Journal of Bioequivalence & Bioavailability - Open Access

JBB/Vol.1 November-December 2009

Research Article | OPEN ACCESS Freely available online | doi:10.4172/jbb.1000019

Pharmacokinetic Profile of Nimesulide in Bovine Calves

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Abstract

The aim of the present study was to investigate pharmacokinetic profile and bioavailability of cyclooxygenase (COX)-2 selective nonsteroidal anti-infalmmatory drug nimesulide in bovine male calves after intravenous (i.v.) and intramuscular (i.m.) administration at a dose of 4.5mg/kg BW. Blood samples were collected by jugular venipuncture at predetermined times following drug administration. Nimesulide in the plasma was assayed by using a validated HPTLC method. Plasma concentration-time data were subjected to compartmental analysis and pharmacokinetic parameters for nimesulide after i.v. and i.m. administration were calculated according to two and one-compartment open models, respectively. Following i.v. administration, a rapid distribution phase was followed by slower elimination phase. The half-lives during distribution phase ($t_{1/2\alpha}$) and terminal elimination phase ($t_{1/2\beta}$) were 0.15±0.005h and 9.02±0.06h, respectively. The steady-state volume of distribution ($v_{d(ss)}$), total body clearance (cl_B) and mean residence time (MRT) of nimesulide were 0.22±0.02L/h/kg, 0.02±0.001 and 11.23±0.04 h, respectively. After i.m administration, maximum plasma concentration (c_{max}) of nimesulide was 35.84±3.04 µg/mL attained at 4.0±0.19 h (t_{max}). Plasma drug levels were not detectable upto 72h. Similarly the $t_{1/2\beta}$ (20.08±0.79h) MRT (13.76±0.09h) of nimesulide after i.m. administration were significantly longer than the i.v administration. The bioavailability of nimesulide was 89.42% after i.m administration. These pharmacokinetic data suggests that nimesulide given intramuscularly may be useful in the treatment of inflammatory disease conditions in bovines.

Introduction

Nimesulide (4-nitro-2-phenoxymethanesulfonanilide) is a non-steroidal anti-inflammatory drug (NSAID) belonging to the sulphonanilide class, and is the first COX-2 preferential inhibitor to be marketed worldwide (Bennett and Villa, 2000). Nimesulide, has been used in humans for primary treatment of patients who need a rapid anti-inflammatory and analgesic action and the drug is among the most prescribed NSAIDs worldwide (Bennett, 1999; Bennett and Villa, 2000; Rainsford, 2006). Unlike most traditional NSAIDs that inhibit both cyclooxygenase COX-1 and COX-2 isoforms, nimesulide selectively blocks COX-2 which is induced in inflammatory conditions (Rainsford, 1999; Rainsford, 2006). Nimesulide has got potent anti-inflammatory activity and the therapy with enrofloxacin and nimesulide was found more efficacious (92.30%) in treating subclinical mastitis in cows (Joshi and Gokhale, 2006). The simultaneous inhibition of COX-1 by the traditional NSAIDs largely accounts for gastrointestinal damage and alterations in the homeostasis functions of the prostanoids preferentially synthesized by this isozyme (Raskin, 1999; Raskin, 2006). It has been demonstrated to cause less gastrointestinal side effects compared to classical NSAIDs and this better tolerability correlates to its preferential COX-2 inhibitory potency (Famaey, 1997; Bennett and Villa, 2000). The therapeutic effects of nimesulide are the result of its multifactorial mode of action, which targets a number of key mediators of the inflammatory process. The drug is considered to be a preferential inhibitor of cyclooxygenase-2 (COX-2), since it also exerts some degree of COX-1 inhibition (Panara et al., 1998) thus blocking the production of prostanoids, many of which are actively involved in the inflammatory process (Tavares et al., 1995). However, in addition to COX inhibition, nimesulide has other pharmacological effects which may contribute to its clinical efficacy in many inflammatory processes.

Pharmacokinetic aspects of nimesulide have been fully documented in human (Bernareggi, 1998) and some animal species. The therapeutic usefulness of nimesulide largely relates to its pharmacokinetic properties in the target species. The pharmacokinetic properties and in vitro potency of nimesulide were investigated in dogs (Toutain et al., 2001), in horses (Villa et al., 2003), in goats (Rao et al., 2007), in sheep (Malik et al., 2008) and more recently, in some companion animals. In bovines nimesulide is used in combination with antimicrobials for treatment of disease condition such as acute mastitis, pneumonia, viral and bacterial respiratory diseases. Pharmacokinetic data provides information about the half-life, bioavailability and elimination profile of the drug which gives an insight into the dosage regimen to be adopted in both normal and in diseased conditions. So pharmacokinetic data for those drugs is essential that are species specific e.g. NSAIDs. Several studies have emphasized that pharmacokinetic data of NSAIDs in different animals cannot be transposed to the bovines. Yet such data are essential

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Received October 31, 2009; **Accepted** December 16, 2009; **Published** December 16, 2009

Citation: Mahapatra L, Sahoo GR, Panda MK, Parija S (2009) Pharmacokinetic Profile of Nimesulide in Bovine Calves. J Bioequiv Availab 1: 121-026. doi:10.4172/jbb.1000019

for rational and judicious use of this drug in bovine medicine. The present investigation was therefore undertaken with the ultimate objective to establish bioavailability and pharmacokinetic parameters of nimesulide following intravenous and intramuscular administration at 4.5 mg/kg BW in bovine calves.

Materials and Methods

Experimental animals

The study was conducted in six clinically healthy male bovine calves of 6.25±0.45 months-old weighing from 60 to 70 kg. Body weight of each animal was recorded on the day prior to initiation of the experiment. The animals were fed concentrates, green fodder and roughage and had free access to water *ad libitum*. All the animals were acclimated for at least 7 days prior to the start of the study. This study was approved by the institutional Animal Ethics committee.

Drug administration

Nimesulide (Nimovet 10%; Indian Immunologicals Ltd. Hyderabed, India) was administered intravenously or Intramuscularly at a dose of 4.5 mg/kg BW as a single dose. In the I.V. study, the drug was injected into the jugular vein using intravenous cannula opposite to the one from which blood samples were collected. Blood samples were also collected by jugular venipuncture following i.m. administration of nimesulide. The study was conducted using two-way crossover design. The same six animals were used for all the studies i.e single intravenous (i.v) and single intramuscular (i.m) administration of the drug .The animals received the drug by i.m route first and then i.v route. A wash out period of three weeks was given between the two treatments.

Sampling

Blood samples were collected into heparinized tubes before drug administration and at 0.033, 0.083, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48 and 72 h after i.v. or i.m. administration of nimesulide. Plasma was separated by centrifugation (3700 g, 10 min at -4°C) within 30 min of sample collection, and aliquot fractions were stored at -20°C until assayed. Before analysis 1ml of Acetonitrile was added to 0.5ml of plasma in a test tube and mixed thoroughly by vertex mixer at high speed for 1min.The samples were centrifuged at 5000rpm for 10min. The supernatant was collected, filtered through 0.22µm nylon membrane filter.

Nimesulide assay

Analysis was carried out by HPTLC using CAMAG linomat 5 operated by WINCATS planar chromatography manager. Plasma samples were prepared using previously described method with little modification (Toutain et al., 2001). About 15µl sample was taken in the Hamilton syringe for spraying on the TLC plate. The glass plates (20×10cm) precoated with silica gel $60F_{254}$ (layer thickness 0.2mm) were used. Samples were sprayed onto the chromatographic layer from the tip of the syringe needle. The syringe volume was 100µl. The gas used for spraying was nitrogen (60-90 psi). The sample was uniformly distributed over the entire length of the band by carefully controlling stage movement. The samples were streaked in form of narrow bands or spots of 6mm with 10mm from the bottom edge and 10mm from the margins. The application volume was 8µl. The distance between the tracks was adjusted basing on the number of samples applied. The mobile phase used was a combination of cyclohexane and ethyl acetate (60:40, v/v) basing on polarity of the analyte. The chromatogram was run upto 90mm. The plates were developed in CAMAG twin trough glass chamber (20×10cm) saturated with the mobile phase. The developed plates were air dried. The analysis was carried out in TLC Scanner3 in absorbance mode. The slit dimension was 6.00×0.30mm and detection wavelength was 220nm. Data resolution was 100µm/step. The source of radiation was deuterium lamp. The scanning speed was 20mm/sec. The peak areas and Rf values were noted for subsequent calculations. Documentation was done in Camag Reprostar 3. Nimesulide was quantified from its peak height and the concentrations in plasma samples were determined by means of calibration curves obtained on analysis of blank bovine plasma samples spiked with nimesulide (external standard) and assayed as per the procedure employed for the experimental samples. The calibration curve constructed for nimesulide in bovine calf blood plasma was found to be linear over the range of 20-900ng/spot. The lower limit of detection (LOD) and lower limit of quantification (LOQ) were found to be 6.64ng and 20.12ng, respectively. The overall recovery of the drug in bovine plasma ranges from 91.3% to 99.96%.

Pharmacokinetic analysis

The individual plasma drug concentration-time profiles were analyzed using a nonlinear interactive curve-fitting computer program PHARMKIT (Sanyal, 1997). The appropriate pharmacokinetic model for each data set was determined by the application of the Akaike's Information Criterion (Yamaoka et al., 1978). In all animals, the disposition kinetics of nimesulide after i.v. and i.m. administration were best fitted by two- and one-compartment open models, respectively, and defined by the equations:

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \text{ (i.v. stydy)}$$

$$Cp = Be^{-\beta t} - A'e^{-kat} \text{ (i.m.stydy)}$$

Where Cp is the plasma concentration of nimesulide at time t, A, A' and B are the zero time intercepts, α , Ka and β are the first order rate constants related to the distribution, absorption and elimination phases, respectively, and e represents the base of natural logarithm.

The pharmacokinetic parameters of nimesulide were calculated according to Gibaldi and Perrier, (1982). The half-lives during the distribution ($t_{1/2\alpha}$), absorption ($t_{1/2Ka}$) and terminal elimination ($t_{1/2\beta}$) phases were calculated as follows:

$$t_{1/2\alpha} = \frac{0.693}{\alpha}$$

$$t_{1/2Ka} = \frac{0.693}{ka}$$

$$t_{1/2\beta} = \frac{0.693}{\beta}$$

The apparent volume of distribution ($V_{d(area)}$), steady- state volume of distribution ($V_{d(ss)}$) and total body clearance (Cl_B) of nimesulide following i.v, administration were calculated accord-

ing to the following equations:

$$Vd\ (area) = \frac{D}{\beta}\ (AUC)$$

$$Cl_B = \frac{D}{(AUC)}$$

Where D is the dose of the drug.

The mean absorption time (MAT), mean residence time (MRT) and bioavailability (F) were calculated using the following formulate:

$$MAT = MRT_{i.m} - MRT_{i.v}$$

$$MRT = \frac{AUMC}{AUC}$$

$$F = \frac{AUC_{im}}{AUC_{iv}} \times 100$$

The area under the plasma concentration-time curve (AUC) and area under the first moment curve (AUMC) were calculated according to the following

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}\ (i.v.\ study)$$

$$AUC = \frac{B}{\beta} - \frac{A'}{K_a}\ (i.m.\ study)$$

$$AUMC = \frac{A}{\alpha^2} + \frac{B}{\beta^2}\ (i.v.\ study)$$

$$AUMC = \frac{B}{\beta^2} - \frac{A'}{Ka^2}\ (i.m.\ study)$$

The maximum plama nimesulide concentration (C_{max}) and the time to reach the maximum plama concentration (t_{max}) were determined from the individual plasma concentration-time profiles.

Time after drug administration (h)	i.v.	i.m.
0.033	107.06±8.37	4.88±1.02
0.083	102.02±10.69	5.86±0.90
0.167	39.87±7.99	8.007±0.56
0.25	39.82±7.03	7.18±0.62
0.5	26.16±2.10	9.23±0.57
1	20.37±2.04	11.07±0.79
1.5	17.73±1.89	16.79±1.44
2	16.52±1.24	21.98±1.90
3	14.96±1.55	30.20±2.59
4	12.65±1.68	35.48±3.04
6	9.37±0.86	11.22±0.96
8	7.33±0.66	5.37±0.46
10	6.15±0.72	2.04±0.18
12	4.94±0.77	1.29±0.21
24	2.10±0.19	0.76±0.10
48	0.53±0.05	0.47±0.12
72	ND	0.31±0.03

Table 1: Mean±SD plasma nimesulide concentration (µg /ml. following i.v. and i.m.administration of 4.5mg/kg BW in bovines (n=6).

Kinetic Parameters	Units	Route of administration	
		i.v.	i.m.
A	µg/ml	88.87±9.82	
A'	µg/ml		482.74±30.07
B	µg/ml	16.54±1.62	2.97±0.18
A	h-1	4.74±0.20	
Ka	h-1		0.84±0.02
ß	h-1	0.08±0.0005	0.04±0.001
$T_{1/2\alpha}$	h	0.15±0.005	
$T_{1/2ka}$	h		0.85±0.008
$T_{1/2ß}$	h	9.02±0.06	20.08±0.79***
AUC	µg.h/ml	229.54±23.24	204.71±13.90
AUMC	µg.h2/ml	2577.18±264.14	2817.90±205.37
MRT	h	11.23±0.04	13.76±0.09**
Vd(area)	L/kg	0.26±0.02	
Vd(ss)	L/kg	0.22±0.02	
Clb	L/h/kg	0.02±0.001	
C_{max}	µg/ml		35.48±3.04
t_{max}	h		4.0±0.19
MAT	h		0.89 ±0.04
F	%		89.42±3.57

Table 2: Mean±SD of the pharmacokinetic parameters of nimesulide following i.v. and i.m.administration of 4.5mg/kg BW in bovines (n=6).

Statistical analysis

Results are presented as mean ± SD for the six calves. Harmonic means and pseudostandard deviations were calculated for the half-lives during the distribution, absorption and terminal elimination phases (Lam et al., 1985). Differences between respective mean values for half-life during the terminal elimination phase, AUC and MRT for the i.v and i.m, routes of administration were compared by unpaired t-test with Welch correction. All P-values <0.05 were considered statistically significant.

Results

The mean plasma concentration of nimesulide at specified time after single i.v. injection at a dose of 4.5mg/kg body has been presented in Table 1. The mean maximum plasma concentration (107.06±8.37 µg/ml, n=6) was observed at 2min (0.033h) and then reduced rapidly upto 1.5hr (17.73±1.89 µg/ml, n=6) and thereafter, the drug concentration in plasma declined gradually till it reached its mean minimum level of 0.53±0.05µg/ml (n=6) at 48h post administration. The concentration of nimesulide was not detected at 72hr interval. Table 2 summerizes the mean pharmacokinetic parameters following i.v. administration. The semi-

logarithmic plot of the observed and fitted plasma concentration of nimesulide vs time (h) after i.v. administration is shown as mean value for six representative bovine calves. The plasma concentration–time curve was best fitted to two compartment open model (Figure 1). The drug was rapidly distributed with $t_{1/2\alpha}$ of 0.15±0.005 h and slowly eliminated with $t_{1/2\beta}$ of 9.02±0.06 h. The apparent volume of distribution based on AUC ($V_{d(area)}$), $V_{d(ss)}$ and MRT were 0.26±0.02 L/kg, 0.22± 0.02L/kg and 11.23±0.04h, respectively. The total body clearance was 0.02±0.001L/h/kg.

The mean plasma concentration of nimesulide at specified time after single i.m. injection at a dose of 4.5mg/kgBW has been presented in Table 1. The mean maximum plasma concentration (35.48±3.04 µg /ml, n=6) was observed at 4.0±0.19h and then reduced rapidly upto 8h to a concentration 5.37±0.46µg/ml (n=6) and thereafter, the drug concentration in plasma declined gradually till it reached its mean minimum level of 0.31±0.03µg/ml (n=6) at 72hr post administration. The semilogarithmic plot of the observed and fitted plasma concentration (µg/ml) of nimesulide vs time (h) after i.m.. administration is shown as mean value for six representative bovine calves. The plasma concentration–time curve was best fitted to one compartment open model (Figure 1). After the i.m. administration, the absorption of nimesulide was rapid as indicated by the mean absorption time (MAT) of 0.89±0.04h (n=6).The MRT, which takes into account the absorption,distribution and elimination phases was 13.76±0.09h indicating that nimesulide persists for a long time in the bovine plasma after i.m. administration. The $t_{1/2\beta}$ (20.08±0.79h) was significantly higher($p<0.001$) than that was collected after the i.v. administration. The mean bioavailability of nimesulide was 89.42±3.57%. Similarly, the MRT was significantly longer ($p<0.005$) than that obtained after i.v. administration (Table 2).

Discussion

The disposition kinetics of nimesulide after i.v. dose of 4.5 mg/kg BW was best fitted by a two-compartment open model. A biexponential plasma concentration-time profile has also been previously reported in dogs given nimesulide @ 5 mg/kg intravenously (Toutain et al., 2001) and in goats given 4mg/kg i.v. (Rao et al., 2007). The half-life during the terminal elimination phase (9.02±0.06 h) of nimesulide in bovines is higher than dogs (8.5±2.1h; Toutain et al., 2001), goats (7.99±2.23h; Rao et al., 2007) and in sheep (7.11±0.83h; Malik et al., 2008). The mean residence time (11.23±0.04h) of nimesulide in bovines is lower than dogs (12.6±3.8h; Toutain et al., 2001),goats (11.72±3.42h; Rao et al.,2007) and higher than sheep (8.73±1.00h; Malik et al., 2008). Relatively shorter $t_{1/2\beta}$ of 6.13 h and MRT of 8.63 h of nimesulide were reported in horses after i.v. administration of nimesulide at 1.5 mg/kg BW (Villa et al., 2003). The variable half-lives encountered in different species may be due to difference in protein binding capacity of the drug in different species. The value of $Vd_{(ss)}$ of (0.22±0.02 L/kg) in bovines is lower than that in goats (0.64 ± 0.13 L/kg; Rao et al., 2007), in sheep (0.53±0.07 L/kg; Malik et al., 2008) and is higher than that in dogs (0.18 L/kg: Toutain et al., 2001a), in horses (0.117 L/kg; Villa et al., 2003) and in humans (0.18-0.39 L/kg; Bernareggi, 1998). Small volume of distribution of nimesulide in most of the species is similar to most NSAIDs, as they are highly bound to plasma proteins. High values of Vd have also been reported for other NSAIDs including flunixin in cows (1.05 L/kg; Hardee et al., 1985), tolfenamic acid in calves (1.79-3.2 L/kg: Lees et al., 1998) and celecoxib in humans (4.5 L/kg; Davies et al., 2000). Highly lipophilic drugs are characterized by a large volume distribution. The large Vd may also be due to altered and high-affinity tissue binding properties (Riviere, 1999). Celecoxib and nimesulide are known to posses high lipophilicity (Seedher and Bhatia, 2003). In bovines the Cl_B was 0.02±0.001L/h/kg lower than in goats (0.06±0.02L/h/kg) and almost similar in dogs (0.015±0.004L/h/kg).

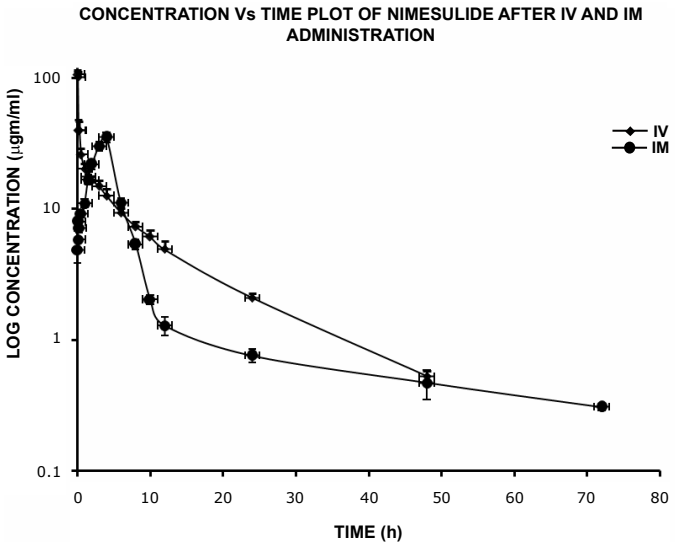

Figure 1: Semilogarithmic plot of the mean plasma nimesulide concentration-time profile following i.v and i.m. administration of nimesulide @ 4.5mg/kg BW. After administration of nimesulide blood samples were collected at 0.033h, 0.083h, 0.167h, 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h,10h,12h, 24h, 48h and 72h both in iv and im route of administration.

Although i.v. is not the most likely route of administration of nimesulide in goats, i.v. pharmacokinetic study was performed to establish disposition kinetic variables, such as $Vd_{(area)}$, $Vd_{(ss)}$ and Cl_B, which could only be obtained after i.v. administration. The values of area under the plasma concentration-time curves obtained after i.v. injection were employed for determination of bioavailability of nimesulide following i.m. administration. Intramuscular administration of nimesulide to bovines at a dose of 4.5 mg/kg BW was associated with rapid appearance of the drug in plasma. Plasma drug concentrations after i.m. injection were more prolonged than after i.v. administration. The maximum plasma drug concentration (C_{max}) of 35.48±3.04 µg/mL was observed at 4h post administration in bovines. A Cmax of 6.1±1.5 µg/mL was observed at 10.9 h in dogs given nimesulide at 5 mg/kg intramuscularly (Toutain et al., 2001). In goats and sheeps,the C_{max} values were reported to be (2.83 + 1.11 µg/mL) at 3.6h (Rao et al., 2007) and 8.65±1.09 µg/mL at 2h (Telang et al., 2008) given nimesulide @4mg/kg BW intramuscularly. Higher value of C_{max} was reported in horses even after oral administration of nimesulide at a dose much lower than that used in the present study. A C_{max} of 3.94 µg/mL at 3.5 h was reported in horses given nimesulide orally at 1.5 mg/kg (Villa et al., 2003). The value of AUC after i.m. administration of nimesulide in bovines (204.71±13.90 µg.h/mL) was 4.3 fold higher than in goats (47.22±14.01 µg.h/mL) at a dose of 4mg/kgBW i.m. In dogs AUC was reported to be (228±54 µg.h/ml) given the drug

at 5 mg/kg intramuscularly (Toutain et al., 2001). The $t_{1/2\beta}$ value after i.m. injection in bovines is 20.08±0.79h is higher than that in goats (13.03±1.71h), in sheep (6.27±0.30h) and in dogs (14.0±5.30h). The higher values of $t_{1/2\beta}$ and AUC in bovines are indicative of higher bioavailability of the drug. The systemic clearance in bovines (0.02±0.001L/h/kg) is similar to that in dogs and about one third of the systemic clearance in goats and in sheeps. Lower clearance in bovines is indicative of longer stay of the drug in the body.

The route of administration appears to influence the $t_{1/2\beta}$ and MRT of nimesulide. In the present study $t_{1/2\beta}$ and MRT of nimesulide after i.m. administration were 20.08±0.79h and 13.76±0.09h were 2.22 and 1.22 times longer, respectively, than the i.v. administration. In goats the $t_{1/2\beta}$ and MRT of nimesulide after i.m. administration were 1.63 and 1.73 times longer respectively than the i.v. route. Markedly longer $t_{1/2\beta}$ (1.6 times) and MRT (2.3 times) after i.m. injection of nimesulide when compared with i.v. administration were also reported in dogs (Toutain et al., 2001). The MAT of 0.89±0.04h was obtained following i.m. administration of nimesulide in bovines was shorter than that reported in dogs (17.6 h), receiving the drug intramuscularly at 5 mg/kg (Toutain et al., 2001) and in goats (8.5h) receiving 4mg/kg BW (Rao et al., 2007). This indicates that longer bioavailability of the drug is not due to decreased elimination but due to increased absorption. It is known that the disposition kinetics of certain drugs administered by extravascular route may exhibit 'flip-flop' phenomenon. Nimesulide administred intramuscularly was shown to follow a 'flip-flop' model in dogs (Toutain et al., 2001). This occurs when the value of elimination rate constant (β) divided by the absorption rate constant (ka) exceeds 3 and resultantly, the terminal slope estimates ka and feathered line β (Notari, 1987). Although terminal half-life of nimesulide was markedly prolonged following i.m. administration in this study, β/ka value of nimesulide after i.m. administration of 4.5 mg/kg was 0.04 suggesting lack of occurrence of the above phenomenon. The systemic availability of nimesulide in bovines after i.m. administration of 4.5 mg/kg was 89.42±3.57% while in goats 68% (Rao et al., 2007), 69% in dogs (Toutain et al., 2001). To the authors' knowledge, absolute bioavailability of nimesulide has not been determined in humans as no i.v. pharmacokinetic data of this drug are available.

Although both COX isoforms are involved in synthesis of prostanoids, COX-1 is constitutively expressed in nearly all cell types while COX-2, which is also constitutive in many tissues, is induced in inflammatory conditions. NSAIDs such as nimesulide that selectively inhibit COX-2 may not affect physiological functions of the prostanoids preferentially synthesized by COX-1 and COX1 inhibition-associated gastrointestinal damage. The present study determined that maximum plasma nimesulide concentration after an i.m. dose of 4.5 mg/kgBW in bovines is 35.48±3.04 µg/mL and that at 24 h is 0.76 + 0.10 µg/mL. The COX inhibitory activity of nimesulide may be instructive of approximating its effective plasma drug concentration, although direct evaluations between in vitro and in vivo findings must be made with caution. Previous studies have emphasized difficulty in comparing data between species as the drugs that are highly selective COX-2 inhibitors in one species may not necessarily exert the same selectively in other species (Pairet and van Ryn, 1998; Brideau et al., 2001).

This is the first report of the pharmacokinetics and bioavailability of nimesulide in bovines. Our findings suggests that there appear to be major differences between the pharmacokinetic properties of nimesulide in bovines and other species. The kinetic data established in this study provide highly useful information and suggest that nimesulide administered by i.m. route may be useful in the treatment of inflammatory disease conditions in bovines. Further studies are needed to determine the efficacy and safety of nimesulide in bovines with various inflammatory disease conditions.

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