DICLOFENAC AND THE ASIAN VULTURE CRISIS

Dr Mark Taggart (ERI-UHI)

International workshop on poisoning and vultures in the European-African bird migration flyway: What is the situation in Africa and how can Europe help?

April 8-11th, 2014, Ronda - Spain
Confirmed in 2004 (India) for wild birds – supported by experiments in South Africa and Spain

Griffon vulture (*Gyps fulvus*) – Least Concern – increasing.


Highly likely that all 8 *Gyps* species are susceptible.

Swan et al., 2006, Biol Letts, 2, 279-282.
Diclofenac now known to be highly toxic to Gyps

*G. fulvus* and *G. africanus* treated with 0.8 mg kg\(^{-1}\) diclofenac – all birds died within 48 hours.

Estimated LD\(_{50}\) for *G. bengalensis*: 0.1-0.23 mg kg\(^{-1}\).

LD\(_{50}\) in rats: strychnine = 16 mg kg\(^{-1}\), K arsenite = 14 mg kg\(^{-1}\); passerines: carbofuran = 0.4 mg kg\(^{-1}\).

Diclofenac exposure pathway in the wild

The ½ life of diclofenac in cattle is fairly long following administration (12.2h in plasma) – hence, if an animal is given the drug in the days preceding death, it can be readily detected in carcass liver tissue samples.
Liver tissue samples are collected, extracted for NSAIDs and analysed using liquid chromatography - triple quadrupole mass spectrometry, and, by ELISA.

Taggart et al., 2007, Env. Poll., 147, 60-65; Taggart et al., 2007, Env. Int., 33, 759-765; Taggart et al., 2009, ES&T, 43, 4561-4566.
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Saini et al., 2012, Env. Poll., 160, 11-16.
Survey work indicated that in 2004-2006, ~1:10 carcasses available to vultures contained diclofenac

Survey 1 – May 04 to July 05
n = 1848 – 10.1%
Mean in all +ve’s – 352ppb

Survey 2 – Apr 06 to Dec 06
n = 1488 – 11.1%

Only 0.13-0.77% need contain a lethal dose of DICLOFENAC to drive the observed decline rate.

Fig. 1. Prevalence of diclofenac in livers of domestic ungulate carcasses from India by state. Assam, Uttarakhand and Meghalaya were surveyed but samples were unavailable. States shown in white were not surveyed. Inset map shows the number of samples collected per state and the number of sites from which they were collected in brackets.

Taggart et al., 2007, Env. Int., 33, 759; Taggart et al., 2009, ES&T, 43, 4561; Green et al., 2004, J. App. Ecol. 41, 793.
Survey work indicated that in 2004-2006, ~1:10 carcasses available to vultures contained diclofenac. Detailed models suggest that “diclofenac is the main, if not the only cause of the widespread declines in vulture populations” seen on the Indian sub-continent.

Finding an alternative to diclofenac that was “vulture safe” became an urgent priority

Table 2. Evidence for NSAID toxicity on vultures, raptors and other scavenging birds indicating the number of birds that died with gout and/or renal failure and total number of birds treated, the ratio of COX-1/COX-2 inhibition in human, equine and canine blood, and the presence of either an –NH, –COOH or both –NH and –COOH groups in the molecular structure. (Data on COX-1/COX-2 ratios come from Brideau et al. (2001) and Lees et al. (2004).)

<table>
<thead>
<tr>
<th>drug</th>
<th>toxicity</th>
<th>died/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspirin</td>
<td>no</td>
<td>0/3</td>
</tr>
<tr>
<td>ketoprofen</td>
<td>no</td>
<td>0/20</td>
</tr>
<tr>
<td>meloxicam</td>
<td>no</td>
<td>0/739</td>
</tr>
<tr>
<td>carprofen</td>
<td>yes</td>
<td>3/40</td>
</tr>
<tr>
<td>diclofenac</td>
<td>yes</td>
<td>28/36</td>
</tr>
<tr>
<td>flunixin</td>
<td>yes</td>
<td>7/24</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>yes</td>
<td>1/1</td>
</tr>
<tr>
<td>phenylbutazone</td>
<td>yes</td>
<td>1/1</td>
</tr>
</tbody>
</table>

Collated zoo, veterinary, rehabilitation centre data on 870 scavenging birds from 79 species - MELOXICAM had been used in a large number of birds/species (including Gyps).

Proven experimentally in S.Africa and India using 3 Gyps species and 4 other scavenging avian species.

With an alternative “vulture safe” drug available, to protect vultures, India, Pakistan and Nepal essentially banned veterinary diclofenac in 2006 (and Bangladesh also followed in 2010).
Is the ban working?

In 2007-10, diclofenac was still very prevalent in the Indian marketplace – 16 bolus brands, 26 injectable.

Cuthbert et al., 2011, ORYX, 45, 420-426.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Bolus</th>
<th>Injectable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>19 (12)</td>
<td>31 (13)</td>
<td>50 (25)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>16 (8)</td>
<td>26</td>
<td>42 (8)</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>1 (1)</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Analgin</td>
<td>9 (1)</td>
<td>6 (1)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Flunixin</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>8 (2)</td>
<td>8 (2)</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Nimesulide</td>
<td>27 (22)</td>
<td>2</td>
<td>29 (22)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Phenyl butazone²</td>
<td>2</td>
<td>5 (1)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>1</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Total with paracetamol as secondary compound</td>
<td>46</td>
<td>18</td>
<td>64</td>
</tr>
</tbody>
</table>

¹Two bolus and three injectable brands of analgin were formulated with phenyl butazone
²One brand of injectable phenyl butazone was formulated with sodium salicylate (aspirin)
What are the wider consequences of vulture loss?

By rapidly disposing of livestock carcasses, vultures provide(d) an invaluable **ECOSYSTEM SERVICE**…

Now almost completely lost - populations of these keystone species are unlikely to rebound to previous levels.

Vultures potentially helped control disease by disposing of infected animals rapidly:

**Anthrax, brucellosis, tuberculosis**
What are the wider consequences of vulture loss?

Dog populations are increasing on/near carcass dumps, significantly increasing the risk of rabies infections in humans (increased by >7 million between 1992 and 2003). India is No.1 in the world for rabies infections already, dog bites being the main source.
What are the wider consequences of vulture loss?

Historically, carcasses were a valuable resource, providing hide for tanning, and CLEAN stripped bone for fertiliser. If India has to switch to burial/incineration, both resources are potentially lost, and disposal costs will be huge (10’s of millions of carcasses/year).
What are the wider consequences of vulture loss?

Historically, the Parsi community allowed vultures and other scavenging birds to dispose of the flesh of their dead at “Towers of Silence” – while Buddhists use similar “Sky Burials” on mountain tops.
What are the wider consequences of vulture loss?

Vultures are very large, very impressive, enigmatic raptors - their loss in itself holds high value (biodiversity, tourism, etc.).
The FUTURE

• **CONSERVATION BREEDING AND RELEASE** – 3 breeding centres in India, 1 in Nepal, 1 in Pakistan – more to follow

• **VULTURE SAFE ZONES** – creation of zones that are “safe” for vultures (diclofenac-meloxicam swapping, education, safe food provision, etc.)

• **CONTINUED ADVOCACY** – remove diclofenac from the market (large vial human formulations especially) – promote meloxicam

• **CONTINUED RESEARCH** – NSAID safety work, population monitoring, carcass surveys, tracking
Some lessons learned (perhaps)?

• CONSERVATION BREEDING critical for long term plans
• Effective ADVOCACY has been critical throughout – in particular, getting the attention of “big players” (large conservation bodies like RSPB are very good at this!)
• RESEARCH has been critical – peer reviewed, International, quality, high profile (Nature!) publications are important (at least in Asia)
• Having a PLAN – the SAVE consortium Recovery Blueprint is very important going forward – signed up to by many stakeholders (conservation, science, government!)
  • IUCN Red List status

• ECOSYSTEM SERVICES aspect has, to date, been somewhat overlooked – potentially extremely important leverage
  • BASELINE data was/is critical in Asia – often lacking
• SECURING/TRANSPORTING SAMPLES for research is(has been significant barrier to progress (extent of problem, analysis required)
  • SAFETY TESTING has simply been too slow (for other NSAIDs)
TO SUM UP

- Declines this fast, on this scale are virtually unprecedented
  - Driven by one rather unremarkable compound
- Critical that diclofenac is removed from the vet market - significant progress made with the ban – far more to do
- That it is not replaced by another equally problematic NSAID
- A combination of social, economic and ecological factors have come together to cause this “Perfect Storm”
THE Perfect Storm (Prof. Pat Redig)

- Superabundance
- Hinduism
- Valuable – old age
- Toxicity
- Extended half-life

In 2004, 52% of vet-NSAID use was with diclofenac - 2007-10, still cheapest
TO SUM UP

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  • Driven by one rather unremarkable compound
• Critical that diclofenac is removed from the vet market - significant progress made with the ban – far more to do
• That it is not replaced by another equally problematic NSAID
• A combination of social, economic and ecological factors have come together to cause this “Perfect Storm”
• Case has highlighted how little we know about the potential effects of pharmaceuticals in the terrestrial environment
• On a possible POSITIVE note – vulture populations “may” now be turning a corner

Diclofenac

Balmford et al., 2013, Science, 339, 653; Prakash et al., 2012, PLoS ONE, 7, e49118
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University of Pretoria: Gerry Swan, Vinny Naidoo

AND MANY MORE…….

Further information:

http://www.save-vultures.org/