

Full Length Research Paper

Pharmacokinetic/Pharmacodynamic (PK/PD) modeling of antipyretic effect of meloxicam: A preferential cyclooxygenase inhibitor in rat

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The main purpose of this study was to predict the efficacy, potency and sensitivity of meloxicam (a preferential cyclooxygenase-2 (COX-2) inhibitor) antipyretic effect by using a simple indirect response model in rat, evaluated by Brewer's yeast induced model. The rats received 1, 3, 7 and 10 mg/kg of meloxicam, after subcutaneous (sc) injection of Brewer's yeast. The plasma concentrations of meloxicam were determined by high performance liquid chromatography-ultraviolet (HPLC-UV) method. Rectal temperature (T_a) was measured for the assessment of the pharmacodynamic (PD) of the meloxicam. Before injection of yeast, basal fever mediator's synthesis (prostaglandin E_2 ; PGE_2) is maintained by physiological mechanism to regulate body temperature which is described by a constant rate synthesis (K_{syn}) and a first order degradation of K_{out} . K_{syn} is calculated by the equation, $K_{syn} = E_0 / K_{out}$, where E_0 is the baseline body temperature. After injection of yeast, the additional fever 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. The pharmacokinetic (PK) parameters showed dose proportionality, with a V_d (4124.52, 4236.73, 4657.15, and 5912.1 ml/kg), CL (78.55, 149.25, 1313.57, and 1519.41 ml/h/kg), and C_{max} (84.72, 258.29, 547.74, and 617.85 ng/ml). Indirect response PD model (inhibitory E_{max} model), estimated K_{IN} (1.43, 0.63, 0.51, and 0.42 1/h), K_{out} (0.005, 0.008, 0.015, and 0.028 1/h), and K_{syn} (0.29, 0.42, 0.076, and 0.03 h); estimates for IC_{50} (concentration of meloxicam in plasma eliciting half of maximum inhibition of IR(t) or K_{IN}) were 146.19, 379.51, 645.05, and 676.44 ng/ml of 1, 3, 7 and 10 mg/kg dose received by groups, respectively. This model appropriately describes the time course of pharmacological response to meloxicam to various doses, in terms of its mechanism of action and pharmacokinetics.

Key words: Brewer's yeast, cyclo-oxygenase-2, fever mediators (PGE_2), meloxicam, pharmacokinetic/pharmacodynamic modeling.

INTRODUCTION

Like other nonsteroidal anti-inflammatory drugs (NSAIDs), meloxicam has been extensively used for the treatment of rheumatoid arthritis (Chen et al., 2008), osteoarthritis (Chen et al., 2008), Alzheimer's disease (Goverdhan et al., 2012) and cancer (Tsubouchi et al., 2000). Meloxicam inhibits preferentially cyclooxygenase 2 (COX-2) isoform

than COX-1 isoform which prevents gastrointestinal bleeding (Hernández-Díaz and García-Rodríguez, 2001; Patringnani et al., 1997). Also, there is a less chance of cardiotoxicity, which may be caused by the selective COX-2 inhibitors (Engelhardt et al., 1995). This preferential inhibition on COX-2 isoform leads to decreased production of prostaglandins which has a crucial role in inflammation, pain, etc. Selection of effective and safe dose for a dosage regimen is very crucial for clinical use. *In vivo* preclinical pharmacokinetic (what drug dose to the body)/pharmacodynamic (what drug dose to the body) (PK/PD) modeling

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is a powerful approach which determines the pharmacodynamic properties of a dosage regimen and explores the safe and effective dose for clinical use. Also, PK/PD modeling can be used to find out sensitive, efficacious and toxic dose. Only limited insights on *in vivo* NSAIDs pharmacokinetics and pharmacodynamics (Toutain et al., 1994, 2001; Lees, 2003) are available, a few preclinical studies have been conducted to model blood or plasma concentration-time profiles. Especially for antipyretic activity, ibuprofen has been modeled in children to biophase concentration (Kelly et al., 1992; Brown et al., 1988) and to plasma concentration (Garg and Jusko, 1994) with indirect response models. To the best of our knowledge, there are only a few reported studies on PK/PD modeling of meloxicam in cat (Giraudel et al., 2005) and pharmacokinetics and pharmacodynamic studies in piglets (Fosse et al., 2008), but till date, there is no modeling studies of meloxicam in rat model.

Injection of various doses of Brewer's yeast into animals induces fever (Kluger, 1991), which is mediated by enhanced formation of cytokines and tumor necrosis factor (TNF- α). Cytokines increase the synthesis of prostaglandin E₂ (PGE₂) in circumventricular organs and organs close to the preoptic hypothalamic area. This PGE₂ via cyclic adenosine monophosphate (AMP) triggers the hypothalamus to increase body temperature (T^a). NSAIDs (meloxicam) suppress this action by inhibiting the PGE₂ synthesis (Engelhardt et al., 1995; Mariona et al., 2001; Oka et al., 1997).

Therefore, the main objectives of the current study was to assess and develop a suitable preclinical PK/PD model for the antipyretic effect of meloxicam and characterization of the full pharmacological profile to predict suitable dosage regimen for animal and other clinical use. For meloxicam's antipyretic effect, an indirect response PK/PD model was hypothesized and Brewer's yeast was used as a pyretic inducer.

MATERIALS AND METHODS

Animals

Male Wistar rats, n = 30, weighing 180 to 270 g were used. Animals were kept under laboratory standard conditions on a 12 h light/dark cycle with light from 8:00 am to 8:00 pm, in a temperature (22°C) controlled room, and were acclimatized for a minimum of 2 days before experiments were performed. They were housed in cages with free access to water. Food was withheld for 12 h before the start of experiments. The experimental protocol of the study was approved by the Institutional Animal Ethical Committee.

Chemicals

Meloxicam and piroxicam (internal standard) were gifted by Dr. Reddy's laboratory, Hyderabad, A.P. India. Acetonitrile, methanol and acetic acid high performance liquid chromatography (HPLC) grade solvents were purchased from Merk India Ltd. Brewer's yeast was purchased from Sigma Aldrich, India.

Experimental protocol

Induction of fever

Animals (n = 30) were randomly divided into five groups. Sterile saline solution (0.5 ml) containing 0.5 mg/kg Brewer's yeast was given subcutaneously (sc) to the groups (I to V) 1 h before the test drug administration (Oforah and Nweke, 2007). Only animals with 0.5 to 1°C and above with increased rectal temperature were used for this study. The yeast solution was prepared at the beginning of the experiment and was injected at 37°C to animals.

PD data collection

Temperature (T^a) was monitored in the rectum once every 30 min for 12 h just before and after the injection of the yeast with a rectal thermometer.

Drug administration

Meloxicam was administered after fever induction as an oral suspension with 0.5% sodium carboxy methyl cellulose at a different doses to the respective groups like 1 mg/kg (group-II), 3 mg/kg (group-III), 7 mg/kg (group-IV) and 10 mg/kg (group-V), whereas group-I (control) receives only 0.5% sodium carboxy methyl cellulose.

PK data collection

From all groups, blood samples (n = 6) of 100 to 200 μ l were withdrawn from the retro-orbital at selected time points up to 12 h. Plasma was obtained by centrifugation at 1000 g/20 min, frozen, and kept at -20°C until analysis. The same volume of withdrawn blood was replaced with sterile saline.

Sample extraction

Meloxicam was extracted from plasma samples by adding 0.5 ml of acetonitrile to 0.5 ml of plasma in 1:1 ratio. This was subjected to vortex mixing at high speed for 1 min, and then centrifuged for 10 min at 9000 \times g. The clear supernatant thus obtained was transferred to clean tube. To 0.5 ml of the supernatant, 0.5 ml of HPLC grade water was added and mixed well. The aliquot was filtered through 0.22 μ m nylon filter and 10 μ l of the aliquot was injected into HPLC system for analysis.

Drug analysis

Measurements of meloxicam in plasma were carried out using HPLC-UV method previously described (Manoj et al., 2007) with some modifications. Briefly, meloxicam and the internal standard (piroxicam) separation were achieved by using the aforementioned method. The mobile phase consisted of a mixture of 65% water:acetic acid (99:1, v/v) and 35% acetonitrile. The flow rate of the mobile phase was adjusted to 0.8 ml/min. Oven temperature was set at 35°C. Meloxicam and piroxicam were detected at 360 nm wavelength (UV-detector). The method was validated prior to the analysis of samples. Stock solution of meloxicam at 1 mg/ml concentration was prepared in acetonitrile:acetic acid (1:1, v/v) and was stored at 4°C. The working standard solutions of meloxicam with internal standard (piroxicam) at 100 μ g/ml 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 μ g/ml for meloxicam

(external standard) were prepared and extracted as described for the experimental samples. 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 1 ml/min flow rate of mobile phase. The limits of detection and quantification in plasma for meloxicam were 0.005 and 0.01 µg/ml, respectively. The signal showed linearity over the range of 50 to 1000 ng/ml with $r^2 = 0.986$. The intra- and inter day coefficients of variation of the assay (meloxicam standards) 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 interferences were detected in the chromatograms of blank plasma samples of the control group at the retention time of meloxicam.

Data analysis

Pharmacokinetic model

Pharmacokinetic parameters for plasma meloxicam were determined by nonlinear least square regression analysis using Phoenix WinNonlin Professional version 6.2.0 (Pharsight Corporation, Cary, NC, USA). A one-compartmental model is enough to describe the pharmacokinetics of orally administered meloxicam.

Pharmacodynamic model

In antipyretic model (Figure 1), after injection with Brewer's yeast, the control group showed a time-varying response. It was modeled using indirect pharmacodynamic response model (Gomathi and Dheeraj, 2012).

$$\frac{dR}{dt} = K_{syn} + IR(t) - K_{out} \times R \quad (1)$$

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} is the first-order rate constant for loss of the response, $IR(t)$ is the input rate function representing the increase in the formation of fever mediators accounting for the temporal increase in response. R is the measured model response which is assumed to be the result from factors controlling either the input or the dissipation of the measured response.

This model assumes that meloxicam (Drug) exerts action by inhibition of the yeast induced fever mediators and this drug effect (Drug) is included in Equation 1 and the resulted equation as follows (Mariona et al., 2001).

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

For this different models were tested for the DRUG: linear model, E_{max} (maximum effect) model and sigmoidal E_{max} models.

Statistical analysis

Results are shown as mean data with their corresponding standard deviations. Comparisons of the observed responses between different groups were made by one way analysis of variance (ANOVA) followed by Tukey's posteriori test. Statistical significance

was set at $P < 0.05$.

RESULTS

Pharmacokinetics of the observed responses

A one-compartment model was used to describe the kinetics of meloxicam in plasma when the drug was given orally. Estimates (from the experiment) 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 as shown in Figure 2. Mean observed peak plasma concentrations of meloxicam was observed after 3 h of the drug administration in all groups with the values 84.72 ± 6.75 , 258.29 ± 23.60 , 547.74 ± 29.24 and 617.85 ± 55.05 ng/ml for 1, 3, 7 and 10 mg/kg, respectively.

Pharmacodynamics of the observed responses

Figure 3 shows the mean observed T^a versus time profiles for all groups injected with Brewer's yeast. Baseline group showed a constant basal body T^a over a 12 h period with a mean \pm standard deviation (SD) value of $38.96 \pm 0.14^\circ\text{C}$. Basal T^a recorded at the time of yeast injection did not differ statistically among groups I to V ($P > 0.05$). In addition, at the times, T^a were recorded between yeast injection and the start of the drug administration; no statistical differences in T^a ($P > 0.05$) were found among groups II to V. A mean maximal increase in body T^a of 38.55 ± 0.12 , 38.48 ± 0.15 , 38.24 ± 0.05 , and $38.11 \pm 0.12^\circ\text{C}$ located at 4, 2, 2, and 2 h after yeast injection was found for group II, group III, group IV and group V, respectively; T^a then returned gradually to baseline in group V at 12 h after yeast injection, while the remaining groups took their time to get to baseline T^a . The onset of the antipyretic effects was fast in the four groups. However, T^a returned to baseline with a 2 to 3 h delay with respect to time to peak plasma concentrations, indicating that the observed effects and plasma drug concentrations could not be related directly.

Pharmacokinetic/Pharmacodynamic modeling

Figure 3 shows the typical model-predicted time course of T^a in all groups on the basis of 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 super imposable; 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} (model predicted), 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

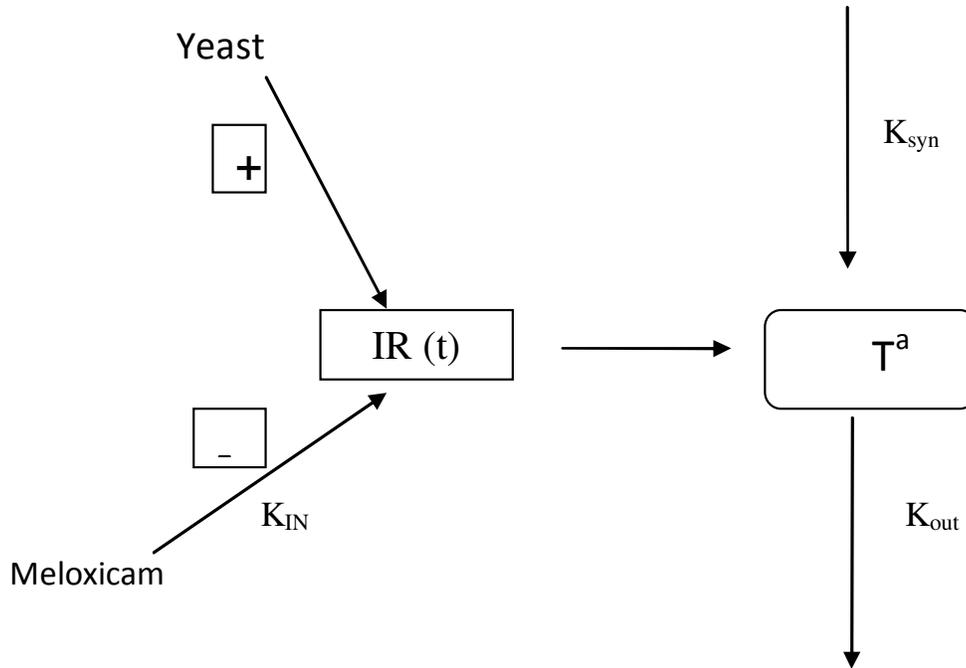


Figure 1. Schematic representation of the pharmacodynamic model used to describe the data of antipyretic study. IR(t), input rate function of fever mediators; K_{syn} zero order rate constant of formation of basal fever; K_{out}, first order rate constant of degradation of fever response.

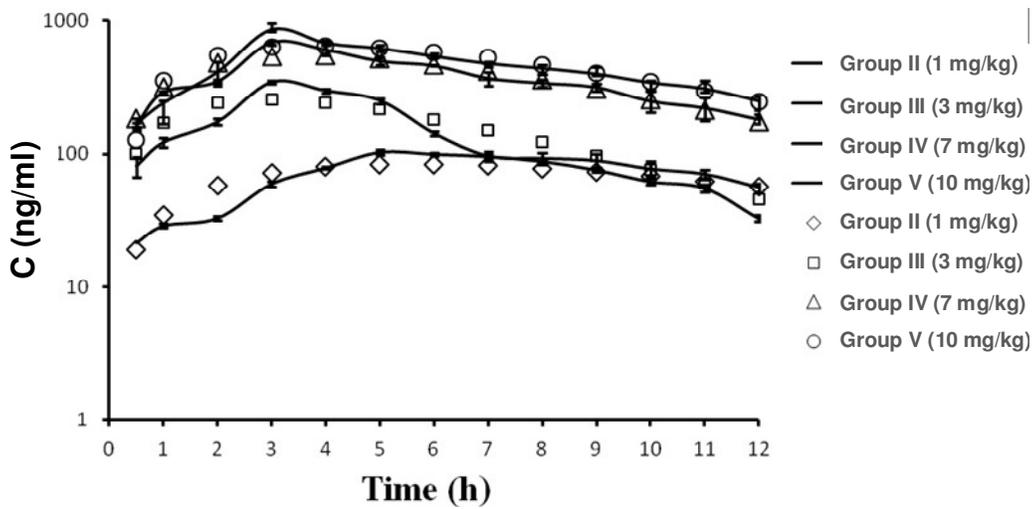


Figure 2. Time course of plasma concentrations of meloxicam in different groups. Symbols represent typical model predictions; line represents mean observed data; and vertical lines represent standard deviation.

after the yeast 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 PD parameter with their inter-animal variability are 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 yeast injection $dT/dt = 0 = K_{syn} - K_{out} \cdot E_0$, where E₀ is the basal temperature (T^a); then K_{syn} = K_{out} · E₀. The typical value of the K_{syn} is computed using the estimates of K_{out} and E₀ (Table 2).

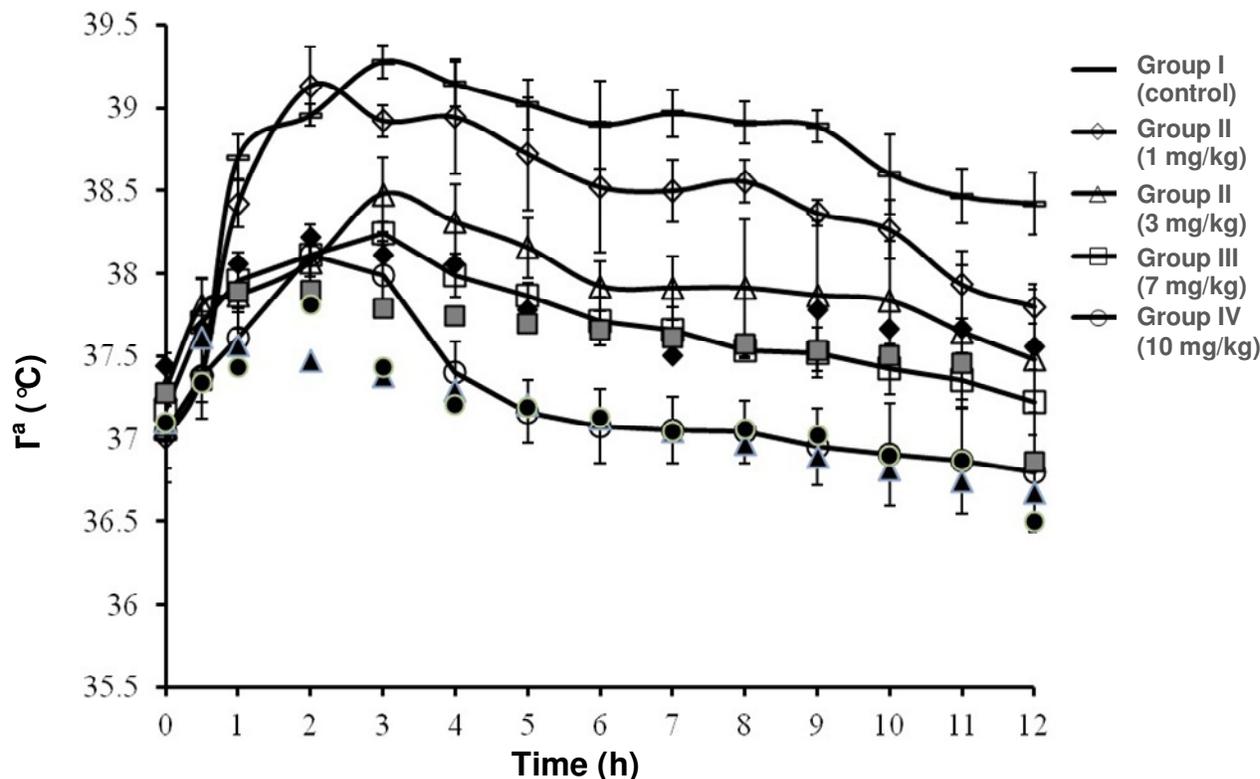


Figure 3. Time course of rectal temperature T^a after yeast injection and meloxicam administration; line with data points represents mean observed data; filled symbols represent typical model predictions, and vertical lines represent standard deviation.

DISCUSSION

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 1271.9, 2013.8, 5328.9, and 6607.0 ng/h/ml for 1, 3, 7, and 10 mg/kg doses, respectively showing dose dependent. Obtained results showed that the time (T_{max}) to reach peak plasma concentrations (C_{max}) is achieved rapidly in all the doses ranging from 3 to 4 h. These results show dose dependent bioavailability where the lowest dose has low bioavailability when compared with higher doses indicating that high AUC values showed longer duration of action.

Pharmacodynamics

For the anti-pyretic effect evaluation, Brewer's yeast

induced pyresis (sc injection) model has been used. We observed maximum mean increase of body temperature at 39.2°C located at 5 h after yeast injection in the control group. This maximum mean temperature is less in the drug treated groups which is indicative of the effect of treatment on the body temperature. Among all groups, higher dose (10 mg/kg) received group showed less increase in body temperature while other groups showed a slight high in body temperature. At the same time, time taken to reach maximum body temperature varies with the administered dose; this is probably because of the pronounced effect of meloxicam on the synthesis of fever mediators. The percent of reduction in body temperature at the end of the experiment, that is, at 12 h is more in the higher doses when compared with lower doses. This reveals that the effect of meloxicam is in dose dependent manner which is proved in the earlier published study (Engelhardt et al., 1995).

Based on observed response versus time profiles, a suitable model should take into consideration the following factors: (i) there is no circadian variation in T_a after yeast injection; (ii) the transient increase in T^a is mainly by an increase in PGE_2 ; (iii) adequate concentration of meloxicam produced inhibition on the increase in T^a ; and (iv) there is no rebound effects.

In our proposed model, from the following equation,

Table 1. Pharmacokinetic parameter estimates of meloxicam given into groups II, III, IV, and V with 1, 3, 7, and 10 mg/kg, respectively.

Group	V (ml/kg)	IAV	CL (mL/h/kg)	IAV	T _{max} (h)	IAV	C _{max} (ng/ml)	IAV	AUC _{0-∞} (h/ng/ml)	IAV
II (1 mg/kg)	4124.52 (0.03)	30.34 (0.43)	78.55 (0.49)	49.57 (0.78)	3.5 (0.24)	15.06 (0.05)	84.72 (0.08)	7.977 (0.08)	1271.96 (0.48)	48.59 (12.71)
III (3 mg/kg)	4236.73 (0.04)	23.43 (0.42)	149.25 (0.15)	14.74 (14.9)	3.86 (0.02)	13.49 (0.03)	258.29 (0.09)	9.14 (2.58)	2013.88 (0.14)	14.72 (20.15)
IV (7 mg/kg)	4657.15 (0.22)	21.88 (0.46)	1313.57 (0.12)	12.07 (13.2)	3.5 (0.11)	11.14 (0.11)	547.74 (0.05)	5.33 (5.58)	5328.98 (0.12)	12.06 (53.39)
V (10 mg/kg)	5912.1 (0.57)	57.06 (0.59)	1519.41 (0.25)	24.81 (15.13)	3.9 (0.2)	20.26 (0.04)	617.85 (0.09)	8.91 (6.18)	6607.05 (0.25)	24.78 (66.08)

Estimates of inter animal variability (IAV) are 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. V, volume of distribution; CL, total plasma clearance; T_{max}, time taken.

Table 2. Pharmacodynamic results obtained from the pharmacokinetic/pharmacodynamic modeling of the antipyretic effect of meloxicam given to different groups of rats; groups II, III, IV and V with 1, 3, 7, and 10 mg/kg respectively.

Group	K _{IN} (1/h)	IAV	K _{OUT} (1/h)	IAV	K _{syn} (h)	IAV	E ₀ (°C)	IAV	IC ₅₀ (ng/ml)	IAV
II (1 mg/kg)	1.43 (0.57)	72.51 (0.011)	0.005 (0.57)	72.6 (0.0001)	0.29 (0.70)	0.18 (0.002)	38.38 (0.71)	0.27 (3.81)	146.19 (0.70)	6.48 (15.95)
III (3 mg/kg)	0.63 (0.70)	39.64 (0.010)	0.008 (0.71)	14.84 (0.0004)	0.42 (0.70)	2.13 (0.004)	38.13 (0.71)	0.98 (11.0)	379.51 (0.71)	4.03 (66.57)
IV (7 mg/kg)	0.51 (0.57)	114.99 (0.002)	0.015 (0.58)	114.88 (0.0004)	0.076 (0.58)	0.06 (0.0007)	37.68 (0.58)	0.28 (3.07)	645.05 (0.58)	8.40 (64.97)
V (10 mg/kg)	0.42 (0.71)	34.28 (0.056)	0.028 (0.71)	34.51 (0.0006)	0.03 (0.70)	0.17 (0.003)	37.28 (0.70)	0.25 (4.09)	676.44 (0.71)	11.86 (40.33)

Estimates of inter animal variability (IAV) are 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. K_{IN}, first order rate constant for release of fever mediators; K_{OUT}, first order degradation of fever mediators; K_{syn}, duration of fever mediators synthesis; E₀, baseline T_a; IC₅₀, meloxicam plasma concentration eliciting half of maximum IR(t) inhibition; IAV, inter animal variability.

$dT/dt=0=K_{syn} - K_{out}$, E₀ predict a time invariant baseline T_a. The estimate of K_{out} (0.028) is very rapid in higher dose (10 mg/kg) than the other doses. Mechanism of action of NSAIDs is to inhibit the synthesis of PGE₂ (Engelhardt et al., 1995). It is estimated by an inhibitory E_{max} model and the values of the IC₅₀ are represented in Table 2.

Conclusion

Conclusively, the use of PK/PD modeling enables accurate assessment of clinical dose. Anti-pyretic

effect of meloxicam was modeled by a simple indirect response model. Raised body temperature (fever) is mainly because of the production of PGE₂ in the brain and inhibition of fever mediator's synthesis is indicative of the level of antipyretic activity of meloxicam (blood brain crossing nature is very important). In spite of this, all the estimated pharmacodynamic (efficacy, potency and sensitivity) and pharmacokinetic parameters describing meloxicam properties were in a dose dependent manner and they showed significant pharmacodynamic properties when administered at high doses. This comparison in different doses demonstrated the usefulness of preclinical PK/PD

modeling approach for predicting a dosage regimen. It is suggested 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.

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ABBREVIATIONS

Vd, Volume of distribution; **Cmax**, maximum plasma concentration; **CL**, clearance; **COX-2**, cyclo-oxygenase-2; **HPLC-UV**, high performance liquid chromatography-ultraviolet.

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