Nimesulide: a vulture-toxic drug

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

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

Aim

This paper, intended for decision-makers involved in drug licensing, presents evidence of the toxicity of nimesulide, 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 nimesulide 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. In two separate studies, nine white-rumped vultures *Gyps bengalensis* were found dead in the wild, and tested positive for nimesulide. Eight of these also showed visceral gout (i.e., a clinical sign of renal failure in birds). One of these tested positive for meloxicam as well as nimesulide, but another vulture that tested positive for meloxicam and not nimesulide showed no visceral gout. Diclofenac was not detected in any of the eight vultures showing visceral gout and nimesulide.
4. In another two separate studies, one conducted in South Africa on Cape Vultures *Gyps coprotheres*, the other in India on Himalayan Griffons *Gyps himalayensis*, those birds given doses of nimesulide all died (two in each experiment). Such experimental safety testing thus showed that nimesulide is toxic to *Gyps* vultures at concentrations likely to be encountered by birds feeding on carcasses in the wild.

5. In contrast to nimesulide, the NSAID meloxicam has been shown to be non-toxic to *Gyps* vultures above the maximum level of exposure (MLE).
6. 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 meloxicam was calculated assuming that cattle in India may typically be dosed with twice the recommended amount.
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. 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. In addition, meloxicam has been shown to increase immune response, pregnancy rate, cow productivity and calf productivity. Negative or mixed effects of meloxicam are rare. In contrast, very few studies have examined the effectiveness and safety of nimesulide to domesticated animals. A single study has compared meloxicam and nimesulide; and found a positive effect for meloxicam and negative effect for nimesulide.
9. To conserve critically endangered *Gyps* vultures, veterinary nimesulide and multipledose 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 seven lines of supporting evidence.

1. Between 2002 and 2015, wildlife forensic investigations examined 62 dead *Gyps* vultures in India. Post-mortem examination included liquid chromatography mass spectrometry screening in 48 vultures. Diclofenac was screened in all years and another eight NSAIDs were screened from 2005 onwards. The organs of 29 vultures screened for NSAIDs showed severe visceral gout. Of these, 25 were positive for diclofenac, three were positive for nimesulide and one was positive for nimesulide and meloxicam. Among the 17 vultures screened for NSAIDs that did not show visceral gout, one was positive for nimesulide, one was positive for meloxicam and 15 were not positive for any NSAID. Further details on pages 8-10.

2. Four vultures were found dead in the Indian state of Gujarat in 2019. Post-mortem examination revealed that all four birds displayed evidence of renal failure, i.e. visceral gout. Toxicological analysis could find no evidence (i.e. all were below the level of detection) for the presence of 32 pesticides. Of 14 drugs tested (13 NSAIDs plus paracetamol), the only drug at concentrations above the level of detection was nimesulide. The concentration of nimesulide in the four birds was 17.2 – 792.1 ng g^{-1} in the liver, 61.0 – 1395.4 ng g^{-1} in the kidney and 195.9 – 1340.7 ng g^{-1} in the gut contents. Further details on P.11-13.

3. In an experiment, two African Cape Vultures *Gyps coprotheres* were given doses orally of nimesulide at the maximum level of exposure that vultures are likely to encounter in cattle carcasses. Both vultures died within 30 hours of dosing. Uric acid concentrations increased 27-79-fold on pre-dose levels. Both birds showed evidence of visceral gout. Further details on P.14-16.

4. In a second safety testing experiment, carried out in India, two Himalayan Griffons were administered nimesulide orally at the maximum likely level of exposure. Both vultures died after 24 hours. There was a 43-75-fold increase in uric acid concentrations, with both birds showing signs of kidney failure and visceral gout. Further details on P.17-21.

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 of 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 22-24.

6. 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 white-rumped 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.

7. A review of studies reporting an effect of nimesulide and meloxicam in veterinary and husbandry situations found a single study for nimesulide and 117 studies for meloxicam. The single study examining the effect of nimesulide compared it to that of meloxicam: while meloxicam had a positive effect; nimesulide had a negative effect. Overall, 79% of studies examining meloxicam treatment reported a positive effect. Meloxicam showed positive effects in cattle, buffalo, horse, goat, sheep and dog; and during castrating, dehorning, general care, handling, infections, limb injuries, reproducing and surgery. In these animals and situations, meloxicam decreased pain, inflammation, stress and dysfunction; increased recovery rate, immune response, pregnancy rate and productivity; and generally resulted in no complications. The proportion of studies examining meloxicam treatment that reported a mixed effect, negative effect, no effect and no conclusion were 9, 3, 7 and 2%, respectively. The studies that reported a negative effect of meloxicam treatment resulted in pregnancy complications, but another eleven studies reported a positive effect of meloxicam treatment on pregnancy rate. Nimesulide treatment was not examined for pregnancy complications. Further details in pages 28-37.

Specific details

Chemical name: **nimesulide**

Systematic name: *N*-(4-Nitro-2-phenoxyphenyl)methanesulfonamide

Formula: $C_{13}H_{12}N_2O_5S$

Molar mass: 308.311 g/mol

Typical formulation: 100, 200 or 400 mg/ml injections in 15 or 30 ml vials, 400 or 1000 mg bolus

Example products (manufacturers): Bangladesh – products are imported

India – Bolin NP (Ruby), Care-NP (Iskon), Diclodec NP (ESPEE), Doloban (Akums), King-NP (Safecon), Nimovet (Indian immunological/Santax), Nimsonex Vet (Stanex), Noxalgin (Nucare), Oxalgin NP (Zydas/ACME)

Nepal – Indian products are imported

Pakistan – products may be imported

Chemical name: **meloxicam**

Systematic name: 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine3carboxamide-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. Post mortem examination of wild *Gyps* vultures finds visceral gout in association with nimesulide residue and not diclofenac residue

Published source

Cuthbert, R. J., Taggart, M. A., Saini, M., Sharma, A., Das, A., Kulkarni, M. D., Deori, P., Ranade, S., Shringarpure, R. N. Galligan, T. H. and Green, R. E. (2015). Continuing mortality of vultures in India associated with illegal veterinary use of diclofenac and a potential threat from nimesulide *Oryx* 50: 104-112.

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). Nimesulide is used to treat domesticated ungulates in South Asia. This examination of carcasses of wild vultures was carried out in India.

Action

Between 2000 and 2012, carcasses of *Gyps* vultures were collected opportunistically from nine Indian states. Post mortem examination focussing on detecting visceral gout was conducted on all carcasses found. Liver and kidney tissue were sampled form most carcasses for NSAIDs screening using liquid chromatography mass spectrometry. For carcasses examined in 20052011, samples were screened for nine NSAIDs, including diclofenac, meloxicam and nimesulide.

For carcasses examined 2000-2004, samples were screened for only diclofenac.

Findings

Sixty-two carcasses of five *Gyps* species were examined for visceral gout. Of these, 48 carcasses of five *Gyps* species were also screened for NSAIDs.

Diclofenac residue and visceral gout were found in 25 carcasses.

Nimesulide residue was found in 5 carcasses; and visceral gout was found in 4 out of these 5 carcasses. Diclofenac residue was not found in any of these carcasses; however, 1 carcass with nimesulide residue and visceral gout also had meloxicam residue.

Another carcass had meloxicam reside but no visceral gout.

Conclusion

Nimesulide caused acute renal failure and death in *Gyps* vultures.

Key figure

Co-occurrence of visceral gout and residue of NSAIDs in carcasses of wild *Gyps* vultures collected in India during 2000-2011. Results are shown separately for a period when assays were only performed on diclofenac (2000-2004) and a later period (2005-2011) when eight other NSAIDs were also assayed. Among these other NSAIDs only meloxicam and nimesulide were detected. The number of fledglings, juveniles, adults and individuals of unknown age, respectively, are shown in brackets.

Species	Gout	Diclofenac	Nimesulide	Meloxicam	Nimesulide & meloxicam	No NSAID
2000–2004						
G. fulvus	Yes	0				0
	No	0				1 (0,1,0,0)
G. himalayensis	Yes	0				0
	No	0				1 (0,1,0,0)
G. indicus	Yes	6 (0,5,1,0)				0
	No	0				3 (0,2,1,0)
G. bengalensis	Yes	7 (0,3,4,0)				0
	No	0				4 (1,1,2,0)
All species	Yes	13 (0,8,5,0)				0
	No	0				9 (1,5,3,0)
2005–2011						
G. fulvus	Yes	0	0	0	0	0
	No	0	0	0	0	0
G. himalayensis	Yes	1 (0,1,0,0)	0	0	0	0
	No	0	0	0	0	1 (0,1,0,0)
G. indicus	Yes	0	0	0	0	0
	No	0	0	0	0	1 (0,1,0,0)
G. bengalensis	Yes	11 (2,1,8,0)	3 (0,1,1,1)	0	1 (0,0,1,0)	0
	No	0	1 (0,0,1,0)	1 (0,0,0,1)	0	4 (1,3,0,0)
All species	Yes	12 (2,2,8,0)	3 (0,1,1,1)	0	1 (0,0,1,0)	0
	No	0	1 (0,0,1,0)	1 (0,0,0,1)	0	6 (1,5,0,0)

2. Further evidence that nimesulide is toxic to vultures: post-mortem examination of more wild White-rumped Vultures *Gyps bengalensis* finds visceral gout in association with nimesulide and not diclofenac residues.

Source

Nambirajan, K., Muralidharan, S., Ashimkumar, A.R. & Jadhav, S. 2021. Nimesulide poisoning in white-rumped vulture *Gyps bengalensis* in Gujarat, India. *Environmental Science and Pollution Research*, https://doi.org/10.1007/s11356-021-14702-y

Background

Diclofenac kills vultures through acute renal failure which, in vultures, as presents as visceral gout (i.e. uric acid deposits on organs and within kidney tubules), and was responsible for the catastrophic declines of *Gyps* vulture populations in south Asia. Another NSAID nimesulide is also used to treat domesticated ungulates in South Asia, residues of which have previously been found in dead vultures with visceral gout.

Action

In 2019, four dead white-rumped vultures were found in the Indian state of Gujarat, in two separate mortality incidents. Post-mortems were carried out, and tissue samples from the liver, kidney and gut contents analysed for 32 toxic pesticides and 13 different NSAIDs, and paracetamol, using liquid chromatography mass spectrometry.

Findings

Evidence of visceral gout was found during post-mortem examination of all four vultures. Residues of 32 pesticides were all below the level of detection in the kidney, liver and gut contents of all four vultures. Of the 14 drugs analysed, only residues of nimesulide were detected in all tissues investigated; all others were below the level of detection. The

concentration of nimesulide in the four birds was 17.2 – 792.1 ng g^{-1} in the liver, 61.0 – 1395.4 ng g^{-1} in the kidney and 195.9 – 1340.7 ng g^{-1} in the gut contents.

Conclusion

Nimesulide caused acute renal failure and death in *Gyps* vultures.

Key figures

Environ Sci Pollut Res

Table 2 Concentration of nimesulide (ng/g, wet weight) recorded in the tissues of white-rumped vultures received dead from Gujarat during 2019

Incident/date/place	Vulture Id	Organ	Concentration of nimesulide (ng/g, wet weight)	Uric acid crystal/visceral gout
Incident 1 4th January 2019 Sanand, Gujarat	White-rumped vulture 1	Liver Kidney Gut content	792.1 1395.4 1108.2	Present
	White-rumped vulture 2	Liver Kidney Gut content	112.5 234.2 1340.7	Present
Incident 2 7th October 2019 Wild Ass Sanctuary, Dhrangadhra, Gujarat	White-rumped vulture 1	Liver Kidney Gut content	731.6 61.0 424.8	Present
	White-rumped vulture 2	Liver Kidney Gut content	17.1 107.7 195.9	Present

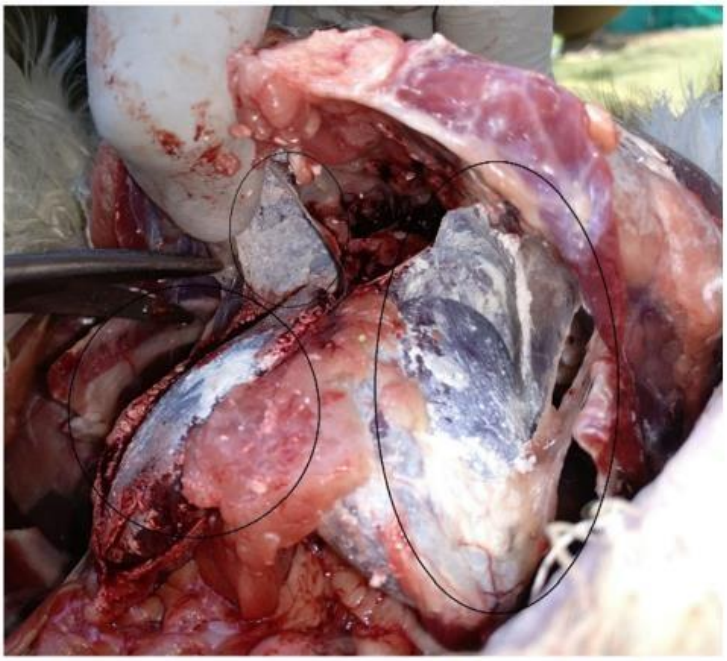


Fig. 1 White chalky uric acid deposit on both the liver lobes of a white-rumped vulture collected from Sanand, Gujarat

3. An experiment finds that doses of nimesulide at the maximum level of exposure causes kidney failure, elevation of blood uric acid levels, visceral gout and death in African Cape Vultures *Gyps coprotheres*.

Source

Galligan, T.H., Green, R.E., Wolter, K., Taggart, M.A., Duncan, N., Mallord, J.W., Alderson, D., Li, Y. & Naidoo, V. 2022. The non-steroidal anti-inflammatory drug nimesulide kills *Gyps* vultures at concentrations found in the muscle of treated cattle. *Science of the Total Environment*, **807,** 150788

Background

Residues of the NSAID nimesulide, in association with visceral gout, have been found in the tissues taken from the carcases of White-rumped Vultures *Gyps bengalensis*, and is therefore likely to be the cause of death of these birds, and therefore toxic to vultures. However, to confirm the toxicity of NSAIDs to *Gyps* vultures, experimental safety testing of drugs needs to be carried out.

Action

Initially, a pharmacokinetic study of nimesulide in cattle was carried out to estimate the maximum level of exposure (MLE) of the drug likely to be encountered by vultures in the wild. Firstly, four cattle were injected with nimesulide at the standard dose (2 mg kg^{-1}), and blood samples taken at regular intervals to identify the time (T_{max}) at which maximum concentrations of the drug were reached. Secondly, double the recommended dose (i.e. 4 mg kg^{-1}, to simulate the behaviour of livestock owners in India) was given to a further four cattle, which were slaughtered at *Tmax*, and tissue samples collected from the neck (injection site), hindquarters, liver and kidney to measure nimesulide concentrations. The MLE was estimated based on mean daily energy use and the maximum likely meal consumed by a vulture. Two African Cape Vultures *G. coprotheres*, a species known to be susceptible to NSAID poisoning and therefore a

suitable surrogate for Asian *Gyps* vultures, were given a dose of injectable nimesulide orally based on the estimated MLE; two other vultures (control group) were given an oral dose of water. Blood samples were taken at regular intervals up to 48 hours after dosing and analysed for nimesulide, uric acid and other biochemical parameters. Post-mortems were carried out on any vulture that died during the experiment.

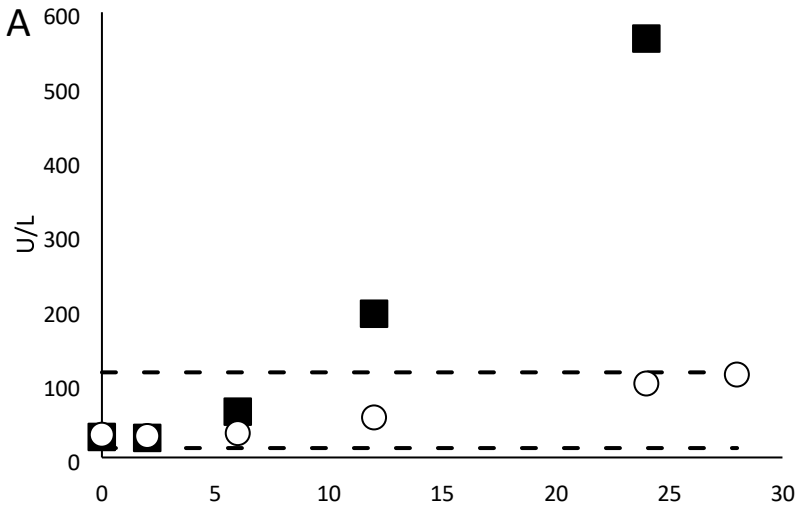
Findings

Both vultures given nimesulide died within 30 hours after dosing; both vultures within the control group were alive and well after 48 hours when the experiment was terminated. Uric acid concentrations showed a 27 – 79-fold increase over their baseline values. Post-mortem examination found visceral gout in both vultures.

Conclusion

Nimesulide is toxic to *Gyps* vultures.

Key figures



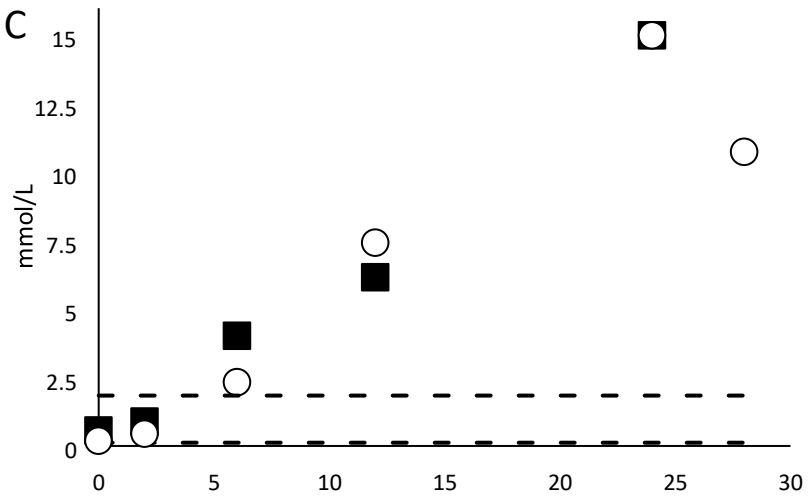


Figure 2: Change over time in plasma alanine transferase (A) and uric acid (C) in two vultures (solid squares = G32745 and open circles = G32746) treated with nimesulide at 17.58 mg kg^{-1} bw. G32746 likely received a lower unknown dose as it was observed expelling liquid immediately after dosing. Also shown is the normal range of concentrations for each biochemical delineated by the lowest and highest measurements taken from two control vultures (dashed lines).

4. An experiment finds that doses of nimesulide at the maximum level of exposure causes kidney failure, elevation of blood uric acid levels, visceral gout and death in Himalayan Griffons *Gyps himalayensis*.

Source

Mathesh, K., Mallord, J.W., Mahendran, K., Manikam, K., Gupta, R., Chutia, K., Pawde, A., Prakash, N.V., Ravichandran, P., Saikia, D., Shringarpure, R., Timung, A., Green, R.E. & Prakash, V.M. *in prep*. Experimental safety testing confirms that the NSAID nimesulide is toxic to *Gyps* vultures in India.

Background

The catastrophic declines of populations of *Gyps* vultures in South Asia was caused by unintentional poisoning by the NSAID diclofenac, which resulted in kidney failure, visceral gout and death in vultures that consumed the contaminated carcasses of domesticated ungulates. Although veterinary use of diclofenac was banned in the region, other NSAIDs are available, such as nimesulide. In addition to residues of nimesulide being found in conjunction with visceral gout in the carcasses of White-rumped Vultures in India, experimental safety testing resulted in the deaths of two African Cape Vultures *G. coprotheres* that were given a dose of the drug at levels that equated to the maximum level of exposure to the drug that would be encountered by vultures feeding on a contaminated carcass, with birds showing elevated uric acid levels in the blood and visceral gout. The aim of the experiment on Himalayan Griffons *G. himalayensis* was to confirm the toxicity of nimesulide to an Asian species of *Gyps* vulture.

Action

Two Himalayan Griffons were given a dose of nimesulide, administered orally, at the maximum likely exposure that was estimated in a pharmacokinetic study on the drug in cattle carried out in South Africa (Galligan *et al*. 2022). The vultures had similar weights (8.0 and 8.2 kg), so the dose was the same for both vultures, 1.5 ml. Two other vultures acted as controls and were

given a dose of benzyl alcohol. Blood samples were taken at 0- (pre-treatment), and 2-, 6-, 12- and 24-hours post-treatment. Nimesulide concentrations were quantified using liquid chromatography tandem mass spectrometry (LC-MS/MS). Various serum constituents associated with changes in kidney function were extracted and measured. Any vulture that died was subjected to post-mortem examination.

Findings

Both vultures that were given nimesulide died after 24 hours. There was rapid absorption of nimesulide in the blood plasma up to 6 hours post-treatment, with a slower elimination thereafter, until death (Fig. 1, below). Both birds showed increases in serum uric acid concentrations compared to the two control birds, which increased steadily until the birds' deaths. Final uric acid concentrations constituted a 43-75-fold increase compared to pre-treatment levels. Uric acid levels in the control birds remained low across the experiment (Fig. 2). Post-mortem necropsy revealed deposition of chalky white crystals on the visceral organs (kidney and liver), i.e., visceral gout, caused by kidney failure (Fig. 4).

Conclusion

The experiment confirmed that nimesulide was toxic to Himalayan Griffons.

Key figures

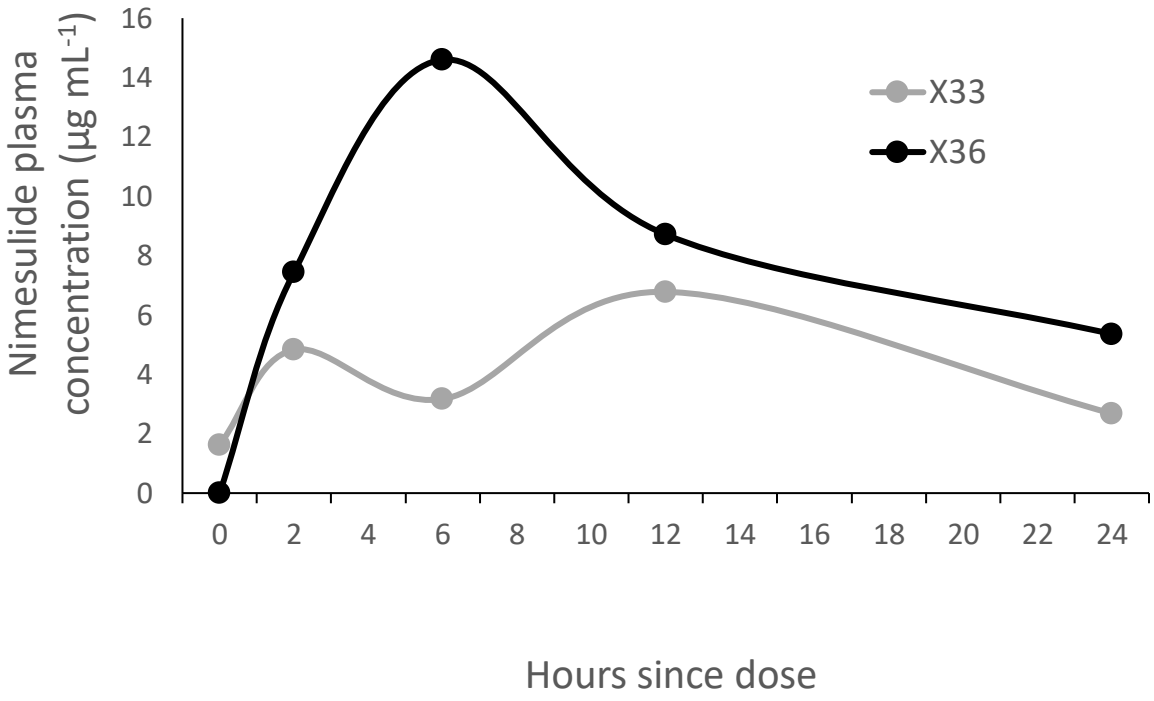


Figure 1. Pharmacokinetic profiles for the two Himalayan Griffons *Gyps himalayensis* treated with nimesulide.

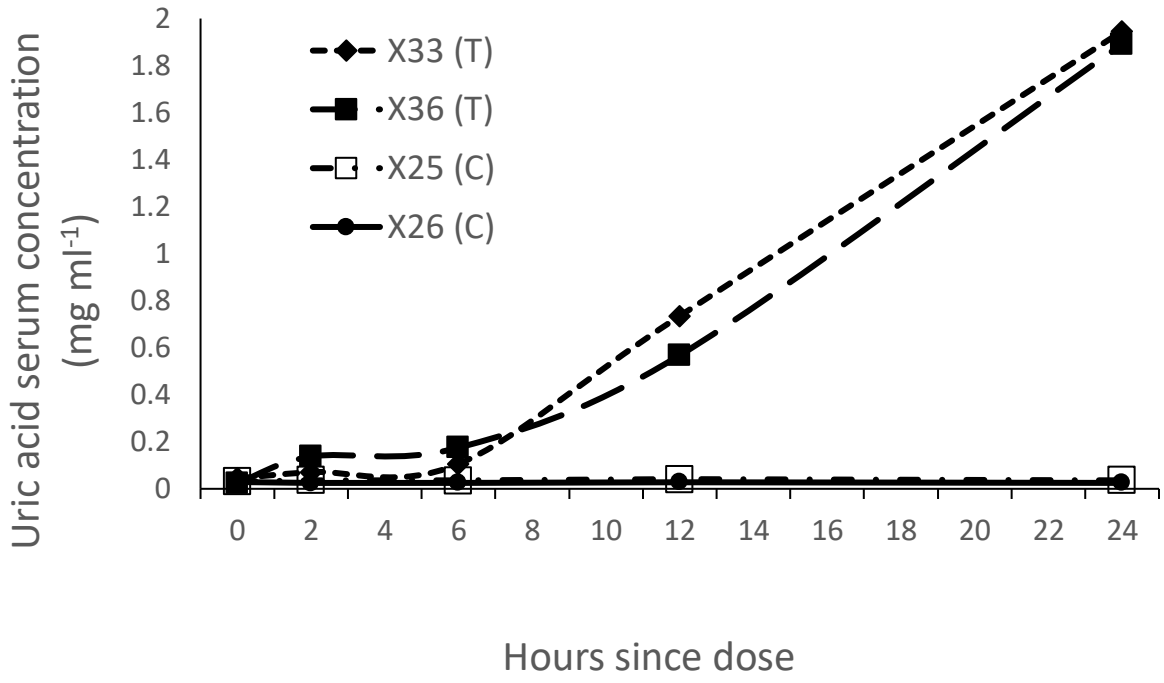


Figure 2. Change over time in plasma uric acid concentrations in two vultures treated with nimesulide (T), in comparison to two vultures assigned to a control group (C) and given a solution of benzyl alcohol / ethanol (the carrier solution for nimesulide in the Nimovet formulation).

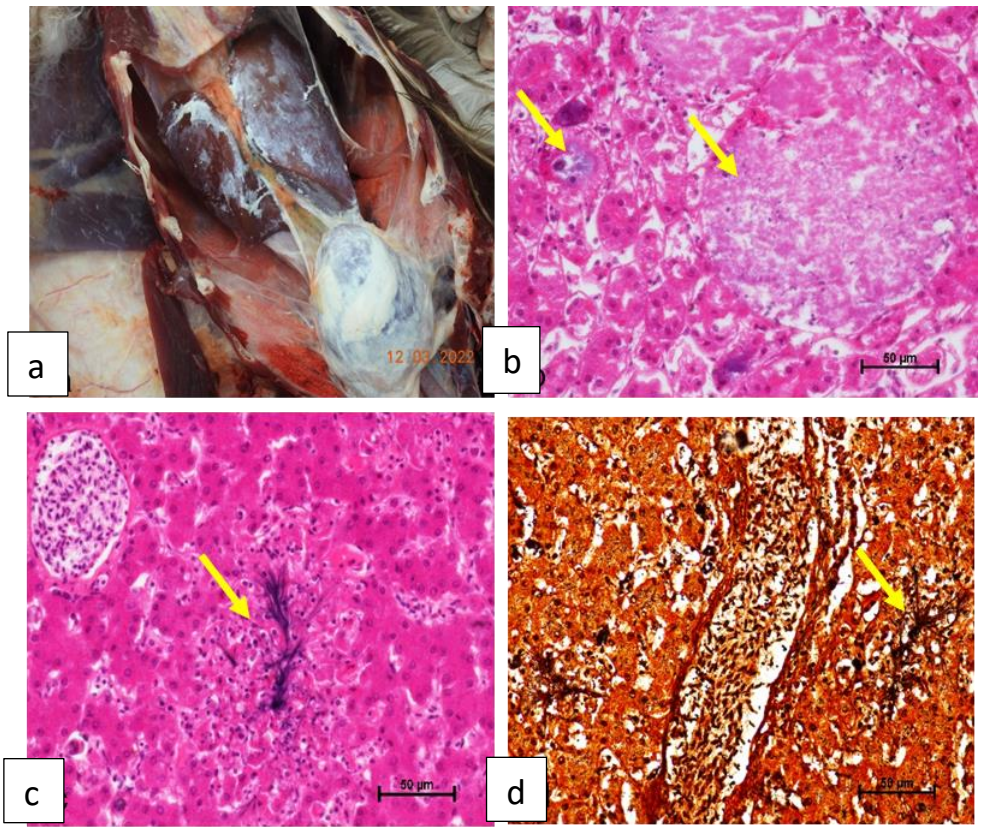


Figure 4. (a) Post-mortem image showing deposition of chalky white urate crystals on visceral organs. Histopathological images of (b) liver and (c) kidney tissues showing deposition of urate crystals, highlighted by Haematoxylin and Eosin (H&E) staining, and (d) silver nitrate / hydroquinone (De Galantha) staining (40 x magnification).

5. An experiment finds doses above the MLE of meloxicam to Asian whitebacked 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

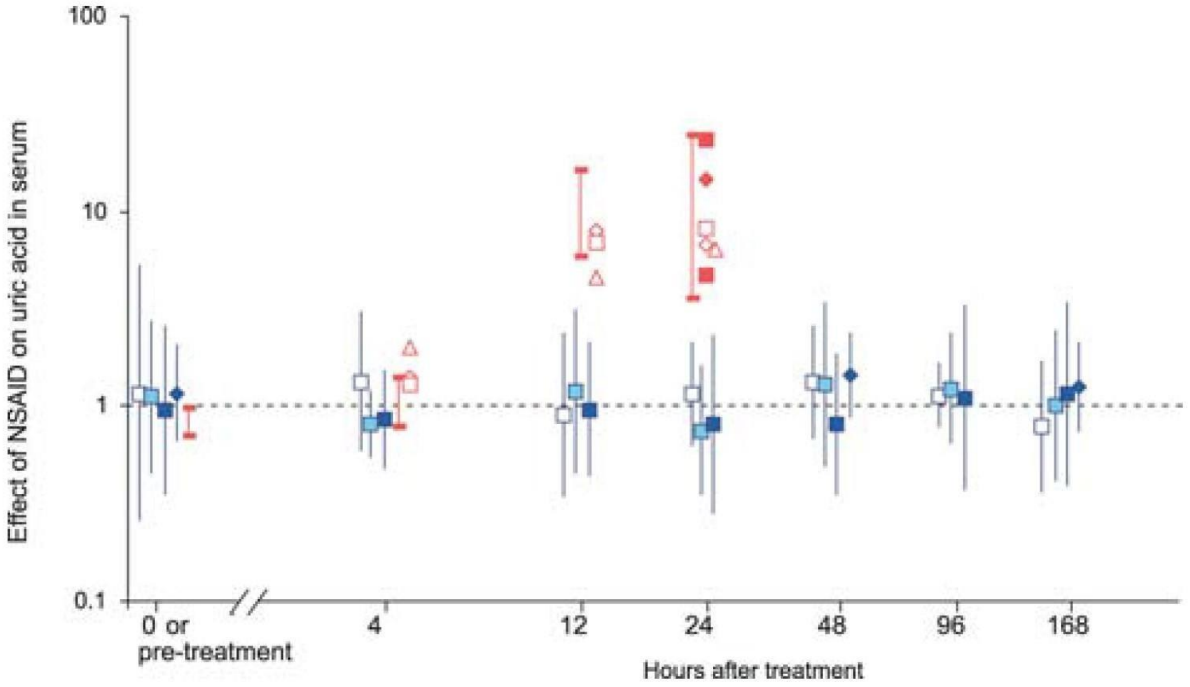
In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived.

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. An experiment finds doses above the MLE of meloxicam to Asian whitebacked 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.

Meloxicamcontaminated 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.

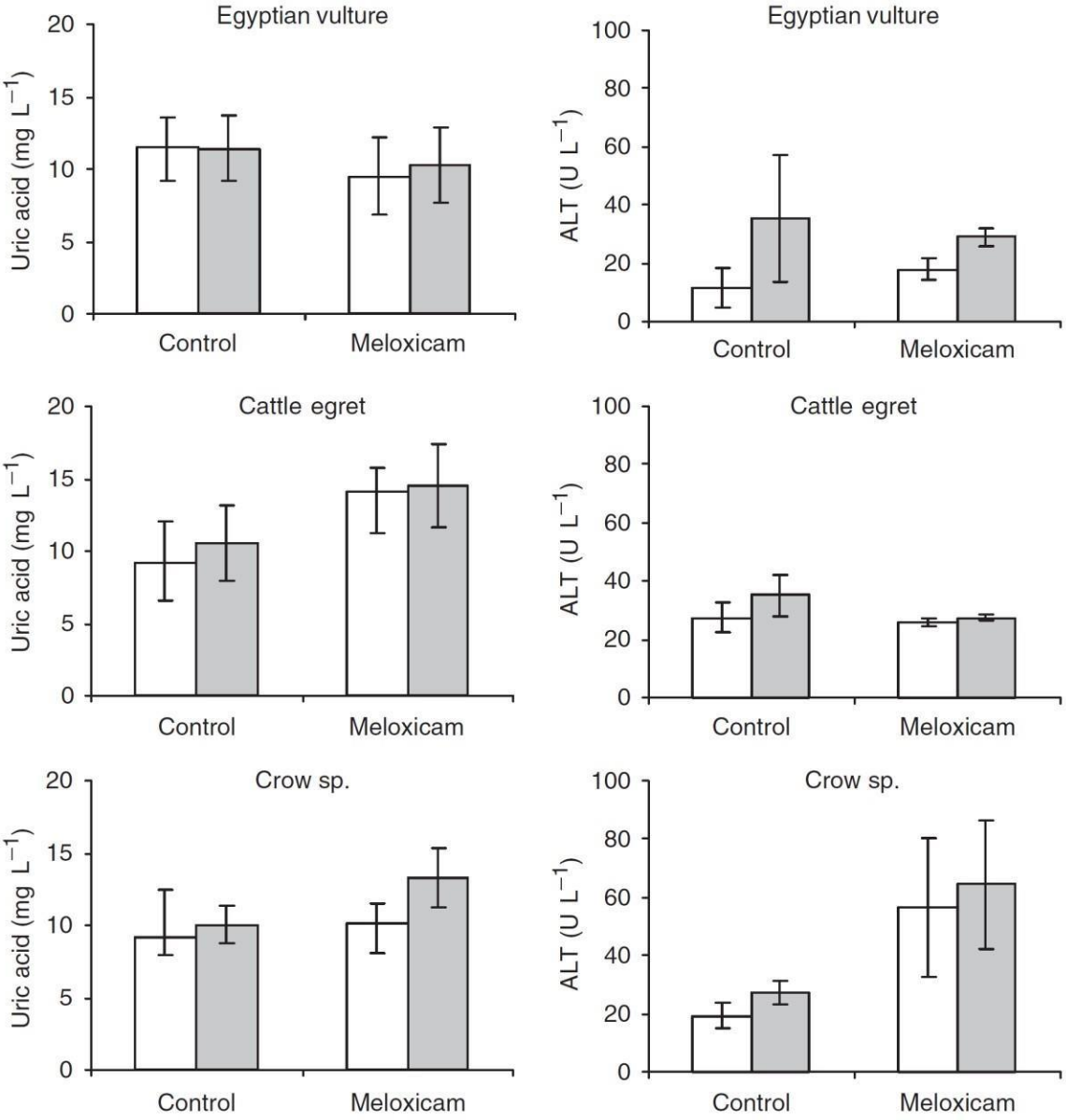
Findings

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).

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

Source

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

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 118 studies: 117 reported an effect of meloxicam treatment; and 1 reported an effect of meloxicam and nimesulide 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 single study comparing meloxicam and nimesulide treatment in dogs reported a positive effect (decreased pain and inflammation) for meloxicam and negative effect (renal complications renal) for nimesulide.

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

Meloxicam showed positive effects: in cattle, buffalo, horse, goat, sheep and dog; and during castrating, dehorning, general care, handling, infections, limb injuries, reproducing and surgery. In these situations, meloxicam decreased pain, inflammation, stress and dysfunction; increased recovery rate, immune response, pregnancy rate and productivity; and generally resulted in no complications.

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

Conclusion

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

Key figure

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

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

Meloxicam	Coetzee et al. 2012b	Cattle	Dehorning	Decrease pain and increase calf productivity	controlled	12	Positive
Meloxicam	Heinrich et al. 2010	Cattle	Dehorning	Decrease pain and stress	controlled	60	Positive
Meloxicam	Heinrich et al. 2009	Cattle	Dehorning	Decrease stress	not controlled	60	Positive
Meloxicam	Bates et al. 2015	Cattle	Dehorning	Increase calf productivity	controlled	202	Positive
Meloxicam	Roy et al. 2015	Cattle	General	Decrease inflammation	controlled	12	Positive
Meloxicam	Carpenter et al. 2016	Cattle	General	Increase cow productivity and longevity	controlled	.	Positive
Meloxicam	Amiridis et al. 2009	Cattle	General	Increase pregnancy rate	controlled	402	Positive
Meloxicam	Cooke et al. 2016	Cattle	Handling	Decrease stress	controlled	943	None
Meloxicam	Guarnieri et al. 2014	Cattle	Handling	Decrease stress	controlled	84	Positive
Meloxicam	Van Engen et al. 2016	Cattle	Handling	Decrease stress	controlled	87	Positive
Meloxicam	Van Engen et al. 2014	Cattle	Handling	Decrease stress	not controlled	97	Positive
Meloxicam	Maslanka et al. 2011	Cattle	Immunisation	Avoid dysfunction	controlled	10	None
Meloxicam	Rodrigues et al. 2015	Cattle	Immunisation	Avoid dysfunction	controlled	21	None
Meloxicam	Bednarek et al. 2002	Cattle	Infection	Decrease inflammation	not controlled	.	Positive
Meloxicam	Konigsson et al. 2002	Cattle	Infection	Decrease inflammation	not controlled	4	Positive
Meloxicam	Bednarek et al. 2003a	Cattle	Infection	Improve recovery	not controlled	30	Positive
Meloxicam	Todd et al. 2010	Cattle	Infection	Increase calf productivity	controlled	62	Positive
Meloxicam	Bednarek et al. 2003b	Cattle	Infection	Increase immune response	controlled	18	Positive

Meloxicam	Bednarek et al. 2005	Cattle	Infection	Increase immune response	not controlled	30	Mixed
Meloxicam	Coetzee et al. 2014	Cattle	Limb injury	Decrease pain	controlled	18	Positive
Meloxicam	Offinger et al. 2013	Cattle	Limb injury	Decrease pain	controlled	19	Positive
Meloxicam	Barrier et al. 2014	Cattle	Reproduction	Decrease pain	controlled	110	Positive
Meloxicam	Fitzpatrick et al. 2013	Cattle	Reproduction	Decrease pain	controlled	24	Positive
Meloxicam	Newby et al. 2013b	Cattle	Reproduction	Decrease pain and stress	controlled	103	Positive
Meloxicam	Mainau et al. 2015	Cattle	Reproduction	Decrease pain and stress	not controlled	60	Mixed
Meloxicam	McDougall et al. 2009	Cattle	Reproduction	Improve recovery	not controlled	727	Positive
Meloxicam	Lopes et al. 2015	Cattle	Reproduction	Increase pregnancy rate	controlled	85	Positive
Meloxicam	Aguiar et al. 2013	Cattle	Reproduction	Increase pregnancy rate	controlled	207	Positive
Meloxicam	Rajkumar et al. 2010	Cattle	Reproduction	Increase pregnancy rate	not controlled	.	Positive
Meloxicam	Erdem et al. 2010	Cattle	Reproduction	No complications	controlled	87	Negative
Meloxicam	Hirsch et al. 2009	Cattle	Reproduction	No complications	controlled	41	Positive
Meloxicam	Newby et al. 2014	Cattle	Reproduction	No complications	controlled	.	Positive
Meloxicam	Beausoleil et al. 2012	Cattle	Surgery	Decrease pain	controlled	18	None
Meloxicam	Blois et al. 2010	Dog	General	Avoid dysfunction	controlled	10	Positive

Meloxicam	Wooten et al. 2009	Dog	General	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Punke et al. 2008	Dog	General	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Gilmour et al. 2012	Dog	General	Decrease inflammation	controlled	15	None
Meloxicam	Gilmour et al. 2009	Dog	General	Decrease inflammation	not controlled	38	Positive
Meloxicam	Hare et al. 2013	Dog	General	No complications	controlled	40	Mixed
Meloxicam	Bostrom et al. 2006	Dog	General	No complications	controlled	8	Positive
Meloxicam	Boston et al. 2003	Dog	General	No complications	controlled	20	Positive
Meloxicam	Narita et al. 2006	Dog	General	No complications	not controlled	15	Positive
Meloxicam	Fusellier et al. 2008	Dog	General	No complications	not controlled	10	Positive
Meloxicam	Viking et al. 2002	Dog	Infection	Decrease pain	controlled	12	Positive
Meloxicam	Brainard et al. 2007	Dog	Limb injury	Avoid dysfunction	not controlled	8	Positive
Meloxicam	Cross et al. 1997	Dog	Limb injury	Decrease inflammation	not controlled	12	Positive
Meloxicam	Van Bree et al. 1994	Dog	Limb injury	Decrease inflammation and no complications	controlled	4	Positive
Meloxicam	Jones et al. 2002	Dog	Limb injury	Decrease pain	controlled	12	Positive
Meloxicam	Moreau et al. 2003	Dog	Limb injury	Decrease pain	controlled	71	Positive

Meloxicam	Matyas et al. 2013	Dog	Limb injury	Decrease pain	controlled	11	Positive
Meloxicam	Borer et al. 2003	Dog	Limb injury	Decrease pain	controlled	60	Positive
Meloxicam	Cozzi and Spensley	Dog	Limb injury	Decrease pain and inflammation	controlled	280	Positive
Meloxicam	Schmid et al. 2010	Dog	Limb injury	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	Walton et al. 2014	Dog	Limb injury	Decrease pain and inflammation	controlled	111	Positive
Meloxicam	Peterson and Keefe 2004	Dog	Limb injury	Decrease pain and no complications	controlled	217	Positive
Meloxicam	Nell et al. 2002	Dog	Limb injury	Decrease pain and no complications	controlled	214	Positive
Meloxicam	Doig et al. 2000	Dog	Limb injury	Decrease pain and no complications	controlled	40	Positive
Meloxicam	Sauve et al. 2003	Dog	Limb injury	No complications	controlled	46	Positive
Meloxicam	Mullins et al. 2012	Dog	Surgery	Avoid dysfunction	not controlled	.	Mixed
Meloxicam	Budsberg et al. 2002	Dog	Surgery	Decrease pain	controlled	40	Positive
Meloxicam	Zanuzzo et al. 2015	Dog	Surgery	Decrease pain	controlled	40	Positive
Meloxicam	Teixeira et al. 2013	Dog	Surgery	Decrease pain	controlled	27	Positive
Meloxicam	Tsai et al. 2013	Dog	Surgery	Decrease pain	controlled	27	Positive

Meloxicam	Teixeira et al. 2013	Dog	Surgery	Decrease pain	controlled	24	Positive
Meloxicam	Leece et al. 2005	Dog	Surgery	Decrease pain	controlled	43	Positive
Meloxicam	Fowler et al. 2003	Dog	Surgery	Decrease pain	controlled	20	Positive
Meloxicam	Caulkett et al. 2003	Dog	Surgery	Decrease pain	controlled	15	Positive
Meloxicam	Moak et al. 2011	Dog	Surgery	Decrease pain	not controlled	25	None
Meloxicam	Gruet et al. 2011	Dog	Surgery	Decrease pain and inflammation	controlled	146	Positive
Meloxicam	Lafuente at al. 2005	Dog	Surgery	Decrease pain and inflammation	controlled	16	Positive
Meloxicam	Yilmaz et al. 2014	Dog	Surgery	Decrease stress	not controlled	24	Positive
Meloxicam	Nakagawa et al. 2007	Dog	Surgery	Increase recovery and no complications	controlled	5	Positive
Meloxicam	Kum et al. 2013	Dog	Surgery	No complications	controlled	18	Positive
Meloxicam	Kazakos et al. 2005	Dog	Surgery	No complications	controlled	38	Positive
Meloxicam	Fresno et al. 2005	Dog	Surgery	No complications	not controlled	20	Positive
Meloxicam	Laredo et al. 2004	Dog	Surgery	No complications	not controlled	32	Positive
Meloxicam	Gruet et al. 2013	Dog	Surgery	Decrease pain and inflammation	not controlled	174	Positive
Meloxicam	Mathews et al. 2001	Dog	Surgery	Decrease pain and no complications	controlled	36	Positive

Meloxicam	Khan and McLean 2012	Dog, cat	General	No complications	controlled	22206	Mixed
Meloxicam	Regan et al. 2016	Donkey	Limb injury	Decrease pain and inflammation	controlled	40	Mixed
Meloxicam	Ingvast-Larsson et al. 2011	Goat	Dehorning	Decrease pain	not controlled	11	None
Meloxicam	van der Heide et al. 2008	Goat	Limb injury	No complications	controlled	18	Positive
Meloxicam	Little et al. 2007	Horse	General	Avoid dysfunction	controlled	18	Positive
Meloxicam	Beretta et al. 2005	Horse	General	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	Raidal et al. 2014	Horse	General	No complications	controlled	9	Mixed
Meloxicam	Nobel et al. 2012	Horse	General	No complications	controlled	33	Positive
Meloxicam	D'Arcy-Moskwa et al. 2012	Horse	General	No complications	controlled	25	Positive
Meloxicam	Raidal et al. 2013	Horse	General	No complications	controlled	10	Positive
Meloxicam	Vander Werf et al. 2012	Horse	General	No complications	not controlled	7	Positive
Meloxicam	Brideau et al. 2001	Horse, Dog	General	Decrease inflammation	controlled	30, 48	Positive
Meloxicam	de Walter et al. 2016	Horse	Limb injury	Decrease inflammation	controlled	24	No conclusion
Meloxicam	de Grauw et al. 2009	Horse	Limb injury	Decrease pain and inflammation	controlled	6	Positive
Meloxicam	Lima et al. 2015	Horse	Reproduction	Increase pregnancy rate	controlled	11	Negative

Meloxicam	Naylor et al. 2014	Horse	Surgery	Decrease pain	controlled	60	Mixed
Meloxicam	Walliser et al. 2015	Horse	Surgery	Decrease pain and inflammation	controlled	66	Positive
Meloxicam	Paull et al. 2012	Sheep	Castration	Decrease pain	controlled	48	Positive
Meloxicam	Small et al. 2014	Sheep	Castration	Decrease pain	controlled	60	Positive
Meloxicam	Colditz et al. 2011	Sheep	Limb injury	Decrease pain and inflammation	controlled	.	Positive
Meloxicam	McKeown et al. 2000	Sheep	Reproduction	Increase pregnancy rate	controlled	.	Positive
Meloxicam	Dorniak et al. 2011	Sheep	Reproduction	No complications	controlled	.	Negative
Meloxicam	Rac et al. 2007	Sheep	Reproduction	No complications	controlled	.	Positive
Meloxicam	Barrett et al. 2016	Cattle	Surgery	Decrease pain	controlled	24	No conclusion
Meloxicam	Newby et al. 2013	Cattle	Surgery	Decrease pain	not controlled	10	Positive
Meloxicam	Deneuche et al. 2004	Dog	General	Decrease pain and no complications	controlled	60	Positive
Meloxicam	Forsyth et al. 1998	Dog	General	No complications	not controlled	24	Positive
Meloxicam	Luna et al. 2007	Dog	General	No complications	not controlled	36	Positive