The diclofenac ban is helping vulture conservation; what further pharmaceutical threats loom ahead?

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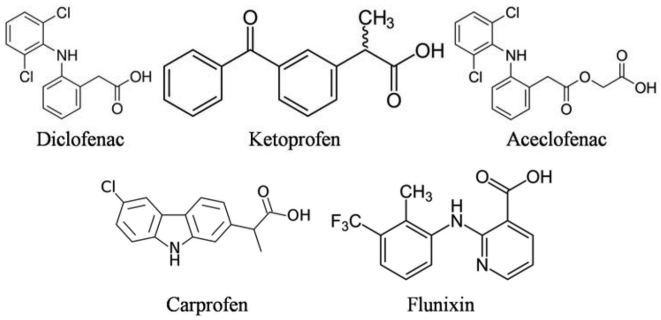
To sustain itself, an ecosystem needs scavengers as much as it needs producers. Despite this, although producers are widely recognized, appreciated, researched and protected by us, scavengers are given less importance. For instance, it was only after vultures started declining drastically in the Indian subcontinent that their ecological importance was realized[1]. Vultures have a suite of adaptations for their scavenging lifestyle, like soaring flight, keen eyesight and extremely low pH of gastric secretions[2]. More than half of the vulture species is on the brink of extinction, with the most dramatic declines observed recently in the Indian subcontinent[3]. While numerous factors have threatened vultures, persecution and poisoning have contributed to their decline[3]. In India, *Gyps* vultures have declined by 99% due to unintentional poisoning by the veterinary drug diclofenac[1].

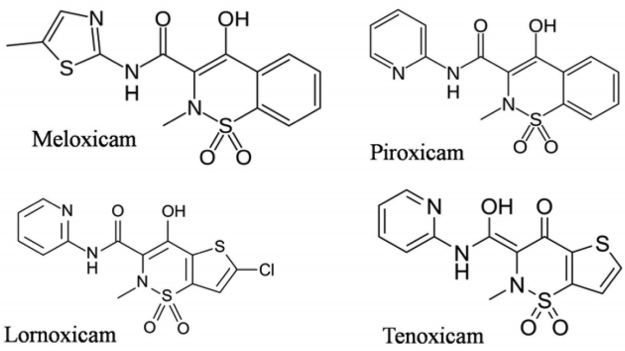
Diclofenac is an out-of-patent non-steroidal anti-inflammatory drug (NSAID) that causes terminal kidney failure in vultures at a very low dose[1]. Vultures ingest diclofenac if they feed on livestock treated with this drug just before death[1]. Hence, the governments of India, Pakistan and Nepal banned the manufacture and sale of diclofenac for veterinary use in 2006. With this ban, a parallel effort was made to identify a replacement drug that could be used for livestock. Meloxicam was identified to be effective for treatment of cattle and safe for vultures, hence meloxicam is now being used as a replacement for diclofenac[4]. This ban, combined with the establishment of conservation breeding centres, has saved vultures from the brink of extinction[5]. This does not, however, mean that the danger is over, because there may be other veterinary drugs that are lethal to vultures. Four such drugs, identified by various researchers are ketoprofen, carprofen, flunixin and aceclofenac (Scheme 1).

Experimental exposure of vultures to ketoprofen produced symptoms similar to diclofenac exposure[6]. Simulations showed that concentration of ketoprofen in livestock carcass was enough to kill vultures, prompting a proposal to ban ketoprofen for veterinary use[7]. While the evidence for harm from ketoprofen is straightforward, risk from three other drugs has been assessed from indirect evidence. Aceclofenac closely resembles diclofenac both structurally and functionally, and is considered by veterinary practitioners as a cost-effective alternative to diclofenac in the Indian subcontinent. However, aceclofenac is metabolized to diclofenac in all tested mammalian models, and this is a clear problem for vultures[8]. Two further drugs of concern are carprofen and flunixin, which produce renal damage in birds. Exposure to flunixin and carprofen caused over 30% mortality in 870 individuals drawn from 79 different species of scavenging birds[9]. Studies have shown that vultures consuming carcasses of livestock treated with carprofen or flunixin are likely to get exposed to lethal doses[9]. It must be noted that all these five NSAIDs are aryl alkanoic acid derivatives (Scheme 1).

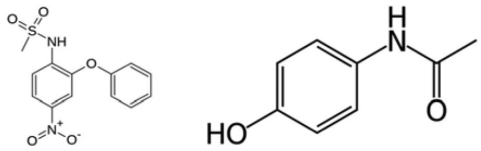
Meloxicam is of low toxicity to a wide number of raptors, including *Gyps* vultures. A detailed survey of scavenging birds revealed that meloxicam was safest among all the NSAIDs administered to scavenging birds. None of the 700 birds across 60 species died on administration of meloxicam[9]. Further, it is also an effective veterinary anti-inflammatory drug. These features make meloxicam the replacement of choice for diclofenac for veterinary use in the Indian subcontinent[4]. Similarly, other oxicam derivatives like piroxicam, tenoxicam and lornoxicam are likely to be safe for vultures as they belong to the same structural group of meloxicam. However, each of these needs to be validated experimentally (Scheme 2).



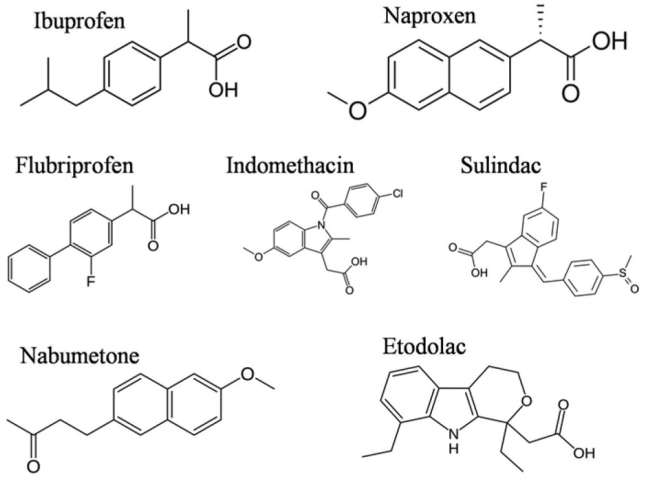
Scheme 1. Structures of non-steroidal anti-inflammatory drugs proved (diclofenac, ketoprofen) or strongly suspected (aceclofenac, carprofen, flunixin) to be toxic to vultures.



Scheme 2. Meloxicam is the only scientifically tested vulture-safe alternative to diclofenac. Other oxicam derivatives are likely to be vulture safe, but need to be tested individually.



Scheme 3. Nimesulide and paracetamol are relatively safe in poultry, and are thus good candidates to test for safety in vultures.



Scheme 4. These NSAIDs are likely to be similar to other aryl alkanoic acid derivatives in their toxicity to vultures.

With dwindling numbers, it is increasingly difficult to test drugs for toxicity directly on vultures. To overcome this limitation, Naidoo *et al.*[10] validated domestic poultry as a model to characterize the mechanism of toxicity of diclofenac. Based on the results, this study suggested that poultry may be used as a model to characterize the mechanism of toxicity of diclofenac as the clinical signs, necropsy findings, histopathological lesions and pathological changes were similar in poultry and vultures. However, toxicity itself was much lower in poultry than in vultures, and the authors[10] also warn about generalizing the results to other non-steroidal anti-inflammatory drugs.

Nevertheless, two comparative studies have showed that although diclofenac induces kidney damage, paracetamol[11] and nimesulide[12] were kidney-safe in poultry. Further, the diclofenac-induced lesions and clinical changes in poultry were similar to those observed in vultures[6]. It is important to understand the implications of these studies for vulture conservation. These studies imply similarity in the response of kidney tissues of vultures and poultry to diclofenac. Considering this, paracetamol and nimesulide, which are safe for poultry, could possibly be safer for vultures (Scheme 3). However, careful studies must be conducted to confirm this. For instance, ketoprofen, which is toxic to vultures, is relatively safe in poultry[13].

It is likely that not only the five NSAIDs shown in Scheme 1, but numerous other NSAIDs that are available in the Indian market, like ibuprofen, naproxen, flubriprofen, indomethacin, sulindac, nabumetone and etodolac (Scheme 4) could pose a serious threat to vultures, as they are also derived from aryl alkanoic acid. Drugs derived from a common skeleton have a high likelihood of following similar pharmacodynamic and pharmacokinetic pathways, though exceptions are common and actual testing is required in each species. Hence, oxicam derivatives, paracetamol and nimesulide could be subjected to testing for efficacy in livestock and safety in vultures, and popularized in veterinary therapeutics to increase the range of possible treatments for inflammatory conditions. This will overcome the continued use of diclofenac – it is still widely utilized even 10 years after being banned for veterinary use, most likely due to lack of a lower cost alternative[5]. These suggestions hold good for all countries across the world which vultures inhabit. Further, owing to recent developments in construction of vulture aviaries in Mumbai for disposal of the dead according to the ritual of Zoroastrianism, terminal administration of vulture-toxic drugs in Parsi community subjects needs to be monitored[14].

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