interval (CI) 1.72 to 3.57, p<0.0001) of hospitalization with a discharge diagnosis of intestinal malabsorption compared with ACEI and a rate ratio of 3.17 (95% CI 2.22 to 4.53, p<0.0001) compared with other ARBs. Therefore, Basson et al. said that olmesartan exposure is associated with an increased risk of hospitalization for intestinal malabsorption and coeliac disease based on an observational cohort study (10).

Sprue-like enteropathy associated with ARBs other than olmesartan have been reported (2-5), so if such a patient is prescribed some kind of ARBs, it is important for general physicians to consider drug-induced enteropathy. We should also pay close attention to other drugs that can cause enteropathy, such as non-steroidal anti-inflammatory drugs, antibiotics, laxatives, vasoconstrictive agents, corticosteroids, chemotherapy agents and so on.

Unfortunately, in the present patient confabulation remained despite treatment with thiamine for 6 months. Therefore, when patients are receiving olmesartan and they complain of nonspecific chronic gastrointestinal symptoms, such as a decreased appetite or a decreased body weight, it is important to consider changing the drugs before serious malabsorption syndrome develops.
The authors state that they have no Conflict of Interest (COI).

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