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COMPARATIVE EVALUATION OF ANTINOCICEPTIVE EFFECTS OF RAMIPRIL, TELMISARTAN, DICLOFENAC AND TRAMADOL IN WISTAR RATS.

Pharmacology

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ABSTRACT

Background:NSAIDs and Opioids are most widely used analgesics but prolonged use causes serious adverse reactions.Studies have shown Renin angiotensin system plays a role in modulating pain.

Aim: Antinociceptive effects of Ramipril and Telmisartan were compared with Diclofenac and Tramadol using tail flick method.

Material and Methods: Study was conducted in Pharmacology department, SGRRIM&HS for 6months.30 Wistar rats were divided in five groups(n=6):Group1(Diclofenac10mg/kg)Group2(Tramadol10mg/kg)Group3(Ramipril1mg/kg)Group4(Telmisartan10mg/kg)andGroup5(Control;Normalsaline0.2ml).Tail flick response was noted at 0,30,60,90,120 and180 minutes after oral administration of drugs. pvalue<0.05 was significant.

Results: Intragroup comparison showed significant results in Groups 1 to 4 during study period($p<0.05$).On intergroup comparison at 90 minutes, Groups1 to 4 showed significant difference when compared with group 5($p< 0.001$).No significant difference was seen between Diclofenac vs Tramadol group($p>0.05$).Significant difference($p<0.001$)was seen when Diclofenac and Tramadol were compared with Ramipril and Telmisartan.

Conclusion: Antinociceptive effects were seen with Ramipril and Telmisartan but showed weaker analgesic effects when compared with diclofenac and tramadol.

KEYWORDS

antinociceptive, Wistar rats Tail flick method, Ramipril, Telmisartan.

Introduction

Pain is one of the most common symptoms in clinical practice and is a major cause of morbidity and mortality, with the economic loss to society being considerable. However, since pain has always been regarded as a symptom, not a disease state, there has been an enormous gap between prevalence and treatment, and it remains largely undertreated.[1,2]Globally, approximately 20% of adults suffer from pain, of which, 10% report persistent pain.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are widely used in the management of various types of pain. It is well established that NSAIDs exert their effect by inhibiting cyclo-oxygenase (COX) enzyme leading to inhibition of prostaglandin synthesis.[4]Wide spread use of NSAIDS is limited due to gastric and renal side effects[5,6]Opioid analgesics are thought to produce analgesia through their action in CNS. Opioid related side effects, i.e. nausea, vomiting, constipation, respiratory depression and abuse liability,also pose greater challenge in pain management.[7,8]

Keeping in mind the limitations of NSAIDs and opioid analgesics, researches are being conducted to look foralternatives for pain management with better safety profile. It is known that Angiotensin Converting Enzyme(ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs) are widely used drugs in various cardiovascular disorders. Angiotensin converting enzyme converts Angiotensin-I to Angiotensin-II, and also degrade the kinins like bradykinin and Substance-P. Evidences indicatethat Angiotensin-II has pro-nociceptive activity and has anti-opioid activity. Involvement of bradykinin in inflammation and pain is well established.[9,10]

Previous studies have shown conflicting anti-nociceptive results of ACE inhibitors & ARBs.[11,12] The effects of ACE inhibitors and ARBs apart from their cardiovascular role has prompted this study to evaluate whether they have antinociceptive effects.

Material and Methods:

The present study was conducted in the department of Pharmacology, Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIM&HS), Dehradun for 6 months from January to June 2017, after the approval from Institutional Animal Ethics Committee (IAEC).Healthy male wistar rats(150-250 gm) were included in the study**.** Female rats and all diseased rats were excluded from the study.30 malerats were divided infive equal groups: Group 1 rats were administered diclofenac; (10 mg/kg), group 2 were administered tramadol;(10 mg/kg), group 3 were administered ramipril;(1mg/kg), group 4 were administered telmisartan;(10mg/kg) and group 5(control group) were administered normal saline;(0.2 ml). All the drugs were administered orally. Animals were housed 3-4 per cage with free access to food and water in temperature controlled facility. Animals were acclimatized to the laboratory conditions for at least 1 hour before testing. Care of animals was as per the guidelines of Committee for The Purpose of Control and Supervision of Experiments on Animals (CPCSEA).[13]

Analgesia was evaluated using tail flick test using analgesiometer.The heat intensity was adjusted such that the control (pre-drug) latencies were 4-5 sec.[14] A 10 second cut off latency was used to prevent tail damage.[15]The initial (control) reaction time was recorded. Reaction time was noted at0, 30, 60, 90, 120 and 180minutesof oral drug administration. Increase in tail flick latency to thermal stimulation was

taken as a measure of analgesia.[14,15]

Procedure:Rats were positioned on the analgesiometer with tail freely projecting out of the holder. Quick withdrawalof the tail called as "tail flick response" was considered as the endpoint of the test. The basal reaction time was taken to radiant heat by placing tail of each rat on radiant heat source of Analgesiometer. The site of application of the radiant heat in the tail was maintained at 2.5 cm from the base of tail.[16]For each animal, the tail flick latency was obtained thrice before drug administration, and mean was used as pre-drug latency.[17]

The statistical analysis was done by using students paired t-test for intragroup comparison and ANOVA test for intergroup comparison using Graph Pad-Instat trial version 3.0. p-value < 0.05 was considered statistically significant.

Results: The values of tail flick response were expressed in Mean±SEM**.** The mean values in tail flick responsein all study groups at baseline **(**0 minute**)**and the progressive changes at 30, 60, 90, 120 and 180 minutes were as shown in table no 1.

Table 1.Tail flick test response at baseline and progressive changes[@]

Group	0 min	30 min	60 min	90 min	120 min	180 min
Group 1 (Diclofenac)	4.17± 0.3	6.83±0.4**	8.5±0.34**	9.17±0.4***	5.67±0.33*	5±0.26*
Group 2 (Tramadol)	3.5±0.43	5.83±0.30**	8±0.36** *	9±0.36** *	6.17±0.48**	5.83±0.60*
Group 3 (Ramipril)	3.83± 0.17	4±0.36 $	5.83±0.31***	6.5±0.34***	4.83±0.4**	4.33±0.42$
Group 4 (Telmisartan)	4±0.26	4.83±0.17*	6±0.36*	6.67±0.33***	5±0.36*	4.5±0.22$
Group 5 (Control)	3.5±0.22	3.5±0.22$	3.5±0.22 $	3.33±0.21 $	3.5±0.22$	3.83±0.17$

(@all values are in seconds)
$= non-significant (p value > 0.05), *= significant (p value< 0.05), **= highly significant (p value< 0.01), ***= extremely significant (p-value< 0.001)

INTERGROUP COMPARISON IN TAIL FLICK RESPONSE.
Statistically the maximum response was seen at 90 minutes, the intergroup comparison was thus done at 90 minutes and at the end of study period i.e. 180 minutes as shown in table 2. At 90 minutes, Groups 1 to 4 showed significant difference when compared with group 5,i.e.control group (p< 0.001). However, no significant difference was seen between Diclofenac group vsTramadol group (p>0.05) andRamipril group vs Telmisartan group (p>0.05). A significant difference (p<0.001) was seen when Diclofenac was compared with Ramipril group andTelmisartan group (p<0.001.Also,significant difference (p<0.001) was seen when Tramadol group was compared with Ramipril group and Telmisartan group.

Table 2. Comparison in Tail Flick Test Response@ at 90 minutes and 180 minutes

Groups	90 minutes	180 minutes
Group1 (Diclofenac)	9.17±0.40	5±0.26
Group2 (Tramadol)	9±0.36	5.83±0.6
Group3 (Ramipril)	6.5±0.34	4.33±0.42
Group4 (Telmisartan)	6.67±0.33	4.5±0.22
Group5 (Control)	3.33±0.21	3.83±0.17
Intergroup comparison	1 vs 2= $ 1 vs 3= *** 1 vs 4= *** 1 vs 5= *** 2 vs 3= *** 2 vs 4= *** 2 vs 5= *** 3 vs 4= $ 3 vs 5= *** 4 vs 5= ***	1 vs 2= $ 1 vs 3= $ 1 vs 4= $ 1 vs 5= $ 2 vs 3= $ 2 vs 4= $ 2 vs 5= ** 3 vs 4= $ 3 vs 5= $ 4 vs 5= $

(@all values are in seconds)
$= non-significant (p-value > 0.05), *= significant (p-value< 0.05), **= highly significant (p-value<0.01), ***= extremely significant (p-value< 0.001)

Discussion: Pain is an unpleasant sensation due to complex neurochemical processes in central and peripheral nervous system. Although NSAIDs and opioids have been the first line drugs for the management of painful conditions, their prolonged use leads to serious adverse reactions such as gastric intolerance and addiction, hence there is need for search of safer alternatives.[18]Renin angiotensin system has been evaluated for its varied effectson pain and its modulation has carved adefinite niche in therapeutics withARBs and ACE Inhibitorswhich are currently being used in treatment of various pathological states like hypertension, congestive heart failure, etc.[19]Some studies have shown that ACE Inhibitorss and ARBs play a role in modifying pain perception.

Hence blockade of Angiotensin II which is a potent pro-nociceptive as seen in previous studies may have antinociceptive effects.18Based on this, in the present study, we compared the antinociceptive effects of commonly prescribed analgesic drugs like diclofenac and tramadol with Ramipril; an ACE inhibitor and Telmisartan; an ARB in Wistar Rats using thermal models.

The mean changes in tail flick test response were noted from 0 to 180 min at an interval of 30 min in all study groups.Maximum antinociceptive response was seen at 90 minutes in all the study groups except the control group (p<0.05). Highly significant improvementwas seen in diclofenac and tramadol group (p<0.001).The antinociceptive effects of diclofenac and tramadol are well established as seen in many previous studies.[20]

In ramipril and telmisartan group the changes in response from 0 min to 90 min were 3.83±0.17 and 6.5± 0.34(p<0.001) and 4±0.26 and 6.67±0.33(p<0.001) respectively. These results were consistent with previous studies where significant improvement has been seen in tail flick test response with ACE inhibitors and ARBs by Jadhav et al.,Salim et aland Indumathy et al. [18,21,22]The possible mechanisms for the antinociceptive effects of ACE inhibitors and ARBs are by blockade of Angiotensin-II synthesis, increasing endogenous opioids in CNS and by modulation of sympathetic transmission.[23]But on intergroup comparison no significant difference was seen at 90 min when diclofenac and tramadol groups were compared(p>0.05) as both the drugs were found to be equally effective.But significant difference was seen when Ramipril and Telmisartan group were compared with Diclofenac and Tramadol group (p<0.001) since both Ramipril and Telmisartan possess weak antinociceptive effects and are not the standard first line analgesic drugs. Intergroup comparison at 180 minutes showed no significant difference in any of the study groups (p>0.05) except when tramadol was compared with control group(p<0.01). This maybe because tail flick test is used in acute pain response and the response of NSAIDs diminishes with the passage of time. Tramadol, being an opioid analgesic,had some sustained effect in our study at 180 minutes.

Study limitations: Involvement of more number of rats in each group in our study may have had shown more consistent results. In our study the antinociceptive effects were determined only at single low dose.Results could have been different by multiple doses or chronic administration of drugs. Lastly, it was an open label study, which has chances of bias.

Conclusion: Diclofenac and tramadol showed significant antinociceptive effects.Both Ramipril and Telmisartan showed antinociceptive effect when tail flick method was used for nociception.However, both these drugs were inferior to diclofenac and tramadol.

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