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AN EXPERIMENTAL EVALUATION OF ANALGESIC ACTIVITY OF TELMISARTAN

Asha D. Jadhav*, Rakesh R. Jadhav, Sudhir L. Padwal, Vinod S. Deshmukh , Swapnil S. Jadhav , Harshal N. Pise

Department of Pharmacology, S.R.T.R. Government Medical College Ambajogai-431517, Maharashtra, India.

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Correspondence to Author:
Dr. Asha Dattatraye Jadhav

At. Makegoan Post – Somnath Borgaon Tq. Ambajogai. Dist – Beed. 431517. Maharashtra. India.

E-mail : ashajadhav700@yahoo.in

ABSTRACT: Aim and Objectives: To study the analgesic activity of telmisartan in graded doses, in tail flick method and acetic acid induced writhing method in rats and mice respectively. **Materials and Methods:** Analgesic activity of telmisartan was evaluated in graded doses tail flick model (for central action) and acetic acid induced writhing model (for peripheral action) of analgesia. Aspirin & tramadol were used as standard drugs. Results were analyzed by one way ANOVA followed by Bonferroni's post hoc test. **Results:** In tail flick method telmisartan showed dose dependent analgesic activity. The tail flick latency time increased from 0 to 60 min. The analgesic activity of telmisartan at dose of 1.5mg/kg was not statistically significant, however it was statistically significant at dose 3mg/kg and 4.5 mg/kg. At the dose of 3mg/kg; telmisartan showed highly significant activity $p<0.01$ at 30, 60 as well as 90 min with maximum effect at 90min, where as the most significant effect $p<0.001$ was observed at the dose of 4.5mg/kg at 60 and 90min. In acetic acid induced writhing method, the telmisartan possessed significant analgesic activity at all three doses (1.5mg/kg, 3mg/kg and 4.5mg/kg) with maximum activity at the dose of 4.5mg/kg. **Conclusion:** Telmisartan an angiotensin II AT1 receptor antagonist possess significant analgesic activity. It should be investigated further as potential treatment option for painful conditions in hypertensive patients.

INTRODUCTION: Pain is an unpleasant sensation localized to a part of the body. This can be both sensation and emotion. Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors. According to the International Association for the Study of Pain, nociception is defined as "the neural processes of encoding and processing noxious stimuli", whereas pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1].

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Drugs commonly used for management of pain are non-steroidal anti-inflammatory drugs and Opioids. Long-term use of these drugs provides only symptomatic relief without curing the underlying pathology. On the contrasy is also with serious adverse effects like gastritis, dependence and addiction. Hence, there is a need for the search for new, safe analgesics. It had been found that; angiotensin II peptide plays a key role in inflammation.

It stimulates the release of pro-inflammatory cytokines, activates Nuclear Factor kappa B (NF – kB), increases oxidant stress, suppresses nitric oxide synthesis and behaves as an inflammatory molecule. It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as chemo attractant protein-1(MCP-1) [2, 3]. Several studies showed that peroxisome proliferated

activated receptor – gamma (PPAR- γ) activation causes blocked the production of inflammatory cytokines [4]. Intrathecal administration of PPAR- γ ligands rapidly (<5min) attenuated mechanical and thermal hypersensitivity associated nerve injury in dose dependent manner that could be blocked with PPAR –y antagonists. Also PPAR –y antagonist itself rapidly increased the mechanical allodynia associated nerve injury, suggest that ligands – dependent, non-genomic activation of spinal PPAR –y decreases behavior signs of inflammatory and neuropathic pain [5].

Telmisartan related research has revealed that it possess PPAR-γ activity [6]. It has also been observed that PPAR-γ agonists like pioglitazone posses anti-inflammatory & analgesic activity, so it would be interesting to find whether telmisartan posses any analgesic activity. One of the study showed that telmisartan attenuates neuropathic pain manifestations in chronic constriction injury model [6].

To the best of our literature search, we have not came across any study evaluating the analgesic activity of telmisartan in thermal and chemical methods of analgesia, hence the present study was conducted to evaluate the analgesic activity of telmisartan in thermal and chemical models of nociception.

MATERIALS AND METHODS:

The present study was carried out after prior approval from Institutional Animal Ethics Committee of our institute. Wistar Albino rats weighing between 200-250gms and adult Swiss albino mice weighing between 20-25g, of either sex were used for the study. Animals were procured from the central animal house of our institute. Animals were acclimatized for 24 hours before study. They were kept in poly propylene cages under controlled temperature of 25±0.5 ^{0}c and humidity. The animals had free access to food and water and were housed under standard light-dark cycle. All the experiments were carried out during day time from 09.00am to 05.00pm.

Drugs and chemicals:

The test drugs, telmisartan was obtained as a gift sample from Cipla Pharmaceutical Ltd., Mumbai. The standard analgesic drugs used were aspirin and tramadol. Carboxy methyl cellulose (CMC) as a suspending agent use to dissolve test drug. The 0.5% carboxy methyl cellulose & Aspirin were obtained as kind gift from Medley Pharmaceuticals, Mumbai. Tramadol and acetic acid was purchased from local pharmacy college. All the drugs were administered by oral route, except tramadol and acetic acid by intraperitoneal route of administration.

Methods:

Tail flick method:

Anti-nociceptive activity was assessed by tail – flick response method using analgesiometer; the method originally described by **D'Amour and Smith** in 1941.[8] The animals were allowed to adapt to laboratory conditions for 24hours before the experiment. Animals were divided into six groups with six animal in each group (n=6) Control group: normal saline 2ml/Kg (p.o.), Standard group: tramadol 10mg/kg (i.p) and aspirin 100mg/kg (p.o), and Test groups: telmisartan [1.5 mg/Kg], telmisartan group [3 mg/Kg], telmisartan group [4.5 mg/Kg] group.

Observations were taken by placing the middle part of the tail on the radiant heat source, that is, heated nichrome wire. The strength of the current passing through the naked nichrome wire was kept constant at 6 amps. The time between placing the tail of the rat on the radiant heat source till its sharp withdrawal was recorded as "reaction time". A cut-off time of 10 seconds in experiments was taken as maximum latency to rule out thermal injury. In all the groups, tail-flick test was performed prior to drug administration and at the end of 30, 60, 90 and 120 minutes after drug administration and the reaction time at each time interval (test latency) was noted.

Acetic acid induced writhing method:

The writhing model represents a chemical nociceptive test based on the induction of peritonitis like condition in animals by injecting irritant substances intraperitoneally [8].

Mice were kept individually in the test cage before acetic acid injection and habituated for 30 minutes. Animals were divided into five groups with six

animal in each group (n=6) Control group: Normal Saline [2ml/Kg] Standard group: Aspirin [300 mg/kg].Test groups: telmisartan [1.5 mg/Kg], telmisartan [3 mg/Kg], telmisartan [4.5 mg/Kg]. All drugs administered orally as a suspension by mixing in carboxy methyl cellulose (CMC).

After 30 minutes of drug administration, the mice were injected with 0.1 ml of 1% acetic acid solution intraperitoneal (i.p.).The mice were placed individually in the big glass beakers and then after five minutes, they were then observed for a period of ten minutes during which the numbers of writhes were recorded for each animal. For scoring purposes, a writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb.

RESULTS:

Tail flick method:

Table 1 and **Graph 1** shows the analgesic activity of telmisartan by tail flick method; in this method telmisartan showed analgesic activity as there was significant increase in tail flick latency time from 0 to 60 min. The analgesic activity of telmisartan at dose of 1.5mg/kg was not statistically significant, however it was statistically significant at dose 3mg/kg and 4.5 mg/kg. At the dose of 3mg/kg; telmisartan showed highly significant activity $p<0.01$ at 30, 60 as well as 90 min with maximum effect at 90min, where as the most significant effect $p<0.001$ was observed at the dose of 4.5mg/kg at 60 and 90min. Tramadol and aspirin used as standard analgesics exerted a highly significant effect ($p<0.001$) at 60min.

TABLE 1: ANALGESIC ACTIVITY OF TELMISARTAN BY TAIL FLICK METHOD.

Group	Drug	Tail flick latency time (mean±SEM)				
		0 min	30 min	60 min	90 min	120 min
I	Control 2ml/kg, p.o	3.117±0.2227	3.650±0.2306	3.867±0.2716	3.967±0.2565	3.667±0.2871
II	Aspirin 100mg/kg, p.o	3.400±0.2082	6.962±0.2220***	8±0.3368***	7.383±0.3429***	6.550±0.3202***
III	Tramadol 10mg/ kg/ p.o	3.067±0.8028	8.392±0.3171***	9.192±0.3176***	6.968±0.2592***	5.865±0.1127***
IV	Telmisartan 1.5mg/kg, p.o	3.650±o.2045	4.483±0.2300	4.867±0.1585	4.867±0.0954	4.666±0.1202
V	Telmisartan 3mg/kg, p.o	3.017±0.2056	5.183±0.4453*	5.833±0.2801**	6.033±0.4910***	4.800±0.2236
VI	Telmisartan 4.5mg/kg, p.o	3.050±0.1996	6.333±0.3451***	6.667±0.3602***	5.217±0.2762	4.600±0.3864

p.o—per oral, * indicates $p<0.05$, **: $p<0.01$, ***$p<0.001$ compared with control

Percentage analgesia of given drug treatment tabulated in **Table 2** and it was calculated by using the formula:

$$\% \text{ Analgesia} = \text{M.P.E} = \frac{\text{T.L.} - \text{B.L.}}{\text{M.L.} - \text{B.L}} \times 100$$

Where, M.P.E. =Maximum possible effect.

M.L. =Maximum latency or cut-off time

T.L. = Test latency or latency at the end of particular period of time

B.L. = Basal latency or control latency.

Among the five group's tramadol and aspirin shows highest percentage of analgesia, difference between two is not statistically significant. The percentage analgesia of telmisartan at all doses (1.5, 3, 4.5mg/kg) is statistically less significant compared to tramadol and aspirin. The percentage analgesia of telmisartan at dose 4.5mg/kg is statistically significant $p<0.05$ compared with telmisartan at dose 1.5mg/kg.

TABLE 2: THE PERCENTAGE ANALGESIA OF DRUG TREATMENT IN TAIL FLICK METHOD

Control	30min	60min	90min	120min
Aspirin (100 mg/kg)	51.48±4.676	66.55±5.971	55.71±6.387	44.28±6.864
Tramadol (10 mg/kg)	74.39±5.146	87.06±4.731	49.6±4.143	34.28±2.444
Telmisartan (1.5mg/kg)	12.84±3.485	15.69±3.769	14.08±4.19	15.13±3.402
Telmisartan (3mg/kg)	24.41±5.502	31.47±5.364	34.19±8.075	16.94±5.324
Telmisartan (4.5mg/kg)	41.06±7.547	44.98±6.343	19.77±6.139	18.25±6.275

Acetic acid induced writhing: As shown in **Table 3** and **Graph 2** the total number of writhes in 10 minutes was highest in control group (23.83) and lowest in telmisartan (4.5mg/kg) group (4.50). Number of writhes in 10 minutes in Telmisartan group was significantly less than control group ($p<0.05$). It was observed that number of writhes reduced by increasing the dose of telmisartan.

$$\% \text{ Inhibition} = \frac{\text{No. of writhes in control group - no. of writhes in test group}}{\text{No. of writhes in control group}} \times 100$$

Among three doses of Telmisartan percentage analgesia was highest in Telmisartan (4,5mg) group (81.11%). In this method telmisartan showed the analgesic activity in dose dependent manner.

TABLE 3 SHOWS THE ANALGESIC ACTIVITY OF TELMISARTAN (ACETIC ACID INDUCED WRITHING METHOD).

Groups	Treatment	Dose	Total no. of writhings (in 10 min)	% inhibition of writhing
I	Normal saline	2 ml/kg, p.o	23.83	-
II	Aspirin	100 mg/kg, p.o	4.833*	79.71
III	Telmisartan	1.5mg/kg, p.o	9.50*	60.13
IV	Telmisartan	3mg/kg, p.o	5.33*	77.63
V	Telmisartan	4.5mg/kg, p.o	4.50*	81.11

Values are mean ± S.E.M; n= 6 in each group.
*p<0.05 when compared to control group. p.o—per oral

DISCUSSION: Telmisartan is highly selective angiotensin receptor antagonist (ARA) most effective for treating hypertension, heart failure 7. Among the all ARAs telmisartan possess highest PPAR-γ agonist activity, and by virtue of this property telmisartan may possess anti-inflammatory and analgesic activity [9].

Present study showed that the telmisartan exerts significant analgesic activity in both central and peripheral model of nociception when compared with control; however this activity is less when compared with tramadol and aspirin in tail flick method and acetic acid induced writhing respectively.

The tail flick response is considered to be a spinal response (Sinclair et. al. 1988) [10, 11] which is co-ordinated and controlled by central mechanism. In present study telmisartan exert dose dependent analgesic activity in tail flick method. Telmisartan could exert central analgesic effect as angiotensin receptor antagonists may modulate the analgesic action by increasing the pain threshold or by central mechanism by altering the pain modulating neurotransmitter level and activation of AT1 receptor with AngII also increases Ca^{++} influx: their blockade leads to analgesic activity.[12] Also Wang JF et. al reported that ARAs produce analgesia on intracerebro-ventricular administration in rats and this action can be blocked by naloxone.[13]

In acetic acid induced abdominal writhing which is visceral pain model, the processor release of arachidonic acid metabolite via cyclooxygenase & prostaglandin biosynthesis plays role in nociception mechanism [14] , result of this study showed that all dose (1.5, 3 & 4.5mg/kg) of telmisartan could exert analgesia by anti-inflammatory mechanism through blockade of angiotensin II, as the later is the main peptide of renin angiotensin system and its activation leads to inflammation by accumulation of neutrophils [15], differentiation of dendritic cells [16,17] .It also stimulates the release of pro-inflammatory cytokines, activates Nuclear Factor kappa B (NF –kB), increases oxidant stress, suppresses nitric oxide synthesis and behaves as an inflammatory molecule.

However it is unclear as to the exact mechanism involved for antinociceptive effect of telmisartan. It could be due to inhibition of sympathetic system since it is proposed that activation of sympathetic system by injury lead to activation of renin angiotensin system, angiotensin AT1 receptor and release of aldosterone which causes pain, therefore it is possible that blockade of AT1 receptor could reduce pain. Also angiotensin II peptide has been reported for its pronociceptive activity and ARAs block the action of angiotensin II by inhibiting its binding with its receptor.

CONCLUSION: Angiotensin II AT_1 receptor antagonists telmisartan is one of the first drug of

choice for treating the essential hypertension and in our study we conclude that it possess significant analgesic activity in both models of nociception. In future this could be investigated for treating painful conditions in hypertensive patients. However, further studies are needed to elucidate the exact mechanism and its extent of analgesia.

REFERENCES:

1. Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M et al. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Pain. 2010; 148(2):215-9.
2. Dai Q, Xu M, Yao M, Sun B; Angiotensin AT1 receptor antagonists exert Anti inflammatory effects in spontaneously hypertensive rats. British journal of pharmacology 2007; 152:1042-1048.
3. Benicky J, Sánchez-Lemus E, Honda M, Pang T, Orecna M, WangJetal.AngiotensinII AT1 receptor blockade ameli orates brain inflammation. Neuropsychopharmacology. 2011; 36(4):857-70.
4. Kamari Y , Harari A, Shaish A, Peleg E, Sharabi Y, Harats D, Grossman E. Effect of telmisartan, angiotensin II receptor antagonist, on metabolic profile in fructose-induced hypertensive, hyperinsulinemic, hyperlipidemic rats. Hypertens Res. 2008; 3:135-40.
5. Jill C. Fehernbacher, Jesse Loverme, William Clarke, Kenneth M. Hargreaves, Daniele Piomelli, Bradley K. Taylor. Rapid pain modulation with nuclear receptor ligands. Brain research review 60 (2009) 114-124.
6. Waleed KG, Al-Hejjaj, Intesar T Numan, Raghdan Z Al-Sa'ad, Saad A. Hussain. Anti-inflammatory activity of telmisartan in rat models of experimentally-induced chronic inflammation: Comparative study with dexamethasone. Saudi Pharmaceutical Journal (2011); 19:29-34.
7. Hafez HM, Elshanawane AA, Abdelaziz LM, Kamal MM. Quantitative Determination of three Angiotensin-II-receptor Antagonists in Presence of Hydrochlorothiazide by RP-HPLC in their Tablet Preparations. Iran J Pharm Res. 2013; 12(4):635-43.
8. Parmer NS, Prakash S. Evaluation of analgesics, anti-inflammatory and anti-pyretic activity. In: Parmar NS, editor. Screening Methods in Pharmacology, New Delhi, India: Narosa Publishing House 2006. p. 225-33.
9. Tao Pang, Julius Benicky, Juan Wang, Martina Orecna, Enrique Sanchez-Lemus et al. Telmisartan ameliorates lipopolysaccharide-induced innate immune response through peroxisome proliferator-activated receptor-γ activation in human monocytes. J Hypertens. 2012; 30(1): 87–96.
10. Sinclair JG, Main CD, Lo GF. Spinal vs. supraspinal actions of morphine on the rat tail-flick reflex. Pain 1988; 33:357-62.
11. Liciane F. Medeiros, Ana Maria O. Battastini, Andressa de Souza, Joanna R. Rozisky, Vinicius S. dos Santos, Wolnei Caumo et al. One-time Exposure to General Anesthetics Alters Nociceptive Response and Nucleotide Hydrolysis in Infant Rats. British Journal of Medicine & Medical Research2014;4(22): 3975-3989
12. Indumathy S, Kavimani S. Antiinflammatroy activity of angiotensin antagonists. Pharmacie Globale (IJCP) 2011; 2(01):1-3.
13. Yamada Y, Ohinata K, Lipkowski AW, Yoshikawa M. Angiotensin AT (2) receptor agonists act as anti-opioids via EP (3) receptor in mice. Peptides. 2009; 30(4):735-9.
14. Berkenkopf JW, Weichman BM. Production of prostacyclin in mice following intraperitoneal injection of acetic acid, phenylbenzoquinone and zymosan: its role in the writhing response. Prostaglandins 1988; 36:693–709.
15. Rasika d. bhalke1 and Subodh c. pal. anti- inflammatory and antinociceptive activity of Pterospermum acerifolium LEAVES. Asian J Pharm Clin Res 2012; 5(2): 23-26.
16. Tobias V. Lanz, Zhaoqing Ding, Peggy P. Ho, Jian Luo, Tony Wyss-Coray, Lawrence Steinman et.al. Angiotensin II sustains brain inflammation in mice via TGF-β. J Clin Invest. 2010; 120(8):2782-2794.
17. MaY, ChenZ, ZouY, GeJ.Atorvastatin represses the angiot ensin 2-induced oxidative stress and inflammatory response in dendritic cells via the PI3K/Akt/Nrf 2 path way. Oxid Med Cell Longev. 2014; 2014:148798.

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