Ketoprofen: a vulture-toxic drug

Summary of evidence that ketoprofen is toxic to vultures; and that meloxicam, an alternative to ketoprofen, is not toxic to vultures as well as a safe and effective veterinary drug

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SAVING ASIA'S VULTURES FROM EXTINCTION

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

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

Aim

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

Executive summary

1. The NSAID ketoprofen has been shown to kill *Gyps* vultures.
2. Wild vultures are exposed to veterinary NSAIDs by feeding on carcasses of domesticated ungulates treated with these drugs shortly before death.
3. The 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 ketoprofen was calculated assuming that cattle in India may typically be dosed with twice the recommended amount. However, other data indicate that this may substantially underestimate the degree of overdosing (see below).
4. The NSAID ketoprofen has been shown to be toxic to *Gyps* vultures at doses at and above the MLE, calculated as described. An experiment showed that oral doses of ketoprofen below the MLE caused hyperuricemia (i.e., elevated uric acid levels), kidney failure and death in one of 11 African white-backed vultures *Gyps africanus*. This experiment also showed oral doses of ketoprofen above the MLE caused hyperuricemia, kidney failure and death in seven of 11 Cape vultures *Gyps coprotheres*.
5. A survey of carcasses of domesticated ungulates at carcass dumps in India found that liver samples from some cattle carcasses available to scavengers were contaminated with ketoprofen. The mean concentration of ketoprofen in the liver was 2.5 times higher than the mean for livers of cattle dosed experimentally on three successive days with twice the standard veterinary dose and slaughtered one hour after the last dose. This indicates that the quantities of ketoprofen administered to cattle close to death

under field conditions in India are typically much higher than was assumed in calculating the MLE. A wild *Gyps* vulture taking a large meal of liver or kidneys from the cattle carcass with the highest measured concentration would have ingested a dose of ketoprofen close to or far above those which killed *Gyps* vulture in the toxicity tests above.

6. In contrast to ketoprofen, the NSAID meloxicam has been shown to be non-toxic to *Gyps* vultures above the maximum level of exposure (MLE).
7. 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 Egyptian vultures *Neophron percnopterus*, cattle egrets *Bubulcus ibis*, crows *Corvus spp.* and common myna *Acridotheres tristis*, which also scavenge.
8. Ketoprofen causes toxicity in *Gyps* vultures by saturation of the metabolic process and thereby drug accumulation. Analysis of the pharmacokinetics of 16 Cape vultures *Gyps coprotheres* used in the ketoprofen toxicity experiment showed greater elimination half-life ($T_{1/2}$), maximum concentration (C_{max}) and area under the curve (AUC) in vultures that died compared to those that did not die.
9. In contrast, meloxicam is rapidly metabolised. Analysis of the pharmacokinetics of 12 Cape vultures *Gyps coprotheres* showed short $T_{1/2}$ and small C_{max} and AUC. Similarly, therapeutic treatment of 11 *Gyps* and non-*Gyps* vultures with meloxicam showed rapid metabolism.
10. Captive vultures are also exposed to NSAIDs through veterinary care. A survey of wildlife veterinarians found neither the use of ketoprofen, meloxicam or ketoprofen plus meloxicam resulted in ill effects in *Gyps* vultures. However, the sample size for ketoprofen (n = 4) was small compared to that for meloxicam (n = 40). The use of ketoprofen plus carprofen and ketoprofen plus flunixin did result in kidney failure and death.
11. Meloxicam is manufactured in Bangladesh, India, Nepal and Pakistan. It has been shown to be an effective treatment for pain, inflammation, stress and dysfunction in a variety of veterinary and husbandry situations and in a variety of domesticated animals. In addition, meloxicam has been shown to increase immune response, pregnancy rate, cow productivity and calf productivity. A positive effect of meloxicam treatment has been reported for a greater variety of veterinary situations than a positive effect of ketoprofen treatment. Negative or mixed effects of meloxicam are rare and fewer than

those for ketoprofen. Meloxicam and ketoprofen have been directly compared nine times: most studies found no difference between the two drugs; but two studies found ketoprofen caused complications while meloxicam did not.

12. To conserve critically endangered *Gyps* vultures, veterinary ketoprofen and multiple-dose vials of human ketoprofen should be banned throughout South Asia. Such a comprehensive ban would not impact livestock healthcare because meloxicam is a safe, effective and widely available alternative to ketoprofen.

Supporting evidence

We present eight lines of supporting evidence.

1. A questionnaire on the consequences of therapeutic use of NSAIDs on *Gyps* vultures was sent to centres holding captive birds worldwide. No deaths were reported where ketoprofen was the sole NSAID administered to three *Gyps* vultures. Single instances in which ketoprofen combined with carprofen and ketoprofen combined with flunixin were administered to *Gyps* vultures both resulted in kidney failure and death, but which of the compounds caused death could not be determined. A *Gyps* vulture treated with both meloxicam and ketoprofen did not die. In contrast, meloxicam did not cause mortalities in 40 *Gyps* vultures and another 700 birds of a variety of species. Further details in pages 10-12.

2. The effect of ketoprofen on *Gyps* vultures was examined in a four-phase partially controlled experiment conducted in South Africa. Phases were: (1) five Cape vultures *Gyps coprotheres* given an oral dose of ketoprofen at doses of 1.3-1.4 mg/kg body weight (bw); (2) five Cape vultures *Gyps coprotheres* fed cattle tissues contaminated with ketoprofen at 0.5-1.0 mg/kg bw; (3) 11 Cape vultures *Gyps coprotheres* given an oral dose of ketoprofen 5.0 mg/kg bw; and (4) two African white-backed vultures *Gyps africanus* given an oral dose of ketoprofen at 1.5 and 1.8 mg/kg bw. The maximum level of exposure (MLE) of ketoprofen to Asian white-backed vulture *Gyps bengalensis* was calculated as 1.54 mg/kg bw. All ketoprofen-treated vultures survived in Phase 1 and 2; however, 7 of the 11 ketoprofen-treated vultures died in Phase 3 (another ketoprofen-treated vulture survived only after remedial treatment). The vulture treated with ketoprofen at 1.50 mg/kg bw (below the MLE) in Phase 4 died as well. All control vultures survived. Elevated uric acid levels in plasma, kidney damage and visceral gout were observed in all ketoprofen-treated vultures that died. Further details in pages 13-15.

3. Blood samples from the ketoprofen toxicity experiment above were used to examine the pharmacokinetics of ketoprofen in 16 Cape vultures *Gyps coprotheres*. The pharmacokinetic profiles of vultures dosed with ketoprofen at 1 mg/kg bw (Group 1), dosed at 5 mg/kg bw and survived (Group 2) and dosed at 5 mg/kg bw and died (Group 3) were modelled and the parameters compared. A number of parameters, including the elimination half-life ($T_{1/2}$) were similar in vultures that survived (Groups 1 and 2), but differed in the vultures that died (Group 3). $T_{1/2}$ was twice as long in Group 3 ($T_{1/2}$ = 7.4 h) compared to Group 2 ($T_{1/2}$ = 3.2 h). All other parameters, including maximum

concentration (C_{max}) and area under the curve (AUC; two measures), were greater in Group 3 than Group 2 and greater in Group 2 than Group 1. C_{max} and AUC were 2 and 3-4 times higher in Group 3 (Cmax = 11 µg/ml; AUC = 50-52 µg/ml h) than Group 2 (Cmax = 21 µg/ml; AUC = 157-208 µg/ml h). Greater $T_{1/2}$, C_{max} and AUC in vultures that died suggests zero-order or near-zero-order metabolism leading to saturation of metabolic process, drug accumulation and toxicity. Further details in pages 16 and 17.

4. The prevalence and concentrations of nine NSAIDs were measured in livers of domesticated ungulates sampled at carcass dumps and other locations in seven Indian states in 2006. Ketoprofen was detected in 13 of 1488 samples (0.8%). The mean and maximum concentrations of ketoprofen measured in livers from cattle carcasses were 0.4 and 5.6 mg/kg, respectively, which are 2.5 and 35 times the mean concentration measured in cattle dosed and sacrificed in the toxicity test above (see supporting evidence 2). This suggests that overdosing of cattle near to death with ketoprofen under field conditions in India may be substantially more extreme than has been assumed. A wild *Gyps* vulture taking a large meal of liver from the cattle carcass with the highest ketoprofen concentration would have received a dose of ketoprofen at 1.21 mg/kg bw, which is close to that which killed a *Gyps* vulture in the toxicity test above (i.e., 1.5 mg/kg bw). Further, although kidneys were not sampled from cattle carcasses, the ketoprofen concentrations in kidneys were certainly higher than those measured in liver. This is because the mean concentration measured in kidneys from cattle dosed and sacrificed in the toxicity test were far greater than that in liver from the same animals (see supporting evidence 2 above). A wild *Gyps* vulture taking a large meal of kidneys from the cattle carcass with the mean and highest concentration of ketoprofen would have received a dose at 3.83 and 53.59 mg/kg bw, respectively, which is close to and far above that which killed *Gyps* vultures in the toxicity test (i.e., 5 mg/kg bw; see supporting evidence 2 above). Further details in pages 18 and 19.

5. 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 body weight (bw); (3-4) 40 African white-backed vultures *Gyps africanus* were given an oral dose of meloxicam at 2.0 mg/kg 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 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 bw. The maximum level of exposure (MLE) of meloxicam to Asian white-backed vulture *Gyps bengalensis*

was calculated as 1.83 mg/kg 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 in pages 20-22.

6. The pharmacokinetics of meloxicam in six *Gyps* vultures was examined in a two-phase uncontrolled experiment in South Africa. Phases were: (1) Cape vultures *Gyps coprotheres* were given an oral dose of meloxicam at 2 mg/kg body weight (bw); and (2) Cape vultures *Gyps coprotheres* were given an intramuscular dose of meloxicam at 2 mg/kg bw. In addition, therapeutic treatment of vultures from four species with meloxicam at 2 mg/kg bw was reported. Oral or intramuscular administered meloxicam was rapidly absorbed (T_{max} = 0.5-0.6 h) and eliminated ($T_{1/2}$ = 0.3-0.4 h) among experimentally and therapeutically treated vultures. The maximum concentration (C_{max} = 3.5-5.3 µg/ml) and area under the curve (AUC = 5.9-6.3 µg/ml h) were relatively small compared to ketoprofen (see above). No vultures showed ill effects and none died. Further details in pages 23-24.

7. 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 *Gyps bengalensis* and four Long-billed vultures *Gyps indicus* were given an oral dose of meloxicam at 0.5 or 2.0 mg/kg 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 bw; and (3) 19 Asian white-backed vultures *Gyps bengalensis* and two long-billed vultures *Gyps indicus* 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 in pages 25-27.

8. A positive effect was reported in more studies examining meloxicam (79%) than studies examining ketoprofen (63%). A mixed effect was reported in less studies examining meloxicam (9%) than studies examining ketoprofen (22%). A similar number of studies examining meloxicam and ketoprofen reported a negative effect (3 and 5%, respectively), no effect (7 and 8%, respectively) and no conclusion (2 and 3%, respectively). Meloxicam showed positive effects for the same animals, situations and objectives that ketoprofen did. In addition, meloxicam uniquely increased immune response, pregnancy rate, breeder productivity and infant productivity. Two of the nine studies that directly compared the effects of the two drugs showed gastrointestinal and

renal complications as a result ketoprofen treatment, but not meloxicam treatment. Three studies reported negative effects of meloxicam treatment resulting in pregnancy complications, but eleven studies reported positive effects of meloxicam treatment resulting in no pregnancy complications. Ketoprofen treatment was no examined for pregnancy complications. Further details in pages 28-39.

Specific details

Chemical name: **ketoprofen**
Systematic name: (RS)-2-(3-benzoylphenyl)propanoic acid
Formula: $C_{16}H_{14}O_3$
Molar mass: 254.281 g/mol
Typical formulation: 100 mg/ml injection in 10, 20, 50 or 100 ml vials
Example products (manufacturers):

Bangladesh – Keto-A Vet (ACME), Keto-Aid (Popular), Kop-Vet (Square), Ketoflam (Opsonin), Ketochem (Chemist lab), Kynol (Eskayef), Renafen (Renata)
India – Ketop (Alembic/Umedica), Ketfen (ethicare), Neoprofen (Pfizer), Profenvet (Vetindia), Vetoprofen (Dosch)
Nepal – Indian product may be imported
Pakistan - Dingalgen (Mylab), Ketoject (Selmore), Keto-P (Star), Profenol (Leads)

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 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*.

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.

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

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.

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.

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 at therapeutic doses. Meloxicam is not toxic to vultures at therapeutic doses. 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

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.

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

2. An experiment finds doses at and above the MLE of ketoprofen to Asian white-backed vultures *Gyps bengalensis* causes kidney failure and death in similar sized African *Gyps* vultures

Source

Naidoo, V., Wolter, K., Cromarty, D., Diekmann, M., Duncan, N., Meharg, A., Taggart M. A., Venter, L. and Cuthbert, R. (2010). Toxicity of non-steroidal anti-inflammatory drugs to *Gyps* vultures: a new threat from ketoprofen. *Biology Letters* 6: 339-341.

Background

A questionnaire survey on the therapeutic use of NSAIDs in vultures found no mortality in three cases involving *Gyps* vultures and ketoprofen. Three cases are too few to conclude ketoprofen is not toxic to *Gyps* vultures. This experiment was undertaken to further examine the toxicity of ketoprofen to *Gyps* vultures.

Action

The effect of ketoprofen on *Gyps* vultures was examined in a four-phase controlled experiment in South Africa.

African *Gyps* vultures were used as less threatened surrogates for Asian *Gyps* vultures. 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).

Two injectable ketoprofen products were used – one manufactured and purchased in India (Phases 1 and 2) and one manufactured and purchased in South Africa (Phases 2-4). Double the recommended dose for cattle in India was used to reflect frequent overdosing behaviour in India.

Phase 1: five Cape vultures *Gyps coprotheres* were given an oral dose of ketoprofen at 1.3-1.4 mg/kg body weight (bw) and three Cape vultures *Gyps coprotheres* were given a control solution.

Phase 2: five Cape vultures *Gyps coprotheres* were fed tissues of cattle dosed with ketoprofen at doses of 0.5-1.0 mg/kg vulture bw and three Cape vultures *Gyps coprotheres* were fed cattle tissues not dosed with ketoprofen. Ketoprofen-contaminated cattle tissues were kidney and liver tissues from five cattle given daily injections of ketoprofen at 6 mg/kg bw for three days and slaughtered 1 h after the final dose.

Phase 3: 11 captive Cape vultures *Gyps coprotheres* were given an oral dose of ketoprofen 5.0 mg/kg bw (no controls). This dose was more than 3 times the maximum level of exposure (1.5 mg/kg bw) estimated for ketoprofen.

Phase 4: two wild African white-backed vultures *Gyps africanus* were given an oral dose of ketoprofen at 1.5 and 1.8 mg/kg bw and two African white-backed vultures *Gyps africanus* were given a control solution.

Blood samples were taken from all vultures in all phases before the experiment and at 10 time points between 5 minutes and 48 h after dosing (except in Phase 2 were the first sample was taken at 16 h). Serum was analysed for uric acid and six other compounds. All dead vultures were examined for cause of death.

The maximum level of exposure to ketoprofen for Asian white-backed vulture *Gyps bengalensis* was calculated using the average body weight (4.75 kg), estimated large meal weight (1.02 kg) and average ketoprofen residue concentration in cattle kidney and liver tissue (7.13 and 0.16 mg/kg bw, respectively); and was equal to 1.54 mg/kg bw.

Findings

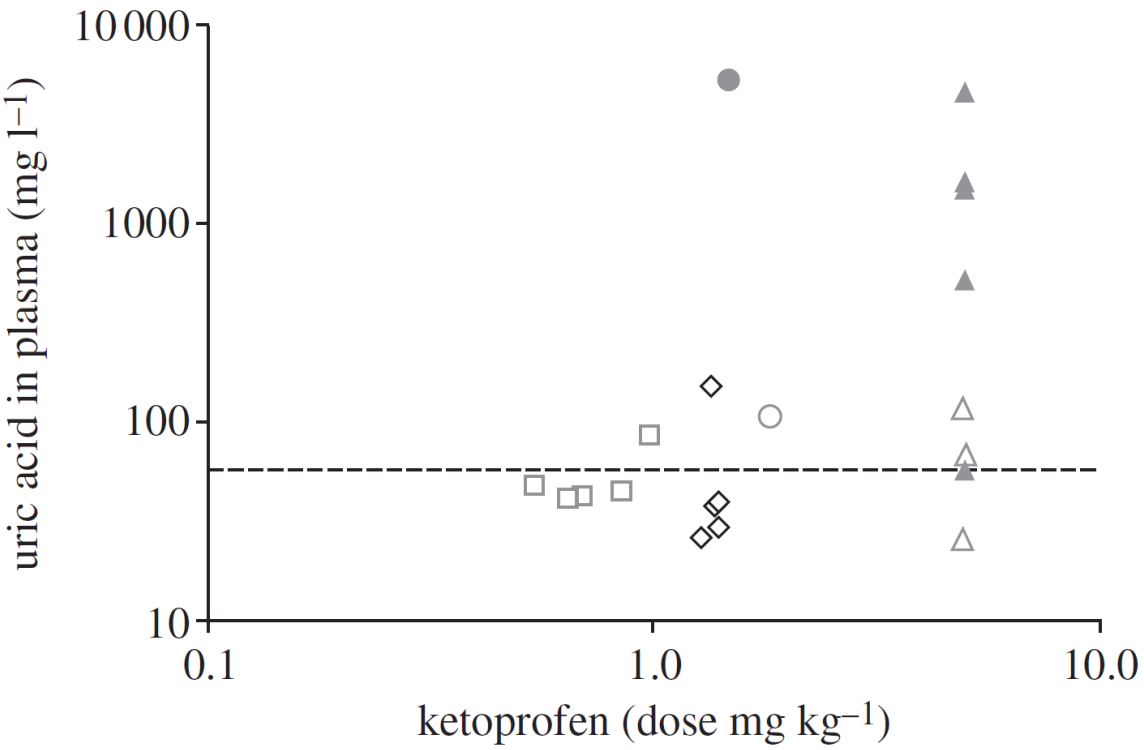
All ketoprofen-treated Cape vultures *Gyps coprotheres* survived low doses in Phase 1 and 2. In Phase 3, 7 of the 11 ketoprofen-treated Cape vultures *Gyps coprotheres* died (one ketoprofen-treated Cape vulture *Gyps coprotheres* survived after remedial treatment). In Phase 4, the African white-backed vulture *Gyps africanus* treated with 1.5 mg/kg died. All control vultures survived.

Elevated uric acid concentrations in plasma were observed at 24 and 48 h in all ketoprofen-treated vultures that died. Kidney damage and visceral gout (i.e., uric acid deposits within kidney tubules; and covering the spleen, liver and lungs) was observed in all ketoprofen-treated vultures that died.

Conclusion

Ketoprofen is toxic to *Gyps* vultures at the maximum level of exposure.

Key figure



The relationship between $\log_{10}$ ketoprofen dose and uric acid concetrations in plasma at 24 h. Squares, triangles and circles denote phases 1, 2 and 3. Unfilled symbols denote dosed vultures that survived and filled symbols denote dosed vultures that died and the horizontal line is the average concentration of uric acid in all vultures prior to dosing. See article for more detail.

3. A pharmacokinetics analysis finds ketoprofen causes toxicity in *Gyps* vultures through zero-order metabolism

Source

Naidoo, V., Venter, L., Wolter, K., Taggart M. A. and Cuthbert, R. (2010). The toxicokinetics of ketoprofen in *Gyps coprotheres*: toxicity due to zero-order metabolism. *Toxicokinetics and metabolism* 84: 761-766.

Background

An experiment was undertaken to determine the toxicity of ketoprofen to *Gyps* vultures (see above). Blood samples were collected during the experiment. This data were used to examine the pharmacokinetics of ketoprofen in Cape vultures *Gyps coprotheres.*

Action

In South Africa, five and eleven Cape vultures *Gyps coprotheres* were given an oral dose of ketoprofen at 1 mg/kg body weight (bw) and 5 mg/kg bw, respectively. Seven of the eleven vultures given the higher dose (5 mg/kg bw) died. All other vultures survived. Blood samples were collected before the experiment and at 10 time points up to 48 h. Ketoprofen concentrations in plasma were determined using liquid chromatography mass spectrometry. The pharmacokinetic profiles of ketoprofen in vultures dosed at 1 mg/kg bw (Group 1), dosed at 5 mg/kg bw and survived (Group 2) and dosed at 5 mg/kg bw and died (Group 3) were modelled and the parameters compared.

Findings

A number of parameters, including the elimination half-life ($T_{1/2}$) were similar in vultures that survived (Groups 1 and 2), but not in vultures that died (Group 3). $T_{1/2}$ was twice as long in Group 3 ($T_{1/2}$ = 7.4 h) compared to Group 2 ($T_{1/2}$ = 3.2 h).

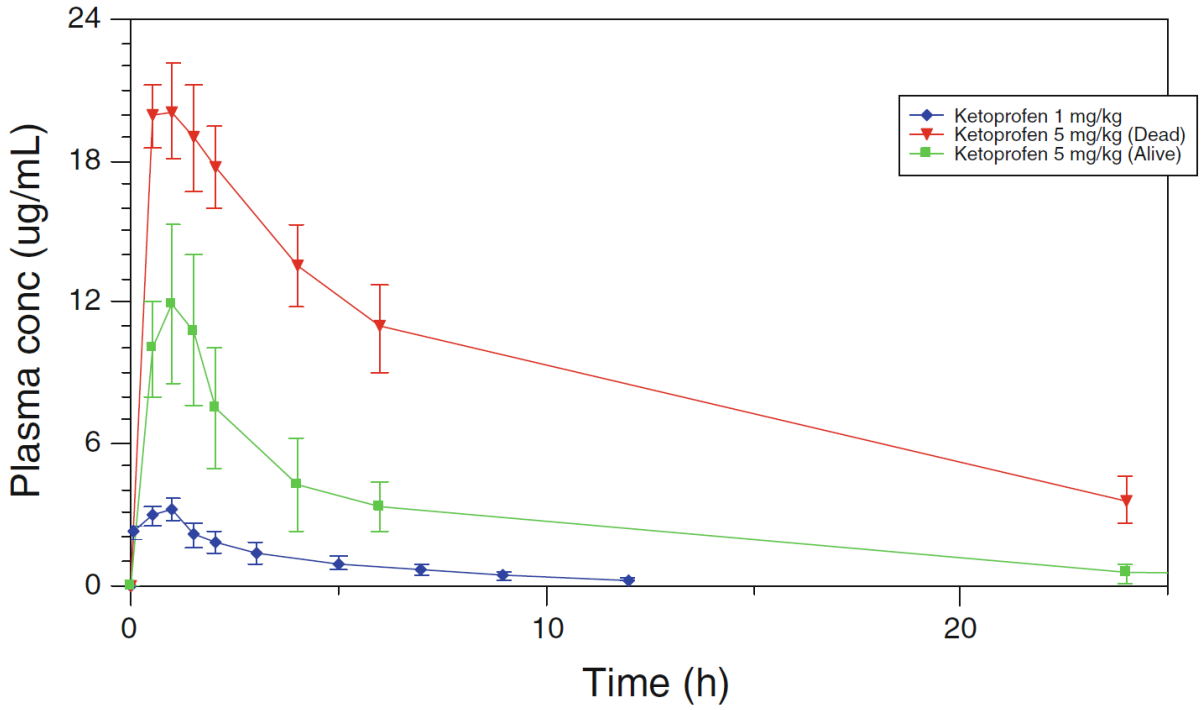
All other parameters, including maximum concentration (C_{max}) and area under the curve (AUC; two measures), were greater in Group 3 than Group 2 and greater in Group 2 than Group 1. C_{max} and AUC were 2 and 3-4 times higher in Group 3 (Cmax = 11 µg/ml; AUC = 50-52 µg/ml h) than Group 2 (Cmax = 21 µg/ml; AUC = 157-208 µg/ml h).

Greater $T_{1/2}$, C_{max} and AUC in vultures that died suggests zero-order or near-zero-order metabolism leading to saturation of metabolic process, drug accumulation and toxicity.

Conclusion

Ketoprofen saturates the metabolic process and thereby accumulates in *Gyps* vultures leading to toxicity.

Key figure



Ketoprofen concentrations (mean ± SE) in plasma versus time, for vultures treated orally at: 1 mg/mg (n = 5; blue); 5 mg/kg and survived (n = 4; green); and 5 mg/kg and died (n = 7; red).

4. A survey of ketoprofen prevalence and concentration in liver samples from carcasses of domesticated ungulates available to scavenger at carcass dumps in India finds that ketoprofen was present and sometimes at high concentrations

Source

Taggart M.A., Senacha K.R., Green R.E., Cuthbert R., Jhala Y.V., Meharg A.A., Mateo R., Pain D.J. (2009). Analysis of Nine NSAIDs in Ungulate Tissues Available to Critically Endangered Vultures in India. Environmental Science & Technology, 43, 4561-4566.

Background

NSAIDs other than diclofenac are used to treat cattle. A survey was conducted to establish which drugs were detectable in liver samples from carcasses of domesticated ungulates at carcass dumps in India.

Action

Liver samples from 1488 domesticated ungulates were collected from 26 sites in seven Indian states in 2006. They were assayed for nine NSAIDs by liquid chromatography-mass spectrometry.

Findings

Ketoprofen was detected in 13 of 1488 samples (0.8%). The maximum concentration of ketoprofen measured in liver from cattle carcasses was 5.6 mg/kg, which is 35 times the mean concentration measured in liver from cattle dosed and sacrificed in the toxicity test (see supporting evidence 2 and 3 above). Cattle in the toxicity test were treated with ketoprofen daily on three days with twice the recommended veterinary dose and slaughtered 1 hour after the last dose. The mean concentration of ketoprofen in liver from cattle carcasses was 0.40 mg/kg, which is 2.5 times the mean concentration measured in liver from cattle dosed and sacrificed in the toxicity test. A wild *Gyps* vulture taking a large meal of liver from the cattle carcass with the highest concentration of ketoprofen would have received a dose at 1.21 mg/kg bw, which is close to that which killed a *Gyps* vulture in the toxicity test (i.e., 1.5 mg/kg bw; see supporting evidence 2 above).

Further, although kidneys were not sampled from cattle carcasses, the ketoprofen concentrations in kidneys were certainly higher than those measured in liver. This is because the mean concentration measured in kidneys from cattle dosed and sacrificed in the toxicity test were far greater than that in liver from the same animals (see supporting evidence 2 above). It follows that the mean and maximum concentrations of ketoprofen in kidneys from cattle carcasses were 2.5 and 35 times that in kidneys from cattle dosed and sacrificed in the toxicity test as well. A wild *Gyps* vulture taking a large meal of kidneys from the cattle carcass with the mean and highest concentration of ketoprofen would have received a dose at 3.83 and 53.59 mg/kg bw, respectively, which is close to and far above that which killed *Gyps* vultures in the toxicity test (i.e., 5 mg/kg bw; see supporting evidence 2 above).

Conclusion

Overdosing of cattle near to death with ketoprofen under field conditions in India may be substantially more extreme than has been assumed. Some wild *Gyps* vultures could ingest sufficient ketoprofen to cause death in a larger meal of liver and/or kidney taken from a cattle carcass with an unusually high but feasible level of contamination.

Key figure

TABLE 2. Prevalence (%) of Diclofenac and Other NSAIDs Detected in Liver Samples from Ungulate Carcasses Sampled in Seven States in India in 2006[a]

state	DIC	MEL	IBU	KET	DIC + MEL	DIC + IBU	DIC + IBU + KET
all States	11.1 (165)	4.0 (60)	0.6 (9)	0.5 (8)	0.9 (13)	0.5 (7)	0.3 (5)
Jammu and Kashmir	3.6 (4)	11.6 (13)	0.9 (1)	–	–	0.9 (1)	–
Gujarat	4.1 (9)	–	–	–	–	–	–
Maharashtra	11.2 (27)	4.6 (11)	–	0.4 (1)	0.8 (2)	–	–
Punjab	12.3 (28)	7.5 (17)	–	–	2.2 (5)	–	–
Madhya Pradesh	12.7 (30)	0.8 (2)	0.4 (1)	–	0.4 (1)	0.4 (1)	–
Rajasthan	14.5 (49)	4.7 (16)	1.5 (5)	2.1 (7)	1.5 (5)	1.5 (5)	1.5 (5)
West Bengal	16.4 (18)	0.9 (1)	1.8 (2)	–	–	–	–

[a] Abbreviaitons are DIC (diclofenac), MEL (meloxicam), IBU (ibuprofen), and KET (ketoprofen). Number of samples containing residues (*n* values) are given in brackets.

5. 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. and 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

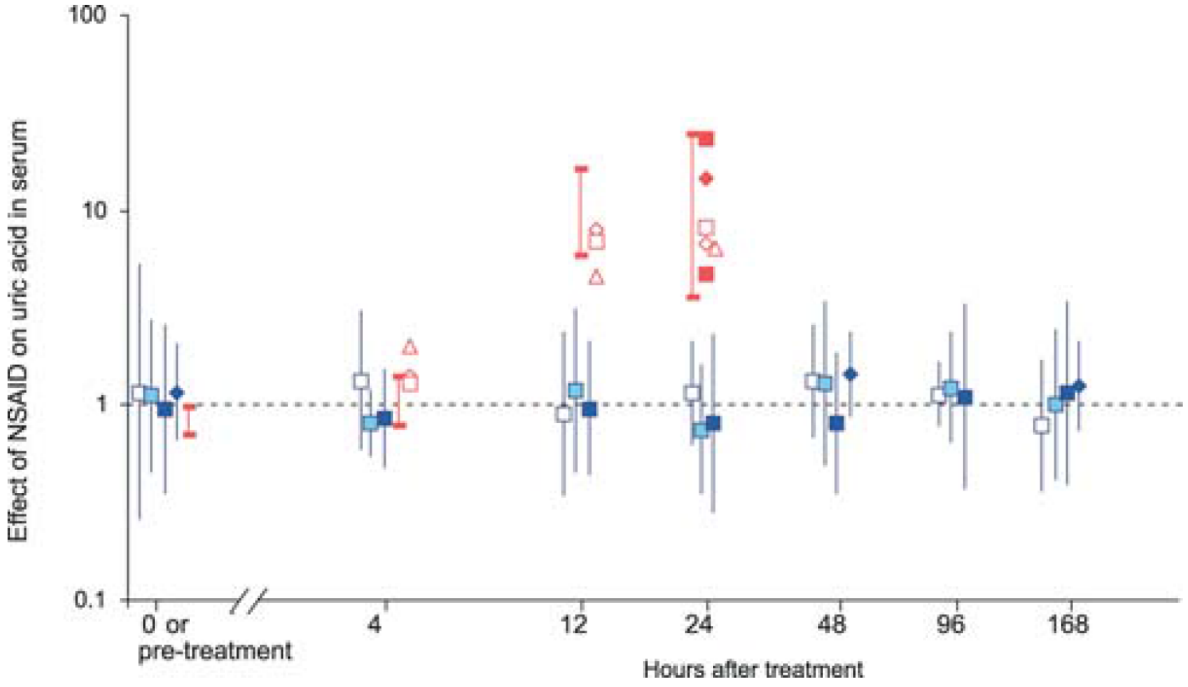
In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived.

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.

6. A pharmacokinetics analysis finds meloxicam is rapidly metabolised and not toxic in *Gyps* and non-*Gyps* vultures

Source

Naidoo, V., Wolter, K., Cromarty, A. D., Bartels, P., Bekker, L., McGaw, L., Taggart M. A., Cuthbert, R. and Swan, G. E. (2007) The pharmacokinetics of meloxicam in vultures. *Journal of Veterinary Pharmacology and Therapeutics* 31: 128-134.

Background

Meloxicam is not toxic to *Gyps* vultures. An experiment was undertaken to examine the pharmacokinetics of meloxicam in Cape vultures *Gyps coprotheres*.

Action

The pharmacokinetics of meloxicam in *Gyps* vultures was examined in a two-phase uncontrolled experiment in South Africa.

In Phase 1, six Cape vultures *Gyps coprotheres* were given an oral dose of meloxicam at 2 mg/kg body weight (bw). In Phase 2, six Cape vultures *Gyps coprotheres* were given an intramuscular dose of meloxicam at 2 mg/kg bw. Blood samples were collected before the experiment and at 8 time points up to 10 h.

In addition, treatment of 12 vultures from four species with meloxicam at 2 mg/kg bw was reported. Eight African white-backed vultures *Gyps africanus* received a single oral dose; whereas, one Cape *Gyps coprotheres*, one African white-backed *Gyps africanus*, one lappet faced *Torgos tracheliotos* and one Egyptian vulture *Neophron percnopterus* received multiple doses at intervals of 24 h. Blood samples were collected before a dose and 8 h after a dose (except in two vultures where additional samples were collected 4 h after a dose).

Meloxicam concentrations in plasma were determined using liquid chromatography mass spectrometry. The pharmacokinetic profiles were modelled and the parameters compared.

Findings

Among experimentally treated vultures, oral or intramuscular administered meloxicam was rapidly absorbed (T_{max} = 0.5-0.6 h) and eliminated ($T_{1/2}$ = 0.3-0.4 h). Among therapeutically

treated vultures, meloxicam was only detected in the two vultures sampled 4 h after a dose, having fully metabolised in vultures first sampled 8 h after a dose.

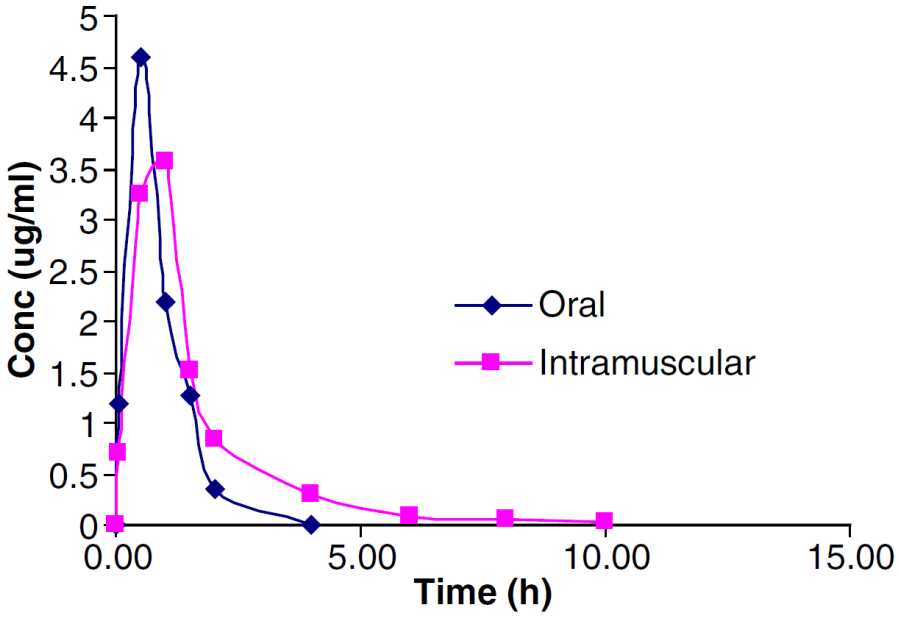
The maximum concentration (C_{max} = 3.5-5.3 µg/ml) and area under the curve (AUC = 5.9-6.3 µg/ml h) were relatively small compared to ketoprofen (see above).

No vultures showed ill effects and none died; however, one Cape vulture *Gyps coprotheres* receiving therapy was euthanized because it was not recovering.

Conclusion

Meloxicam does not saturate the metabolic process and thereby does not accumulate in vultures.

Key figure



Mean plasma concentration versus time curve following oral and intramuscular meloxicam administration in adult Cape vultures *Gyps coprotheres.*

7. 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* and four Long-billed vultures *Gyps indicus* were given an oral dose of meloxicam at 0.5 or 2.0 mg/kg body weight (bw); and two Asian white-backed vultures *Gyps bengalensis* and two Long-billed vultures *Gyps indicus* 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 *Neophron percnopterus*, four cattle egrets *Bubulcus ibis*, five crows *Corvus spp.* and five common myna *Acridotheres tristis* were given sterilised water.

Phase 3: 19 Asian white-backed vultures *Gyps bengalensis* and two long-billed vultures *Gyps indicus* were fed tissue from buffalo dosed with meloxicam; and five Asian white-backed

vultures *Gyps bengalensis* 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 *Acridotheres tristis*); 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

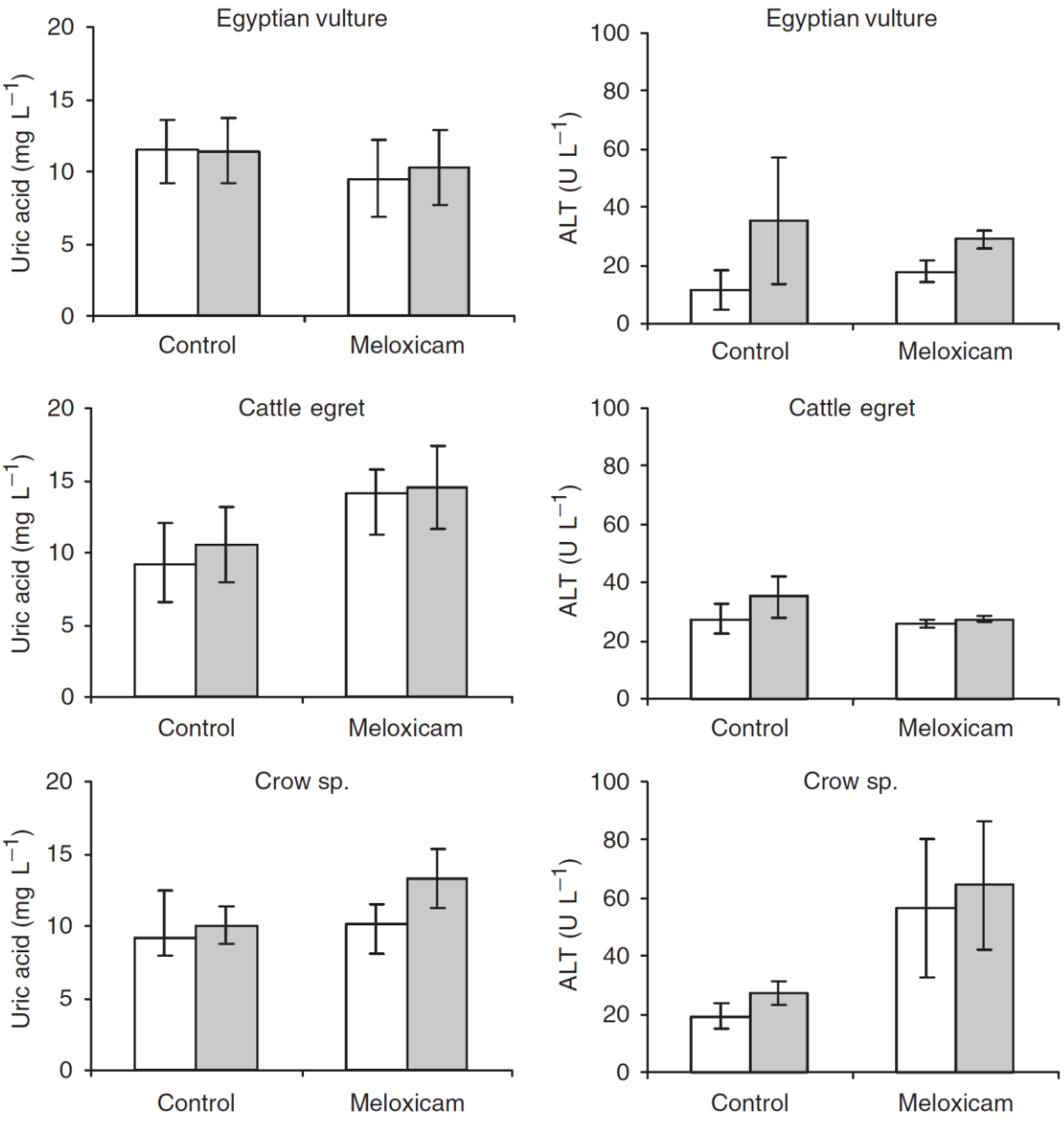
In all Phases, all meloxicam-treated birds survived with no ill effects. All control birds survived.

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).

8. 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 domesticated animals

Background

Meloxicam is not toxic to vultures. Therefore, meloxicam is vulture-safe alternative to ketoprofen. This review of literature was undertaken to assess the safety and effectiveness of meloxicam as an alternative to ketoprofen 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 ketoprofen and/or meloxicam in the following domesticated animals: cattle; water buffalo; horse; donkey; camel; goat; sheep; and dog.

Findings

Among 173 studies: 65 reported an effect of ketoprofen treatment; 117 reported an effect of meloxicam treatment; and nine reported an effect of both meloxicam and ketoprofen treatment.

All studies were grouped into broad veterinary and husbandry situations for treatment (e.g. infection, surgery, reproducing); broad objectives of treatment (e.g. decrease pain, increase reproductive rate, no complications); 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 more studies examining meloxicam (79%) than studies examining ketoprofen (63%). A mixed effect was reported in less studies examining meloxicam (9%) than studies examining ketoprofen (22%). A similar number of studies examining meloxicam and ketoprofen reported a negative effect (3 and 5%, respectively), no effect (7 and 8%, respectively) and no conclusion (2 and 3%, respectively).

Meloxicam and ketoprofen showed positive effects in cattle, buffalo, horse, goat, sheep and dog. Meloxicam and ketoprofen showed positive effects in castrating, dehorning, general care, infections, limb injuries, reproducing and surgery. Meloxicam and ketoprofen treatment decreased pain, inflammation, stress and dysfunction; increased recovery rate; and resulted in no complications.

Meloxicam uniquely increased immune response (two studies), pregnancy rate (five studies), cow productivity (one study) and calf productivity (two studies). In addition, meloxicam showed a positive effect in handling cattle (i.e., transporting).

Nine studies directly compared the effects of meloxicam and ketoprofen. Six of the nine studies showed no difference in effect between the two drugs – both decreased pain and inflammation and resulted in no complications – in cattle, horses, goats and dogs. Two of the nine studies showed negative effects of ketoprofen treatment in dogs – one showed gastrointestinal complications and the other renal complications – but not meloxicam treatment. One of the nine studies was inconclusive.

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). Further, only one study examined the effect of ketoprofen on pregnancy and this was on a post-natal situation (i.e., mastitis).

Conclusion

Meloxicam is as safe as and probably more effective than ketoprofen in a variety of veterinary and husbandry situations in a variety of animals.

Key figure

One-hundred and seventy-three studies reported an effect of either meloxicam, ketoprofen or meloxicam and ketoprofen 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
Ketoprofen	Ting et al. 2003	Cattle	Castration	Decrease pain	controlled	50	Positive
Ketoprofen	Moya et al. 2014	Cattle	Castration	Decrease pain and increase calf productivity	not controlled	150	Mixed
Ketoprofen	Stafford et al. 2002	Cattle	Castration	Decrease pain and stress	not controlled	.	Positive
Ketoprofen	Early et al. 2002	Cattle	Castration	Decrease stress and immune response	controlled	40	Positive
Ketoprofen	Milligan et al. 2004	Cattle	Dehorning	Decrease pain	controlled	40	Mixed
Ketoprofen	McMeekan et al. 1998	Cattle	Dehorning	Decrease pain	controlled	100	Positive
Ketoprofen	Sutherland et al. 2003	Cattle	Dehorning	Decrease pain	not controlled	.	Positive
Ketoprofen	Faulkner et al. 2000	Cattle	Dehorning	Decrease pain	not controlled	20	Positive
Ketoprofen	Duffied et al.2010	Cattle	Dehorning	Decrease pain	not controlled	40	Positive
Ketoprofen	Da Silva et al.1998	Cattle	General	Avoid dysfunction	controlled	.	Positive
Ketoprofen	Bastos et al. 1997b	Cattle	General	Avoid dysfunction	controlled	6	Positive
Ketoprofen	Bastos et al. 1997a	Cattle	General	Avoid dysfunction	not controlled	7	Positive
Ketoprofen	Donalisio et al. 2013	Cattle	General	Decrease pain	controlled	12	Positive
Ketoprofen	Pyörälä et al. 1999	Cattle	General	No complications	controlled	5	Positive
Ketoprofen	Fenwick et al. 1996	Cattle	Infection	Avoid dysfunction	controlled	16	Mixed
Ketoprofen	Roussel et al. 1993	Cattle	Infection	Avoid dysfunction	controlled	16	Positive

Ketoprofen	Semrad 1993	Cattle	Infection	Avoid dysfunction	not controlled	9	Mixed
Ketoprofen	Van de Weerdt et al. 1999	Cattle	Infection	Avoid dysfunction	not controlled	6	Positive
Ketoprofen	Lockwood et al. 2003	Cattle	Infection	Decrease pain	controlled	66	Positive
Ketoprofen	Banting et al. 2008	Cattle	Infection	Decrease pain	controlled	27	Positive
Ketoprofen	Chapinal et al. 2010	Cattle	Limb injury	Decrease pain	controlled	47	Mixed
Ketoprofen	Whay et al. 2005	Cattle	Limb injury	Decrease pain	controlled	40	None
Ketoprofen	Flower et al. 2008	Cattle	Limb injury	Decrease pain	controlled	68	None
Ketoprofen	Thomas et al. 2015	Cattle	Limb injury	Decrease pain	controlled	.	Positive
Ketoprofen	Janßen et al. 2016	Cattle	Limb injury	Decrease pain and stress	controlled	21	None
Ketoprofen	Shpigel et al. 1994	Cattle	Reproduction	Improve recovery	controlled	.	Positive
Ketoprofen	Panter et al. 1992	Cattle	Reproduction	Increase pregnancy rate	controlled	.	Mixed
Ketoprofen	Short et al. 1995	Cattle	Reproduction	Increase pregnancy rate	not controlled	.	Mixed
Ketoprofen	Newby et al. 2014	Cattle	Surgery	Decrease pain	controlled	.	Mixed
Ketoprofen	Newby et al. 2013	Cattle	Surgery	Decrease pain	controlled	.	Mixed
Ketoprofen	Forsyth et al. 2000	Dog	Castration	No complications	not controlled	30	Positive
Ketoprofen	Daminet et al. 2003	Dog	General	Avoid dysfunction	not controlled	18	Positive
Ketoprofen	Saritas et al. 2015	Dog	General	Decrease pain	controlled	17	Positive
Ketoprofen	Fantoni et al. 2015	Dog	General	Decrease pain	controlled	.	Positive
Ketoprofen	Baltoyiannis et al. 2002	Dog	General	No complications	controlled	25	Negative
Ketoprofen	Narita et al. 2005	Dog	General	No complications	controlled	9	Positive
Ketoprofen	Paquette et al. 1997	Dog	Infection	Avoid dysfunction	controlled	16	Positive

Ketoprofen	Hazewinkel et al. 2003	Dog	Limb injury	Decrease inflammation and no complications	controlled	16	Positive
Ketoprofen	Grisneaux et al. 1999	Dog	Surgery	Decrease pain	controlled	96	Mixed
Ketoprofen	Lemke et al. 2002	Dog	Surgery	Decrease pain	controlled	22	None
Ketoprofen	Grisneaux et al. 2003	Dog	Surgery	Decrease pain	controlled	55	Positive
Ketoprofen	Morgaz et al. 2013	Dog	Surgery	Decrease pain	controlled	75	Positive
Ketoprofen	Agner et al. 2008	Dog	Surgery	Decrease pain	not controlled	426	Positive
Ketoprofen	Pibarot et al. 1997	Dog	Surgery	Decrease pain	not controlled	70	Positive
Ketoprofen	Martins et al. 2010	Dog	Surgery	Decrease pain and no complications	not controlled	46	Positive
Ketoprofen	Lobetti et al. 2000	Dog	Surgery	No complications	controlled	40	Mixed
Ketoprofen	Mozaffari et al. 2010	Donkey	General	No complications	controlled	20	Negative
Ketoprofen	Viles et al. 2013	Donkey	Reproduction	Increase pregnancy rate	controlled	6	Mixed
Ketoprofen	Karademir et al. 2016	Goat	Castration	Decrease stress	controlled	16	None
Ketoprofen	Benbarek et al 2012	Horse	General	Decrease stress	controlled	.	Mixed
Ketoprofen	MacAllister et al. 1993	Horse	General	No complications	controlled	16	Mixed
Ketoprofen	Owens et al. 1995	Horse	Limb injury	Decrease pain	not controlled	7	Positive
Ketoprofen	Owens et al. 1996	Horse	Limb injury	Decrease pain and inflammation	not controlled	24	Positive
Ketoprofen	Sigurdsson et al. 1993	Sheep	Infection	Decrease stress	controlled	28	Positive
Ketoprofen	Marini et al. 2015	Sheep	Limb injury	Decrease pain	controlled	40	No conclusion
Ketoprofen	Stafford et al. 2006	Sheep	Surgery	Decrease stress	controlled	30	Positive
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	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	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	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 & ketoprofen	Barrett et al. 2016	Cattle	Surgery	Decrease pain	controlled	24	No conclusion
Meloxicam & ketoprofen	Newby et al. 2013	Cattle	Surgery	Decrease pain	not controlled	10	Positive
Meloxicam & ketoprofen	Deneuche et al. 2004	Dog	General	Decrease pain and no complications	controlled	60	Positive
Meloxicam & ketoprofen	Forsyth et al. 1998	Dog	General	No complications	not controlled	24	Positive
Meloxicam & ketoprofen	Borges et al. 2013	Dog	General	No complications	not controlled	24	Positive for meloxicam, negative for ketoprofen
Meloxicam & ketoprofen	Luna et al. 2007	Dog	General	No complications	not controlled	36	Positive for meloxicam, negative for ketoprofen
Meloxicam & ketoprofen	Mathews et al. 2001	Dog	Surgery	Decrease pain and no complications	controlled	36	Positive
Meloxicam & ketoprofen	van der Heide et al. 2008	Goat	Limb injury	No complications	controlled	18	Positive
Meloxicam &	Brideau et al. 2001	Horse,	General	Decrease inflammation	controlled	30, 48	Positive

ketoprofen	Dog