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EVALUATION OF CENTRAL AND PERIPHERAL ANALGESIC ACTIVITY OF CETRIZINE IN MICE: A RANDOMIZED CONTROL STUDY.

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ABSTRACT

Background
Pain management is challenging due to the subjective nature of pain and the limitations of existing analgesics. Histamine and serotonin pathways play a role in pain modulation, suggesting potential analgesic effects of cetirizine and amitriptyline. While amitriptyline has shown some efficacy, cetirizine's role in pain relief remains unclear. This study evaluates their analgesic potential of cetrizine individually and with diclofenac in mice.

Methods
Albino Swiss mice (n=24) were divided into four groups to evaluate the analgesic effects of amitriptyline and cetirizine, compared to diclofenac. Pain response was assessed using the tail flick (thermal), tail clip (physical), and writhing (chemical) tests at multiple time points. Drugs were administered orally, and the percentage inhibition of writhing was calculated.

Results
Amitriptyline exhibited the highest analgesic effect in the tail flick test (13.50±0.342 sec at 90 min), followed by diclofenac (11.00±0.365 sec) and cetirizine (8.00±0.365 sec). In the tail clip test, diclofenac and amitriptyline showed peak response times of 12.66±0.323 sec and 12.16±0.342 sec, respectively. Cetirizine was less effective in both tests. In the writhing test, diclofenac had the highest inhibition (65.85%), followed by cetirizine (41.46%), while amitriptyline showed the least effect (19.50%). These findings confirm significant analgesic properties of all tested drugs, with varying efficacy.

Conclusion
Amitriptyline showed the most prolonged analgesic effect in thermal and mechanical pain models, while diclofenac was most effective in visceral pain inhibition. Cetirizine demonstrated moderate analgesic activity.

Recommendation
Cetirizine may be considered as a supportive analgesic agent, especially when conventional NSAIDs pose risks, warranting further studies on its analgesic mechanisms and clinical applications.

Keywords: *Analgesic activity, Amitriptyline, Cetirizine, Diclofenac, Tail flick test, Tail clip test, Writhing test.*
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INTRODUCTION

Pain is a common symptom of numerous diseases, often necessitating treatment with analgesics. However, pain management remains a significant challenge due to its subjective nature, as its intensity does not always correspond to the nociceptive inputs that trigger it. Pain perception varies among individuals, with some tolerating stimuli that others find unbearable. Furthermore, pain is not a consistent feeling, as evidenced by its various descriptors such as sharp, dull, aching, burning, or throbbing. Notably, pain can persist even after the resolution of an injury or may occur in the absence of any detectable tissue damage. Under normal physiological conditions, pain is transmitted through small-diameter C and Aδ primary afferent fibers in peripheral nerves, which respond to mechanical, thermal, and chemical stimuli. C fibers, being unmyelinated, are primarily associated with dull and burning pain, whereas myelinated Aδ fibers transmit sharp and well-localized pain. These nociceptive fibers convey signals from muscles, viscera, and the skin, playing a critical role in pain perception and modulation [1].

Analgesics, or pain relievers, are essentially divided into two types: opioids, which operate centrally, and nonsteroidal anti-inflammatory medications (NSAIDs), which work peripherally. Analgesics' effectiveness varies by individual, and their use is frequently limited due to

their short therapeutic window and risk of side effects. Diclofenac, a strong NSAID from the phenylacetic acid class, is commonly given for inflammatory and painful disorders, including postoperative pain. Its analgesic and anti-inflammatory properties are due to its ability to inhibit cyclooxygenase (COX), an enzyme that converts arachidonic acid into prostaglandins. This process has been demonstrated in vitro by a considerable decrease in the synthesis of prostaglandins, prostacyclin, and thromboxane in a variety of biological tissues, including sheep seminal vesicles, guinea pig stomach, and bovine cerebral cortex [2,3]. Despite their efficacy, NSAIDs have substantial adverse effects like bleeding in the gastrointestinal tract, ulceration, and renal toxicity, prompting the quest for better analgesic alternatives [4].

Cetirizine, a second-generation H1 antihistamine, is widely used to treat allergy disorders such as rhinitis, urticaria, and conjunctivitis because of its selective action and favourable pharmacokinetic profile. Interestingly, histamine is also involved in pain modulation, with studies showing that activation of H1 receptors can enhance sensitivity to painful stimuli. This shows that the histaminergic system has an important function in central nociceptive processing [5,6]. Furthermore, a substantial link has been found between chronic pain and depression, with data indicating that differences in brain serotonin levels may underpin both illnesses. Tricyclic antidepressants, such as amitriptyline, have been shown to have analgesic qualities in patients with diverse pain syndromes, even when depression is not present [7,8]. However, antidepressants are not routinely recommended for pain management due to uneven results, underlining the need for further research.

This study seeks to investigate the analgesic potential of cetirizine, a second-generation antihistamine, in mice. It will also be compared to the analgesic effects of amitriptyline, a tricyclic antidepressant, which will be evaluated both separately and in combination with diclofenac to determine their effectiveness in pain reduction. The analgesic activity will be assessed using experimental models such as the tail flick test (thermal approach), tail clip test (physical method), and writhing test (chemical method). By investigating these medications' analgesic efficacy, this study hopes to develop novel therapeutic techniques that give effective pain relief with fewer adverse effects [9,10].

METHODS

Study Design

This was a randomized controlled experimental study conducted using adult Albino Swiss mice. Animals were randomly assigned to different treatment groups to compare the analgesic effects of test drugs with a standard reference drug and a control.

Study Setting

The study was carried out at the Department of Pharmacology, NIMS Medical College and Hospital, Jaipur, a well-established tertiary medical teaching institution in Rajasthan, India, equipped with a CPCSEA-approved animal house facility and standard laboratory infrastructure for preclinical pharmacological experiments.

Study Drugs and Chemicals

Amitriptyline, cetirizine, and the standard medication diclofenac were among the test medications. These were purchased from a nearby drugstore.

Experimental Animals

Albino Swiss mice were used due to their ease of maintenance and handling. The study involved 24 healthy adult mice (3–4 months old, 20–25 g) of either sex, housed in polypropylene cages at NIMS Medical College, Jaipur. This study was conducted over 10 months, from January 2024 to October 2024. Except for the time spent experimenting, they were housed in a typical laboratory setting and provided with an open diet of pellets and water.

Inclusion and Exclusion Criteria

Inclusion criteria included healthy albino mice (3–4 months old, 20–25 g). Exclusion criteria included mice outside this weight and age range, pregnant or recently delivered mice, and those previously used in other experiments.

Intervention

Mice were divided into four groups (G1–G4, six mice each, total = 24):
G1 (Control): Received distilled water.
G2 (Standard): Received diclofenac (10 mg/kg p.o.).
G3 (Test 1): Received amitriptyline (10 mg/kg p.o.).
G4 (Test 2): Received cetirizine (1 mg/kg p.o.).
All drugs were administered orally via gavage using an oral feeding needle. Drug administration was carried out once, and analgesic activity was assessed at predetermined time intervals post-administration.

Methods for Analgesic Activity Evaluation

Analgesic activity of amitriptyline and cetirizine was compared with diclofenac using three methods:

Radiant Heat Method (Thermal Method): Pain was induced using a heated nichrome wire (52±0.5°C) in an analgesiometer. Tail flick response time was recorded, with a cutoff of 15 seconds to prevent injury. Mice showing baseline responses beyond 6 seconds were

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excluded. Readings were taken at 0, 30, 60, and 90 minutes post-administration.

Tail Clip Method (Physical Method): Pain was induced using an artery clip with rubber tubing, applied 2 cm from the tail base. Mice responding within 10 seconds were selected. The reaction time was recorded at 0, 30, 60, and 90 minutes, with a 15-second cutoff.

Writhing Test (Chemical Method): Acetic acid (0.6% p.o., 10 mg/kg) was used to induce abdominal writhing, characterized by abdominal contractions and limb extension. The number of writhes was counted over 20 minutes, starting 5 minutes post-injection. Percentage inhibition was calculated using the formula:

Inhibition (%) = [(Writhes in Control - Writhes in Treatment) / Writhes in Control] × 100

Statistical Analysis

Results were expressed as Mean ± SEM. One-way ANOVA was used for multiple comparisons, and if significant, Bonferroni's post hoc test was applied to determine differences between groups. A p-value of ≤0.05 was considered statistically significant.

The CPCSEA guidelines were strictly adhered to during this work with proper approval from the Institutional Animal Ethics Committee (IAEC). Ethical approval was obtained from the IAEC of NIMS Medical College, Jaipur.

RESULTS

All 24 mice included in the study were healthy adult Albino Swiss mice of either sex, aged between 3–4 months and weighing between 20–25 g. There were no statistically significant differences in mean age or weight across the four groups at baseline, ensuring comparability (Table 1).

Table 1: Baseline characteristics of experimental groups (Mean ± SEM)

PARAMETER	CONTROL (n=6)	DICLOFENAC (n=6)	AMITRIPTYLINE (n=6)	CETIRIZINE (n=6)
Age (months)	3.3 ± 0.2	3.4 ± 0.3	3.2 ± 0.2	3.3 ± 0.3
Weight (g)	22.1 ± 0.5	21.9 ± 0.6	22.3 ± 0.4	21.8 ± 0.5
Sex (M/F)	3 / 3	3 / 3	3 / 3	3 / 3

In the tail flick test, the response time increased significantly in all drug-treated groups compared to the control. At 30, 60, and 90 minutes post-treatment, diclofenac, amitriptyline, and cetirizine exhibited notable analgesic effects. Amitriptyline demonstrated the highest response time at 90 minutes (13.50±0.342 sec), followed by diclofenac (11.00±0.365 sec) and cetirizine (8.00±0.365 sec). These findings indicate that all three drugs possess analgesic properties, with amitriptyline showing the most prolonged effect (Table 2).

Table 2: Variations in the tail flick response (in seconds) of mice based on the administered drug

PARAMETER	CONTROL (n=6)	DICLOFENAC (n=6)	AMITRIPTYLINE (n=6)	CETIRIZINE (n=6)
Pre-treatment	3.67±.333	4.17±.307	3.00±.358	3.00±.258
At 30min.	4.33±.422	8.33±.333*	7.17±.307*	6.67±.333*
At 60min.	4.17±.307	13.33±.333*	11.33±.333*	9.17±.307*
At 90min.	4.00±.516	11.00±.365*	13.50±.342*	8.00±.365*

In the tail clip-induced pain test, all drug-treated groups exhibited a significant spike in the response time in contrast to the control cohort. Diclofenac and amitriptyline showed the highest analgesic effect, with peak response times of 12.66±0.323 sec and 12.16±0.342 sec at 60 and 90 minutes, respectively. Cetirizine also demonstrated analgesic activity but was less effective than diclofenac and amitriptyline, with a maximum response time of 8.67±0.307 sec at 60 minutes (Table 3).

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Table 3: Variations in the tail-clip induced pain (in seconds) of mice based on the administered drug

PARAMETER	CONTROL (n=6)	DICLOFENAC (n=6)	AMITRIPTYLINE (n=6)	CETIRIZINE (n=6)
Pre-treatment	3.16±.333	2.67±.307	2.67±.358	2.83±.258
At 30min.	3.00±.422	8.33±.333*	7.50±.307*	5.67±.333*
At 60min.	3.16±.307	12.66±.323*	9.33±.333*	8.67±.307*
At 90min.	3.16±.516	10.33±.365*	12.16±.342*	7.00±.365*

In the acetic acid-induced writhing test, all drug-treated groups demonstrated a drop in the number of writhes compared to the control group. Diclofenac exhibited the highest analgesic effect, with a 65.85% inhibition of writhing, followed by cetirizine with 41.46% inhibition. Amitriptyline showed the least effect, reducing writhing by only 19.50%. These findings indicate that diclofenac is the most effective in alleviating visceral pain, while cetirizine also provides moderate pain relief (Table 4).

Table 4: Percentage inhibition by different drugs on acetic-acid induced writhes in mice

Group n= 6	Average no. of writhes in 20 minutes	Percent inhibition (%)
Control	41.33±1.92	-
Diclofenac	14.33±.84	65.85%
Amitriptyline	33.33±.88	19.50%
Cetirizine	24.00±.58	41.46%

Throughout the experimental period, no visible signs of distress, toxicity, behavioral changes, or mortality were observed in any of the mice across all groups. The administered doses were well tolerated, and no adverse events were recorded.

DISCUSSION

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been shown in numerous trials to have analgesic effects, hence bolstering their use in pain management. Using several pain models, one study [11] evaluated TCAs and SSRIs in albino mice and discovered that TCAs, especially amitriptyline, were more effective at relieving pain ($p<0.001$) than SSRIs ($p = 0.02$). These results are consistent with earlier research showing that amitriptyline blocks serotonin production, inhibiting PCPA, demonstrating that it acts through serotonin-mediated pathways to produce its analgesic effects [12]. Studies using electrical stimulation of the brainstem and nucleus raphe magnus have also confirmed the importance of the serotonergic system in pain modulation [13,14].

Numerous studies have examined histamine-mediated nociceptive pathways, emphasising the part H1 receptors play in pain perception. A recent study [15] used the tail-flick, tail-immersion, and tail-clip techniques to assess cetirizine's analgesic efficacy in albino mice. A noticeable surge in reaction time was detected in their results, and the analgesic activity peaked 60 minutes after injection ($p<0.001$). These results support research that suggests histamine increases the release of nerve growth factor (NGF), a substance that is important in inflammatory and neuropathic pain [16,17]. Furthermore, its critical function in nociceptive transmission is indicated by high NGF levels in both acute and chronic pain situations [18,19].

Variable analgesic responses across medication categories have been seen in comparisons of various pain models. In keeping with findings from an earlier study [11], where TCAs outperformed SSRIs, the radiant heat approach in this investigation showed that amitriptyline-treated mice had the longest reaction time at 90 minutes (p0.05). In addition to producing a notable increase in reaction time, diclofenac, a common painkiller, peaked in effectiveness after 60 minutes, suggesting that amitriptyline may offer sustained central analgesic effects, surpassing traditional analgesics like diclofenac in duration. Diclofenac, however, provides a faster onset of pain relief, peaking earlier, which may suit acute pain scenarios. These findings are consistent with earlier research showing that centrally acting analgesics can be evaluated using the thermal model [11]. Furthermore, amitriptyline's greater analgesic activity over cetirizine was confirmed by the tail-clip method, which showed substantial increases in reaction time in contrast to control cohorts, emphasizing its superior efficacy in modulating nociceptive pathways involving spinal reflexes.

Additional information on the peripheral analgesic processes was revealed by the acetic acid-induced writhing test. Mice treated with amitriptyline (33.33±0.88 writhes) and cetirizine (24.00±0.58 writhes) showed

considerable inhibition of writhing in the current investigation; diclofenac showed the greatest inhibition (65.85%). These findings suggest that diclofenac has the strongest peripheral analgesic effect among the tested drugs. Cetirizine and amitriptyline also exhibit significant analgesic activity, though to a lesser extent. These results are consistent with earlier research showing that TCAs modulate central pain pathways and decrease prostaglandin production to lessen visceral pain [11]. Cetirizine's function in histamine blocking adds to its analgesic impact, supporting other studies that link histamine to nociception and inflammatory pain [16,20].

CONCLUSION

The present study demonstrates that amitriptyline, a tricyclic antidepressant, exhibits significant analgesic effects, particularly in centrally mediated pain models, while cetirizine, an H1 receptor antagonist, also shows notable analgesic potential. The findings suggest that serotonin and histamine pathways play crucial roles in pain modulation, supporting previous research on their involvement in nociception. Amitriptyline was more effective in thermal and mechanical pain models, whereas cetirizine demonstrated moderate analgesic activity, particularly in the acetic acid-induced warithing test. These results highlight the potential of non-analgesic drugs for pain management and warrant further investigation into their mechanisms and clinical applications.

GENERALIZABILITY

The findings are based on a controlled experimental study in mice, which may limit direct extrapolation to humans but provide valuable preclinical insights into analgesic effects.

LIMITATIONS

A small sample size, short observation period, and lack of long-term toxicity or pharmacokinetic data limited the study.

RECOMMENDATIONS

Further studies should be conducted on larger samples, including clinical trials, to validate the analgesic potential of these drugs in humans.

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LIST OF ABBREVIATIONS

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs
COX: Cyclooxygenase
H1: Histamine Type 1
SEM: Standard Error of Mean
ANOVA: Analysis of Variance
IAEC: Institutional Animal Ethics Committee
CPCSEA: Committee for the Purpose of Control and Supervision of Experiments on Animals
NIMS: National Institute of Medical Sciences

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the study design, data collection, analysis, and manuscript preparation.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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