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# 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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colonoscopy groups, respectively. Most patients were aged between 50 and 69 years (range, 50-93 y). The proportion of patients taking any antihypertensive was 46% (968/2088) of the patients in the EGD group and 42% (5267/12428) of the patients in the colonoscopy group. The use of olmesartan in particular was reported by 22 (1%) of the EGD and 83 (0.7%) of the colonoscopy study patients, while use of nonolmesartan ARB was reported by 228 (11%) of the EGD and 1048 (8%) of the colonoscopy patients.

Univariate (Table 2) and multivariate (Table 3) analyses demonstrated that there was no statistically significant association between the use of olmesartan and diarrhea among those undergoing EGD (multivariate OR, 1.99; 95% CI, 0.79-5.00) or colonoscopy (multivariate OR, 0.63; 95% CI, 0.23-1.74). Associations that reached statistical significance on multivariate analysis were an increased risk of diarrhea with older age (EGD OR for ≥70 y vs 50-59 y, 1.35; 95% CI, 1.01-1.80; colonoscopy OR, 2.22; 95% CI; 1.86-2.65) and female sex (EGD OR, 1.48; 95% CI, 1.16-1.90; colonoscopy OR, 1.69; 95% CI, 1.45-1.97). In addition, there was a decreased risk of diarrhea among EGD patients taking calcium channel blockers (OR, 0.61; 95% CI, 0.38-0.98) and angiotensin-converting enzyme inhibitors (OR, 0.67; 95% CI, 0.50-0.92) as well

**TABLE 1. Characteristics of Study Patients[a,b]**

| Characteristic | EGD (n=2088) | Colonoscopy (n=12,428) |
|---|---|---|
| Age (y) | | |
| 50-59 | 779 (37) | 5621 (45) |
| 60-69 | 763 (37) | 4141 (33) |
| 70+ | 546 (26) | 2666 (21) |
| Sex | | |
| Female | 1364 (65) | 7387 (59) |
| Male | 724 (35) | 5041 (41) |
| Procedure indication | | |
| Diarrhea (cases) | 393 (19) | 867 (7) |
| Reflux (controls) | 1695 (82) | - |
| CRC Screening (controls) | - | 11,561 (93) |
| HTN medications | | |
| None | 1120 (54) | 7161 (58) |
| Any | 968 (46) | 5267 (42) |
| Olmesartan | 22 (1) | 83 (0.7) |
| Any ARB | 228 (11) | 1048 (8) |
| Any ACEI | 418 (20) | 2235 (18) |
| HCTZ/chlorthalidone | 218 (10) | 1539 (12) |
| Beta blocker | 404 (19) | 2245 (18) |
| Calcium channel blocker | 171 (8) | 921 (7) |

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; CRC = colorectal cancer; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).

**TABLE 2. Univariate Analysis of Factors Associated With Diarrhea[a,b]**

| Factor | EGD | | | Colonoscopy | | |
|---|---|---|---|---|---|---|
| | Diarrhea | Control | *P* | Diarrhea | Control | *P* |
| Age (y) | | | .38 | | | <.001[c] |
| 50-59 | 139 (18) | 640 (82) | | 290 (5)[c] | 5331 (95)[c] | |
| 60-69 | 140 (18) | 623 (82) | | 297 (7)[c] | 3844 (93)[c] | |
| 70+ | 114 (21) | 432 (79) | | 280 (11)[c] | 2386 (89)[c] | |
| Sex | | | | | | |
| Female | 285 (21)[c] | 1079 (79)[c] | <.001[c] | 608 (8) | 6779 (92)[c] | <.001[c] |
| Male | 108 (15) | 616 (85) | | 259 (5) | 4782 (95) | |
| Any antihypertensive | 158 (16)[c] | 810 (84)[c] | .006[c] | 369 (7) | 4898 (93) | .91 |
| No antihypertensive | 235 (21) | 885 (79) | | 498 (7) | 6663 (93) | |
| Olmesartan | 7 (32) | 15 (68) | .12 | 4 (5) | 79 (95) | .44 |
| Any ARB | 34 (15) | 194 (85) | .11 | 87 (8) | 961 (92) | .08 |
| Any ACEI | 60 (14)[c] | 358 (86)[c] | .009[c] | 142 (6) | 2093 (94) | .20 |
| HCTZ/chlorthalidone | 34 (16) | 184 (84) | .20 | 84 (5) | 1455 (95)[c] | .01[c] |
| Beta blocker | 74 (18) | 330 (82) | .77 | 175 (8) | 2070 (92) | .09 |
| Calcium channel blocker | 22 (13)[c] | 149 (87)[c] | .04[c] | 66 (7) | 855 (93) | .81 |

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide.
[b]Values are No. (percentage).
[c]Exposures meeting statistical significance.

**TABLE 3. Multivariate Analysis of Factors Associated With Diarrhea[a]**

| Factor | EGD | | Colonoscopy | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age (y) | | | | |
| 50-59 | 1.0 | - | 1.0 | - |
| 60-69 | 1.12 (0.86-1.45) | .41 | 1.44 (1.22-1.71)[b] | <.001[b] |
| 70+ | 1.35 (1.01-1.80)[b] | .04[b] | 2.22 (1.86-2.65)[b] | <.001[b] |
| Sex | | | | |
| Female | 1.48 (1.16-1.90)[b] | .002[b] | 1.69 (1.45-1.97)[b] | <.001[b] |
| Male | 1.0 | - | 1.0 | - |
| Any antihypertensive | 0.72 (0.57-0.90)[b] | .005[b] | 0.90 (0.76-1.04) | .14 |
| Olmesartan | 1.99 (0.79-5.00) | .14 | 0.63 (0.23-1.74) | .37 |
| Any ARB | 0.73 (0.49-1.09) | .12 | 1.17 (0.92-1.49) | .20 |
| Any ACEI | 0.67 (0.50-0.92)[b] | .01[b] | 0.89 (0.73-1.08) | .23 |
| HCTZ/chlorthalidone | 0.87 (0.58-1.30) | .49 | 0.66 (0.51-0.84)[b] | <.001[b] |
| Beta blocker | 1.07 (0.80-1.43) | .66 | 1.11 (0.93-1.33) | .25 |
| Calcium channel blocker | 0.61 (0.38-0.98)[b] | .04[b] | 0.97 (0.75-1.27) | .84 |

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; EGD = esophagogastroduodenoscopy; HCTZ = hydrochlorothiazide.
[b]Exposures meeting statistical significance.

as among colonoscopy patients taking thiazide diuretics (OR, 0.66; 95% CI, 0.51-0.84).

Of the 393 patients who presented for upper endoscopy because of diarrhea, 70 (18%) had biopsy results consistent with celiac disease and 2 (0.5%) of those were taking olmesartan. When compared with EGD patients who presented because of diarrhea without a diagnosis of celiac disease on biopsy, there was no statistically significant association between the use of olmesartan and the diagnosis of celiac disease (*P*=.61) (Table 4).

Of the 867 patients who presented for colonoscopy because of diarrhea, 762 (88%) underwent biopsy and 59 of these had a diagnosis of microscopic colitis. None of the diagnoses of microscopic colitis, however, was associated with current use of olmesartan (Table 5). When compared with colonoscopy cases without a diagnosis of microscopic colitis on biopsy, there was no statistically significant association between the use of olmesartan and the diagnosis of microscopic colitis (*P*=1.0).

**TABLE 4. Antihypertensive Use in EGD Cases With/Without Diagnosis of Celiac Disease on Biopsy[a,b]**

| Antihypertensive | Diagnosis celiac disease (n=70) | No diagnosis celiac disease (n=323) |
|---|---|---|
| HTN medication, any | 23 (33) | 135 (42) |
| Olmesartan[c] | 2 (3) | 5 (2) |
| Any ARB | 2 (3) | 32 (10) |
| Any ACEI | 11 (16) | 49 (15) |
| HCTZ/chlorthalidone | 7 (10) | 27 (8) |
| Beta blocker | 10 (14) | 64 (20) |
| Calcium channel blocker | 2 (3) | 20 (6) |

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).
[c]*P*=.61.

## DISCUSSION

In this case-control study, we sought to examine the recently described association between the use of olmesartan and chronic severe diarrhea using a large sample of patients presenting for endoscopy at a tertiary referral medical center. Previous data on the risk of diarrhea among individuals taking olmesartan come from the original trial comparing the use of olmesartan to placebo in patients with diabetes. Data from that trial suggested no increased gastrointestinal adverse effects of the drug; however, the risk of diarrhea with the use of olmesartan was not a primary end point of the study.[7] To our knowledge, this is the first study to compare the rate of use of olmesartan and biopsy findings in patients with symptomatic chronic diarrhea vs asymptomatic individuals presenting for endoscopic evaluation.

We found that neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy. Other antihypertensives were negatively associated with diarrhea, possibly as a result of their known constipating effects. Analysis of the biopsy results of those patients who presented for endoscopy because of diarrhea similarly resulted in negative findings: there was no statistically significant association between patients whose biopsy results were consistent with a diagnosis of celiac disease or microscopic colitis and the use of olmesartan. Notably, most of the individuals in the initial case series who developed sprue-like enteropathy associated with the use of olmesartan were HLA DQ2 or DQ8 positive, suggesting potential predisposing factors in certain individuals; however, the underlying mechanism remains unknown.

Strengths of this study include the large sample size as well as the comprehensive and protocoled, direct, in-person solicitation of home medication use immediately preceding each endoscopic procedure. Limitations of this study include its retrospective nature, although it examines a large sample size for a rare event

that may not be amenable to a prospective design. There was also a relatively small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis. Because the upper bound of our 95% CI was 5.00 in the EGD analysis and 1.74 in the colonoscopy analysis, a meaningful association between olmesartan and diarrhea may exist that was not detectable because of the relative rarity of use of olmesartan.

## CONCLUSION

Our findings suggest that the spruelike enteropathy recently associated with olmesartan is a rare event and milder presentations causing diarrhea among substantial numbers of outpatients are unlikely. Future studies should focus on the mechanisms by which olmesartan causes severe spruelike enteropathy, and the identification of patient-related risk factors that predispose for this rare but serious outcome.

**Abbreviations and Acronyms:** **ARB** = angiotensin receptor-blocker; **EGD** = esophagogastroduodenoscopy; **OR** = odds ratio

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**TABLE 5. Antihypertensive Use in Colonoscopy Cases With/Without Microscopic Colitis on Biopsy[a,b]**

| Antihypertensive | Microscopic colitis (n=59) | No microscopic colitis (n=703) |
|---|---|---|
| HTN medication, any | 24 (41) | 296 (42) |
| Olmesartan[c] | 0 (0) | 4 (0.6) |
| Any ARB | 5 (8) | 71 (10) |
| Any ACEI | 13 (22) | 109 (16) |
| HCTZ/chlorthalidone | 6 (10) | 63 (9) |
| Beta blocker | 8 (14) | 137 (19) |
| Calcium channel blocker | 2 (3) | 53 (8) |

[a]ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor-blocker; HCTZ = hydrochlorothiazide; HTN = hypertension.
[b]Values are No. (percentage).
[c]$P=1.0$.

## REFERENCES

1. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.
2. Dreifuss SE, Tomizaka Y, Farber NJ, Davison JM, Sohnen AE. Spruelike enteropathy associated with olmesartan: an unusual case of severe diarrhea. *Case Rep Gastrointest Med*. 2013;2013:618071.
3. Nielsen JA, Stephen A, Lewin M. Angiotensin-II inhibitor (olmesartan)-induced collagenous sprue with resolution following discontinuation of drug. *World J Gastroenterol*. 2013;19(40):6928-6930.
4. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. *Am J Gastroenterol*. 2013;108(5):647-653.
5. Rubio-Tapia A, Talley NJ, Gurudu SR, Wu TT, Murray JA. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol*. 2010;8(4):344-349.e3.
6. Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. *Mayo Clin Proc*. 2012;87(12):1231-1232; author reply 1232.
7. Menne J, Haller H. Olmesartan and intestinal adverse effects in the ROADMAP study. *Mayo Clin Proc*. 2012;87(12):1230-1231; author reply 1232.