Diclofenac: a vulture-toxic drug

Summary of evidence that diclofenac is toxic to vultures and is the main, if not sole, cause of catastrophic vultures declines in South Asia; and that meloxicam, an alternative to diclofenac, is not toxic to vultures, as well as a safe and effective veterinary drug

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SAVE is an international consortium of conservation and research organisations whose mission is to respond to the vulture crisis in Asia by striving to halt vulture population declines and working to minimise their negative impacts on ecological and human health. For further details go to www.save-vultures.org

Diclofenac is toxic to *Gyps* vultures; however, meloxicam is not toxic to *Gyps* vultures and an effective alternative for veterinary purposes

Aim

This paper, intended for decision-makers involved in drug licensing, presents evidence of the toxicity of diclofenac, a non-steroidal anti-inflammatory drug (NSAID), to *Gyps* vultures; and the safety, to both vultures and domesticated animals, and effectiveness, in domesticated animals, of meloxicam, an alternative NSAID.

Executive summary

1. The NSAID diclofenac was found to be the main, if not sole, cause of the decline of G*yps* vultures in South Asia. Wild vultures are exposed to NSAIDs when feeding on carcasses of domesticated ungulates treated with these drugs shortly before death.

2. Beginning in the mid-1990s, dead and dying vultures were being found with visceral gout. A breakthrough in our understanding of the vulture declines occurred when a perfect association was found between the presence of visceral gout and diclofenac residues in vulture carcasses found in Pakistan. Experimental evidence confirmed that diclofenac was toxic to White-rumped vultures *Gyps bengalensis*.

3. These findings were repeated across a large proportion of the species range in India and Nepal, and was extended to a second *Gyps* species, Long-billed Vulture *G. indicus*.

4. Diclofenac was experimentally shown to be toxic to two other members of the *Gyps* genus, White-backed Vulture *G. africanus* and Eurasian Griffon *G. fulvus*, suggesting that it is likely to be toxic to all *Gyps* species.

5. The proportion of cattle carcasses required to be contaminated with diclofenac residues to explain the extent of the reduction in vultures numbers was estimated to be only between 1:130 and 1:760, strongly suggesting that diclofenac poisoning was at least a major cause of the population declines.

6. Experimental evidence showed that, although diclofenac concentrations decline rapidly within the tissues of treated cattle, enough of the drug remains to cause appreciable mortality if birds were to take a large meal from a carcass from an animal that was given its last dose within a few days of death.

7. Further refinements of population models demonstrated that most if not all excess mortality was caused by diclofenac poisoning. Therefore, it could be concluded that diclofenac poisoning was the main, if not the sole, cause of the declines of *Gyps* vultrues across the Indian subcontinent.

8. Captive vultures are also exposed to NSAIDs through veterinary care. A survey of wildlife veterinarians found the use of diclofenac caused visceral gout and death in 28 out of 36 cases involving a captive *Gyps* vulture.

9. The maximum level of exposure (MLE) of a given drug to a *Gyps* vulture is intended to reflect the largest dose of the drug likely to be encountered by that species in the wild. The MLE for an NSAID is calculated from the body weight of a given vulture species, the weight of a large meal for that species and highest tissue-specific residue concentration of the NSAID in tissues of a

domesticated ungulate treated with the drug. The MLE for meloxicam was calculated assuming that cattle in India may typically be dosed with twice the recommended amount.

10. In contrast to diclofenac, the NSAID meloxicam has been shown to be non-toxic to *Gyps* vultures above the MLE.

11. Two experiments showed that oral doses of meloxicam above the MLE did not cause hyperuricemia or any other ill effects in 50 individual *Gyps* vultures from three species: African white-backed vultures *Gyps africanus*, Asian white-backed vultures *Gyps bengalensis* and long-billed vultures *Gyps indicus*. These experiments also showed that tissues from cattle and buffalo dosed with meloxicam with some doses at the MLE did not cause hyperuricemia or any other ill effects in *Gyps* vultures. Further, oral doses of meloxicam above the MLE did not cause hyperuricemia or any other ill effects in other scavenging species, including Egyptian vultures *Neophron percnopterus*, cattle egrets *Bubulcus ibis*, crows *Corvus spp.* and common myna *Acridotheres tristis*.

12. Meloxicam is manufactured in Bangladesh, India, Nepal and Pakistan. Experimental and clinical studies have shown largely positive effects of meloxicam treatment domestic animals. Meloxicam has been shown to be an effective treatment for pain, inflammation, dysfunction and stress in a variety of veterinary and husbandry situations. In addition, meloxicam has been shown to increase recovery, pregnancy rate, productivity and survival in a variety of domesticated animals. Findings of negative, mixed and no effects for meloxicam treatment are rare.

13. To conserve critically endangered *Gyps* vultures, veterinary and multiple- dose vials of human diclofenac were banned throughout South Asia. Such a comprehensive ban has had a positive effect on the population trends of Critically Endangered *Gyps* vultures, and is unlikely to impact

livestock healthcare because meloxicam is a safe, effective and widely available alternative to diclofenac.

Supporting evidence

We present several lines of supporting evidence.

1. Post-mortems were carried out on 259 Oriental White-backed Vultures (OWBV) that died in Pakistan, 85% of which had visceral gout. Further necropsies on a subset of these birds (n = 42) showed that those with visceral gout (n = 28) also had detectable levels of diclofenac residues in the blood, while those with no visceral gout (n = 14) had no diclofenac. Initial enquiries to veterinarians and pharmacists highlighted that a non-steroidal anti-inflammatory drug (NSAID) diclofenac had recently come onto the market and was known to cause kidney failure. Experimental dosing of vultures with diclofenac demonstrated that the drug was toxic to vultures and that birds also displayed severe visceral gout along with detectable diclofenac residues in the blood. This suggested that diclofenac was likely to be the cause of the vulture declines (further details, pp. 11-14).

2. Post-mortems and analysis of liver and kidney samples were carried out on a smaller number (n = 28) of both OWBV and Long-billed Vultures *G. indicus* (LBV) found in India and Nepal, 18 (72%) of which had extensive visceral gout. All birds that had visceral gout also had detectable diclofenac, but none was found in birds without visceral gout. This repeat of the results from Pakistan demonstrated that the effects of diclofenac extended over much of the vultures' range and was now confirmed for a second species, LBV (further details, pp. 15-17).

3. In South Africa, a single-phased controlled experiment examined toxicity of diclofenac to African white-backed vultures *Gyps africanus* and Eurasian griffon vultures *G. fulvus*. Vultures were given an oral dose of diclofenac at 0.8 mg kg^{-1} body weight. Blood samples were taken for

analysis of uric acid and other biochemical components; and all vultures that died and one that survived, but was euthanized, were given full post-mortem examinations. All diclofenac-treated individuals died; whereas, all control individuals survived. Elevated uric acid and ALT concentrations in plasma were observed in diclofenac-treated vultures, but not the control individuals. Kidney damage and visceral gout was observed in all diclofenac-treated vultures, but not the control individual that was euthanised. These results suggested that diclofenac poisoning is likely to be a common result in all *Gyps* vultures (further details, pp. 18-19).

4. A simulation model of vulture demography demonstrated that the excess mortality responsible for the observed rates of population decline of vultures across the Indian subcontinent could be caused by contamination with a lethal level of diclofenac in a small proportion of ungulate carcasses available to vultures. This figure was between 1:130 and 1:760. The proportion of vultures found with signs of diclofenac poisoning was similar to model predictions if this was the sole cause of vulture declines (further details, pp. 20-22).

5. Cattle were experimentally dosed with either 1.0 or 2.5 mg kg^{-1}, to assess how concentrations of diclofenac changed within carcasses in relation to the time elapsed between the cow's death and its last injection. Based on the earlier dose-response model of Swan *et al*. (2006), it was possible to estimate the relationship between the rate of diclofenac-induced mortality and the dose of the drug consumed. Although diclofenac concentrations decline rapidly within the tissues of treated cattle, enough of the drug remains to cause appreciable mortality if birds were to take a large meal from a carcass from an animal that was given its last dose within a few days of death (further details, pp. 23-25).

6. Based on the distribution of diclofenac concentrations in ungulate carcasses, the probability of a bird dying given a certain concentration of the drug, and the interval between meals, we estimated the death rate per meal was 2.66% (for a feeding interval of 2 days) or 3.23% (for 3 days). From these figures it was estimated that the rate of decline would be between 80-99% if diclofenac was the only cause, which was higher than the actual decline of 48% discovered

through road transect surveys. However, the precision of the model estimates was low, and there was no significant difference between the two values, suggesting that diclofenac poisoning was the main, if not the sole, cause of the decline of *Gyps* vultures across the Indian subcontinent (further details, pp. 26-28).

7. A questionnaire on the consequences of therapeutic use of NSAIDs on *Gyps* vultures was sent to centres holding captive birds worldwide. Diclofenac caused visceral gout and death in 28 out of 36 *Gyps* vultures. In contrast, meloxicam did not cause mortalities in 40 *Gyps* vultures and another 700 birds of a variety of species (further details, pp. 29-32).

8. The effect of meloxicam on *Gyps* vultures was examined in a six-phase partially controlled experiment conducted in South Africa and India. Phases were: (1-2) 10 African white-backed vultures *Gyps africanus* were given an oral dose of meloxicam at 0.5-1.0 mg kg^{-1} body weight (bw); (3-4) 40 African white-backed vultures *Gyps africanus* were given an oral dose of meloxicam at 2.0 mg kg^{-1} bw; (5) six African white-backed vultures *Gyps africanus* were twice fed meloxicam-contaminated cattle tissue and once given an oral dose of meloxicam at >0.01-1.98 and 1.18-2.45 mg kg^{-1} bw, respectively; and (6) six Asian white-backed vultures *Gyps bengalensis* and four long-billed vultures *Gyps indicus* were given an oral dose of meloxicam 0.5-2.0 mg kg^{-1} bw. The maximum level of exposure (MLE) of meloxicam to Asian white-backed vulture *Gyps bengalensis* was calculated as 1.83 mg kg^{-1} bw. In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived. Uric acid concentrations in plasma in all meloxicam-treated vultures remained within the normal range (further details, pp. 33-35).

9. The effect of meloxicam on *Gyps* vultures and other common scavenging birds was examined in a three-phase controlled experiment in India. Phases were: (1) six Asian white-backed vultures (OWBV) *Gyps bengalensis* and four Long-billed vultures *Gyps indicus* (LBV) were given an oral dose of meloxicam at 0.5 or 2.0 mg kg^{-1} bw; (2) five Egyptian vultures *Neophron percnopterus*, five cattle egrets *Bubulcus ibis*, five crows *Corvus* spp. and five common myna

Acridotheres tristis were given an oral dose of meloxicam at 2.0 mg kg^{-1} bw; and (3) 19 OWBV and two LBV were fed tissue from buffalo dosed with meloxicam. In all Phases, all meloxicam-treated birds survived with no ill effects. All control birds survived. Uric acid and ALT concentrations in serum in all meloxicam-treated birds was not significantly different to that of control birds (further details, pp. 36-38).

10. A total of 117 studies reported an effect of meloxicam treatment, 79% of which were positive. A negative, mixed, no effect or no conclusion was reported in only 2, 8, 7 and 2%, respectively. Meloxicam showed a positive effect for most husbandry and veterinary situations, treatment objectives and types of domesticated animal. Overall, only three studies reported negative effects of meloxicam treatment resulting in breeding complications; however, two studies reported positive effects of meloxicam treatment resulting in no breeding complications and five studies reported positive effects of meloxicam treatment resulting in increased pregnancy rates (further details, pp. 39-43).

Specific details

Chemical name: **diclofenac**

Systematic name: 2-(2,6-dichloranilino) phenylacetic acid

Formula: $C_{14}H_{11}Cl_2NO_2$

Molar mass: 296.1 g mol^{-1}

Typical formulation: 50 or 83 mg/ml injection in 1-3 ml vials or in tablet form

Example products (manufacturers):

Manufacture, import / export and use for veterinary purposes banned by the Governments of India, Pakistan and Nepal in 2006; and Bangladesh in 2010. Recently also banned in Cambodia (2019), Iran (2019) and Oman (2020).

Chemical name: **meloxicam**

Systematic name: 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide

Formula: $C_{14}H_{13}N_3O_4S_2$

Molar mass: 351.403 g/mol

Typical formulation: 5 or 10 mg/ml injection in 30, 50 or 100 ml vials; and 100 mg bolus

Example products (manufacturers):

Bangladesh – Mel-Vet (ACME), Meximol (Ethical drugs), MP-Vet (Chemist Laboratories)

India – Diclovet-M and Melodic (Umedica), Melonex (Intas), Melosafe and Meloxicon (Safecon), Melovet (Zee), Proxyvet-MP (Health Biotech), Xyclofen (Iskon)

Nepal – Melocam (CTL), Melox (Medivet), Molfen (Qumed)

Pakistan – Camilox and Meloxi-10 (Selmore), Diclostar (Star), Diclosym and Melocsym (Symans), Metrym (Nawan)

1. A perfect association between the presence of visceral gout and diclofenac residues in dead wild Oriental White-backed Vultures, and experimental evidence that demonstrates toxicity of diclofenac to OWBV, suggests that this widespread drug is the cause of the decline of *Gyps* vultures across South Asia.

Published source

Oaks, J. L., Gilbert, M., Virani, Z., Watson, R. T., Meteyer, C. U., Rideout, B. A., Shivaprasad, H. L., Ahmed, S., Chaudhry, M. J. I., Arshad, M., Mahmood, S., Ali, A. and Khan, A. A. (2004). Diclofenac residues as the cause of vulture population declines in Pakistan. Science 427: 630-633.

Background

Gyps vultures had been declining in South Asia since the mid-1990s. Many dead vultures had been found with signs of kidney failure and visceral gout but, as these could be symptoms of various agents, the race was on to determine the cause of the declines.

Action

Post-mortem analysis was carried out on 259 adult and subadult Oriental White-backed Vultures *Gyps bengalensis* (OWBV), followed by detailed necropsies and diagnostic testing on 42 OWBV that had been found within 24 hours of death.

Given negative results for all tested substances, viruses etc, it was hypothesised that ingested veterinary pharmaceuticals may be responsible; given the combination of renal failure and the necessity of oral consumption, a survey of 74 veterinarians and pharmacies in the local area identified diclofenac (a non-steroidal anti-inflammatory drug, or NSAID) as the only drug that met these criteria. Using liquid chromatography and mass spectroscopy, samples were tested for diclofenac. A further survey of 84 drug retailers and veterinarians found that 77 sold it daily, and that the 71 reported that it had become available in the last five years.

To verify renal toxicity of diclofenac in OWBVs, oral doses of the drug were administered to four birds, two given a high dose of 2.5 mg kg^{-1}, corresponding to the mammalian label dose, and two given a low dose of 0.25 mg kg^{-1}.

Finally, to verify that carcasses of treated livestock would contain sufficient diclofenac concentrations to cause renal failure and death in scavenging vultures, twenty OWBVs were fed meat from livestock treated with varying doses of diclofenac shortly before death. Based on the product of the concentration of the drug in the meat and the amount of meat consumed, vultures received doses ranging from 0.007 – 0.940 mg kg^{-1} (see *Key figure*).

Findings

Post-mortems were carried out on 259 OWBV, of which, 219 (85%) had visceral gout.

Following necropsy, 28/42 OWBV had visceral gout, 14 did not. Combination of visceral gout and lack of histopathological lesions indicative of acute renal failure or infectious disease suggested a toxic cause.

The following causes of avian renal disease were ruled out: cadmium, lead and mercury poisoning; avian influenza, infectious bronchitis and West Nile viruses; toxic concentrations of arsenic and toxic or deficient concentrations of copper, iron, manganese, molybdenum and zinc. Carbamate and organophosphate pesticides, organochlorine pesticides and polychlorinated biphenyls were either not detected or were detected at below toxic concentrations. No viruses from the kidney, spleen, lung or intestine were isolated.

Diclofenac residues (0.051-0.643 µg g^{-1}) were detected in 25 (100%) vultures that died of renal failure, and in 0/13 (0%) of vultures that died of other causes.

Of 20 vultures fed meat from a buffalo or goat that had been treated with therapeutically recommended doses of diclofenac, 13 died, all showing signs of renal failure and visceral

gout. Three (of six) vultures fed uncontaminated meat showed no signs of renal failure or visceral gout.

Conclusion

Diclofenac was the cause of the symptoms (renal failure and visceral gout) found in dead wild vulture, and is toxic to OWBV. Given the widespread veterinary use of the drug, it is likely to be the cause of the vulture declines across the Indian subcontinent.

Key figure

Table 2 **Results of experimentally feeding meat from diclofenac-treated animals to OWBVs**

Vulture no	Exposure (mg kg^{-1})	Result	Diclofenac residues (μg g^{-1})
11	0.007	Gout	0.38
12	0.025	Survived	ND
8	0.027	Survived	ND
10	0.028	Survived	ND
7	0.029	Survived	ND
9	0.029	Survived	ND
D	0.140	Gout	0.07
F	0.240	Survived	BDL (8 days)
H	0.550	Gout	0.25
B	0.600	Survived	BDL (8 days)
64	0.820	Gout	0.54
65	0.820	Gout	ND
62	0.840	Gout	0.22
63	0.840	Gout	0.12
70	0.860	Gout	0.74
67	0.860	Gout	ND
68	0.860	Gout	ND
66	0.880	Gout	0.26
73	0.910	Gout	0.91
72	0.940	Gout	ND
1	None (control)	Survived	ND
2	None (control)	Survived	ND
3	None (control)	Survived	ND
4	None (control)	Survived	ND
cc1	None (control)	Survived	BDL (8 days)
cc2	None (control)	Survived	BDL (8 days)

Values in parentheses in the last column indicate time after exposure. OWBVs that died and displayed gross characteristics of visceral gout on necropsy are labelled as 'Gout' in the third column. BDL, below detection limit of diclofenac assay (0.005–0.01 μg g^{-1}); ND, analysis not done.

2. Evidence for the impact of diclofenac on *Gyps* vulture mortality found in a second species and extended to a large proportion of the species' ranges across the Indian subcontinent.

Published source

Shultz, S., Baral, H.S., Charman, S., Cunningham, A.A., Das, D., Ghalsasi, G.R., Goudar, M.S., Green, R.E., Jones, A., Nighot, P., Pain, D.J. & Prakash, V. 2004. Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. *Biology Letters*, **271,** S458-S460.

Background

Evidence from a previous study of *Gyps bengalensis* in Pakistan strongly implicated mortality caused by poisoning by the veterinary NSAID diclofenac as the major cause of vulture declines, not only in Pakistan but potentially across the Indian subcontinent. It found a perfect association between visceral gout (and renal failure) and diclofenac residues in the kidneys. The aim of this study was to assess whether diclofenac poisoning was the cause of the decline over a much wider area.

Action

Liver and kidney samples were taken from recently dead vultures (15 Oriental White-backed Vultures (OWBV) and 13 Long-billed Vultures (LBV)) collected between 2000 and 2004 in India and Nepal. Post-mortems were carried out. Of 13 OWBV and 12 LBV for which the presence or absence of visceral gout could be determined, tissues of 11 OWBV and 7 LBV were also analysed for diclofenac residues. Diclofenac was extracted from 0.5 g samples of kidney or liver tissue, and analysed by HPLC-MS-MS.

Findings

Eighteen (72%) of the 25 birds had extensive visceral gout (see *Key figure*). Proportions of OWBV and LBV were similar. Diclofenac was detected at concentrations in the range 0.004-

0.16 µg g^{-1}. Seventy-seven percent (10/13) of the OWBV and 63% (5/8) of the LBV had detectable residues.

All 14 birds with gout had detectable diclofenac, but diclofenac was not found in the four birds without gout, a result that significant for each species individually (Fishers exact test: OWBV, $p = 0.018$; LBV, $p = 0.048$).

Conclusions

The complete and highly significant association between the presence of diclofenac and that of visceral gout (see *Key figure*) mirrored the results from the previous study in Pakistan, and demonstrated that the effects of diclofenac on mortality of *Gyps* vultures extended over a large proportion of the species range on the Indian subcontinent, where populations were in steep decline. The study also extends the impact of diclofenac to a second species, and was now confirmed for OWBV and LBV.

Key figure

Table 1. Numbers of dead oriental white-backed (OWBV) and long-billed (LBV) vultures collected in India and Nepal with and without visceral gout.
(The table shows numbers of individuals. Subscripts represent numbers of juveniles, subadults and adults, respectively.)

species	gout	no gout
OWBV	$10_{(1,3,6)}$	$3_{(0,2,1)}$
LBV	$8_{(2,3,3)}$	$4_{(0,1,3)}$
both species	18	7

Table 2. Co-occurrence of diclofenac residues and visceral gout in oriental white-backed (OWBV) and long-billed (LBV) vultures in India and Nepal.
(The table shows numbers of individuals. Subscripts represent numbers of juveniles, subadults and adults, respectively.)

	species	diclofenac	no diclofenac
gout	OWBV	$9_{(1,3,5)}$	0
	LBV	$5_{(2,2,1)}$	0
	both species	14	0
no gout	OWBV	0	$2_{(0,1,1)}$
	LBV	0	$2_{(0,1,1)}$
	both species	0	4

3. A toxicity experiment finds diclofenac causes kidney failure and death in two additional species of *Gyps* vultures

Published source

Swan, G. E., Cuthbert, R. J., Quevedo, M., Green, R. E., Pain, D. J., Bartels, P., Cunningham, A. A., Duncan, N., Meharg, A. A., Oaks, J. L., Parry-Jones, J., Shultz, S., Taggart, M. A., Verdoorn, G., Wolter, K. (2006). Toxicity of diclofenac to *Gyps* vultures. *Biology Letters* **2**: 279-282

Background

Diclofenac is toxic to Asian white-backed vultures *Gyps bengalensis*. This experiment was undertaken to examine toxicity of diclofenac to other species of *Gyps* vulture.

Action

A single-phased controlled experiment was undertaken in South Africa.

Two African white-backed vultures *Gyps africanus* and three Eurasian griffon vultures *Gyps fulvus* were given an oral dose of diclofenac at 0.8 mg/kg body weight (bw); and another two white-backed and three Eurasian griffon vultures *Gyps fulvus* were given an oral dose of sterilized water.
Blood samples were taken from all vultures before and 4, 12 and 24 h after dosing. Plasma was

analysed for uric acid and other biochemical components. All vultures that died and one that survived, but was euthanized, were given full post mortem examinations. Liver and kidney samples were analysed for diclofenac residue using liquid chromatography mass spectrometry.

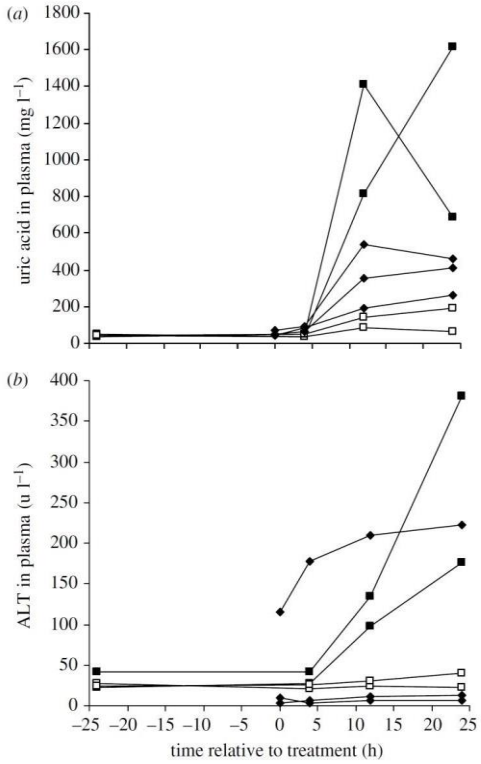
Findings

All diclofenac-treated individuals died; whereas, all control individuals survived. Elevated uric
acid and ALT concentrations in plasma were observed at 12 and 24 h in diclofenac-treated vultures, but not the control individuals. Kidney damage and visceral gout was observed in all diclofenac-treated vultures, but not the control individual that was euthanised.

Conclusion

Diclofenac is toxic to *Gyps* vultures in general.

Key figure



(a) Uric acid and (b) ALT concentrations in plasma measured before and after oral treatment of vultures with 08 mg/kg of diclofenac. Lines connect data for the same bird. Results are shown for two diclofenac-dosed (filled squares) and two sham-treated (open squares) G*yps africanus* and for three diclofenac-dosed *Gyps fulvus* (filled diamonds).

4. Diclofenac poisoning is sufficient to explain decline of *Gyps* vultures across the Indian subcontinent.

Published source

Green, R.E., Newton, I., Shultz, S., Cunningham, A.A., Gilbert, M., Pain, D.J. & Prakash, V. 2004. Diclofenac poisoning as a cause of vulture population declines across the Indian subcontinent. *Journal of Applied Ecology*, **41,** 793-800.

Background

Vulture populations across the Indian subcontinent has been declining since the mid-1990s. Unintentional poisoning through consumption of the NSAID diclofenac when feeding on the carcasses of cattle treated with the drug shortly before death was identified as a probable cause of the decline. However, previous studies had not evaluated whether diclofenac poisoning was sufficient, on its own, to cause the very rapid rates of population decline observed across the subcontinent.

Actions

Post-mortem and clinical analysis of vulture carcases collected in India, Nepal and Pakistan to identify causes of death. The presence of visceral gout and / or diclofenac residues was considered indicative of diclofenac poisoning.

Estimation of population trends of OWBV and LBV between 2000 and 2003 across northern India based on road transect surveys, and on counts of active nests in Punjab province in Pakistan.

Demographic model: using assumptions about vulture demographic rates and foraging ecology based on scientific literature and expert opinion, it is possible to estimate the rate of population change and proportion of vultures killed by diclofenac in relation to the proportion of ungulate carcasses that contain a lethal level of diclofenac.

Findings

A simulation model of vulture demography demonstrated that the observed rates of population decline could be caused by contamination with lethal level of diclofenac in a small proportion (between 1:130 and 1:760) of ungulate carcasses available to vultures.

Proportions of adult and subadult vultures found dead or dying in the wild that had signs of diclofenac poisoning were similar to the proportions of deaths expected from the model if the observed population decline was due entirely to diclofenac poisoning. The proportion of excess mortality required to cause the observed population declines that could be attributable to diclofenac was estimated to be between 71% and 100% depending on model assumptions. However, across all or most of the plausible range of assumed values for adult survival, the upper 95% confidence limit for the proportion of excess mortality due to diclofenac was 100%.

Conclusions

Available data are consistent with diclofenac poisoning being at least the major cause, and possibly the only cause, of rapid population declines of *Gyps* vultures across the Indian subcontinent.

Key figure

(F = interval, in days, between successive meals, i.e. the more frequent that vultures feed, the steeper the decline in the rate of population change with respect to the proportion of ungulate carcasses contaminated with a lethal level of diclofenac.)

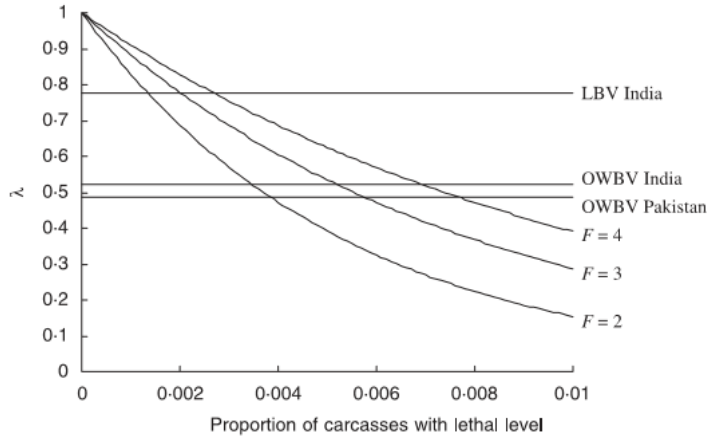


Fig. 1. Modelled relationship of the rate of population change, λ, to the proportion of ungulate carcasses contaminated with a lethal level of diclofenac for three assumed values of the feeding interval, *F*. Adult survival rate before the population decline and in the absence of diclofenac is assumed to be 0·95. Horizontal lines show values of λ estimated from population survey data for 2000–03.

5. Diclofenac concentrations in experimentally-treated cattle are enough to cause appreciable vulture mortality for up to four days after a cow received its last injection.

Published source

Green, R.E., Taggart, M.A., Das, D., Pain, D.J., Kumar, C.S., Cunningham, A.A., & Cuthbert, R. 2006. Collapse of Asian vulture populations: risk of mortality from residues of the veterinary drug diclofenac in carcasses of treated cattle. *Journal of Applied Ecology*, **43,** 949-956.

Background

The likely cause of the rapid declines of *Gyps* vultures in the Indian subcontinent was poisoning by the veterinary non-steroidal anti-inflammatory drug (NSAID) diclofenac. Typical symptoms of visceral gout and diclofenac residues have been found in the majority of vulture carcasses found since the decline, the proportion being consistent with diclofenac being possibly the only cause of the declines.

However, no detailed studies have been made previously of the exposure of vultures to diclofenac and the risk of death posed consuming by a meal of contaminated meat. The risk will be dependent on the concentration of the drug in cattle tissues and the time between treatment and death of the treated animal.

Action

Three experiments were conducted:

1) ten cattle were given a diclofenac injection (1 mg kg^{-1}, the typical dose in India), with two being slaughtered after 21, 46, 71, 167 and 334 hrs after treatment. Samples were taken from the intestine, kidney, liver and muscle from the opposite side to the injection site.

2) 16 cattle were given diclofenac injection (2.5 mg kg^{-1}, the typical dose in Pakistan), and four were slaughtered at 2-4, 12, 24 and 144 hrs after treatment. Samples were taken from fat, kidney, liver and triceps muscle.

3) Eight cattle were given diclofenac injection (2.5 mg kg^{-1}), and four were slaughtered at 2-96 and 176 hrs after treatment. Samples were taken from fat, kidney, liver and triceps muscle.

Diclofenac concentrations were measured for each tissue, and then averaged over all parts of the cattle carcass that would be available to vultures as food. Changes in the concentration of diclofenac were modelled in relation to the time since the last injection, for both individual tissues and averaged over the whole carcass.

The ingested dose was calculated based on the size of a typical meal (1.023 kg), which would sustain a vulture for three days and the average concentration of diclofenac, which was assumed to be as the average for the whole carcass. This was multiplied by 1.023 and divided by OBWB body weight (4.75 kg). A dose-response model from Swan *et al*. (2006) was used to estimate the relationship between the rate of diclofenac-induced mortality and the dose of diclofenac ingested. Two versions of this model were used, one of them excluding data from an outlier, a bird in the original study that died after receiving a very low dose of diclofenac.

Findings

Diclofenac concentration declined rapidly in all tissues (slower in muscle) up to the transition time (25-46 hrs) after which it declined more slowly (half-life 35-57 hrs). Concentrations were higher in kidney and liver, followed by intestines, fat and muscle (Fig. 2).

The average diclofenac concentrations were sufficient to cause appreciable mortality in vultures that fed on the carcass of an animal that died within 1-4 days of the last treatment (Fig. 3), i.e. > 10% of birds if a treated cow had died within 33 hrs or 59 hrs of the last injection, depending on the experiment; if the version of the model excluding the outlier (see above) the times are 9 and 19 hrs.

Vultures that fed exclusively on tissues with higher than average concentrations of diclofenac would be at risk over a much longer interval after treatment. The corresponding figures are > 10% mortality within 56 / 105 hrs; and 19 and 28 hours of the last injection.

Conclusions

Although diclofenac concentrations decline rapidly within the tissues of treated cattle, enough of the drug remains to cause > 10% mortality in vultures **(PER MEAL)** if birds were to take a large (but typical) meal from a carcass from an animal that was given its last dose within a few days of death.

Fey figure

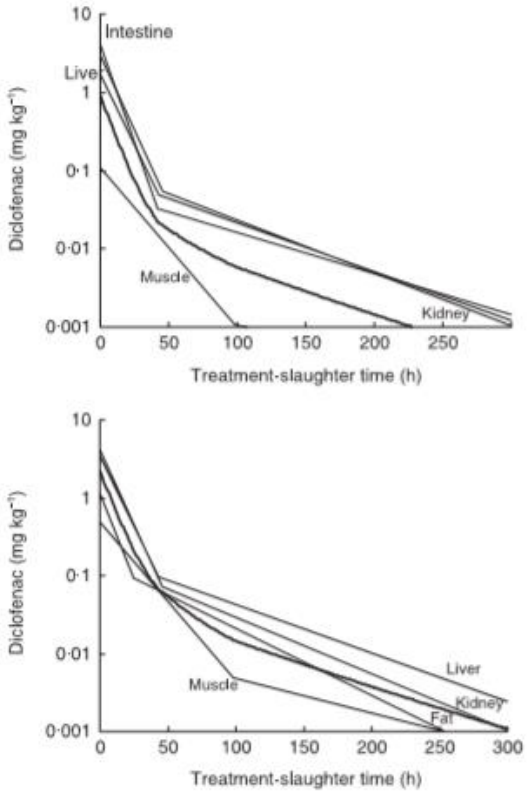


Fig. 2. Concentration of diclofenac in various cattle tissues in relation to the time between administration of the final injection of a course of the drug and slaughter. Models are the same as those presented in Fig. 1. The thin lines on each panel represent results for different tissues. The thick line shows the estimated diclofenac concentration averaged over all parts of a carcass that are available to vultures (see text). The upper panel shows results from experiment 1 with *Bos indicus* and the lower panel shows results from experiment 2 with young *Bos taurus*.

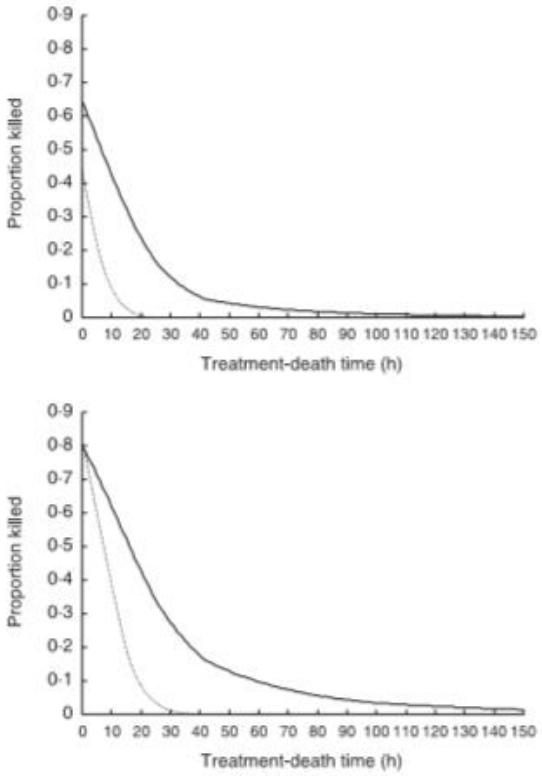


Fig. 3. Proportion of *Gyps bengalensis* estimated to be killed by diclofenac in relation to time between administration of the final injection of a course of the drug and the death of the treated cow (see text). Results are shown separately for a dose–response model fitted to all data from the experiments of Oaks *et al.* (2004) (solid line) and after excluding an outlier (dotted line). The upper panel shows results from experiment 1 with *Bos indicus* and the lower panel shows results from experiment 2 with young *Bos taurus*.

6. Diclofenac poisoning is the main, if not the sole, cause of the decline of *Gyps* vultures across the Indian subcontinent.

Published source

Green, R.E., Taggart, M.A., Senacha, K.R., Raghavan, B., Pain, D.J., Jhala, Y. & Cuthbert, R. 2007. Rate of decline of the Oriental White-backed Vulture population in India estimated from a survey of diclofenac residues in carcasses of ungulates. *PLoS One*, **2(8),** e686.doi:10.1371/journal.pone.0000686.

Background

The non-steroidal anti-inflammatory drug (NSAID) diclofenac has been identified as a major cause of the population declines of *Gyps* vultures across the Indian subcontinent. Vultures are exposed to diclofenac, formerly widely used in the region, by feeding upon carcasses of domesticated ungulates that were treated with the drug shortly before death

However, no large-scale surveys have been made of the amount of diclofenac in tissues of ungulates available to vultures. There has also not been a method for estimating the effect of a given level of diclofenac contamination on vulture population trends.

Action

We fitted a distribution model to the measurements of diclofenac concentrations in ungulate liver samples.

Based on the relationship between diclofenac concentrations in liver and other tissues, we estimated the average concentration of diclofenac in the whole carcass based on the observed value for liver.

From the average meal size and body weight of oriental white-backed vultures (OWBV), we estimated the dose of diclofenac ingested per unit vulture body weight from a single meal of

mixed tissues from a carcass with diclofenac concentration averaged across the whole carcass.

We used experimental data for captive OWBV from Swan *et al*. (2006) to fit a dose-response model relating the proportion of birds killed by diclofenac to the dose of the drug administered per unit vulture body weight. Two models were fitted, with and without an outlier, a bird that died with visceral gout, after ingesting a very small dose of diclofenac.

The above steps were combined to obtain a dose-response model relating the proportion of OWBV that are killed by taking a single meal of mixed tissues from a contaminated ungulate carcass to the concentration of diclofenac in the liver.

Based on the distribution of diclofenac concentrations in liver, the probability of a bird dying given a certain concentration of the drug, and the interval between feeding, we calculated the average proportion of vultures dying from diclofenac poisoning per meal of mixed carcass tissues. The estimated death rate per meal was 2.66% (for feeding interval 2 days) or 3.23% (for 3 days) if the outlier was used in fitting the dose-response model, and 0.86% and 1.37% if not.

Using the vulture population model from Green *et al*. (2004) and the values in this study of the proportion of vultures likely to die per meal of contaminated tissue, we estimated the expected annual rate of change of the OWBV population in 2004–2005. We expect high rates of population decline (98% per year) when the dose-response model includes the outlier, whereas lower rates of decline (80–83% per year) are expected when not.

Based on road transect surveys, the average rate of decline of between 2000–2003 was 48% per year (95% CL 34–62%), which is much lower than those (80–99% per year) calculated from diclofenac levels in carcasses using the dose-response model. The rate of decline derived from carcass surveys was significantly higher ($P < 0.021$) when the dose-response curve including the outlier was used; whereas, there was no significant difference between the estimates derived from the carcass and road transect surveys, when the alternative model was used (48% vs 80-83%, $P > 0.10$).

Based on the population trend obtained from road transect surveys, it is possible to calculate the excess mortality necessary to explain such a decline. Following this, it is possible to calculate the proportion of that excess mortality attributable to diclofenac alone. The best estimate from this model is that diclofenac poisoning was the sole cause of the decline. The level of support for this hypothesis exceeded 84%, while support for the hypothesis that it was the main cause exceeded 92%

Conclusions

Diclofenac poisoning is the main, if not the sole, cause of the decline of *Gyps* vultures across the Indian subcontinent.

Key figure

Table 5. Estimates of death rate per meal *C* of oriental white-backed vultures, the annual rate of decline of the vulture population and the percentage of excess vulture mortality that is attributable to diclofenac poisoning *E*, based upon concentrations of diclofenac in liver samples taken from ungulate carcasses.

Model specification			Death rate per meal *C* %		Annual rate of decline %			% of excess mortality caused by diclofenac E_{diclo}		Percent support for diclofenac as	
Gb11 included?	*F*	S_0	Estimate	95% C.L.	Estimate	95% C.L.	Different from road transects? *P*	Estimate	95% C.L.	Main cause of decline	Sole cause of decline
Yes	2	0.90	2.66	0.40–5.72	99	57–100	0.018	100	100–100	99.4	98.2
Yes	2	0.97	2.66	0.40–5.72	99	53–100	0.021	100	100–100	99.5	97.9
Yes	3	0.90	3.23	0.56–6.45	98	54–100	0.014	100	100–100	99.6	98.6
Yes	3	0.97	3.23	0.56–6.45	98	51–100	0.016	100	100–100	99.5	98.4
No	2	0.90	0.86	0.07–3.11	81	19–100	0.136	100	19–100	93.7	86.4
No	2	0.97	0.86	0.07–3.11	80	14–100	0.156	100	17–100	92.9	84.4
No	3	0.90	1.37	0.19–4.05	83	28–99	0.100	100	40–100	95.9	90.0
No	3	0.97	1.37	0.19–4.05	82	23–99	0.114	100	35–100	95.4	88.6

A significance test of the difference between the rate of population decline estimated from diclofenac surveys and road transect counts of vultures and the level of support (% of bootstrap/Monte Carlo replicates) for diclofenac poisoning being the main cause (>50% of excess mortality) or the sole cause (100% of excess mortality) of the vulture decline are also shown. Results are given for calculations that used a dose-response model including and excluding an outlying datum (Gb11), for two plausible values of the interval between meals *F* (days) and for the bounds of the likely range of pre-decline annual adult survival probability S_0.
doi:10.1371/journal.pone.0000686.t005

7. A questionnaire survey finds diclofenac, carprofen, flunixin, ibuprofen and phenylbutazone vulture-toxic; and meloxicam vulture-safe; but cannot classify aspirin, dexamethasone and ketoprofen because of small samples.

Source

Cuthbert, R. J., Parry-Jones, J., Green, R. E. and Pain, D. J. (2007) NSAIDs and scavenging birds: potential impacts beyond Asia's critically endangered vultures *Biology Letters* 3: 90-93.

Background

Throughout South Asia, approximately twelve non-steroidal anti-inflammatory drugs (NSAIDs) are available to treat livestock. Some of these NSAIDs are used to treat birds throughout the world. This survey was undertaken to gather information on NSAIDs associated deaths in *Gyps* vultures and other scavenging birds.

Action

A questionnaire on NSAID use and consequences was sent to zoos, wildlife rehabilitation centres and public veterinaries worldwide. Key information sought were species and number of vultures treated, injury or illness, NSAID and dosage used and outcome of treatment, including post-mortem examination results. Results from experimental safety tests for diclofenac and meloxicam were included. The number of cases was tallied, where a case represented a course of treatment in an individual bird and therefore could include the use of more than one NSAID.

Findings

Thirty-one institutions responded. They provided 870 cases involving 8 types of NSAID (and 1 type of steroidal anti-inflammatory: dexamethasone) and 79 species of bird. Of these, 106 involved 5 types of NSAID (plus dexamethanasone) and 6 species of *Gyps* vultures, including *Gyps bengalensis*.

Diclofenac treatment resulted in visceral gout and death in 28 out of 36 cases involving a *Gyps* vulture. No other cases were reported.

Meloxicam treatment resulted in no mortality in 39 cases involving a *Gyps* vulture; and no mortality in a further 700 cases involving 60 other species, including scavenging raptors. Meloxicam plus ketoprofen treatment resulted in no mortality in 1 case involving a *Gyps* vulture. No other cases were reported.

Aspirin treatment resulted in no mortality in 3 cases involving 3 species, including scavenging raptors.

Carprofen treatment resulted in visceral gout and death in 1 out of 17 cases involving a *Gyps* vulture; and visceral gout and death in a further 4 out of 23 cases involving 11 other species, including scavenging raptors.
Carprofen plus ketoprofen treatment resulted in visceral gout and death in 1 case involving a *Gyps* vulture. No other cases were reported.

Flunixin treatment resulted in visceral gout and death in 2 out of 4 cases involving a *Gyps* vulture; and visceral gout and death in a further 6 out of 20 cases involving 11 other species, including scavenging raptors.

Flunixin plus ketoprofen treatment resulted in visceral gout and death in 1 case involving a *Gyps* vulture. No other cases were reported.

Dexamethasone treatment resulted in no mortality in 1 case involving a *Gyps* vulture; and 9 cases involving other species, including scavenging raptors.

Ibuprofen treatment resulted in visceral gout and death in 1 case involving a non-*Gyps* vulture species. No other cases were reported.

Ketoprofen treatment resulted in no mortality in 3 cases involving a *Gyps* vulture; and no mortality in a further 17 cases involving 10 other species, including scavenging raptors.

Phenylbutazone treatment resulted in visceral gout and death in 1 case involving a non-*Gyps* vulture species. No other cases were reported.

Conclusion

Diclofenac, carprofen, flunixin, ibuprofen and phenylbutazone are toxic to vultures. **Meloxicam** is not toxic to vultures. Sample sizes for cases involving aspirin, dexamethasone and ketoprofen are too small to show these drugs are toxic of not toxic to vultures.

Key figure

Questionnaire results indicating drug used, toxicity, number of cases, range of doses and species treated.

drug	toxicity	*N* cases	dose (mg kg^{-1})	species treated ($n>1$)
aspirin	no	3	5.4–6.4	*Aegypius monachus*, *Ciconia ciconia*, *Corvus corax*
dexamethasone[a]	no	10	0.2–5.0	*Gyps himalayensis*, *Leptoptilos crumeniferus*, *Bubulcus ibis*, *Vultur gryphus* (2), *Ciconia ciconia* (4), *Tyto alba*
ketoprofen	no	20	1.0–7.7	*Gyps fulvus* (2), *Gyps rueppellii*, *Aegypius monachus*, *Necrosyrtes monachus*, *Buteo jamiacensis* (2), *Geranoaetus melanoleucus* (2), *Vultur gryphus* (2), *Leptoptilos crumeniferus* (2), *Corvus ossifragus*, *Asio flammeus flammeus* (2), *Bubo virginianus* (2), *Otus asio* (2)
meloxicam	no	739	0.1–0.75	60 species treated (see electronic supplementary material for details on species and dose rates)
ketoprofen and meloxicam	no	1	ket 1.0, mel 0.2	*Gyps africanus*
carprofen	yes	5	1.0–5.0	*Gyps fulvus*, *Parabuteo unicinctus* (2), *Aegolius acadicus* (2)
carprofen	no	35	1.5–7.6	*Gyps africanus* (3), *Gyps bengalensis* (2), *Gyps fulvus* (5), *Gyps himalayensis* (3), *Gyps rueppellii* (2), *Gyps rueppellii x africanus*, *Aegypius monachus* (3), *Necrosyrtes monachus*, *Torgus tracheliotus*, *Buteo jamiacensis Haliaeetus leucocephalus* (7), *Ciconia ciconia*, *Ephippiorhynchus senegalensis*, *Bugeranus carunculatus*, *Grus vipio*, *Ardeotis kori* (2)
diclofenac	yes	28	0.1–2.5	*Gyps bengalensis* (23), *Gyps africanus* (2), *Gyps fulvus* (3)
diclofenac	no	8	0.25–0.6	*Gyps bengalensis* (8)
flunixin	yes	7	1.0–4.5	*Gyps rueppellii*, *Cariana cristata*, *Leptoptilos crumeniferus*, *Platalea alba*, *Aegypius monachus* (3)
flunixin	no	16	0.5–12.0	*Gyps fulvus*, *Gyps rueppellii*, *Haliaeetus leucocephalus*, *Terathopius ecaudatus*, *Parabuteo unicinctus*, *Leptoptilos crumeniferus*, *Aegypius monachus*, *Vultur gryphus* (2), *Ciconia ciconia* (2), *Buteo jamiacensis* (5)
ibuprofen	yes	1	—	*Aegypius monachus*
phenylbutazone	yes	1	—	*Torgus tracheliotus*
flunixin or ketoprofen	yes	1	—	*Gyps africanus*
carprofen and ketoprofen	yes	1	car 7.2, ket 4.3	*Gyps africanus*

[a] Dexamethasone is a steroidal anti-inflammatory drug, not an NSAID.

8. An experiment finds doses above the MLE of meloxicam to Asian white-backed vultures *Gyps bengalensis* does not cause kidney failure, death or elevation of blood uric acid levels in African and Asian *Gyps* vultures

Source

Swan, G., Naidoo, V., Cuthbert, R., Green, R. E., Pain, D. J., Swarup, D., Prakash, V., Taggart M. A., Bekker, L., Das, D., Diekmann, J., Diekmann, M., Killian, E., Meharg, A., Patra, R. C., Saini, M. & Wolter, K. (2006). Removing the threat of diclofenac to critically endangered Asian vultures. *PLoS Biology* DOI: 10.1371/journal.pbio.0040066.

Background

A previous questionnaire survey on the use of NSAIDs in vultures, found no mortality in 39 cases of meloxicam treatment involving six species of *Gyps* vultures. This experiment was undertaken to further examine the toxicity of meloxicam to *Gyps* vultures.

Action

The effect of meloxicam on *Gyps* vultures was examined in a six-phase partially controlled experiment in South Africa and India.

African and Asian *Gyps* vultures were used. The African white-backed vulture *Gyps africanus* and the Asian white-backed vulture *Gyps bengalensis* are of similar size (4-7 and 3.5-7.5 kg, respectively).

One injectable meloxicam product, manufactured and purchased in India, was used.

Double the recommended dose for cattle in India was used to reflect frequent overdosing behaviour in India.

Phases 1-2: 10 African white-backed vultures were given an oral dose of meloxicam at 0.5-1.0

mg/kg body weight (bw); and six African white-backed vultures were given sterilised water.

Phases 3-4: 40 African white-backed vultures *Gyps africanus* (including 21 wild vultures) were given an oral dose of meloxicam at 2.0 mg/kg bw; and three captive and four wild African white-backed vultures *Gyps africanus* were given sterilised water.
Phase 5: six African white-backed vultures *Gyps africanus* were twice fed tissue from cattle dosed with meloxicam and once given an oral dose of meloxicam at >0.01-1.98 and 1.18-2.45 mg/kg bw, respectively. Meloxicam-contaminated cattle tissues were muscle and liver from three cattle given daily injections of meloxicam at 1 mg/kg bw for five days and slaughtered 8 h after the final dose.
Phase 6: six Asian white-backed vultures *Gyps bengalensis* and four long-billed vultures *Gyps indicus* were given an oral dose of meloxicam 0.5-2.0 mg/kg bw; and two Asian white-backed vultures *Gyps bengalensis* and three long-billed vultures *Gyps indicus* were given sterilised water.
Blood samples were taken from all vultures in Phases 1-5 before the experiment and at up to six time points up to 168 h after dosing. Serum was analysed for uric acid and three other biochemicals.
The maximum level of exposure of meloxicam to Asian white-backed vultures *Gyps bengalensis*

was calculated using the average body weight (4.75 kg), estimated large meal weight (1.02 kg) and highest meloxicam residue concentration in cattle liver tissue (8.54 mg/kg bw); and was equal to 1.83 mg/kg bw.

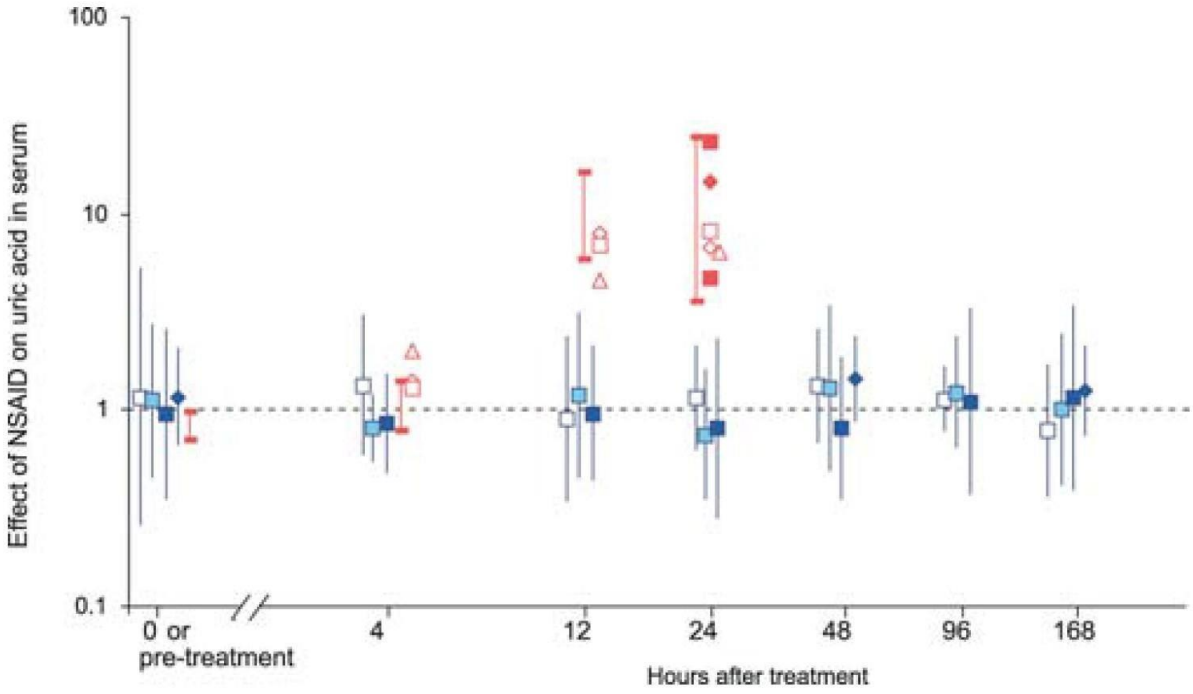
Findings

In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived.
Uric acid concentrations in serum in all meloxicam-treated vultures remained within a 95% range calculated from measurements from these vultures before treatment and control vultures.

Conclusion

Meloxicam is not toxic to *Gyps* vultures at the maximum level of exposure.

Key figure



The effect of adminstration of meloxicam and diclfoenac by [oral dose] on uric acid in serum of vultures. Blue symbols show the ratio of the geometric mean (with 95% confidence interval) serum concentration of uric acid for a group of *Gyps* vultures treated with meloxicam to that for a control group sampled at the same time. Each group of blue symbols show the effects of increased doses of meloxicam, from left to right. Red symbols and vertical lines show the equivalent ratio but for vultures given diclofenac. See article for more detail.

9. An experiment finds doses above the MLE of meloxicam to Asian white backed vultures *Gyps bengalensis* does not cause kidney failure, death or elevation of blood uric acid levels in Gyps vultures and other common scavenging birds native to South Asia

Source

Swarup, D., Patra, R. C., Prakash, V., Cuthbert, R., Das, D., Avarti, P., Pain, D. J., Green, R. E., Sharma, A.K., Saini, M. Das, D. and Taggart M. A. (2007). Safety of meloxicam to critically endangered *Gyps* vultures and other scavenging birds of India. Animal Conservation **10,** 192 198.

Background

Meloxicam is not toxic to Gyps vultures. This experiment was undertaken to further examine the toxicity of meloxicam to Gyps vultures and other common scavenging birds of South Asia.

Action

The effect of meloxicam on Gyps vultures and other common scavenging birds was examined in a three-phase controlled experiment in India.

One injectable meloxicam product, manufactured and purchased in India, was used. Double the recommended dose for buffalo in India was used to reflect frequent overdosing behaviour in India.

Phases 1: six Asian white-backed vultures *Gyps bengalensis* (OWBV) and four Long-billed Vultures (LBV) *Gyps indicus* were given an oral dose of meloxicam at 0.5 or 2.0 mg/kg body weight (bw); and two OWBV and two LBV were given sterilised water.

Phases 2: five Egyptian vultures *Neophron percnopterus*, five cattle egrets *Bubulcus ibis*, five crows *Corvus* spp. and five common myna *Acridotheres tristis* were given an oral dose of meloxicam at 2.0 mg/kg bw; and four Egyptian vultures, four cattle egrets, five crows and five common myna were given sterilised water.

Phase 3: 19 OWBV and two LBV were fed tissue from buffalo dosed with meloxicam; and five OWBV were fed tissue from goats not dosed with meloxicam. Meloxicam-contaminated buffalo tissues were muscle and liver representing doses of 0.3-2.1 mg/kg bw from two buffalo given daily injections of meloxicam at 1 mg/kg bw for five days and slaughtered 8 h after the final dose.

Blood samples were taken before dosing and 48h after dosing from all birds in Phases 1 and 2 (except common myna); and only 48h after dosing from birds in Phase 3. Serum was analysed for uric acid and other biochemical components. All birds were observed for seven days for symptoms of toxicity.

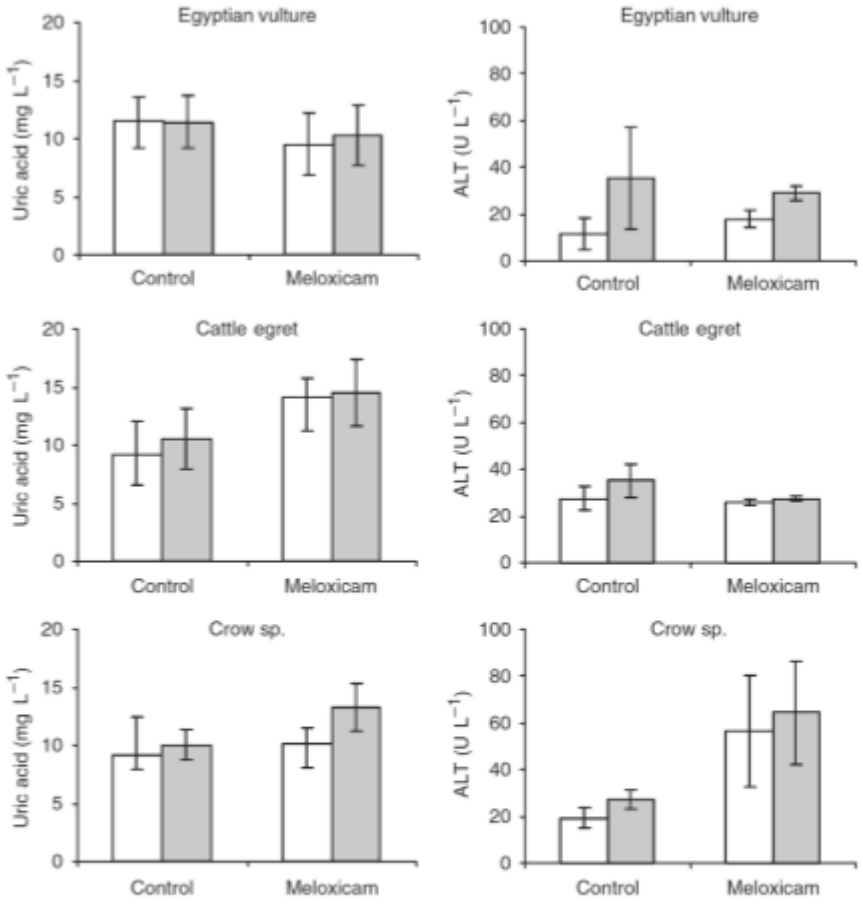
Findings

In all Phases, all meloxicam-treated birds survived with no ill effects. All control birds survived. Uric acid and ALT concentrations in serum in all meloxicam-treated birds was significantly different to that of control birds.

Conclusion

Meloxicam is not toxic to Gyps vultures and other common scavenging birds at the maximum level of exposure.

Key figure



Concentration of uric acid and ALT in serum of Egyptian vultures *Neophron percnopterus*, cattle egrets *Bubulcus ibis* and crows *Corvus spp.* given an oral dose of meloxicam at 2.0 mg/kg bw (filled columns) or sterilised water (open columns).

10. A review of the literature finds that meloxicam is a safe and effective treatment for domesticated animals.

Source

Galligan, T.H. (unpublished). Vulture-safe meloxicam is a safe and effective treatment for a variety of ailments in cattle.

Background

Meloxicam is not toxic to vultures. Therefore, meloxicam is a vulture-safe alternative to diclofenac and other vulture-toxic NSAIDs. This review of literature was undertaken to assess the safety and effectiveness of meloxicam for the treatment of domesticated animals.

Action

The PubMed literature databases (online and open access) were surveyed for *in vivo* experimental and clinical studies reporting an effect of meloxicam in the following domesticated animals: cattle, water buffalo, horse, donkey, camel, goat, sheep and dog.

Findings

A total of 117 studies reported an effect of treatment with meloxicam. Studies were grouped into broad veterinary and husbandry situations for treatment (e.g. infection, surgery, reproduction); broad objectives of treatment (e.g. pain reduction, increase reproductive rate); and categorised as having a: positive effect; negative effect; mixed effect (partially positive and negative); no effect; or no conclusion.

A positive effect was reported in 79% of studies. The proportion of studies examining meloxicam treatment that reported a mixed effect, a negative effect, no effect or no conclusion was 9, 3, 7 and 2%, respectively.

Meloxicam showed positive effects: in cattle, buffalo, horse, goat, sheep and dog; and during castrating, dehorning, general care, handling, infections, limb injuries, reproducing

and surgery. In these situations, meloxicam decreased pain, inflammation, stress and dysfunction; increased recovery rate, immune response, pregnancy rate and productivity; and generally resulted in no complications.

Overall, three studies reported negative effects of meloxicam treatment resulting in pregnancy complications (one each in cattle, horse and sheep). However, eleven studies reported positive effects of meloxicam treatment resulting in no pregnancy complications (nine in cattle and two in sheep).

Conclusion

Meloxicam is a safe and effective NSAID for use in a variety of veterinary and husbandry situations in a variety of animals.

Key figure

One-hundred and eighteen studies reported an effect of either meloxicam or meloxicam and nimesulide treatment in domesticated animals. Data provided are: NSAID(s) examined; reference for the study; domesticated animal; veterinary or husbandry situation; objective of treatment; experimental method; total sample size (n); and effect reported.

NSAID	Study	Animal	Situation	Objective	Method	n	Effect
Meloxicam & nimesulide	Borges et al. 2013	Dog	General	No complications	not controlled	24	Positive for meloxicam, negative for nimesulide
Meloxicam	Roberts et al. 2016	Cattle	Castration	Decrease pain	controlled	83	Mixed
Meloxicam	Roberts et al. 2015	Cattle	Castration	Decrease pain	controlled	30	Positive
Meloxicam	Olson et al. 2016	Cattle	Castration	Decrease pain	controlled	60	Positive
Meloxicam	Coetzee et al. 2012a	Cattle	Castration	Decrease pain	controlled	258	Positive
Meloxicam	Brown et al. 2015	Cattle	Castration	Decrease pain and increase calf productivity	controlled	62	Positive
Meloxicam	Repenning et al. 2013	Cattle	Castration	Decrease pain and stress	controlled	157	None
Meloxicam	Allen et al. 2013	Cattle	Dehorning	Decrease pain	controlled	30	Positive
Meloxicam	Stewart et al. 2009	Cattle	Dehorning	Decrease pain	controlled	46	Positive
Meloxicam	Clapp et al. 2015	Cattle	Dehorning	Decrease pain	not controlled	25	Mixed
Meloxicam	Theurer et al. 2012	Cattle	Dehorning	Decrease pain	not controlled	12	Positive
Meloxicam	Coetzee et al. 2012b	Cattle	Dehorning	Decrease pain and increase calf productivity	controlled	12	Positive

Meloxicam	Heinrich et al. 2010	Cattle	Dehorning	Decrease pain and stress	controlled	60	Positive
Meloxicam	Heinrich et al. 2009	Cattle	Dehorning	Decrease stress	not controlled	60	Positive
Meloxicam	Bates et al. 2015	Cattle	Dehorning	Increase calf productivity	controlled	202	Positive
Meloxicam	Roy et al. 2015	Cattle	General	Decrease inflammation	controlled	12	Positive
Meloxicam	Carpenter et al. 2016	Cattle	General	Increase cow productivity and longevity	controlled	.	Positive
Meloxicam	Amiridis et al. 2009	Cattle	General	Increase pregnancy rate	controlled	402	Positive
Meloxicam	Cooke et al. 2016	Cattle	Handling	Decrease stress	controlled	943	None
Meloxicam	Guarnieri et al. 2014	Cattle	Handling	Decrease stress	controlled	84	Positive
Meloxicam	Van Engen et al. 2016	Cattle	Handling	Decrease stress	controlled	87	Positive
Meloxicam	Van Engen et al. 2014	Cattle	Handling	Decrease stress	not controlled	97	Positive
Meloxicam	Maslanka et al. 2011	Cattle	Immunisation	Avoid dysfunction	controlled	10	None
Meloxicam	Rodrigues et al. 2015	Cattle	Immunisation	Avoid dysfunction	controlled	21	None
Meloxicam	Bednarek et al. 2002	Cattle	Infection	Decrease inflammation	not controlled	.	Positive
Meloxicam	Konigsson et al. 2002	Cattle	Infection	Decrease inflammation	not controlled	4	Positive
Meloxicam	Bednarek et al. 2003a	Cattle	Infection	Improve recovery	not controlled	30	Positive
Meloxicam	Todd et al. 2010	Cattle	Infection	Increase calf productivity	controlled	62	Positive
Meloxicam	Bednarek et al. 2003b	Cattle	Infection	Increase immune response	controlled	18	Positive
Meloxicam	Bednarek et al. 2005	Cattle	Infection	Increase immune response	not controlled	30	Mixed
Meloxicam	Coetzee et al. 2014	Cattle	Limb injury	Decrease pain	controlled	18	Positive
Meloxicam	Offinger et al. 2013	Cattle	Limb injury	Decrease pain	controlled	19	Positive
Meloxicam	Barrier et al. 2014	Cattle	Reproduction	Decrease pain	controlled	110	Positive
Meloxicam	Fitzpatrick et al. 2013	Cattle	Reproduction	Decrease pain	controlled	24	Positive
Meloxicam	Newby et al. 2013b	Cattle	Reproduction	Decrease pain and stress	controlled	103	Positive
Meloxicam	Mainau et al. 2015	Cattle	Reproduction	Decrease pain and stress	not controlled	60	Mixed
Meloxicam	McDougall et al. 2009	Cattle	Reproduction	Improve recovery	not controlled	727	Positive
Meloxicam	Lopes et al. 2015	Cattle	Reproduction	Increase pregnancy rate	controlled	85	Positive
Meloxicam	Aguiar et al. 2013	Cattle	Reproduction	Increase pregnancy rate	controlled	207	Positive
Meloxicam	Rajkumar et al. 2010	Cattle	Reproduction	Increase pregnancy rate	not controlled	.	Positive
Meloxicam	Erdem et al. 2010	Cattle	Reproduction	No complications	controlled	87	Negative
Meloxicam	Hirsch et al. 2009	Cattle	Reproduction	No complications	controlled	41	Positive
Meloxicam	Newby et al. 2014	Cattle	Reproduction	No complications	controlled	.	Positive
Meloxicam	Beausoleil et al. 2012	Cattle	Surgery	Decrease pain	controlled	18	None
Meloxicam	Blois et al. 2010	Dog	General	Avoid dysfunction	controlled	10	Positive
Meloxicam	Wooten et al. 2009	Dog	General	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Punke et al. 2008	Dog	General	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Gilmour et al. 2012	Dog	General	Decrease inflammation	controlled	15	None
Meloxicam	Gilmour et al. 2009	Dog	General	Decrease inflammation	not controlled	38	Positive
Meloxicam	Hare et al. 2013	Dog	General	No complications	controlled	40	Mixed
Meloxicam	Bostrom et al. 2006	Dog	General	No complications	controlled	8	Positive
Meloxicam	Boston et al. 2003	Dog	General	No complications	controlled	20	Positive
Meloxicam	Narita et al. 2006	Dog	General	No complications	not controlled	15	Positive
Meloxicam	Fusellier et al. 2008	Dog	General	No complications	not controlled	10	Positive
Meloxicam	Viking et al. 2002	Dog	Infection	Decrease pain	controlled	12	Positive
Meloxicam	Brainard et al. 2007	Dog	Limb injury	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Cross et al. 1997	Dog	Limb injury	Decrease inflammation	not controlled	12	Positive
Meloxicam	Van Bree et al. 1994	Dog	Limb injury	Decrease inflammation and no complications	controlled	4	Positive

Meloxicam	Jones et al. 2002	Dog	Limb injury	Decrease pain	controlled	12	Positive
Meloxicam	Moreau et al. 2003	Dog	Limb injury	Decrease pain	controlled	71	Positive
Meloxicam	Matyas et al. 2013	Dog	Limb injury	Decrease pain	controlled	11	Positive
Meloxicam	Borer et al. 2003	Dog	Limb injury	Decrease pain	controlled	60	Positive
Meloxicam	Cozzi and Spensley	Dog	Limb injury	Decrease pain and inflammation	controlled	280	Positive
Meloxicam	Schmid et al. 2010	Dog	Limb injury	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	Walton et al. 2014	Dog	Limb injury	Decrease pain and inflammation	controlled	111	Positive
Meloxicam	Peterson and Keefe 2004	Dog	Limb injury	Decrease pain and no complications	controlled	217	Positive
Meloxicam	Nell et al. 2002	Dog	Limb injury	Decrease pain and no complications	controlled	214	Positive
Meloxicam	Doig et al. 2000	Dog	Limb injury	Decrease pain and no complications	controlled	40	Positive
Meloxicam	Sauve et al. 2003	Dog	Limb injury	No complications	controlled	46	Positive
Meloxicam	Mullins et al. 2012	Dog	Surgery	Avoid dysfunction	not controlled	.	Mixed
Meloxicam	Budsberg et al. 2002	Dog	Surgery	Decrease pain	controlled	40	Positive
Meloxicam	Zanuzzo et al. 2015	Dog	Surgery	Decrease pain	controlled	40	Positive
Meloxicam	Teixeira et al. 2013	Dog	Surgery	Decrease pain	controlled	27	Positive
Meloxicam	Tsai et al. 2013	Dog	Surgery	Decrease pain	controlled	27	Positive
Meloxicam	Teixeira et al. 2013	Dog	Surgery	Decrease pain	controlled	24	Positive
Meloxicam	Leece et al. 2005	Dog	Surgery	Decrease pain	controlled	43	Positive
Meloxicam	Fowler et al. 2003	Dog	Surgery	Decrease pain	controlled	20	Positive
Meloxicam	Caulkett et al. 2003	Dog	Surgery	Decrease pain	controlled	15	Positive
Meloxicam	Moak et al. 2011	Dog	Surgery	Decrease pain	not controlled	25	None
Meloxicam	Gruet et al. 2011	Dog	Surgery	Decrease pain and inflammation	controlled	146	Positive
Meloxicam	Lafuente at al. 2005	Dog	Surgery	Decrease pain and inflammation	controlled	16	Positive
Meloxicam	Yilmaz et al. 2014	Dog	Surgery	Decrease stress	not controlled	24	Positive
Meloxicam	Nakagawa et al. 2007	Dog	Surgery	Increase recovery and no complications	controlled	5	Positive
Meloxicam	Kum et al. 2013	Dog	Surgery	No complications	controlled	18	Positive
Meloxicam	Kazakos et al. 2005	Dog	Surgery	No complications	controlled	38	Positive
Meloxicam	Fresno et al. 2005	Dog	Surgery	No complications	not controlled	20	Positive
Meloxicam	Laredo et al. 2004	Dog	Surgery	No complications	not controlled	32	Positive
Meloxicam	Gruet et al. 2013	Dog	Surgery	Decrease pain and inflammation	not controlled	174	Positive
Meloxicam	Mathews et al. 2001	Dog	Surgery	Decrease pain and no complications	controlled	36	Positive
Meloxicam	Khan and McLean 2012	Dog, cat	General	No complications	controlled	22206	Mixed
Meloxicam	Regan et al. 2016	Donkey	Limb injury	Decrease pain and inflammation	controlled	40	Mixed
Meloxicam	Ingvast-Larsson et al. 2011	Goat	Dehorning	Decrease pain	not controlled	11	None
Meloxicam	van der Heide et al. 2008	Goat	Limb injury	No complications	controlled	18	Positive
Meloxicam	Little et al. 2007	Horse	General	Avoid dysfunction	controlled	18	Positive
Meloxicam	Beretta et al. 2005	Horse	General	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	Raidal et al. 2014	Horse	General	No complications	controlled	9	Mixed
Meloxicam	Nobel et al. 2012	Horse	General	No complications	controlled	33	Positive
Meloxicam	D'Arcy-Moskwa et al. 2012	Horse	General	No complications	controlled	25	Positive

Meloxicam	Raidal et al. 2013	Horse	General	No complications	controlled	10	Positive
Meloxicam	Vander Werf et al. 2012	Horse	General	No complications	not controlled	7	Positive
Meloxicam	Brideau et al. 2001	Horse, Dog	General	Decrease inflammation	controlled	30, 48	Positive
Meloxicam	de Walter et al. 2016	Horse	Limb injury	Decrease inflammation	controlled	24	No conclusion
Meloxicam	de Grauw et al. 2009	Horse	Limb injury	Decrease pain and inflammation	controlled	6	Positive
Meloxicam	Lima et al. 2015	Horse	Reproduction	Increase pregnancy rate	controlled	11	Negative
Meloxicam	Naylor et al. 2014	Horse	Surgery	Decrease pain	controlled	60	Mixed
Meloxicam	Walliser et al. 2015	Horse	Surgery	Decrease pain and inflammation	controlled	66	Positive
Meloxicam	Paull et al. 2012	Sheep	Castration	Decrease pain	controlled	48	Positive
Meloxicam	Small et al. 2014	Sheep	Castration	Decrease pain	controlled	60	Positive
Meloxicam	Colditz et al. 2011	Sheep	Limb injury	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	McKeown et al. 2000	Sheep	Reproduction	Increase pregnancy rate	controlled	.	Positive
Meloxicam	Dorniak et al. 2011	Sheep	Reproduction	No complications	controlled	.	Negative
Meloxicam	Rac et al. 2007	Sheep	Reproduction	No complications	controlled	.	Positive
Meloxicam	Barrett et al. 2016	Cattle	Surgery	Decrease pain	controlled	24	No conclusion
Meloxicam	Newby et al. 2013	Cattle	Surgery	Decrease pain	not controlled	10	Positive
Meloxicam	Deneuche et al. 2004	Dog	General	Decrease pain and no complications	controlled	60	Positive
Meloxicam	Forsyth et al. 1998	Dog	General	No complications	not controlled	24	Positive
Meloxicam	Luna et al. 2007	Dog	General	No complications	not controlled	36	Positive