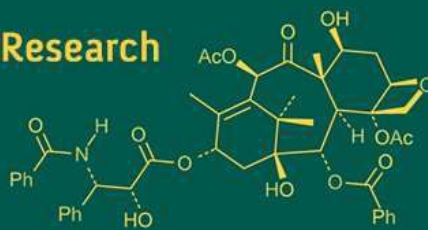
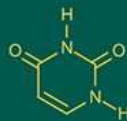


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## Disposition kinetics of meloxicam in goats following single intramuscular administration

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### Abstract

Disposition kinetics of meloxicam (0.5 mg/kg) was studied following intramuscular administration in female Barberi goats. Meloxicam concentration in plasma was measured using HPLC assay and kinetic parameters were determined using PHARMKIT software. Semi-logarithmic plot of the observed plasma levels indicated that plasma levels data could be best fitted to one-compartment open model. The observed mean peak plasma concentration of meloxicam in goats was  $0.94 \pm 0.03 \mu\text{g} \cdot \text{ml}^{-1}$  at 120 min (2 h) which gradually declined to  $0.16 \pm 0.08 \mu\text{g} \cdot \text{ml}^{-1}$  at 18 h. Determination of different pharmacokinetic variables revealed that the value of  $C_{\text{max}}$  was  $0.84 \pm 0.01 \mu\text{g}/\text{ml}$  and  $T_{\text{max}}$  was  $105.43 \pm 10.89$  min while the elimination half-life was  $446.19 \pm 56.20$  min, and bioavailability was almost 100%. Based on the values of different PK determinants, the loading dose of meloxicam @ 1.12 mg/kg body weight may be used in goats by intramuscular route followed by the maintenance dose of 0.68 mg/kg body weight and be repeated at 12-hour interval.

**Keywords:** Goats, meloxicam, intramuscular, HPLC, pharmacokinetics, bioavailability

### Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) showing preferential inhibition of cyclo-oxygenase-2 (COX-2) enzyme and comparatively lesser gastrointestinal toxicity potential relative to nonselective NSAIDs (Davies., 1999) <sup>[1]</sup>. Non-steroidal anti-inflammatory drugs are being commonly used to manage pain and inflammation in animals. Meloxicam has high bioavailability and results in fewer negative side effects compared to other NSAIDs (Coetzee, 2013) <sup>[2]</sup>. It has been reported to show positive impact in cases of diarrhoea (Todd *et al.*, 2010) <sup>[3]</sup>, dehorning (Heinrich *et al.*, 2009, 2010) <sup>[4, 5]</sup>, castration, and respiratory diseases (Coetzee *et al.*, 2009) <sup>[6]</sup>. The pharmacokinetics (PK) of meloxicam has been studied following different routes of administration in horses (Lees *et al.*, 1991; Toutain *et al.*, 2004) <sup>[7, 8]</sup>, dogs (Busch *et al.*, 1998; Montoya *et al.*, 2004) <sup>[9, 10]</sup>, piglets (Fosse *et al.*, 2008) <sup>[11]</sup>, yak (Ahmad *et al.*, 2015) <sup>[12]</sup> calves (Kovács *et al.*, 2022) <sup>[13]</sup>, and sheep (Woodland *et al.*, 2019; Gungor *et al.*, 2023) <sup>[14, 15]</sup>. Pharmacokinetics of meloxicam has been studied in goats following intravenous administration (Shukla *et al.*, 2007; Yadav *et al.*, 2014) <sup>[16, 17]</sup>, subcutaneous administration (Karademir *et al.*, 2016) <sup>[18]</sup> and following intramuscular administration (Sharman *et al.*, 2018; De Vito *et al.*, 2018) <sup>[19, 20]</sup>. But in view of the large variations in values of different pharmacokinetic determinants of meloxicam in goats after intramuscular administration, as reported by these scientists, we had undertaken the present study following intramuscular administration (IM) in goats.

### Materials and Methods

Three (3) healthy female Barberi goats, aging between 1.2 and 2.0 years and weighing 18 to 22 kg, were used in the present study. Experimental goats were housed in well-ventilated and clean goat-sheds of the Department of Veterinary Physiology. Animals were straw and seasonal green-fodder along with concentrate as per standard managemental practice and had ad-lib access to clean drinking water. Experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) as per guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

An injectable formulation of meloxicam, Melonex®; Intas Pharmaceutical Ltd., Ahmedabad, India, was intramuscularly injected @ 0.5 mg/kg body weight on the ventro-lateral aspect of neck of experimental goats. Blood samples (2.0-3.0 ml) were collected from jugular vein of goats into heparinised test tubes before drug administration and at 2.5, 5, 10, 15, 30, 45 minutes and 1, 1.5, 2, 3, 6, 8, 12, 18, 24, 30, 36 and 48 h after drug administration. Blood samples were centrifuged at 3,000 rpm for 20 min and plasma was separated, aliquoted into cryo-vials, and stored at -80 °C until assayed. HPLC Assay method of Neilson and Gyrd-Hansen (1997) [21] with certain modifications was used to extract meloxicam from plasma samples.

### Assay method

Meloxicam reference standard was purchased from Sigma Aldrich (St. Louis, USA). A stock solution (100 µg/ml) of meloxicam was prepared in HPLC grade water and stored at -80 °C. HPLC system (Waters™, USA), having photodiode array detector with Empower software and C<sub>18</sub> reverse phase column (particle size 5 µm; 4.6 x 250 mm, Waters Spherosorb®), was used for assay of meloxicam in plasma, employing the modified HPLC method of Dasandi *et al.* (2002) [22].

Before running the HPLC system, the mobile phase, standards and different samples were filtered through 0.22 µm Millipore cellulose acetate membrane. The volume of sample injected was 20 µl and the flow rate maintained was 1.2 ml/min. Retention time was 4.6±0.1 min for meloxicam, with a total run time of 7 min. Working plasma standards were prepared from the stock solution (100 µg/ml) of meloxicam in pooled plasma from untreated goats. The detection wavelength was set at 355 nm. The limits of detection (LOD) and limits of quantification (LOQ) for meloxicam were 0.05 µg/ml and 0.10 µg/ml, respectively. The assay was sensitive, consistent and reproducible with a linear standard curve in the range of 0.1 to 6.40 µg/mL of meloxicam with the correlation coefficient (R<sup>2</sup>) value of 0.999.

### Pharmacokinetics and statistical analysis of data

The pharmacokinetic variables were determined using PHARMKIT software. Other parameters were calculated using the equations described by Baggot (1977) [23] and

Gibaldi and Perrier (1982) [24]. Evaluation of the plasma concentration-time profile of meloxicam following IM administration revealed that the data could be best fitted to one-compartment open model with first order absorption and adequately described by the equation:

$$C_p = B e^{-\beta t} - A' e^{-K_a t}$$

where  $C_p$ , plasma concentration of meloxicam at time  $t$ ;  $B$  and  $A'$ , zero time plasma drug concentration intercepts of the elimination and absorption phases;  $\beta$  and  $K_a$ , elimination and absorption phase rate constants respectively; and  $e$ , base of the natural logarithm. Data were expressed as mean±SE except for  $t_{1/2K_a}$  and  $t_{1/2\beta}$  which were expressed as harmonic mean values. Statistical analysis was performed using Student's *t*-test. The dosage regimen of meloxicam was computed using the equations suggested by Baggot (1977) [23].

### Results

Plasma levels of meloxicam as a function of time in goats after intramuscular administration of meloxicam @ 0.5 mg.kg<sup>-1</sup> are shown in Fig. 1. The mean peak plasma meloxicam level of 0.94±0.03 µg.ml<sup>-1</sup> was observed at 120 min which gradually declined to 0.16±0.08 µg.ml<sup>-1</sup> at 18 h. Observed plasma levels of meloxicam suggested mono-exponential decline in plasma levels and thus could be best fitted to one-compartment open model with the first-order absorption. Mean values (±SE) of different pharmacokinetic parameters are summarized in Table 1.

The absorption rate constant ( $K_a$ ) values in different goats ranged from 0.019 to 0.042 min<sup>-1</sup> and the mean value was found to be 0.03±0.006 min<sup>-1</sup> while the corresponding half-life values ( $t_{1/2K_a}$ ) ranged from 16.69 to 35.93 min with the mean value of 22.79±5.68 min. The mean elimination rate constant ( $\beta$ ) value was calculated to be 0.0013±0.00 min<sup>-1</sup> and the mean elimination half-life was found to be 446.19±56.20 min (Table 1). The mean value of area under plasma concentration time curve (AUC) was 601.05±49.82 µg.ml<sup>-1</sup>min, and the calculated values of  $C_{max}$  (0.84±0.01 µg.ml<sup>-1</sup>) and  $t_{max}$  (105.43±10.89 min) were very close to the corresponding observed value of 0.94±0.03 µg.ml<sup>-1</sup> and 2 h, respectively.

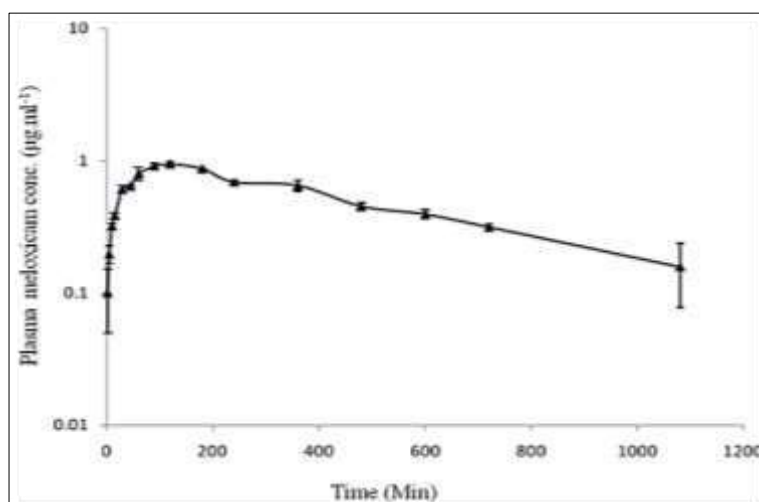


**Fig 1:** Semilogarithmic plot of plasma meloxicam concentrations versus time data following a single intramuscular administration of meloxicam (0.5 mg.kg<sup>-1</sup>) in goats on the ventro-lateral aspect of neck. Each point represents the mean±SE of 3 animals

**Table 1:** Pharmacokinetic parameters of meloxicam following a single intramuscular administration of meloxicam (0.5 mg.kg<sup>-1</sup>) in goats on the ventro-lateral aspect of the neck

| Parameters (Units)                             | Mean±S.E.         |
|------------------------------------------------|-------------------|
| B (µg.ml <sup>-1</sup> )                       | 1.06±0.08         |
| K <sub>a</sub> (min <sup>-1</sup> )            | 0.030±0.006       |
| β (min <sup>-1</sup> )                         | 0.0013±0.00       |
| t <sub>1/2ka</sub> (min)                       | *22.79±5.68       |
| t <sub>1/2β</sub> (min)                        | *446.19±56.20     |
| AUC (µg.ml <sup>-1</sup> min)                  | 601.05±49.82      |
| AUMC (µg.ml <sup>-1</sup> min <sup>2</sup> )   | 496576.2±92857.56 |
| MRT (min)                                      | 722.44±90.21      |
| MAT (min)                                      | 392.71±75.28      |
| C <sub>max</sub> (calc) (µg.ml <sup>-1</sup> ) | 0.84±0.01         |
| t <sub>max</sub> (calc) (min)                  | 105.43±10.89      |

\*Harmonic mean value B: Zero time intercept of the least square regression line of the elimination phase (β) and represent the expected zero time plasma concentration of the drug; K<sub>a</sub>: Absorption rate constant; β: elimination rate constant, t<sub>1/2ka</sub>, and t<sub>1/2β</sub> (min): Absorption, and elimination half-lives, respectively; AUC: Total area under the plasma drug concentration time curve, AUMC: Total area under the first moment of plasma drug concentration-time curve; MRT: The mean residence time; MAT: The mean absorption time; C<sub>max</sub>: Observed peak plasma concentration of the drug; t<sub>max</sub>: Time period at which the peak plasma concentration is observed

## Discussion

Non-steroidal anti-inflammatory drugs, including meloxicam, are being extensively used in veterinary clinical practice to manage pain and inflammation in animals. Meloxicam was administered intramuscularly on ventro-lateral aspect of the neck of goats. Absorption of meloxicam appeared to be faster and better from ventro-lateral aspect of neck as meloxicam could be detected in plasma within 2.5 min of drug administration and peak plasma level (C<sub>max</sub>) was found to be 0.94±0.03 µg.ml<sup>-1</sup> at 120 min (2 h) after injection. Absorption half-life value of meloxicam in goats in the present study was calculated to be 22.79±5.68 min. The absorption half-life value of meloxicam in our study is in agreement with the value of 0.33 h/19.8 min (Shrman *et al.*, 2018) [19] after IM administration in goats, and much shorter than the value of 2.26 h in buffalo calves reported by Mody *et al.*, 2007 [25].

Following intramuscular administration of meloxicam in goat, elimination half-life was found to be 446.19±56.20 min which is almost comparable to the value of 7.34 h reported by Shrman *et al.* (2018) [19], however, it was shorter than the value of 10.82 hours in goats (De Vito *et al.*, 2018) [20] and many folds shorter than the value of 37.88 h reported in buffalo calves (Mody *et al.*, 2007) [25]. Possibility of such a difference in elimination half-life due to differences in the site of drug administration (gluteal muscle) and/or the species and breed of animals cannot be ruled out. These observations evidently suggest that compared to buffalo calves, goats are fast eliminators. This possibility is also supported by the value of mean residence time (MRT) of meloxicam after intramuscular administration in goat (722.44 min) compared to the much higher corresponding value of MRT in buffalo calves (60 h) reported by Mody *et al.* (2007) [25]. Following intravenous administration of meloxicam also shorter MRT value of 336.31±14.61 minutes has been reported in goats from our laboratory (Yadav *et al.*,

2014) [17]. The AUC value of meloxicam in goats in the present study (674.95±49.82 µg.ml<sup>-1</sup>min) was almost similar to the AUC value of 14.29h/857.40 min in goats reported by Shrman *et al.*, (2018) [19], however, lower than reported in buffalo calves (105 µg.ml<sup>-1</sup>h; Mody *et al.*, 2007) [25].

To calculate the bioavailability (F) of meloxicam following intramuscular administration in goats, we considered the pharmacokinetic data of our own laboratory following intravenous administration of meloxicam in goats (Yadav *et al.*, 2014) [17]. Bioavailability of meloxicam in goats following intramuscular administration in the neck region was found to be almost 100% (99.05±0.08 %) which is almost equal to the F value of 100 % reported in goats (De Vito *et al.*, 2018) [20]. Therefore, our findings evidently suggest that meloxicam can be effectively administered by IM route for the treatment of various disease conditions in goats.

There is no data on clinically effective plasma or tissue concentration of meloxicam except for in horses where it has been reported to be 0.73 µg/ml (Toutain *et al.*, 2004) [8]. Therefore, considering the same effective plasma concentration of meloxicam for goats as well and the PK determinants as generated in the present study, intramuscular loading and maintenance doses of meloxicam for goats were calculated to be 1.12 and 0.68 mg/kg body weight, respectively, and be repeated at 12 h interval.

## Conclusion

Disposition kinetics data of meloxicam suggest that this drug has almost 100% bioavailability following intramuscular administration and it should be used at the loading dose rate of 1.12 mg/kg while the maintenance dose rate of 0.68 mg/kg body weight in goats and the drug administration be repeated at 12 h interval for satisfactorily clinical outcome.

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