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Eco-Friendly Meloxicam Replaces Eco-Demaging Diclofenac Sodium in Veterinary Practice in South Asia - A Review

K T Mahmood[1] , M.Ashraf[2] and M. U. Ahmad[3],

[1]Drug Testing Laboratory, Health Department, Punjab, Lahore [2]Department Of Pharmacology and Toxicology, Faculty of Biosciences, [3]Department of Epidemiology and Public Health, University of Veterinary and Animal Sciences, Lahore.

Abstract

Meloxicam is a non-steroidal anti inflammatory drug (NSAIDs). It has been reported as a safe substitute of diclofenac sodium which has been banned for veterinary use in Pakistan, Nepal and India due to its relay toxicity associated with the catastrophic and unprecedented decline in vulture population during last 17 years. Diclofenac was very cheap and commonly used drug and it was highly toxic when dose of 0.8 mg /kg was administered directly to the vulture in captivity. Although diclofenac is now regarded as a devastating environmental toxicant in recent times, but it is still used in veterinary practice. Meloxicam was safe for vultures up to the dose of 2 mg/Kg which is more than its likely maximum level of exposure (MLE) to wild vultures. Marked inter-species differences in the pharmacokinetics (PK) of NSAIDs had been reported and pharmacokinetic data could not be extrapolated from one species to another. However, consequent upon to relentless International pressures for elimination of diclofenac sodium from veterinary practice, the governments in the subcontinent are freely registering meloxicam for veterinary use without giving any due consideration to species specific PK-data. Manufacturers are selling veterinary injections of meloxicam without giving animal specific dosage. There is need to study pharmacokinetics of meloxicam in the domestic target species under local conditions, to enable its rational clinical use.

Keywords: *Meloxicam, eco-friendly, diclofenac, eco-damaging, veterinary use, inter-species variation.*

Introduction:

Vultures have great significance for human well-being from the ecological, social and religious viewpoints. The veterinary use of diclofenac sodium, a NSAID has been linked to the catastrophic decline in South Asian vulture population (95% plus since 1993). These birds were exposed to diclofenac sodium when scavenging on carcass of animal treated with diclofenac. The scavengers had died due to renal failure resulting from visceral gout related to relay toxicity of diclofenac. The present review paper briefly describes a major ecological damage by pharmaceutical product diclofenac sodium and subsequent finding of meloxicam as its safe and ecofriendly alternate in veterinary practice.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

NSAIDs are agents having anti-inflammatory analgesic and antipyretic effects[1].These drugs are used frequently and commonly in humans as well as in animals to manage pain, fever and inflammation for the treatment of different clinical conditions such as rheumatic disorders, musculo-skeletal disorders, sports injuries, menstrual cramps and other syndromes involving pain and inflammation [1,2]. These drugs have analgesic action at low dose and anti inflammatory action at high dose. As a class, NSAIDs account for about 5% of all prescriptions in Europe and the United States [3]. Many athletes self-administer NSAIDs prior to athletic participation to prevent pain and inflammation before it occurs [4]. NSAIDs are usually co administered as an adjunct to antimicrobial therapy in veterinary practice [5].

Sir John Vane (1927-2004), was awarded Noble prize in 1971 as he had clarified mechanism of action of NSAIDs. He discovered that NSAIDs had unique property of cyclooxygenase (COX) inhibition. The key enzyme COX plays vital role in prostaglandin (PG) formation. The prostaglandins produced within the body are directly concerned with inflammation, pain, fever, platelet aggregation and gastro protective action. His theory proposed in 1971, that the inhibition of prostaglandin (PG) formation by NSAIDs is the basis for

their therapeutic actions as well as for their side effects has gained general acceptance [6]. In the early 1990s, two COX isoenzymes, named COX-1 and COX-2, were identified which had different molecular structures and were encoded by different genes. Subsequent studies showed that COX-1 is constitutive and catalyses the production of prostaglandins involved in GI mucosal protection and other physiological activities. Whereas COX-2, mostly inducible, is responsible for the production of prostaglandins that mediate inflammation, pain and fever. Thus, COX-2 inhibition is usually responsible for the therapeutic effects of these drugs, whereas the typical adverse reactions are attributable to COX-1 inhibition [7, 8, 9].

The irrational and liberal use of NSAIDs adversely effect gastrointestinal tract and renal system. The most common adverse events related to the use of NSAIDs, include dyspepsia, heartburn and abdominal discomfort, GI haemorrhage, peptic ulcer and perforation [10]. NSAIDs-induced small bowel injury has also been reported [11]. The renal adverse events include fluid and electrolyte disturbances, tubulointerstitial nephritis, papillary necrosis, glomerular lesions and acute renal failure [12].

Vultures crisis:

There are nine species of vultures in the Indian subcontinent. These are the *Neophron percnopterus* (Egyptian Vulture), *Sarcogyps calvus* (Red Headed Vulture), *Gyps fulvus* (Indian Griffon Vulture), *Gyps himalayensis* (Himalayan Griffon), Aegypius monachus (Cinereous Vulture) and *Gypaetus barbatus* (Bearded Vulture) *Gyps bengalensis* (Oriental White-backed Vulture), *Gyps tenuirostris* (Slender billed Vulture*), Gyps indicus* (Long billed Vulture). These are strong birds in wild, having big wingspan and very good eye sight. They fed on carcasses of cattle. They tear apart flesh with their large, powerful beaks with hooked tips. The distinctive head of these scavengers is designed especially for eating carcasses, a fully feathered head would be difficult to keep clean from the blood and body fluids encountered in corpses. These birds are capable of digesting decaying meat at any stage of decay and withstand diseases that would lethal for any other living creature. Vultures are very sensitive to environmental changes because they are long-lived, need large territories, have selective diet, are at the top of the food chain and have a low breeding rate. Therefore, they are excellent indicators of the state of health within ecosystems. Indian society benefited from the rapid and hygienic removal of dead livestock by vultures, a flock of which can pick a cow carcass lean in a matter of minutes [13,14].

Vultures have great significance for human well-being from the ecological, social and cultural viewpoints especially in Pakistan, India Bangladesh, Nepal and South Africa. These scavengers are eco-cleaners and play a vital role in environmental health by consuming/disposing off carcasses of dead animals and thus reducing the risk of livestock born diseases. An absence of vultures scavenging on carcasses of animals would disturb the balance of ecosystem. Consequently, there would be great danger of spread of diseases such as brucellosis, tuberculosis, and anthrax [15]. Vultures are very important for Parsi and Tibetan communities for there religious custom of "sky burial "in tower of silence [16].

The population of South Asian had declined drastically during last 17 years (more then 95%). Three species of vultures namely *Gyps bengalensis, G. indicus and G. tenuirostris* native to Asia, were at high risk of global extinction in the wild. Decline of vulture populations was first recorded at the Kealadeo Ghana National Park, Rajasthan in

India during mid 1980's to mid 1990's. The International Union for Conservation of Nature, (IUCN) is the world's main authority on the conservation status of species. The IUCN Red List of Threatened Species founded in 1948, is the world's most comprehensive inventory of the global conservation status of plant and animal species. All of these three vulture species are on IUCN Red list as 'Critically Endangered', since 2000. It is the IUCN highest category of endangerment. [17,18]. Research work in Pakistan and India has indicated that extinction crisis of vultures had escalate [19,20]. The vulture population in South Asia has declined catastrophically in the last 2 decades, with population decreases since 1992 reported to be over 97% [21].

Diclofenac-as a cause of death

The internationally supported collaborative research sponsored by United States–based Peregrine Fund was carried out in Pakistan. The scientist had made a breakthrough by identifying the cause of the declines to be diclofenac, an anti-inflammatory drug commonly and frequently used in livestock in Asia since mid-1990s. Vultures were exposed to diclofenac when they consume carcasses of animals that were treated with this drug, a few days before death. Diclofenac caused death as it was responsible for elevated uric acid concentrations in serum causing visceral gout leading to kidney failure of vulture. The drug diclofenac reaches within body of these scavengers through dead livestock's treated with this drug prior to death. Experiments showed that captive vultures are highly susceptible to diclofenac, and are killed by kidney failure within a short time of feeding on the carcass of an animal treated with the normal veterinary dose. Residue analysis in kidney samples had shown a perfect 100% correlation between gout and diclofenac residues. Vultures fed either diclofenac or treated buffalo carcasses, died of gout. Thus, scientific link between the diclofenac and dramatic fall in the raptor numbers was established. A dose of 0.8 mg kg^{-1} was highly toxic to vulture. The estimated LD 50 was 0.1-0.22 mg kg^{-1}. [Lethal Dose LD50 is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals. The LD50 is one way to measure the short-term poisoning potential (acute toxicity) of a material. Vultures succumb to kidney failure and visceral gout when they eat a dead animal that has been treated with diclofenac [22, 23, 24]. It is added that normal therapeutic anti inflammatory dose for human is 3-4 mg / kg.

The precise mechanism of diclofenac toxicity in Gyps vulture is associated with decreased uric acid excretion [25]. It has been demonstrated that vulture susceptibility to diclofenac results from a combination of an increased reactive oxygen species, interference with uric acid transport and the duration of exposure. All these factors ultimately lead renal failure responsible for vulture's mortality [26].

The relay toxicity of diclofenac sodium (NSAIDs) may thus be taken as first clear cut case of eco- damage by a pharmaceutical product.

Broiler chicken experimental model

The University of Veterinary and Animal Sciences (UVAS), Lahore was requested by WWF Pakistan to evaluate toxicity of diclofenac. Consequently, a broiler chicken experimental model was designed and developed to study toxicity of diclofenac at Department of Pharmacology and Toxicology, UVAS, Lahore in April 2004 Different doses (1—16 mg kg^{-1}/bodyweight /day) of the drug were tried on broiler chicken. Study showed that diclofenac sodium was toxic in broiler chicken at dose

of 1.0 mg kg^{-1}. Signs and symptoms of morbidity/ postmortem findings were similar to those which were reported for vulture i.e. neck drooping, lethargy, visceral gout and renal failure as a consequence of uric acid deposit. A mortality of 60-80% was observed at therapeutical dose. This work had revealed that broiler chicken could serve as a good surrogate avian species for carrying out various toxicological studies at experimental level. The broiler chicken model was a very good model due to reproducibility, free availability and low price [27].

This model was used for screening of different NSAIDs in a pilot project UVAS Lahore. The result had shown that diclofenac was toxic whereas meloxicam, piroxicam and mefnamic acid were safe in broiler chicken [28].

Ban on diclofenac sodium

There was a relentless International pressure for putting ban on veterinary use of diclofenac. The Ministry of Environment, Pakistan had requested Ministry of Health (MOH), to look into the possibility for banning the use of diclofenac on priority basis. The MOH, Islamabad was provided details regarding environmental disaster emerging from relay toxicity of diclofenac which was linked with catastrophic / unprecedented decline in population of vulture in Pakistan. The issue was discussed in detail at the 199th meeting of the Drug Registration Board Ministry of Health, Government of Pakistan, Islamabad which was held on 23rd & 24th August, 2006. After listening to all stakeholders and keeping in view of the published /research carried out, Registration Board, MOH, Government of Pakistan had de-registered all the formulations of diclofenac used in veterinary practice. The diclofenac for veterinary use was also banned in India and Nepal in 2005 and 2006 respectively [29, 30, 31].

The corresponding author is conducting a survey in Pakistan to explore misuse of "formulations of diclofenac for human" in veterinary practice. Initial results were shocking showing that pharmaceutical malpractice of this misuse is common in Pakistan. It was also reported that after ban on diclofenac for veterinary use in India, freely available inexpensive formulations of diclofenac for human use are being misused on animals [32]. Liberal and wide use of diclofenac in veterinary practice is also affecting vulture populations in South Africa [33].

The affect of this ban was assessed and evaluated in India by taking 1488 liver samples from carcasses of livestock across seven Indian states. The residues of different NSAIDs were determined by means of the liquid chromatography-mass spectrometry. Result had indicated that diclofenac was present in 11.1% of samples taken between April and December 2006, and meloxicam (4%), ibuprofen (0.6%), and ketoprofen (0.5%) were also detected [34]. These observation had shown that NSAIDs were identified in 241 out of 1488, indicating that 68% of samples contained diclofenac residue whereas 24% of samples contained meloxicam residue. This assessment clearly indicated that ban on veterinary use of diclofenac was not effective. However, it was positive aspect that livestock sector was also using meloxicam which was reported as safe substitute of diclofenac.

Meloxicam, an alternate to diclofenac sodium:

Extensive research was followed for search of suitable alternate to veterinary diclofenac. The criteria was that alternate drug should be effective for animals but safe for vulture.

The pharmacokinetic characteristics like good absorption, longer half-life and

optimum bioavailability of meloxicam in human make it an ideal and suitable NSAID for use in animal [35]. Meloxicam was already registered for human use in Pakistan. It was also registered for use in small animals in the United Kingdom and USA prior to vulture crisis.

Studies at UVAS, Lahore

A pilot project was designed in December 2005, for carrying out toxicological studies on meloxicam at Department of Pharmacology and Toxicology, UVAS, Lahore, Pakistan. The result had indicated that the drug meloxicam was safe in chicken at dose of 1.6 mg kg^{-1}/day. The experiment was repeated during a PhD research project at Department Of Pharmacology and Toxicology, UVAS, Lahore, Pakistan, by administering different doses to the chicken up to the level 3.2 mg kg^{-1}/Day. Result had indicated that drug was safe at this high dose [36].

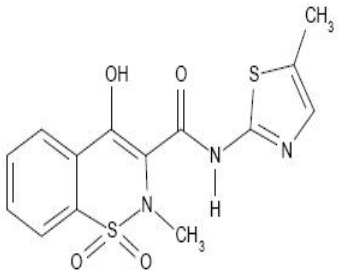
Direct administration of meloxicam to vultures in captivity

Since the three resident Gyps species in Asia (G. bengalensis, G. indicus and G. tenuirostris) were critically endangered and rare. These were not available for extensive safety study on meloxicam. So, African white-backed vulture *Gyps africanus* was identified as a surrogate species for Asian Gyps vultures. This is the closest relative of Oriental white-backed vulture *G. bengalensis* and is widespread and abundant in Africa. Captive, injured individuals destined for euthanasia were available for safety testing. The same clinical symptoms as *G. bengalensis* were obtained from diclofenac exposure, confirming at a 98% level of significance that diclofenac is as toxic for *G. africanus* as for *G. bengalensis*, and hence a suitable surrogate species [37]. A phased programme of safety testing for an alternative drug, meloxicam, was started on 24 vultures in 3 groups of 8 birds. All birds in phase's I-III survived and no adverse reactions were observed in vultures at any administered dose. There was no loss of body weight related to treatment, all blood parameters measured remained within their normal ranges, and there were no significant sub-lethal effects. Meloxicam was thus found to be safe at 2.5 x LD50 of diclofenac To increase confidence in safety of meloxicam a larger sample of vultures was required to be treated with meloxicam at an estimated maximum level of exposure (MLE). All birds survived at a higher dose of meloxicam and no loss of body weight was observed over 7 days. All blood parameters measured remained within their normal ranges (at 2 and 7 days after exposure). Further trials involving a total of 78 individuals from six Gyps species treated with meloxicam provide strong evidence that meloxicam are safe to Gyps vultures with no sub-lethal effects reported. More than 700 individuals from 43 species of birds have since been clinically treated with meloxicam, indicating that it is safe for a wide range of species. In the final phase, ten Asian vultures of two of the endangered species (*Gyps bengalensis, Gyps indicus*) were dosed with meloxicam by gavage, five of them at more than the likely MLE dosage. All meloxicam-treated birds survived all treatments, and none suffered any obvious clinical effects. Serum uric acid concentrations remained within the normal limits throughout, and were significantly lower than those from birds treated with diclofenac in other studies. The dose of drug was progressively increased from 0.5 to 1 mg /Kg vulture body weight and then to the highest dose of 2 mg kg^{-1} which exceeded likely maximum level of exposure (MLE) of meloxicam to wild vultures. It was concluded that meloxicam was of low toxicity to *Gyps* vultures and that its use in place of diclofenac would reduce vulture

mortality substantially in the Indian subcontinent [38, 39]. A recent reported study had indicated that meloxicam is eliminated from vulture at very fast rate. Thus less residual time indicates safety of meloxicam in vultures [40].

Meloxicam

It is an oxicam derivative, a member of the enolic acid group of NSAIDs. Meloxicam is a pale yellow crystalline solid. It is slightly soluble in acetone, soluble in dimethylformamide, very slightly soluble in ethanol (96%) and in methanol. It is insoluble in water at an acid-neutral pH and very highly soluble at a basic pH. Meloxicam has pKa values of 1.09 and 4.18 at pH values of 0 to 3 and 2.5 to 6.5, respectively .it is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. It has the following structural formula [41,42].



$C_{14}H_{13}N_3O_4S_2$.
M. wt. 351.4 dalton

Meloxicam is approved for human use in more than 70 countries including UK, USA, Europe and Canada. In Pakistan, 7.5 mg or 15 mg meloxicam tablets for oral administration are registered and available for human uses whereas Injection meloxicam 5mg/ml have been registered after ban of diclofenac for veterinary use.

Meloxicam preferentially inhibits COX-2 over COX-1. COX-2 is the inducible isoenzymes implicated in the inflammatory response, whereas COX-1 has cytoprotective effects in the gastric mucosa. Therefore, a preferential selectivity for one isoenzyme over another, as displayed by meloxicam, may have implications in the clinical setting in terms of a more favorable risk benefit profile [43]. This selectively inhibition of cyclooxygenase-2 is responsible pathophysiological conditions rather than cyclooxygenase-1, which is responsible for physiological processes [44]. It is binds strongly to plasma proteins (99.5%) and displays linear pharmacokinetics, with a half-life of 20-24 hours in human [45]. It has a favourable tolerability profile as compared to other NSAIDs. The therapeutic index of meloxicam is higher than that of other NSAIDs, including piroxicam, diclofenac, and indomethacin. Meloxicam forms four metabolites that undergo fast elimination, leading to a shorter half life ($t_{1/2}$) in comparison with piroxicam and tenoxicam. The pharmacologically inactive metabolites do not change renal blood flow and therefore have no capability for nephrotoxicity. A potent inhibitor of prostaglandin synthesis, meloxicam is used for the treatment of acute and chronic inflammation associated with musculoskeletal disease, and for the management of postoperative pain. Meloxicam has better safety and efficacy, in comparison to piroxicam and diclofenac sodium [46, 47, 48, 49, 50, 51].

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration. Tablets, oral suspension and capsules were shown to be bioequivalent. Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage

forms (capsules and tablets). With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/ml for 7.5 mg doses and 0.8 - 2.0 µg/ml for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Meloxicam is ~ 99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. It is almost completely metabolized and four pharmacologically inactive metabolites are found & excreted in urine and feces of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%) [52, 53].

Clinical trials in over 5000 patients with osteoarthritis and rheumatoid arthritis had shown that efficacy of meloxicam was comparable to piroxicam, diclofenac and naproxen. However, it has better safety profile. Meloxicam had produced significantly fewer gastrointestinal (GI) side effects than the comparators ($p < 0.05$). Perforations, ulcerations and bleedings occurred in 0.1%, 0.2%, 1.2%, 0.6% and 2.1% of meloxicam 7.5 mg, 15 mg, patients respectively ($p < 0.05$ for piroxicam and naproxen compared with meloxicam). Thus, safety profile may be likely to be due to its selective inhibition of COX-2 relative to COX-1 [54].

Pharmacokinetic-Pharmacodynamic (PK - PD) relationships and dose effects for meloxicam was studied in horses in order to propose a suitable dosage for use in clinical studies. The study was done on 6 adult horses conducted by use of a randomized, Latin-square design. Arthritis was induced in the right carpal joint of each horse by administration of Freund's complete adjuvant. Various dosages of meloxicam (0, 0.25, 0.5, 1.0, and 2.0 mg kg^{-1}, IV) were then administered. Validated endpoints including stride length and overall clinical lameness score (scale of 0 to 20) were used to assess the effect of meloxicam. The dose-effect relationship was quantified by use of a maximum possible effect (Emax) model. For stride length (expressed as a relative percentage increase from control values), the median effective dose (ED_{50}) was 0.120 mg kg^{-1} for an Emax of 11.15%. For clinical lameness score (expressed as an absolute increase from the control value), the ED_{50} was 0.265 mg kg^{-1} for an Emax of 9.16 units. The PK-PD analysis allowed calculation of a median effective concentration of 130 ng/mL for stride length and 195 ng/mL for lameness score. Use of the Emax model predicted a maximal possible increase in effect of 19.5% for stride length and 13.91 units for lameness score. For stride length and lameness score, the Hill coefficient (slope) was extremely high, which suggested a steep dose-effect relationship. Results of this study suggest that meloxicam is a potent anti-inflammatory drug in horses. A dosage of 0.6 mg kg^{-1}/d would be appropriate for use in a clinical study [55].

Meloxicam was evaluated for post operative pain management fallowing stifle joint surgery in dogs after intravenous administration and it was reported as useful NSAIDs [56].

The analgesic efficacy of an epidural morphine/mepivacaine combination alone versus epidural morphine/mepivacaine in combination with meloxicam administered prior to the onset of anesthesia was assessed in 20 dogs. Administration of meloxicam in addition to epidural morphine plus mepivacaine conveys improved analgesia as

compared with epidural morphine/mepivacaine combination alone. Postoperative analgesia was reliably maintained for 24 hours following administration [57]. Meloxicam has now been registered in USA for use on cat. For the control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy and castration when administered prior to surgery [58].

Ketoprofen Found Toxic to Vultures:

In search for alternate to diclofenac sodium for veterinary use, safety-testing experiments for ketoprofen, were carried out on Gyps vultures, an NSAID already in use in South "Mortalities occurred at dose levels of 1.5 and 5mg kg21 vulture body weight (within the range recommended for clinical treatment) with the same clinical signs as observed for diclofenac. Surveys of livestock carcasses in India indicate that toxic levels of residual ketoprofen are already present in vulture food supplies [59]. Ketoprofen, has been clearly shown to be toxic to Gyps vultures,

Pharmacokinetics:

The study of absorption, distribution, metabolism and excretion (ADME) of the drug is of great significance for evaluation of clinical outcome of any drug therapy. Therapeutic and toxic effects of drugs depend on the drugs concentration at the site of action. Pharmacokinetics is the discipline dealing with the rates of movement of a drug or it's metabolites into and out of the body [60].

Inter-ethnic and inter-species variations in clinical response to meloxicam

The genetics and environmental factors have strong impact on drug disposition in man [61]. This impact on ADME of drug is responsible for inter-individual and inter-species variations to clinical response.

In vitro activities of cytochromes P450 (7-alkyl/aryloxyresorufin dealkyl(aryl)ases, testosterone hydroxylase/oxidase, 6-chlorzoxazone hydroxylase, 7-methoxy-4-trifluoromethyl-coumarin demethylase, and lauric acid hydroxylases), reductases of carbonyl group (toward metyrapone, daunorubicin, glyceraldehyde, and 4-pyridine-carboxaldehyde) and conjugation enzymes (p-nitrophenol-UDP-glucuronosyl transferase, 1-chloro-2,4-dinitrobenzene glutathione-S-tranferase) in young adults, males, non-castrated (N=6) farm animals were studied and compared. Presence of proteins cross-reacting with anti-human CYP3A4, CYP2C9, and CYP2E1 IgG was detected in all farm species. Bovine microsomes differed from other microsomes of farm species in very high 7-ethoxyresorufin-O-deethylase activity (CYP1A1/2). Significantly higher 7-methoxy-4-trifluoromethyl-coumarin demethylase (2–3 times) and 12-lauric acid hydroxylases (4–10 times) activities (probably corresponding to CYP2C and CYP4A, respectively) were found in ovine microsomes. The highest 6β-testosterone hydroxylase activity, which is usually considered to be a CYP3A activity marker, was found in pig. Reductases of all farm animals display considerable ability to reduce carbonyl group of xenobiotics. Significant differences in level and activity of many biotransformation enzymes tested suggest that extrapolation of pharmacokinetic data obtained in one species to another (even related) could be misleading [62].

There are differences in the efficiency, safety and tolerability of NSAIDs among races and species. These differences may be due to variability in pharmacokinetics, protein binding, drug interaction and renal or hepatic disorder [55, 63].

The pharmacokinetic profile of the meloxicam was investigated in a number of animal species, including mice, rats, dogs,

mini-pigs, and baboons, after administration of [^{14}C] meloxicam. The plasma concentration-time profiles for meloxicam in rats and dogs were comparable to that in humans, whereas there were marked differences between humans and mice, mini-pigs, and baboons [35].

It had also been reported that disposition of meloxicam varied even among different avian species. Three Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [sodium salicylate, flunixin (FLU) and meloxicam (MEL)] were administered intravenously to broiler chickens. Plasma concentrations were determined by high-performance liquid chromatography methods and pharmacokinetic parameters were calculated. After intravenous administration of sodium salicylate (50 mg kg^{-1}), FLU (1.1 mg kg^{-1}) and MEL (0.5 mg kg^{-1}), these drugs were eliminated from plasma with a mean half-life of 04.04, 05.45 and 03.20 h, respectively. Apparent volumes of distribution (0.39, 0.08 and 0.12 l/kg, respectively) indicated that tissue distribution was limited for the three drugs. Total body clearance was 70 ml/h kg for sodium salicylate and 10 and 25 ml/kg h for FLU and MEL, respectively. Based on the pharmacokinetic parameters these NSAIDs may offer possibilities for treatment of various conditions in chickens, [64].

Similarly variations in elimination half-lives for meloxicam were reported in pigeons (2.4 h), ducks (0.72 h), turkeys (0.99 h) and ostriches (0.5 h) after intravenous administration of meloxicam at 0.5 mg kg^{-1} [65] whereas $t_{1/2}$ of 2.7 h reported in piglets [66]. The half life of meloxicam in vulture is about one hour [40].

The pharmacokinetics of meloxicam was studied in female rabbit. The single oral doses of 0.3 and 1.5 mg kg^{-1}/day were given and repeated for 5 days to female rabbits (n = 5/group) to define the optimal dose and dosing interval for clinical use. Clinical signs, body weight, and serum chemistry parameters (sodium, potassium, chloride, total protein, urea, creatinine, glucose, alkaline phosphatase, gamma glutamyl transferase and alanine aminotransferase) were evaluated before and 5 d after dosing to monitor safety at the 2 dose levels in both studies. Plasma samples were collected serially, and concentrations were determined by high performance liquid chromatography. After single oral dosing at 0.3 or 1.5 mg kg^{-1}, maximal plasma concentrations of meloxicam were achieved at 6 to 8 h and were 0.14 and 0.3 microgram/ml, respectively. Plasma drug levels decreased rapidly to near-undetectable levels by 24 h. There was moderate interindividual variability in plasma meloxicam concentrations with less than proportional increases in peak plasma concentration and area under the concentration curve values at the higher dose after the single and repeat dosing. The elimination half-life was approximately 8 h at both dose levels, suggesting that metabolism was not saturated. Oral clearance of meloxicam is high in rabbits, indicating rapid metabolism and elimination. There was no accumulation of meloxicam when given at 0.3 or 1.5 mg kg^{-1} for 5 d, and meloxicam was rapidly eliminated after discontinuation of dosing. Rabbits may require a dose exceeding 0.3 mg kg^{-1} given once daily to achieve optimal plasma levels of meloxicam over a 24-h interval [67].

A study was done in goats and sheeps to compare pharmacokinetics of meloxicam. The results had shown that sheep eliminate meloxicam slower than do goat [68]. It is added that variation in pharmacokinetics of oxytetracycline, ampicillin and gentamicin have already been reported in Nubian goats and desert sheep [69]. The variation in two related speices clearly suggest that

extrapolation of PK.data of this NSAID from one species to another species would be misleading and study in target speices is vital to ensure rational drug therapy.

Inter ethnic differences in response to many drug therapies have been reported in human. Marked gender -dependent racial differences in disposition of cyclosporine among healthy African American and white subjects were observed [70].

In a study marked differences in pharmacokinetics of meloxicam were observed in Chinese populations. It was reported that pharmacokinetic profile of meloxicam in Chinese volunteers was different from white population. They carried out Pharmacokinetic profile of single doses of meloxicam in healthy volunteers. The plasma concentrations of meloxicam after an oral dose of 15 mg to twenty healthy Chinese male volunteers were analyzed by means of a validated HPLC method. The twenty volunteers can be classified into extensive metabolizers and poor metabolizers according to pharmacokinetic parameters. The main parameters in the two groups obtained were as follows: $t_{1/2}$ were 21 $\pm$ 4 and 38 $\pm$ 9 h, AUC 0-infinity were 49 $\pm$ 10 and 110 $\pm$ 8 $\mu g.h.mL^{-1}$, respectively. Even the AUC data in extensive metabolizers was 1.7 times as that reported in White volunteers following the same doses of meloxicam. There were significant individual differences in the pharmacokinetics of meloxicam in Chinese volunteers, which may be due to the genetic polymorphism of CYP2C9 [71]. In another study it is reported that Germans and Indian have different pharmacokinetic characteristics [72].

Pharmacokinetics of Meloxicam in Different Species, A Study at Uvas, Lahore:

The pharmacokinetic parameters of meloxicam were characterized in various domestic animals dogs, horses, donkeys, buffalo and goats, at the Department of Pharmacology and Toxicology, UVAS, Lahore. The main aim of the study was to explore inter species variations of meloxicam pharmacokinetic parameters under local conditions of Pakistan in order to make recommendation for rational drug therapy with meloxicam. The statistical analyses of the results were performed by applying ANOVA and LSD test for multiple comparisons. The results had indicated that lot of variations existed in pharmacokinetic behavior of meloxicam among dogs, horses, donkeys, buffalos and goats. The respective mean$\pm$ SE half lives ($t_{1/2}$) were 23.40$\pm$0.40, 8.17$\pm$0.60,1.00 $\pm$ 0.01,15.43$\pm$0.63 and 7.34$\pm$0.31 h [73].

Conclusion and Recommendations:

The vultures are of great significance for maintaining balance of ecosystem in South Asia including Pakistan and India. It had been established scientifically that relay toxicity of a non-steroidal anti-inflammatory drug diclofenac sodium was responsible for catastrophic / dramatic fall in Asian vulture population within Indian subcontinent.

Eco-damaging diclofenac sodium responsible was banned for veterinary use in Pakistan, India and Nepal during 2005-06. However, an efficient mechanism should be developed to prevent misuse of formulations of diclofenac for human use being used on animals.

The ecofriendly meloxicam is suitable alternate to diclofenac for veterinary use. But interspecies variations in pharmacokinetic of meloxicam limit the extrapolation of data from one species to another. There is need to study pharmacokinetic profile in the domestic target species under local conditions, to enable its rational clinical use.

The livestock sector is fully aware that better high quality yields of meat, milk and

other diary product depend on better health of animals. The infections, inflammations and pain may adversely affect livestock sector. So, we need to carry out trials for assessment of minimum effective plasma concentration of meloxicam for management of different pains emerging from clinical conditions. The interaction with antibiotics must be studied as NSAIDs are usually co administered as an adjunct to anti microbial therapy in veterinary practice.

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