SHORT COMMUNICATIONS

J. Raptor Res. 50(2):207–210

POTENTIAL TOXICITY OF FENBENDAZOLE TO *GYPS* VULTURES ON THE INDIAN SUBCONTINENT: A REVIEW

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KEY WORDS: *White-rumped Vulture*; Gyps bengalensis; *White-backed Vulture*; Gyps africanus; *fenbendazole*; *Indian subcontinent*; *toxicity*; *vultures*.

Fenbendazole is an antihelminthic compound belonging to the benzimidazole class that is commonly used both for treatment and prophylaxis of various species of nematode, trematode, cestode, and a few protozoan endoparasites in livestock (Bowman 1995). Fenbendazole is one of the most widespread and common antiparasitic agents used in veterinary medicine due to its efficacy, broad spectrum, and ease of oral administration. Fenbendazole is a tasteless compound and does not affect palatability of feed, and is therefore suited to oral administration.

Fenbendazole acts by binding to β-tubulins of nematode cells, thereby interfering in dimerization of β-tubulins to α-tubulins. This consequently inhibits polymerization of tubulins into microtubules, which are required for protein synthesis and various metabolic processes (Martin 1997) including cell division. Interruption of these processes arrests normal biochemical and physiological functioning of cells of parasites, resulting in death. The drug is considered safe in livestock and other mammalian species because of its selective inhibition of β-tubulins of nematode cells over mammalian β-tubulins (Friedman and Platzer 1980, Reinemeyer and Courtney 2001). However, marked bone marrow suppression and adverse effects on gut mucosa were also reported in some mammalian species (Gary et al. 2004, Weber et al. 2006).

The Long-billed Vulture (*Gyps indicus*), White-rumped Vulture (*G. bengalensis*) and Slender-billed Vulture (*G. tenuirostris*) are endemic to the Indian subcontinent, and are critically endangered due to toxicity caused by residual diclofenac in carcasses of various species of livestock, which were treated by diclofenac prior to their death (Oaks et al. 2004, Swan et al. 2006). Remaining populations are extremely small and fragmented and these vultures remain vulnerable to diclofenac-induced mortalities (Taggart et al. 2007). A survey of the literature revealed fenbendazole toxicity in many species of domesticated, as well as wild, birds. Residue of fenbendazole in carcasses of livestock could be ingested by *Gyps* vultures, as diclofenac was. Considering the dwindling population of *Gyps* vultures and the proven toxicity of diclofenac through livestock carcasses, I here provide a brief review of potential toxicity of fenbendazole to *Gyps* vultures.

TOXICITY IN BIRDS

Fenbendazole was initially found to be safe with respect to effects on various avian species (Kirsch 1983, Santiago et al. 1985). More recently, however, studies have documented fenbendazole toxicity episodes causing mortalities in different domestic as well as wild species (Taylor et al. 1983, Pedersoli et al. 1989, Latimer 1994, Rivera et al. 2000, Wiley et al. 2009). No empirical data are available in the literature on the extent of selective binding of fenbendazole to parasitic β-tubulin over avian β-tubulin, which raises concerns about the safety of fenbendazole use in avian species (Howard et al. 2002). Results of multiple studies have suggested that metabolism of fenbendazole varied across avian species and differed relative to fenbendazole metabolism in mammals (Short et al. 1988, Howard et al. 2002). Consequently, there is uncertainty about the safety profile of fenbendazole, as it appears that some avian species are more susceptible to fenbendazole toxicity than others.

In terms of pathological findings, leukopenia resulting from bone-marrow hypoplasia and intestinal crypt cell necrosis was common in the multiple toxicity episodes caused by fenbendazole in phylogenetically distinct species of birds. These species included pigeons and doves (Howard et al. 2002, Gozalo et al. 2006), Painted Storks (*Mycteria leucocephala*; Weber et al. 2002), and more specifically African White-backed Vultures (*G. africanus*), Lappet-faced Vultures (*Torgos tracheliotus*), and Marabous (*Leptoptilos crumenifer*; Bonar et al. 2003). The similarity of pathological lesions in different avian species suggests the underlying mechanisms of fenbendazole toxicity in some birds could be similar in that it involves bone marrow and intestinal crypts, both of which have cells that undergo

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rapid multiplication by cell division (mitosis), indicating that the toxic effects could be associated with the pronounced inhibitory effect of fenbendazole, or its metabolites, on avian β-tubulins.

PHARMACOKINETICS OF FENBENDAZOLE IN BOVINES AND VULTURES

Fenbendazole is used orally as an antiparasitic agent in animals with internal helminthic infestations and, more importantly, in prophylaxis as well, which extends its use to healthy animals. Use of antiparasitic agents, such as fenbendazole, is fairly common in modern dairy, meat, and poultry farming. The use of fenbendazole in veterinary institutions, and its availability in pharmacies without a prescription contribute to its widespread use. Furthermore, febantel, another antihelmintic of the benzimidazole class, is biotransformed into fenbendazole inside the body by metabolic processes (McKellar and Scott 1990).

Vultures mostly feed on carcasses of domestic animals on the Indian subcontinent (Pain et al. 2008). Residual availability of fenbendazole in carcasses of cattle and buffalo depends on pharmacokinetic parameters of fenbendazole in these species. T_{max} is defined as time taken by a drug to achieve maximum concentration in blood serum after administration. Mean T_{max} values of fenbendazole and its metabolites were in the range of 30–36 hr in cattle and 18–38 hr in buffalo after a single standard dosing of 7.5 mg/kg body weight, and fenbendazole and its metabolites could be detected up to 120 hr post-dosing (Sanyal 2011); residues of diclofenac in cattle were detectable up to 71 hr post-dosing (Taggart et al. 2007). Comparison of pharmacokinetics of fenbendazole and diclofenac reveals relatively higher temporal persistence of fenbendazole and its metabolites in livestock after administration, increasing the probability of ingestion by vultures, compared to diclofenac, which has been proven to be toxic to *Gyps* vultures. It is evident based on these factors that vultures are likely to ingest varying amounts of residual fenbendazole in livestock carcasses on a regular basis. Dosing of fenbendazole in a range of 47–60 mg/kg resulted in toxicity in Lappet-faced Vultures and White-backed Vultures (Bonar et al. 2003). Because of the absence of quantitative information on the lethal dose (LD_{50}) of fenbendazole for *Gyps* vultures, I urge investigation of the concentration of residual fenbendazole in livestock carcasses lethal to *Gyps* vultures.

POTENTIAL TOXICITY IN *GYPS* VULTURES

White-backed Vultures are phylogenetically similar to White-rumped Vultures, and this similarity suggests that other or perhaps all *Gyps* vultures could be similarly susceptible to diclofenac toxicity based on their phylogenetic relationships and previously observed toxicity in four species of *Gyps* vultures (Johnson et al. 2006, Naidoo et al. 2009b). Toxicity testing *in vivo* of diclofenac in White-backed Vultures and White-rumped Vultures resulted in similar increased and lethal levels of uric acid in blood of the two species; increased uric acid led to visceral gout and subsequent death in affected vultures post-diclofenac dosing (Swan et al. 2006). Further, *in vivo* diclofenac toxicity trials in Cape Griffons (*G. coprotheres*) revealed that toxicity was similar to that observed in three species of *Gyps* vultures from the Indian subcontinent (Oaks et al. 2004). Also, ketoprofen had toxic effects in White-backed Vultures and Cape Griffons (Naidoo et al. 2009a), highlighting the metabolic similarities and possible susceptibility to certain compounds within the *Gyps* genus. Moreover, similar toxicity of fenbendazole in White-backed Vultures and Lappet-faced Vultures (*Torgos tracheliotus*; Bonar et al. 2003), which belong to different genera, suggests that other vultures, apart from the *Gyps* genus, may be susceptible to fenbendazole toxicity. Metabolic processes and pathological lesions involved in fenbendazole toxicity are different from those of diclofenac, yet metabolic similarities and phylogenetic relationships among species in the *Gyps* genus suggest that fenbendazole toxicity observed in White-backed Vultures may be of concern across the *Gyps* genus.

Vultures are obligate scavengers, and they have a robust immune system, which facilitates carcass-feeding by providing protection from various infective and pathological microbes. Fenbendazole induces intestinal cell necrosis, which can facilitate entry of intestinal bacteria into systematic circulation (Howard et al. 2002). Concomitant immuno-suppression due to leukopenia significantly reduces the defense mechanisms of the body, and lesions mutually supplement and predispose septicaemia, which increases the probability of mortality. Prolonged ingestion of residual fenbendazole in livestock carcasses below a toxic level may also adversely affect *Gyps* vultures in unknown ways. Furthermore, as three species of *Gyps* vultures are critically endangered, any pharmacological agent with potential toxicity to these vultures should be evaluated comprehensively to minimize risk to critically endangered White-rumped Vulture, Long-billed Vulture, and Slender-billed Vulture and possibly other vultures on the Indian subcontinent.

TOXICIDAD POTENCIAL DEL FENBENDAZOL PARA BUITRES DEL GÉNERO *GYPS* EN EL SUBCONTINENTE INDIO: UNA REVISIÓN

RESUMEN.—El fenbendazol es un compuesto antihelmíntico de amplio espectro utilizado con fines profilácticos y terapéuticos en medicina veterinaria. El fenbendazol actúa por inhibición selectiva de las β-tubulinas en las células helmínticas sobre las β-tubulinas de los mamíferos. El alcance de la unión selectiva del fenbendazol sobre las β-tubulinas de las aves no se conoce, poniendo en duda su seguridad en esta clase. Evidencia reciente sugiere que el fenbendazol podría ser tóxico para varias especies de aves incluyendo a *Gyps africanus*, cercano filogenéticamente a otras especies del género *Gyps* que se encuentran en peligro crítico en el subcontinente indio. Pruebas de toxicidad de diclofenaco y ketoprofeno, ambos compuestos analgésicos utilizados

en medicina veterinaria y para los cuales se probó la toxicidad en buitres del género *Gyps* en sus formas residuales en cadáveres de ganado, revelaron notables similitudes metabólicas para diferentes especies del género *Gyps*. El fenbendazol residual, al igual que el diclofenaco y el ketoprofeno, podría ser tóxico para los buitres del género *Gyps*, en base a la toxicidad mostrada en *G. africanus*, así como en base a las similitudes metabólicas y filogenéticas a lo largo del género *Gyps*. Además, las correlaciones de los hallazgos patológicos de la toxicidad del fenbendazol con sus propiedades farmacológicas y farmacocinéticas sugieren que este compuesto puede ser tóxico para los buitres, lo que debería dar lugar a pruebas para evaluar su toxicidad.

[Traducción del equipo editorial]

ACKNOWLEDGMENTS

I thank K.S. Gopisundar and A.M. Goswami for their assistance with the literature. Two anonymous reviewers provided comments that improved an earlier version of this report.

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Received 14 June 2015; accepted 14 December 2015
Associate Editor: Joseph B. Buchanan