Scene setting - literature review on known impacts of veterinary medicines on vultures

LIFE Re-Vultures International Workshop on Vultures & Veterinary Drugs
*Dadia, Greece, 19th February 2019*

Louis Phipps
*VCF Research Officer*
Introduction

- **Aim:** To set the scene by reviewing existing knowledge of the effects of veterinary medicines on vultures
  - Overview of current knowledge
  - Coverage of some recent research
  - Identify knowledge gaps
  - Recommendations for future work
Release pathways of pharmaceuticals:

Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment

Anekwe Jennifer Ebele, Mohamed Abou-Elwafa Abdallah, Stuart Harrad

Ebele et al. 2017
Emerging Contaminants 3 (2017) 1e16

Fig. 2. Illustration of sources of environmental contamination with PPCPs.
Release pathways of pharmaceuticals:

Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment

Anekwe Jennifer Ebele *, Mohamed Abou-Elwafa Abdallah **, Stuart Harrad *

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- NSAID concentrations in surface water samples from different countries

![Graph showing NSAID concentrations in surface water samples from different countries]

Fig. 3. Concentrations (ng/L) of non-steroidal anti-inflammatory drugs (NSAIDs)* reported in surface water samples from different countries**.

* NSAIDs include Ibuprofen, Naproxen, Diclofenac, Ketoprofen and Acetaminophen.

** Data from [116], [86], [85], [87], [144], [18], [111], [112], [177], [122], [52], [165], [23], [24], [67], [33], [7].
Release pathways of veterinary pharmaceuticals (VPs):
Discovering the threat of NSAIDs

Catastrophic collapse of Indian white-backed *Gyps bengalensis* and long-billed *Gyps indicus* vulture populations

V. Prakash\(^a\), D.J. Pain\(^b,\ast\), A.A. Cunningham\(^c\), P.F. Donald\(^b\), N. Prakash\(^a\), A. Verma\(^a\), R. Gargi\(^a\), S. Sivakumar\(^a\), A.R. Rahmani\(^a\)

- Late 1990s-2000s, >95% decline of three species:
  - Indian/long-billed vulture - *Gyps indicus*
  - Slender-billed vulture - *Gyps tenuirostris*
  - White-rumped vulture - *Gyps bengalensis*
Discovering the threat of NSAIDs

A Cautionary Tale: Diclofenac and Its Profound Impact on Vultures

Ngaio L Richards, Working Dogs for Conservation, Bozeman, MT, United States; University of Florida, Gainesville, FL, United States
Martin Gilbert, Cornell University, Ithaca, NY, United States
Mark Taggart, University of the Highlands and Islands, Inverness, United Kingdom
Vinny Naidoo, University of Pretoria, Pretoria, South Africa

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- Narrative of the Asian vulture crisis:
  - Hypotheses and investigations: pathology and epidemiology
  - Captive trials confirm sensitivity
  - Diclofenac mode of action and *Meloxicam* safety testing
  - Conservation and research actions
Discovering the threat of NSAIDs

Diclofenac residues as the cause of vulture population decline in Pakistan

J. Lindsay Oaks1, Martin Gilbert2, Munir Z. Virani3, Richard T. Watson4, Carol U. Meteyer5, Bruce A. Rideout1, H. L. Shivaprasad5, Shakeel Ahmed6, Muhammad Jamshed Iqbal Chaudhry6, Muhammad Arshad6, Shahid Mahmood6, Ahmad Ali6 & Aleem Ahmed Khan6

Toxicity of diclofenac:

- Kidney function impeded > uric acid accumulates > visceral gout
- Death within 48 hours
- Mortality of >10% birds/carcass
- Low no. of treated carcasses cause declines
Safety testing of meloxicam

Removing the Threat of Diclofenac to Critically Endangered Asian Vultures

Gerry Swan¹, Vinasan Naidoo¹, Richard Cuthbert², Rhys E. Green²,³, Deborah J. Pain², Devendra Swarup⁴, Vibhu Prakash⁵, Mark Taggart⁶, Lizette Bekker¹, Devojit Das⁶, Jörg Diekmann⁷, Maria Diekmann⁷, Elmarie Killian¹, Andy Meharg⁶, Ramesh Chandra Patra⁶, Mohini Saini⁶, Kerri Wolter⁶

- Initial tests on *G. africanus* and *G. coprotheres*
- Subsequent tests on *G. bengalensis* and *G. indicus*
- No clinical effects: conclude low toxicity and safe alternative
- Supports calls to ban diclofenac

- Team of >20 people working across 4 countries
- Costly and labour intensive
- 1-2 years to complete
Other harmful NSAIDs: ketoprofen

- Tests on *G. africanus* and *G. coprotheres*
- Mortalities occurred at dose levels of 1.5 and 5 mg kg/vulture body weight
- Same clinical signs as diclofenac
Other harmful NSAIDs: flunixin, phenylbutazone, carprofen

The Safety and Pharmacokinetics of Carprofen, Flunixin and Phenylbutazone in the Cape Vulture (Gyps coprotheres) following Oral Exposure

https://doi.org/10.1371/journal.pone.0141419
Tamsyn Fourie¹, Duncan Cromarty², Neil Duncan³, Kerri Wolter², Vinny Naidoo¹*

1 Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria, Pretoria, South Africa, 2 Department of Pharmacology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa, 3 Vulture Programme (VulPro), Plot 121, Rietfontein, 0046, South Africa

- Initial tests on G. coprotheres
- No lethal effect but toxic clinical signs, clinical pathological changes and/or long half-lives of elimination
- Safety concern: potential toxicity after repeated administration
Other harmful NSAIDs: carprofen

The use of toxicokinetics and exposure studies to show that carprofen in cattle tissue could lead to secondary toxicity and death in wild vultures

V. Naidoo, M.A. Taggart, N. Duncan, K. Wolter, J. Chipangura, R.E. Green, T.H. Galligan


- Generally low risk unless tissue from injections sites is consumed
- Remains a safety concern
Other harmful NSAIDs: aceclofenac

Metabolism of aceclofenac in cattle to vulture-killing diclofenac

T. H. Galligan, M. A. Taggart, R. J. Cuthbert, D. Svobodova, J. Chipangura, D. Alderson, V. M. Prakash, V. Naidoo

First published: 02 March 2016 | https://doi.org/10.1111/cobi.12711 | Cited by: 10

- Metabolises to diclofenac
- At 12 h ~80% aceclofenac had been converted into diclofenac
- Poses the same risk as diclofenac
Other harmful NSAIDs: flunixin

Suspected flunixin poisoning of a wild Eurasian Griffon Vulture from Spain

Irene Zorrilla, Rosa Martinez, Mark A. Taggart, Ngaio Richards

First published: 09 October 2014 | https://doi.org/10.1111/cobi.12417 | Cited by: 18

- Wild *G. fulvus* found dead in Andalucia in 2012
- Visceral gout
- Elevated levels of flunixin
- First recorded mortality of wild vulture after exposure to non-diclofenac NSAID
Confirmed threat of NSAIDs

**Pharmaceuticals in the Environment**

**Impacts of Pharmaceuticals on Terrestrial Wildlife**

MARK A. TAGGART,* NGAI O RICHARDS AND CHAD A. KINNEY
Beyond NSAIDs: antiparasitics

Risk assessment of bearded vulture (*Gypaetus barbatus*) exposure to topical antiparasitics used in livestock within an ecotoxicovigilance framework

Rafael Mateo a,*, Inés S. Sánchez-Barbudo a, Pablo R. Camarero a, José M. Martínez b


- 2004-2013: 486 scavenger poisoning cases investigated in the Pyrenees
- 4/24 bearded vultures positive for topical antiparasitics:
  - 3 with diazinon and 1 with permethrin
- 71.4% of lambs feet tested had residues of various antiparasitics
- Risk assessment suggests diazinon possible effect on thermoregulation
- Recommended washing lamb/sheep feet at feeding stations
- More research needed
Beyond NSAIDs: antibiotics

Oral mycoses in avian scavengers exposed to antibiotics from livestock farming

Aida Pitarch a, Concha Gil a, Guillermo Blanco b, c

Science of the Total Environment 605–606 (2017) 139–146

- Assessed oral lesion occurrence in wild nestlings:
  - Cinereous: 77.8%, n = 9
  - Egyptian: 28.6%, n = 21
  - Griffon: 66.7%, n = 48
  - Golden eagles: 28.6%, n = 7

- Yeast infections in 100% of affected nestlings (14 yeast species)

- Possibly linked to exposure to antimicrobials, disrupting normal and protective microbiota
Oral mycoses in avian scavengers exposed to antibiotics from livestock farming

Aida Pitarch, Concha Gil, Guillermo Blanco

Science of the Total Environment 605–606 (2017) 139–146

Fig. 1. Examples of lesions caused by yeast-like fungi in the oral cavity of vulture nestlings in central Spain. (A and B) cinereus vulture, (C) griffon vulture and (D and E) Egyptian vulture.

Fig. 2. Frequency of (A) nestlings with yeast-like fungal lesions in the oral cavity, and (B) lesions in each category of location in the four sampled scavenger species. Sample sizes are shown above the bars.
Beyond NSAIDs: antibiotics

Food safety in scavenger conservation: Diet-associated exposure to livestock pharmaceuticals and opportunist mycoses in threatened Cinereous and Egyptian vultures. Ecotoxicology and Environmental Safety 135 (2017) 292–301

Guillermo Blanco, Alexandra Junza, Dolores Barrón

- Used livestock fluoroquinolones (used to treat respiratory and urinary infections) as indicators of pharmaceutical burden in carrion
- Higher concentration of fluoroquinolones in cinereous vulture nestlings than Egyptian vulture nestlings > greater reliance on livestock
- Ingestion of antibiotics during nestling development proposed as a plausible cause of oral lesions
- More research required on impact on nestling survival and fitness > population dynamics
Beyond NSAIDs: antibiotics

Livestock farming practices modulate vulture diet-disease interactions

Guillermo Blanco a,*, Ainara Cortés-Avizanda b, c, Óscar Frias a, Eneko Arrondo b, José A. Donázar b

Assessed oral lesion occurrence in wild nestlings, high vs low intensity farming:

- Cinereous: 75%, n = 16 vs 39%, n = 13
- Egyptian: 46%, n = 13 vs 6%, n = 17
- Griffon: 61%, n = 28 vs 7%, n = 14

Positive relationship between occurrence of oral lesions and frequency of high intensity livestock (swine, poultry) in the diet

Promote widespread monitoring oral lesions and pharmacovigilance
Beyond NSAIDs: antibiotics

Determination of fluoroquinolone antibiotic residues in the plasma of Eurasian griffon vultures (*Gyps fulvus*) in Spain

Encarna Casas-Díaz, Carles Cristòfol, Rafaela Cuénta, Susana Agustí, Manuela Carneiro, Ignasi Marco, Santiago Lavin, Antoni Margalida


- Fluoroquinolone residues detectable in 65% (n = 106) of *G. fulvus* in Navarra and Catalonia
  - 15% (10/106) > enrofloxacin quantifiable
  - 6% > (6/106) > ciprofloxacin quantifiable
- Increased exposure in areas of high density of livestock deposited at feeding sites
- Levels were likely too low to cause intoxication
- **Increased monitoring required**
Beyond NSAIDs: euthanasia drugs / barbiturates

VIGILANCE POISON: Illegal poisoning and lead intoxication are the main factors affecting avian scavenger survival in the Pyrenees (France)

Philippe Berny, Lydia Vilagnes, Jean-Marc Cugnasse, Olivier Mastain, Jean-Yves Chollet, Guy Joncour, Martine Razel
Ecotoxicology and Environmental Safety 118 (2015) 71-82

5 turkey vultures die after being poisoned by vet euthanasia drug

By ASSOCIATED PRESS  NOV 07, 2017  |  7:25 PM

LA Times

IN PRESS: A review of secondary pentobarbital poisoning in scavenging wildlife, companion animals and captive carnivores

Wells, Butterworth & Richards

- Euthanasia drug residues detected in 9/120 dead G. fulvus in France
- Pentoarbital
- Global survey
- 125 cases, 432 animals
Improved surveillance is required

Development of a QuEChERS method for simultaneous analysis of antibiotics in carcasses for supplementary feeding of endangered vultures  

doi: 10.1016/j.scitotenv.2018.01.060


● QuEChERS = Quick + Easy + Cheap + Effective + Rugged + Safe

● Assessed risk of exposure to antibiotics for cinereous vultures at supplementary feeding sites (SFS) in SE Portugal

● 87 samples of liver, muscle and kidney from 7 goats and 25 sheep disposed at feeding sites

● According to questionnaires farmers had not treated livestock with antibiotics

● Analyses revealed residues in 29% of samples; higher in goats (42.9%) than sheep (24.2%)

● Low concentrations but proves unexpected exposure, with unknown health consequences
Knowledge gaps and future research

Forensic Research

Review Article

Merging Wildlife and Environmental Monitoring Approaches with Forensic Principles: Application of Unconventional and Non-Invasive Sampling in Eco-Pharmacovigilance

Ngaio L. Richards1,2,3, Sarah W. Hall2,3, Nancy M. Harrison2,4, Lota Gautam5,6, Karen S. Scott7, Geraldine Dowling4, Irene Zorilla4 and Itígo Fadjardo8

● Highlights promising approaches for pharmacovigilance, promoting non-invasive methods
● Feathers, bones, eyes, pellets, faeces
● Faeces: Are Egyptian vultures exposed to VPs through consumption of livestock dung?
  ○ The importance of coprophagy in EV diet is unknown/unquantified
  ○ Observations and tracking data from the Douro region (Spain-Portugal) suggest possible route of exposure when EVs consume faeces from calf scours and/or dung heaps > requires further research
Conclusions

● Vultures are exposed to multiple veterinary pharmaceuticals
● Toxicity of NSAIDs is well established
● Toxicity of additional veterinary pharmaceuticals regularly established over time
● Vultures in Europe are regularly exposed to antibiotics
● The direct and indirect effects of antibiotic exposure are not fully known
  ○ There is a link between antibiotic exposure and occurrence of oral lesions
● Further research is required into exposure and toxicity of antiparasitics, antibiotics, euthanasia drugs
  ○ Risk of exposure at supplementary feeding sites?
● Widespread, standardized monitoring / pharmacovigilance is required
  ○ e.g. EU COST Action ‘European Raptor Biomonitoring Facility’
Thanks for listening

info@4vultures.org

Together for Vultures

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