

Olmesartan, Other Antihypertensives, and Chronic Diarrhea Among Patients Undergoing Endoscopic Procedures: A Case-Control Study

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Abstract

Objective: To investigate a recent association between the use of the angiotensin receptor-blocker (ARB) olmesartan and a severe enteropathy resembling celiac disease.

Patients and Methods: We searched our endoscopy database for all outpatient esophagogastroduodenoscopy (EGD) or colonoscopy examinations in patients aged at least 50 years during the period January 1, 2007, to March 31, 2013. Cases were those whose examination indication was diarrhea, and controls were those whose examination indication was esophageal reflux (EGD) or colorectal cancer screening (colonoscopy). We compared cases with controls with regard to the proportion of those listing olmesartan among their medications. Secondary exposures were the proportion of those taking non-olmesartan ARBs or other antihypertensive medications. We also examined biopsy results to determine whether there were histologic changes associated with the use of olmesartan.

Results: We identified 2088 patients undergoing EGD and 12,428 patients undergoing colonoscopy meeting inclusion criteria. On multivariate analysis, there was no statistically significant association between olmesartan and diarrhea among those undergoing EGD (odds ratio, 1.99; 95% CI, 0.79-5.00) or colonoscopy (odds ratio, 0.63; 95% CI, 0.23-1.74). Review of pathology reports of the EGD and colonoscopy groups showed no association between the use of olmesartan and the histologic diagnosis of celiac disease ($P=.61$) or microscopic colitis ($P=1.0$), respectively.

Conclusion: Our findings suggest that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy. The spruelike enteropathy recently associated with olmesartan is likely a rare adverse effect and milder presentations are unlikely.

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A number of recent reports in the literature have implicated olmesartan, an angiotensin II receptor-blocker (ARB) commonly prescribed for the treatment of hypertension, in the development of a severe form of chronic diarrhea and intestinal villous atrophy resembling celiac disease.¹⁻³ In an initial case series, 22 individuals were diagnosed with refractory celiac disease because of chronic diarrhea and villous atrophy on histology, although all lacked the diagnostic markers of celiac disease and derived no clinical improvement from a gluten-free diet.¹ These individuals were observed to be taking olmesartan and experienced significant clinical and histological improvement with the cessation of the drug, suggesting a strong association between olmesartan and the development of a severe form of spruelike enteropathy.

A recent review of individuals with villous atrophy of unclear etiology also observed that a number of those originally considered to have unclassified sprue (negative celiac disease serologies despite evidence of villous atrophy on duodenal biopsy) were taking olmesartan.⁴ As in the previous study, all these patients had symptomatic improvement after the discontinuation of the drug. Similarly, a case series of patients with collagenous sprue at the Mayo Clinic reported that of 30 patients with collagenous sprue, 27% had been taking olmesartan.⁵ Although the diagnosis of celiac disease is made on duodenal biopsy, the finding of microscopic colitis (lymphocytic and/or collagenous colitis) in the large intestine is associated with a diagnosis of celiac disease. Thus, a positive association between microscopic colitis and the use of olmesartan could suggest a

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spectrum of histologic changes associated with the drug. In addition, lymphocytic colitis was present in 22% of the initial case series describing olmesartan-associated spruelike enteropathy.¹

Another recent case report described similar findings of negative serologic markers despite mild villous atrophy in a patient taking olmesartan; however, unlike the previous reports, this patient exhibited no symptoms of diarrhea, suggesting that olmesartan may produce a spectrum of disease with preclinical or asymptomatic histologic changes.⁶

It is unclear whether these cases described in the literature highlight a very rare reaction to olmesartan, or whether patients with severe disease represent the most clinically overt sample, with milder forms of olmesartan enteropathy left undetected. It is also unclear whether olmesartan alone is associated with this phenomenon or whether other members of its drug class share similar effects. We therefore performed a case-control study with the aim of investigating a possible association between diarrhea and the use of olmesartan among patients undergoing endoscopic procedures. As a secondary aim, we measured for associations between diarrhea and other antihypertensive medication exposures.

METHODS

Patients

Using an electronic endoscopy database, we identified all outpatient esophagogastroduodenoscopy (EGD) or colonoscopy examinations in patients aged at least 50 years during the 75-month period spanning the dates January 1, 2007, and March 31, 2013, at Columbia University Medical Center, a hospital-based endoscopy suite in New York City. As part of routine preendoscopy protocol, all patients were interviewed in person by a nurse and asked to provide a list of all their current medications (prescription as well as nonprescription). Cases were defined as those whose examination indication was listed as diarrhea, and controls were defined as those whose examination indication was esophageal reflux (in those undergoing EGD) or colorectal cancer screening (in those undergoing colonoscopy). We compared cases with controls with regard to the proportion of those who listed olmesartan among their

medications. Secondary exposures were the proportion of those taking nonolmesartan ARBs or other antihypertensive medications. We used multivariate logistic regression, adjusting for age and sex, to quantify the association between these drug exposures and case status, that is, diarrhea.

To determine whether there were histologic changes associated with the use of olmesartan, we examined the biopsy results of both the EGD and the colonoscopy groups. We examined the upper endoscopy cases (ie, patients who presented for EGD because of diarrhea) to determine whether there were any diagnoses of celiac disease and whether there was an increased proportion of olmesartan use among those who underwent small intestinal biopsy during the procedure. To do so, we identified patients with celiac disease (either newly diagnosed or previously diagnosed) in this data set using a query for the *International Classification of Diseases, Ninth Revision* code for celiac disease (579.0) followed by manual review of the chart of each case with this diagnosis code. Using the search terms “microscopic colitis” or “lymphocytic colitis” or “collagenous colitis,” we also manually reviewed the biopsy reports of colonoscopy cases (ie, patients who underwent colonoscopy because of diarrhea) to determine whether there was an increased proportion of microscopic colitis among patients taking olmesartan.

Statistical Analyses

For the primary outcome, we performed multiple logistic regression, controlling for age and sex, and calculated adjusted odds ratios (ORs) and their corresponding 95% CIs. All reported *P* values are 2-sided. We used SAS version 9.2. When comparing the use of olmesartan among cases diagnosed with celiac disease or microscopic colitis, we used the Fisher exact test. The Institutional Review Board at Columbia University Medical Center approved this study.

RESULTS

We identified 2088 patients undergoing EGD and 12,428 patients undergoing colonoscopy who met the inclusion criteria. Cases as defined by those undergoing endoscopy because of diarrhea were 393 (19%) in the EGD and 867 (7%) in the colonoscopy cohort (Table 1). Women composed 65% and 59% of the EGD and

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