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The anti-inflammatory activity of Azilsartan in animal models of experimentally-induced chronic and granulomatous inflammations

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ABSTRACT

It is well documented that blockade of angiotensin II type 1 receptor may interfere with the progression of the inflammatory processes. The present study aims to evaluate the dose-response relationship of the anti-inflammatory activity of azilsartan in rat models of chronic and granulomatous inflammation. The study includes two parts: First part: 42 rats were allocated into 7 groups, each containing six rats, to evaluate the anti-inflammatory activity of different doses of azilsartan in the rat model of formalin-induced chronic inflammation. Second part: 42 rats were allocated as in 1st group to evaluate the anti-inflammatory activity of azilsartan in the rat model of cotton pellet-induced granuloma. Azilsartan in a dose-dependent pattern (0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg), significantly attenuated inflammation in both rat models utilized in the study with maximum effect achieved with 1.0 mg/kg, which is comparable to that reported for dexamethasone and relative linearity within the lowest dose range. In conclusion, azilsartan decreased formalin-induced chronic inflammation and cotton-pellet induced granuloma in rats in a dose-dependent pattern. Therefore, it may be considered as a potential candidate for treating chronic inflammatory conditions in human.



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INTRODUCTION

Inflammation is an important physiological response initiated against a variety of insults (biological or physical trauma) for the aim of limiting tissue damage and promoting repair (Fobes and Rosenthal, 2014). It needs the involvement of many cell types expressing and reacting to diverse

chemical signals through a highly organized sequence (Malik and Kanneganti, 2017). Although the inflammatory response is beneficial to establish defence of the host against insults, it may escape the control of the biological system and contribute to the pathogenesis of common chronic inflammatory diseases such as atherosclerosis, insulin resistance, and arthritis (Viola and Soehnlein, 2015; Zhao *et al.*, 2015; Chimenti *et al.*, 2015). After the acute response to the insult, chronic inflammatory cascades started a few days later and may sustain for longer periods due to many reasons including persistence of the stimulus, impaired healing process, repeated cycles of low-grade inflammation or continued overexpression of the immune response mediators (Germolec *et al.*, 2018). It is well-established that angiotensin II (Ang II), the major component of the renin-angiotensin system (RAS), can induce a state of oxidative stress and inflammation by activating the angiotensin II type 1 (AT1) receptor (Shim *et al.*, 2018). The locally or

systematically expressed Ang II represents the active component of the RAS. Many tissues and organs, including the immune system, respond directly or indirectly to the overexpressed Ang II through initiating different types of biochemical changes including exaggerated inflammatory reactions (Lam *et al.*, 2014). The involvement of RAS components in the pathogenesis of chronic inflammatory disorders in experimental animals and human have been well recognized through the finding that blockade of AT1-R attenuates many inflammation-related conditions in the heart, kidney and liver (Pialoux *et al.*, 2011; Azhar Omaran, 2017). The RAS blockade not only restores the impaired hemodynamic responses in cardiovascular disorders but also limits tissue injury through the attenuation of the deleterious inflammatory responses (Hussain *et al.*, 2017; Mahmood *et al.*, 2018). The newly approved angiotensin receptor blocker (ARB) azilsartan is a highly selective AT1-receptor blocker and prescribed for the treatment of hypertension. However, it acts as a partial agonist on the nuclear peroxisome proliferator-activated receptor- γ (PPAR- γ) with profound antioxidant and anti-inflammatory activities (Kurta and Kajiya, 2012; Toba *et al.*, 2006). Recently, azilsartan has been reported to improve many metabolic and inflammatory disorders and preserves the functions of various organs (Sukumaran *et al.*, 2017; Michel *et al.*, 2016). Although azilsartan demonstrates an influential role on many inflammatory reaction cascades, the dose-response relationship in animal models of inflammation is not clear enough to predict the required dose for such effect. Therefore, the present study was conducted to evaluate the dose-response relationship of the anti-inflammatory activity of azilsartan in animal models of chronic and granulomatous inflammation (Al-Nashi *et al.*, 2013).

MATERIALS AND METHODS

Animals and study design

Azilsartan powder (Apollo Healthcare Resources, Singapore) was suspended in 0.5% carboxymethylcellulose (CMC) as a vehicle and used for the preparation of different doses according to the body weight of the rats (0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg). Wistar rats weighing 180-220 g of both sexes were purchased from the animal house of the College of Pharmacy, University of Baghdad. The rats were kept in the Experimental Animals Lab of the Faculty of Pharmacy, Al-Rafidain University College at 25 \pm 2°C for 1 week before starting the experiments. The animals were fed a standard rodent chow, and the food was withdrawn 12 hr before the experiments, while the access to drinking water was allowed *ad libitum*. All the experiments

were conducted by the adopted guidelines of laboratory animal care and the related ethics of working on the experimental animals. The study protocol was approved by the local research ethics committee of the Faculty of Pharmacy, Al-Rafidain University College. In the present study, 84 Wistar rats were randomly allocated into 12 groups (six rats each); the study protocol involves two parts: in the first part, 42 rats were allocated into 7 groups for the evaluation of the anti-inflammatory activity of different doses of azilsartan in the model of formalin-induced chronic inflammation. In the second part, the other 42 rats were allocated into 7 groups to study the anti-inflammatory activity of azilsartan in cotton pellet-induced granulomatous inflammation. In both parts, 1 mg/kg of dexamethasone (American reagent, USA) was utilized as a standard anti-inflammatory agent for comparison.

The model of formalin-induced paw oedema

The model of formalin-induced paw oedema (Motevalian *et al.*, 2017) was utilized for the evaluation of the dose-response relationship of the anti-inflammatory activity of azilsartan. In this part, 0.1 ml of 2% formalin (Sigma-Aldrich, UK) was injected into the sub-plantar region of the right hind paw of the rats after mild anaesthesia with diethyl ether. The rats were administered either a vehicle (2 ml CMC) as a control, 1 mg/kg dexamethasone as comparator, and different doses of azilsartan medoxomil (0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg body weight) 30 min before induction of paw oedema with formalin and continued for seven consecutive days. The azilsartan, dexamethasone and the vehicle were administered orally once daily with the aid of an oral gavage needle. The change in paw thickness was evaluated at zero time (before induction of paw oedema) and 6 days after the induction of paw oedema using a digital Vernier calliper (Joseph *et al.*, 2005). The increase in paw thickness (mm) was calculated and presented as mean \pm SD, while the anti-inflammatory activity of azilsartan and dexamethasone was expressed as a percentage of inhibition of the paw oedema (Singh *et al.*, 2010; Al-Grawi *et al.*, 2018).

The model of cotton pellet-induced granuloma

The dose-response relationship of the anti-inflammatory activity of azilsartan was assessed utilizing the standard method of cotton pellets-induced granuloma (Santos *et al.*, 2004). In this method, four sterile cotton pellets (10 \pm 2 mg) were subcutaneously implanted into the central region, two in either side, in each rat after mild anaesthesia. All doses of the drugs and the vehicle (as indicated previously) were administered orally as a single daily dose (before the implantation of the cotton pellets) for seven consecutive days. On the 8th day, the implanted pellets with the granuloma tissue

were carefully removed under anaesthesia and rendered free from extraneous tissues. After weighing the wet pellets to measure the wet weight, they were incubated at 60°C for 18 hr to obtain a constant dry weight. The amount of exudate (mg) was calculated by subtracting the dry weight from the original wet weight of the pellet. The weight of the granuloma was calculated by subtracting the original pellet weight (10 mg) from the dried weight calculated after dryness. The anti-inflammatory activity was expressed as percentage inhibition of the exudate and granuloma tissue formation (Al-Thahab *et al.*, 2018).

Statistical analysis

The results were statistically evaluated utilizing Graph Pad software version 5.1 (Graph Pad Software Inc., California, US). All data were expressed as mean \pm SD. The significance of differences between treated groups was determined using unpaired Student's *t*-test and one-way analysis of variance (ANOVA) and Bonferroni's *post hoc* test. *P*-values < 0.05 were considered significant (Lateef *et al.*, 2018).

RESULTS

Table 1 shows that both dexamethasone and all the administered azilsartan doses (0.125, 0.25, 0.5, 1.0, and 2.0 mg/kg bwt) decreased significantly and

dose-dependently the increases in paw thickness compared with the vehicle-treated group; maximum effect (31%) was obtained by the dose of 2.0 mg/kg, which was found comparable to that produced by 1.0 mg/kg dexamethasone ($P>0.05$). Although all the azilsartan doses significantly attenuated the increase in paw thickness compared with control, only the 2.0 mg/kg dose achieved a response comparable to that produced by dexamethasone. Meanwhile, figure 1 demonstrates the dose-response relationship of the anti-inflammatory activity of azilsartan and found to be relatively linear within the dose ranges utilized in this study, with the best linearity between 0.125 and 1.0 mg/kg. In table 2, 1 mg/kg of dexamethasone inhibits the exudate formation significantly compared to controls, and represents the largest anti-inflammatory activity effect (49.8%) compared with control, and comparable to that produced by 2.0 mg/kg azilsartan. Moreover, all the given azilsartan doses decreased the formation of the inflammatory exudate significantly in a dose-dependent pattern compared with the vehicle-treated group ($P<0.05$). The maximum response was produced by 1.0 and 2.0 mg/kg doses (40.4% and 48.6%, respectively), and found to be non-significantly different when compared with each other. In Figure 2, the dose-response relationship

Table 1: Effects of different doses of azilsartan on the paw thickness of rats in formalin-induced chronic inflammation model

Treatment groups	Baseline paw thickness (mm)	Paw thickness at day 7 (mm)	Δ Paw thickness (mm)	Inhibition of paw oedema (%)
Control (Vehicle)	3.1 \pm 0.33	7.12 \pm 0.55*	4.0 \pm 0.53 ^a	-
Dexamethasone (1mg/kg)	3.8 \pm 0.3	4.43 \pm 0.42*	0.67 \pm 0.16 ^b	37.7 \pm 5.8 ^a
Azil (0.125mg/kg)	3.5 \pm 0.26	6.9 \pm 0.42*	3.43 \pm 0.48 ^a	4.22 \pm 3.7 ^b
Azil (0.25mg/kg)	3.4 \pm 0.31	6.4 \pm 0.21*	2.97 \pm 0.44 ^a	10.4 \pm 2.9 ^b
Azil (0.5mg/kg)	3.32 \pm 0.21	5.9 \pm 0.22*	2.53 \pm 0.38 ^c	17.9 \pm 3.0 ^c
Azil (1mg/kg)	3.3 \pm 0.16	5.4 \pm 0.1*	2.1 \pm 0.14 ^d	25.1 \pm 1.5 ^d
Azil (2mg/kg)	3.26 \pm 0.22	4.9 \pm 0.39*	1.69 \pm 0.33 ^e	31.0 \pm 5.5 ^a

Values are expressed as mean \pm SD; n= 6 rats in each group; * significantly different compared with the corresponding baseline value (paired *t*-test, $P<0.05$); values with non-identical superscripts (a,b,c,d,e) among groups are significantly different (ANOVA, $P<0.05$); Azil: azilsartan.

Table 2: Effects of different doses of azilsartan on the weight of exudate in cotton-induced granulomatous inflammation model in rats

Treatment groups	Weigh of Exudate (mg)	Change in Exudate (%)
Control (Vehicle)	108.2 \pm 8.8 ^a	-
Dexamethasone (1 mg/kg)	49.7 \pm 2.2 ^b	54.1 \pm 2.0 ^a
Azil (0.125 mg/kg)	91.7 \pm 5.7 ^c	15.3 \pm 5.3 ^b
Azil (0.25 mg/kg)	77.8 \pm 3.9 ^d	28.3 \pm 3.4 ^c
Azil (0.5 mg/kg)	72.2 \pm 4.5 ^d	33.3 \pm 4.2 ^c
Azil (1 mg/kg)	64.7 \pm 2.1 ^e	40.4 \pm 1.8 ^d
Azil (2 mg/kg)	55.7 \pm 2.3 ^e	48.6 \pm 2.0 ^{3a}

Values are expressed as mean \pm SD; n= 6 rats in each group; * significantly different compared with the control (unpaired *t*-test, $P<0.05$); values with non-identical superscripts (a,b,c,d,e) among groups are significantly different (ANOVA, $P<0.05$); Azil: azilsartan.

Table 3: Effects of different doses of azilsartan on the weight of granuloma in cotton-induced granulomatous inflammation model in rats

Treatment groups	Weigh of Granuloma (mg)	Change in Granuloma (%)
Control (Vehicle)	32.2±8.8 ^a	-
Dexamethasone (1mg/kg)	12.0±1.1 ^{*b}	62.8±3.3 ^a
Azil (0.125mg/kg)	21.9±0.7 ^{*c}	31.9±2.3 ^b
Azil (0.25mg/kg)	19.6±0.4 ^{*d}	39.0±1.1 ^c
Azil (0.5mg/kg)	18.9±0.6 ^{*d}	41.3±1.9 ^c
Azil (1mg/kg)	14.8±0.8 ^{*e}	54.2± 2.3 ^d
Azil (2mg/kg)	12.5± 0.5 ^{*b}	61.0±1.5 ^a

Values are expressed as mean±SD; n= 6 rats in each group; * significantly different compared with the control (unpaired *t*-test, $P<0.05$); values with non-identical superscripts (a,b,c,d,e) among groups are significantly different (ANOVA, $P<0.05$); Azil: azilsartan.

of the anti-inflammatory effects (in terms of decreasing the formation of inflammatory exudate) of azilsartan appears to be

relatively linear within the utilized doses in the present study. Meanwhile, azilsartan significantly decreased dose-dependently the formation of granuloma compared with the vehicle-treated group, with the maximum response produced by 2.0 mg/kg dose (61.0%), which was comparable to that produced by 1.0 mg/kg of the standard anti-inflammatory agent dexamethasone (62.8). The dose of 1.0 mg/kg dexamethasone significantly inhibited the formation of granuloma compared to the vehicle-treated group (Table 3). Figure 3 demonstrates the dose-response relationship of the anti-inflammatory activity (in terms of the inhibition of granuloma formation) of azilsartan; the effect was found to be relatively linear within the doses used in the present study, and the best linearity was achieved within the lowest doses range (0.125-0.25 mg/kg).

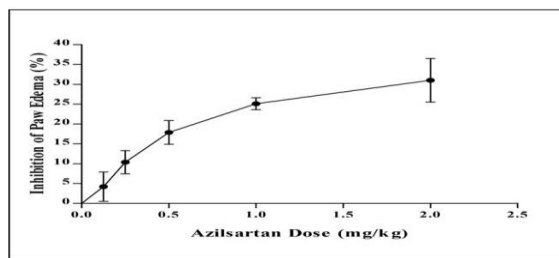


Figure 1: Dose-response relationship of the effect of azilsartan on the paw oedema in formalin-induced chronic inflammation in rats

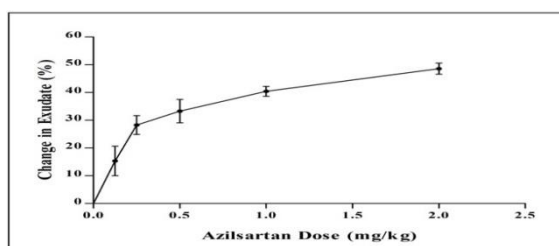


Figure 2: Dose-response relationship of the effect of azilsartan on the weight of the exudate in cotton-induced granulomatous inflammation in rats

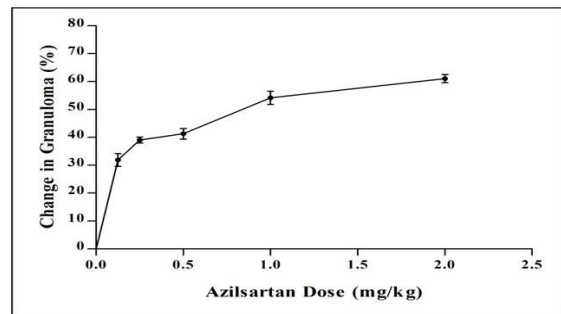


Figure 3: Dose-response relationship of the effect of azilsartan on the weight of the granuloma in cotton-induced granulomatous inflammation in rats

DISCUSSION

The expression of Ang II receptors was found to be increased significantly during experimentally induced inflammation, indicating a potential role for AT1 receptor in the initiation and progression of the inflammatory reaction (Chon *et al.*, 2011). Moreover, stimulation of AT1 receptors increases the production of reactive oxygen species (ROS) and enhances the expression of many inflammatory cytokines (Gabriele *et al.*, 2017; Guo *et al.*, 2011). In the present study, the formalin and the cotton pellet-induced inflammation is similar to that observed during the pathogenesis of arthritis. Accordingly, the utilized animal models are considered as a standard approach for the assessment of therapeutic agents with suspected anti-arthritis activity (Okoli *et al.*, 2008). Since the administration of azilsartan attenuates the inflammatory cascades significantly in these models of inflammation, one can suggest that this ARB may have potential anti-arthritis and anti-proliferative activities. During the initiation of an inflammatory process, the associated tissue injury induces a series of cellular responses at the lesion area, accompanied with the expression and release of many pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, prostaglandins and other substances, which are consequently, followed by the appearance of the inflammatory changes (Sadik and Luster,

2012). It has been proved that the activation of nuclear receptor PPAR γ with various ligands, including certain types of ARBs, demonstrates the ability to decrease the expression of many inflammatory mediators with consequent modulation of certain types of inflammatory cascades (Sauer, 2016; Villapol, 2018). Additionally, the dose-dependent anti-inflammatory activity of telmisartan was previously reported in an experimental model similar to that utilized in the current study, where the results seem to be in tune with the current data (Al-Hejjaj *et al.*, 2011). Azilsartan, the selective AT1 receptor blocker, was found effective in decreasing ROS production and the expression of many pro-inflammatory mediators. The antioxidant and anti-inflammatory effects of azilsartan are mostly attributed to its ability to prevent the activation of the nuclear factor- κ B signalling pathway that enables the transcription of NADPH oxidase, TNF- α and inducible nitric oxide synthase genes (de Araújo *et al.*, 2015; Liu *et al.*, 2016). The present results are consistent with previously mentioned data and revealed that treatment with azilsartan significantly interferes with the formation of inflammatory oedema and granulation tissue due to the challenge with formalin or subcutaneous implantation of cotton pellets. Moreover, other mechanisms beyond AT1 receptor antagonism may be responsible for the antioxidant and anti-inflammatory activities of azilsartan. Azilsartan acts as a partial agonist at the PPAR γ (Kajiya *et al.*, 2011) and this effect was accompanied with the induction of catalase gene expression and the inhibition of NF- κ B, thus combating oxidative stress and down-regulating most of the pro-inflammatory responses (Blessing *et al.*, 2008). Additionally, the reported anti-inflammatory effects of azilsartan in the present study can be positively correlated with its PPAR γ agonist activity.

Activation of PPAR γ downregulates the transcription of many genes that encode many inflammatory cytokines, growth factors, proteolytic enzymes, adhesion molecules, and chemotactic factors (Tian *et al.*, 2009). The positive effect of azilsartan treatment on inflammatory disorders is also supported by clinical trials which involved patients with different pathologies of inflammatory nature including arthritis, metabolic syndrome and liver diseases (Mahmood *et al.*, 2018; Skibitskiy *et al.*, 2016; Hussain *et al.*, 2017). Additionally, Leung *et al.* showed that the ARB losartan decreases the expression of TGF- β 1, most likely through the prevention of binding of Ang II with its receptors in Browicz-Kupffer cells (Leung *et al.*, 2003). These observations encourage the efforts to evaluate the anti-inflammatory effect of many potent PPAR γ ligands, including azilsartan and other ARBs, when the safety concern of these agents was

completely resolved. Therefore, the possible involvement of PPAR γ in the anti-inflammatory response observed for azilsartan in the experimental models of chronic inflammation used in the present study cannot be ignored. However, more investigations are required to confirm this outcome.

CONCLUSION

Azilsartan, in a dose-dependent pattern, shows the efficacy to attenuate formalin-induced paw oedema and cotton-pellet-induced granuloma in rat models of chronic inflammation. Therefore, it could be evaluated as a potential candidate for the treatment of chronic inflammatory disorders in humans.

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Conflicts of interest

There are no conflicts of interest.

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