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ARBs-correlated Celiac-Like Enteropathy

YELDA KOMESLI[1]; BEKIR UGUR ERGUR[2]; ERCUMENT KARASULU[3,4]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Altinbas University, Istanbul, Turkey,
[2]Department of Histology and Embryology, Faculty of Medicine, University of Kyrenia, Kyrenia, Cyprus
[3]Department of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, Ege University, Izmir, Turkey
[4]Center for Drug R&D and Pharmacokinetic Applications (ARGEFAR), Ege University, Izmir, Turkey

**Corresponding Author: Yelda Komesli, Altinbas University, Kartaltepe Mah. İncirli cad. No:11 Bakırköy / Istanbul*
E-mail: yelda.komesli@altinbas.edu.tr Tel: +90 505 571 82 01

1. INTRODUCTION

Olmesartan medoxomil (OM) is an angiotensin receptor blocker antihypertensive drug and is used at a single oral dose. Celiac-like enteropathy side effect of OM were accepted by the FDA (According to safety announcement UCM359496). Link between OM and celiac effect was first defined by Rubio-Tapia et al in 2012 [1]–[3] This histopathological findings of celiac-like side effects are severe intestinal villous atrophy with intraepithelial lymphocytosis, increased subepithelial collagen and inflammation of lamina propria. The cessation of OM causes complete improvement of both clinical and histological features. The diagnosis of celiac disease is supported by a positive antibody test (deamidated gliadin peptide, antiendomysial antibodies and tissue transglutaminase) and symptomatic and histological response to a gluten-free diet [4]–[9] It is difficult to differentiate OM and other ARB-related enteropathy findings and histopathology from celiac disease. Many cases of celiac-like enteropathy have been reported after long-term use of OM in humans. 55 million patients worldwide are using OM and the world sales volume is $ 5.5 billion. Many of lawsuits filed against this side effect result in the compensation payment of the originator company. In this study, we compared the histopathological findings of the OM-SMEDDS and OM suspension administered group of rats compared to the control group that received no medication. We correlated celiac-like enteropathy caused by OM and other ARBs with clinical observations and concluded that would be beneficial for clinicians.

Preparation of OM-SMEDDS: Preparation of OM-SMEDDS: The experiments were carried out using our previous standardized and optimized SMEDDS and validated HPLC method that reported in our previous article [10]

Histopathological findings in olmesartan-related celiac-like entropathy in rats: Histological studies were performed on albino 18 male normotensive Wistar Rats (160-180 g). In our study, after one month of exposure of OM Self microemulsifying drug delivery system that we developed (SMEDDS) and Olmesartan plain drug suspen-

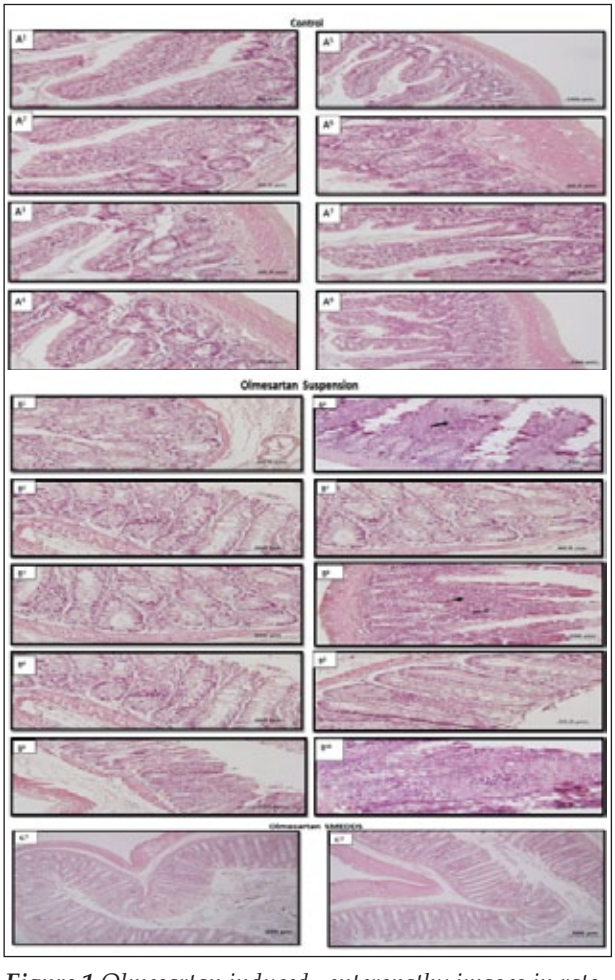

Figure 1 *Olmesartan induced enteropathy images in rats. There is intense mononuclear cell infiltration and villous atrophy at the OM suspension administereted group.*

sion, histochemical findings of the intestinal samples were taken from control group, SMEDDS administered and OM suspension administered rats. The duodenum was used as the intestinal segment [11]. Histological examinations of rat intestine indicated that SMEDDS-treated rats and control group had no enteropathy findings while the OM suspension-treated group showed enteropathy findings with increased mononuclear cell infiltration (***Figure 1***). We believe our transport system reduced the contact of OM with the intestines because of its lipophilic characteristics. This effect of SMEDDS can be explained by increased bile secretion in the gastrointestinal tract, dividing into mixed micelles, increasing lymphatic transport, and modulating enterocyte-based enzyme and carrier systems [12]. Throughout the NIBP experiment, SMEDDS did not cause diarrhea or weight loss compared to suspension. This finding suggests that the SMEDDS will prevent celiac-like enteropathy. SMEDDS does not cause side effects .

Clinical findings and Case Results in olmesartan-related celiac-like entropathy

In a systematic review performed by Burbure, findings from different case series were evaluated. In a total of 104 cases, patients who had been using OM for 1 month to 11.5 years were examined. HLDQ / HLDQ8 gene was detected in 70%, villous atrophy was detected in 100% and IEL was detected in 70% of the cases. 30% collagen sprue, 27% microscopic colitis and 41% lymphocytic or collagen gastritis were detected in cases. 95% of patients recovered after discontinuation of OM treatment [13]–[20]

Clinical findings and Case Results in other non-olmesartan-related celiac-like entropathy: Case reports of patients taking other angiotensin receptor blockers like valsartan, irbesartan, telmisartan, eprosartan, losartan, and candesartan demonstrated a profound celiac-like enteropathy findings and villous atrophy are also exist [20], [21], [30], [31], [22–29]

2. CONCLUSION

Our olmesartan-induced celiac rat model experiment has given us hope that in the future we will learn more about celiac disease with celiac animal models caused by ARB. In addition, our results demonstrated histopathologically that olmesartan induces celiac-like enteropathy in animals. Since antihypertensive ARBs have a celiac side effect, it is very important for clinicians to be aware of the histopathological and histochemical changes associated with ARB enteropathy. In the future, further studies of olmesartan and other angiotensin receptor blockers in humans and animals should be performed on a histopathological, genetic and histochemical basis. This will resolve unexplained enteropathy cases.

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