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A comparative study of analgesic effect of Flunarizine and Cinnarizine in albino rats, using digital analgesiometer

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Abstract: *Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is frequently classified as physiologic or acute pain and pathologic or chronic pain, which includes inflammatory pain and neuropathic pain. Acute pain typically has a sudden onset and recedes during the healing process. Analgesics are the drugs which possess significant pain relieving properties by acting on CNS or on peripheral pain receptors without significantly affecting consciousness.Analgesic drugs are divided into two groups. They are 1. Opioid analgesics 2.Non opioid analgesics.Ca^{2+} channel antagonists also called Ca^{2+} entry blockers are drugs that inhibit Ca^{2+} channel functions. Voltage sensitive Ca^{2+} channels mediate the entry of extracellular Ca^{2+} influx into the smooth muscles, cardiac myocytes,sinoatrial (SA) and atrio-ventricular (AV) nodal cells in response to electricaldepolarization. In both smooth muscle and cardiac myocytes, $Ca^{2+}$is trigger for contraction. All Ca^{2+} channel blockers (CCB) approved for clinical use decrease coronary vascular resistance and increase coronary blood flow. They have acquired and maintained an important position in the drug therapy of cardiovascular diseases, hypertension, angina pectoris and arrhythmias.But some journals revealed the anti-nociceptive property of these CCB's in which the results suggest that CCB's can induce analgesia and increase morphine analgesia, possibly through a decrease in cellular calcium availability. So the main aimof this study is tocompare the analgesic effect ofFlunarizine andCinnarizine in rats using Analgesiometer (digital).*
Objectives:*1. To study the analgesic effect of Flunarizine, Cinnarizine in rats using Analgesiometer (digital). 2.To Compare the analgesic effect of Flunarizine, Cinnarizine in rats using Analgesiometer (digital).*
Materials & Methods: *A Randomized controlled trail was conducted in the Dept. of Pharmacology, DrPinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance. Total rats were divided into 3 groups consisting of 6 rats in each group. First group of rats (control group) were treated with 0.2 ml normal saline. Second group were considered as test drug-1 and were treated with Flunarizineat a dose of 2.6mg/kg body weight. Third group were considered as test drug-2 and treated with Cinnarizine ata dose of 3.5mg/kg body weight.*
Conclusion: *The result showed that Cinnarizine has analgesic property, and it is less when compared to Flunarizine. However the above preclinical experiments only give us an idea about the analgesic effect of Cinnarizine&Flunarizinebut large scale clinical trials are necessary for final assessment.*

I. Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1][2]. Pain is frequently classified as physiologic or acute pain and pathologic or chronic pain, which includes inflammatory pain and neuropathic pain. Acute pain typically has a sudden onset and recedes during the healing process. Acute pain can be considered as 'good pain' as it serves an important protective mechanism like withdrawal reflex. Chronic pain can be considered as 'bad pain' because it persists long after recovery from an injury and is often refractory to common analgesic agents. Analgesics are the drugs which possess significant pain relieving properties by acting on CNS or on peripheral pain receptors without significantly affecting consciousness.Analgesic drugs are divided mainly into two groups. They are 1. Opioid analgesics 2.Non opioid analgesics.Ca^{2+} channel antagonists also called Ca^{2+} entry blockers are drugs that inhibit Ca^{2+} channel functions.Voltage sensitive Ca^{2+} channels mediate the entry of extracellular Ca^{2+} influx into the smooth muscles, cardiac myocytes,sinoatrial (SA) and atrio-ventricular (AV) nodal cells in response to electrical depolarization. In both smooth muscle and cardiac myocytes, Ca^{2+} is trigger for contraction.. All Ca^{2+} channel blockers approved for clinical use decrease coronary vascular resistance and increase coronary blood flow and have acquired and maintained an important position in the drug therapy of cardiovascular diseases, hypertension, angina pectoris and arrhythmias. But some journals revealed the anti-nociceptive property of these CCB's in which the results suggest that CCB's can induce analgesia and increase

morphine induced analgesia, possibly through a decrease in cellular calcium availability. Similarly the journal of Indianjournal of experimental biology(2001)[3] and European journal of pharmacology(2002)[4] gave information about the analgesic activity of Flunarizine and Cinnarizine.So the main aim of this study is to compare the analgesic effect of Flunarizine and Cinnarizine in rats using Analgesiometer (digital).

Flunarizine: Flunarizineis a non-selective calcium channelblocker[5] and has histamine H_1 blocking activity. It is effective in the prophylaxis of migraine[6], occlusive peripheral vascular disease, vertigo of central and peripheral origin, and as an adjuvant in the therapy of epilepsy.**Mechanism of action:**Inhibits the influx of extracellular calcium through myocardial and vascular membrane pores by physically plugging the channel. Decrease in intracellular calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased after load [7].

Cinnarizine: Cinnarizine is an anti-histaminic drug and is also a calcium channel blocker. It is mainly used for the control of vomiting due to motion sickness and can inhibit smooth muscle contraction by blocking calciumchannels. It is a piperazine derivative, H1 histamine antagonist. **Mechanism of action:** Cinnarizine is a polyvalent non-competitive antagonist of vasoconstrictive agents, and reduces the vascular response to epinephrine, norepinephrine, serotonin, angiotensin, dopamine, and other vasoactive hormones. It is a long-acting, potent inhibitor of potassium chloride-depolarization-induced peripheral vasoconstriction, acting via selective inhibition of calcium influx into depolarized cells, thereby reducing the availability of free calcium ions for induction and maintenance of contraction in smooth muscle. Directly antagonizes the stimulated influx of extracellular calcium,modifyingintracellular calciumadenosinetriphosphate balance in erythrocytes, thus increasing theirflexibility and decreasing whole blood viscosity [8].

Objectives: 1. ToStudy the analgesic effect of Flunarizine, Cinnarizine in rats using Analgesiometer (digital). 2. To Compare the analgesic effect of Flunarizine, Cinnarizine in rats using Analgesiometer (digital).

II. Methodology

A Randomized controlled trail was conducted in the Dept. of Pharmacology, DrPinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance.Total Male albino rats were divided into 3 groups consisting of 6 rats in each group. Animals are weighed with the help of weighing machine. The animals weighing 250gms on average were selected for the experiment. First group of rats (control group) were treated with 0.2 ml normal saline intra peritoneally. Second group were considered as test drug-1 and treated with Flunarizine at dose of 2.6mg/kg body weightintraperitoneally. Third group were considered as test drug-2 and treated with Cinnarizine at dose of 3.5mg/kg body weightintraperitoneally.

Tail flick time was taken as the reaction time. Normal reaction time was noted for 5 times in each animal before starting the experiment. Average of all the 5 readings were taken as mean reaction time at 0 minutes. After recording of normal reaction time, normal saline was administeredintraperitoneally to control group, Flunarizinewas administered intraperitoneallyto test drug-1 group of animals, Cinnarizine was administered intraperitoneally to test drug-2 group. For the above mentioned drugs, reaction time was recorded after administration to their respective groups at 30 minutes, 60 minutes and 90 minutes. All recordings were tabulated separately.

Equipments: Digital Analgesiometer, Insulin syringes,Measuring jar, Glass, beaker,Animal weighing balance, Mortar & pestle ,Spirit ,Cotton ,Stop watch

Chemicals & Solutions: Flunarizine,Cinnarizine,Double distilled water,Normal saline,Dimethyl sulfoxide

Animals: Male Albino wistar rats weighing about 250gm.

Instrument Descripition: Digital Analgesiometer is the instrument meant for studying the analgesic effect of pain by observing the flicking of tail due to heat. It is provided with an arrangement for holding the tail of the rat. A wire is connected between two terminals through which heat is generated. The instrument is also provided with a metallic rat carrier for proper holding of rat. This also facilitates easy positioning of the tail of rat in the grooveprovided for holding the tail above the heater wire. Analgesiometer operates on 220/230V, 50HZ.

The Tail Flick Method[9]: The tail flick procedure was originally described byD'amor&smith[10](1941) for testing analgesics in both rats and mice. Total Male albino rats were divided into 3 groups consisting of 6 rats in

each group. Animals are weighed with the help of weighing machine. The animals weighing 250gms on average were selected for the experiment. First group of rats (control group) were treated with 0.2 ml normal saline.

Second group were considered as test drug-1 and treated with Flunarizine at dose of 2.6mg/kg body weight. Third group were considered as test drug-2 and treated with Cinnarizine at dose of 3.5mg/kg body weight.

Reaction time after giving the drug was recorded at 30 minutes, 60 minutes and 90 minutes. All recordings were tabulated separately.

For identification each group was marked with different colors. A portion of the tail, was darkened using ink, at approximately 3 cm from the tip of the tail. Control group of animals were marked with black ink, test-1 with red ink and test-2 with blue ink. Prior to the experiment all animals normal reaction time for heat on analgesiometer was tested for at least 5 times and reaction time was tabulated.

The timer in the analgesiometer will automatically record the tail flick latency. The instrument was operated at 2.5 amps current throughout the experiment. The rat is inserted in the metallic rat holder and the tail of the rat was taken outfrom the slit provided in the rat holder. The tail of the rat was positioned in the groove provided. The mains plug was inserted in to the mains socket for powering the analgesiometer. the set current knob was rotated anti-clock wise fully. the instrument was switched on with the help of switch marked with mains on the front panel. Mains ON indicator starts glowing. Current meter will start indicating current in the meter. Now the desired level was set by observing the color of the wire connected between the two terminals below the tail of the rat. It shall be near to red hot.

The flicking of the tail of the rat was observed and the time taken for flicking of the tail after heat is applied was noted. A cut off period of 20 seconds is observed to prevent damage to tail. Any animal failing to withdraw its tail within cut off period is rejected from the study. At least 3-5 reading for each rat was taken at a gap of 5 minutes to the normal behavior of the animal. Next, First group of rats (control group) were treated with 0.2 ml normal saline. Second group were considered as test drug-1 and treated with Flunarizine at dose of 2.6mg/kg body weight. Third group were considered as test drug-2 and treated with Cinnarizine at dose of 3.5mg/kg body weight. Tail flick latency was recorded for the three groups of animals after 30 minutes, 60 minutes and 90 minutes after administration of drugs after Imposing a cutoff time at each test time period. The results were tabulated.

Statistical Analysis: Mean, SD, SE, 95% Confidence limits, ANOVA, Tuckey HSD, Paired t-test were applied.

III. Results and Discussion

Table-1: Descriptive and inferential statistics of reaction time of each drug at 0, 30, 60 and 90 min.

Time	Drug	Mean	SD	SE	95% Confidence Interval	
					Lower Bound	Upper Bound
At 0	Normal	7.0	0.32	0.13	6.63	7.30
	Flunarizine	7.5	0.62	0.25	6.89	8.18
	Cinnarizine	6.8	0.66	0.27	6.07	7.46
At 30	Normal	7.5	0.55	0.22	6.93	8.08
	Flunarizine	10.7	0.82	0.33	9.81	11.52
	Cinnarizine	9.8	0.75	0.31	9.04	10.62
At 60	Normal	6.7	0.82	0.33	5.81	7.52
	Flunarizine	12.0	0.63	0.26	11.34	12.66
	Cinnarizine	10.3	0.82	0.33	9.48	11.19
At 90	Normal	7.7	0.52	0.21	7.13	8.21
	Flunarizine	13.2	0.75	0.31	12.38	13.96
	Cinnarizine	11.3	0.52	0.21	10.79	11.88

Fig-1: Mean reaction time of each drug at 0, 30, 60 and 90 min

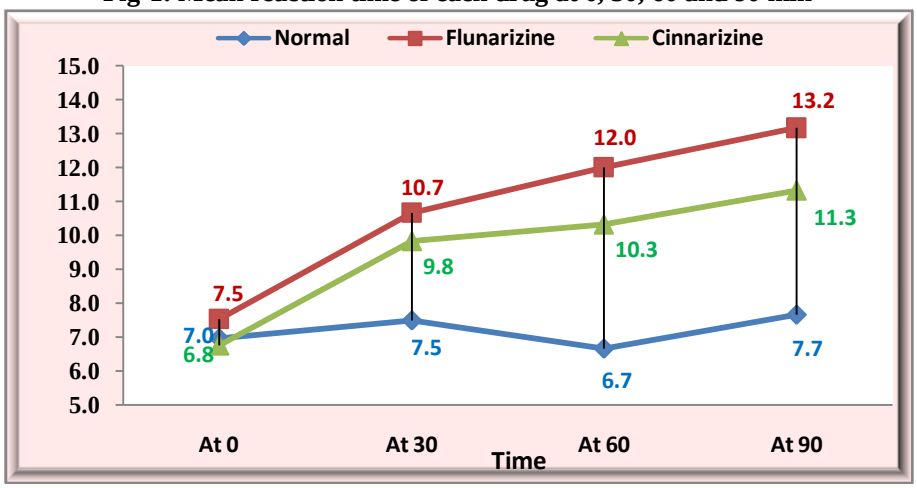

Table-2: Comparison of mean reaction time among the drugs at 0, 30, 60 and 90 min.

Time	Comparison	Sum of Squares	Df	Mean Square	F	P-value	Inference
At 0	Between Groups	1.898	2	0.949	3.094	0.075	NS
	Within Groups	4.6	15	0.307			
	Total	6.498	17	-			
At 30	Between Groups	32.333	2	16.167	31.63	<0.01	HS
	Within Groups	7.667	15	0.511			
	Total	40	17	-			
At 60	Between Groups	89.333	2	44.667	77.308	<0.01	HS
	Within Groups	8.667	15	0.578			
	Total	98	17				
At 90	Between Groups	94.111	2	47.056	128.333	<0.01	HS
	Within Groups	5.5	15	0.367			
	Total	99.611	17	-			

In control group with 0.2 ml of normal saline there was no significant change in mean reaction time at 0 minutes, 30 minutes, 60 minutes and 90 minutes but it was significant in both the test groups

Table-3: Comparison of mean reaction time between the drugs at 30, 60 and 90 min

Time	(I) Group	(J) Group	Mean Difference (I-J)	P-value	Inference
At 30	Normal	Flunarizine	-3.1667*	<0.01	HS
		Cinnarizine	-2.3333*	<0.01	HS
	Flunarizine	Cinnarizine	0.8333	0.142	NS
At 60	Normal	Flunarizine	-5.3333*	<0.01	HS
		Cinnarizine	-3.6667*	<0.01	HS
	Flunarizine	Cinnarizine	1.6667*	<0.01	HS
At 90	Normal	Flunarizine	-5.5000*	<0.01	HS
		Cinnarizine	-3.6667*	<0.01	HS
	Flunarizine	Cinnarizine	1.8333*	<0.01	HS

In test drug-1 group of rats treated with Flunarizineat dose of 2.6mg/kg body weight, there was significant change in mean reaction time at 30, 60 and 90 minutes and similar result was observed in test drug-2 group treated withCinnarizineat dose of 3.5mg/kg body weight.

Table-4: Pair wise comparison of mean reaction time between time intervals in each drug.

Drug	Pair	t-value	P-value	Inference
Normal	At 0 to 30 min	-2.902	0.03	S
	At 30 to 60 min	2.076	0.09	NS
	At 60 to 90 min	-2.739	0.04	S
Flunarizine	At 0 to 30 min	-5.959	0.00	HS
	At 30 to 60 min	-3.162	0.03	S
	At 60 to 90 min	-3.796	0.01	S
Cinnarizine	At 0 to 30 min	-12.207	0.00	HS
	At 30 to 60 min	-1.168	0.30	NS
	At 60 to 90 min	-3.873	0.01	S

In comparison between two test drugs, it was found that mean reaction time increased gradually after 30 minutes, 60 minutes and 90 minutes of drug administration for both the drugs. Better results were observed with test drug-1 Flunarizine than with test drug-2 Cinnarizine.

IV. Conclusion

The result showed that Cinnarizine has analgesic property, and it is less when compared to Flunarizine. However the above preclinical experiments only give us an idea about the analgesic effect of Cinnarizine&Flunarizinebut large scale clinical trials are necessary for final assessment.

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