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ORIGINAL ARTICLE

Attenuation of PTZ Induced Generalized Clonic and Myoclonic Seizures by Meloxicam

Kalpana[1], Sayyed Mudasar Hussain[1], Uzair Nisar[1]*, Md. Jamal[2], Shabana Usman Simjee[3]

[1]Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, Ziauddin University Karachi.

[2]Department of Pharmacy, City University of Science and Information Technology, Peshawar, Pakistan.

[3]H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan

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Address of Correspondence:

Email: uzair.nisar@zu.edu.pk

ABSTRACT

Background: Millions of people worldwide suffer from epilepsy, a condition marked by repeated seizures, with about one-third of patients not being well controlled by the antiepileptic medications now on the market. In experimental settings, the Pentylenetetrazol (PTZ) model is frequently employed to cause seizures, offering a framework for assessing possible therapies. Since inflammation is a key factor in the epilepsy etiology, nonsteroidal anti-inflammatory medications (NSAIDs) with specific COX-2 inhibitors like meloxicam may have neuroprotective effects.

Objective: To evaluate meloxicam's anticonvulsant qualities in a mouse model of PTZ-induced seizures is the main aim of this study.

Materials & Methods: Five groups of male NAVAL MEDICAL RESEARCH INSTITUTE(NMRI) mice were established: control, diazepam + PTZ, meloxicam (25 mg/kg) + PTZ, meloxicam (15mg/kg) + PTZ, and PTZ only. Tukey and ANOVA's post-hoc test were used for the statistical analysis of the observed parameters for seizure onset, duration, severity, and post-seizure outcomes.

Results: When compared to the PTZ-only group, meloxicam exhibited improved survival rates, decreased seizure length and severity, and markedly delayed the start of the first myoclonic jerk and generalized seizures. With a 90% survival rate, the high-dose meloxicam group (15 mg/kg) showed the most noticeable effects.

Discussion: In the acute PTZ model, meloxicam significantly reduced the occurrence of generalized clonic and myoclonic seizures, indicating its potent anticonvulsant effects. This outcome is likely due to meloxicam's COX-2 inhibition and TgF beta inhibition, which reduces the neuroinflammation and stabilizes neuronal excitability. By lowering pro-inflammatory prostaglandins that contribute to seizure susceptibility, meloxicam not only modulates seizure activity but may also offer neuroprotective benefits. These findings suggest meloxicam's potential as a therapeutic option in epilepsy.

Conclusion: Meloxicam has demonstrated potential as an anticonvulsant medication in PTZ-induced seizures, indicating the need for additional research into its long-term effectiveness and procedures of action in the epilepsy'streatment.

Keywords: Epilepsy, Pentylenetetrazol (PTZ), Meloxicam, Neuroinflammation, COX-2 inhibitor, Seizure model, Neuroprotection

INTRODUCTION

Epilepsy is a medical disorder that, as statistics have previously outlined, affects millions of people and is marked by prominently appearing seizures. Coming with such situation is the enormous progress made towards the invention of antiepileptic drugs for seizure control, still, one in three or more patients will have seizures suggesting that further drug development is warranted [1]. To elicit seizures in their animal models, researchers frequently employ pentylenetetrazol (PTZ), which is known to induce convulsive and myoclonic seizures, and therefore is a great model for generalized seizures elicitation [2, 3]. This experimental design is important when testing anti-epileptic strategies because it gives a chance to see if the test compounds have malignant-induced convulsions and investigate their potential neuroprotective action.

While previously inflammation had generally been overlooked in studies focused on epilepsy, there has been more recognition of its significance over the last few years. It is known that inflammation within the brain can lead to a more severe seizure intensity and can contribute to epileptogenesis [4, 5]. Nonsteroidal anti-inflammatory drugs have for many years been used to relieve pain, inflammation and fever, which is why studies are being done to find out if they can also provide any relief for cyanosis [6, 7]. It is expected that some drugs may affect the neuroinflammation pathways and hence the progressive nature of the epilepsia conditions [6].

Meloxicam is an NSAID that selectively inhibits COX-2 and primarily used for the treatment of arthritic pain and inflammation, but literature studies reveals that COX-2 inhibitors also involved in many other neurological disorders including epilepsy [8, 9, 10] Meloxicam has been studied previously in the pilocarpine induced model but in the present work we aim to investigate its anticonvulsant activity against PTZ induced seizure. Moreover, we also focus on the anticonvulsant effect of meloxicam on different acute seizure behavior including Generalized ClonicSeizures (GCS),MycolonicSeizure respectively.

Earlier, it has been shown that the application of anti-inflammatory drugs has a tendency to decrease the number of attacks and their severity [8, 9]. Given meloxicam's anti-inflammatory properties, it may lessen seizure intensity and improve outcomes in this acute seizure model [10, 11]. The aim of this study is toexamine the potential of repurposing meloxicam as an antiepileptic medication, providing new insights into its therapeutic possibilities.

MATERIALS & METHODS

Animal Selection & Ethical Compliance

Whereas PTZ stands for Pentylenetetrazole DZP for Diazepam and MLX for meloxicam.

Male mice of the naval medical research institute(NMRI) strain weighing between 25 and 30 grams were used in the research and obtained from an approved animal provider source for the study'spurpose.The mice were kept in a laboratory environment with a regular, alternating pattern of 12 hours of light and 12 hours of darkness in addition to a temperature of 22 °C ± 2°C and humidity from 50 to 60%. These species were able to obtain food and water for the whole period of the investigation. The Ziauddin university (Approved Animal ethical committee number2024-003/KJ/FOP)'s Institutional Animal Care and Use Committee (IACUC) granted all the experimental methods and they were carried out in the laboratory according to ethical principles for use and care of laboratory animals.

Table I: Grouping of treated animals with doses and routes of administration

Groups	Treatment	Dose	Route of Administration
Group-I	Normal saline	0.5 mg/kg	I.P.
Group-II	PTZ	80 mg/kg	I.P.
Group-III	DZP/PTZ	7.5 mg/kg	I.P.
Group-IV	MLX/PTZ	15 mg/kg	I.P.
Group-V	REPSOX+MLX/PTZ	25mg/lg+15 mg/kg+80 mg/kg	I.P.

Experimental Design

Using an acute PTZ seizure paradigm, the trial sought to evaluate the anticonvulsant effects of repurposed medications. Thirty mice in total were categorized into five (5) groups of six (N=6) mice each at random (Table **1**). The hierarchies of the groups were as follows:

Group I: Control Group

To address the injection stress and handling effects in mice, an intraperitoneal (i.p.) injection of 0.2 ml of saline was administered to this group. PTZ or any other test chemical was not given to this group.

Group II: Positive Control (PTZ Only)

To induce seizure, 80 mg/kg was given via intraperitoneal.

Group III: Standard Treatment (Diazepam + PTZ)

This group of mice received diazepam intraperitoneally at a dose of 2 mg/kg 30 minutes before receiving PTZ at a dose of 80 mg/kg. A well-known anticonvulsant called diazepam was used as a reference medication to evaluate the efficacy and validate the seizure model.

Group IV: Test Compound No. 01 (Meloxicam 25 mg/kg + PTZ)

Mice in this group received a 25 mg/kg intraperitoneal injection of meloxicam. Thirty minutes later, PTZ (80 mg/kg) was given to assess the anticonvulsant capability of meloxicam at a reduced dosage.

Group V: Test Compound No. 02 (Meloxicam 15 mg/kg + PTZ)

15 mg/kg dose of meloxicam was given to this group via intraperitonealinjection. In line with Group IV, PTZ (80 mg/kg) was administered 30 minutes following meloxicam administration in order to evaluate the influence of meloxicam's dose-response on seizures caused by PTZ.

PTZ Administration Protocol

On the day of the experiment, pentylenetetrazol (PTZ) was made fresh by dissolving it in saline to the appropriate concentration. All groups received it intraperitoneally (i.p.) at a dose of 80 mg/kg, with the exception of Group I, which served as the control. By using this method, the test compounds' ability to modulate seizures was assessed in relation to both the control and diazepam-treated groups.

Observation and Data Recording

After receiving PTZ, every mouse was housed in a separate observation cage, and for half an hour, their behavior was observed to document any seizures. The following variables were recorded:

Latency to First Clonic Seizure: The interval between the first clonic seizure and the PTZ injection time was noted. This metric made it easier to evaluate how well the treatments worked to postpone the onset of seizures.

Duration of Clonic Seizures: Each mouse's observed total length of clonic seizures was calculated. This information shed light on how severe the seizures were.

Seizure Severity: A modified Racine scale, which rates seizures from stage 0 (no response) to stage 5 (generalized clonic-tonic seizures with loss of posture), was used to assess the seizures severity.

Mortality: To assess the test drugs' ability to prevent seizure-induced mortality, the survival rate of the mice after PTZ-induced seizures was noted.

Data Analysis

All data representation was made via Standard deviation (SD) or mean ± SD. After this, the post-hoc test of Tukey was used to find if the variances among the groups were significant (in the case of one-way ANOVA, the group means). p value less than 0.05 was the threshold for statistical significance. The IBM Corp's SPSS software, version 25, was used forstatistical.

Ethical Approval

In order to ensure conformity to the ethical standards established in the "National Institutes of Health Guide for the Care" and utilization of Laboratory Animals, "Institutional Animal Care and Use Committee" (IACUC) of Ziauddin University(Approved Animal Ethical Committee number 2024-003/KJ/FOP)reviewed and approved all experimental protocols.

RESULTS

Meloxicam'sEffect on PTZ-Induced Seizures in Mice

First Myoclonic Jerk (FMJ)

The control group experienced an early onset of the first myoclonic jerk (FMJ) at 90.84 ± 17.22 seconds after PTZ injection due to the administration of PTZ (80 mg/kg). The onset of FMJ was considerably delayed in mice pretreated with 15 mg/kg of meloxicam; the delay was 1719.17 ± 16.26 seconds ($p < 0.01$). Meloxicam appears to have a significant preventive effect against the initial phases of seizure activity based on this delay (Table **2**).

Hind Limb Tonic Extension (HLTE)

Mice in the control group displayed HLTE, which indicated significant seizure activity, with an average length of 852 ± 12.47 seconds. Pretreated mice with 15 mg/kg of meloxicam did not exhibit any HLTE during the examination period, indicating a significant decrease in the seizures severity ($p < 0.01$). This finding suggests that meloxicam successfully reduces the severity of seizures generated by PTZ (Table **2**).

Table II: Effect of meloxicam on First Myoclonic Jerk (FMJ) and Hind Limb Tonic Extension (HLTE)

Groups	Treatment	Dose	FMJ (Sec)	HLTE (Sec)
Group-I	Normal saline	0.5 mg/kg	0.00	0.00
Group-II	PTZ	80 mg/kg	90.84 ±17.22***	852 ±12.47***
Group-III	DZP/PTZ	7.5+80 mg/kg	0.00	0.00
Group-IV	MLX/PTZ	15+80 mg/kg	1719.17 ±16.26***	0.00
Group-V	REPSOX+MLX/PTZ	25+15+80 mg/kg	1685.84 ±47.32***	0.00

Table III: Effect of meloxicam on Onset of Generalized Seizures (GS)

Groups	Treatment	Dose	Onset of GS (sec)	Frequency of Myoclonic Jerks
Group-I	Normal saline	0.5 mg/kg	0.00	0.00
Group-II	PTZ	80 mg/kg	130±17.22***	5
Group-III	DZP/PTZ	7.5+80 mg/kg	0.00	0.00
Group- IV	MLX/PTZ	15+80 mg/kg	No GCS	1
Group-V	REPSOX+MLX/PTZ	25+15+80 mg/kg	No GCS	1

Onset of Generalized Seizures (GS)

When PTZ was administered to the control group, the average onset time of generalized seizures (GS) was 130 ± 17.22 seconds. Meloxicam (15 mg/kg)-treated mice exhibited a considerable delay in the start of generalized seizures (GS), and no GS was seen during the research period. This result emphasizes how meloxicam may be able to stop seizures from getting worse and leading to more widespread convulsions (Table **3**).

Myoclonic Jerks

Myoclonic jerks occurred five times per session on average in the control group, lasting 22 ± 2 seconds and with an average onset time of 58 ± 2.5 seconds. The group that was administered meloxicam, on the other hand, experienced a decreased frequency of three myoclonic jerks per session, a shorter duration of 17 ± 1 seconds, and a delayed onset of 82 ± 2 seconds ($p < 0.05$). According to Table **3** findings, meloxicam appears to lessen both the frequency and intensity of myoclonic seizures in mice.

DISCUSSION

This study investigated the meloxicam'seffect, a nonsteroidal anti-inflammatory drug (NSAID), on seizures triggered by PTZ in mice. Meloxicam lowered the seizures duration and frequency, improved survival rates in treated mice, and significantly delayed the

onset of both generalized convulsive seizures (GCS)and myoclonic jerks. These data

Survival Rate

The PTZ-only control group had a 0% survival rate, which is indicative of the significant mortality linked to the severe seizure activity that PTZ induces. On the other hand, mice who received meloxicam at a dose of 15 mg/kg showed a considerably better survival rate of 90% ($p< 0.01$). Meloxicam's promise as an anticonvulsant drug is further supported by this significant improvement, which shows that it has a protective effect against PTZ-induced mortality (Figure **1**).

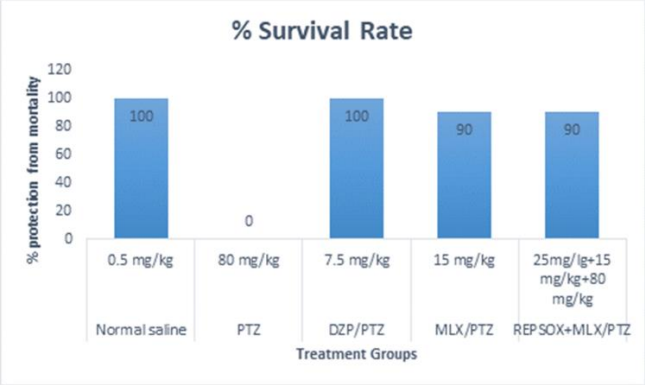

Figure 1. Effect of Meloxicam on Percent Survival Rate

suggested that meloxicam may have anti-convulsant properties, making it effective in the seizures and epilepsy treatment.

Epilepsy is a complicated neurological conditionindicated by spontaneous and repeated seizures. For many years, inflammatory pathways have been linked to epilepsy pathology. Epileptic seizures originate and worsen due to neuro-inflammation, typically triggered by the overexpression of enzymes like COX-2 and pro-inflammatory cytokines [8]. Neuroinflammation can also exacerbate excitability of neurons and reduce seizure thresholds [12, 13]. Due to their anti-inflammatory qualities, NSAIDs have been proposed as prospective adjuvant therapies for epilepsy, particularly for reducing the neuroinflammatory element of the illness [14, 15].

Meloxicam was selected for this research due to its known inflammatory effects in central nervous system (CNS) conditions and its capability to pass through the blood brain barrier [16]. The results of our study are consistent with research suggesting that COX inhibitors can lower seizure occurrence by alleviating inflammation. Studies, on animal epilepsy models have demonstrated that selective COX inhibitors can lessen both the frequency and intensity of seizures. [17, 18].

Our research findings indicate that mice given meloxicam showed a delay, in the start of seizures and involuntary muscle twitches when compared to the group that did not receive the treatment implying that meloxicam could potentially help in stabilizing nerve cells and slowing down the overly excitable condition triggered by PTZ. Meloxicam therapy was observed to reduce the occurrence and length of seizures, confirming its potential anti-convulsant characteristics.

These findings are consistent with prior studies showing that anti-inflammatory medications can lower seizure frequency and severity by blocking inflammation pathways and modifying neurotransmitter systems [19, 20].

Meloxicam significantly increased the survival rate of mice with PTZ-induced seizures in addition to altering the features of seizures. Meloxicam's capacity to preserve neuronal tissue and lessen the overall load of seizures may be the cause of this improvement. Because the medication reduces oxidative stress and excitotoxicity, two major processes that lead to death of neurons in epilepsy, it may be able to lessen seizure-induced neuronal damage [21, 22].

Furthermore, meloxicam's established ability to lowerapoptosis and oxidative stress in models of neuro-degenerative diseases gives validity to the drug's neuroprotective benefits shown in our study [23]. Meloxicam inhibits COX-2, which increases prostaglandin production and neuronal excitability in epilepsy. Meloxicam may thus exert anticonvulsant effects via a number of pathways, including the suppression of oxidative damage and inflammatory mediators [24].

Nonetheless, owing of various research limitations, these results, should be regarded with caution. Although useful for studying the early effects of potential anticonvulsant drugs, the acute seizure model used here may not accurately reflect the chronic nature of epilepsy. Study on safety and long-term efficacy of meloxicam as an antiepileptic agent is needed [25].

CONCLUSION

In conclusion, this work shows that, in the PTZ-induced seizure paradigm in mice, meloxicam may have anticonvulsant effects. Meloxicam exhibits potential as a therapeutic drug for treating seizures by postponing the onset of seizures, decreasing their duration and frequency, and increasing the rate of survival. This effect may be attributed to its neuroprotective and anti-inflammatory properties. Subsequent studies ought to delve more into the possible mechanisms of action of meloxicam and examine its long-term effects in models of chronic epilepsy.

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