International Journal of Therapeutic Applications, Volume 9, 2013, 1-10

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODELING OF ANTI-INFLAMMATORY EFFECT OF MELOXICAM, A PREFERENTIAL CYCLOOXYGENASE-2 INHIBITOR, IN RATS

Dheeraj Gopu*, [1] Harish Kaushik K, [2]Gomathi P
Division of Pharmacokinetics and Pharmacodynamics,
Department of Pharmacology, Vaagdevi College of Pharmacy, K.U .Warangal, A.P. INDIA.

Abstract:
Objective: To establish a suitable Pharmacokinetic / Pharmacodynamic (PK/PD) model for the meloxicam's anti-inflammatory activity for predictions about efficacy, potency and sensitivity by using a complex indirect response model in the rat, where carrageenin used as a inflammogen.
Methods: The rats were divided into different groups and received 1, 3, 7 and 10 mg/kg of meloxicam, after sub-plantar injection of carrageenin to the right hind paw. The plasma concentrations of meloxicam were determined by RP-HPLC-UV method and pharmacodynamics (paw edema volume) measured by plethesmography.
PK/PD model: Before injection of carrageenin, basal inflammatory mediator's synthesis (PEI_2) is maintained by physiological mechanism which is described by a constant rate synthesis (K_{syn}) and a first order degradation (K_{out}). K_{syn} is computed by equation $K_{syn} = E_0 . K_{out}$. After injection of carrageenin, the additional inflammatory mediators' synthesis is regulated by input rate (IR (t)). This process is governed by a first order rate constant (K_{IN}), which can be inhibited by meloxicam.
Results: The PK parameters showed dose proportionality, with a Vd, 2101, 3761, 4754and 5321 mL/kg; CL, 774, 1738, 1872 and 1913mL/hr/kg; C_{max}, 175, 290, 544and 731ng/mL. Indirect response PD model (inhibitory E_{max} model), estimated K_{IN} 1.24, 1.96, 1.95 and 1.89 1/hr; K_{out} 0.012, 0.019, 0.021 and 0.025 1/hr; K_{syn} 0.0032, 0.0039, 0.0038, and 0.0026 h; estimates for IC_{50} (concentration of meloxicam in plasama eliciting half of maximum inhibition of IR(t) or K_{IN} were 418.5, 565.91, 832.96 and 1482.7 ng/mL of group II, group III, group IV and group V respectively.
Conclusion: This hypothetical model appropriately described the time course of pharmacological response of meloxicam in various doses.

Keywords: carrageenin, inflammogen, inflammatory mediators, meloxicam, Pharmacokinetic / Pharmacodynamic modeling.

Abbreviations: Vd, volume of distribution; Cmax, a maximum plasma concentration; CL, clearance; COX-2, cyclo-oxygenase-2; RP-HPLC-UV, reverse phase high performance liquid chromatography-ultraviolet.

Introduction

Selection of effective and safe dose for a dosage regimen is very crucial for clinical use. *In vivo* preclinical pharmacokinetic / pharmacodynamic (PK/PD) modeling is a powerful mathematical approach which determines the relationship of pharmacokinetic and pharmacodynamic properties of a dosage regimen and also explores the safe and effective dose for clinical use [1]. Often, PK/PD studies conducted for the determination of three properties of a drug, they are sensitivity, potency and efficacy. PK/PD modelling in a non-human species offers a valuable approach to dosage regimen predic-tion for human use.

Meloxicam, preferential cyclooxygenase-2 (COX-2) inhibitor, a enolic derived new NSAID has 3-72 folds greater affinity towards COX-2 over the COX-1 [2, 3] and have less GI toxicity [2, 4] cardiotoxicity[4] and more neuroprotection.[5] Its therapeutic index is relatively higher than that of other NSAIDs including piroxicam, diclofenac, and indomethacin [3]. Although meloxicam showed advantageous pharmacodynamic effects but

Corresponding author :
dheerajgopu@gmail.com

prediction of an effective and safe clinical dose regimen is essential for clinical use. Various preclinical models available to relate the pk and pd, but there is a limited insight on *in-vivo* NSAIDs pharmacokinetics and pharmacodynamics [2, 6-8], a few preclinical researches conducted to model blood or plasma concentration-time profiles.

The main objective of the current study is to assess and develop a suitable preclinical PK/PD model for the anti-inflammatory effect of meloxicam and characterization of the full pharmacological profile to predict suitable dosage regimen for animals and other clinical use. To achieve this we used carrageenin induced inflammation as a PD model and meloxicam as a test substance, because of preferential inhibition on COX-2. Injection of different doses of carrageenin to the rat paw showed time-dependent bi-phasic inflammatory response. In first phase release of histamine, 5-HT and bradykinin etc occurs where as in second phase synthesis of inflammatory mediators like PGE_2, PGI_2 and other leukotrienes (LTs) by inducing the release of COX-2 enzyme [7,8]. These mediators increase the vascular permeability which enhances the edema formation and leukocyte infiltration to the inflamed region by increasing the blood flow to the site. Most probably meloxicam inhibits the second phase in inflammation by showing action preferentially on COX-2.

To best of our knowledge there are only a few reported studies on PK/PD modeling of meloxicam in cat [9, 10], dog [11] and piglet [12] but till- now there is no modeling studies in the rat.

1. Materials and Methods

2.1 Chemicals

Meloxicam and Piroxicam (internal standard) were kindly supplied by Dr.Reddy's labs India. Acetonitrile, methanol and acetic acid HPLC grade solvents were purchased from Merk India ltd. Carrageenin purchased from Sigma Aldrich, India. All the materials used in this were analytical grade.

2.2 Animals

Male Wistar rats, weighing 180 to 270 g were used in this study. Animals were kept under laboratory standard conditions on a 12-hlight/dark cycle with light from 6:00AM to 6:00PM, in a temperature (22°C) controlled room, and were acclimatized for a minimum of 7days before experiment was performed. They were housed in cages with free access to water. Food was withheld for12h before the start of experiments.

2.3 Experimental Protocol

The study protocol was keenly observed and approved by the Institutional Animal Ethical Committee (IAEC20111/10/12).

2.3.1 Induction of paw inflammation: Animals (n= 30) were randomly allocated into five groups. For inflammation induction all animals were injected subcutaneously with 0.1ml of a 1% carrageenin suspension in 0.9% saline into right hind paw.

2.3.2 PD data collection: Induced inflammation was measured by plethysmography as described [7]. Paw swelling was determined once just before and every hour during the 6h to carrageenin and drug administration.

2.3.3 Drug administration: Animals were treated orally with meloxicam 1mg/kg (groupII), 3 mg/kg (groupIII), 7mg/kg (group IV) and 10mg/kg (groupV), suspended in 0.5% sodium carboxy methyl cellulose suspesnsion just before carragenin administration. Group I (control) received only 0.5% sodium carboxy methyl cellulose suspension.

2.4 Sample collection

From all groups, blood samples (n = 30) of 100 µl were withdrawn at selected times for 6h. Group I (control) blood samples were taken to study the influence of sampling on the time course of paw swelling. Plasma was obtained by centrifugation at1000g/20min, frozen, and kept at -20°C until analysis. The same volume of withdrawn blood was replaced with sterile saline.

2.5 Sample extraction

Meloxicam was extracted from plasma samples by adding 0.5mL of acetonitrile to 0.5mL of plasma in 1:1 ratio. This was subjected to vortex mixing at high speed for1min, and then centrifuged for 10min at 9000×g. The clear

supernatant thus obtained was transferred to clean tube. To 0.5mL of supernatant, 0.5mL of HPLC grade water was added and mixed well. The aliquot was filtered through 0.22 µm nylon filter and 10 µl of the aliquot was injected into HPLC system for the analysis.

2.6 Drug analysis

Measurements of meloxicam concentrations in plasma were carried out using previously described RP-HPLC-UV method [13] with some modifications. Briefly, meloxicam and the internal standard (piroxicam) separation were achieved by using a Waters 510 HPLC pump, a Rheodyne injector with a 20 ?L loop, reversed phase C_{18} column (300mm X 3.9mm I.D., 10 ?m ?Bondapak) with a guard column [Merk KGaA, Darmastadt, Germany] with a ultraviolet detector. The mobile phase consisted of a mixture of 65% water: aceticacid (99:1, V/V) and 35% acetonitrile. The flow rate of the mobile phase was adjusted to 1.0 mLmin−1.Oven temperature was set at 35°C. The method was validated prior to the analysis of samples. Stock solution of meloxicam at 1mgmL−1 concentration was prepared in acetonitrile: acetic acid (1:1, v/v) and stored at 4°C. The working standard solutions of meloxicam with internal standard (piroxicam) at 100µg mL^{-1} prepared daily were used to spike blank plasma samples of rat. Plasma standards at 1, 0.5, 0.25, 0.1, 0.05, 0.01, 0.005 and 0.001 µgmL−1 for meloxicam (external standard) were prepared and extracted as described for the experimental samples. Meloxicam and piroxicam was detected at 360nm wavelength (UV-detector). Meloxicam was quantified from its respective peak area and the concentrations in plasma samples were determined by means of calibration curves obtained on analysis of blank plasma samples spiked with meloxicam. The retention time for meloxicam and piroxicam were 5.90 and 5.0 respectively at 1mL min^{-1}. Flow rate of mobile phase. The limits of detection and quantificationin plasma for meloxicam were 0.005 and 0.01 µgmL−1 respectively. The signal showed linearity over the range 05 to1000 ng/ml with r^2=0.986. The intra-and inter day coefficients of variation of the assay were 3.14 and 4.94%, respectively. The respective limits of detection and quantification were determined as 3 and 10 times the signal to noise ratio at the time of elution of the meloxicam. No endogenous

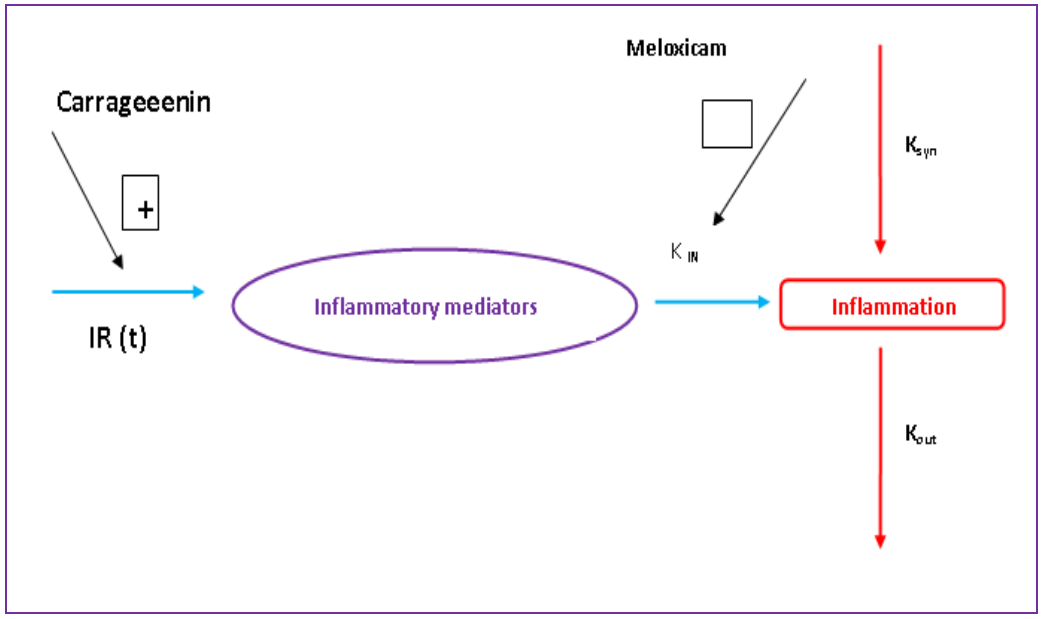

Figure-1: Schematic representation of the pharmacodynamic model used to describe the data of anti-inflammatory study. IR(t), input rate function of inflammatory mediators; K_{syn} zero order rate constant of formation inflammatory response; $K_{IN,}$ first order rate constant of release of inflammatory mediators into the inflammation compartment; K_{out}, first order rate constant of degradation of inflammatory response.

interferences were detected in the chromatograms of blank plasma samples of control group at the retention time of meloxicam.

2.7 Data analysis:

2.7.1 Pharmacokinetic model: A one compartment model is enough to describe the pharmacokinetic parameters of the meloxicam when it is administered through oral route. Pharmacokinetic parameters for plasma meloxicam were determined by nonlinear least square regression analysis using Phoneix WinNonlin® Professional version 6.2.0 (Pharsight Corporation, Cary, NC, USA) from the obtained drug concentration vs time profile.

2.7.2 Pharmacodynamic model: In anti-inflammatory model (figure-1), after injection with carrageenin control group showed a time-varying response. It was modeled using indirect pharmacodynamic response model. For inflammation a more complex physiological indirect response model is need to explain the delayed increase in inflammation in drug treated groups when compared with control group.

Especially this model assumes that a) carrageenin injection provoke transient formation of inflammatory mediators (M), which is described by the input rate function IR(t). b) the mediatior induced inflammatory response is governed by a first order rate constane (K_{IN}), which can be inhibited by meloxicam in plasma; and c) in absence of carrageenin and/or drug in the body, a certain degree of inflammation (baseline level) is maintained by the balance between the production (represented by the first order rate constant, K_{syn}) and the degradation represented by the first order rate constant, K_{out}) of inflammatory response. This model is represented by the following set of differential equations:

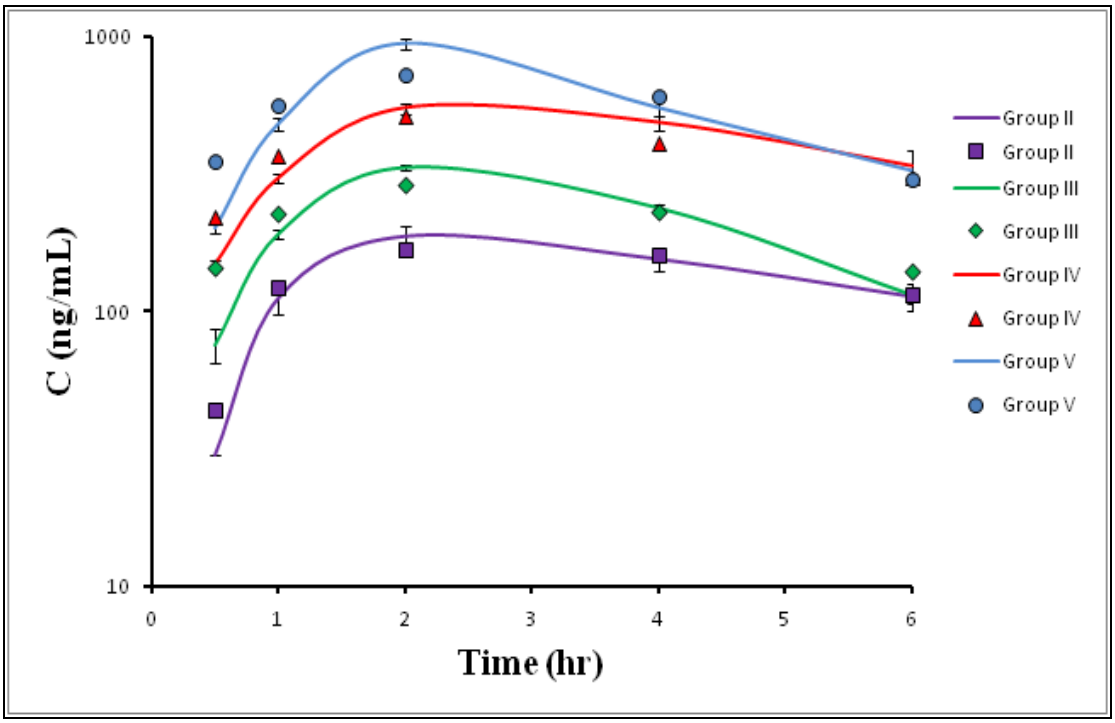

Figure-2: Time course of plasma concentrations of meloxicam in different groups. line represents mean observed data; Symbols represent typical model predictions, and vertical lines represent standard deviation.

$$\frac{dM}{dt} = IR\,(t) - K_{IN} \times (1\text{-}DRUG) \times M \qquad (1)$$

This model assumes that meloxicam (DRUG) exerts action by inhibition of the carrageenin induced mediators and this drug effect (DRUG)

is included in equation 1 and the resulted equation as follows.

$$\frac{dR}{dt} = K_{IN} \times (1\text{-DRUG}) \times M + K_{syn} - K_{out} \times R \quad (2)$$

Where dR/dt is the rate of change of the response over time (T^a), K_{syn} represents the zero-order rate constant for production of the response and K_{out} the first-order rate constant for loss of the response, IR(t) is the input rate function representing the increase in the formation of Inflammatory mediators accounting for the temporal increase in response. R is measured model response which is assumed to be result from factors controlling either the input or the loss of the measured response. For this different models were tested for the DRUG: linear, E_{max} and sigmoidal E_{max} models.

1.8 Statistical analysis:

Results are shown as mean data with their corresponding standard deviations. Comparisons of the observed response of different groups were made by one way ANOVA followed by Tukey's posteriori test with Graph Pad Prsim V 5.0. Statistical significance was set at $p<0.05$.

2. Results

3.1 Pharmacokinetics:

A one-compartment model was used to describe the kinetics of meloxicam in plasma when the drug was given orally. Estimates of the typical pk parameters and their values of inter-animal variability are listed in table-1. Mean observed and typical model predicted plasma concentration versus time profiles are shown in figure-2. Mean observed maximum plasma concentrations of meloxicam was observed after 2hr of the drug administration in all groups with the values 175.73±13.89, 290.29±30.43, 544.74±44.13 and 731.64±13.12 ng/mL for the 1, 3, 7 and 10 mg/kg respectively.

3.2 Pharmacodynamics:

Figure-3 shows the mean observed paw swelling versus time profiles for all groups injected with carrageenin. Baseline group showed a constant basal body inflammation over a 6h period. Mean basal swelling values did not differ statistically among groups I to V (p

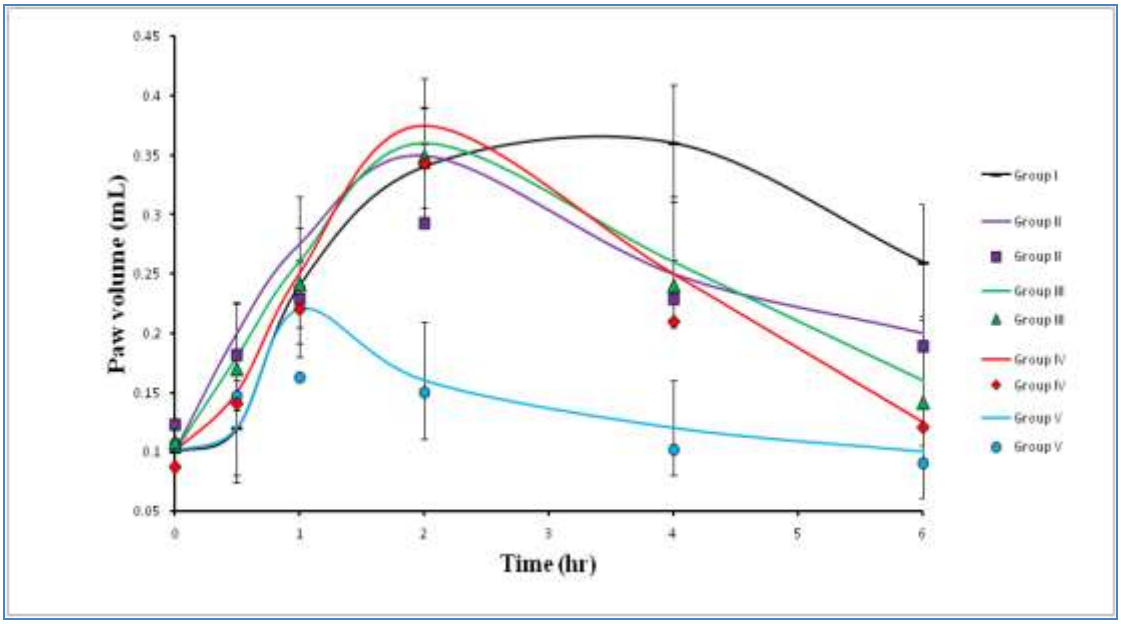

Figure-3: Time course of inflammation of after carrageenin injection and meloxicam administration; line represents mean observed data; Symbols represent typical model predictions; and vertical lines represent standard deviation.

>0.05). In addition, at the times paw selling were recorded between Carrageenin injection and the start of the drug administration no statistical differences in T^a ($p > 0.05$) were found among groups I to V. A mean maximum of paw swelling of 0.36 ± 0.05, 0.356 ±0.15, 0.36±0.04, 0.375±0.16 and 0.22±0.04 after carrageenin injection was found for group I, group II, group III, group IV and group V respectively; then paw volume returned gradually to baseline in group V at 6h after carrageenin injection remaining groups taken time to come baseline paw volume. The onset of the anti-inflammatory effects was fast in the four groups. However, base line paw volume returned to baseline with a 2-to3-h delay with respect to time to peak plasma concentrations, indicating that observed effects and plasma drug concentrations could not be related directly.

3.3 Pharmacokinetic/Pharmacodynamic Modeling:

Figure-3 showed the typical model-predicted time course of inflammation response in all groups using the model described in figure-2 (top) and by equations.1 and 2. It can be observed that model predictions for groups II, III, IV and V are almost superimposable; the fact that plasma drug concentrations for both groups at early times after administration of doses were 9 to 11 times higher than the estimated value of IC_{50} (per group), together with the high inter-individual variability, could explain this issue. This result should be interpreted as an almost instantaneous increase in the synthesis of fever mediators after the carrageenin injection. The effect of meloxicam plasma concentrations on the inhibition of IR (t) was described by an inhibitory E_{max} model. Estimates of the parameters of the linear spline and pharmacodynamic parameter with their inter-animal variability were listed in table-2 with an adequate precision. During the model building process E_{max} was estimated close to the 1; for that reason, its value was fixed. At times before Carrageenin injection $dT/dt=0=K_{syn}-K_{out}.E_0$,

Table 1

Pharmacokinetic parameter estimates of meloxicam given in to group II, group III, group IV and group V with 1mg/kg, 3mg/kg, 7mg/kg and 10mg/kg respectively.

Estimates of inter animal variability (IAV) expressed as coefficients of variation (%). Precision of the estimates is expressed as relative standard error in parentheses. Relative standard error is standard error divided by the parameter estimate.

Group	V (mL/kg)	IAV	CL (mL/hr /kg)	IAV	T_{max} (hr)	IAV	C_{max} (ng/mL)	IAV	AUC0-∞ (hr*ng /mL)	IAV
II (1mg/kg)	2101 (0.12)	11 (2.1)	774 (0.034)	34 (0.77)	2.7 (0.09)	9 (0.03)	175 (0.08)	7.90 (1.75)	1290 (0.34)	34 (12.9)
III (3mg/kg)	3761 (0.04)	44.54 (0.38)	1738 (0.02)	29.46 (1.73)	2.18 (0.19)	19.7 (0.02)	258 (0.10)	10.48 (2.90)	1725 (0.29)	29.43 (17.25)
IV (7mg/kg)	4754 (0.11)	10.68 (4.75)	1872 (0.04)	38.63 (1.67)	2.83 (0.09)	9.32 (0.03)	544 (0.08)	8.10 (5.44)	4184 (0.38)	38.68 (41.84)
V (10mg/kg)	5321 (0.63)	57.06 (0.59)	1913 (0.024)	24.81 (15.13)	2.37 (0.25)	25.28 (0.02)	731 (0.17)	17.93 (7.31)	4517 (0.52)	52.62 (45.17)

V, volume of distribution; CL, total plasma clearance; T_{max}, time taken to reach maximum concentration; C_{max}, maximum plasma concentration observed; IAV inter animal variability.

where E_0 is the basal paw volume; then K_{syn}= K_{out}. E_0. The typical value of the K_{syn} is computed using the estimates of K_{out} and E_0 and listed in table-2.

3. Discussion

4.1 Pharmacokinetics:

The estimates obtained for pharmacokinetic parameters are difficult to compare across different study of the compound in the rat model because of different design and doses. Computed area under the plasma concentrations ($AUC_{0-\infty}$) of the mean plasma concentration of the different doses versus time profile showed linearity when they were plotted AUC_{dose} against dose administered. These AUC_{dose} predicted values are 1290.32, 1725.34, 4184.34 and 4517.23 ng.hr/mL for 1, 3, 7 and 10mg/Kg dose respectively. Obtained results s1howed that the time (T_{max}) to reach peak plasma concentrations (C_{max}) achieved rapidly in all the doses ranging from 2-3hrs. These results showing linearity and these are have dose dependent bioavailability where the lowest does has low bioavailability when compared with higher doses which indicating that high AUC values showed longer duration of action.

4.2 Pharmacodynamics:

It is well elucidated that preferential COX-2 inhibitor exert their pharmacological action through a reversible inhibition of COX-2 over COX-1. By basing on previous studies that COX-2 expression was experimentally induced in the footpad by carrageenin and that the elicited inflammation could be blocked by a selective COX-2 inhibitor [8]. Meloxicam does not affect the rate of synthesis and release of COX-2 enzyme it only competes with the arachidonic acid for binding to COX-2 preferentially over COX-1. This hampers the formation of inflammatory mediators' synthesis by expressed COX-2, such as prostaglandins [3].

The Carrageenin induced edema has long been used to evaluate the anti-inflammatory

Table 2

Pharmacodynamic results obtained from the Pharmacokinetic/pharmacodynamic modeling of the anti-inflammatory effect of meloxicam given to different groups of rats; group II, group III, group IV and group V with 1mg/kg, 3mg/kg, 7mg/kg and 10mg/kg respectively.
Estimates of inter animal variability (IAV) expressed as coefficients of variation (%). Precision of the estimates is expressed as relative standard error in parentheses. Relative standard error is standard error divided by the parameter estimate.

Group	K_{IN} (1/hr)	IAV	K_{out} (1/hr)	IAV	K_{syn} (hr)	IAV	E_0 (mL)	IAV	IC_{50} (ng/mL)	IAV
II (1mg/kg)	1.24 (0.45)	7.31 (0.08)	0.012 (0.57)	1.37 (0.005)	0.00329 (0.007)	NE	0.27 (0.28)	24.4 (0.003)	418.5 (0.18)	37.35 (2.59)
III (3mg/kg)	1.96 (0.44)	20.4 (0.043)	0.019 (0.45)	4.93 (0.002)	0.0039 (0.041)	NE	0.20 (0.49)	49.32 (0.002)	565.91 (0.08)	17.88 (2.08)
IV (7mg/kg)	1.95 (0.45)	19.30 (0.045)	0.02 (0.58)	5.24 (0.002)	0.0038 (0.043)	NE	0.19 (0.59)	59.48 (0.002)	832.96 (0.07)	14.18 (4.16)
V (10mg/kg)	1.89 (0.45)	26.02 (0.032)	0.019 (0.58)	3.90 (0.003)	0.0026 (0.70)	NE	0.14 (0.42)	41.66 (0.0014)	1482.7 (0.09)	20.69 (6.63)

$K_{IN,}$ first order rate constant for release of inflammatory mediators per hour; Kout, first order degradation of inflammatory mediatiors; K_{syn}, duration of inflammation mediators synthesis, E_0, baseline paw volume of respective group animals; IC_{50}, meloxicam plasma concentration eliciting half of maximum IR(t) inhibition; IAV, inter animal variability.

effect of the NSAIDs. The time profile of the paw swelling found for the control group in our study was similar to that of published previous studies [7 & 14] on the same strain, sex, and age received same dose of carrageenin. They found maximum paw swelling increase of 38% located after 4hr [15] and 46.2% after 4h [14] after carrageenin injection, whereas we observed 36.4% after 4hr after injection of carrageenin. At the end of experiment, average paw volume had been declined to 32.8% in our study, 35% [14] and 34.3% [15].

Ideally, drug effect, production of the absolute endpoint should be solely related to its pharmacodynamic properties (efficacy, potency and sensitivity). These pharmacodynamic properties may be influenced by inflammation induction, progression and recovery. This confusing factor deserves special attention for the drugs such as meloxicam. In present study, anti-inflammatory effect of meloxicam, decrease in the paw swelling of 1mg/kg meloxicam treated group is less than that of 3mg/kg, 7mg/kg and 10mg/kg treated group and the observed pharmacodynamic effect of 1mg/kg and 10mg/kg treated groups very similar to that of published study [15]. Reduction in the paw edema volume by meloxicam is a time and dose dependent manner. However this significant inhibition in the paw volume observed after 1hr of carrageenin injection by meloxicam because carrageenin elicits inflammation in two phases, where first phase (0-1hr) of edema (attributed to release of 5-HT, hisatamine and bradykinin) is not inhibited by NSAIDs. In contrast, the second phase (1-6hr) has been correlated with the elevated synthesis of the inflammatory mediators (PGs) {drug} and more recently due to the induction of COX-2 enzyme this will be inhibited by meloxicam and along this meloxicam also inhibit the leukocyte migration [16].

While linking pharmacokinetics with pharmacodynamic we adapted indirect response model where the drugs acts through the inhibition of input rate function of fever mediator synthesis (K_{IN}). Our PK/PD model assumes that delay in the synthesis of inflammatory mediators is computed by model which is earlier explained equation and it is denoted by K_{syn}. The robustness of the model was confirmed by both the accuracy and precision of the estimates. Best of our knowledge there is no PK/PD model on the meloxicam in the rat, however estimates of IC_{50} values were found to be very significant.

It is important to notice that our hypothetical and validated model was unable to explain the raise in the first peak of paw swelling. As earlier discussed this effect may be due to the local histamine, bradykinin or 5-HT effect whose activity is insensitive to the meloxicam. Therefore lack of the predictability of this model is irrelevant to the pharmacodynamic parameters of the meloxicam.

In summary, the use of PK/PD modeling enables accurate assessment of the anti-inflammatory effect, considering a more complex indirect response model to describe the delay in the anti-inflammatory effect of meloxicam by including the another parameter (K_{syn}). All the estimated pharmacodynamic (efficacy, potency and sensitivity) and pharmacokinetic parameters describing meloxicam properties were in a dose dependent manner. This comparison in different doses demonstrated that the usefulness of preclinical PK/PD modeling approach for predicting a dosage regimen. It is foreboded that PK/PD modeling can provide a more robust rationale for dose selection of COX inhibitors, not only in the target species but also in the humans.

Conflict of interest

Authors declares no conflict of interest

Acknowledgements:

The authors thank Phoenix WinNonlin® Corporation CA, USA for providing academic user license and they also heartily thankful to Dr. D.R. Krishna, Dr. P.Goverdhan and Dr. J. Vidyasagar for their inspiration and support for the study.

References:

1. Dheeraj, G., Gomathi, P, 2011. Pharmacokinetic / Pharmacodynamic modeling: An investigational tool for drug development. International Journal of Pharmacy and Pharmceutical Sciences, 2012; 4(3): 30-37.

2. Noble, G., Edwards, S., Lievaart, J., Pippia, J., Boston, R., Raidal, S.L, 2012. Pharmacokinetics and safety of single and multiple oral doses of meloxicam in adult horses. Journal of Veterinary Internal Medicine, 26(5):1192-201
3. Engelhardt, G., Homma, D., Schlegel, K., Utzman, R., Schnitzler, C, 1995. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam a new non-steroidal anti-inflammatory agent with favorable gastrointestinal tolerance. Inflammation Research, 44:423–433.
4. Mandery, K., Bujok, K., Schmidt, I., Wex, T., Treiber, G., Malfertheiner, P., Rau, T.T., Amann, K.U., Brune, K., Fromm, M.F., Glaeser, H, 2010. Influence of cyclooxygenase inhibitors on the function of the prostaglandin transporter orfanic anion-transporting polypeptide 2A1 expressed in human gastroduodenal mucosa. Journal of Pharmacology and Experimental Therapeutics, 332 (2):345-351.
5. Goverdhan, P., Sravanthi, A., Mamatha, T, 2012. Neuroprotective Effects of Meloxicam and Selegiline in Scopolamine-Induced Cognitive Impairment and Oxidative Stress. International Journal of Alzheimers Disease, 1-8.
6. Vasquez-Bahena, D.A., Salazar-Morales, U.E., Ortiz, M.I, 2010. Castaneda-Hernadez G, Troconiz IF. Pharmacokinetic / pharmacodynamic modeling of the analgesic effects lumiracoxib, a selective inhibitor of cyclooxygenase-2 in rats. British Journal of Pharmacology, 159(1): 176-187.
7. Mariona, J., Jose-pe, U., Javier, R., Dios-Vie Itez, C., Gilberto, C.F., Flores-Murriecta, A, 2001. Pharmacokinetic /Pharmacodynamic Modeling of Antipyretic and Anti-Inflammatory Effects of Naproxen in the Rat. *Journal of Pharmacology and Experimental Therapeutics,* 297:198–205
8. Krekels, E.H., Angesjö, M., Sjögren, I., Möller, K.A., Berge, O.G., Visser, S.A, 2011. Pharmacokinetic-pharmacodynamic modeling of the inhibitory effects of naproxen on the time-courses of inflammatory pain, fever, and the ex vivo synthesis of TXB2 and PGE2 in rats. Pharmlcological Research, 28(7): 1561-1576.
9. Giraudel, J.M., Diquelou, A., Laroute, V., Lees, P, 2005. Pharmacokinetic and Pharmacodynamic Modelling of NSAIDs in Cat model of reversible inflammation in the cat. British Journal of Pharmacology, 146: 642-653.
10. Giraudel, J.M., King, J.N., Jeunesse, E.C., Lees, P., Toutain, P.L, 2009. Use of a pharmacokinetic / pharmacodynamic approach in the cat to determine a dosage regimen for the COX-2 selective drug robenacoxib. Journal of Veterinary Pharmacology and Therapeutics, 32:18–30.
11. Jeunesse, E.C., Bargues, I.A., Toutain, C.E., Lacroix, M,Z., Letellier, I.M., Giradel, J.M., Toutain, P.L, 2011. Paw inflammation model in dogs for preclinical pharmacokinetic / pharamcodynamic investigations of nonsterioidal anti-inflammatory drugs. Journal of Pharmacology and Experimental Therapeutics, 338:548-558.
12. Fosse, T.K., Haga, H.A., Hormazabal, V., Haugejorden, G., Horsberg, T.E., Ranheim, B, 2008. Pharmacokinetics and pharmacodynamics of meloxicam in piglets. Journal of Veterinary Pharmacology and Therapeutics, 31: 246-252.
13. Manoj, S., Gurpreet Singh, B.G., Sindhura, A.G., Telang, G.S Rao., Malik, J.K, 2001. Comparative plasma pharmacokinetics of meloxicam in sheep and goats following intravenous administration. Comparative Biochemistry and Physiology C, 145:528–532.
14. Seibert, K., Zhang, Y., Leahy, K., Hauser, S., Masferrer, J., Perkins, W., Lee, L., Isakson, P.C, 1994. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. Proceedings of the National Academy of Sciences of

the United States of America, 91:12013–12017.

15. Dudhgaonkar, P.S., Surendra, K,T., Shakoor Bhat, A., Sachin, H.J., Dinesh K, 2006. Synergistic anti-inflammatory interaction between meloxicam and aminoguanidine hydrochloride in carrageenan-induced acute inflammation in rats. Life Sciences, 78:1044-1048.
16. Haken, T., Zafer, B.M., Ersoy, T., Isail, K., San, T., Arbak, S, 2008. Anti-inflammatory effect of meloxicam on experimental vasospasm in the rat femoral artery. Journal of Clinical Neuroscience, 15:55-59.