Flunixin: a vulture-toxic drug

Summary of evidence that flunixin is toxic to vultures; and that meloxicam, an alternative to flunixin, 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

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

Aim

This paper, intended for decision-makers involved in drug licensing, presents evidence of the toxicity of flunixin, 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 flunixin has been found in dead wild *Gyps* vultures.

2. Wild vultures are exposed to NSAIDs when feeding on carcasses of domesticated ungulates treated with these drugs shortly before death.
3. Published data from wildlife forensic investigations in Spain shows visceral gout (i.e., a clinical sign of renal failure in birds) and flunixin residue, but not diclofenac residue, in carcasses of four Eurasian griffon vultures *Gyps fulvus*.
4. Captive vultures are also exposed to NSAIDs through veterinary care.

5. A survey of wildlife veterinarians found the use of flunixin caused visceral gout and death in 2 out of 4 cases involving a captive *Gyps* vulture.
6. 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.

7. An experiment showed that oral doses of flunixin above the MLE caused observable symptoms of toxicity, hyperuricemia (i.e., elevated uric acid levels) and elevated alanine transferase (ALT) in two Cape vultures *Gyps coprotheres*.
8. Two captive Rüppell's Vultures found dead at a Rome zoo were found to have extensive visceral gout and kidney lesions typical of NSAID toxicity. Analysis of kidney and liver samples demonstrated that flunixin was the only NSAID detected in all samples. Concentrations of flunixin ranged from 16-39 µg/kg in kidney and liver samples, and <5-38.5 µg/kg in muscle, the latter in samples taken from a White-backed Vulture also found dead at the zoo. Concentrations of flunixin in beef fed to the vultures was 31,350 µg/kg, 1.8-3.5 times the recommended therapeutic dose for cattle
9. The NSAID diclofenac has been shown to be toxic to *Gyps* vultures. Experiments show that oral doses of diclofenac caused hyperuricemia, kidney failure and death in *Gyps* vultures.
10. In contrast to flunixin, 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 Egyptian vultures *Neophron percnopterus*, cattle egrets *Bubulcus ibis*, crows *Corvus spp.*

and common myna *Acridotheres tristis*, which also scavenge.

12. Meloxicam is manufactured in Bangladesh, India, Nepal and Pakistan. More experimental and clinical studies have shown a positive effect of meloxicam treatment than that of flunixin treatment. 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 nimesulide and multiple-dose vials of human nimesulide 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 nimesulide.

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. Flunixin caused visceral gout and death in 2 out of 4 *Gyps* vultures. A single instance where flunixin in combination with ketoprofen was administered to a *Gyps* vulture resulted in kidney failure and death, but which of the compounds caused death could not be determined. Further, flunixin caused mortalities in 6 out of 20 other birds of a variety of species. In contrast,

   meloxicam did not cause mortalities in 40 *Gyps* vultures and another 700 birds of a variety of species. Further details in pages 8-10.

2. In Spain, wildlife forensic investigations found a dead Eurasian griffon vulture *Gyps fulvus*. Post-mortem examination included liquid chromatography mass spectrometry screening for seven NSAIDs. Organs showed moderate autolysis and severe visceral gout. Pesticide screening was negative. NSAID screening was positive for flunixin, but negative for all other NSAIDs, including diclofenac.

3. Further wildlife forensic investigations in Spain discovered a further three dead Eurasian griffon vultures *Gyps fulvus* with visceral gout and flunixin. Further details in pages 17 and 18.

4. The effect of flunixin on *Gyps* vultures was examined in controlled experiment conducted in South Africa. Two Cape vultures *Gyps coprotheres* were given oral doses of flunixin at 1 mg/kg body weight (bw). The maximum level of exposure (MLE) of

flunixin to Cape vulture *Gyps coprotheres* was calculated as 0.35 mg/kg bw. Both treated and control vultures survived with no pathological signs of toxicity at post mortem following euthanasia; however, observable symptoms of toxicity and elevated uric acid levels were found in one vulture and elevated levels of ALT in both vultures. Further details in pages 13-15.

5. The cause of death of two captive Rüppell's Vultures G*yps rueppellii* and one Whitebacked Vulture *G. africanus* at a Rome zoo was determined to be flunixin poisoning. Post-mortems of the two *G. rueppellii* showed extensive visceral gout and kidney lesions, typical of NSAID toxicity, while chemical analysis demonstrated that flunixin was the only NSAID present in all samples. All three birds were fed with the same beef, which had a flunixin concentration of 31,500 µg/kg (1.8-3.5 times recommended therapeutic dose for cattle); concentrations of the drug in kidney and liver samples of *G. rueppellii* were 16-39 µg/kg, while concentrations within muscle were <5 µg/kg (*G. rueppellii*) – 38.5 µg/kg (*G. africanus*).

6. In South Africa, a single-phased controlled experiment examined toxicity of diclofenac to African white-backed vultures *Gyps africanus* and Eurasian griffon vultures *Gyps fulvus*. Vultures were given an oral dose of diclofenac at 0.8 mg/kg body weight (bw). 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. Further details in pages 16-17.

7. 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 18-20.

8. Among 201 studies, a positive effect was reported in more studies examining meloxicam (81%) than those examining flunixin (44%). A negative, mixed or no effect was reported in less studies examining meloxicam (2, 8 and 7%, respectively) than studies examining

flunixin (9, 15 and 28%, respectively). A similar number of studies examining meloxicam and flunixin reported a no conclusion (2 and 3%, respectively). Meloxicam showed a positive effect for more husbandry and veterinary situations, treatment objectives and types of domesticated animal than Flunixin. Six of the 11 studies that directly compared the effects of meloxicam and flunixin showed no difference in effect (positive) between the two drugs; however, three studies showed positive effects of flunixin and either mixed or no effect of meloxicam; and one study showed a positive effect of meloxicam and a negative effect of flunixin. Overall, 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 in pages 21-34.

Specific details

Chemical name: **flunixin**

Systematic name: 2-[[2-Methyl-3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid

Formula: $C_{14}H_{11}F_3N_2O_2$

Molar mass: 296.24 g/mol

Typical formulation: 50 or 83 mg/ml injection in 50 or 100 ml vials

Example products (manufacturers):

Bangladesh – Korean products imported

India – Flizik (Sequest)

Nepal – products may be imported

Pakistan – Loxin (selmore), Nixsym (Symans), Maxin (Star), Phonix (mylab), Tricure (ICI)

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. 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

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. A post-mortem examination of wild *Gyps* vultures finds visceral gout and flunixin residue, but not diclofenac residue

Source

Zorrilla, I., Martinez, R., Taggart, M. A. and Richards, N. (2014). Suspected flunixin poisoning of a wild Eurasian griffon vulture from Spain. *Conservation Biology* 29: 587-592.

Background

Diclofenac kills vultures through acute renal failure. In vultures, acute renal failure presents as visceral gout (i.e., uric acid deposits on organs and within kidney tubules). Flunixin is used to treat cattle, horses and pigs in Spain. The Government of Andalusian, Spain, carry out forensic investigations on all wild birds of prey that are found dead. The Eurasian griffon vulture *Gyps fulvus* is a native species in Pakistan and belongs to the same genus as the critically endangered *Gyps* vulture species in Pakistan.

Action

A Eurasian griffon vulture carcass was found in Andalusia, Spain. Post-mortem examination included chromatographic screening for pesticides (e.g. carbonates, organophosphates, strychnine) and liquid chromatography mass spectrometry screening for seven non-steroidal anti-inflammatory drugs (NSAIDs: carprofen, diclofenac, flunixin, indomethacin, ketoprofen, meloxicam, naproxen and nimesulide). A 5 g sample of tongue, crop mucosa and ventricle mucosa combined was used to screen for pesticides. Two samples were used to screen for NSAIDs: a 5 g sample of liver and a 5 g sample of kidney. NSAID screening was performed in two independent laboratories (one in Spain and one in the United Kingdom).

Findings

The carcass was of a mature female in good condition. Examination occurred approximately 5-

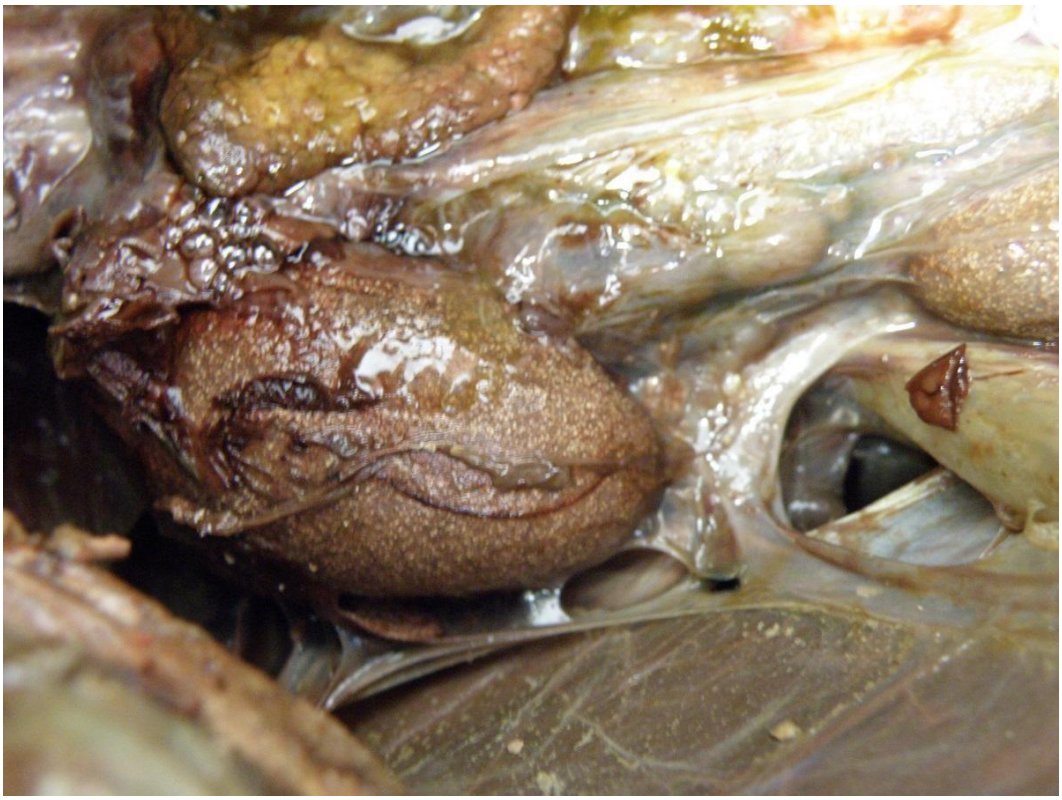
6 h after death. Organs showed moderate autolysis and severe visceral gout (i.e., uric acid covering the kidney, liver, and pericardium, and throughout the kidney tubules).
Pesticide screening was negative.

NSAID screening was positive for flunixin, but negative for all other NSAIDs.

Conclusion

Flunixin caused acute renal failure and death in a Eurasian griffon vulture.

Key figure



Photograph of the right (centre) and left (top right) kidney of a wild Eurasian griffon vulture found dead in the field, showing uric acid deposits on the kidney mucosa. This vulture tested positive for flunixin, but no other NSAID or pesticide.

3. Examination of livestock and avian carcasses in Iberia detects ongoing threat from NSAIDs in scavenger food supply and further cases of flunixin poisoning in *Gyps* vultures

Source

Herrero-Villar, M., Velarde, R., Camarero, P.R., Taggart, M.A., Bandeira, V., Fonseca, C., Marco, I. and Mateo, R. 2020. NSAIDs detected in Iberian avian scavengers and carrion after diclofenac registration for veterinary use in Spain. *Environmental Pollution*, **266,** doi.org/10.1016/j.envpol.2020.115157

Background

Previous work has identified flunixin residues and visceral gout in a dead Eurasian Griffon (EG) in Spain. The veterinary use of diclofenac was registered in Spain, Europe's main vulture stronghold, in 2013. This was partly based on the assumption that contaminated meat would not find its way into the vulture food chain.

Action

Muscle, liver and kidney from a total of 228 livestock carcasses that had been provided to vultures at designated feeding sites, were sampled and analysed using liquid chromatography with mass spectrometry (LCMS) for ten different NSAIDs. These included carprofen, diclofenac, flunixin, indomethacin, ketoprofen, meloxicam, naproxen, phenylbutazone, suxibuzone and tolfenamic acid.

For each NSAID, the risk of exposure to vultures was calculated as the toxicity exposure ratio (TER = LD_{50}/ETE), with LD_{50} values (i.e. median lethal dose at which 50% of birds died) taken from previous studies on vultures, and the estimated theoretical exposure (ETE) based on NSAID concentrations detected in carrion in this study, the weight of the vulture and its average daily intake of meat (analogous to MLE). A widely used metric to measure exposure to a chemical substance, a TER value <10 represents an acute toxicity risk to wild birds.

In addition, the carcasses of 389 scavenging birds, including 344 vultures, from forensic cases admitted to wildlife rehabilitation centres, were analysed for NSAIDs and post-mortems carried out to look for clinical signs of NSAID poisoning, e.g. visceral gout.

Findings

Of the livestock carcasses, seven (3.07%), either sheep or pig, contained NSAID residues, including flunixin (n = 4, 1.75%), ketoprofen, diclofenac and meloxicam (each n = 1, 0.44%).

All estimated TER values were above 10, except for the one sample that tested positive for diclofenac, and one of the four that tested positive for flunixin; the TER value of the latter ranged between 0.22-1 (i.e. <<<10), indicating a very high risk of poisoning.

Of the avian scavenger carcasses, 14 were found with NSAID residues in the liver and/or kidney. Eleven EG (3.59%) tested positive for NSAIDs (meloxicam, n = 7, 2.29%; flunixin, n = 4, 1.30%).

Of 306 dead EG, 10 had degenerative lesions in the kidney and/or liver, and four of these (1.31%) presented extensive visceral gout, of which two had elevated flunixin levels in tissue (liver, 11.32 mg kg^{-1} & 4.91 mg kg^{-1}). A third bird showing kidney degeneration had a flunixin level of 0.33 mg kg^{-1}. Furthermore, a bird that died in a rehabilitation centre was also tested as it was suspected to have died of iatrogenic flunixin poisoning, and found to have elevated flunixin levels in the liver (2.83 mg kg_{-1}) and visceral gout. Two other EG with visceral gout had no detectable NSAID residues in their tissues.

Conclusion

Flunixin was associated with visceral gout and/or kidney damage in three (0.98%) dead EG, with residues of no other NSAID present, confirming poisoning by ingestion of flunixin.

Key figure

Table 2. Positive cases of NSAIDs with the region of origin, presumptive diagnosis, NSAID concentrations by tissue.

Bird	Species	Year	Region	Diagnosis	NSAID	Concentration (mg kg^{-1})		
						Liver	Kidney	Muscle
1	Eurasian griffon	2010	Aragon	Traumatism/ Renal degeneration	Flunixin	0.33	-	-
2	Eurasian griffon	2015	Madrid	Indeterminate/ Visceral gout	Flunixin	4.91	-	-
3	Eurasian griffon	2017	Extremadura	Feather disease	Flunixin	0.023	-	-
4	Eurasian griffon	2018	Catalonia	Indeterminate/Visceral gout	Flunixin	11.32	20.35	-
5	Eurasian griffon	2015	Extremadura	Iatrogenic[a]	Flunixin	2.83	-	0.44
6	Eurasian griffon	2018	Catalonia	Traumatism	Meloxicam	0.641	0.264	-
7	Eurasian griffon	2018	Catalonia	Traumatism	Meloxicam	0.159	0.231	-
8	Eurasian griffon	2019	Aragon	Traumatism/Pb intoxication	Meloxicam	2.44	<LOQ	-
9	Eurasian griffon	2019	Cantabria	Indeterminate	Meloxicam	1.84	-	-
10	Eurasian griffon	2019	Aragon	Suspected Pb intoxication	Meloxicam	1.06	-	-
11	Eurasian griffon	2019	Aragon	Suspected Pb intoxication	Meloxicam	0.887	<LOQ	-
12	Eurasian griffon	2019	Extremadura	Traumatism	Meloxicam	-	0.829	-
13	Black kite	2019	Catalonia	Indeterminate	Meloxicam	0.033	0.046	-
14	Egyptian vulture	2018	Castile and Leon	Carbofuran intoxication	Meloxicam	0.141	-	-
15	Common buzzard	2018	Catalonia	Electrocution	Meloxicam	0.838	1.245	-

LOQ: limit of quantification.
[a] Soler et al. (2016).

Journal Pre-proof

4. An experiment finds doses of carprofen, flunixin and Phenylbutazone cause symptoms and signs of toxicity in Cape vultures *Gyps coprotheres*

Source

Fourie, T., Cromarty, D., Duncan, N., Wolter, K. and Naidoo, V. (2015) The safety and pharmacokinetics of carprofen, flunixin and Phenylbutazone in the Cape vulture (*Gyps coprotheres*) following oral exposure. *PLoS ONE* 10: e0141419.

Background

A questionnaire survey on the therapeutic use of NSAIDs in vultures found carprofen, flunixin and Phenylbutazone to be toxic to *Gyps* vultures. Three dead vultures recovered in Spain showed visceral gout in association with flunixin residue (and not diclofenac residue). This experiment was undertaken to further examine the toxicity of carprofen, flunixin and Phenylbutazone to *Gyps* vultures.

Action

The effect of carprofen, flunixin and Phenylbutazone on *Gyps* vultures was examined in a controlled experiment in South Africa. Cape vultures *Gyps coprotheres* were used as less threatened surrogates for Asian *Gyps* vultures.
Injectable carprofen, flunixin and phenylbutazone products manufactured in South Africa were

used. For carprofen, which is used as a therapeutic drug for birds of prey, vultures were exposed to the recommended dose for birds of prey. For flunixin and Phenylbutazone, vultures were exposed to twice the maximum residue level in horse and cattle, respectively, given the recommended dose in South Africa for; to reflect frequent overdosing behaviour in South Asia.

Two Cape vultures *Gyps coprotheres* were given an oral dose of carprofen at 10 mg/kg body weight (bw); two Cape vultures *Gyps coprotheres* were given an oral dose of flunixin at 1 mg/kg; two Cape vultures *Gyps coprotheres* were given an oral dose of phenylbutazoneat 1.5 mg/kg; and two Cape vultures *Gyps coprotheres* were given an oral dose of control solution. The maximum level of exposure (MLE) to flunixin for the Cape vulture *Gyps coprotheres* was calculated using the average body weight (8 kg), estimated large meal weight (1.42 kg) and average flunixin residue concentration in cattle liver tissue (1.95 mg/kg); and was equal to 0.35mg/kg bw.

The MLE to phenylbutazone for the Cape vulture *Gyps coprotheres* was calculated using the average body weight (8 kg), estimated large meal weight (1.42 kg) and average phenylbutazone residue concentration in horse kidney tissue (3.4 mg/kg); and was equal to 0.60 mg/kg bw. Observations were made during a 48 h period. A series of blood samples were taken from all vultures from before the experiment to 48 h after dosing. Plasma was analysed for elimination behaviour and serum was analysed for uric acid, alanine transferase (ALT) and other biochemical compounds associated with toxicity. All vultures were euthanized immediately after 48 h and examined post mortem.

Findings

All Cape vultures *Gyps coprotheres* survived treatment with carprofen at the recommended therapeutic dose; and flunixin and phenylbutazone at doses above the MLE. All control vultures survived.

Symptoms of toxicity (lethargy and depression) were observed in some treated vultures; however, no pathological signs of toxicity were detected at post mortem.

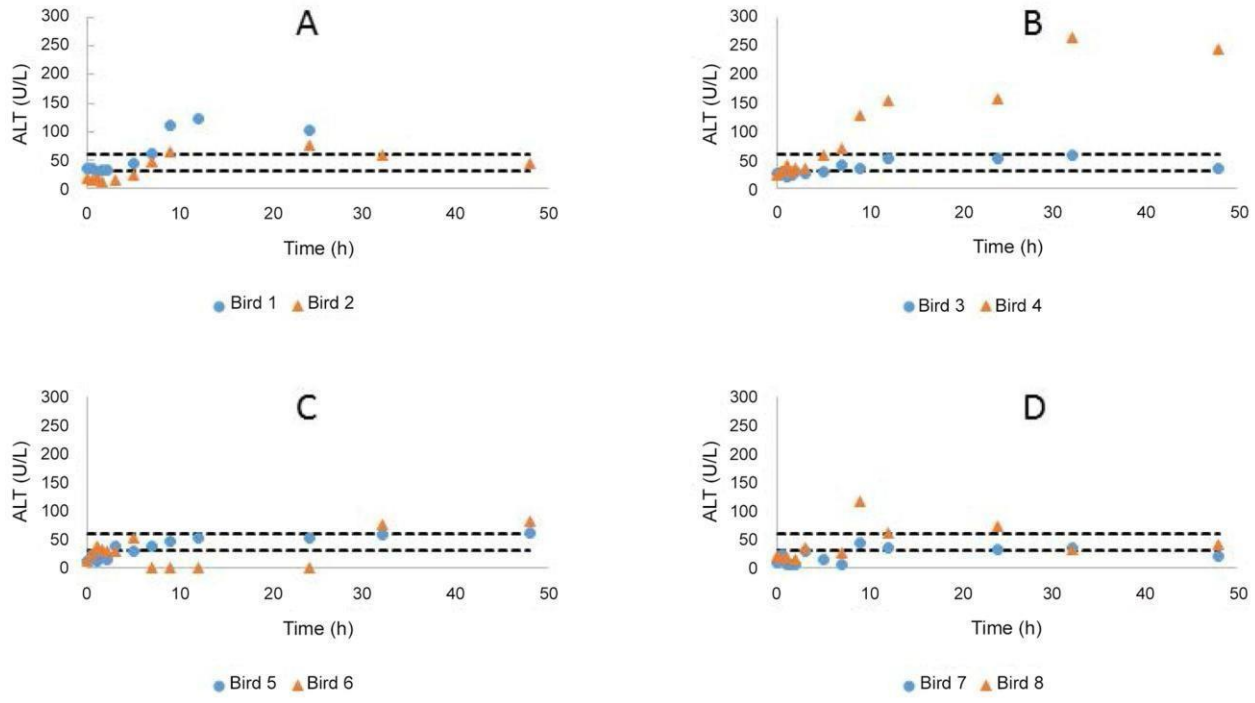
All treated vultures showed elevated levels of ALT. One carprofen-treated and one flunixin-treated vulture showed elevated levels of uric acid. Carprofen and phenylbutazone showed

long elimination half-lives. These three findings are clinical signs of toxicity and are seen in vultures exposed to diclofenac and ketoprofen.

Conclusion

Carprofen, flunixin and phenylbutazone are probably toxic to *Gyps* vultures. *Gyps* vultures exposed to carprofen, flunixin and phenylbutazone above the MLE show some clinical signs of toxicity. Sample sizes in this study are too small to confirm that these drugs are not toxic to vultures.

Key figure



Changes in ALT activity for the individuals vultures r treated with carprofen (A), flunixin (B), phenylbutazone (C) and control vultures (D). Dashed lines represent normal range of activity.

5. Post-mortem analysis of two captive Ruppell's Vultures *Gyps rueppellii* and one captive White-backed Vulture *G. africanus* found flunixin poisoning to be cause of death.

Source

Eleni, C., Neri, B., Giannetti, L., Grifoni, G., Meoli, R., Stravino, F., Friedrich, K. G., Scholl, F., Di Cerbo, P & Battisti, A. (2019) Death of captive-bred vultures caused by flunixin poisoning in Italy. *Environmental Toxicology and Pharmacology* 68: 91-93

Background

Poisoning by the NSAID diclofenac is the main, or sole, cause of the catastrophic decline of populations of three species of South Asian *Gyps* vultures. Diclofenac kills vultures through renal failure, which manifests itself as visceral gout. Although diclofenac has been banned, there are several other NSAIDs still widely available that are potentially toxic to vultures, including flunixin, which is also used to treat livestock. Rüppell's *Gyps rueppellii* and White-backed *G. africanus* Vultures are native species of Africa within the same genus as those that suffered declines in Asia. Like Asian *Gyps* species, White-backed Vultures are known to be susceptible to diclofenac poisoning.

Action

Two captive Rüppell's and one White-backed Vultures at Rome zoo were found dead two, three and 23 days, respectively, after feeding on beef from the same bovine carcass. Samples of muscle, liver and kidney were collected from both Rüppell's Vultures, and muscle from the White-backed (internal organs were not present due to the advanced state of putrefaction of this bird), to screen for NSAIDs, as was a sample of the beef on which the birds had fed.

Findings

Post-mortem results showed that both Rüppell's Vultures showed extensive visceral gout and severe renal lesions (organs of the White-backed Vulture were not available).

Chemical analysis showed that flunixin was the only NSAID detected in all samples. Concentrations in the kidney and liver ranged between 16 & 39 µg/kg. In the muscles of Rüppell's Vultures, flunixin levels were <5 µg/kg, while in the White-backed Vulture, it was 38.5 µg/kg.

Flunixin concentration in the beef fed to the vultures was very high – 31,350 µg/kg – although this may have been inflated due to desiccation as samples were not taken until 7 days after the meat was fed to the vultures.

Conclusions

Extensive visceral gout and kidney lesions observed in this study similar to other published cases of NSAID toxicity in vultures.

Study demonstrates that high dosages of flunixin, equating to ca.3,875 µg/kg (recommended therapeutic dose for cattle is 1,100-2,200 µg/kg), may be highly toxic and capable of causing death. Concentrations detected in vulture organs in this study were substantially lower than that reported for Eurasian Griffon Vulture *Gyps fulvus* (16-29 µg/kg v 2,700-3,500 µg/kg).

6. 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.

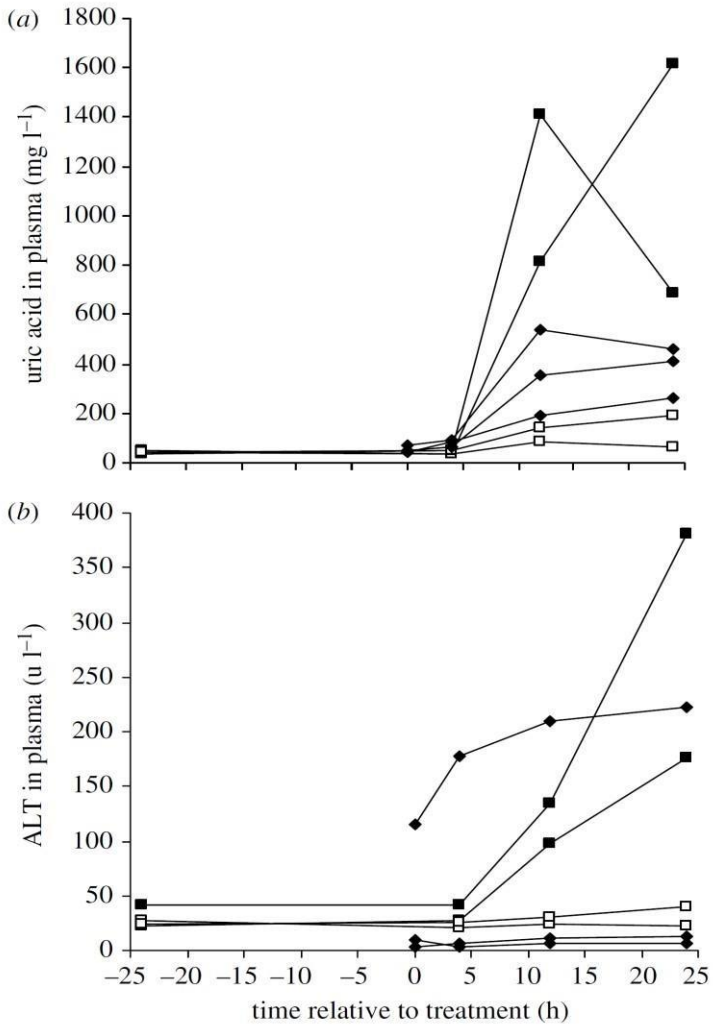
Findings

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).

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 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

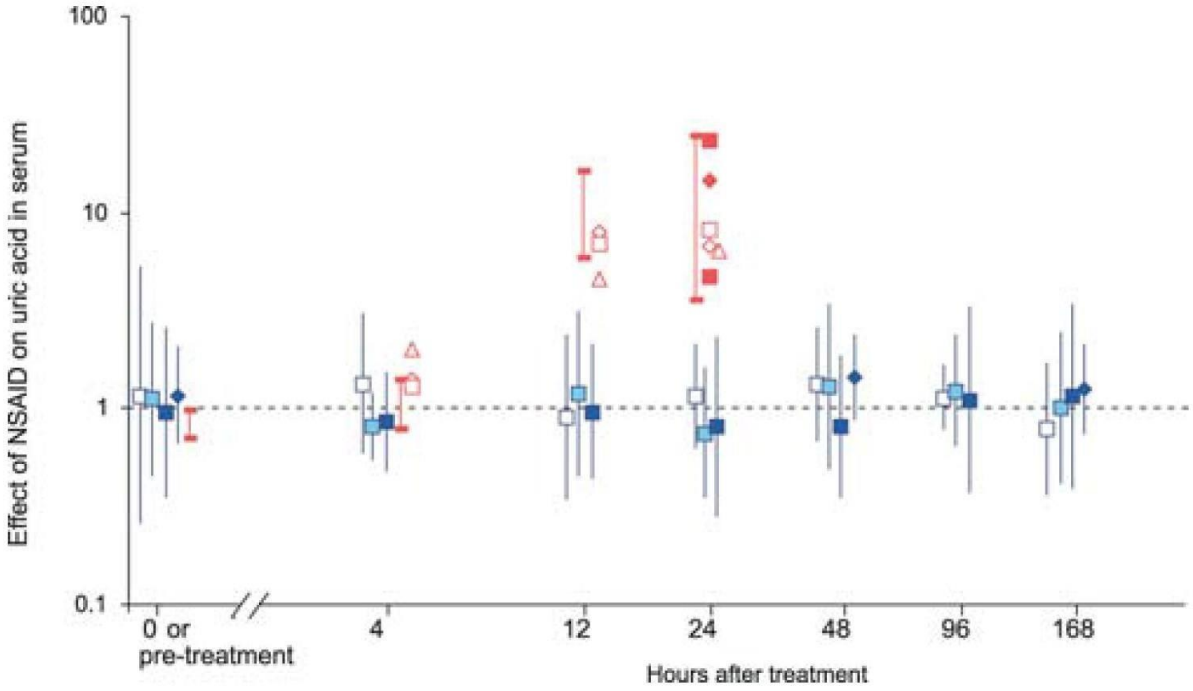
In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived.

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.

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

Source

Galligan, T. H. (2016). Unpublished.

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 flunixin 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 flunixin and/or meloxicam in the following domesticated animals: cattle; water buffalo; horse; donkey; camel; goat; sheep; and dog.

Findings

Among 202 studies: 123 reported an effect of meloxicam treatment; 90 reported an effect of flunixin treatment; and 11 reported an effect of both meloxicam and flunixin treatment. Studies were grouped into:

1) Seven broad veterinary and husbandry situations for treatment: breeding, general, infection and injury, inoculation, husbandry, surgery (veterinary) or surgery (husbandry). 2) Ten broad objectives of treatment: decrease pain, decrease inflammation, decrease dysfunction, decrease stress, increase pregnancy rate, increase recovery, increase productivity, increase survival, no immunosuppression or no complications. 3) Five effects: positive, negative, mixed, none or no conclusion.

A positive effect was reported in more studies examining meloxicam (81%) than studies examining flunixin (44%). A negative, mixed or no effect was reported in less studies examining meloxicam (2, 8 and 7%, respectively) than studies examining flunixin (9, 15 and 28%, respectively). A similar number of studies examining meloxicam and flunixin reported a no conclusion (2 and 3%, respectively).

Meloxicam showed positive effects in six of the eight animals examined (cattle, buffalo, horse, goat, sheep and dog); whereas, flunixin showed positive effects in four of the eight animals examined (cattle, horse, sheep and dog). Meloxicam showed positive effects in six of the seven situations examined (breeding, general, husbandry, infections and injuries, surgery (husbandry) and surgery (veterinary)); whereas, flunixin showed positive effects in five of the seven situations examined (breeding, general, infections and injuries, surgery (husbandry) and surgery (veterinary)). Meloxicam showed positive effects in 10 of the 10 objectives of treatment (decreased pain, inflammation, dysfunction and stress; increased pregnancy rate, recovery rate, productivity and survival; and no immunosuppression and complications); whereas, flunixin showed positive effects in 9 of the 10 objectives of treatment (decreased pain, inflammation,

dysfunction and stress; increased pregnancy rate, recovery rate and productivity; and no immunosuppression and no complications).

Eleven studies directly compared the effects of meloxicam and flunixin. Six of the 11 studies showed no difference in effect (positive) between the two drugs. Three of the 11 studies showed positive effects of flunixin treatment and either mixed or no effect of meloxicam treatment. One of the 11 studies showed a positive effect of meloxicam treatment and a negative effect of flunixin treatment.

Overall, three studies reported negative effects of meloxicam treatment resulting in breeding complications (in cattle, horse and sheep). However, two studies reported positive effects of meloxicam treatment resulting in no breeding complications (in cattle and sheep); and five studies reported positive effects of meloxicam treatment resulting in increased pregnancy rates (in cattle, horse and sheep).

Conclusion

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

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Key figure

Flunixin	Skidmore et al. 2002	Camel	Breeding	Increase pregnancy rate	Controlled	21	None
Flunixin	Burford et al. 1998	Cattle	Breeding	Increase pregnancy rate	Controlled	10	None
Flunixin	Odensvik et al. 1993	Cattle	Breeding	Increase pregnancy rate	Controlled	11	Positive
Flunixin	Guzeloglu et al. 2007	Cattle	Breeding	Increase pregnancy rate	Controlled	52	Positive
Flunixin	Drillich et al. 2007	Cattle	Breeding	Increase pregnancy rate	Controlled	238	None
Flunixin	Gonzales et al. 2012	Cattle	Breeding	Increase pregnancy rate	Controlled	247	None
Flunixin	Geary et al. 2010	Cattle	Breeding	Increase pregnancy rate	Controlled	325	None
Flunixin	Chapinal et al. 2010	Cattle	Breeding	Increase pregnancy rate	Controlled	391	None
Flunixin	Merrill et al. 2007	Cattle	Breeding	Increase pregnancy rate	Controlled	483	Positive
Flunixin	Gonzales et al. 2011	Cattle	Breeding	Increase pregnancy rate	Controlled	719	None
Flunixin	Rossetti et al. 2011	Cattle	Breeding	Increase pregnancy rate	Controlled	975	None
Flunixin	Gonzales et al. 2010	Cattle	Breeding	Increase pregnancy rate	Controlled	1221	Negative
Flunixin	Kim et al. 2014	Cattle	Breeding	Increase pregnancy rate	Controlled	?	Positive
Flunixin	Odensvik et al. 1998	Cattle	Breeding	Increase pregnancy rate	Non-controlled	12	Positive
Flunixin	Geary et al. 2012	Cattle	Breeding	Increase pregnancy rate	Non-controlled	40	Non-conclusive
Flunixin	Purcell et al. 2005	Cattle	Breeding	Increase pregnancy rate	Non-controlled	484	Mixed

Flunixin	Shwartz et al. 2009	Cattle	General	Decrease inflammation and increase productivity	Controlled	26	Mixed

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

NSAID	Study	Animal	Situation 2	Objective	Method	n	Effect

Flunixin	Pyorala et al. 1999	Cattle	General	No complications (irritation)	Non-controlled	5	Negative
Flunixin	Cooke et al. 2013	Cattle	Husbandry	No complications	Controlled	45	Mixed
Flunixin	Semrad 1993	Cattle	Infection and injury	Decrease dysfunction	Controlled	10	Positive
Flunixin	Wilson et al. 2015	Cattle	Infection and injury	Decrease dysfunction	Controlled	320	None
Flunixin	Jarlov et al. 1992	Cattle	Infection and injury	Decrease dysfunction	Non-controlled	4	Positive
Flunixin	Yeiser et al. 2012	Cattle	Infection and injury	Decrease dysfunction and increase productivity	Controlled	24	Mixed
Flunixin	Luthman et al. 1989	Cattle	Infection and injury	Decrease dysfunction and increase recovery	Non-controlled	?	Mixed
Flunixin	Anderson et al. 1986	Cattle	Infection and injury	Decrease inflammation	Controlled	12	Positive
Flunixin	Wilson et al. 2007	Cattle	Infection and injury	Decrease inflammation and dysfunction	Controlled	9	None
Flunixin	Anderson et al. 1989	Cattle	Infection and injury	Decrease inflammation and increase productivity	Controlled	21	Mixed
Flunixin	Schulz et al. 2011	Cattle	Infection and injury	Decrease pain and inflammation	Controlled	10	Positive
Flunixin	Chapinal et al. 2013	Cattle	Infection and injury	Decrease pain and inflammation	Controlled	19	None
Flunixin	Margolis et al. 1987	Cattle	Infection and injury	Decrease shock	Controlled	14	None
Flunixin	Giri et al. 1991	Cattle	Infection and injury	Increase pregnancy rate	Controlled	8	Positive

Flunixin	von Krueger et al. 2010	Cattle	Infection and injury	Increase productivity	?	?	Positive
Flunixin	Anderson et al. 1986c	Cattle	Infection and injury	Increase productivity	Controlled	13	None
Flunixin	Wagner eta l. 2004	Cattle	Infection and injury	Increase productivity	Controlled	30	None
Flunixin	Lockwood et al. 2003	Cattle	Infection and injury	Increase recovery	?	66	Positive
Flunixin	Selman et al. 1984	Cattle	Infection and injury	Increase recovery	?	?	Mixed
Flunixin	Lohuis et al 1989	Cattle	Infection and injury	Increase recovery	Controlled	9	Positive
Flunixin	Odensvik et al. 1996	Cattle	Infection and injury	Increase recovery	Controlled	11	Mixed
Flunixin	Roussel et al. 1988	Cattle	Infection and injury	Increase recovery	Controlled	11	Mixed
Flunixin	Badnarek et al. 2003	Cattle	Infection and injury	Increase recovery	Controlled	18	Positive
Flunixin	Anderson et al. 1996	Cattle	Infection and injury	Increase recovery	Controlled	22	Negative
Flunixin	Verhoeff et al. 1986	Cattle	Infection and injury	Increase recovery	Controlled	23	None
Flunixin	Barnett et al. 2003	Cattle	Infection and injury	Increase recovery	Controlled	115	Positive
Flunixin	Scott 1994	Cattle	Infection and injury	Increase recovery	Controlled	144	None
Flunixin	Balmer et al. 1997	Cattle	Infection and injury	Increase recovery	Controlled	187	Positive
Flunixin	Rantala et al. 2002	Cattle	Infection and injury	Increase recovery	Non-controlled	6	Positive
Flunixin	Thiry et al. 2014	Cattle	Infection and injury	Increase recovery	Non-controlled	210	Positive
Flunixin	Uren et al. 1989	Cattle	Infection and injury	Increase recovery	Non-controlled	?	None
Flunixin	Green et al. 1997	Cattle	Infection and injury	Increase survival	Controlled	54	None
Flunixin	Webster et al. 2013	Cattle	Surgery (Husbandry)	Decrease pain	Controlled	30	Positive

Flunixin	Stilwell et al. 2008	Cattle	Surgery (Husbandry)	Decrease pain	Controlled	40	Mixed
Flunixin	Paull et al. 2015	Cattle	Surgery (Husbandry)	Decrease pain	Controlled	40	None
Flunixin	Tacker et al. 2014	Cattle	Surgery (Husbandry)	Decrease pain	Controlled	48	None
Flunixin	Myers et al. 2010	Cattle	Surgery (Husbandry)	Decrease pain	Controlled	66	Non-conclusive

				Decrease	Controlled		
Flunixin	Huber et al. 2013	Cattle	Surgery (Husbandry)	pain		80	None
Flunixin	Mintline et al. 2014	Cattle	Surgery (Husbandry)	Decrease pain and inflammation	Controlled	48	None
Flunixin	Currah et al. 2009	Cattle	Surgery (Husbandry)	Decrease pain and inflammation	Controlled	101	Positive
Flunixin	Wittek et al. 2008	Cattle	Surgery (Veterinary)	Increase productivity	Controlled	45	None
Flunixin	Williams et al. 1999	Dog	Breeding	No complications	Controlled	?	Positive
Flunixin	McKellar et al. 1989	Dog	General	Decrease inflammation	Non-controlled	?	Positive
Flunixin	Dow et al. 1990	Dog	General	No complications (gastrointestinal)	Controlled	?	Negative
Flunixin	Mathews et al. 1996	Dog	General	No complications (hepatic)	Controlled	64	Negative
Flunixin	Regnier et al. 1986	Dog	Infection and injury	Decrease inflammation	Controlled	?	Positive
Flunixin	Hardie et al. 1983	Dog	Infection and injury	Decrease inflammation and increase survival	Controlled	24	None
Flunixin	Hardie et al. 1987	Dog	Infection and injury	Increase recovery	Controlled	12	Positive

Flunixin	Dobromylskyj et al. 1992	Dog	Infection and injury	Increase recovery	Controlled	16	Mixed
Flunixin	Stegelmeier et al. 1988	Dog	Infection and injury	Increase recovery and no complications	Controlled	12	Mixed
Flunixin	Davidson et al. 1992	Dog	Infection and injury	No complications (irritation)	Controlled	?	Negative
Flunixin	Krohne et al. 1987	Dog	Infection and injury	Decrease inflammation	Non-controlled	?	Positive
Flunixin	Anderson et al. 1991	Goat	Infection and injury	Decrease inflammation and increase recovery	Controlled	18	Mixed
Flunixin	Cetin et al. 2014	Goat	Breeding	Increase pregnancy rate	Controlled	123	Negative
Flunixin	Dwinger et al. 1984	Goat	Infection and injury	Increase recovery	?	?	Non-conclusive
Flunixin	Aiumlamai et al. 1990	Sheep	Breeding	No complications (reproduction)	Controlled	14	Positive
Flunixin	Cheng et al. 1998	Sheep	General	Decrease inflammation	Non-controlled	?	Positive
Flunixin	Grant et al. 1996	Sheep	General	Decrease pain	Non-controlled	?	None
Flunixin	Chambers et al. 1995	Sheep	Infection and injury	Decrease inflammation	Controlled	?	Positive
Flunixin	Welsh et al. 1995	Sheep	Infection and injury	Decrease pain	Controlled	47	Positive
Flunixin	Welsh et al. 1994	Sheep	Infection and injury	Decrease pain	Controlled	?	Positive
Flunixin	Paull et al. 2007	Sheep	Surgery (Husbandry)	Decrease pain	Controlled	32	Positive

				Decrease	Controlled		
Flunixin & meloxicam	Maslanka et al. 2010	Cattle	General	No immunosuppression	Controlled	24	Positive
Flunixin & meloxicam	Bednarek et al. 2003	Cattle	Infection and injury	Increase recovery	Controlled	18	Positive
Flunixin & meloxicam	Friton et al. 2004	Cattle	Infection and injury	Increase recovery and no complications	Controlled	201	F=mixed, M=positive
Flunixin & meloxicam	Fraccaro et al. 2014	Cattle	Surgery (Husbandry)	Decrease pain and inflammation	Non-controlled	?	F=positive, M=mixed
Flunixin & meloxicam	Glynn et al. 2013	Cattle	Surgery (Husbandry)	Decrease pain, inflammation and stress	Controlled	24	F=positive, M=negative
Flunixin & meloxicam	Luna et al. 2007	Dog	General	No complications (gastrointestinal)	Controlled	18	F = negative, M = posiitve
Flunixin & meloxicam	Gilmour et al. 2012	Dog	Infection and injury	inflammation		15	F=positive, M=mixed
Flunixin &		Dog	Surgery			24	F=positive,

meloxicam	Yilmaz et al. 2014		(Husbandry)	Decrease stress	Controlled		M=none
Flunixin & meloxicam	Little et al. 2007	Horse	Surgery (Veterinary)	Decrease pain and inflammation	Controlled	18	Positive
Flunixin & meloxicam	Naylor et al. 2014	Horse	Surgery (veterinary)	No complications (gastrointestinal and survival)	Non-controlled	60	Positive
Flunixin & meloxicam	Paull et al. 2012	Sheep	Surgery (Husbandry)	Decrease pain	Controlled	48	Positive
Meloxicam	Barrier et al. 2014	Cattle	Breeding	Decrease pain	Controlled	110	Positive
Meloxicam	Mainau et al. 2015	Cattle	Breeding	Decrease pain and stress	Controlled	60	Mixed
Meloxicam	Newby et al. 2013b	Cattle	Breeding	Decrease pain and stress	Controlled	103	Positive
Meloxicam	Lopes et al. 2015	Cattle	Breeding	Increase pregnancy rate	Controlled	85	Positive
Meloxicam	Aguiar et al. 2013	Cattle	Breeding	Increase pregnancy rate	Controlled	207	Positive
Meloxicam	Rajkumar et al. 2010	Cattle	Breeding	Increase pregnancy rate	Controlled	?	Positive
Meloxicam	Hirsch et al. 2009	Cattle	Breeding	No complications	Controlled	41	Positive
Meloxicam	Erdem et al. 2010	Cattle	Breeding	No complications	Controlled	87	Negative
Meloxicam	Newby et al. 2014	Cattle	Breeding	No complications	Controlled	?	Positive
Meloxicam	Roy et al. 2015	Cattle	General	Decrease inflammation	Controlled	12	Positive
Meloxicam	Amiridis et al. 2009	Cattle	General	Increase pregnancy rate	Controlled	402	Positive

				Decrease	Controlled		
Meloxicam	Carpenter et al. 2016	Cattle	General	Increase productivity and longevity	Controlled	?	Positive
Meloxicam	Guarnieri et al. 2014	Cattle	Husbandry	Decrease stress	Controlled	84	Positive

				Decrease	Controlled		
Meloxicam	Van Engen et al. 2016	Cattle	Husbandry	stress		87	Positive
Meloxicam	Van Engen et al. 2014	Cattle	Husbandry	Decrease stress	Controlled	97	Positive
Meloxicam	Cooke et al. 2016	Cattle	Husbandry	Decrease stress	Controlled	943	None
Meloxicam	Konigsson et al. 2002	Cattle	Infection and injury	Decrease inflammation	Non-controlled	4	Positive
Meloxicam	Bednarek et al. 2002	Cattle	Infection and injury	Decrease inflammation	Non-controlled	?	Positive
Meloxicam	Coetzee et al. 2014	Cattle	Infection and injury	Decrease pain	Controlled	18	Positive
Meloxicam	Offinger et al. 2013	Cattle	Infection and injury	Decrease pain	Controlled	19	Positive
Meloxicam	Fitzpatrick et al. 2013	Cattle	Infection and injury	Decrease pain	Controlled	24	Positive
Meloxicam	Todd et al. 2010	Cattle	Infection and injury	Increase productivity	Controlled	62	Positive
Meloxicam	Bednarek et al. 2005	Cattle	Infection and injury	Increase recovery	Controlled	30	Mixed
Meloxicam	Bednarek et al. 2003a	Cattle	Infection and injury	Increase recovery	Controlled	30	Positive
Meloxicam	McDougall et al. 2009	Cattle	Infection and injury	Increase recovery	Controlled	727	Positive
Meloxicam	Maslanka et al. 2011	Cattle	Innoculation	Decrease dysfunction	Controlled	10	None
Meloxicam	Rodrigues et al. 2015	Cattle	Innoculation	Decrease dysfunction	Controlled	21	None

				Decrease		Controlled		
Meloxicam	Theurer et al. 2012	Cattle	Surgery (husbandry)	Decrease pain		Controlled	12	Positive
Meloxicam	Allen et al. 2013	Cattle	Surgery (husbandry)	Decrease pain		Controlled	30	Positive
Meloxicam	Roberts et al. 2015	Cattle	Surgery (husbandry)	Decrease pain		Controlled	30	Positive
Meloxicam	Stewart et al. 2009	Cattle	Surgery (husbandry)	pain			46	Positive
Meloxicam	Olson et al. 2016	Cattle	Surgery (husbandry)		Decrease pain	Controlled	60	Positive
Meloxicam	Roberts et al. 2016	Cattle	Surgery (husbandry)		Decrease pain	Controlled	83	Mixed
Meloxicam	Coetzee et al. 2012a	Cattle	Surgery (husbandry)		Decrease pain	Controlled	258	Positive
			Surgery					

Meloxicam				Decrease pain			Positive
Meloxicam	Clapp et al. 2015	Cattle	(husbandry)	Decrease pain	Non-controlled	25	Mixed

				Decrease	Controlled		
Meloxicam	Coetzee et al. 2012b	Cattle	Surgery (husbandry)	Decrease pain and increase productivity	Controlled	12	Positive
Meloxicam	Brown et al. 2015	Cattle	Surgery (husbandry)	Decrease pain and increase productivity	Controlled	62	Positive
Meloxicam	Heinrich et al. 2010	Cattle	Surgery (husbandry)	Decrease pain and stress	Controlled	60	Positive
Meloxicam	Repenning et al. 2013	Cattle	Surgery (husbandry)	Decrease pain and stress	Controlled	157	None
Meloxicam	Heinrich et al. 2009	Cattle	Surgery (husbandry)	Decrease stress	Controlled	60	Positive
Meloxicam	Bates et al. 2015	Cattle	Surgery (husbandry)	Increase productivity	Controlled	202	Positive

Meloxicam				Decrease pain			Positive
Meloxicam	Beausoleil et al. 2012	Cattle	Surgery (veterinary)	Decrease pain	Controlled	18	None
Meloxicam	Barrett et al. 2016	Cattle	Surgery (veterinary)	Decrease pain	Controlled	24	Non-conclusive
	Newby et al. 2013	Cattle	Surgery (veterinary)		Non-controlled	10	
Meloxicam	Bednarek et al. 2005	Cattle	Infection and injury	Increase recovery and no immunosuppression	?	?	Positive
Meloxicam	Wooten et al. 2009	Dog	General	Decrease dysfunction	Controlled	8	Positive
Meloxicam	Blois et al. 2010	Dog	General	Decrease dysfunction	Controlled	10	Positive
Meloxicam	Punke et al. 2008	Dog	General	Decrease dysfunction	Non-controlled	8	Positive
Meloxicam	Deneuche et al. 2004	Dog	General	Decrease pain and no complications	Controlled	60	Positive
Meloxicam	Bostrom et al. 2006	Dog	General	No complications	Controlled	8	Positive
Meloxicam	Fusellier et al. 2008	Dog	General	No complications	Controlled	10	Positive
Meloxicam	Boston et al. 2003	Dog	General	No complications	Controlled	20	Positive
Meloxicam	Borges et al. 2013	Dog	General	No complications	Controlled	24	Positive
Meloxicam	Forsyth et al. 1998	Dog	General	No complications	Controlled	24	Positive
Meloxicam	Hare et al. 2013	Dog	General	No complications	Controlled	40	Mixed
Meloxicam	Narita et al. 2006	Dog	General	No complications	Non-controlled	15	Positive
Meloxicam	Luna et al. 2007	Dog	General	No complications	Non-controlled	36	Positive
Meloxicam	Brideau et al. 2001	Dog	General	Decrease inflammation	Controlled	48	Positive

				Decrease	Controlled		
Meloxicam	Khan and McLean 2012	Dog	General	No complications	Non-controlled	2220 6	Mixed
Meloxicam	Brainard et al. 2007	Dog	Infection and injury	Decrease dysfunction	Non-controlled	8	Positive
Meloxicam	Gilmour et al. 2009	Dog	Infection and injury	Decrease inflammation	Controlled	38	Positive
Meloxicam	Cross et al. 1997	Dog	Infection and injury	Decrease inflammation	Non-controlled	12	Positive
Meloxicam	Van Bree et al. 1994	Dog	Infection and injury	Decrease inflammation and no complications	Non-controlled	4	Positive

Meloxicam				Decrease pain			Positive
	Jones et al. 2002	Dog	Infection and injury		Controlled	12	
Meloxicam	Viking et al. 2002	Dog	Infection and injury	Decrease pain	Controlled	12	Positive
Meloxicam	Borer et al. 2003	Dog	Infection and injury	Decrease pain	Controlled	60	Positive
Meloxicam	Moreau et al. 2003	Dog	Infection and injury	Decrease pain	Controlled	71	Positive
Meloxicam	Matyas et al. 2013	Dog	Infection and injury	Decrease pain	Non-controlled	11	Positive
Meloxicam	Cozzi and Spensley	Dog	Infection and injury	Decrease pain and inflammation	Controlled	280	Positive
Meloxicam	Schmid et al. 2010	Dog	Infection and injury	Decrease pain and inflammation	Controlled	?	Positive
Meloxicam	Walton et al. 2014	Dog	Infection and injury	Decrease pain and inflammation	Non-controlled	111	Positive
Meloxicam	Peterson and Keefe 2004	Dog	Infection and injury	Decrease pain and no complications	Controlled	217	Positive
Meloxicam	Doig et al. 2000	Dog	Infection and injury	Decrease pain and no complications	Non-controlled	40	Positive
Meloxicam	Nell et al. 2002	Dog	Infection and injury	Decrease pain and no complications	Non-controlled	214	Positive
Meloxicam	Sauve et al. 2003	Dog	Infection and injury	No complications	Controlled	46	Positive
Meloxicam	Mullins et al. 2012	Dog	Surgery (veterinary)	Decrease dysfunction	Non-controlled	?	Mixed
Meloxicam	Caulkett et al. 2003	Dog	Surgery (veterinary)	Decrease pain	Controlled	15	Positive
Meloxicam	Fowler et al. 2003	Dog	Surgery (veterinary)	Decrease pain	Controlled	20	Positive
Meloxicam	Teixeira et al. 2013	Dog	Surgery (veterinary)	Decrease pain	Controlled	24	Positive

Meloxicam							Positive
Meloxicam	Moak et al. 2011	Dog	Surgery (veterinary)	Decrease pain	Controlled	25	None
Meloxicam	Budsberg et al. 2002	Dog	Surgery (veterinary)	Decrease pain	Controlled	40	Positive
Meloxicam	Zanuzzo et al. 2015	Dog	Surgery (veterinary)	Decrease pain	Controlled	40	Positive
Meloxicam	Leece et al. 2005	Dog	Surgery (veterinary)	Decrease pain	Controlled	43	Positive
Meloxicam	Teixeira et al. 2013	Dog	Surgery (veterinary)	Decrease pain	Non-controlled	27	Positive
	Tsai et al. 2013	Dog	Surgery (veterinary)		Non-controlled	27	
Meloxicam	Lafuente at al. 2005	Dog	Surgery (veterinary)	Decrease pain and inflammation	Controlled	16	Positive
Meloxicam	Gruet et al. 2011	Dog	Surgery (veterinary)	Decrease pain and inflammation	Non-controlled	146	Positive
Meloxicam	Mathews et al. 2001	Dog	Surgery (veterinary)	Decrease pain and no complications	Controlled	36	Positive
Meloxicam	Nakagawa et al. 2007	Dog	Surgery (veterinary)	Increase recovery and no complications	Non-controlled	5	Positive
Meloxicam	Kum et al. 2013	Dog	Surgery (veterinary)	No complications	Controlled	18	Positive
Meloxicam	Fresno et al. 2005	Dog	Surgery (veterinary)	No complications	Controlled	20	Positive
Meloxicam	Laredo et al. 2004	Dog	Surgery (veterinary)	No complications	Controlled	32	Positive
Meloxicam	Kazakos et al. 2005	Dog	Surgery (veterinary)	No complications	Controlled	38	Positive
Meloxicam	Gruet et al. 2013	Dog	Surgery (veterinary)	Decrease pain and inflammation	Non-controlled	174	Positive
Meloxicam	Regan et al. 2016	Donkey	Infection and injury	Decrease pain and inflammation	Controlled	40	Mixed

Meloxicam				Decrease pain			Positive
Meloxicam	van der Heide et al. 2008	Goat	Infection and injury	No complications	Controlled	18	Positive
Meloxicam	Ingvast-Larsson et al. 2011	Goat	Surgery (husbandry)	Decrease pain	Controlled	11	None
Meloxicam	Lima et al. 2015	Horse	Breeding	Increase pregnancy rate	Non-controlled	11	Negative
Meloxicam	Beretta et al. 2005	Horse	General	Decrease pain and inflammation	Non-controlled	?	Positive
Meloxicam	D'Arcy-Moskwa et al. 2012	Horse	General	No complications	Controlled	25	Positive
Meloxicam	Vander Werf et al. 2012	Horse	General	No complications	Non-controlled	7	Positive
Meloxicam	Raidal et al. 2014	Horse	General	No complications	Non-controlled	9	Mixed
	Raidal et al. 2013	Horse	General	No complications	Non-controlled	10	
Meloxicam	Nobel et al. 2012	Horse	General	No complications	Non-controlled	33	Positive
Meloxicam	de Walter et al. 2016	Horse	Infection and injury	Decrease inflammation	Controlled	24	Non-conclusive
Meloxicam	de Grauw et al. 2009	Horse	Infection and injury	Decrease pain and inflammation	Controlled	6	Positive
Meloxicam	Walliser et al. 2015	Horse	Surgery (veterinary)	Decrease pain and inflammation	Non-controlled	66	Positive
Meloxicam	Brideau et al. 2001	Horse	General	Decrease inflammation	Controlled	30	Positive
Meloxicam	McKeown et al. 2000	Sheep	Breeding	Increase pregnancy rate	Controlled	?	Positive

Meloxicam							Positive
Meloxicam	Rac et al. 2007	Sheep	Breeding	No complications	Controlled	?	Positive
Meloxicam	Dorniak et al. 2011	Sheep	Breeding	No complications	Non-controlled	?	Negative
Meloxicam	Colditz et al. 2011	Sheep	Infection and injury	Decrease pain and inflammation	Non-controlled	?	Positive
Meloxicam	Small et al. 2014	Sheep	Surgery (husbandry)	Decrease pain	Controlled	60	Positive