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Research Article

ANALGESIC ACTIVITY OF ANGIOTENSIN AT_1 RECEPTOR ANTAGONIST: CANDESARTAN IN RATS AND MICE

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ABSTRACT

Objective: The objective was to evaluate analgesic activity of candesartan in graded dose in tail flick method in rats and acetic acid-induced writhing in mice.

Methods: Wistar Albino rats of either sex weighing 200-250 g or Swiss Albino mice of either sex weighing 20-25 g. Analgesic activity of candesartan (5 mg/kg, 10 mg/kg, 15 mg/kg.) was evaluated in graded dose and compared with tramadol (10 mg/kg) and aspirin (100 mg/kg) using tail flick response method and acetic acid-induced writhing of analgesia. Study was conducted after approval from the Institutional Animal Ethics Committee, which is an approved body by Committee for the Purpose of Control and Supervision of Experiments on Animals letter no. 78 dated October 18, 2012.

Results: In the present study, oral administration of candesartan showed analgesic activity at high dose compared to the control and less analgesic activity as compared to the standard in analgesic methods. In tail-flick method, after 30-90 minutes of drug administration, tail flick latency of candesartan (15 mg/kg) was significant ($p<0.05$) compared with control but less than that of tramadol and aspirin. In acetic acid induced writhing method, the analgesic activity of candesartan was significant only at high dose (15 mg/kg) compared to the control.

Conclusion: Candesartan possesses analgesic activity only at high dose. However, further studies need to be carried out to see underlying mechanism candesartan in analgesia and to know the extent of analgesia.

Keywords: Acetic acid induced writhing method, Angiotensin II receptor blockers, Candesartan, Tail flick method.

INTRODUCTION

Pain being the most common complaint faced by the physicians; its characterization is of major importance in the diagnosis and management of various diseases. Pain is an unpleasant sensation that is due to complex neurochemical process in central and peripheral nervous system. Although nonsteroidal anti-inflammatory drugs and opioids have been used for decades to treat painful conditions, their prolonged use often leads to serious adverse reactions such as gastric intolerance addiction tolerance to opioids, hence, search of safe new analgesic drug is mandatory.

At present, medicinal practice is based on the use of highly effective drugs with least side effects. The chronic painful conditions like osteoarthritis affects majority of the geriatric population. The presence of both osteoarthritis and essential hypertension is common in that population [1], and they are more beneficient using less number of drugs.

It is reported that angiotensin (AT)-II possesses pronociceptive activity. AT-II the central product of the renin-AT system induces oxidative stress, inflammation, and apoptosis by activating the AT-1 receptor [2]. AT receptor antagonists block the action of AT-II by inhibiting it's binding with its receptor may exert the antinociceptive activity. Candesartan binds selectively and noncompetitively to the AT-II receptor.

Type 1, thus preventing the actions of AT-II by virtue of this property it might showed the antinociceptive activity, hence the present study was planned to investigate the analgesic property of candesartan in graded dose in tail flick method and acetic acid-induced writhing method of analgesia.

METHODS

Experimental animals

Wistar rats weighing between 200 and 250 g and adult Swiss albino mice weighing between 20 and 25 g of either sex were used for the studies. Animals were procured from the central animal house of our institute. Animals were acclimatized for 2 day before the study. They were kept in polypropylene cages under controlled temperature 25±0.5°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 the daytime from 09.00 am to 05.00 pm.

Drugs and chemicals

Candesartan was obtained as gift samples from Cipla Pharmaceutical Ltd., Mumbai. The 0.5% carboxymethyl cellulose was used as suspending agent. The 0.5% carboxy methyl cellulose and aspirin were obtained as a kind gift from Medley Pharmaceuticals, Mumbai. Tramadol and acetic acid were purchased from local pharmacy college. All the drugs were administered by oral route, except tramadol which was administered by intraperitoneal route.

Methods

Tail flick method [3]

Anti-nociceptive activity was assessed by tail flick method as described by D'amour and Smith (1941). The temperature of nichrome wire was kept constant at 52±0.5°C. The time taken by rat to withdraw its tail from the noxious stimulus is measured. A cut off time of 10 seconds is set to prevent the injury to the animal. The animals were divided into six groups with six animals in each group. Group one serves as a control and received normal saline. Group two received tramadol in doses of 10 mg/kg as standard treatment. Group three received

Table 1: Tail flick method

Group	Treatment	Dose	Tail flick latency time(s) (mean±SEM)				
			0 minute	30 minutes	60 minutes	90 minutes	120 minutes
I	Normal saline	2 ml/kg, p.o	3.01±0.12	2.95±0.23	3.96±0.10	3.90±0.13	3.46±0.65
II	Tramadol	10 mg/kg, i.p.	3.06±0.80	7.99±0.52***	8.89±0.67***	7.83±0.11**	6.73±0.53**
III	Aspirin	100 mg/kg, p.o	3.33±0.30	6.83±0.33***	8±0.546***	6.97±0.53***	6.57±0.12***
IV	Candesartan	5 mg/kg, p.o	2.91±0.10	4.91±0.28	5.23±0.39	4.66±0.17	4.30±0.22
V	Candesartan	10 mg/kg, p.o	2.75±0.85	4.11±0.22	5.25±0.36	5.23±0.28	3.90±0.29
VI	Candesartan	15 mg/kg, p.o	3.50±0.17	4.78±0.20*	7.03±0.30***	4.70±0.28	4.20±0.13

Values are mean±SEM, n=6 in each group. *p<0.05, **p<0.01, ***p<0.001 compared with control. SEM: Standard error mean

aspirin in doses of 100 mg/kg. Group four, five, and six received candesartan in doses of 5 mg/kg, 10 mg/kg, and 15 mg/kg. On the 1st day, the animals were habituated to the tail flick apparatus taking three different measurements. On day 2, the baseline tail flick latency was measured before administration of drugs. The animals which have shown readings more than 5 seconds were discarded. The test drugs were given orally to the animals immediately after basal readings. The animals were subjected to tail flick apparatus 30 minutes after administration of drugs. Further readings were recorded at 60 minutes, 90 minutes, and 120 minutes. Data for tail flick method were expressed as mean±standard error of the mean. The percentage maximum possible effect was calculated using formula:

% maximum permissible exposure = (test drug latency − basal latency/ cut off time − basal latency) × 100.

Acetic acid-induced writhing method [4]

In acetic acid-induced writhing method, Swiss albino mice of either sex were divided into five groups. Group I (control group) was given normal saline 0.2 ml orally Group II (standard group) was given aspirin at the dose of 100 mg/kg orally. Group III, IV, and V (test group) received candesartan in doses of 5, 10, and 15 mg/kg orally; all the drugs were given 30 minutes before the experiment. After 30 minutes, 0.1 ml 1% acetic acid was given i.p. The mice were placed individually into glass beakers, and 5 minutes were allowed to elapse. The mice were then observed over the period of 10 minutes, and total number of writhes counted. For a scoring purpose, a writhe was indicated by stretching of the abdomen with simultaneous stretching of one of hind limb. % inhibition of writhing was counted using formula:

% inhibition = (total number of writhings in control group − total number of writhings in test group/total number of writhings in the control group) × 100.

Statistical analysis

The data were expressed as mean±standard error of the mean. The data were evaluated by one-way analysis of variance followed by Bonferroni's post-test. The p<0.05 was considered statistical significant.

RESULTS

In tail flick method, the analgesic activity of candesartan was significant (p<0.05) compared to control and less compared to the tramadol and aspirin at (15 mg/kg) after 30 and 60 minute after the drug administration. At low dose of candesartan (5 mg and 10 mg/kg) did not show analgesic activity. Table 1 shows the tail-flick latency (i.e., mean reaction time) in all the six groups in the tail flick model of analgesia in rats.

In acetic acid-induced writhing method, candesartan showed decrease number of writhing compared to control the group but less than the aspirin group.

Table 2 shows the total number of writhes was the highest in the control group (23.83) and lowest in the aspirin group (4.833). Number of writhes in 10 minutes in three doses of candesartan groups were

Table 2: Effect of different drugs in acetic acid-induced writhing models in mice

Groups	Treatment	Dose	Total number of writhings (in 10 minutes)	% inhibition of writhing
I	Normal saline	2 ml/kg, p.o	21.76	-
II	Aspirin	100 (mg/kg p.o)	4.833*	79.71
VI	Candesartan	5 (mg/kg p.o)	12.66*	46.87
VII	Candesartan	10 (mg/kg p.o)	10.83*	54.55
VIII	Candesartan	15 (mg/kg p.o)	9.50*	60.13

Values are mean±SEM; n=6 in each group, *p<0.05 when compared to control group. SEM: Standard error mean

significantly less than the control group (p<0.05) but was significantly more when compared to aspirin (p<0.05). Maximum percentage analgesia among three doses of candesartan was at 15 mg/kg and least in candesartan (5 mg/kg) group (46.87%).

DISCUSSION

Candesartan is selective AT-II receptor antagonist use for the treatment of hypertension and heart failure. AT-II is one of the key peptides in inflammation whose levels get increased in plasma and tissues like brain, heart, kidney, liver, including stomach during the inflammatory process. AT-II generates reactive oxygen species [5] which cause cell damage and increased expression of the proinflammatory cytokines; intracellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor (TNF-α) along with neutrophils infiltration and leukocyte migration in the mucosa [6]. Furthermore, AT-II stimulates the release of proinflammatory cytokines, activated nuclear factor kappa β, increases oxidant stress, suppress nitric oxide synthesis and behave as inflammatory molecule [7]. In the present study, the candesartan shows analgesic activity only at high dose could be by antagonizing AT-II.

The other possible mechanism for antinociceptive effect could be due to anti-inflammatory activity. Pain is one of the cardinal signs of inflammation and by decreasing inflammation it could help to reduce pain sensation. Bregonzio et al. (2003) [8]. demonstrated the anti-inflammatory effects of candesartan in preventing stress-induced gastric injury suggesting its protective role by decreased expression of stress-induced TNF-α and ICAM-1 and reducing neutrophils infiltration in the gastric mucosa, so candesartan is non-peptide AT-II AT-1 receptor antagonist might modulates visceral pain by preventing the inflammation.

In the present study, candesartan showed the antinociceptive activity at high dose with no analgesic effect at lower dose which was similar to study conducted by Abdel et al. 2007 [9]. It has been observed that many AT receptor antagonists including telmisartan, candesartan, irbesartan, and losartan serve as peroxisome proliferated activated receptor-gamma (PPAR-γ) agonistic activity. The telmisartan possess the highest whereas candesartan had lowest PPAR-γ agonist activity [10].

The analgesic and anti-inflammatory activity of AT receptor antagonists could be exerted by agonist action on PPAR-γ. Candesartan had weak PPAR-Y agonist activity, and this could be the reason for that no analgesic effect of candesartan lower doses. Takai et.al also reported that AT receptor antagonist Losartan, Irbesartan, and Valsartan does not have an antinociceptive effect at low doses while on chronic administration produces antinociceptive effect [11].

CONCLUSION

Candesartan possesses analgesic activity only at high dose. However, further studies need to be carried out to see underlying mechanism candesartan in analgesia and to know the extent of analgesia.

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