

Treatment of Joint Inflammatory Diseases in the Lamé Backyard Chickens with NSAIDs

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Abstract: The effects of several Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) were determined in 200 mature backyard chickens with clinical signs of lameness. The NSAIDs, diclofenac, carprofen, ketoprofen and meloxicam with doses 0.5, 1, 2, 3 and 4 mg/kg were used in these groups, orally. Chickens were monitored on a daily basis for general condition, joint inflammation reduction and mortality. Diclofenac, carprofen and ketoprofen were associated with mortality. In contrast, there were no reported mortalities for the NSAID, meloxicam in this study. Results of the current study revealed that the meloxicam was the drug of choice with relative safety for treatment of joint inflammatory diseases in chickens.

Key words: Backyard chickens, inflammation, joint, NSAIDs

INTRODUCTION

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are commonly used for the diagnosis and treatment of inflammatory musculoskeletal disease in both humans and animals (Hocking *et al.*, 2005). NSAIDs act by inhibiting cyclo-oxygenase activity and thereby reducing the synthesis of prostaglandins but information on their effectiveness and optimum dose in avian species is limited (Hocking *et al.*, 2005). Both sodium salicylate and acetaminophen have anti-nociceptive properties in pigeons in the same order of magnitude as that seen in some mammalian species (Brune *et al.*, 1974). Indomethacin has been shown to have anti-inflammatory effects in the chicken (Ito and Bohn, 1986) and antinociceptive effects in pigeons (Benzi *et al.*, 1966). The propionic acid class of NSAIDs include carprofen and ketoprofen and have been used in bird species for analgesia (McGeowm *et al.*, 2000). Ketoprofen is most commonly prescribed for musculoskeletal pain from soft-tissue injury, osteoarthritis or other bone and joint problems (Naidoo *et al.*, 2010b). Carprofen, has been shown to affect the walking ability of lame broiler chickens (McGeowm *et al.*, 2000) and lame birds selected this drug preferentially in a feed-choice experiment (Danbury *et al.*, 2000). Diclofenac is an important non-steroidal anti-inflammatory drug (NSAID) in human medicine and is commonly used in the management of pain and inflammation associated with the joints (Naidoo *et al.*, 2010a). In South Asia, diclofenac is also used in veterinary medicine as an analgesic, anti-pyretic and anti-inflammatory drug in cattle. Whilst the drug is

probably as effective as many other available NSAIDs (such as ketoprofen, meloxicam, flunixin, carprofen), diclofenac has been very commonly used across the Asian sub-continent due to its widespread availability and cheap price (Naidoo *et al.*, 2010a). Meloxicam is also a COX-2 inhibitor NSAID and belongs to the oxacam group. Meloxicam is used to reduce the inflammation and pain of joint diseases and muscle injuries in birds. Safety testing has established that the NSAID meloxicam is an effective and vulture safe alternative to diclofenac (Swan *et al.*, 2006). Information on their effectiveness and optimum dose of NSAIDs in avian species is limited and we conducted a experiments to evaluate NSAIDs such as diclofenac, carprofen, ketoprofen and meloxicam for their effectiveness and optimum dose for treatment of joint inflammation and articular pain in the backyard chickens with clinical signs of lameness.

MATERIALS AND METHODS

Experimental design: Two-hundred mature backyard chickens with clinical signs of lameness (one-legged standing, limping and resting) were obtained from a backyard flocks with history of naturally articular pain between July 2010 to November 2010. They were equally divided in 5 treatment groups, with 20 birds in each group. Each treatment group had one control with 20 chickens in it. All treatment and control groups were placed in the same test environment, in the animal house of veterinary research laboratory and were fed ad libitum. Water was freely available at all times. The drugs selected for this experiment were, diclofenac (0.15 mg/mL, oral

suspension, Razi drug company, Iran), carprofen (2.5 mg/mL, oral suspension, Razi drug company, Iran), ketoprofen (5 mg/mL, oral suspension, Razi drug company, Iran) and meloxicam (0.2 mg/mL, oral suspension, Razi drug company, Iran) at a dose rate of 0.5, 1, 2, 3 and 4 mg/kg PO twice daily in drinking water was given for 5 days and then maintained once daily for the next 10 days. Drinking water free from any drugs was used in control groups. All chickens were monitored on a daily basis for general condition, joint inflammation reduction and mortality. The behaviour of the birds was recorded for maximum 15 days. The birds were observed for 1 h behind a one-way screen by an observer who was not aware of the treatment of the bird.

RESULTS AND DISCUSSION

All chickens treated with 0.5-4 mg/kg of diclofenac, carprofen and ketoprofen survived and showed no symptoms of toxicity or mortality after initial 5 days treatment, but at the dose of 3-4 mg/kg of mentioned drugs in days 7, 10 and 11 post-treatment, 25, 15 and 5% mortality in backyard chickens were seen. Diclofenac, carprofen and ketoprofen affected some aspects of behaviour at the 2mg/kg dose and the responses were similar at this dose. These drugs should be used for treatment of joint inflammation and lameness for short periods with low doses. Ketoprofen increased grooming activity. Birds treated with diclofenac and carprofen spent less time standing and tended to spend more time resting whereas ketoprofen and meloxicam tended to produce the opposite effect. The minimum effective dose for diclofenac, carprofen, ketoprofen and meloxicam with obvious behavioural change in lame chickens was 3, 2, 2 and 0.5 mg/kg, respectively. At these doses, diclofenac, carprofen, ketoprofen and meloxicam have similar effects on birds' behaviour with satisfactory results after 5, 4, 3 and 3 days, respectively. Meloxicam at all doses has good effects on pain-related behaviour in the backyard chickens without any symptoms of toxicity or mortality until the end of the behavioural observation period. The survey also highlights the relative safety of meloxicam for treatment of joint inflammation, lameness and pain relief in backyard chickens. According to the results of this study, meloxicam was the drug of choice for treatment of inflammatory conditions such as lameness and articular pain in backyard chickens with minimum side effects. Meloxicam with low doses and in short period of time has the best effects on pain relief in the lame backyard chickens, but it is more expensive than other three NSAIDs. For this reason, although meloxicam is now used in South Asia and the manufacture and sale of veterinary diclofenac has been banned, meloxicam remains more expensive and human formulations of diclofenac are being used to treat livestock (Naidoo *et al.*, 2010b). Whilst the drug is probably as

effective as many other available NSAIDs (such as ketoprofen, meloxicam, flunixin, carprofen), diclofenac has been very commonly used across the Asian sub-continent due to its widespread availability and cheap price (Oaks *et al.*, 2004; Swan *et al.*, 2006).

Unfortunately, this widespread use is now acknowledged to have led to what may be described as one of the worst environmental catastrophes in the twenty-first century: the complete devastation of resident Gyps vulture populations across the Asian subcontinent (Oaks *et al.*, 2004), so meloxicam remains the only NSAID where both safety testing and clinical data demonstrate convincing safety to Gyps vultures and a wider range of avian scavengers (Cuthbert *et al.*, 2007; Swan *et al.*, 2006; Naidoo *et al.*, 2010b). To date, the once ubiquitous Oriental white-backed vulture (*Gyps bengalensis*) population, which used to number tens-of-millions of birds, has declined by a staggering 99.9% in about 15 years as the result of their exposure to diclofenac residues in the cattle carcasses (Green *et al.*, 2007; Prakash *et al.*, 2007). Further, controlled toxicity studies have now shown that diclofenac is also toxic to three other Gyps vulture species, as well as the domestic chicken (*Gallus gallus*), although at a higher dose for the latter (Swan *et al.*, 2006; Naidoo *et al.*, 2007, 2009). Experiments show that they die from kidney failure within days of exposure and have extensive visceral gout at post-mortem (Oaks *et al.*, 2004; Swan *et al.*, 2006). In the survey for understanding the toxicity of non-steroidal anti-inflammatory drugs to Gyps vultures, all vultures treated with 0.5-1.4 mg/kg of ketoprofen and sham-dosed birds survived and showed no symptoms of toxicity or detectable abnormalities in blood parameters. However, one of the two experimental birds dosed with 1.5 mg/kg died, as did 7 of the 11 birds dosed with 5 mg/kg (Naidoo *et al.*, 2010b).

This has been demonstrated clinically in male Eider ducks where ketoprofen has been reported to be lethal (Mulcahy *et al.*, 2003). Whilst the mechanism behind ketoprofen's toxicity in ducks is unknown, it is plausible that ketoprofen toxicity is due to oxidative damage to the renal tubular epithelial cells (Naidoo *et al.*, 2010a). Similar findings (gout and/or kidney damage) were also recorded in mortality cases reported in raptors following treatment with the NSAIDs flunixin and carprofen (Cuthbert *et al.*, 2007). This suggests that a common mechanism of toxicity may be responsible for NSAID-related mortality across different orders of birds. Deficiencies in the CYP450 system in Gyps may also explain the toxicity we observe for ketoprofen and diclofenac, as this would allow the accumulation of the primary drugs, which are known to induce free radical cellular damage via the inhibition of the COX pathway or via other mechanisms (Mahmud *et al.*, 1996; Galati *et al.*, 2002). Nephropathy is a common adverse effect of NSAID and necropsy reports of Siberian

Crane given flunixin meglumine (5 mg/kg) demonstrated renal ischemia and necrosis (Paul-Murphy and Ludders, 2001). In a study using the Bobwhite quail given flunixin for 7 days there was histological evidence of renal damage at doses as low as 0.1 mg/kg (Hocking *et al.*, 2005).

From pharmacokinetic studies (Baert and De Backer, 2003) the half-life of flunixin in the chicken was ten times as long as in other birds studied (ostrich, duck, turkey and pigeon). The optimum doses of carprofen, flunixin, ketoprofen and sodium salicylate for the treatment of inflammatory pain in domestic fowl using the microcrystalline sodium urate model of articular pain, were determined 30, 3, 12, and 100-200 mg/kg, respectively (Hocking *et al.*, 2005). Carprofen and flunixin meglumine were associated with mortality of Gyps vultures and other species, with a reported mortality of 13 and 30%, respectively. Two instances of mortality with renal disease and gout are reported for ibuprofen and phenylbutazone (Cuthbert *et al.*, 2007). There were no mortalities following treatment with meloxicam. For Gyps vultures, 39 individuals from six species have been treated and a minimum of 700 birds from 54 other raptors and scavenging species were given meloxicam. Meloxicam doses ranged from 0.1 to 0.75 mg/kg bw, with a median dose of 0.5 mg/kg. Meloxicam was administered by intramuscular injection (57% of treatments), orally (32%) or through a combination of one intramuscular injection followed by oral dosing (11%). Treatment ranged from 1 to 120 days (median 5 days) (Cuthbert *et al.*, 2007).

CONCLUSION

Avian species vary in their responses and pharmacokinetics to NSAIDs (Baert and De Backer, 2003; Baert *et al.*, 2002) and different disease states may also affect the relative effectiveness of the recommended doses. Although, less information is available on the safety of NSAIDs in domestic backyard chickens (*Gallus gallus*), results of our study revealed that the meloxicam is better than the other NSAIDs for treatment of joint inflammatory disease, lameness and other pain related behaviour in backyard chickens with high marginal safety and minimum side effects.

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