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Neglected ecological and health risks associated with the use of diclofenac in veterinary medicine: A mini-review

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Abstract

There is sufficient scientific evidence to support that residues of diclofenac, a non-steroidal anti-inflammatory drug (NSAID) administered to livestock raised in the open, can cause fatal renal crystallization in vultures' species, and perhaps other birds such as eagles, if treated animals enter the trophic chain. This phenomenon caused the population of vultures to decline sharply, on the brink of extinction, in India, Pakistan, Tibet, and many countries in the Middle East. For this reason, except for Spain, this medication has been prohibited for veterinary use in the rest of Europe, the United States of America, Canada, Japan, Australia, New Zealand, and many other countries. In contrast, in Latin America, diclofenac is available for veterinary use in various preparations alone or combined with antibacterial drugs. The precise impact this is generating on the native species of vultures and other birds that feed on animals that die in open pastures and are not incinerated is unknown. Given the nature of our livestock production via small producers and extensive farming, most animals medicated with this NSAID can enter the natural food chain and become part of the vulture diet. Most researchers who have studied this ecological problem have recommended that countries adhere to the precautionary principle of prohibiting its sale until there is concrete evidence of the magnitude of the damage that the permissive use of diclofenac in veterinary medicine may cause in Latin America. In Mexico, the official standard NOM-064-ZOO-2000, *Lineamientos para la clasificación y prescripción de los productos farmacéuticos veterinarios por el nivel de riesgo de sus ingredientes activos*, recommends incinerating animals treated with diclofenac, a command that does not fit our daily reality. The question is: shall Latin American countries remain inactive despite a hitherto invisible ecological disaster? Research in Latin America needs to be carried out that supports or rejects the possible impact of diclofenac on wild species, including vultures. However, many countries on the continent, including Mexico, have adhered to the 11th Declaration of Rio for Sustainable Development in the 21st century. Based on this, we propose that action should be taken without delay to avoid or limit an ecological disaster by banning diclofenac in veterinary medicine.

Keywords: Vultures; Diclofenac; Ecology; Toxicity; Legislation; Prohibition.

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The current state of the environmental health threat

Diclofenac, a non-steroidal anti-inflammatory pharmaceutical agent, is a very commonly prescribed drug in human medicine, and in some countries, it has been incorporated into veterinary medicine. However, it was responsible for the death of countless *Gyps* vultures in Pakistan,[1] the Himalaya,[2] the Indian sub-region,[3] and neighboring countries, with the safety of other non-steroidal anti-inflammatory drugs (NSAIDs) being questionable until proven otherwise, i.e., nimesulide,[4] the diclofenac derivative acecoflenac,[5,6] and flunixin.[7] Furthermore, diclofenac may also be toxic to other wild-living avian species, i.e., eagles such as the *Aquila nipalensis*.[8] Along with other pharmaceutical chemicals, diclofenac has been classified as a contaminant of potential importance for Mexico based on its use volumes, toxicological interest, mechanisms of action, and relevance to public health.[9] The accepted fact is that the toxicity of diclofenac in vultures is idiosyncratic and most likely the result of species-specific metabolism.[10] However, this drug is regularly included in drug preparations in Latin America destined for food-producing animals that may get in contact with these scavenger birds. The lethal effects on vultures when they feed on animals that die unattended in the field are easily observed. For example, world evidence shows that it caused the decline of > 95 % of vultures of the *Gyps* genus in Southern Asia, and a direct cause–effect was demonstrated by determining tissue and blood concentrations of diclofenac in various species of vulture.[11] Consequently, the inclusion of this drug in any formulation was banned in 2006 in India, Pakistan, and other countries in the South Asian continent,[3,12-14] and an evident recovery of vulture species has since been demonstrated.[15] Despite this experience, three drug preparations were allowed in Spain in 2013.[7] Although critical diclofenac poisoning has not been observed in Spain and Portugal,[16] this may be related to well-managed carrion disposal and appropriate veterinary risk labeling medicines containing diclofenac and other potentially dangerous pharmaceuticals to avian scavengers. That is, the Spanish authorities have made clear that Veterinarians should not prescribe or administer these drugs to animals whose carcasses are going to be used or can get in contact with necrophagous birds, such as livestock outdoor-reared, and that in the event of death or slaughter of the diclofenac-treated animals, they should be disposed of, making them unavailable to wildlife.[17] Despite this, the first fatal case of a cinereous vulture fledgling (*Aegypius monachus*), classified as 'near threatened' by the International Union for Conservation of Nature, was reported, and diclofenac concentrations found were 26.5 ng/g in the liver and 51.4 ng/g in the kidney. Necropsy findings were compatible with diagnosing fatal gout caused by diclofenac intoxication.[18] These authors concluded that there is a risk of diclofenac intoxication for vultures in Spain and support the earlier proposal that indicates that due to the possibility of causing an important impact on vulture populations, a precautionary ban on the veterinary use of diclofenac should be enforced in Spain while encouraging the use of safer alternative drugs.[19,20]

The reality of livestock production in Latin America is far from adhering to the production policies imposed in Spain. Often animals are neglected for days or weeks in the field, and if the carcass contains diclofenac, vultures will be immediately in danger. In fact, it has been calculated that the use of diclofenac resulted in global declines in vultures and related species nearing 99.9 %.[21] It has been proposed that the precautionary principle in the veterinary use of diclofenac be applied

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to maintain a zero-risk approach. For example, considering that diclofenac is almost certainly toxic to all *Gyps* vultures' species,[22,23] researchers have pronounced themselves to ensure that veterinary diclofenac products are not licensed or introduced to the African continent.[24] Hence authorities in Latin America should implement and enforce a total ban on the use of this drug.[24] Diclofenac is an additional threat to the conservation of vultures as they are already illegally poisoned, can suffer lead and other intoxications, and are illegally shot by poachers and farmers.[25,26] In an extensive review, Mahapatro and Arunkumar (2014) state that more scrupulous monitoring and cross-checking of veterinary drugs such as diclofenac, ketoprofen, aceclofenac, and meloxicam are necessary, focusing on toxicities not only in farm animals but in scavengers in general. Also, the presence of pollutants such as diclofenac, ibuprofen, ketorolac, and pentachlorophenol within the toxic ranges, has already been confirmed in wastewater in Mexico, adding a threat to these species.[26] In some regions of Mexico, bioaccumulation of diclofenac has been shown in coastal fauna, including birds. However, further studies are necessary to characterize the impact of these findings on local fauna, including native vulture species.[27]

The link between diclofenac use in livestock and vultures toxicity

Many pharmaceutical preparations in Mexico and Latin America contain diclofenac alone or combined with antibacterial drugs. They all indicate its use in ruminants, pigs, and sometimes even in small species and horses. In cattle, oral administration of diclofenac at a dose of 1 mg/kg is rapidly absorbed with a $T_{1/2}ab$ of 1.61 ± 0.61 h. In a single-dose study, elimination half-life ($T_{1/2}\beta$) was relatively rapid 1.51 ± 0.38 h, and bioavailability was close to 100 %.[28] In pigs, the pharmacokinetics of diclofenac it appears to be reasonably similar.[29] However, a more recent study found a long half-life when defining the pharmacokinetics of a combined preparation of oxytetracycline and diclofenac with values of elimination half-life ($T_{1/2}\beta$) of 30.48 ± 9.42 h.[30] In all veterinary species studied so far, and in humans, diclofenac is eliminated following almost complete biotransformation by hydroxylation (CYP2C9) and by conjugation with glucuronic acid or sulfate.[31,32] The main hydroxylation product is 4-hydroxy-diclofenac.[32] Then, metabolites and the parent molecule are excreted through the urine.[33] The European Medicines Evaluation Agency (EMEA) has established a maximum residue level (MRL) of 1-10 ppb in porcine and cattle tissues. However, withdrawal times must be established for each pharmaceutical preparation given the vast array of vehicles involved in different pharmaceutical preparations. Thus, according to the prolonged $T_{1/2}\beta$ mentioned of 35.48 h[30] or considering another less extreme value obtained for cattle of $T_{1/2}\beta$ of 9.46 h,[34] a minimum theoretical withdrawal time of 8 to 26 days would be advisable based on the empirical formula proposed of $T_{1/2}\beta \times 20$.[35] Nevertheless, commercially available products recommend slaughter withdrawal times ranging from 3 to 6 days when diclofenac is administered alone. Suppose an animal is treated with a single dose of diclofenac and left unattended for several days. In that case, there is a strong possibility that it will enter the trophic chain of scavenging birds, and indirectly the metabolites mentioned above of diclofenac will

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enter the vultures and other scavenging bird organisms. In this context, the *Gyps* vulture population declined in the Middle East, and the phenomenon was linked to the disposition of diclofenac in goats and cattle in 2007.[36] The authors demonstrated that diclofenac and metabolites could be detected in cattle liver, kidney, and intestine at least three days after the last dose of the drug. However, as presented above, other analytical techniques may find more prolonged periods of dangerous exposure of diclofenac metabolites to avian scavenging species.[30,34] Hence, the determination of diclofenac-dependent death of vultures when scavenging on livestock treated with diclofenac varies among researchers. Nevertheless, despite these differences, all researchers agree that vultures are susceptible to developing kidney damage with increased serum uric acid concentrations and visceral gout.[28] As already stated, diclofenac is exceptionally toxic to vulture populations, causing fatalities a few days after exposure to minimal quantities.[2,23] Furthermore, to complete the vicious cycle of diclofenac and vulture death, diclofenac and its metabolites have been found in most dead vultures in the field.[11,37] It has been established that the probability of death of a *G. bengalensis* vulture receiving a single dose of 0.8 mg/kg will be 0.9284, and the survival probability is only 0.0051.[22] When *Gyps bengalensis* vultures voluntarily ate 0.007–0.940 mg/kg of diclofenac as residue in a single meal of goat or buffalo tissues, they all eventually died of renal failure with acute severe necrosis of proximal convoluted tubules.[38]

Proposed mechanism for toxicity

The pathology of diclofenac toxicity in vultures has been extensively described. All vultures show extensive visceral gout and renal microscopic lesions at necropsy and necrosis of proximal convoluted tubules compatible with the formation of microcrystals.[23,39] The lethal dose 50 is approximately 0.1 mg/kg to 0.2 mg/kg.[22,29] As stated before, it has been concluded that the tissues of cattle treated with diclofenac are a hazard to wild vultures that feed on an animal that dies within a few days after treatment. The intestine, kidney, and liver have the highest diclofenac concentrations, but the concentration averaged across all the edible tissues of the carcass is also hazardous to this species.[40,41] In contrast, the mechanism by which the referred toxicity occurs has not been fully characterized. It has been postulated that toxicity could be related to the unique avian renal vascular structure known as the renal portal valve and that diclofenac altered valve functionality with subsequent renal ischemia.[7,42] The vulture's vasculature was almost identical to that of the domestic chicken, with the valva *renalis portalis* present in the *iliaca externa* vein between the *renalis renalis cranialis* and the *renalis caudalus* veins. The valve is ring-shaped with finger-like processes and is histologically composed of smooth muscle. Hence, the proposed mechanism of toxicity was anatomically possible.[42] Supporting the crucial role of these valves, other authors have proposed that the toxicity caused by diclofenac at the kidney level is caused by inhibiting the modulating effect of prostaglandin on angiotensin II-mediated adrenergic stimulation. Renal portal valves open in response to adrenergic stimulation, redirecting portal blood to the caudal vena cava and bypassing the kidney. Prostaglandins modulate this phenomenon. If diclofenac interferes with the modulating action of prostaglandins on

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the renal portal valves, their over-activation redirects blood supply away from the renal cortex, causing severe ischemic necrosis.[43] That is, diclofenac alters both renal perfusion and renal plasma flow, with death associated with tubular secretion being reduced to negligible functionality for a prolonged period.[44] This is supported by histopathological studies demonstrating tubular necrosis, urate deposits in cortical tubules of kidneys, and no in the kidney's medulla. Also, some urate tophi were seen in various parenchymatous organs. In all cases, mild to moderate degenerative changes manifest in the kidneys and liver, indicating obstructive nephropathy as the cause of visceral gout observed.[45] Nevertheless, other researchers claim that a decreased uric acid excretion better explains diclofenac toxicity in *Gyps* vulture, together with a duration of this effect added to increased production of reactive oxygen species and not so much to renal portal vasoconstriction,[23] and also due to a deficient phase 1 cytochrome P450 – dependent metabolism of vultures.[40] In any case, a specific physiological pathway is being inhibited, which may depend on biphasic concentrations instead of only metabolic capacity.[10] In either case, toxicity is always consistent. Nevertheless, the differential sensitivity of European Eastern or African vultures compared to the turkey vulture of America (*Cathartes aura*) suggests a much lesser susceptibility to toxicity due to diclofenac in the latter.[46] However, the authors recognize that additional studies seem warranted.

Diclofenac is widely used as an analgesic, antiarthritic, and antirheumatic compound in human medical care. It is accepted that approximately 15 % of it is excreted unchanged via urine. Hence, it is expected to be a residue in the environment. In fact, it is one of the most frequently detected pharmaceuticals in urban wastewater. Under natural conditions, diclofenac decomposition in the environment is done through oxidative and reductive processes producing approximately 26 byproducts. It has been proposed that diclofenac and byproducts are toxic to vultures.[47]

Diclofenac has shown half-lives in vulture species that range from 10 to 22 h, with zero-order cumulative pharmacokinetics.[23,39]

State of the problem and proposals

Along with intensive livestock producers, Latin America is emerging as a major world supplier of livestock protein. However, Latin America has a sizable sector of extensive livestock production. In such cases, animals are reasonably free in the pastures, and under these conditions, a small farmer cannot isolate sick animals, and they remain in the open. If a fatality occurs, carcasses are susceptible to being consumed by vultures and other birds. Nevertheless, a knowledge gap exists for NSAID threats linked to American scavenger birds. However, no substantial differences in ecosystems or physiological features of potentially affected birds justify a different course of action. The ban on diclofenac in veterinary medicine should be imposed in Latin America.[48] Diclofenac toxicity toward vulture species has been referred to as the paradigmatic example of the adverse effects of an active principle.[49] Thus, this potential or real ecological disaster can be prevented or mitigated if the regional and hopefully worldwide ban on the manufacture and/or sale of veterinary diclofenac is enforced. Then, proven and safer NSAID derivatives may be allowed for livestock.[22] Veterinarians and producers should guaranty that fatal cases of animals treated with

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diclofenac should be adequately disposed of to prevent contact with scavenging birds. However, being realistic, this regulation is almost impossible to enforce in Latin America.[49] In contrast, the ban on veterinary diclofenac has proven to be an effective management tool for reversing vulture population declines.[50] Neither in the United States of America nor in Canada diclofenac-containing preparations have been approved, except the topical 2 % ointment for horses.[51] With some notable exceptions already commented upon in Europe, veterinary uses of diclofenac are greatly restricted.[52] Then, why is diclofenac allowed in various pharmaceutical forms for systemic effect in food-producing species in Latin America? Furthermore, Chinese companies can make diclofenac preparations available online on our continent. Mexico and most Latin American countries have signed the so-called Rio Principles for Sustainable Development in the 21st century.[53] According to this document, many actions are needed under the concepts of one planet living, i.e., to reduce our ecological debt, care for the living, and produce food in harmony with one's ecological surroundings in a sustainable manner. The Rio Declaration on Environment and Development specifies: "States shall enact effective environmental legislation. Environmental standards, management objectives, and priorities should reflect the environmental and developmental context to which they apply."[54] The authorities in Latin American countries are then urged to act without further delay to avoid or limit the ecological disaster that seems to be brewing by the use of diclofenac in veterinary medicine.

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Data availability

All relevant data are in the manuscript and its supporting information files.

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Conflicts of interest

The authors confirm that they do not have any conflicts of interest.

Author contributions

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