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The Availability of the Vulture toxic Non-steroidal anti-inflammatory Drugs in the proposed Vulture Safe Zone of Moyar Valley in Tamil Nadu state of India

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ABSTRACT

The three Gyps Vultures endemic to South Asia declined due to use of the veterinary non-steroidal anti-inflammatory drug diclofenac (NSAID). The drug diclofenac was banned in India for veterinary purposes from 2006. The drugs namely aceclofenac, carprofen, flunixin, ketoprofen and nimesulide are identified as toxic drugs for vultures. A total of 73 pharmacy shops in the year 2019 and 77 pharmacy shops in the year 2020 were surveyed in the vulture area covering three districts Coimbatore, Erode and The Nilgiris of Tamil Nadu. The aceclofenac, diclofenac, flunixin, meloxicam, nimesulide, phenylbutazone tolfenamic acid and ketoprofen were available on sale in the pharmacies in the proposed vulture safe zone of Tamil Nadu. The drug meloxicam was the most commonly encountered drug, sold in 69.6% (2019) and 71.8% (2020) in the pharmacy shops for veterinary usage. The availability of vulture toxic drugs is fast becoming popular in the vulture zones, particularly nimesulide 10.1% (2019) and 7.1% (2020) and the availability of recently announced another safest drug for vultures tolfenamic acid also available in the few pharmacy shops in the provisional vulture zone of Coimbatore, Erode and The Nilgiri district. Although the large number of manufacturers and availability of meloxicam is encouraging, the availability of wide range of untested NSAIDs in the proposed vulture zone of Tamil Nadu is a major source of concern. We recommend that banning of the identified vulture toxic NSAIDs drugs for veterinary usage in order to provide safety zone for vultures in Tamil Nadu.

Key words: Gyps Vulture, Decline, Conservation, Diclofenac, Meloxicam, Tamil Nadu

Introduction

Vulture species are threatened across the large area of India (Prakash *et al.*, 2012) and in most parts of the world (Oganda *et al.*, 2012). Major reason for vulture decline is the use of non-steroidal anti-inflammatory drug (NSAID) diclofenac on livestock (Oaks *et al.*, 2004; Green *et al.*, 2004). The drug diclofenac was banned in India for veterinary purposes from 2006

(Prakash *et al.*, 2007). The repeated road transects surveys of vultures across the much of former range have shown at least a slowing of declines since the recovery in the population of White-rumped vulture (Prakash *et al.*, 2017). Similarly, both the prevalence and the concentration of diclofenac in the cattle carcasses sampled throughout the same area declined between 2006 and 2009 (Cuthbert *et al.*, 2014a). Another harmful drug ketoprofen for vultures banned

for veterinary usage within the vultures foraging home range of Tamil Nadu in order to save a small population of vultures in southern India (Venkitachalam *et al.*, 2016). The NSAID drugs, such as aceclofenac, carprofen, flunixin, ketoprofen, nimesulide and phenylbutazone evidence to the toxicity for vultures and so far meloxicam the only safest drug for vultures (Prakash *et al.*, 2012). In addition, recently tolfenamic acid was identified as another safest drug for vulture (save-vultures.org). After diclofenac ban on its veterinary use in 2006 (India, Pakistan, Nepal) and 2010 (Bangladesh), residues of diclofenac have continued to be found in cattle carcasses and in dead vultures. The toxic drugs and banned diclofenac drug for vultures are also available in India for livestock treatment.

A detailed reconnaissance of non-steroidal anti-inflammatory open drug prevalence survey was carried out within the vulture foraging and breeding ranges of the vulture zone in Tamil Nadu (Map 1) to understand the availability of banned NSAIDs drug diclofenac, recently identified as vulture toxic drugs and the safest drug meloxicam availability in the pharmacy shops within 100 km radius of vulture zone in Tamil Nadu, India

Materials and Methods

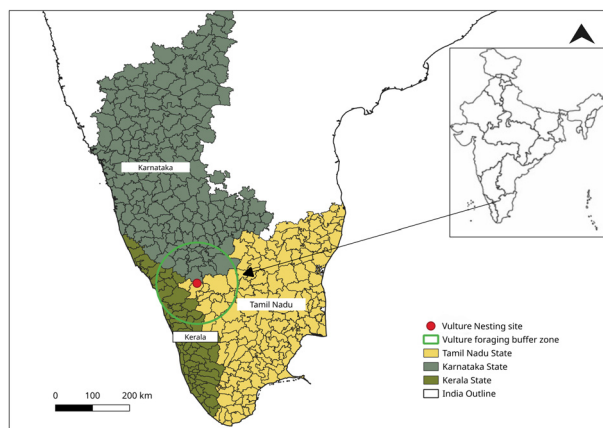
The repeated pharmacy surveys were carried out for two years 2019 and 2020 (January - December) in the pharmacy shops within 100 km radius of The Nilgiris, Coimbatore and Erode of Tamil Nadu. The field biologist and trained volunteers visited the pharmacies and also asked to buy NSAIDs for treating livestock. A standard questionnaire forms were used to get information on availability of different NSAIDs for treating livestock and geographical coordinates of each pharmacy, the date of the visit, pharmacy name and complete address of the shop and license number were recorded. Simultaneously, the details of the type of NSAID, number of brands, if the drugs were an injectable or bolus (oral tablet) form, manufacturing date and price also recorded. The shopkeepers were questioned on whether they were aware of the ban on banned diclofenac drug for veterinary purpose and recently identified vulture killer NSAIDs and its role in the vulture decline. The different teams gathered information on the NSAIDs by visiting same pharmacies shops during 2019 and 2020 subsequent years.

Statistical Analysis

Basic statistics *viz.* arithmetic mean, standard deviation and standard error were calculated for all the replicative variables and are given as $X \pm SD$ or $X \pm SE$. Statistical analyses were performed by using Windows based statistical package *viz.* Microsoft Excel, MINITAB (Ryan *et al.*, 1992) and SPSS (Statistical Package for Social Science: Nie *et al.*, 1975). The significance of the Pearson correlation coefficient was tested using t test. The non-parametric test used was Chi-square test for testing the association between variables. For hypothesis testing $P < 0.05$ and $P < 0.01$ were considered and these levels of significance are indicated as appropriate. Although chi-square results are given in many tables and graphs where the data were used in percentage, the analyses were done only on frequencies.

Results and Discussion

In total 12873.69 km² area falls within the provisional vulture safe zone of Tamil Nadu (Map 1). A total of 73 pharmacy shops in 2019 and 77 pharmacy shops in 2020 were surveyed within 100 km radius. The vulture toxic drugs meloxicam, nimesulide accounted for the majority of NSAID sold, the remainder of six other drugs; ketoprofen, flunixin, aceclofenac, phenylbutazone, carprofen and diclofenac (Table 2), paracetamol was most frequently combined with both injectable and bolus forms of meloxicam and with bolus forms of nimesulide and diclofenac (Table 1). There were significant reductions in the proportion of NSAID sold that were identified as toxic drugs for vultures



Map 1. Map showing the potential vulture foraging areas of Tamil Nadu, Kerala and Karnataka.

(< 5%) between 2019 and 2020 (Fig. 1, Table 2). The proportions of diclofenac and ketoprofen (banned in 2015 in three districts namely The Nilgiris, Coimbatore and Erode of Tamil Nadu) significantly dropped to < 2% (n=2) after the ban (Fig. 1). The meloxicam was the most commonly offered drug overall during the survey and a significant increases in proportions of visits in the pVSZ of Tamil Nadu (Table 2). The meloxicam sold in 15 different trade names such as Doloban plus vet, Intas, Martin, Proxyvet mp, Pyridase Bolus, Ailanto My-Bio-science, Bluemelox-p, Coxpara, Melotop-p-vet, Le-Mantus, Vet mankind, Limagesic-P, Lemonte, Zentek, Vetoquinol, Melozine-P, Metaflam, Meloxicam Plus. The Nimesulide had the second highest sales in the proposed vulture zone of TamilNadu (Table 2) and available in different trade names are Vet mankind, Cipla, ABAD 55, Doloban Plus Vet, Pyridase, Cargill. The phenylbutazones also available in different trade names are Zydus and Cargill. The drugs aceclofenac available in trade

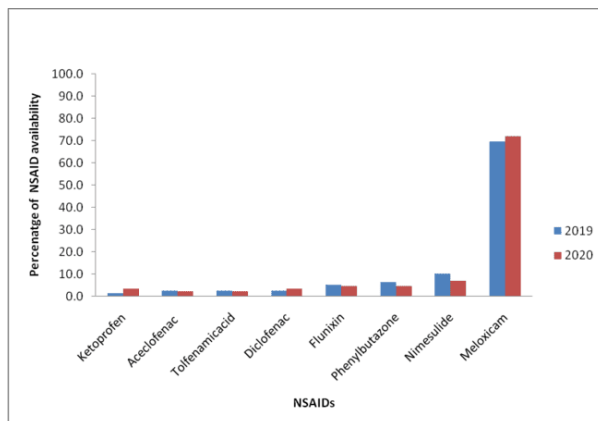


Fig. 1. Prevalence of eight NSAIDs in the vulture zone of Tamil Nadu

name of Afenak-100, Acimol-SR, and the trade name of ketoprofen are Zydus AIT; the trade name of diclofenac is Ranbaxy and Tolfenamic acid also available in the trade name of Maxxtol and Tolfine.

Availability of diclofenac and other NSAIDs

A major concern arising from this study is the widespread availability of recently identified toxic drugs for sale for veterinary use in the vulture zones of Moyar Valley in Tamil Nadu. While national legislation has been effective at removing most veterinary formulations of diclofenac from the country, the ban on diclofenac is being circumvented through the sale of forms. A systematic open non-steroidal anti-inflammatory vulture survey was carried out for the first time between 2019 and 2020 in the three districts namely Coimbatore, Erode and The Nilgiris and these districts. We recorded the harmful drugs for vultures namely diclofenac, nimesulide, ketoprofen, flunixin, aceclofenac, phenylbutazone, meloxicam and importantly banned drug for veterinary usage diclofenac on sale these districts and indicating that despite national legislation to ban the veterinary use of diclofenac the drug remains available for sale.

While illegal selling of banned diclofenac is of major concern, there is no evidence that any compounds were mislabelled by manufacturers and all NSAIDs purchased were manufactured in India and labelled in English with appropriate detail on the concentration of active ingredients and date of manufacture. Recently, 100 cases were registered against suppliers, distributors, manufacturers and retailers of diclofenac (save-vultures.org). The ketoprofen is the proved to be another toxic drug to vultures and found in livestock carcasses in India

Table 1. Number of brands of Bolus and Injectable Formulations of NSAIDs and the combined total from the survey in the Proposed Vulture Safe Zone between 2019 and 2020.

Active ingredient	Injectable	Bolus	Total
Aceclofenac		2	2
Diclofenac	1	1 (1)	2 (1)
Flunixin	4		4
Meloxicam	16 (5)	35 (32)	51 (37)
Nimesulide		8 (7)	8(7)
Phenylbutazone	5		5
Tolfenamicacid	1	1	2
Ketoprofen	1		1
Total with paracetamol as secondary compound	5	40	45

Number in parenthesis indicates the number of brands in which paracetamol was a secondary active ingredient.

Table 2. Percentage of (all NSAIDs stocked) of eight available for use on cattle, during open surveys of pharmacies in the proposed pVSZ in Tamil Nadu between 2019 and 2020.

Formulations	2019		2020	
	Bolus	Injectable	Bolus	Injectable
Aceclofenac	3.9	-	1.8	3.6
Diclofenac	2.0	3.6	3.5	3.6
Flunixin	-	14.3	0.0	14.3
Meloxicam	76.5	57.1	77.2	60.7
Nimesulide	15.7	-	10.5	-
Phenylbutazone	-	17.9	-	14.3
Tolfenamic Acid	2.0	3.6	1.8	3.6
Ketoprofen	-	3.6	5.3	-
	$\chi^2_T = 14.067$ P < 0.05		$\chi^2_T = 14.067$ P < 0.05	

(Naidoo *et al.*, 2010; Taggart *et al.*, 2007). The flunixin, which may be toxic to scavenging birds (Cuthbert *et al.*, 2015), was recorded in the pharmacies. Nothing is known of the safety or toxicity of phenylbutazone despite the widespread availability of these NSAIDs in pharmacies. The safety or toxicity of paracetamol (acetaminophen) to vultures and other scavenging birds is unknown but this compound is frequently used in combination in other drugs, both injectable and bolus formulation in meloxicam in the veterinary pharmaceuticals.

The rise of meloxicam

Meloxicam is the only safest NSAID that has been shown through safety testing (Swarup *et al.*, 2007) to be non-toxic to Gyps vultures at doses they are likely to be exposed to in the wild. In Tamil Nadu, although the availability of meloxicam was increased within the three districts namely Coimbatore, The Nilgiris and Erode. The meloxicam was rarely the most common NSAID sold.

The appearance of new NSAIDs

There are many other NSAIDs that are widely available with different brand names, some which are known to be toxic for vultures, the most prevalent being nimesulide and ketoprofen. With the decline of the once-ubiquitous diclofenac, there are now gaps in the market that pharmaceutical companies are keen to fill with alternatives. Availability of the nimesulide now increased in the pharmacy shops in the vulture zone. The aceclofenac, flunixin and phenylbutazone, usually at low prevalence, but including several known or suspected to be toxic to vultures. These drugs are available in both injectable and bolus forms. Several formulations are already available, so it could become a major veterinary

drug in the future. The recently identified one more safest and nontoxic drug for vulture tolfenamic acid which is used for livestock treatment particularly in the vulture safe zone of TamilNadu. The recent finding addition of the alternative drug may strengthen the vulture conservation of vultures in India. Number of brands of bolus and injectable formulations of NSAIDs and the combined total from the survey in the proposed vulture safe zone between 2019 and 2020.

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Conflict of Interest

The authors declare no competing interests.

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