
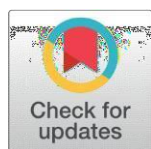


# Evaluation of the anticonvulsant properties of flurbiprofen in pilocarpine-induced convulsions in mice

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## ABSTRACT

**Background and objective:** Flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID), possesses non-selective COX inhibition properties. Some NSAIDs exhibit anticonvulsant effects and provide analgesic benefits for seizure patients. This study aimed to assess the potential anticonvulsant action of flurbiprofen in mice.

**Methods:** Twenty-five mature male mice were divided into five groups for the study. To prevent peripheral cholinergic activation, mice in each group were injected intraperitoneally with atropine sulfate (1 mg/kg) subcutaneously one hour after dosing. Seizures were induced ten minutes later using an intraperitoneal injection of 300 mg/kg of pilocarpine. Following pilocarpine injection, the animals were monitored for 1 hour. Seizure severity was assessed using the Racine scale.

**Results:** Oral administration of flurbiprofen at doses of 0, 10, 20, and 40 mg/kg resulted in a significant decrease in convulsion onset and a substantial reduction in convulsion duration compared to the control group. Flurbiprofen at 20 and 40 mg/kg inhibited seizure scores in pilocarpine-injected mice in a dose-dependent manner. A high dose of flurbiprofen (40 mg/kg) significantly reduced the duration of convulsions, delayed convulsion onset, and decreased seizure scores in mice ( $p < 0.05$ ).

**Conclusions:** Flurbiprofen exhibits significant dose-dependent anticonvulsant activity. Further studies are necessary to determine the primary mechanism of action.

**Keywords** Convulsion, Flurbiprofen, Mice, Pilocarpine

## INTRODUCTION

Epilepsy, a group of severe neurological conditions, is characterized by a propensity for recurrent, unprovoked seizures, or abnormally high levels of synchronous brain waves.<sup>1</sup> There are currently diverse kinds of epilepsy, with temporal lobe epilepsy being one of the

most difficult to treat with medication.<sup>2,3</sup> Status epilepticus (SE), a potentially fatal episode of prolonged seizure activity, can occur in some patients with epilepsy if they are not treated or are not responding to medication.<sup>4,5</sup> Effective seizure control cannot be achieved with the currently available antiepileptic drugs.<sup>6</sup> Despite 20 new drugs being introduced for epilepsy management, the seizure rate has not changed, necessitating additional work to develop more advanced medications to treat epilepsy.<sup>7</sup>

Convulsions associated with nonsteroidal anti-inflammatory drug (NSAID) overdoses have rarely been documented.<sup>8</sup> Flurbiprofen, an NSAID, rapidly crosses the blood-brain barrier, with ibuprofen having a saturable transport component.<sup>9</sup> Plasma protein binding restricts NSAID uptake by the brain by reducing the free amount of NSAID in the bloodstream.<sup>9</sup> Flurbiprofen has various therapeutic effects against pain, inflammation, fever, coagulation, cancer, and Alzheimer's disease, with its mechanism of action mainly attributed to the inhibition of the COX enzyme.<sup>10</sup> Propionic acid's anti-inflammatory and antipyretic properties have been the subject of some studies to treat convulsions associated with fever; however, only ibuprofen has been explored for its antiepileptic effects.<sup>11</sup>

The goal of this study is to investigate the effect of flurbiprofen on pilocarpine-induced convulsions in mice. We hypothesized that flurbiprofen could aid in the development and prevention of convulsions.

## MATERIALS AND METHODS

### Animals

Male mice were acquired from the Laboratory Animal Facility of University of Mosul's College of Veterinary Medicine. The mice were housed in a climate-controlled environment, maintaining a constant temperature of  $22\pm 2^{\circ}\text{C}$  and a 12-hour light/dark cycle, with lights on at 08:00. Animals were placed in plastic cages, with 4 to 6 mice per cage, and provided *ad libitum* access to water and food, except during the experimental procedures.

The protocol for the study was reviewed and approved by the Scientific Committee of the Branch of Physiology, Biochemistry, and Pharmacology at the Faculty of Veterinary Medicine, University of Mosul (Mosul, Iraq).

### Drugs

Flurbiprofen (100mg fortine film-coated tablet, Bilim Pharmaceuticals Industry, Turkey) was dissolved in distilled water and administered orally. Atropine sulfate (VAPCO Product Manufacturing Co. Ltd., Jordan) and pilocarpine hydrochloride (API, Jordan) were diluted in distilled water. These medications were administered intraperitoneally (i.p.) at a volume of 2 ml/kg body weight. Flurbiprofen was given orally 60 minutes prior to the test. Control groups received distilled water in the same manner as the treatment groups.

## Study design

Twenty-five mice were divided into five groups as follows: The 1<sup>st</sup> group, serving as the control, received distilled water orally. The 2<sup>nd</sup> group was administered 1 mg/kg diazepam intraperitoneally and was considered the standard group. The 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> groups were given flurbiprofen orally at doses of 10 mg/kg, 20 mg/kg, and 40 mg/kg, respectively.

## Pilocarpine-induced seizure

One hour after administering the doses to all groups, the mice received a subcutaneous injection of 1 mg/kg atropine sulfate to suppress peripheral cholinergic signaling. Roughly ten minutes later, an intraperitoneal injection of 300 mg/kg pilocarpine was given to induce seizures. The mice were then observed for one hour following the pilocarpine injection.<sup>12</sup> Key parameters recorded included the onset of convulsions, the number of convulsions, and the survival percentage.

The anticonvulsant effects of flurbiprofen were evident through the extended seizure onset time, decreased number of hind-limb extensions, and enhanced protection against death.<sup>13,14</sup> The fatality rate was tracked for 24 hours after the administration of pilocarpine.<sup>15</sup> To safeguard the mice from any adverse effects related to epileptic seizures, each mouse received a 1 mg injection of diazepam upon the experiment's completion. The severity of the convulsions was evaluated using a modified Racine's scale (phases 1-5)<sup>16</sup> with the following classifications: 0 for no reaction; 1 for ear and facial twitching; 2 for myoclonic body jerks; 3 for clonus seizures; 4 for tonic-clonic convulsions; and 5 for generalized clonic convulsions or status epilepticus.

## Statistical analyses

Data were statistically analyzed and expressed as mean  $\pm$  standard error. All data were subjected to one-way analysis of variance (ANOVA), followed by a post-hoc least significant difference (LSD) test for multiple comparisons. A p-value of  $\leq 0.05$  was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc, version 16).

## RESULTS

Pilocarpine-induced convulsions were observed in all groups of mice, but the onset and duration varied between groups. Acute flurbiprofen treatment significantly delayed the onset of convulsion episodes and decreased the number of convulsion attacks compared to the control group ( $p \leq 0.05$ ). Flurbiprofen at 20 and 40 mg/kg reduced the mortality rate by 100% compared to the control group and flurbiprofen at 10 mg/kg (Table 1).

**Table 1**  
Effect of flurbiprofen on pilocarpine-induced convulsion in mice.

Group	Onset of convulsion	Number of convulsions	Survival percentage
Control	7.56±1.30	38.40±4.38	80%
Diazepam (1mg)	11.63±0.84*	23.60±3.60*	100%
Flurbiprofen (10mg)	14.95±1.73*	41.00±3.80 <sup>a</sup>	80%
Flurbiprofen (20mg)	13.00±0.55*	29.60±4.29 <sup>b</sup>	100%
Flurbiprofen (40mg)	14.55±1.94*	21.00±2.54 <sup>*b</sup>	100%

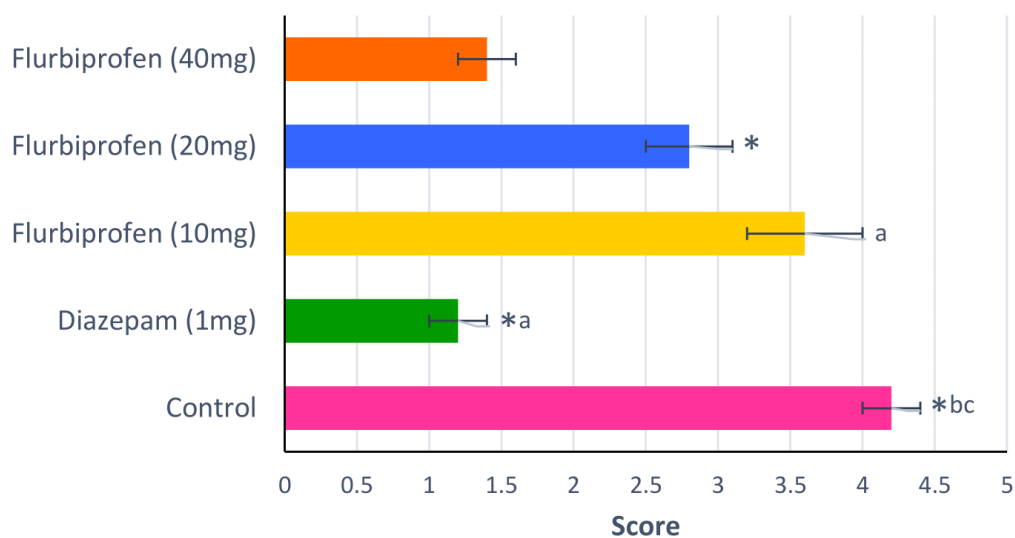
Data presented as (mean±SE), n=5 mice (in each group). \*Meaningfully dissimilar from the control group,  $p \leq 0.05$ . <sup>a</sup>Meaningfully dissimilar from the mean of the diazepam 1 mg/kg group,  $p \leq 0.05$ . <sup>b</sup>Meaningfully dissimilar from the mean of the flurbiprofen 10mg group,  $p \leq 0.05$ .

Seizure scores were significantly attenuated in a dose-dependent manner by flurbiprofen at 20 and 40 mg/kg orally in pilocarpine-injected mice. High-dose flurbiprofen (40 mg/kg) markedly inhibited the seizure score, similar to that of diazepam (Table 2 and Figure 1).

**Table 2**  
Effect of flurbiprofen on seizure score in mice.

Group	Seizure Score
Control	4.2±0.2
Diazepam (1mg)	1.2±0.2*
Flurbiprofen (10mg)	3.6±0.4 <sup>a</sup>
Flurbiprofen (20mg)	2.8±0.3 <sup>*a</sup>
Flurbiprofen (40mg)	1.4±0.2 <sup>*bc</sup>

Data presented as (mean±SE), n=5 mice (in each group). \*Meaningfully dissimilar from the control group,  $p \leq 0.05$ . <sup>a</sup>Meaningfully dissimilar from the mean of the diazepam 1 mg/kg group,  $p \leq 0.05$ . <sup>b</sup>Meaningfully dissimilar from the mean of the flurbiprofen 10mg group,  $p \leq 0.05$ . <sup>c</sup>Meaningfully dissimilar from the mean of the flurbiprofen 20mg group,  $p \leq 0.05$ .



**Figure 1 The anticonvulsant score of flurbiprofen.** \*Meaningfully dissimilar from the control group,  $p \leq 0.05$ . <sup>a</sup>Meaningfully dissimilar from the mean of the diazepam 1 mg/kg group,  $p \leq 0.05$ . <sup>b</sup>Meaningfully dissimilar from the mean of the flurbiprofen 10mg group,  $p \leq 0.05$ . <sup>c</sup>Meaningfully dissimilar from the mean of the flurbiprofen 20mg group,  $p \leq 0.05$ .

## DISCUSSION

Cyclooxygenase 2 (COX-2) has garnered significant attention as a potential target for the creation of analgesic and anti-inflammatory drugs.<sup>17,18</sup> This is in contrast to the ubiquitously expressed cyclooxygenase-1 (COX-1), which plays a vital role in maintaining homeostasis and physiological processes.<sup>19,20</sup> COX-2 is usually present in low amounts, but its activation can occur in response to events such as surgical procedures, injury, convulsions, or infections. This enzyme is a key contributor to inflammation and pain in a wide range of peripheral inflammatory disorders.<sup>21,22</sup> An increasing body of research suggests that COX-2 is also substantially elevated in brain-related conditions linked to injury, including traumatic brain injuries,<sup>23</sup> epilepsy,<sup>24</sup> and ischemic stroke<sup>25</sup>.

Many efforts have been directed towards understanding COX-2's involvement in seizures by modifying its expression or function.<sup>26</sup> Research on the influence of non-steroidal anti-inflammatory drugs (NSAIDs) targeting COX-1 and COX-2 on acute convulsions has been conducted using various rodent models of seizures and epilepsy, yielding mixed outcomes.<sup>26,27</sup> A comprehensive observational study in Taiwan from 2000 to 2011 revealed that long-term NSAID treatments reduced the occurrence of epileptic seizures in individuals with rheumatoid arthritis.<sup>28</sup> The findings of our investigation are consistent with a related study that assessed the anticonvulsant properties of ibuprofen against pentylenetetrazol-induced seizures, demonstrating a reduction in epileptic events in a rat model.<sup>11</sup>

Some studies have indicated that not all NSAIDs possess antiepileptic effects in animal models, particularly paracetamol, which has not demonstrated such an effect.<sup>27</sup> Another study compared the anticonvulsant effects of aspirin and diclofenac, non-selective COX enzyme inhibitors, with selective COX-2 inhibitor Celecoxib in a picrotoxin-induced convulsion model in mice.<sup>29</sup> Celecoxib was found to be more effective as an anticonvulsant. Selective COX-2 inhibitors or nonselective NSAIDs demonstrated positive effects in the pilocarpine epilepsy model, including hippocampal neuroprotection, diminished mossy fiber sprouting, reduced morbidity, and functional mortality.<sup>30-33</sup>

One significant limitation of our study is that we only used the pilocarpine model for inducing convulsions and did not assess the impact of chronic flurbiprofen administration on convulsions. Like any experimental study, ours has limitations, such as not using more than one model to induce epilepsy. We aimed to reduce the number of laboratory animals used in our study in accordance with international recommendations on the ethics of dealing with laboratory animals.

## CONCLUSIONS

The flurbiprofen demonstrates an anticonvulsant effect in a pilocarpine-induced convulsion mouse model, implying that flurbiprofen may be beneficial and potentially effective against febrile seizures, possibly through central COX-2-mediated inhibition.

## LIST OF ABBREVIATIONS

ANOVA= one-way analysis of variance, COX 1= Cyclooxygenase 1, COX 2=Cyclooxygenase 2, LSD= least significant difference, NSAIDs= nonsteroidal anti-inflammatory drug, SPSS= Statistical Package for Social Sciences.

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## DECLARATIONS

### Authors' contributions

Both authors contributed equally to the design, execution, and interpretation of the research, as well as the drafting and revision of the manuscript. All authors approved the final version of the manuscript and are responsible for its content.

### Conflict of interest

The authors declare that they have no potential conflicts of interest.

### Data availability

The data that support the findings of this study are available on request from the corresponding author, ASN.

### Ethical approvals and consent

The official approval for the study protocol was received from the Committee of Postgraduate Studies at the College of Medicine, University of Mosul, Iraq. This approval was in accordance with institutional regulations governing animal handling and use in research.

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No external funding was received for this study.

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