ANTI-NOCICEPTIVE OUTCOMES OF ANTICONVULSANT/ ANTIDEPRESSANT MEDICINES IN THE MANAGEMENT OF FORMALIN INDUCED PAIN IN GROUP OF MICE

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ABSTRACT

Background: Anti-depressant is used to treat various disorders like neuropathic pain, migraine etc. Anticonvulsant drugs may have a role in the modulation of changes include inhibition of voltage gated ion channels at sites of spinal, supraspinal and peripheral.

Objectives: An experimental observational study was carried out to find the role of anti-nociceptive outcomes of anticonvulsant/antidepressant medicines in the management of formalin induced pain in group of mice.

Methods: A total of 20 albino mice weighed 20-30 gm. were taken. Pain was induced by formalin. Animals were divided in 4 groups (05/ group) group no 1: Control, group no 2: Paracetamol, group no 3: Fluvoxamine, group no 4: Lamotrigine. Number of counts of licking paw and paw-lifting of mice during first phase and second phase was noted. Percentage effectiveness was calculated by the formula. The palliative action of the medicine was evaluated by calculating the latency moment in reaction to stimulus of heat.

Results: Effect of diverse doses of anti-depressants & anticonvulsant on licking / lifting of paw showed that high dose PCM completely defended 2nd stage of lifting / licking paw but in 1st stage defense was seen. FLX exhibited rising upshot with period in both licking / lifting of paw. Lamotrigine with high dose showed increase protection in licking of paw in 1st stage as compared to 2nd stage. The impact of medicines on latency period showed that high doses PCM and FLX exhibit a rise is latent period of time to react to stimulus of heat. LTG offer time-based defense against nociceptive ache.

Conclusion: Our study shows the anti-nociceptive outcomes (relieving pain) of antidepressant fluvoxamine was better than paracetamol and lamotrigine in the treatment of formalin induced pain in group of mice.

Key Words: Anti-nociceptive effects, Fluvoxamine, Lamotrigine, Mice.

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INTRODUCTION

Anti-depressant /Anti-epileptic drugs are used globally to treat various disorders other than problem of epilepsy, like neuropathic pain, bipolar disorder and migraine. Anticonvulsant drugs may have a role in the modulation of changes (after operation) include inhibition of channels of sodium and calcium and receptor of glutamate at sites of spinal, peripheral and supra-spinal.[1] The adjuvant medicines specified by the WHO are: anticonvulsants, antidepressants, steroids and anesthetics.[2] Neuropathic pain can be divided into positive and negative symptom categories. Antidepressants and anticonvulsants are prescribed for neuropathic pain with negative and positive symptoms, respectively. The anticonvulsants play an important role in blockade of sodium and calcium channel.[3] The analgesic role of antidepressants is blocking the reuptake of norepinephrine or serotonin.[4,5]

Additionally clinical studies suggested that anticonvulsants may lessen immediate and movement-evoked pain, and also reduce the need of opioid in post operate cases. These drugs may also ease postoperative anxiety, increase functional postoperative recovery and decrease postsurgical ache.[5].

Paracetamol is used globally for its antipyretic and analgesic actions. It behaves like NSAIDs as it acts as inhibitor of COX-2. However, Paracetamol is, a feeble pain killer than NSAIDs but is preferred due to its good tolerance.[6,7]

Lamotrigine (LTG) is second-generation anticonvulsants with analgesic properties. It acts as voltage-stimulated sodium channels, stable the pre-synaptic neuronal membranes and blocking the release of pre-synaptic aspartate and glutamate.[8] LTG was found to show the tolerance of extended release as compared to tolerance of immediate release from the pain. The most known side effects are diplopia, dizziness, ataxia and nausea and somnolence and rash.[9] However, a study found no evidence of the therapeutic role of LTG in neuropathic pain & fibromyalgia.[10]

Fluvoxamine (FLX) is an antidepressant, functions as an inhibitor of reuptake of serotonin. It is easily available, well-tolerated, and cheap inhibitor. It blocks the reuptake of serotonin at the serotonin transporter of the neuronal membrane, increasing the role of serotonin on its auto receptors. It is thought that FLX stops the binding of serotonin by inhibiting the binding site of substrate and stabilizing the SERT transporter.[11] FLX has small affinity for alpha and beta adrenergic, dopamine, opiate and receptors of 5-HT1/ 5-HT2. FLX may use in problems of anxiety like disorders such as stress and panic chaos.[12]

Injection of formalin give high "long" lever-press reactions in experimental animals compared to injection of saline. It is suggested that formalin-induced pain lengthened the time duration.[13] Neuropathic ache is usually unbearable; decrease the routine activities of patients. Characteristically, neuropathic pain is not easy to manage and, may progress into chronic states and in many cases refractory to medical management.

An experimental observational study was conducted to find the role of anti-nociceptive outcomes of anticonvulsant/ antidepressant medicines in the management of formalin induced pain in group of mice.

METHODS

Animals: A total of 20 albino mice weighed 20-30 gm. were taken from animal dwelling of The University of Lahore. Mice were kept at temperature of 22 ± 20 ^{0}C and prohibited from humidity. The animals were kept on cycle of 12-hour day / night. Food and were supplied ad libitum and were not given twelve hours before experiment.

Chemicals: Formalin solution (Sigma Company) from general stock whereas Paracetamol tablet (PCM), and Fluvoxamine medicine (FLX) were donated by Unison Chemical Company Lahore. Lamotrigine (LTG) was taken from High Noon Laboratories, Lahore.

Acute pain model:

Formalin test: Formalin induced pain was judged by observing the lifting of paw and behavior. Animals were comprised in four groups (5 mice in each group); group no 1: control, group no 2: PCM (400mg/kg), group no 3: FLX tablet (40mg/kg), group no 4: LTG tablet (70mg/kg). Oral medicine to groups of mice and normal saline to control group. After the period of an hour the doses of medicine about 20 µl of 5.0 % solution of formalin was injected in the facade of paw. Number of counts of licking and lifting of paw of mice during the period of first phase (15-20 minutes) and in 2nd phase (31-45 minutes) was noted. Formula used for finding the % age effectiveness.[14]

% of effectiveness= (control worth – tested medicine worth / control worth) multiply by 100

Hot plate experiment: The painkiller action of the medicine was evaluated by calculating the latency period in reaction to stimulus of heat. Same groups of mice were used for evaluating the latency time. The animals were positioned on hot plate (temperature 53℃) at time interval 0 min, 30 min, 60 min & 90 min subsequently the administration of drug. The Latency period until animal began either jumping or licking was noted. Latency time should not be more than 60 seconds (to avoid tissue damage). Formulation for % age of utmost possible effects was as follow.[15]

% age possible effects = (Post medicine latency-Pre medicine latency / discontinue period-Pre medicine latency) multiply 100

Statistics of results was analyzed by SPSS 20. Data was expressed as mean±SEM. One way ANOVA was used to find the significance difference in effect of antidepressant/anticonvulsant drugs relieving the pain in groups of mice. P less than 0.05 (significant).

RESULTS

Table 1 shows the effect of diverse doses of anti-depressants & anticonvulsant on licking / lifting of paw. PCM with dose of 400mg/kg 100 % defended 2nd stage (15 to 40 minutes) of lifting / licking paw but in 1st stage (0 to 5 min) no defense was seen in licking / lifting of paw. FLX 40mg/kg exhibited rising upshot with period in both licking / lifting of paw. Lamotrigine medicine with dose of 70mg/kg showed increase protection in licking of paw (84%) at 0 to 40 min whereas decline of effectiveness in lifting of paw at 15 - 45 min (50%).

Table 1: Effect of medicines on licking / lifting of paw behavior in group of mice

Test Medicine	Licking o Paw		Lifting of Paw		
Time Duration	15-30(min)	31-45 (min)	15-30 (min)	31-45 (min)	*P- value
Normal/ Control	4.3 ± 0.52	7.7 ± 0.57	1.9 ± 0.21	1.21 ± 0.21	NS
PCM (400 mg/kg)	0 ± 0 (100 %)	0 ± 0 (100 %)	0 ± 0 (100 %)	0 ± 0 (100 %)	-
FLX (40 mg/kg)	0.20 ± 0.20 (95.45 %)	0 ± 0* (100 %)	0 ± 0* (100 %)	0 ± 0* (100 %)	<0.05
LTG (70 mg/kg)	1.1 ± 0.31* (77.28 %)	1.21 ± 0.21 (84.63 %)	0 ± 0 (100 %)	0.6 ± 0.2 (50 %)	<0.05

Data was expressed as mean ± SEM (with number of mice 05) *p<0.05 taken as significant in comparison to normal / control. The number in brackets shows % values of effectiveness.

Table 2. Impact of medicine on latency period to hot platter persuaded lifting / jumping actions in group of mice.

Test medicine	Latency Period of Time		
	30-- min	60-- min	90-- min
Normal group	11.21 ± 0.70	10.9 ± 0.38	11.0 ± 0.45
P C M (400 mg / kg)	31.10 ± 1.38 (63.0 %)	34.80 ± 0.16 (67.06 %)	39.40 ± 2.66 (71.09 %)
FLX (15 mg/kg)	39.1 ± 0.90* (71.3 %)	40.11 ± 2.35* (73.08 %)	40.61 ± 1.97* (72.92 %)
LTG (40mg/kg)	30.4±0.51 (62 %)	34.4±1.5 (67 %)	37.40±1.36 (71 %)

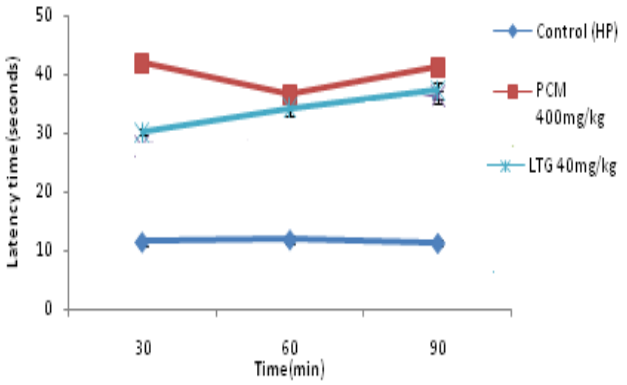

Fig 1: Effect of LTG on hot plate bring thermal feeling

Data are expressed as mean±SEM (no of mice in each group 5.0, *P less than 0.05 taken as significant in comparison to normal mice group. The figures in brackets showed maximum % effect quantities.

The impact of medicines on latency period in hot plate is existing (Table 2 & Fig 1). PCM with a dose of 400 mg / kg exhibit a rise is latent period of time to react to stimulus of heat, highest rising was seen (72%) at time period of 90 minutes. FLX 15mg/kg showed similar propensity of protection against hot stimuli (71-71.5 %). LTG 40mg/ kg offer time-based defense against nociceptive ache persuaded by stimulus of heat, the highest effect of 71 % attained at time of 90 min after given the dose.

DISCUSSION

We observed oral doses of anti-depressants and anti-convulsant on-licking / lifting of paw. PCM with a dose of 400 mg/ kg 100% defended 2nd phase (15 to 45 min) of lifting/licking of paw. In comparison of our study, an experimental study was carried out in group of mice, by administering paracetamol and compared its effect with ibuprofen. Study found a significant antinociceptive effect (blocking painful stimulus) in case of paracetamol whereas ibuprofen, showed no anti-nociceptive action, in the primary phase of the formalin test. Their results confirm the analgesic function of paracetamol.[16,17] However a study proved that Paracetamol even at high doses is ineffective to relieve pain due to headache /backache.[18]

According to our study, FLX with dose of 40 mg / kg exhibited rising outcome with time period in both licking / lifting of paw. It is known that fluvoxamine increased analgesic effect at the opioid receptor. A study was carried out to find the effect of fluvoxamine and other antidepressant drugs including methadone in a group of mice using hot plate assay. Study found that fluvoxamine unaccompanied induces an anti-nociceptive effect and it is arbitrated by non-opioid mode of action. However, fluvoxamine with sub-threshold dose persuaded a synergistic effect with a dose of methadone.[19] It is proposed that antidepressant drugs mildly attenuating the action of pro-inflammatory cytokine and improved the symptoms of depression.[20]

We found that Lamotrigine with a dose of 70mg/kg initially increase the response of protection in paw-licking (84%) whereas diminished effectiveness in lifting paw at time 15 - 45 min (50%). Our study is in contrast with trail base study. According to clinical trials lamotrigine is used to cure fibromyalgia or neuropathic pain for weeks. The trial includes half of the study subjects, who had pain in their limbs due to injured nerves caused by type 2 diabetes. Seven diverse painful neuropathic states were also noted. Study found that lamotrigine showed no Anti-nociceptive effects and not differ from placebo apart from causing more side effects than placebo.[21]

Most studies give contradictory reports on the role of lamotrigine in controlling neuropathic pain began with primary doses of 125 mg range to 200 mg and end with dose of 400 mg/day. One of the studies evaluated twelve studies with 1500 study subjects and found the role of lamotrigine in curing neuropathic ache with no proof to recommend the medicine lamotrigine for curing neuropathic pain.[21,22] However a study showed, function of lamotrigine for managing neuropathic ache in damaged spinal cord. Study included 147 individuals with neuropathic pain (NP) and used lamotrigine. The anti-convulsant drug lamotrigine with quantity of 25. 50 & 100 mg two times/ day was prescribed. Assessment of NP was carried out at initial period and thereafter at 1 week, 2 week & 3 weeks using Short-form MC Gill Pain Questionnaire-2 scores. Study found a significant difference between the values of the SFMPQ2 score at initial period and those 1,2 and 3 weeks for lamotrigine. These findings proved that lamotrigine can be used in controlling the NP after damage of spinal cord.[23]

CONCLUSION

Our study shows the anti-nociceptive outcomes (relieving pain) of antidepressant fluvoxamine was better than paracetamol and lamotrigine in the treatment of formalin induced pain in group of mice. On the other hand the anticonvulsant effect of lamotrigine is disputed. Further studies are needed to conform the safety and efficacy of these drugs in treating acute / neuropathic pain.

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AUTHOR'S CONTRIBUTIONS

SS: Study design, manuscript writing, data analysis,
AS: Interpretation of data, **c**ritical analysis, **c**ritical review

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