MedPress
Psychiatry & Behavioral Sciences

Flurbiprofen is Effective in Suppressing Inflammatory Pain in Mice

Research Article

Yanming Chen[1], Xinyi Xiao[1] and Jinsong Chen[2]*

[1] Peking University Health Science Center, China

[2] Xuzhou Food and Drug Supervision and Inspection Center, China

***Corresponding author**
Chen J,
Xuzhou Food and Drug Supervision and Inspection Center, Xuzhou 221000, China,
Tel: +8619504491979;
Email: cjs13952205318@163.com

Article Information
Received: 28-December-2023;
Accepted: 03-January-2024;
Published: 05-January-2024.

Abstract

Inflammatory pain is a clinically common but difficult to treat pain condition. Currently, an increasing number of studies are using animal models to evaluate drugs for the treatment of inflammatory pain. Flurbiprofen is a non-steroidal anti-inflammatory drug with analgesic and anti-inflammatory effects. The aim of this study was to investigate the analgesic effects of flurbiprofen (Flurbiprofen) on inflammatory pain in mice. In this study, mouse models of visceral inflammatory pain (acetic acid torsion test), skin inflammatory pain (carrageenan-induced inflammatory pain) and joint inflammatory pain (iodoacetic acid-induced arthritis model) were constructed to simulate human inflammatory pain, and the effects of different doses of flurbiprofen on inflammatory pain in mice were observed. The experimental results showed that flurbiprofen could significantly reduce inflammatory pain in mice, and its analgesic effect was positively correlated with the dose. The results of this study provide new ideas for the treatment of inflammatory pain, and also provide data to support the clinical application of flurbiprofen.

Keywords: Flurbiprofen; Inflammatory pain; Analgesic effect

Introduction

The International Association for the Study of Pain (IASP) defines chronic pain as "pain that lasts longer than the normal tissue healing time (usually 3 months)" [1]. Chronic pain, due to its long duration and prolonged healing, can lead to dysfunction of the patient's body, decrease immunity and induce a variety of complications, and lead to a series of psychological, behavioural, familial and social problems, which seriously affects the patient's quality of life [2]. Chronic pain is one of the most prominent causes of disability worldwide and a major challenge for public health [3]. The presence of inflammation is a common underlying mechanism of chronic pain [4]. In recent years, the treatment of inflammatory pain has been a hot topic in clinical medical research.

Existing guidelines recommend paracetamol (acetaminophen) as a first-line analgesic. However, this is not ideal for chronic inflammatory pain as paracetamol lacks anti-inflammatory activity [5]. Flurbiprofen is an NSAID that has both analgesic and anti-inflammatory properties [6]. Compared with other NSAIDs, flurbiprofen has relatively few side effects and is widely used [7]. In recent years, flurbiprofen has gradually gained attention as a therapeutic agent for inflammatory pain. It has been shown that flurbiprofen can exert analgesic effects by inhibiting prostaglandin synthesis and release, reducing the production of inflammatory mediators and neuronal sensitivity to them, such as post-surgical pain and arthritis pain [7-9]. However, studies on the analgesic effect of flurbiprofen on inflammatory pain in mice are limited and the results are controversial. Therefore, the present study aimed to investigate the analgesic effect of flurbiprofen on inflammatory pain in mice, to provide scientific basis and data support for the application of this drug as a therapeutic agent for inflammatory pain, and also to provide reference value for further research on the therapeutic effect of flurbiprofen on other types of pain.

Material and Methods

Animals

Seventy-two 6- to 8-week-old ICR mice (weighing 20-30 g, both males and females) were purchased from Dongfang Breeding Co. Ltd, Pizhou City, Jiangsu Province (Xuzhou, China), and were housed at room temperature in an SPF-grade animal house, with regular alternation of day and night (12 h/12 h), and were given adequate water, food, and free space to move around. Experiments were conducted after 5 days of acclimatisation.

Drug Preparation and Administration

Flurbiprofen (batch number: 100725-200401, purity ≥98%) (Flurbiprofen, Flu) was purchased from Aladdin Reagent (Shanghai) Co. Ltd. in a volume of 0.1 mL/10 g. Saline was given to the control group. Acetic acid (batch no.: 20211205, analytically pure) was purchased from Tianjin Yongda Chemical Reagent Co. Ltd; carrageenan (batch no.: L10017, 98% pure) was purchased from Shanghai Blue Season Science and Technology Development Co. Iodoacetic acid (Batch No. A12410, purity 98%) was purchased from Shanghai Anegi Chemical Co.

Visceral Inflammatory Pain (acetic acid torsion test)

ICR mice were weighed and randomly grouped (blank control group, flurbiprofen 20 mg/kg, flurbiprofen 50 mg/kg, flurbiprofen 100 mg/kg), 8 mice in each group. Mice in each group were injected intraperitoneally with 1% acetic acid solution 0.5 h after the drug was given by gavage, and the number of twisting of the mice 0-45 min after the injection of acetic acid was observed and recorded as a means of analysing the inhibitory rate of flurbiprofen on inflammatory pain of the viscera. The mice showed characteristic responses such as inward concavity of the abdomen, elongation and twisting of the trunk, elevation of the buttocks, and extension of the hind limbs, which were recorded as one torsion response [10].

Inhibition rate = [(average number of twists in blank control group - average number of twists in drug treated group)/average number of twists in blank control group] × 100%.

Inflammatory Pain in the Skin (Carrageenan Gum-Induced Inflammatory Pain)

Mice were randomly divided into blank group, model group, flurbiprofen 20 mg/kg, flurbiprofen 50 mg/kg, flurbiprofen 100 mg/kg, 8 mice in each group. In a quiet room, the mice were placed in a test chamber on an elevated metal grid, and after the mice were acclimatised for 30 min, the pre-modelling baseline values (Baseline) were measured using a plantar mechanical pinprick pain system, model SA708 (Jiangsu Saiance Biotechnology Co., Ltd.). Then 1% carrageenan gum (20 µL) was injected into the subcutaneous tissue of the plantar foot of the right hind paw using a 1710 TLL Hamilton micro syringe and a 301/2-gauge needle, and waited for 3 h. Different compounds or saline were given to the mice by gavage after the foot was sufficiently swollen, and the thresholds of mechanical reduction of the foot were measured at the five time points of 30, 60, 90, 120, and 180 min after the administration of flurbiprofen, in order to analyse the Inhibition rate of flurbiprofen on inflammatory skin pain [11]. Inhibition rate == [(Maximum mechanical foot reduction threshold after flurbiprofen administration - Post-modelling baseline)/(Pre-modelling baseline - Post-modelling baseline)] × 100%.

Inflammatory Pain in Joints (Iodoacetic Acid-Induced Arthritis Model)

Mice were anaesthetised by tail vein injection of etomidate emulsion (2 mg/kg, 0.1 mL/10 g), fixed in the supine position on a wooden board, with the knee joints shaved and flexed at an angle of 90°, and then iodoacetic acid (20 µL, 10 mg/mL) dissolved in saline was injected into the knee joint space [12]. The pre-modelling baseline (Baseline) of the mice was determined before injection of iodoacetic acid, and the post-modelling baseline (Pre-Flu) of the mice was recorded at 24 h after injection of iodoacetic acid. Briefly, a SA708 plantar mechanical needle was lifted and a linearly increasing force was applied to the hind paw of the mice, and a stop signal was automatically obtained when the animal removed the paw , and the threshold of foot reduction after mechanical stimulation was automatically recorded in grams. Each group (blank group, model group, flurbiprofen 20 mg/kg, flurbiprofen 50 mg/kg, flurbiprofen 100 mg/kg) was given the therapeutic drug by gavage, and the blank control group was given an equal volume of saline by gavage. Subsequently, the inhibition rate of flurbiprofen on inflammatory joint pain was analysed by determining the mechanical foot-shrinkage threshold of the mice in each group at 30, 60, 90, 120 and 180 minutes after the administration of the drug.

Inhibition rate == [(Maximum mechanical foot reduction threshold after flurbiprofen administration - post-modelling baseline)/(pre-modelling baseline - post-modelling baseline)] × 100%.

Data processing

Data were expressed as mean ± S.E.M. and analysed by GraphPad Prism 9.3 (San Diego, CA, USA). The trapezoidal rule was applied to calculate the area under the time course curve (AUC). Multiple comparisons were analysed using one-way or two-way ANOVA followed by Dunnett's test for multiple comparisons.

Results

Analgesic Effects of Flurbiprofen in an Acetic Acid-Induced Torsional Pain Model

Mouse acetic acid torsion test is a pain experimental model used to evaluate the analgesic activity of a variety of different mechanisms and links of analgesic drugs have positive results, commonly used in the preliminary screening of analgesic active components of the experimental research, with high sensitivity, stability and other advantages [13,14]. There was no significant difference in the body weight of the mice in each group before the acetic acid torsion experiment, and the average number of torsions in the blank control group (saline group) was 69.5 times. The experimental results are shown in Figure 1, compared with the blank control group, flurbiprofen (20 mg/kg, 50 mg/kg, 100 mg/kg) inhibited the number of mouse torsion in a dose-dependent relationship, and the mean number of torsion in the low, medium and high dose groups was 53.33, 27.83 and 13.50 times, with %MPE of 23.26%, 59.95% (**** P < 0.001), 80.58% (**** P < 0.0001).

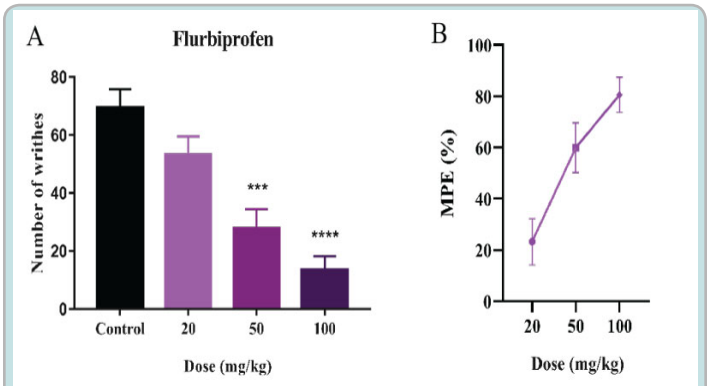

Figure 1: Effect of flurbiprofen on the number of twists in mice. ***P < 0.001, ****P < 0.0001 vs. Control. Comparison was made by one-way ANOVA followed by Dunnett's test. The data are expressed as the mean ± SEM; n=8.

Analgesic Effect of Flurbiprofen in Carrageenan-Induced Inflammatory Pain Model

Plantar subcutaneous injection of carrageenan has also been widely used to produce a model of local inflammatory pain. Subcutaneous injection of plantar carrageenan into experimental animals results in a series of responses similar to acute inflammation in humans, including local capillary dilation, increased vascular permeability, exudation, and oedema; because of the stability and reproducibility of this model, it has been commonly used to screen for anti-inflammatory pain medications [15]. Animals show early pain responses such as foot licking and foot lifting, followed by persistent mechanical pain sensitisation [16]. Prior to carrageenan gum injection to induce inflammation,

the mechanical foot-shrinkage thresholds of the mice were measured every 10 minutes until three stable readings were obtained. The mechanical foot-shrinkage threshold of mice was significantly reduced at 3 hours after 1% carobacillin injection. Subsequently, the mechanical foot-retraction thresholds of each group were determined in each mouse at 30, 60, 90, 120, and 180 min after flurbiprofen gavage, and the mean values were calculated and plotted as time-response curves as shown in Figure 2. Flurbiprofen (20 mg/kg, 50 mg/kg, 100 mg/kg) reversed the mechanical hypersensitivity behaviour in a dose-dependent relationship, and the analgesic effects of the low, medium and high dose groups were 34.06%, 53.28% and 81.35%, respectively.

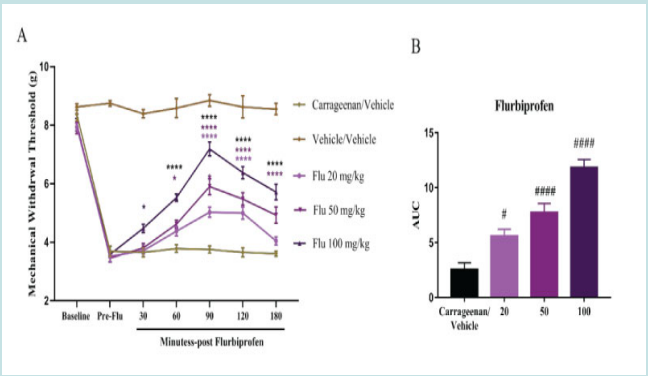

Figure 2: Analgesic effects of flurbiprofen in a carrageenan-induced inflammatory pain model. *P < 0.05, ****P < 0.0001 vs. carrageenan/vehicle by two-way ANOVA followed by Dunnett's test (A). #P < 0.05, ####P < 0.0001 vs. carrageenan/vehicle by one-way ANOVA followed by Dunnett's test (B). Data are shown as the mean ± S.E.M (n = 8).

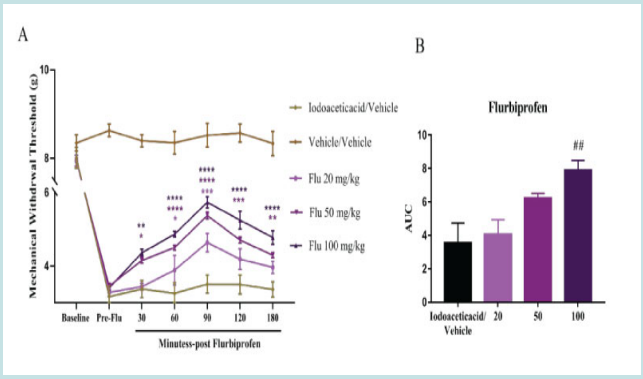

Figure 3: The anti-nociceptive effects of flurbiprofen in iodoaceticacid-evoked osteoarthritis model. *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001 vs. iodoaceticacid/vehicle by two-way ANOVA followed by Dunnett's test (A). ##P < 0.01 vs. iodoaceticacid/vehicle by one-way ANOVA followed by Dunnett's test (B). The data are expressed as the mean ± SEM (n = 8).

Analgesic Effects of Flurbiprofen in a Model of Iodoacetic Acid-Induced Osteoarthritis

Intra-articular injection of iodoacetic acid into the joints of animals is a recognised and effective method of inducing osteoarthritis. iodoacetic acid is an inhibitor of glyceraldehyde-3-phosphate dehydrogenase activity, which induces chondrocyte cell death and thus produces cartilage damage, with loss of proteoglycan matrix and functional joint damage similar to that seen in human osteoarthritis. As shown in Figure 3, there were no significant differences in mechanical foot reduction thresholds between groups of animals before injection of iodoacetic acid into mouse knee joints. Compared with the pre-modelling baseline, at 24 hours after iodoacetic acid injection, the mechanical foot reduction thresholds of the mice were significantly lower, indicating that inflammatory mechanical allodynia had occurred. Flurbiprofen was able to reverse mechanical hypersensitivity behaviour in a dose-dependent relationship (Figure 3A), with results expressed as AUC (Figure 3B). In the flurbiprofen group, the analgesic effect of low, medium and high doses of 20, 50 and 100 mg/kg was 29.13%, 42.79% and 51.38%, respectively.

Discussion

Chronic pain lasts for a long time and seriously affects patients' ability to perform their daily tasks and quality of life, as well as affecting their mental state and creating a global healthcare burden [17]. Inflammatory pain is one of the most common forms of chronic pain, and the three organ systems that are particularly susceptible to inflammatory pain are viscera, skin and joints [18]. In this study, we investigated the analgesic effect of flurbiprofen in visceral inflammatory pain (acetic acid torsion test), cutaneous inflammatory pain (keratan gum-induced inflammatory pain), and joint inflammatory pain (iodoacetic acid-induced arthritis model).

The results of this study showed that flurbiprofen could significantly reduce the degree and duration of inflammatory pain in mice, and the analgesic effect was positively correlated with the dose, i.e., as the dose of flurbiprofen was increased, its analgesic effect was also gradually increased, and the pain behaviour of the mice was significantly improved. This is due to the fact that the higher dose can inhibit the production of more prostaglandins, thus reducing the production of relevant inflammatory mediators and the sensitivity of neurons to them, and thus achieving better analgesic effects.

Although the results of the present study showed that flurbiprofen alone has been able to significantly reduce the degree and duration of inflammatory pain in mice, the analgesic effect of flurbiprofen may be further exerted by the combined application of other drugs under certain circumstances. For example, the combination of drugs with analgesic effects, such as opioids, may improve the analgesic effect of flurbiprofen and also reduce its adverse effects.

While the inflammatory pain model used in this study is highly reproducible and comparable, there are some differences from the actual human inflammatory conditions. Therefore, in future studies, different types of inflammatory pain models should be compared and evaluated in more detail to more accurately assess the therapeutic effects of flurbiprofen on different types of pain.

Conclusions

The results of this study showed that flurbiprofen, as a non-steroidal anti-inflammatory drug, has a good analgesic effect and can significantly reduce the degree and duration of inflammatory pain in mice. This provides a scientific basis and theoretical support for its application in the treatment of inflammatory pain. Meanwhile, the methods and techniques used in this study can also provide references for the study of other types of pain treatment drugs, which can help to explore their mechanism

of action and therapeutic effects in depth and provide a more scientific theoretical basis for clinical application.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, et al. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 161: 1976-1982.

2. Ho KY, Gwee KA, Cheng YK, Yoon KH, Hee HT, et al. (2018). Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice. Journal of Pain Research. 2018: 1937-1948.

3. Ilari S, Giancotti L A, Lauro F, Dagostino C, Gliozzi M, et al. (2020). Antioxidant modulation of sirtuin 3 during acute inflammatory pain: The ROS control. Pharmacological Research. 157: 104851.

4. Yam MF, Loh YC, Tan CS, Adam SK, Manan NA, et al. (2018). General pathways of pain sensation and the major neurotransmitters involved in pain regulation. International Journal of Molecular Sciences. 19: 2164.

5. Brauer S. (2012). Hand, hip, and knee osteoarthritis. Journal of Physiotherapy. 58: 203.

6. Buisseret B, Guillemot-Legris O, Ben Kouidar Y, Paquot A, Muccioli GG, et al. (2021). Effects of R-flurbiprofen and the oxygenated metabolites of endocannabinoids in inflammatory pain mice models. The FASEB Journal. 35: e21411.

7. Sun M, Cong X, Chang E, Miao M, Zhang J, et al. (2020). Efficacy of flurbiprofen for postoperative pain in Chinese surgical patients: a meta-analysis. Journal of Surgical Research. 252: 80-88.

8. Li M, Zhang K, Li T, Chen Y, Znag H, et al. (2023). Sciatic Nerve Block Combined with Flurbiprofen Inhibits Spinal Cord Inflammation and Improves Postoperative Pain in Rats with Plantar Incision. Journal of Pain Research, 2023: 1533-1546.

9. Li P, Li H, Shu X, Wu M, Liu J, et al. (2020). Intra-articular delivery of flurbiprofen sustained release thermogel: improved therapeutic outcome of collagenase II-induced rat knee osteoarthritis. Drug Delivery. 27: 1034-1043.

10. Mansouri M T, Naghizadeh B, Ghorbanzadeh B. (2015). Ellagic acid enhances the antinociceptive action of venlafaxine in mouse acetic acid-induced pain: An isobolographic analysis. Pharmacological Reports. 67: 473-477.

11. Teng B, Song Y, Zhang F, Ma T-Y, Qi J-L, et al. (2016). Activation of neuronal Kv7/KCNQ/M-channels by the opener QO58-lysine and its anti-nociceptive effects on inflammatory pain in rodents. Acta Pharmacologica Sinica. 37: 1054-1062.

12. Bishop T, Hewson DW, Yip PK, Fahey MS, Dawbarn D, et al. (2007). Characterisation of ultraviolet-B-induced inflammation as a model of hyperalgesia in the rat. Pain. 131: 70-82.

13. Tsai PY, Lin KC. (2015). Insight into the photodissociation dynamical feature of conventional transition state and roaming pathways by an impulsive model. The Journal of Physical Chemistry A. 119: 29-38.

14. Carneiro JG, Rodrigues JAG, de Sousa Oliveira Vanderlei E, Souza RB, Quindere ALG, et al. (2014). Peripheral Antinociception and Anti-Inflammatory Effects of Sulphated Polysaccharides from the Alga Caulerpa mexicana. Basic & Clinical Pharmacology & Toxicology. 115: 335-342.

15. Karthikeyan R. (2020). Analgesic and Anti-Inflammatory Activity Screening of Ethanolic Extract of Chromolaena Odorata Root. RVS College of Pharmaceutical Sciences, Coimbatore.

16. Annamalai P, Thangam EB. (2022). Vitex trifolia L modulates inflammatory mediators via down-regulation of the NF-κB signaling pathway in carrageenan-induced acute inflammation in experimental rats. Journal of Ethnopharmacology. 298: 115583.

17. Turk DC, Fillingim RB, Ohrbach R, Patel KV. (2016). Assessment of psychosocial and functional impact of chronic pain. The Journal of Pain, 17: T21-T49.

18. Burma NE, Leduc-Pessah H, Fan CY, Trang T. (2017). Animal models of chronic pain: advances and challenges for clinical translation. Journal of Neuroscience Research. 95: 1242-1256.

Citation: Chen Y, Xiao X and Chen J. Flurbiprofen is Effective in Suppressing Inflammatory Pain in Mice. Medp Psychiatry Behav Sci. 2023; 3(2): mppbs–2023120001.