Carprofen: a vulture-toxic drug

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

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

Aim

This paper, intended for decision-makers involved in drug licensing, presents evidence of the toxicity of carprofen, 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 carprofen can be toxic to *Gyps* vultures at high, but realistic, concentrations.
2. Captive vultures are exposed to NSAIDs through veterinary care.

3. A survey of wildlife veterinarians found that treatment with carprofen resulted in visceral gout and death in 1 out of 17 cases involving a *Gyps* vulture.
4. 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 carprofen was calculated assuming that cattle in India may typically be dosed with twice the recommended amount.

5. Although both Cape Vultures *Gyps coprotheres* survived, an experiment showed that oral doses of carprofen at the recommended therapeutic dose caused observable symptoms of toxicity, including elevated uric acid levels (hyperuricemia) in one bird, and elevated alanine transferase (ALT) levels and long elimination half-lives in both.
6. Although the drug was largely harmless at lower doses, another experiment on Cape Vultures showed that high doses of carprofen, based on the concentrations found at the injection site in cattle, resulted in the death of one of two vultures, and was associated with severe visceral gout and elevated uric acid and ALT levels
7. 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.
8. In contrast to carprofen, the NSAID meloxicam has been shown to be non-toxic to *Gyps* vultures above the MLE.

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

10. 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 carprofen 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.

11. To conserve critically endangered *Gyps* vultures, use of carprofen on cattle and other domestic animals should be discouraged throughout South Asia. Such actions would not impact livestock healthcare because meloxicam is a safe, effective and widely available alternative to vulture-toxic NSAIDs.

Supporting evidence

We present six 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. Carprofen caused visceral gout and death in 1 out of 17 *Gyps* vultures. A single instance where carprofen in combination with ketoprofen was administered to a *Gyps* vulture also resulted in kidney failure, visceral gout and death, but which of the compounds caused death could not be determined. Furthermore, treatment with carprofen resulted in visceral gout and death in 4 out of 23 cases involving 11 other species, including scavenging raptors. In contrast, meloxicam did not cause mortalities in 40 *Gyps* vultures and another 700 birds of a variety of species.

2. The effect of carprofen, flunixin and phenylbutazone on *Gyps* vultures was examined in controlled experiment conducted in South Africa. Two Cape vultures *Gyps coprotheres* were given oral doses of carprofen at 10 mg/kg body weight (bw), the recommended dose when treating raptors. 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.

3. Further experiments were carried out on Cape Vultures to assess the toxicity of carprofen to *Gyps* vultures. Fourteen birds given doses ranging from 0.87 – 4.4 mg kg^{-1} bw all survived with no observable or clinical signs of toxicity. Two further birds were given oral doses of 64 mg kg^{-1} bw, which equated to the average carprofen concentration at the injection site in cattle. One of these birds died, showing elevated uric acid and ALT levels and severe visceral gout.

4. 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.

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

6. A total of 123 studies were found on the effect of meloxicam on domestic animals, which were positive in 81% of cases. A negative, mixed or no effect was reported in just 2%, 8% and 7%, respectively, with no conclusion being reached in 2% of cases.

Specific details

Chemical name: **carprofen**

Systematic name: 2-(6-Chloro-9H-carbazol-2-yl) propanoic acid

Formula: $C_{15}H_{12}ClNO_2$

Molar mass: 273.71 g/mol

Typical formulation: 50 mg ml^{-1} injection in 50- or 100-ml vials; and 25-100 mg tablets

Example products (manufacturers):

Bangladesh – Rimadyl (Zoetis)

India – Carprofen Injectable Solution (Nicosia Int'l)

Nepal – products may be imported

Pakistan – products may be imported

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*.

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.

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

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 or not toxic to vultures.

Key figure

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

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

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

2. 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* (CV) 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 CV were given an oral dose of carprofen at 10

mg kg^{-1} body weight (bw); two CV were given an oral dose of flunixin at 1 mg kg^{-1}; two CV were given an oral dose of phenylbutazone at 1.5 mg/kg; and two CV were given an oral dose of control solution.

The maximum level of exposure (MLE) to flunixin for the CV 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 CV 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

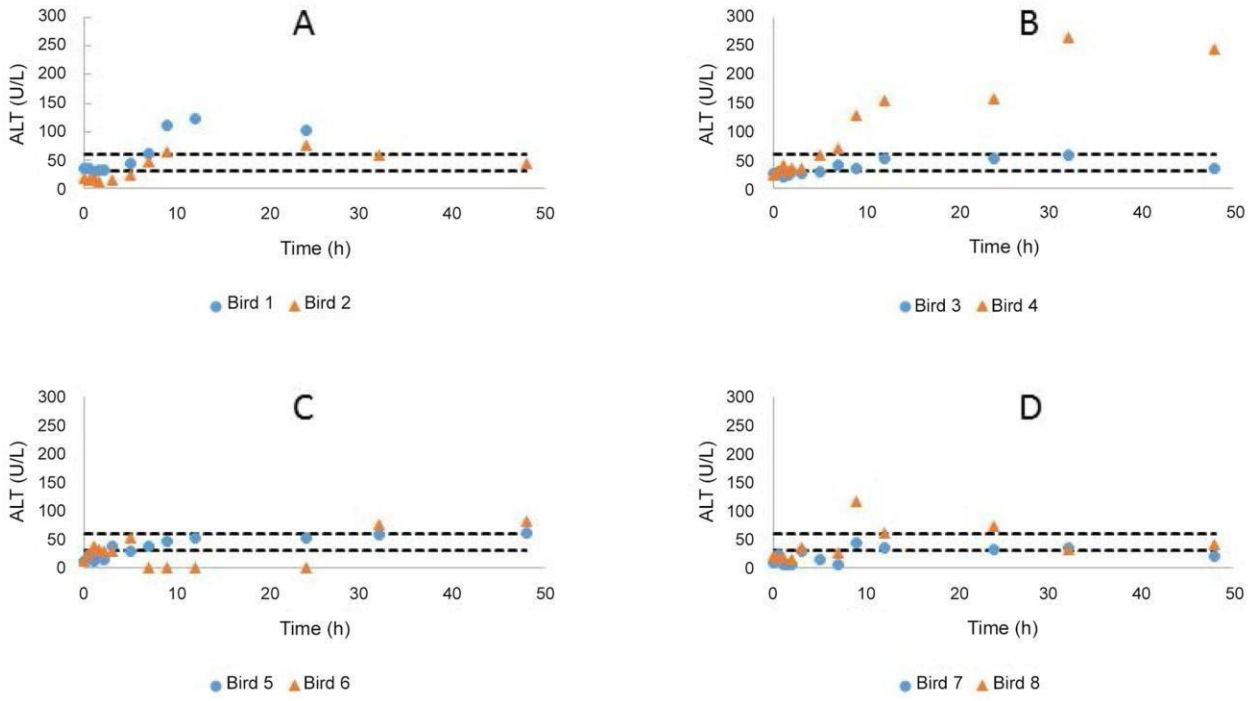
All Cape vultures *Gyps coprotheres* survived treatment with carprofen at the recommended therapeutic dose; and flunixin and phenylbutazone at doses above the MLE. All control vultures survived. Symptoms of toxicity (lethargy and depression) were observed in some treated vultures; however, no pathological 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.

3. An experiment finds high but realistic doses of carprofen can cause death and other symptoms and signs of toxicity in Cape vultures *Gyps coprotheres*

Source

Naidoo, V., Taggart, M.A., Duncan, N., Wolter, K., Chipangura, J., Green, R.E. & Galligan, T.H. 2018. The use of toxicokinetics and exposure studies to show that carprofen in cattle tissue could lead to secondary toxicity and death in wild vultures. *Chemosphere*, **190,** 80-89

Background

Given the proven role of diclofenac in the decline of Asian *Gyps* vultures, there is concern over the toxicity of other NSAIDs, of which less is known. A questionnaire survey on the therapeutic use of NSAIDs in vultures found that, along with other NSAIDs, carprofen was in some cases toxic to *Gyps* vultures. Further experiments showed that, although no birds died, vultures exposed to carprofen above the MLE showed clinical signs of toxicity. Sample sizes in that study were too small to confirm that carprofen was not toxic to *Gyps* vultures.

Action

Four aspects to study:

Pharmacokinetic study in cattle to identify maximum NSAID concentration (C_{max}) and time at which this was achieved in cattle (T_{max}). Cattle were treated with the recommended dose, 1.4 mg kg^{-1} bw, and slaughtered at T_{max}, at which time C_{max} was measured. Blood samples collected and analysed

Pharmacokinetics of carprofen in *Gyps* vultures (n = 6), split into three groups of two, which were either dosed orally, or by intramuscular or intravenous injection. Blood samples collected and analysed.

Tissue residue study of carprofen in cattle, given twice the recommended dose (to reflect common practice in South Asia), 2.8 mg kg^{-1} bw. At T_{max} (12 hrs), cattle slaughtered, and 3 sample replicates taken from liver, kidney, hind leg muscle, omental fat and muscle from the injection site on neck.

Toxicity of carprofen to *Gyps* vultures was determined with a four-phase cross-over study, where groups of four vultures were alternately either given a dose of the drug or were used as controls. In Phases 1 and 2, treated birds were either given 1 kg of kidney or muscle from animals treated with carprofen or not. In Phase 3, vultures were given carprofen orally at the theoretical MRE (MLE) in kidney (water used a s control). In Phase 4, two birds were given carprofen orally at the average concentration found at the injection site (64 mg kg^{-1}), and two at the MRE calculated from cattle kidneys.

Blood was sampled from vultures in Phases 3 and 4, before and at 2, 8, 24 and 48 hours post-treatment.

Plasma and tissue analysis: carprofen concentration was determined using a liquid chromatography electrospray ionisation triple quadrupole mass spectrometry system (LC-ESI-MS/MS). Serum samples were analysed for activities of alanine transferase (ALT) and alkaline phosphatase (ALP); and concentrations of Potassium (K), sodium (Na), and uric acid (UA).

Findings

Pharmacokinetics of carprofen in Gyps *vultures*. Dosed at 5 mg kg^{-1}, either orally, or by injection intramuscularly or intravenously, carprofen was well tolerated in all exposed vultures.

Tissue residue study of carprofen (2.8 mg kg^{-1}) in cattle. The concentrations of carprofen in liver, fat, kidney, muscle (leg) and injection site muscle ranged from 3.74 (fat) to 289.05 (injection site) mg kg^{-1}. In kidney it was 7.72 mg kg^{-1}. For study of toxicity in vultures, MRE based on kidney concentrations was used, along with mean concentration in injection site tissue.

Toxicity study of carprofen in Gyps *vultures*. Problems getting vultures to eat kidney and muscle tissue in Phases 1 and 2, resulted in low doses effectively being administered, the highest dose levels being 0.87 (kidney) and 0.9 (muscle) mg kg^{-1}. No observable or clinical signs of toxicity were evident in any of the treated birds.

Six vultures (four in Phase 3m one in Phase 4) were given an oral dose of carprofen at 4.4 mg kg^{-1} bw. There were no observable or clinical signs of toxicity, although all pharmacokinetic parameters showed substantial variability.

In Phase 4, two birds were given an oral dose of carprofen at 64 mg kg^{-1} bw, which equated to the average carprofen concentration at the injection site of cattle (289.05 mg kg^{-1}). One bird died, showing a 27-fold increase in uric acid levels, and an increase in ALT and K levels and, clinically, severe visceral gout.

Conclusion

At double the recommended dose for cattle (as is common in South Asia), carprofen was generally harmless to *Gyps* vultures, although there was considerable variation in how individual birds' metabolism responded to the drug. However, when given a much higher dose, which equated to injection site concentrations, one of two birds died showing all the symptoms of NSAID (carprofen) poisoning.

Therefore, if a vulture were to consume tissue from the injection site from a cow treated with carprofen just prior to death, then it could ingest a very high concentration of the drug and could die as a result.

Key figure

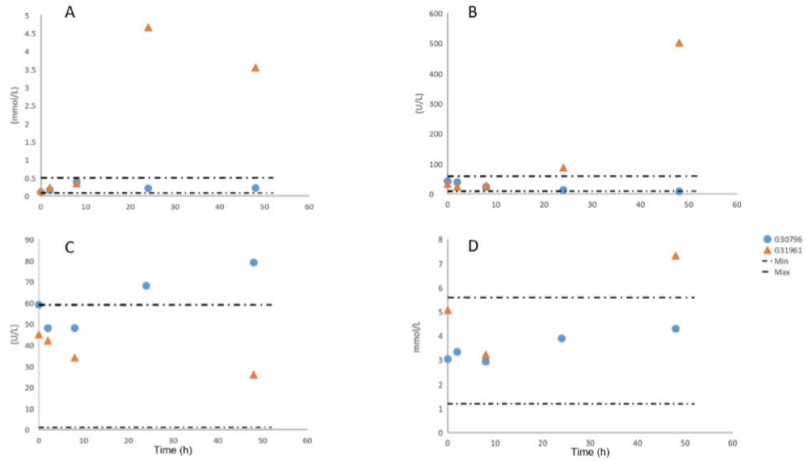


Figure 1: Change in concentrations of uric acid (A), ALT (B), ALP (C) and potassium (D) concentrations in the two bird exposed to carprofen at 64 mg/kg. Bird G31961 (triangle) died from exposure

4. 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.

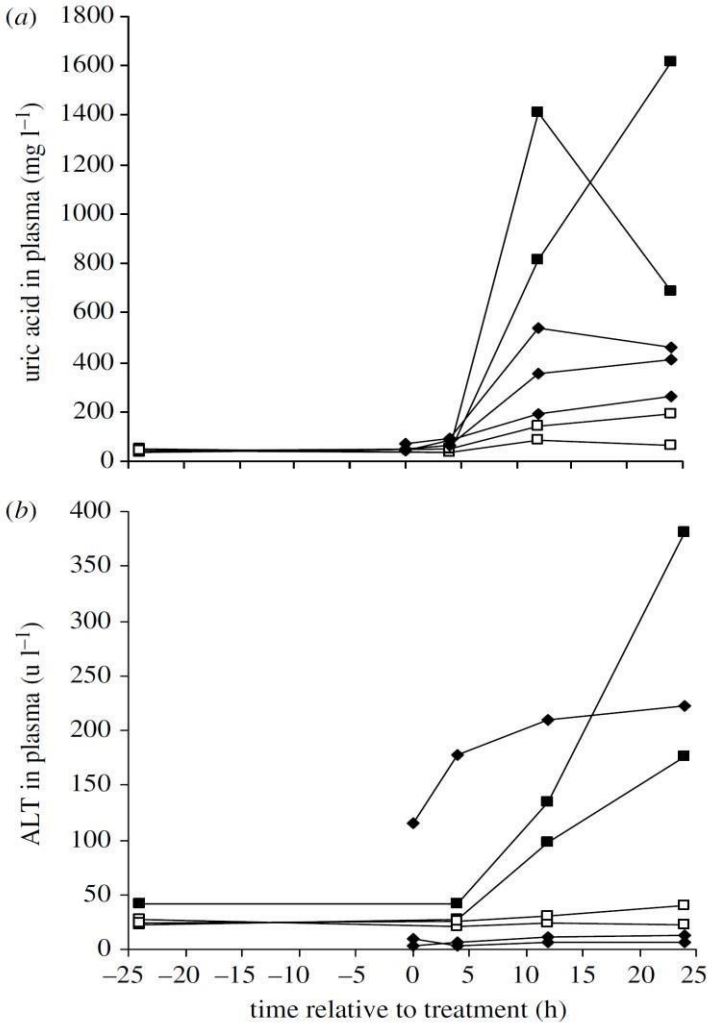
Findings

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).

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

Source

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

Background

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

Action

The effect of meloxicam on *Gyps* vultures was examined in a six-phase partially controlled experiment in South Africa and India. African and Asian *Gyps* vultures were used. The African white-backed vulture *Gyps africanus* and the Asian white-backed vulture *Gyps bengalensis* are of similar size (4-7 and 3.5-7.5 kg, respectively).

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

Phases 1-2: 10 African white-backed vultures were given an oral dose of meloxicam at 0.5-1.0 mg/kg body weight (bw); and six African white-backed vultures were given sterilised water.

Phases 3-4: 40 African white-backed vultures *Gyps africanus* (including 21 wild vultures) were given an oral dose of meloxicam at 2.0 mg/kg bw; and three captive and four wild African white-backed vultures *Gyps africanus* were given sterilised water.

Phase 5: six African white-backed vultures *Gyps africanus* were twice fed tissue from cattle dosed with meloxicam and once given an oral dose of meloxicam at >0.01-1.98 and 1.18-2.45 mg/kg bw, respectively. Meloxicam-contaminated cattle tissues were muscle and liver from three cattle given daily injections of meloxicam at 1 mg/kg bw for five days and slaughtered 8 h after the final dose.

Phase 6: six Asian white-backed vultures *Gyps bengalensis* and four long-billed vultures *Gyps indicus* were given an oral dose of meloxicam 0.5-2.0 mg/kg bw; and two Asian white-backed vultures *Gyps bengalensis* and three long-billed vultures *Gyps indicus* were given sterilised water.

Blood samples were taken from all vultures in Phases 1-5 before the experiment and at up to six time points up to 168 h after dosing. Serum was analysed for uric acid and three other biochemicals.

The maximum level of exposure of meloxicam to Asian white-backed vultures *Gyps bengalensis* was calculated using the average body weight (4.75 kg), estimated large meal weight (1.02 kg) and highest meloxicam residue concentration in cattle liver tissue (8.54 mg/kg bw); and was equal to 1.83 mg/kg bw.

Findings

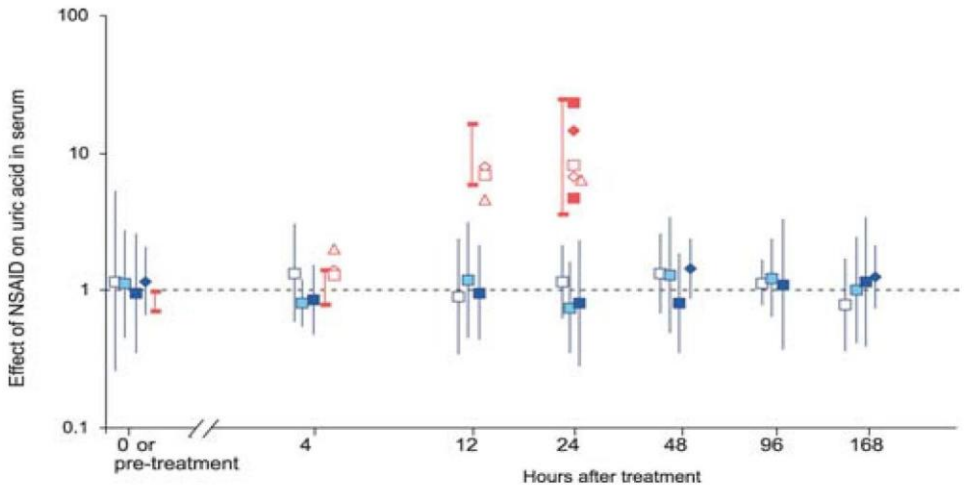
In all Phases, all meloxicam-treated vultures survived with no ill effects. All control vultures survived. Uric acid concentrations in serum in all meloxicam-treated vultures remained within

a 95% range calculated from measurements from these vultures before treatment and control vultures.

Conclusion

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

Key figure



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

6. A 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 other known and potentially-toxic NSAIDs. This review of literature was undertaken to assess the safety and effectiveness of meloxicam as an alternative vulture-toxic NSAIDs for the treatment of domesticated animals.

Action

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

Findings

A total of 123 studies reported an effect of meloxicam 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 81% of studies examining the effect of meloxicam (81%). A negative, mixed or no effect was reported in just 2%, 8% and 7% respectively. No conclusion was reached in 2% of cases.

Meloxicam showed positive effects in six of the eight animals examined (cattle, buffalo, horse, goat, sheep and dog) and in six of the seven situations examined (breeding, general, husbandry, 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).

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 a safe as effective NSAID in a variety of veterinary and husbandry situations in a variety of domesticated animals.