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Flurbiprofen: Determination of safety profile, analgesic effect, and interaction with lipoic acid in murine

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Abstract

our study aimed study aimed to detect and investigate the safety profile of flurbiprofen and evaluate the analgesic effects of the tail immersion and writhing tests, as well as its interaction with lipoic acid as an analgesic for visceral pain in mice. The up-and-down manner described by Dixon was utilized to determine the median lethal dose (LD_{50}) and the median analgesic dose (ED_{50}), the safety criteria were calculated, mathematical equations were applied, and the interaction between flurbiprofen and alpha-lipoic acid was evaluated using the writhing test. The LD_{50} of oral flurbiprofen was 1147.4 mg/kg, and the ED_{50} of oral flurbiprofen was 8.6 mg/kg using the tail immersion test. The therapeutic index was 133, and the standard safety margin was 35%. The highest analgesia time was one h after dosing, which faded after 24 h. Administration of flurbiprofen 10, 20, and 40 mg/kg had an analgesic effect in a dose-dependent manner. Flurbiprofen relieved visceral pain when dosed at 20, 40, and 80 mg/kg, with analgesic efficacies of 53, 56, and 65%, respectively. The simultaneous administration of flurbiprofen and alpha-lipoic acid had a synergistic analgesic effect on visceral pain. From our results, we conclude that flurbiprofen has a wide range of safety and is an effective analgesic for peripheral and visceral pain. The synergistic effect between flurbiprofen and alpha-lipoic acid may have clinical benefits, including reducing the dose of flurbiprofen when used together.

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Introduction

Flurbiprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. However, its analgesic activity was for mild to moderate pain, similar to other NSAIDs, and it has recently been clinically used to treat various neoplastic nociception (1). Flurbiprofen is a non-selective cyclooxygenase inhibitor, both centrally and peripherally, which results in the cutoff of the sequence of inducible and housekeeping prostaglandins from arachidonic acid (2). In addition, flurbiprofen inhibits the nuclear factor (NF-κB) and activator protein 1 (AP-1) (3). The pharmacological effects of steroidal anti-inflammatory drugs are attributed to the inhibitory effects of NF-κB, either by direct interaction with the NF-κB p65 subunit (4) or by increasing transcription of its inhibitor (I-κB-α) (5). Pharmacokinetic data on flurbiprofen has been studied in various animal models and humans (6,7); however, it is well absorbed orally, reaching a maximum concentration in the blood in approximately 1.5 hours (range 0.5-4 hours) (8,9). Flurbiprofen was eliminated within 24 hours of the last administered dose (10). Alpha-lipoic acid is an antioxidant agent that has a clinical benefit in treating neuropathic disorders, especially in patients with diabetes (11). Lipoic acid has potent painkiller efficacy for mild pain (12), an anti-chronic inflammation effect (13), a hypothermic effect (13), and a depression effect on the CNS of poultry (14), and alpha-lipoic acid can treat hepatic and renal damage caused by diclofenac (15).

This study aimed to evaluate the therapeutic index of flurbiprofen, as well as the analgesic effects of two different methods for assessing analgesia in peripheral and visceral pain and its interaction with alpha-lipoic acid in mice.

Materials and methods

Animals and ethical approval

Male Swiss albino mice weighing 25-32 g were purchased from the laboratory animal house of the Faculty of Veterinary Medicine. Mice were housed at a temperature of 20±2°C with a 12/12 hours light/dark cycle, with water and food ad libitum. The Scientific Committee ethically approved this study by the Physiology, Biochemistry, and Pharmacology Department. It is worth noting that this study is a part of my master's thesis.

Drugs and solvent

Flurbiprofen (Fortine®) was purchased from the local market as a tablet (100 mg) and was dissolved in distilled water. Alpha-lipoic acid (Lipoic-Forte by AMS®) in the form of a dry capsule (600 mg) was dissolved in propylene glycol (Sigma Chemical Co. 99%). Acetic acid (Sigma Chemical Co., 99%) was diluted to 1% with distilled water.

Calculation of the median lethal dose of flurbiprofen when administered orally in up-down manner

The median lethal dose for oral administration of flurbiprofen by the up-and-down method was previously described by Dixon (16), and the mice were individually checked for 24 h for the onset of signs of acute toxicity and death. The initial dose (800 mg/kg) was selected based on a preliminary study and previous studies.

Calculation of the median effective dose for analgesia of flurbiprofen in tail immersion test by the up-down method

The up-and-down approach was used to calculate the median analgesic effective dose of flurbiprofen for oral administration, and five male mice were used in the tail immersion test (17), the principle of which is the thermal stimuli by hot water in a water bath. At the beginning of the heat adjustment in 55-56 of the water bath then, we hold the mice gently and immerse two-thirds of the tail in a water bath and record by stopwatch the time in milliseconds required to withdraw the tail in response to thermal pain then, we oral administered this mouse an initial dose of flurbiprofen (10 mg/kg), after half hour we re-examination the pain response in a water bath, if there is an increase in withdrawal time this mean analgesic effect began and give this mouse symbol (X) if not (0).

Measurement of flurbiprofen safety indices

The following equations were used to interpret and extrapolate the safety of flurbiprofen based on the calculated ED_{50} and LD_{50} values: Therapeutic index T I = LD_{50} /ED_{50} (higher TI values are associated with a safe drug); standard safety margin SSM = (LD_1 /ED_{99} - 1) × 100 (LD_1 is the lowest lethal dose in 1% of the experimental sample, and ED_{99} is the lowest dose required to produce a therapeutic effect in 99% of the experimental sample; higher SSM values are associated with greater drug safety) (18).

Determination of the best time for analgesia after a single dose of flurbiprofen

Six male mice were used and orally administered flurbiprofen at 10 mg/kg body weight. The time required to withdraw the tail was measured in the tail immersion test at zero and 0.5, 1, 2, 4, and 24 hours.

Determination of the dose-response relationship after multiple doses of flurbiprofen

Twenty male mice were separated into four groups and treated with flurbiprofen at 0 (distilled water), 10, 20, and 40 mg/kg body weight orally. The time required to withdraw the tail was measured in the tail immersion test after an hour of administration for each mouse in all groups.

The analgesic activity of flurbiprofen in the visceral pain model-writhing method

Twenty mice were divided into four groups. The 1st group: was administered distilled water orally (control). The 2nd group: flurbiprofen at 20 mg/kg orally. The 3rd group: flurbiprofen at 40 mg/kg orally. The 4th group: flurbiprofen at 80 mg/kg orally. One hour after dosing in all groups, mice were intraperitoneally injected with acetic acid (1%) at 0.01 ml, and the onset and number of writhing events for 30 min were calculated (19).

Determination of the antinociceptive impacts after coadministration of flurbiprofen and lipoic acid in the visceral pain model-writhing method

Twenty mice were used and divided into four groups. The 1st group: was orally dosed with distilled water (control). The 2nd group: flurbiprofen at 20 mg/kg orally. The 3rd group: lipoic acid at a dose of 100 mg/kg orally. The 4th group: flurbiprofen at 10 mg/kg and lipoic acid at 50 mg/kg orally. An hour after the dosing of all groups, mice were injected with acetic acid (1%) at 0.01 ml intraperitoneally; the onset and the number of writhing for 30 minutes were calculated.

Data Analytics

The statistical software package SPSS (IBM, version 16.0) was employed for statistical data analysis. Data were analyzed using one-way ANOVA, accompanied by the least significant difference test. Data are presented as mean + SE standard error, $p \leq 0.05$, regarded as statistically significant.

Results

Calculation of the median lethal dose of flurbiprofen when administered orally by the up-down method

The median lethal dose of flurbiprofen was 1147 mg/kg orally, and the mice showed signs of acute poisoning within 5-15 minutes of dosing. These signs were characterized by lethargy, increased respiration, and Straub tail, which ended in nervous convulsions and death (Table 1).

Calculation of the median effective dose for analgesia of flurbiprofen in tail immersion test by the up-down method

To find the median analgesic dose of flurbiprofen in mice, a tail immersion test was used for five mice, and the median analgesic dose was 8.6 mg/kg body weight (Table 2).

Table 1: Median Lethal Dose (LD_{50}) of oral flurbiprofen by up and down method

Variables	Results
LD_{50}	1147.4 mg/kg
The average of the doses administered	1200-800=400 mg/kg
Primary dose	800 mg/kg
Last dose	1000 mg/kg
Increase or decrease in the dose	200 mg/kg
No. of chicks and their symbols	(OOXOXO) 6
The onset of toxicity signs	5-15 minutes
Sings of toxicity	Lethargy, increased respiration, Straub tail, nervous convulsions and death

X: Death, O: Live, The LD_{50} was determined by the up-and-down manner.

Table 2: Median Effective Dose (ED_{50}) of orally flurbiprofen by tail immersion test

Variables	Results
ED_{50}	8.6 mg/kg
Average of the doses utilized	10-8=2 mg/kg
First dose	10 mg/kg
Last dose	10 mg/kg
Increment or decrement in the dose	2 mg/kg
No. of chicks and their symbols	(XOXOX) 5

X: Positive response of antinociception, O: Negative response of antinociception, The ED_{50} were determined by the up-and-down manner.

Measurement of flurbiprofen safety indices

The results of the third experiment, wholly dependent on the results of the first and second experiments, were as follows: the values of safety parameters were dependent on the application of equations, where the therapeutic index was 133, meaning doubling the median effective dose 133 times to kill 50% of mice, and the standard margin of safety was 35% (Table 3).

Determination of the best time for analgesia after a single dose of flurbiprofen

Flurbiprofen at10 mg/kg produces an analgesic effect after an hour of oral administration, which is expressed as a significant increase in the tail-raising period compared with the tail-raising time at time zero. When comparing the pain threshold after 24 h of oral administration of flurbiprofen, we noticed that the analgesic effect faded compared to time 1 and 2 h, and we demonstrated that the highest analgesic impact was one hour after the treatment (Table 4).

Table 3: Flurbiprofen drug safety as measured by safety indices

Measurement times	The time required to withdraw immersed tail from hot water bath (sec)
0	3.30±0.19
0.5	3.57±0.15
1	4.37±0.18 *ab
2	4.13±0.14 *b
4	3.87±0.23
24	3.26±0.33

Values are mean ± SE of 6 mice/time. *The value varies significantly with time zero, $P \leq 0.05$. a the value varies significantly with the time half an hour, $P \leq 0.05$. b the value varies significantly with time 24 hours, $P \leq 0.05$.

Table 4: Determination of the best time for analgesia after a single dose of flurbiprofen

Safety index	Parameters
Therapeutic index	133
Standard safety margin	35%

Determination of the dose-response relationship after multiple doses of flurbiprofen

Flurbiprofen at 10, 20, and 40 mg/kg produced an analgesic effect after an hour of oral administration, which was expressed as a significant increase in the tail-raising

period compared to the control group. The analgesic efficacy percentages were 26, 33, and 37% respectively (Table 5).

The analgesic activity of flurbiprofen in the visceral pain model-writhing method

Flurbiprofen at 20, 40, and 80 mg/kg produced an analgesic effect after an hour of oral administration, which was expressed as a significant dose-dependent increase in the onset of writhing compared to the control group. Furthermore, there was a significant decrease in the number of writhing events compared to that in the control group. The analgesic efficacy percentages were 53, 56, and 63% respectively (Table 6).

Determination of the analgesic activity of flurbiprofen and Alpha-lipoic acid coadministration in the visceral pain model-writhing method

The combination of flurbiprofen 10 mg/kg + alpha-lipoic acid 50 mg/kg produced a synergistic analgesic effect, with a significant decrease in the writhing response number in comparison with the control, flurbiprofen 20 mg/kg, and alpha-lipoic acid 100 mg/kg groups. Flurbiprofen used alone at a dose of 20 mg/kg produced significant analgesic, with the writhing number reduced to 61.4±1.40 during the 30 min period, while Alpha-lipoic acid 100 mg/kg reduced the writhing number to 77.0±1.58, compared with control 102.0±4.64 (Table 7).

Table 5: Determination of the dose-response relationship after multiple doses of flurbiprofen

Groups	Latency to lift tail (seconds)	Percentage of Analgesic efficacy
Control	3.61±0.45	-
Flu 10mg/kg	4.88±0.28*	26%
Flu 20mg/kg	5.38±0.14*	33%
Flu 40mg/kg	5.76±0.24*	37%

Values are mean ± SE of 5 mice/time. * Significantly different from the control data, P≤0.05. a Significantly different from the data of the flurbiprofen 20 mg/kg group, P≤0.05.

Table 6: The analgesic activity of flurbiprofen in the visceral pain model-writhing method

Groups	The onset of writhing (seconds)	Numbers of writhing	Percentage of Analgesic efficacy
Control	1.4±0.25	112.0±12.81	-
Flu 20mg/kg	4.0±0.45*	53.2±5.30*	53%
Flu 40mg/kg	5.4±0.60*	49.8±1.72*	56%
Flu 80mg/kg	5.6±0.68*a	41.6±0.68*	63%

Values are mean ± SE of 5 mice/group. * Significantly different from the control data, P≤0.05. a Significantly different from the data of the flurbiprofen 20 mg/kg group, P≤0.05.

Table 7: Analgesic activity of flurbiprofen and Alpha lipoic acid coadministration in the visceral pain model-writhing method

Groups	Onset of writhing (seconds)	Numbers of writhing	% Analgesic efficacy
Control	1.2±0.52	102.0±4.64	-
Flu 20mg/kg	4.4±0.24*	61.4.4±1.40*	40 %
ALA 100mg/kg	3.8±0.37*	77.0±1.58*a	25 %
Flu 10mg/kg+ ALA 50mg/kg	5.2±0.37*b	53.4±3.98*b	49 %

Values are mean ± SE of 5 mice/time. * Significantly different from the control data, P≤0.05. a Significantly different from the of the flurbiprofen 20 mg/kg group, P≤0.05. b Significantly different from the data of the Flu 10mg/kg+ ALA 50mg/kg group, P≤0.05.

Discussion

One of the most important factors that must be taken into account when researching drugs is to determine the median lethal dose (20), through which you will have an idea of the doses that can be used. We determined the median lethal dose of flurbiprofen using the up-and-down method, which is considered the most ethical method in this approach because a minimum number of animals have been used compared with other approaches (21). The LD_{50} of flurbiprofen in mice was 1147.4 mg/kg orally, which is higher than that in other studies that determined the LD_{50} of flurbiprofen at 640 mg/kg orally in mice, and the reason for its higher value may be attributed to the difference in the method of determination of LD_{50}. Based on the material safety data for flurbiprofen, the oral LD_{50} in mice, rats, and rabbits was 640, 117, and 290 mg/kg, respectively, whereas the percutaneous LD_{50} in rabbits was 500 mg/kg. The tail immersion test and tail-flick response were used previously for the evaluation of the analgesic effect of NSAIDs in mice (22) and rats (23); therefore, we used this reliable method to determine the median effective dose of flurbiprofen analgesia, which was 8.6 mg/kg orally, and it was close to the median analgesic dose of flurbiprofen in rats which was 7.2 mg/kg orally) (23). After determining the safety index criteria, flurbiprofen appears to be a safe drug, but its adverse effects have not been fully studied in our research. Our findings refer to the peak analgesic effect after the hour, six mice that were orally administered flurbiprofen at 10 mg/kg, which is in agreement with studies that indicated that the

blood concentration of flurbiprofen was after an hour of oral administration (24-26). Flurbiprofen showed a linear dose-response relationship concerning the analgesic-to-immersion test in a mouse model, which is in agreement with a previous study on flurbiprofen plasma levels in volunteers, which revealed a linear dose-response relationship concerning gastric injury and serum drug levels (27). Another study on the analgesic effect of graded doses of flurbiprofen in post-episiotomy pain revealed a linear effect when administered orally at 25, 50, and 100 mg (28). The analgesic activity of flurbiprofen is attributed to its inhibitory effect on cyclooxygenase enzymes (COX 1 and COX2), which are responsible for the production of prostaglandins; flurbiprofen has specificity for COX-1 in inhibiting PGE2 production, which plays a role in causing pain by stimulating nerve endings (29). However, another mechanism of the analgesic effect of flurbiprofen was demonstrated in rats, which claimed that flurbiprofen increases the upregulation of β-endorphin (1). β-endorphin is an important inhibitory neurotransmitter in the nociception regulation pathway, and markedly inhibits the effect of the sensory neurotransmitter substance P, So, the deficiency of β-endorphin may lead to a certain degree of hyperalgesia (30). The analgesic efficacy of flurbiprofen was screened by acetic acid writhing test-induced visceral pain after an hour of oral administration at three different doses 20, 40, and 80 mg/kg body weight. Flurbiprofen showed a significant drop in writhing induced by acetic acid before oral administration in a dose-dependent manner, where the percent inhibitions were compared with control values and were found to be 53%, 56%, and 63%, respectively, in agreement with a study conducted on mice and rats that compared the analgesic effect of flurbiprofen and LFP83 (a prodrug of flurbiprofen) by using a writhing test (31). The synergistic interaction between alpha-lipoic acid and flurbiprofen is due to their unique mechanism of action on nuclear factor NF Kappa B (NF-κB) and activator protein 1. Recent studies have demonstrated the inhibitory effect of flurbiprofen on nuclear factor kappa B (3,32), and one of the mechanisms of action of alpha-lipoic acid is its inhibition of nuclear factor kappa and activated protein 1 (33,34).

Conclusions

We conclude from our results that flurbiprofen has a wide range of safety and is an effective analgesic for peripheral and visceral pain. The peak effect was after an hour of administration, which may be attributed to the route of administration. Alpha-lipoic acid has an analgesic effect, but is less potent than flurbiprofen. The synergistic effect between flurbiprofen and alpha lipoic acid may have clinical benefits, including reducing the dose of flurbiprofen when used together.

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Conflict of interest

We have no conflicts of interest to disclose.

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الفلوربيبروفين: تحديد خصائص الأمان والتأثير المسكن والتداخل مع حمض الليبويك في الفئران

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الخلاصة

كان الهدف من دراستنا هو الكشف والتحري عن ملف الامان لعقار الفلوربيبروفين وتقييم الفعل المسكن عن طريق التحفيز الحراري والألم الحشوي وتداخله مع حمض الالفا ليبويك كمسكن للألم الحشوي في الفئران. استخدمت طريقة الصعود والنزول المكتشفة بواسطة دكسون لإيجاد الجرعة المميتة الوسطية والجرعة المسكنة الوسطية ولإيجاد معايير السلامة تم تطبيق معادلات رياضية ولتقييم التداخل بين الفلوربيبروفين وحمض الالفا ليبويك تم استخدام اختبار التلوي الحشوي. كانت الجرعة المميتة الوسطية ١١٤٧,٤ملغم/كغم عن طريق الفم وكانت الجرعة المسكنة الوسطية ٨,٦ ملغم/كغم باستخدام اختبار غمر الذيل وكان مؤشره العلاجي هو ١٣٣ وهامش الأمان القياسي ٣٥%. اعلى وقت للتسكين كان بعد ساعة من التجريع وتلاشى بعد ٢٤ ساعة. أدى إعطاء الفلوربيبروفين بجرعة ١٠ و٢٠ و٤٠ ملغم/كغم تأثيرا مسكنا للألم معتمدا على الجرعة. وأدى الفلوربيبروفين الى تسكين الألم الحشوي عند تجريعه بجرعة ٢٠ و٤٠ و٨٠ بنسبة تسكين بلغت ٥٣ و٥٦ و٦٥ % على التوالي وكان الإعطاء المتزامن للفلوربيبروفين وحمض الالفا ليبويك ذو تأثير تأزري للتأثير المسكن للألم الحشوي. نستنتج من نتائجنا أن الفلوربيبروفين له مدى واسع من الأمان وهو مسكن فعال للآلام المحيطية والحشوية. إن التأثير التارزي بينه وبين حمض الالفا ليبويك قد تكون له فوائد سريرية من ضمنها تقليل جرعة الفلوربيبرويفين عند استعمالهما سوية.