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Olmesartan, other anti-hypertensives, and chronic diarrhea among patients undergoing endoscopic procedures; a case-control study

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Abstract

Objective—To investigate a recent association between 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 at least 50 years of age during the dates 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 to 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 anti-hypertensive medications. We also examined biopsy results to determine if there were histologic changes associated with olmesartan use.

Results—We identified 2088 patients undergoing EGD and 12428 patients undergoing colonoscopy meeting inclusion criteria. On multivariate analysis, there was no statistically-significant association between olmesartan and diarrhea among those undergoing EGD (OR 1.99 95% CI 0.79–5.00) or colonoscopy (OR 0.63 95% CI 0.23–1.74). Review of pathology reports of the EGD and colonoscopy groups showed no association between olmesartan use and the histologic diagnosis of celiac disease (p=0.61) or microscopic colitis (p=1.0), respectively.

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

INTRODUCTION

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.[1,2,3] In an initial case series, 22 individuals were diagnosed with refractory celiac disease due to 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 sprue-like 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 prior study, all of 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 also associated with a diagnosis of celiac disease. Thus, a positive association between microscopic colitis and olmesartan use could suggest a spectrum of histologic changes associated with the drug. In addition, lymphocytic colitis was present in 22% of the initial case series describing olmesartan-associated sprue-like 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 prior reports, this patient exhibited no symptoms of diarrhea, suggesting that olmesartan may produce a spectrum of disease with pre-clinical 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 measuring for a possible association between diarrhea and olmesartan use among patients undergoing endoscopic procedures. As a secondary aim, we measured for associations between diarrhea and other anti-hypertensive medication exposures.

METHODS

Patients

Using an electronic endoscopy database, we identified all outpatient esophagogastroduodenoscopy (EGD) or colonoscopy examinations in patients at least 50 years of age 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 pre-endoscopy protocol, all patients were interviewed in person by a nurse and asked to provide a list of all of their current medications (prescription as well as non-prescription). 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 to controls with regard to the proportion of those who listed olmesartan among their medications. Secondary exposures were the proportion of those taking non-olmesartan ARBs or other anti-hypertensive medications. We used multivariate logistic regression, adjusting for age and gender, to quantify the association between these drug exposures and case status, i.e. diarrhea.

In order to determine if there were histologic changes associated with olmesartan use, we examined the biopsy results of both the EGD and the colonoscopy groups. We examined the upper endoscopy cases (i.e. patients who presented for EGD due to diarrhea) to determine if 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. In order to do so, we identified patients with celiac disease (either newly-diagnosed or previously diagnosed) in this dataset using a query for the International Classification of Diseases 9 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 (i.e. patients who underwent colonoscopy due to diarrhea) to determine if there was an increased proportion of microscopic colitis among patients taking olmesartan.

Statistical Analysis

For the primary outcome, we performed multiple logistic regression, controlling for age and gender, and calculated adjusted odds ratios (OR) and their corresponding 95% confidence intervals. All reported p values are 2-sided. We used SAS version 9.2 (Cary, NC). When comparing olmesartan use amongst cases diagnosed with celiac disease or microscopic colitis, we used Fisher’s exact test. The Institutional Review Board at Columbia University Medical Center approved this study.

RESULTS

We identified 2,088 patients undergoing EGD and 12,428 patients undergoing colonoscopy who met the inclusion criteria. Cases as defined by those undergoing endoscopy due to diarrhea were 393 (19%) in the EGD and 867 (7%) in the colonoscopy cohort. [Table 1] Females composed 65% and 59% of the EGD and colonoscopy groups, respectively. Most

patients were between 50–69 years of age (range 50–93). The proportion of patients taking any anti-hypertensive was 46% of the EGD and 42% of the colonoscopy patients. Olmesartan use in particular was reported by 22 (1%) of the EGD and 83 (0.7%) of the colonoscopy study subjects, while non-olmesartan ARB use was reported by 228 (11%) of the EGD and 1048 (8%) of the colonoscopy subjects.

Univariate [Table 2] and multivariate analyses [Table 3] demonstrated that there was no statistically significant association between olmesartan use 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 vs. 50–59, 1.35 95% CI 1.01–1.80; Colonoscopy OR 2.22 95% CI 1.86–2.65) and female gender (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 ACE inhibitors (OR 0.67 95% CI 0.50–0.92) as well as among colonoscopy patients taking thiazide diuretics (OR 0.66 95% CI 0.51–0.84).

Of the 393 subjects who presented for upper endoscopy due to diarrhea, 70 (18%) had biopsy results consistent with celiac disease, and 2 (0.5%) of those were taking olmesartan. When compared to EGD subjects who presented due to diarrhea without a diagnosis of celiac disease on biopsy, there was no statistically significant association between olmesartan use and the diagnosis of celiac disease (p= 0.61). [Table 4]

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

DISCUSSION

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

We found neither olmesartan nor other ARBs were associated with diarrhea among patients undergoing endoscopy. Other anti-hypertensives 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 due to 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, the majority of individuals in the initial case series who developed sprue-like enteropathy associated with olmesartan use 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 is 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 olmesartan use (0.7–1%) among study subjects, limiting the power of this analysis. Since the upper bounds of our 95% confidence interval was 5.00 in the EGD analysis and 1.74 in the colonoscopy analysis, a meaningful association between olmesartan and diarrhea may exist which was not detectable due to the relative rarity of olmesartan use.

CONCLUSION

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

ABBREVIATIONS

ARB	angiotensin receptor-blocker
EGD	esophagogastroduodenoscopy

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Table 1

Characteristics of Study Subjects

	EGD (n=2,088)	Colonoscopy (n=12,428)
Age		
50–59	779 (37)	5621 (45)
60–69	763 (37)	4141 (33)
70+	546 (26)	2666 (21)
Gender		
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)	--	11561 (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)

ARB: angiotensin receptor-blocker. ACEI: angiotensin-converting enzyme inhibitor. HCTZ: hydrochlorothiazide.

Table 2

Univariate Analysis of Factors Associated with Diarrhea.

	EGD			Colonoscopy		
	Diarrhea	**Control**	**p value**	**Diarrhea**	**Control**	**p value**
Age			0.38			**<0.001**
50–59	139 (18)	640 (82)		**290 (5)**	**5331 (95)**	
60–69	140 (18)	623 (82)		**297 (7)**	**3844 (93)**	
70+	114 (21)	432 (79)		**280 (11)**	**2386 (89)**	
Gender						
Female	**285 (21)**	**1079 (79)**	**<0.001**	608 (8)	**6779 (92)**	**<0.001**
Male	108 (15)	616 (85)		259 (5)	4782 (95)	
Any anti-hypertensive	**158 (16)**	**810 (84)**	**0.006**	369 (7)	4898 (93)	0.91
No anti-hypertensive	235 (21)	885 (79)		498 (7)	6663 (93)	
Olmesartan	7 (32)	15 (68)	0.12	4 (5)	79 (95)	0.44
Any ARB	34 (15)	194 (85)	0.11	87 (8)	961 (92)	0.08
Any ACEI	**60 (14)**	**358 (86)**	**0.009**	142 (6)	2093 (94)	0.20
HCTZ/Chlorthalidone	34 (16)	184 (84)	0.20	84 (5)	**1455 (95)**	**0.01**
Beta Blocker	74 (18)	330 (82)	0.77	175 (8)	2070 (92)	0.09
Calcium Channel Blocker	**22 (13)**	**149 (87)**	**0.04**	66 (7)	855 (93)	0.81

Exposures meeting statistical significance are shown in **bold**.

Table 3

Multivariate Analysis of Factors Associated with Diarrhea

	EGD		Colonoscopy	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Age				
50–59	1.0	--	1.0	--
60–69	1.12 (0.86–1.45)	0.41	**1.44 (1.22–1.71)**	**<0.001**
70+	**1.35 (1.01–1.80)**	**0.04**	**2.22 (1.86–2.65)**	**<0.001**
Gender				
Female	**1.48 (1.16–1.90)**	**0.002**	**1.69 (1.45–1.97)**	**<0.001**
Male	1.0	--	1.0	--
Any anti-hypertensive	**0.72 (0.57–0.90)**	**0.005**	0.90 (0.76–1.04)	0.14
Olmesartan	1.99 (0.79–5.00)	0.14	0.63 (0.23–1.74)	0.37
Any ARB	0.73 (0.49–1.09)	0.12	1.17 (0.92–1.49)	0.20
Any ACEI	**0.67 (0.50–0.92)**	**0.01**	0.89 (0.73–1.08)	0.23
HCTZ/Chlorthalidone	0.87 (0.58–1.30)	0.49	**0.66 (0.51–0.84)**	**<0.001**
Beta Blocker	1.07 (0.80–1.43)	0.66	1.11 (0.93–1.33)	0.25
Calcium Channel Blocker	**0.61 (0.38–0.98)**	**0.04**	0.97 (0.75–1.27)	0.84

Exposures meeting statistical significance are shown in **bold**.

Table 4

Anti-hypertensive use in EGD cases with/without diagnosis of celiac disease on biopsy

Anti-hypertensive	Diagnosis celiac disease (n = 70)	No diagnosis celiac disease (n = 323)
HTN medication, any	23 (33)	135 (42)
Olmesartan*	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)

* p = 0.61

Table 5

Anti-hypertensive use in colonoscopy cases with/without microscopic colitis on biopsy

Anti-hypertensive	Microscopic colitis (n = 59)	No microscopic colitis (n = 703)
HTN medication, any	24 (41)	296 (42)
Olmesartan*	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)

* p = 1.0