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Non-steroidal anti-inflammatory drug use in South Africa and possible effects on vultures

Mark D. Anderson[a*], Steven E. Piper[b] and Gerry E. Swan[c]

IT HAS RECENTLY BEEN SHOWN THAT A NON-steroidal anti-inflammatory drug (NSAID), sodium diclofenac (diclofenac), has been responsible for the catastrophic decline in the populations of three species of vultures in south Asia. Though diclofenac is not used or authorized for veterinary purposes in South Africa, a large number of other NSAIDs are widely employed for analgesic, anti-inflammatory and antipyretic indications in animals. As the carcasses of NSAID-treated livestock are often available to vultures, especially at 'vulture restaurants', conservationists in South Africa are concerned about the potential impact of these drugs on this threatened group of birds. A research project, to determine whether South African vultures are equally susceptible to diclofenac and other NSAIDs, has recently been launched.

Asian vulture crisis

In the past decade, populations of three *Gyps* vulture species have collapsed catastrophically[1–3] in south Asia, leaving them on the brink of extinction. Oriental white-backed vultures (*G. bengalensis*), long-billed vultures (*G. indicus*) and slender-billed vultures (*G. tenuirostris*) are currently listed as 'critically endangered' by BirdLife International.[4] Mortalities were first observed in 1997 among oriental white-backed vultures nesting in Keoladeo National Park in northwestern India. The number of breeding pairs dropped from 150 in the 1996/97 nesting season to zero today.[3,5] Subsequent investigations indicated that vulture populations throughout the Indian subcontinent have declined by about 95%.[1,3]

These population declines are cause for concern, because vultures play an integral role in the region as scavengers of carcasses of wild and domestic ungulates. They consume the carcasses of cattle (sacred to Hindus), which are not normally eaten by humans.[6] Parsis, descendants of the Zoroastrians of Persia, rely on vultures to dispose of human corpses,[7–9] to avoid contamination of the earth, fire and water. Vultures are important in the control of livestock diseases (such as anthrax, tuberculosis and brucellosis), rapidly disposing of infected carcasses, thus inactivating pathogens.[10] The niche occupied by vultures may be taken over by other animals, such as feral dogs, cats and rats, and this may result in new disease threats, such as rabies and plague. There have also been reports of depredations of feral dogs on humans (D. Pain, pers. comm.).

Since the late 1990s, various organizations have attempted to determine the cause of the high mortality rates of these vulture species.[1,3] Various hypotheses were proposed and tested to determine the origin of the vulture deaths. These include lack of food, intervention by aviation authorities, pesticides, direct or secondary poisoning, human persecution, environmental factors and an infectious disease.[11] In Pakistan and India, necropsies of birds that had died suddenly, in good physical condition, indicated that most had suffered from visceral gout, the result of renal failure, leading to hyperuricaemia and the deposition of uric acid crystals on and within the internal organs.[12] Initially, a disease hypothesis was viewed as the most plausible reason for the observed mortalities.[13] This raised concern that African vultures might eventually become infected, because of the movements of *G. fulvus* between Europe/Asia and Africa.[11] Exhaustive testing of tissue samples from newly dead vultures in Pakistan and India resulted in no evidence of viral or bacterial infection, pesticides, poisons, heavy metals or nutritional deficiency as possible causes of renal failure in the dead birds.[12] Surveys of veterinarians and veterinary pharmaceutical retailers in south Asia indicated that diclofenac, introduced as a painkiller and anti-inflammatory agent for humans in the 1970s, had more recently come into widespread use in Pakistan as a veterinary medicine. Oaks *et al.*[12] found the kidneys of vultures dying with symptoms of visceral gout contained residues of diclofenac, whereas vultures dying of other, known, causes did not. Captive vultures, fed meat from domestic animals treated with diclofenac, died with the same symptoms as observed in wild birds. Diclofenac is a widely used veterinary drug in India, Nepal and Bangladesh.[6,14] It is classified as a non-steroidal anti-inflammatory drug (NSAID), and used as an analgesic, anti-inflammatory and antipyretic.[15]

The discovery that the veterinary use of diclofenac can have an acute toxic effect on wildlife (that is, vultures), over a large area in a short time, is extraordinary and equivalent to the recognition of the effects of the DDT derivative, DDE (dichlorodiphenyldicloroethylene), on raptors and other birds in the 1960s.[16–18] Though it is a very different toxin, the recent diclofenac findings[12] are likely to have an equivalent impact to those resulting from DDT research. The effect on vultures may, however, be significantly different because, unlike DDT, where alternative pesticides were available, the potential NSAID substitutes for diclofenac are related drugs that act in a similar way.[19,20] They suppress inflammation and pain by inhibiting the production of the cyclo-oxygenase enzymes, which are necessary in the formation of prostaglandins.[21]

NSAIDs represent a new environmental threat and serve as a warning to scientists and conservationists about the potential impact of other veterinary drugs on wildlife populations. Although the use of diclofenac in the Indian subcontinent is widespread,[12,14] a simulation model of

[a]Department of Tourism, Environment and Conservation, Private Bag X5018, Kimberley 8300, South Africa.
[b]School of Botany and Zoology, University of KwaZulu-Natal, Private Bag X01, Scottsville, Pietermaritzburg 3209, South Africa.
[c]Wildlife Research Programme, Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria, Onderstepoort 0110, South Africa.
*Author for correspondence.
E-mail: manderson@half.ncape.gov.za

vulture demography demonstrated that the observed rates of population decline could be caused by contamination with a lethal level of diclofenac in a small proportion (between 1:130 and 1:760) of ungulate carcasses available to vultures.[22]

It is currently a race against time to save south Asian vultures and urgent remedial action is needed. Current actions include meetings with appropriate governmental and non-governmental organizations, a study to determine substitute, safer drugs, implementation and enforcement of a ban on diclofenac, the quarantining of viable population of each species, a captive breeding programme, and establishment of 'vulture restaurants'[6,22,23] (Gilbert, in litt.).

Although there is very limited use of NSAIDs in Africa, there is concern that the continent's vultures may be affected, albeit to a limited extent. A recent study[24] has shown that vulture populations in rural areas in Sudano-Sahelian savannas of West Africa's Burkina Faso, Mali and Niger have decreased by an average of 95% during the past 30 years, with the reasons for the declines being unknown.

Non-steroidal anti-inflammatory drug use in South Africa

There are no reports of diclofenac use in birds,[12] but other NSAIDs, such as indomethacin,[25] flunixin meglumine[26] and ketoprofen,[12] may cause renal disease in chickens, cranes, quails and African white-backed vultures.[12,27,28] Although diclofenac is not registered for veterinary use in South Africa, a wide variety of other non-steroidal anti-inflammatory drugs are widely used, including phenylbutazone (used in cattle, especially dairy cows (P. Dommit, pers. comm.), horses, pigs and dogs), flunixin meglumine (horses, cattle, pigs, dogs and cats), eltenac (horses), carprofen (dogs and cats), meloxicam (dogs and cats) and vedaprofen (cattle, horses, pigs and dogs).[29] NSAIDs have anti-inflammatory, analgesic and antipyretic activity[19,20] and are particularly used for painful musculoskeletal conditions and treatment of tissue inflammation in all animal species. They are indicated more specifically for the treatment of inflammatory conditions associated with respiratory disease and mastitis in cattle and endotoxaemia in horses and cattle. In addition, NSAIDs prevent platelet aggregation and blood clotting through the inhibition of thromboxane.

Although diclofenac has been shown to be toxic to vultures,[12] it is not known whether other NSAIDs have similar nephrotoxic effects. Various NSAIDs have been shown to cause nephrotoxicity in other bird species such as northern bobwhites,[27] and whooping cranes (*Grus americanus*), Siberian cranes (*G. leucogeranus*) and red-crowned cranes (*G. japonensis*).[28] In contrast, studies of flunixinin-treated chickens, ducks, turkeys, pigeons, and ostriches did not reveal any serious side effects.[30] This research has highlighted the variation in bird species' sensitivity and responses to different analgesic drugs.[28] Thus, assessing the safety and efficacy of an NSAID in one bird species may not reliably be used to predict its impact on another.

Vulture conservation and vulture restaurants in South Africa

Nine species of vultures occur in South Africa, some only marginally and in very low numbers.[31,32] Seven species are listed in *The Red Data Book of Birds of South Africa, Lesotho and Swaziland*.[33] Two *Gyps* species, the Cape vulture (*Gyps coprotheres*) and the African white-backed vulture (*G. africanus*) are the most widespread and most commonly observed. The Cape vulture is endemic to southern Africa and during the past three decades various initiatives have been undertaken to promote the conservation of this localized and threatened species.[31] Threats include inadvertent poisoning, powerline electrocution, drowning in farm reservoirs and, importantly, a declining food source.[33] To address the last threat, vulture restaurants have been established at various localities in South Africa.[34] Here, the carcasses of livestock and other animals are provided, with the source usually being local farms, abattoirs and feedlots. During a recent study,[34] the carcasses of horses and dairy cows were found to be a major component of the food provided at these restaurants, animals likely to be treated with NSAIDs. There are records of dairy cows, previously treated with phenylbutazone, being provided at vulture restaurants (P. Dommit, pers. comm.).

Although no mortalities have been observed, it is possible that vultures have been killed. A small proportion of contaminated carcasses can result in significant population declines.[22] Until it is proven that other non-steroidal drugs locally used in cattle and horses are safe for vultures, these drugs should be regarded as potentially lethal. It would be in the best interests of vultures and other scavengers to prevent exposure to these drugs by disposing of carcasses of animals treated prior to death with NSAIDs in a manner that will prevent access by vultures.

There were about 225 formal vulture restaurants in southern Africa in 2002 and, of these, some 120 were active. The number of active vulture restaurants is growing annually by about 9% and therefore there were predicted to be about 140–145 by the start of 2005. Most of these are provisioned by commercial livestock and dairy farmers seeking a cost-effective and safe method of disposing of their dead animals. The majority of carcasses are cattle, horses and sheep, and occasionally other species. Generally, the livestock have died naturally, except in the case of horses, which are generally killed using a firearm. Until recently, no record was kept of the cause of death of the livestock brought to feed the birds, except for the stipulation that no carcasses carrying barbiturates or other poisons which could harm vultures can be used to provision a vulture restaurant.

Proposed research and conservation in South Africa

Studies are currently been undertaken at the Faculty of Veterinary Science, University of Pretoria, in collaboration with the Royal Society for the Protection of Birds, the Vulture Study Group of the Endangered Wildlife Trust, and the Vulture Unit of De Wildt, to assess the risk of NSAID residues in carcasses to vultures. An initial study has established that the African white-backed vulture is as sensitive (or possibly more sensitive) to the toxic effects of diclofenac as the oriental white-backed vulture (G.E. Swan, unpubl. data). Further studies have been designed to identify NSAIDs that would not pose a threat to vulture populations, in particular in Asia but also in South Africa. The African white-backed vulture will be used as a surrogate for the Asian species. Studies will also be undertaken to explain the apparent extreme sensitivity of vultures to diclofenac and possibly other NSAID drugs as well as to examine other potential risks to vulture populations from carcass residues.

The information derived from these studies will guide veterinary and conservation practices in South Africa (and elsewhere in Africa), especially with respect to the provisioning of NSAID-treated livestock at vulture restaurants. In the interim, it is important that dead livestock that have previously been treated with these drugs should be disposed of in a manner which makes them unavailable to vultures. Once it is known what the residence time is of NSAIDs, it may be possible to develop a policy for the disposal of drug-treated livestock.

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Further correspondence concerning *Sahelanthropus tchadensis*

Sir — Readers following the debate about *Sahelanthropus tchadensis* in this journal need to know that the principal argument in the response by M. Brunet *et al.* to an article of ours is based on a series of CT scans and digital photos which reveal contradictions between the figure and its legend.[1] In our reply to this response,[2] we did not mention these contradictions, because we considered that it would be unlikely that they would be published as submitted. However, it is clear that:

1) There is an error in the scales, because hominid teeth a few millimetres long, as suggested by the scale, are unknown. The error is 1 to 10.

2) There is an error in the orientation of the CT scans A, for which the legend reads 'sagittal sections with mesial side at right'.

The root of M_3, which descends towards the right in the scans, indicates that this is not the mesial surface but the distal one. In lower third molars, the mesial root is vertical and the distal one is inclined towards the rear of the mandible, where there is no other tooth to hinder its development. This point is clearly illustrated by photograph G in the same figure. In addition, in the two central images in line A, the planar interstitial facet, which is on the mesial surface of the third molar, occurs on the left in the image, whereas the rounded surface characteristic of the distal part of the tooth is to the right.

Examination of the sagittal section 'shot at 3.33 mm from the buccal edge of the tooth' (the CT scan at the right-hand end) and photographs E and G, and in particular the fractures and wear pattern that the tooth possesses, show that the sagittal sections were taken respectively from the lingual margin of the tooth.

3) There is an error in orientation of the CT scans in line B, which the legend indicates are 'transversal sections with lingual side at right — from right to left, CT scans are respectively shot at 2.67 mm, 3.69 mm, 4.11 mm, and 9.36 mm from the mesial edge of the tooth'.

If the lingual surface is to the right as indicated in the legend, then the photograph is of a left tooth. If this is so, then the text becomes incomprehensible in relation to the CT scans. Apart from that, in hominids, mastication can give rise to aberrant wear patterns. The perceived inclination of the occlusal surface can also depend on the preparation of the remnants of the roots still present just beneath the cervix of the crown and those solidly anchored in the mandible, prior to gluing the pieces together.

White[3] has clearly shown the problems that can be encountered during the process of sticking fragments of fossils together. In general, it is difficult to find perfect contacts between a crown and its roots if these have been separated for millions of years, encrusted separately in a hard matrix and then recently subjected to intense aeolian abrasion and strong temperature changes, which often break the teeth into fragments or polish the exposed surfaces, as has happened in the case of the mandible, or have been cleaned in the laboratory, as happened to the isolated third molar.

Comparison with photograph E reveals that, from right to left, the sections were taken respectively from the distal margin of the tooth.

4) There is an error in orientation of the