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Effect of Joint Inflammation on Piroxicam Pharmacokinetics in Rats

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PIROXICAM IS one of the nonsteroidal anti-inflammatory drugs of the oxicam class commonly used in both veterinary and human medicine. Anti-inflammatory and pharmacokinetics of piroxicam (20 mg/kg b. wt.) via intramuscular (i.m) injection were studied in normal and joint inflamed male rats. Injection of complete Freund's adjuvant in the right hind rat's paw resulted in biphasic edematous inflammatory thickness, immediate acute phase started at the 4th day followed by a chronic phase with marked edema at day 14 of injection. Treatment with piroxicam (20mg/kg b.wt.) for 28 day resulted in significant decrease in thickness of edema by 46.15, 57.40, 47.16, 53.57, 45.65 and 51.13% in days 4, 10,17,21,24 and 28 days, respectively.

Treatment of arthritic rat with 20 mg/kg b. wt i.m piroxicam for 28 days showed a significant decrease in the arthritic index (2.00 ± 0.09 and 0.80±0.01) from day 10 to day 28 as compared with arthritic index in non-treated (2.80 ± 0.18 and 6.20 ± 0.15), respectively.

Plasma samples were collected after 2,4,6,8,10,12,24 and 48 hours for analysis of plasma piroxicam concentration. The obtained data showed a non-significant increase in plasma piroxicam concentration in joint inflamed rats than that of normal rats. The calculated pharmacokinetic parameters revealed a short t0.5 absorption (t0.5ab) 2.10 ± 0.345 hrs and 1.75 ± 0.100 hrs, and prolonged elimination half-life time (t0,5el) 14.01 ± 0.730 and 20.61 ± 0.921 hrs in normal and joint inflamed rats, respectively. Slow elimination rate (Cl/F) (0.12 ± 0.003 and 0.08 ± 0.003 (mg/kg)/ (μg/ml)/h), t0.5el as well as prolonged MRT (23.24 ± 0.666 and 32.26 ± 1.261 hrs) in normal and joint inflamed rats, respectively.

In conclusion: Piroxicam in dose of 20mg/kg/ b.wt via i.m has an anti-inflammatory effect in rat with joint inflammation and has non-significant higher and prolonged plasma concentration in inflamed joint rats than in normal.

Keywords: Piroxicam, Anti-inflammatory, Pharmacokinetics, Rat, Arthritis.

Introduction

Piroxicam is a nonsteroidal anti-inflammatory drug of the oxicam class used to relieve the symptoms of painful, inflammatory conditions like arthritis, surgery, cancers in dogs and cats [1], horse [2] andgoats[3], as well as mastitis in goat and cattle [4]. Piroxicam hasantipyretic, anti-inflammatoryand analgesic properties with advantage of once-a-day dosing and so can be used for acute or long term therapy of arthritis. Also, it has anti-cancer property against cell carcinoma of urinary bladder [5,6].

As the therapeutic activityas anti-inflammatory, analgesic and antipyretic has advantage of once-a-day dosing,therefore itwas recommended to be used for acute or long term therapy of inflammatory arthritis and the response increases over several weeks [7].

Various anti-arthritic agents are commonly evaluated using rate adjuvant induced arthritis (AIA). AlA is induced in rats by single injection of Freund's adjuvant [8]. Complete Freund's adjuvant (CFA) contains heat-killed *Mycobacterium Tuberculosis* or its cell wall

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suspended in paraffin oil [9]. Complete Freund's adjuvant is the most effective in potentiating cellular immunity and humeral antibody response to injected immunogenic agents. This activity is a result of sustained release of antigen from the oily adjuvant deposit which stimulates local innate immune response resulting in enhanced adaptive immunity [10-12].

Rapid onset and progression of polyarticular inflammation are the major characters of AIA. CFA injection into rat's paws resulting in an acute non-specific inflammation and swelling which lasts during the first week. In the non-injected hind paw a second immunologically-induced swelling occurs thereafter and lasts up to 4 weeks after adjuvant injection [13]. Cartilage damage is less severe than that in rheumatic arthritis, while bone destruction is more prominent, AIA arthritic rats, activated T cells can be detected in the inflamed joints. The infiltrating T cells into inflamed joint originate from the spleen, draining lymph nodes. Peyer's patches and the recirculating T cell pool [14].

Bioavailability of the drug not interferedwith food and antacids. Piroxicam is approximately 99%bound to plasma proteins. Despite its high plasma binding, the drug readily penetrates into synovial fluid. piroxicam has a long elimination half-life of about 50 h. Elimination of the parent drug is mainly the result of biotransformation. The elimination of piroxicam is impaired in some elderly patients, resulting in a high interindividual variability in average steady state levels following a standard 20 mg/day dosage regimen [15].

It was suggested that the drug has entrohepatic circulation [16]. Concentration maximum(C_{max}= 543.2 ± 64.4 µg/ml), absorption rate constant (α = 1.2 ± 0.4 h), and elimination rate constant (β = 0.4 ± 0.2 h of the male West African Dwarf (WAD) goats were significantly higher ($p < 0.05$) in comparison with C_{max} (376.9 ± 61.2 µg/ml), α (0.8 ± 0.3 h) and β (0.3 ± 0.1 h) of the female goats, respectively [4].

Serial blood samples were collected for quantification of piroxicam in plasma. Piroxicam was readily absorbed at both dosages, and no adverse effects were observed. Plasma concentrations peaked at 3.67 hr with a concentration of 4.00 µg/ml for the lower dosage, and at 0.83 hr at 8.77 µg/ml for the higher dosage [17].

Aim of study: It planned to studyclinical pharmacology that can provide comparative information about the pharmacokinetics of piroxicam in arthritic rat as compared with normal one to explore the possible effect of disease.

Material and Methods

Animals

Adult male albino rats weighing 200-250 gm, purchased from privet animal house, animals were kept for acclimatization at 25°C humidity 60% and natural light condition. Rats were fed on balanced ration and allowed for access to water.

Induction of chronic inflammation

Experimental chronic arthritic inflammation was induced according to the methodof Philippe et al.[18], by single subcutaneous injection of 100 µl of heat-killed *Mycobacterium tuberculosis* suspended (Sigma, USA) in a sterile paraffin oil (10 mg/ml)) into the subplantar region of rat'sright hind paw. This model is thought to share many features with human rheumatoid arthritis. It is considered as one of the most widely used models for evaluating the anti-inflammatory and the anti-arthritic activities of compounds.

Inflammation assessment

The edemathickness was measured by mean of micrometer(mm) immediately before arthritisinduction on day zero (basal thickness) and on days 4, 7, 10, 14, 17, 21, 24, and 28, thereafter results are plotted graphically versus time [19].

Arthritic assessment

Induction of arthritic inflammation (as edemathickness) was measured by micrometer immediately before arthritisinduction on day zero (basal thickness) and after Freund's adjuvant injection [19].

Arthritic index (score)

For determination of arthritic index, the degree of arthritis severity was monitored daily and scored as follows: 0 = normal paw, 1 = mild erythema and swelling. 2 = moderate erythema and swelling. 3= severe erythema and swelling. The maximal possible score per animal was 12 [20]**.**After complete detection of arthritis induction, Piroxicam was injected, intramuscularly, at day 4. Blood samples were collected at different time intervals for measuring of piroxicam concentration from 2 to 48 hours. Moreover, piroxicam administration continued daily for 28 days for evaluation of piroxicam

anti-inflammatory activity in adjuvant induced arthritis.

Determination of Piroxicam plasma concentration

Plasma piroxicam concentrations were determined in plasma spectrophotometrically according to the method described byHobbs and Twomey [16].Blood samples were withdrawn from the retro-orbital vein at 0, 2, 4 6, 8, 10, 12, 24 and 48 h, in heparinized tubes, after treatment.. The samples were centrifuged at 2000 xg for 15 minutes, 0.2 m1 of plasma were acidified with 0.05 ml 1N HCl then extracted with 1 ml dichloroethane. The organic layer was extracted with 0.5 ml carbonate buffer (pH 9) and the optical density of the latter was determined at 355 nm in a spectrophotometer. Standard curve was prepared by spiked Plasma from non-treated animals with different concentrations of piroxicam and treated with the same procedures as treated samples.

Pharmacokinetic (PK) and statistical analyses

The pharmacokinetic analysis of the data was performed using a non-compartmentalmodel using commercially available software program (WinNonlin® software, version 5.2, Pharsight Corporation). A non-compartmental model was fitted to the concentration-time data separately for each rat.The area under the curve (AUC) and the area under the first moment curve (AUMC) were calculated for normal and joint inflamed rats from the piroxicam concentration-time relationship using the trapezoidal method, with the area from the last time point extrapolated to infinity using the last measured plasma piroxicam concentration and.AUMC to AUC after adjustment for the difference in dosage. Absorption rate constant (kab), absorption half-life (t.5ab), theelimination rate constant (Kel), and the apparent terminal plasma half-life (t0.5el) were calculated using the following standard equations: kab = 1/MAT (/h), absorption half-life (t0.5.ab); T.ab = 0.693×MAT (h).The apparent terminal plasma half-life (t0.5 el) was calculated as: t0.5 el = 0.693×MRT.The elimination rate constant kel was calculated as kel = 1/MRT. The apparent volume of distribution of the central compartment (V/f) was calculated as: V/f= Dose/C0, where C0 was the extrapolated plasma concentration immediately after injection (time = 0 min) assuming instantaneous mixing. The time to reach peak concentration (Tmax) following i.m administration of piroxicam was calculated using the following equation:The tmax = 2.303×loge (kab/kel)/(kab - kel) (h), where loge is the natural logarithm. The peak concentration (Cmax) was calculated using the following equation: Cmax = [(F×Dose×kab)/(V/f ×(kab - kel)]×[*e*-kel×tmax - *e*-kab×tmax210] (µg/ml) where**:** *e* = the base of natural logarithm [21].

Results and Discussion

Piroxicam is anti-inflammatory drug frequently prescribed in animals to reduce pain, fever and inflammation and in the treatment of different clinical conditions such as rheumatoid and mastitis [21]. Inflammatoryassessment,A rthriticassessment, Plasma concentration and Pharmacokinetics of piroxicam were studied in normal and experimentally joint inflamed rats after a single i. m injection of 20 mg/kg b.wt.

The obtained results of inflammatory assessment after i.m. injection of piroxicam 20mg/kg b.wt daily for 28 days were presented in Table1 and Figure 1. These results revealed increase in edema thickness allover 28 days is following injection of complete Freund's adjuvant in the right hind rat's paw. The inflammatory edema was biphasic 1. Immediate acute phase with increase in edema thickness starts at the 4thday after adjuvant injection. 2. Followed by chronic phase with marked increase on edema thickness at day 14 of injection.

Treatment with piroxicam (20mg/kg b.wt.) for 28 day resulted in significant decrease in edema thickness allover 28 days of treatment and by 46.15, 50.09, 55.42, 57.40, 47.16, 53.57, 45.65 and 51.13% in days 4, 7, 10, 14, 17, 21, 24 and28, respectively. Piroxicam has therapeutic effects including anti-inflammatory, analgesic and antipyretic with advantage of once-a-day dosing and therefore, it can be used for acute or long term therapy of arthritis and the response increases over several weeks [2, 5,6].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly effectively used drug to relive pain and decrease inflammation in RA, acute arthritis, osteoarthritis and other inflammatory conditions. Pyroxy cam is one of the NSAIDs has analgesic, anti-inflammatory and antipyretic activities in mice [25] and rats [26]. CFA arthritic rats treated with piroxicam (20 mg/kg b. wt i.m) showed significant decrease in inflammatory in paw edema and arthritic index, these findings confirmed by Matson et al. [27], Williams et al. [28]) and Sigurdardottir [29].

The arthritic index (Table 2 and Fig. 2) showed progressive increase in combined

TABLE 1. Paw edema thickness (mm)of normal, arthritic and arthritic piroxicam treated rats (20 mg/kg b. wt for 28 days (N=10, Mean ± SD)

Treatment	Time in days							
	4	7	10	14	17	21	24	28
Normal	2.10 ± 0.09	2.12 ± 0.08	2.00 ± 0.06	2.11 ± 0.08	2.10 ± 0.06	2.08 ± 0.09	2.17 ± 0.06	2.19 ± 0.09
Arthritis	5.20 ± 0.18 a	5.21 ± 0.17 a	5.07 ± 0.18 a	5.40 ± 0.20 a	5.30 ± 0.23 a	5.17 ± 0.21 a	4.60 ± 0.10 a	4.50 ± 0.11 a
Arthritis + piroxicam (20 mg/kg b.wt)	2.80 ± 0.20 b	2.60 ± 0.25	2.26 ± 0.27 b	2.30 ± 0.19 b	2.80 ± 0.12 b	2.40 ± 0.18 b	2.50 ± 0.15 b	2.19 ± 0.13 b
% Decrease in oedema thickness	46.15	50.09	55.42	57.40	47.16	53.57	45.65	51.13

a. Significant from normal at $P < 0.05$ b. Significant from arthritis at $P < 0.05$.

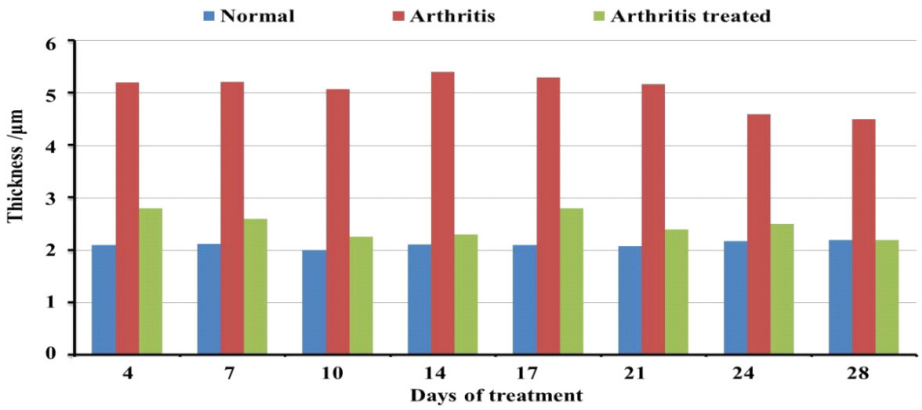

Fig. 1. Levels of paw edema thickness (µm) of normal, arthritic and arthritic piroxicam treated rats (20 mg/kg b. wt for 28 days

TABLE 2. Arthritic index of arthritic and arthritic piroxicam treated rats (20 mg/kg b. wt for 28 days (N=10, Mean ± SD)

Treatment	Time in days							
	4	7	10	14	17	21	24	28
Arthritis	2.20 ± 0.0.1	2.21 ± 0.10	2.80 ± 0.18 a	4.40 ± 0.12	4.80 ± 0.10	5.22 ± 0.20	5.60 ± 0.17	6.20 ± 0.15
Arthritis + piroxicam (20 mg/kg b.wt)	2.80 ± 0.12	2.14 ± 0.11	2.20 ± 0.27	2.00 ± 0.09 a	2.01 ± 0.02 a	2.02 ± 0.03 a	0.91 ± 0.01 a	0.80 ± 0.01 a

a. Significant from arthritis at $P < 0.05$.

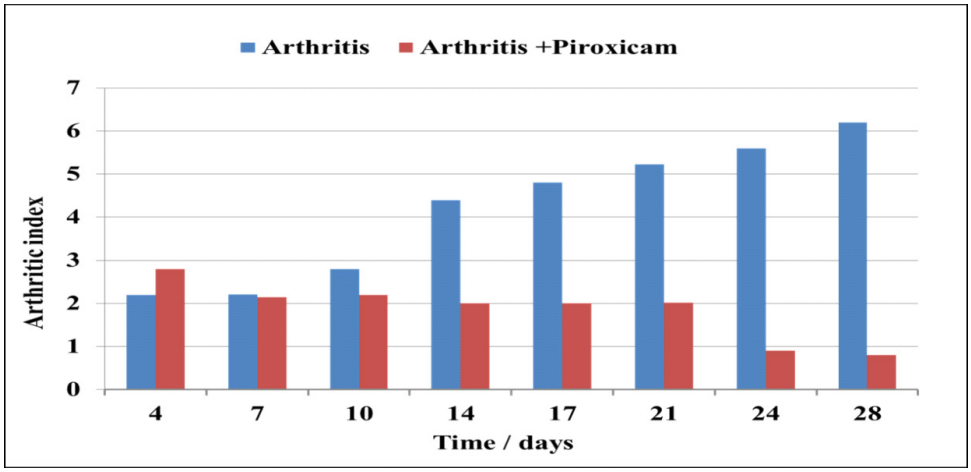

Fig.2. Levels of arthritic index of arthritic and arthritic piroxicam treated rats (20 mg/kg b. wt) for 28 days

adjuvant induced arthritic rat from 10 to 28 days. Treatment with piroxicam (20 mg/kg b. wt i.m) for 28 days in arthritic rats (Table 2)revealed a significant decrease from 10 to 28 days.

Chronic rheumatic arthritis is an inflammatory condition characterized by synovial hyperplasia and progressive joint damage [23]. Researchers suggested that i.m injection of the Complete Freund's Adjuvant (CFA) in rats induce inflammatory condition most closely similar to that in human condition**).**Injection of CFA in rats induced arthritis characterized by acute increase in paw edema thickness and arthritis index, the acute phase was followed by chronic phase with permanent inflammatory edema persisted up to the 4thweak. These results are agreed with that obtained by Swingle [13] and Cook and Nickerson [24].

Plasma piroxicam concentration after i.m injection (20 mg/kg b.wt.) started by 2 hrs after injection (3.36 ± 0.62), the highest level was at 8 hrs (6.31± 0.01) followed by gradual decrease to reach 1.98 ± 0.01 at 48 hrs in normal rats; while in joint inflamed rate it was 4.50 ± 0.02 at 2 hrs to reach highest level at 8 hrs (7.89± 0.22) and at 48 hrs (2.67 ± 0.17) in joint inflamed rats. This result showed that piroxicam plasma concentration was generally higher in joint inflamed rats than normal ones at all intervals (Table 3, Fig 3). Maximum plasma concentrations were reached within 6-8 h, this time was reported to be varied between 1 and 6 h [30]. Plasma concentration persisted until 48 hours in both normal and joint inflamed rats. These results showed a non-significant increase in piroxican plasma concentrations in joint inflamed than normal rats.

TABLE 3. Plasma piroxicam concentration after i.m injection (20 mg/kg b.wt.) in normal and joint inflamed rats (N=10, Mean ± SD)

Time/ hrs	Normal		Joint inflamed	
	Mean ± SD		Mean ± SD	
2	3.36	0.62	4.50	0.02
4	5.67	0.54	6.30	0.32
6	6.31	0.01	7.22	0.04
8	6.31	0.01	7.89	0.22
10	5.66	0.19	6.82	0.29
12	5.12	0.08	5.80	0.01
24	2.19	0.05	3.61	0.01
48	1.98	0.01	2.67	0.17

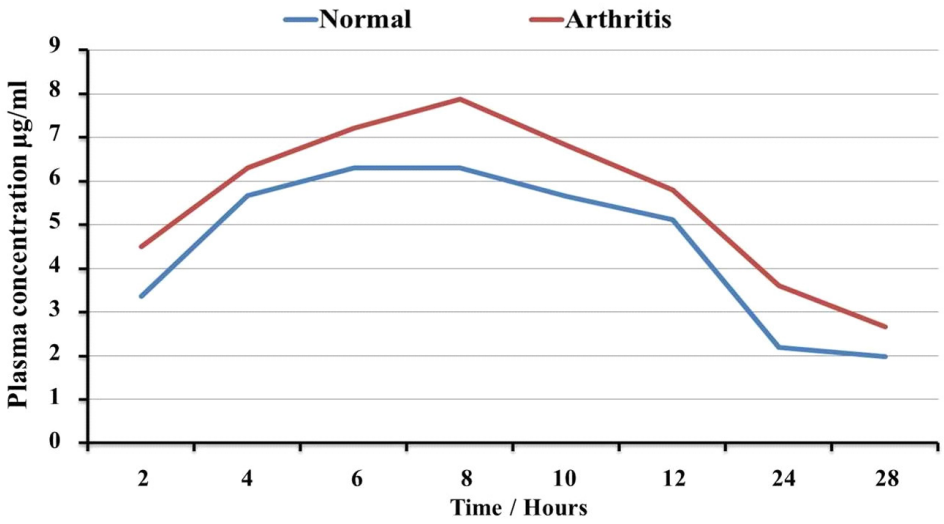

Fig. 3. Plasma piroxicam concentration after i.m injection (20 mg/kg b.wt.) in normal and joint inflamed rats (N=10, Mean ± SD)

The calculated pharmacokinetic parameters (Table 4) showed a short t0.5 absorption (t0.5ab) 2.10 ± 0.345 hrs and 1.75 ± 0.100 hrs, and prolonged elimination half-life time (t0,5el) 14.01 ± 0.730 and 20.61 ± 0.921 in normal and joint inflamed rats, respectively. The obtained data showed slow elimination rate (Cl/F) (0.12 ± 0.003 and 0.08 ± 0.003 (mg/kg)/(µg/ml)/h), which supported by the prolonged t0.5el as well as prolonged MRT (23.24 ± 0.666 and 32.26 ± 1.261 hrs) in normal and joint inflamed rats, respectively.

The pharmacokinetic profiles of piroxicam (20mg/kg b.wt i.m) in male rates showed that the Cmax in joint inflamed rat (7.08 ± 0.059µg/ml) is higher than that of normal (6.06 ± 0.146µg/ml) at long Tmax 6.80±0.234 hrs in inflamed joint than in normal (6.72±0.683hrs) (Table 2). The maximum tolerated dose in dog was 1 mg/kg every 48 h. But the acceptable dose for dog is 0.3 mg/kg per os every 24 h [31]. The time of peak concentration in rats is 2.56 h [32].

Piroxicam is rapid absorbed in inflamed joint rats with short absorption half-life (1.75 ± 0.100 h) than in normal rats (t0.5ab = 2.10± 0.345 h). The elimination half-life time (t0.5el) is longer (20.61±0.921 hrs) in inflamed joint rats than in normal (14.01±0.730 hrs) with prolonged mean residence time (MRT) 32.26 ± 1.261 h in diseased rats in comparison with normal 23.24 ± 0.666 h. The half-life was 2–9 h in piroxicam dose of 3 and 10 mg/kg body weight in rabbit, rats and rhesus monkey as well as 45 h in beagle dog [19, 33, 34] The plasma half-life of Piroxicam (1–2 mg/kg per os) is 1.7 h in mice [35]. Piroxicam is bound to plasma proteins, and has a half-life of 50 h in humans and is also excreted in urine and faces [36].

These results indicated rapid absorbed and slow eliminated of Piroxicam in inflamed joint rats than normal ones. These results supported by prolonged higher plasma concentration in inflamed joint rats than in normal and higher area under curve AUC0–t (206.86± 3.414 µg/ml/h and 152.17 ± 2.352µg/ml/h) AUC0and –inf (264.46± 8.689 325 µg/ml/h and 170.92± 4.325µg/ml/h in inflamed joint than in normal rats, respectively.

All obtained results are compatible with the obtained body clearance (CL/F) which was slow in inflamed joint rats (0.08± 0.003µg/ml /h) than in normal (0.12± 0.003µg/ml /h).

Since, piroxicam causes hyper-bilirubinaemia [37] and bilirubin competes for same binding site with piroxicam, the elimination of piroxicam may likely be delayed, and so accounting for 81.9-99% plasma protein bound [4,15,30].

The obtained results showed higher volume of distribution in normal and inflamed joint rats which supported by slow elimination [38, 39] and high effective as anti-inflammatory due to its preferential distribution in inflamed tissue [40].

The differences in the pharmacokinetic

TABLE 4. Pharmacokynetic parameters of piroxicam after i.m injection (20 mg/kg b.wt) in normal and joint inflamed rats (N =10, Mean ± SD)

Parameter	Unit	Normal		Inflamed Joints	
		Mean ±	SD	Mean ±	SD
A	µg/ml	10.00	0.578	9.73	0.230
Kab	1/h	0.34	0.075	0.40	0.022
Kel	1/h	0.05	0.002	0.03	0.002
T0.5ab	h	2.10	0.345	1.75	0.100
T0.5el	h	14.01	0.730	20.61	0.921
V/F	(mg/kg)/(µg/ml)	2.36	0.070	2.25	0.038
CL/F	(mg/kg)/(µg/ml)/h	0.12	0.003	0.08	0.003
Tmax	h	6.72	0.683	6.80	0.234
Cmax	µg/ml	6.06	0.146	7.08	0.059
AUC 0-t	µg/ml/h	152.17	2.352	206.86	3.414
AUC 0-inf	µg/ml/h	170.92	4.325	264.46	8.689
AUMC	µg/ml/h^2	3975.48	211.712	8542.20	604.079
MRT	h	23.24	0.666	32.26	1.261

parameters can be attributed to routes of administration [41]. Since about 99% of piroxicam is bound to proteins, its distribution is limited primarily to the extracellular spaces. Nevertheless, it readily penetrates the synovial fluid and is found in concentrations that are approximately 40-50 % [15, 30, 42].

Pharmacokynetic profile of drugs affecting by animal species**,** diseased condition, age, sex, values of Cmax are lower in male than female rat using i.m route [43] and was 543.2 ± 64.4 µg/ml in male goats as compared with 376.9 ± 61.2 µg/ml in female goats [4, 43].

In conclusion: Piroxicam in dose 20mg/kg b.wt i.m has anti-inflammatory effect in rat with joint inflammation and has non-significant higher and prolonged plasma concentration in inflamed joint rats than in normal.

Ethical approval

This study was approved from Institutional Animal Ethics Committee and in accordance with local laws and regulations.

Authors' Contributions

AMA and HAM designed and planned this study, drafted and revised the manuscript, shared, samples collection, performing the tests, manuscript writing and data analysis. M.I. collects tissue samples and histological study. Authors read and approved the final manuscript.

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Conflict of Interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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تاثير التهاب المفاصل على المسارالدوائي للبريكسيكام في الفئران

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البريكسيكام هو واحد من الأدوية المضادة للالتهابات غير الستيرويدية (Nonsteroidal) من مجموعه الأوكسيكام المستخدمة عادة في كل من الطب البيطري والطب البشري. تم دراسة تضاد الالتهابات والمسار الدوائي للبيروكسيكام (20 مجم / كجم بالوزن) المعطي بالحقن العضلي.

ادي حقن مساعد فرويند الكامل في مخلب الفئران الأيمن إلى سمك التهابي اوديمي ثنائي الطور ، بدأت المرحلة الحادة الفورية في اليوم الرابع تليها مرحلة مزمنة مع واوديما واضحة في اليوم 14 من الحقن. أدى العلاج بالبيروكسيكام (20 مجم / كجم من وزن الجسم) لمدة 28 يومًا إلى انخفاض كبير في سمك الاوديما بنسبة 46.15 و 57.40 و 47.16 و 53.57 و 45.65 و 51.13٪ في الأيام 4 و 24،21،17،10 و 28 يومًا على التوالى.

علاج التهاب المفاصل بالبريكسيكام 20 مج / كم وزن حى لمدة 28 يومًا أسفرت عن انخفاضًا ملحوظًا في مؤشر التهاب المفاصل (2.00 ± 0.09 و 0.80 ± 0.01) من يوم 10 إلى يوم 28 مقارنةً بمؤشر التهاب المفاصل غير المعالج (2.80 ± 0.18 و 6.20 ± 0.15) ؛ على التوالي.تم جمع عينات البلازما بعد 24،12،10،8،6،4،2 و 48 ساعة لتحليل تركيز البريكسيكام. وأظهرت البيانات التي تم الحصول عليها زيادة غير كبيرة في تركيز البريكسيكام في بلازما الفئران الملتهبة المفاصل عن الفئران الطبيعيه. كشفت المعلمات الحركية الدوائية المحسوبة عن امتصاص قصير 0.345 ± 2.10 (t0.5ab) t0.5 ساعة و 1.75 ± 0.100 ساعة ، وفترة نصف عمر التخلص اطول t0،5el)) 14.01 ± 0.730 و 20.61 ± 0.921 في الفاران ذات المفاصل الملتهبه عن الفئران الطبيعيه ،على التوالي. معدل الازاله بطيء (Cl / F) (0.12 ± 0.003 و 0.08 ± 0.003 (مجم / كجم) / (µg / ml) / (h) و t0.5el بالإضافة إلى MRT المطول (23.24 ± 0.666 و 32.26 ± 1.261 ساعة) فئران الملتهبة المفاصل و طبيعية ، على التوالي.

في الختام: البريكسيكام بجرعة 20 مجم / كجم وزن حى له تأثير مضاد للالتهابات المفاصل في الفئران وله تركيز بلازما أعلى وأطول غير معنوى في الفئران ذات المفاصل الملتهبة عن الطبيعيه.