

*Full Length Research Paper*

# Comparative study between effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on acetic acid- induced ulcerative colitis in rats

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Accumulating data suggest the involvement of renin angiotensin system (RAS) in the pathogenesis of inflammatory bowel disease. The aim of the present study was to evaluate the potential protective and therapeutic effects of captopril and valsartan on acetic acid induced- ulcerative colitis in rats. The results were assessed by macroscopic and microscopic examinations of colonic tissues as well as by biochemical measurement of malondialdehyde (MDA), tumor necrosis factor alpha (TNF- $\alpha$ ), transforming growth factor- beta1 (TGF- $\beta$ 1), angiotensin converting enzyme (ACE), reduced glutathione (GSH) and platelet activating factor (PAF) levels in colonic tissues. Oral treatment with captopril or valsartan in a dose of 30 mg kg<sup>-1</sup> body weight, starting one day before induction of colitis and continuing for 1 week (prophylactic groups) or starting one week after induction of colitis and continuing for another one week (therapeutic groups), significantly reduced MDA, TNF- $\alpha$ , PAF, TGF- $\beta$ 1 and significantly increased colonic GSH in colonic tissues as compared to acetic acid control groups. Captopril and valsartan attenuated the macroscopic and microscopic colonic damage induced by acetic acid. No significant difference between the effect of either drug could be detected other than the significant decrease in ACE activity in colonic tissue exerted by captopril and not by valsartan, These results suggest that either captopril or valsartan may be effective in prophylaxis as well as in treatment of ulcerative colitis through targeting RAS.

**Keywords:** Ulcerative colitis, captopril, valsartan, angiotensin converting enzyme, reduced glutathione, tumor necrosis factor alpha, transforming growth factor beta.

## INTRODUCTION

Inflammatory bowel disease (IBD), comprising both

### Abbreviations

ACE, angiotensin converting enzyme; II, Ang II, angiotensin II; Ang II type 1, AT<sub>1</sub>; ARB, angiotensin receptor blocker; IBD, inflammatory bowel disease; GSH, reduced glutathione; MDA, malondialdehyde; PAF, platelet activating factor; RAS, renin angiotensin system; TGF-, transforming growth factor beta; TNF-, tumor necrosis factor alpha.

ulcerative colitis and Crohn's disease, is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract (Israeli et al., 2005). Both conditions result in inflammation, ulceration, edema, bleeding and diarrhea (Sands, 2007). Although many treatments are currently available for IBD, these are only effective for ameliorating the signs and symptoms of the disease. There is, as yet, no cure for this condition. The most commonly used therapies include aminosalicylates, antibiotics, corticosteroids and immunosuppressants, all of which have disadvantages (Sartor, 2004). It is therefore important to find better

treatment options with fewer side effects.

While the cause of ulcerative colitis remains unknown, a number of findings in recent years point to an over stimulation or inadequate regulation of the mucosal immune system as a major pathophysiologic pathway (Israeli et al., 2005). Thus, any treatment which is able to inhibit the activation of these immunological and inflammatory effectors mechanisms is likely to lead to an improvement in the patient's symptoms and to a decrease in the inflammatory reactions (Rama et al., 2005). In recent years, data are accumulating suggesting involvement of renin angiotensin system (RAS) in the pathogenesis of IBD (Fändriks, 2010). Colonic mucosal levels of both Ang II and I are reported to be greater in patients with Crohn's disease, and appear to correlate with the degree of inflammation with the source most likely to be a local angiotensin cascade, or the endothelium of the microvasculature (Jaszewski et al., 1990). Indeed, (Hirasawa et al., 2002) reported colonic localization of RAS.

Ang II receptors are found throughout the intestine. Binding for the Ang II type 1 (AT<sub>1</sub>) receptor has been demonstrated in the muscularis mucosa, enteric nerves and epithelial cells of the colon, and specifically within the intestine of Sprague-Dawley rats [Sechi et al., 1993]. Angiotensin II (Ang II) is a proinflammatory hormone that has been shown to participate in several key events of the inflammatory response, raising the possibility of its contribution to intestinal ulceration (Dagenais et al., 2005). Ang II increases vascular permeability (via release of prostaglandins and vascular endothelial cell growth factor/vascular permeability factor), and it participates in the recruitment of infiltrating inflammatory cells into tissues by their direct activation, or by regulation of the expression of platelet activating factor (PAF) (Neuwirth et al., 1989), cytokines, adhesion molecules and chemokines by resident cells (Suzuki et al., 2000). Accumulating evidence also indicates that AT<sub>1</sub> receptor activation has proinflammatory effects. Ang II activates the nicotinamide adenine dinucleotide oxidase system, resulting in production of reactive oxygen species such as superoxide and hydrogen peroxide (Touyz and Schiffrin, 2004). Moreover, Ang II is known to regulate motility in the intestine, as well as ion and water absorption via receptors in the mucosa and muscle (Johansson et al., 2001). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are two distinct pharmacologic classes that both reduce the actions of Ang II at the AT<sub>1</sub> receptor (Goodfriend et al., 1996). ACE inhibitors, by blocking kininase II, also inhibit the breakdown of bradykinin (Cruden et al., 2004). On the other hand, the reflex increase in Ang II, resulting from blockade of the AT<sub>1</sub> receptor, is believed to lead to enhanced stimulation of the unblocked AT<sub>2</sub> receptor (Horiuchi et al., 1999). Augmentation of bradykinin and stimulation of the AT<sub>2</sub>

receptor may have additional vascular (e.g., vasodilator) and non-vascular e.g. (fibrinolytic and growth effects (Cruden et al., 2004; Horiuchi et al., 1999). The aim of the current study was to assess and compare the possible protective and therapeutic effects of an ACE inhibitor, namely captopril, and an ARB, namely valsartan, on the extent and severity of ulcerative colitis induced by acetic acid in rats and to study the possible underlying mechanism of action of these drugs.

## MATERIALS AND METHODS

### Animals

Seventy male Wistar albino rats (150-200 g) were used throughout this work (supplied from animal house, King Saud University). The animals were maintained in a room under standard conditions of light, feeding and temperature. The study was conducted in accordance with the standards established by the guide for the care and use to laboratory animals of the College of Medicine Research Centre. After one week of acclimatization, the animals were randomly divided into the following groups each of (10) rats.

**Group I:** Normal control group.

**Group II:** Acetic acid control group received 0.5ml kg<sup>-1</sup> 2% gum acacia p.o. once daily starting one day before acetic acid-induced colitis and continued for one week. This group served as control for groups IV and VI.

**Group III:** Acetic acid control group received 0.5ml kg<sup>-1</sup> 2% gum acacia p.o. once daily starting one week after acetic acid-induced colitis and continued for one week. This group served as control for groups V and VII.

**Group IV:** Rats received captopril HCl (Capoten-Bristol-Myers Squibb) suspended in 2% gum acacia at a dose of 30 mg kg<sup>-1</sup> p.o. once daily starting one day before acetic acid-induced colitis and continued for one week.

**Group V:** Rats received captopril HCl suspended in 2% gum acacia at a dose of 30 mg kg<sup>-1</sup> p.o. once daily starting one week after acetic acid-induced colitis and continued for one week.

**Group VI:** Rats received valsartan (Diovan, Novartis Pharmaceuticals, Basel, Switzerland) suspended in 2% gum acacia at a dose of 30 mg kg<sup>-1</sup> p.o. once daily starting one day before acetic acid-induced colitis and continued for one week.

**Group VII:** Rats received valsartan suspended in 2% gum acacia at a dose of 30 mg kg<sup>-1</sup> p.o. once daily starting one week after acetic acid-induced colitis and continued for one week.

All drugs were given by oral gavage syringe. The doses of valsartan and captopril were selected based on other studies reporting cytokine suppressing effect of these drugs at these doses (Xu et al., 2006; Kassab et al., 2006; Constantinescu et al., 1995).

**Table 1:** Effects of captopril (30 mg kg<sup>-1</sup>) and valsartan (30 mg kg<sup>-1</sup>), administered prophylactically and therapeutically, on: colonic malodialdehyde(MDA), reduced glutathione(GSH), tumor necrosis factor-alpha (TNF- $\alpha$ ), transforming growth factor-beta 1(TGF- $\beta$ 1) and platelet activating factor(PAF) concentrations as well as angiotensin converting enzyme (ACE) activity (mean  $\pm$  S.E.M.) in acetic acid-induced colitis in rats.

Groups	MDA nmol/mg tissue	GSH nmol/g tissue	TNF- $\alpha$ pg/g wet tissue	TGF- $\beta$ 1 pg/g wet tissue	PAF pg/g wet tissue	ACE nmol/min/g wet tissue
(Group I) Normal control	0.257 $\pm$ 0.021	1436 $\pm$ 57	1.47 $\pm$ 0.021	0.40 $\pm$ 0.21	12.6 $\pm$ 0.48	0.27 $\pm$ 0.07
(Group II) Acetic acid control received gum starting one day before colitis and continued for one week	0.540 $\pm$ 0.034*	639 $\pm$ 46*	13.92 $\pm$ 0.28*	0.93 $\pm$ 0.4*	27.08 $\pm$ 0.88*	0.91 $\pm$ 0.40*
(Group III) Acetic acid control received gum starting one week after colitis and continued for one week	0.635 $\pm$ 0.052*	650 $\pm$ 36*	10.78 $\pm$ 0.52*	1.49 $\pm$ 0.3*	25.07 $\pm$ 0.77*	0.89 $\pm$ 0.35*
(Group IV) Captopril starting one day before colitis and continued for one week	0.300 $\pm$ 0.021 <sup>^</sup>	850 $\pm$ 87 <sup>^</sup>	6.32 $\pm$ 0.64 <sup>^</sup>	0.50 $\pm$ 0.3 <sup>^</sup>	17.04 $\pm$ 0.31 <sup>^</sup>	0.40 $\pm$ 0.03 <sup>^</sup>
(Group V) Captopril starting one week after colitis and continued for one week	0.295 $\pm$ 0.010 <sup>&amp;</sup>	930 $\pm$ 65 <sup>&amp;</sup>	5.21 $\pm$ 0.88 <sup>&amp;</sup>	0.69 $\pm$ 0.2 <sup>&amp;</sup>	16.05 $\pm$ 0.34 <sup>&amp;</sup>	0.34 $\pm$ 0.04 <sup>&amp;</sup>
(Group VI) Valsartan starting one day before colitis and continued for one week	0.290 $\pm$ 0.021 <sup>^</sup>	950 $\pm$ 56 <sup>^</sup>	6.63 $\pm$ 0.66 <sup>^</sup>	0.51 $\pm$ 0.2 <sup>^</sup>	16.92 $\pm$ 0.51 <sup>^</sup>	0.82 $\pm$ 0.05
(Group VII) Valsartan starting one week after colitis and continued for one week	0.289 $\pm$ 0.022 <sup>&amp;</sup>	987 $\pm$ 62 <sup>&amp;</sup>	4.98 $\pm$ 0.47 <sup>&amp;</sup>	0.63 $\pm$ 0.4 <sup>&amp;</sup>	17.12 $\pm$ 0.23 <sup>&amp;</sup>	0.85 $\pm$ 0.03
F value	56.65	70.23	43.65	53.21	62.12	36.56
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

\*: Significant as compared to normal control group I.

<sup>^</sup>: Significant as compared to group II.

<sup>&</sup>: Significant as compared to group III.

S.E.M: standard error mean

## Induction of experimental colitis in rats

Acetic acid-induced colitis was performed using modification of the method described by (Millar et al., 1996). The animals were starved for 24 hours with access to water ad libitum. Each rat was anaesthetized by intraperitoneal injection of pentobarbitone Na (40mg kg<sup>-1</sup>). An infant feeding tube (Pennine Health Care FT-1608/40, outside diameter 2mm) was inserted into the colon to 8 cm. 2ml of acetic acid (3%v/v in 0.9% saline) was infused into the colon. The acetic acid was retained in the colon for 30 seconds, after which the fluid was withdrawn.

At the end of the experimental period, animals were exsanguinated. Colonic biopsies were immediately taken for macroscopic scoring, histopathological and biochemical studies.

## Assessment of colitis

### Macroscopic scoring

At post-mortem laparotomy, 6 cm of colon extending proximally for 2 cm above the anal orifice was removed. It was immediately transferred into Krebs buffer (pH 7.5), which was gently bubbled with O<sub>2</sub> and 5% CO<sub>2</sub>. The colon was gently incised along its mesenteric border, washed and placed later (mucosal surface upwards) on a glass dish containing the buffer for macroscopic evaluation (colonic damage score). The severity of inflammation for each specimen was evaluated by two experienced observers unaware of the treatments, using 5 point scale ranging from 0 to 4 as follows: (0) No macroscopic change, (1) Mucosal erythema alone, (2) Mild mucosal oedema, slight bleeding or small erosion, (3) Moderate oedema, bleeding ulcers or erosion and (4) Severe ulceration, erosions, oedema and tissue necrosis (Appleyard and Wallace, 1995).

### Histopathological study

Full thickness biopsy specimens (one specimen per each animal) were fixed in 10% formal saline prior to wax embedding sectioning, and staining with haematoxylin and eosin. Histological assessment by light microscope was carried out by two observers unaware of the treatments.

### Biochemical study

Colonic samples were put immediately in liquid nitrogen then stored at -20 °C till analysis. Tissue samples were homogenized and used for assessment of:

## Lipid peroxidation

By measuring an end product of lipid peroxidation, namely malondialdehyde (MDA), by a colorimetric method described by (Buege and Aust, 1978). In brief, 2.5% (w/v) colonic biopsy homogenates was prepared in phosphate buffer pH 7.2 reacted with thiobarbituric acid (TBA) reagent containing 0.375% TBA, 15% trichloroacetic acid and 0.25 N HCl. Samples were boiled for 15 minutes, cooled and centrifuged. Absorbance of the supernatant was spectrophotometrically measured at 532nm. MDA concentration was calculated by the use of 1,1,3,3 tetraethoxypropane as a standard and expressed as nmole MDA/g wet tissue.

## Reduced glutathione (GSH)

Measured by a colorimetric method described by (Owens and Belcher, 1965) and based on the reaction of 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB) with the GSH present. The absorbance was measured at 412 nm in a Shimadzu double beam spectrophotometer (UV200S). The amount of GSH present in the sample was calculated using a standard solution of GSH containing 1 mg of GSH/1ml of 3% metaphosphoric acid. The increase in the extinction at 412 nm was proportional to the amount of GSH present.

## Tumor necrosis factor alpha (TNF- $\alpha$ )

Measured by enzyme-linked immunoabsorbent assay (ELISA) kit (Genzyme Diagnostics, Cambridge, Mass., USA). Briefly, colonic samples were homogenized in 100 mg sample/0.9 ml PBS (pH 7.4) containing 0.75 mg/ml PMSF, 1 mg/ml leupeptin and 5 mg/ml aprotinin for 30 s. They were then centrifuged at 12,000 rpm for 20 min. 100  $\mu$ l of the supernatant was added to the 96-well microtiter plate precoated with monoclonal antimouse TNF- antibody and incubated for 2 h at 37°C. After thorough washing, the substrate solution was added. Color development was allowed for 10 min and the reaction was stopped by application of stop solution. Color absorbance was read in an MRX microplate reader (Dynex Technologies, Chantilly, VA, USA) at 450 nm (Ramesh and Reeves, 2002).

## Transforming growth factor beta 1 (TGF- $\beta$ <sub>1</sub>)

Assessed by ELISA kit (DuoSet®; R&D Systems, Minneapolis, MN, USA). Briefly, colonic samples were homogenized in 100 mg sample/0.9 ml PBS (pH 7.4) containing 0.75 mg/ml PMSF, 1 mg/ml leupeptin and 5 mg/ml aprotinin for 30 s. They were then centrifuged at

12,000 rpm for 20 min. 100 µl of the supernatant was added to the 96-well microtiter plate precoated with monoclonal antimouse TGF-β1 antibody and incubated for 2 h at 37°C. After thorough washing, the substrate solution was added. Color development was allowed for 10 min and the reaction was stopped by application of stop solution. Color absorbance was read in an MRX microplate reader (Dynex Technologies, Chantilly, VA, USA) at 450 nm (Javelaud and Mauviel, 2004).

### **Platelet activating factor (PAF)**

Assessed in an aggregometer by the aggregation of aspirin treated washed rabbit platelets in the presence of adenosine diphosphate scavengers after preparing the platelets by differential centrifugation (Wallace et al., 1989).

### **Angiotensin converting enzyme (ACE) activity**

Measured by a kinetic assay at 37°C using a test reagent kit for ACE (Sigma, MO, USA) (Holmquist et al., 1979). The procedure utilizes the ACE calibrator i.e. lyophilized porcine ACE and the synthetic tripeptide substrate N-(2-furyl) acryloyl-L-phenyl alanyl-glycyl glycine. The latter is hydrolyzed by ACE to furyl acryloyl phenyl -alanine and glycyl glycine resulting in a decrease in absorbance read at 340nm. The activity of ACE in the samples was assessed by comparing the sample reaction rate with that of the ACE calibrator and the results are expressed as nmol/min /gm wet tissue .

### **Statistical Analysis**

All data were expressed as mean ± standard error of the mean (S.E.M) for ten rats per each experimental group. Statistical group analysis was performed with SPSS 17.0 statistical software. One-way analysis of variance (ANOVA) was used to compare the mean values of quantitative variable among the groups. Bonferroni test was used to identify the significance of pair wise comparison of mean values among the groups. As the outcome variable for gross lesion score is a qualitative variable, a nonparametric statistical test ;Kruskal-Wallis test was used to compare the mean ranks of scores among the different groups. Statistically significant differences were accepted at P < 0.05(Winer, 1971).

## **RESULTS**

### **Biochemical results**

Administration of either captopril or valsartan before or

after induction of colitis caused a significant reduction in MDA, TNF-α , TGF-β 1, and PAF as well as a significant increase in GSH in colonic tissues as compared to acetic acid control group. Captopril, but not valsartan, resulted in significant decrease -more than 50% in ACE activity as compared to acetic acid control group (table 1).

### **Macroscopic results**

Acetic acid treatment induced severe macroscopic inflammation in the colon, as assessed by the colonic damage score. Administration of captopril or valsartan significantly reduced the severity of the gross lesion score (table 2).

### **Histological results**

The histopathological features of untreated rats revealed transmural necrosis, oedema, and diffuse inflammatory cell infiltration in the mucosa. There were focal ulceration of the colonic mucosa extending through the muscularis mucosa, desquamated areas and loss of the epithelium. The architecture of the crypts was distorted and the lamina propria was thickened in peripheral areas of distorted crypts especially in basal areas. An infiltrate consisting of mixed inflammatory cells was also observed (Figure.1.A and B). Administration of captopril or valsartan either as prophylaxis or therapy attenuated the extent and severity of the histological signs of cell damage (Figure.1. C and D).

## **DISCUSSION**

The critical role of inappropriate inflammation is becoming accepted in many diseases including cardiovascular diseases, inflammatory and autoimmune disorders. The RAS from an evolutionary point of view is a very old system with pro-inflammatory effects on different tissues. In addition to endocrine effects, it also has paracrine and autocrine actions (Thomas and Mendelsohn, 2003). It is becoming evident that RAS is a key mediator of inflammation, with the AT<sub>1</sub> receptors governing the transcription of proinflammatory mediators both in resident tissue and in infiltrating cells such as macrophages (Suzuki et al., 2003). Activation of AT<sub>1</sub> receptors also causes the expression of TGF-β<sub>1</sub> which is a multifunctional cytokine (Li et al., 2009; Rosenkranz, 2004; Teacher, 2001). In this study, we used acetic acid model to induce ulcerative colitis in animals. Acetic acid produced a large inflammatory response as evidenced by the macroscopic and the microscopic damage and by the significant increase in the inflammatory mediator; PAF and in the inflammatory cytokines; TGF-β<sub>1</sub> and TNF- . A significant oxidative stress could be observed in the

**Table (2):** Effects of captopril ( $30 \text{ mg kg}^{-1}$ ) and valsartan ( $30 \text{ mg kg}^{-1}$ ), administered prophylactically and therapeutically, on gross lesion score (mean  $\pm$  S.E.M.) in acetic acid-

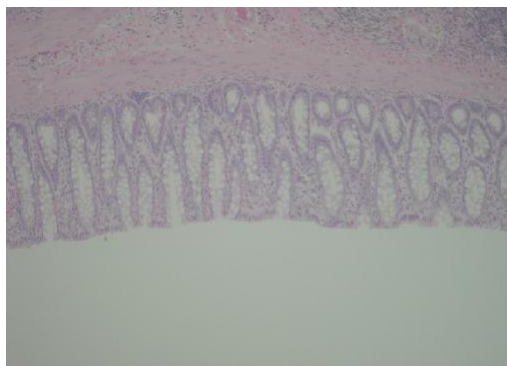
Groups	Gross lesion score
(Group I) Normal control	0.00 $\pm$ 0.00
(Group II) Acetic acid control received gum starting one day before colitis and continued for one week	3.83 $\pm$ 0.17 *
(Group III) Acetic acid control received gum starting one week after colitis and continued for one week	3.80 $\pm$ 0.18*
(Group IV) Captopril starting one day before colitis and continued for one week	1.63 $\pm$ 0.18 <sup>^</sup>
(Group V) Captopril starting one week after colitis and continued for one week	1.67 $\pm$ 0.20 <sup>&amp;</sup>
(Group VI) Valsartan starting one day before colitis and continued for one week	1.59 $\pm$ 0.19 <sup>^</sup>
(Group VII) Valsartan starting one week after colitis and continued for one week	1.62 $\pm$ 0.23 <sup>&amp;</sup>
F value	47.98
P	<0.001

\*: Significant as compared to normal control group I.

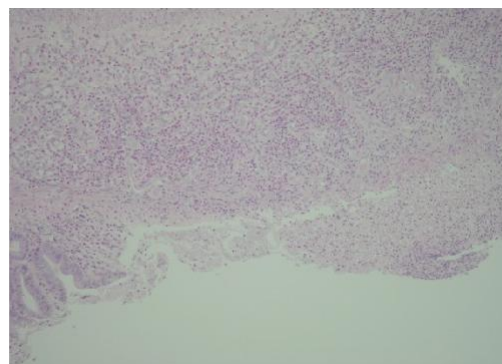
<sup>^</sup>: Significant as compared to group II.

<sup>&</sup>: Significant as compared to group III.

S.E.M: standard error mean

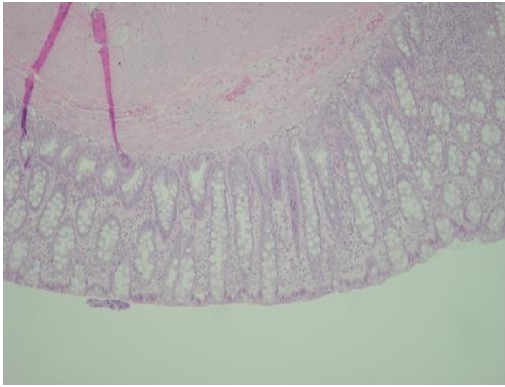


**Figure 1 (A)** Normal control group. Photomicrograph of the haematoxylin & eosin stained section of rat colon showed intact epithelial surface x 100.

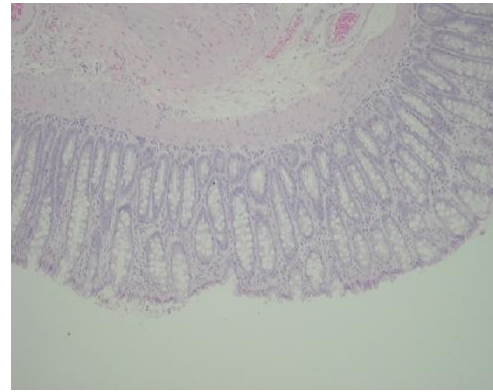


**Figure 1 (B)** Acetic acid treated animals, colonic mucosa showed massive necrotic destruction of epithelium, submucosal oedema, hemorrhages and inflammatory cellular infiltration x 100.





**Figure 1 (C)** Valsartan treated group, showed protection against acetic-acid induced damage x 100.



**Figure 1 (D)** Captopril treated group showed moderate protection compared to 100.

current study as evidenced by a significant increase in colonic MDA as well as a significant decrease in colonic GSH.

Rats that received captopril or valsartan, prophylactically and therapeutically, showed significant amelioration in these parameters as compared to the acetic acid group. No significant difference was observed between the effects exerted by either drug, giving the evidence that the effect of either drug is mainly related to interfering with RAS. Thus, our data suggest that an ACE inhibitor or an ARB can decrease the colonic inflammation in the acetic acid animal model. Both drugs probably exerted a beneficial effect via modulation of the immune system, as shown by a suppression of TGF- $\beta_1$  and TNF- $\alpha$  as well as via decreasing oxidative stress as shown by decreasing MDA and increasing GSH. In addition, as considerable evidence has shown that fibrogenic response to injury is mediated through Ang II induction of TGF- $\beta_1$  expression in a number of tissues (Xu et al., 2006) including intestine (Beck et al., 2003). Thus, blockade of Ang II mediated TGF- $\beta_1$  induction by ACE inhibitors or ARBs could be a beneficial therapeutic target through reduction of this fibrogenic cytokine in colitis.

Supporting the role of RAS in ulcerative colitis is the demonstration in the current study of a significant increase in ACE activity in acetic acid induced colitis. These results support the contention that ACE may be a potential new option for treating inflammatory bowel disease (Koga et al., 2008).

Our findings are in support of other investigators who have recently identified potential benefit in blocking the RAS pathway in inflammatory bowel disease. Santiago et al., 2008 reported beneficial effect of valsartan in two models of colitis. In dextran sulfate sodium– induced

colitis in mice, captopril significantly reduced epithelial cell apoptosis and mucosal expression of TNF- $\alpha$ . The histopathologic grade of colitis was also significantly lowered in ACE-I treated mice (Ariel et al., 2007) and rats (Byrnes et al., 2009). Amelioration of induced colitis in angiotensinogen gene knockout mice has been also demonstrated (Inokuchi et al., 2005). A recent study reported that in a murine colitis model the degree of colitis was much milder in AT1R gene knockout mice (Mizushima et al., 2010). It has been reported that AT $_1$  receptor regulates the expression of adhesion molecules, like vascular addressin cell adhesion molecule 1, under colonic inflammatory conditions through regulation of the translocation of NF-kappaB into the nucleus (Mizushima et al., 2010). Indeed, an Australian-based analysis of the angiotensinogen-6 variant found a significant association with Crohn's disease, also supporting the therapeutic potential for either ACE inhibitors or ARBs (Hume et al., 2006). In summary, our results demonstrate that specific targeting of RAS whether by ACE inhibitors or ARBs can reduce some of the parameters associated with intestinal inflammation. This study suggests a possible anti-inflammatory effect for captopril and valsartan in colitis via modulation of the immune system, as well as via antioxidant action. The fact that the use of these drugs does not have any associated immunosuppressive side effects may allow this therapy to be provided in conjunction with reduced doses of immunomodulating therapies in inflammatory bowel disease.

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