Avian Analgesia
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Abstract
Avian pain is likely analogous to pain experienced by most mammals. Approach to pain management for the avian patient involves considering the duration, type, and extent of injury along with physical, environmental, and behavioral management. Invasive, painful procedures should always be accompanied by appropriate analgesia and anesthesia. Although pain management in birds is in its infancy, research and clinical studies demonstrate benefit for use of opioids, steroidal and nonsteroidal anti-inflammatory drugs, as well as other analgesics such as α2-agonists, ketamine, and local anesthetics. Ongoing assessment of pain and analgesic efficacy is extremely important, because the dosage and choice of analgesic may vary widely between species.

Key words: Analgesia; α2-agonists; ketamine; local anesthetics; nonsteroidal anti-inflammatory drugs; pain; preemptive; steroidal anti-inflammatory drugs; opioids

The recognition and appropriate treatment of pain in birds are difficult tasks for the practitioner. Although there are lists of analgesics and dosages available in the literature, there are only a few investigations that document the analgesic efficacy of these drugs. Birds represent the most abundant and diverse class of air-breathing vertebrates, consisting of approximately 9,700 species. Considerable variation in behavioral responses to pain occurs between species, breeds, strains, or individuals, and there is no reliable or universal indicator of pain.1 Also, birds do not indicate pain in an obvious manner because, as prey species, they are less likely to display overt pain-associated behavior that may attract the attention of predators.2 Recognition of pain and anxiety is critical to the appropriate selection of a pain-management strategy. Recognizing pain, treating it appropriately, and evaluating the efficacy of administered treatments can be one of the greatest challenges facing avian practitioners.

Birds possess the neurologic components that allow them to respond appropriately to a painful stimulus and have endogenous antinociceptive mechanisms to modulate pain. Treatment with pharmacologic agents used in mammals modulates pain pathways and behavioral responses to painful stimuli.1,3 Appropriate pain relief should always be provided, because lack of timely administration of analgesics can have a negative effect on homeostasis and healing.1,3 Birds should be treated for pain like any mammal when dealing with conditions that are known to be painful in humans.6 If the procedure or injury involves tissue damage and/or there are changes in posture (guarding), temperament (aggressive or passive), or normal behavior (that is, a decline in feeding or activity), the veterinarian should assume that the bird is experiencing pain.7

Analgesics decrease stimulation of ascending spinal pathways or activate endogenous descending
pain modulation pathways. Controlling pain not only involves drug administration but should also include physical, environmental, and behavioral management. Proper care and nonpharmacologic methods of analgesia include support or bandaging of the traumatized area, appropriate environmental modification with proper choice and location of perches, provision of appropriate bedding, food, water, and a dry, warm, quiet, stress-free environment. Reduction of fear and anxiety with anxiolytics, tranquilizers, and muscle relaxants can also reduce muscle tension and central nervous system (CNS) activity that may contribute to the experience of pain in birds.

### Approaches to Analgesic Therapy in Birds

#### Preemptive Analgesia

The provision of analgesia before injury can reduce the intensity of pain. Tissue injury can induce prolonged changes in CNS activity that later influence the responses to subsequent input, which contribute to postoperative pain. Nociceptive (pain) stimulation that reaches the spinal cord can produce a state of spinal neuron hyperexcitability known as central sensitization. In mammals, neural changes induced by nociceptive stimulation can be prevented by administration of analgesics before tissue insult. Once established, central sensitization can also reduce analgesic efficacy. Presumably, preemptive administration of analgesics reduces the magnitude of the pain experienced by an animal as a result of tissue damage. Thus, if at all possible, analgesia should be administered to patients before surgery. When injury occurs before surgical intervention, analgesia should be administered as soon as practically possible and maintained as long as the bird displays behavior that is indicative of pain.

#### Balanced Anesthesia

Balanced anesthesia refers to administration of several drugs to prevent more profound physiologic alterations associated with administration of larger doses of a single drug during or after anesthesia. A balanced approach to anesthetizing birds can minimize the adverse effects of any single drug. Balanced anesthesia techniques normally include preemptive administration of an analgesic. Administration of appropriate analgesics perioperatively reduces the required dose of inhaled anesthetics, which decreases the risk of a negative outcome. In chickens, μ and κ opioid agonists decrease the requirement for isoflurane in a dose-dependent manner. However, care should be taken when combining opioids with isoflurane because of the potential for respiratory depression.

Most birds are usually anesthetized solely with inhaled anesthetics, frequently isoflurane or sevoflurane. During anesthesia, the CNS is depressed sufficiently to prevent perception of pain, but this depression does not provide analgesia. In fact, all inhaled anesthetics can be hyperalgesic (produce extreme sensitivity to pain) at very low concentrations (that is, concentrations that would be obtained at some point during recovery from anesthesia) by enhancing C-fiber (unmyelinated pain fiber) activity. The sometimes violent recoveries from inhalant anesthesia that have been noted in birds may be due, in part, to hyperalgesia produced by low concentrations of inhaled anesthetics. Thus, provision of appropriate perioperative analgesia may improve recovery in avian species.

### Analgesic Selection

In mammals, opioids and α2-agonists are often chosen for acute pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat inflammatory, chronic pain. NSAIDs may also be used effectively for postoperative pain. The duration, severity, and type of injury and quality of pain will direct selection of an appropriate pain-management strategy.

#### Opioids

Opioid actions are mediated by specific membrane receptors that are distributed throughout the CNS and peripheral nervous system. The μ receptor is most commonly associated with analgesic therapy, but specific δ and κ agonists can also modulate nociceptive transmission at spinal and supraspinal sites. Opioids can be used effectively in birds, but the literature contains variable, and sometimes conflicting, reports. The clinical use of opioids in birds has been hindered by this lack of consistent, published information and concerns related to interspecies differences in response to opioids.

Differences in the response of animals to opioid analgesics may be related to the interspecies differences in opioid receptor populations. Unique distributions of opioid receptors in birds may account for differences in response to opioids between mammals and birds. In contrast to the population of opioid receptors in the mammalian nervous system, κ receptors predominate in the pigeon fore brain.
In mammals, µ and κ opioid agonists are often used to provide analgesia and CNS depression during anesthesia. The concurrent administration of opioid agonists during inhaled anesthesia reduces requirements for inhaled anesthesia. In the pigeon, the effect of µ and κ opioid receptor stimulation appears to be similar to that observed in mammals. Side effects such as sedation and respiratory depression can be readily reversed with naloxone or naltrexone, but this also terminates analgesia.

Early investigations of the analgesic efficacy of morphine in chickens demonstrated a significant effect after administration of 200 mg/kg. More recent investigations, using a toe-pinch model of pain assessment, demonstrate a significant analgesic effect at much lower dosages of 5 to 30 mg/kg. Interestingly, chickens can be trained to associate color with the presence of analgesics. Chickens (both healthy and lame) select food with the highest dose of morphine when given a choice of food containing 3 different doses of morphine (8.6, 49, and 430 mg/kg food). Chickens without lameness show an obvious preference for morphine, perhaps because of euphoric effect. Genetic factors play an important role in determining sensitivity to opioid analgesic effects. Morphine can produce either hypoalgesia or hyperalgesia during thermal and chemical nociceptive tests in chickens. Hyperalgesia is strain-dependent and naloxone-sensitive, and mediated primarily by µ receptor activation at CNS loci.

Buprenorphine is a partial agonist that binds readily to µ receptors and has some κ antagonist properties. As a partial agonist, it does not induce the same degree of effect as a full agonist, such as morphine, and is only effective for treating mild to moderate pain. Buprenorphine has been reported to be clinically effective in birds, but in African grey parrots, large doses produce no significant analgesic effect. Antinociception has been reported in other species after the administration of high doses of buprenorphine. In a recent investigation, buprenorphine (0.1 mg/kg intramuscularly) administered to African gray parrots failed to produce plasma concentrations that are associated with analgesia in humans.

Butorphanol is a weak µ receptor antagonist but a strong κ agonist. It is used commonly in small and large animal anesthesia for premedication and analgesia. In mammals, butorphanol produces analgesia in a dose-dependent manner with less respiratory depression than that produced by morphine. In parrots, administration of butorphanol (1 mg/kg) with isoflurane decreases the amount of isoflurane required to prevent response to a painful stimulus.

The reduction in isoflurane requirement is most profound in cockatoos (25% reduction), less so in African grey parrots (11% reduction), and not significant in blue-fronted Amazon parrots. However, reductions in isoflurane requirements may be indicative of sedation rather than analgesia. In halothane-anesthetized turkeys, administration of butorphanol (0.1 mg/kg) does not significantly reduce inhalant requirements during surgery. Butorphanol (0.1 mg/kg) increases the threshold of response to electrical stimulation in African gray parrots.

Fentanyl is a µ receptor agonist and is used in mammals to treat more severe pain. In white cockatoos, the administration of fentanyl (0.02 mg/kg intramuscularly) produces plasma concentrations for at least 2 hours that are considered to be analgesic in humans. However, no significant difference was found in analgesic response between birds given saline solution and those receiving fentanyl, which suggests differences between humans and birds in the plasma concentrations required to produce analgesia. Fentanyl (0.2 mg/kg) does produce significant analgesia in some birds, but administration of this large dose is not recommended because of the large injectate volume and excitement seen in some birds.

**Steroidal Anti-Inflammatory Drugs (Corticosteroids)**

Corticosteroids may reduce pain by suppressing inflammatory responses to tissue damage through reductions in fibroblast proliferation and macrophage response to migration inhibition factor, sensitization of lymphocytes, and responses to mediators of inflammation. The combination of a long-acting local anesthetic (for example, bupivacaine) and a corticosteroid has been shown to reduce postoperative discomfort in humans. Betamethasone is a powerful steroidal anti-inflammatory drug that reduces pain associated with degenerative hip disorders in adult male turkeys. Betamethazone decreases inflammation associated with sodium urate–induced synovitis in chickens, and betamethasone (0.04 mg/kg), dexamethasone (0.06 mg/kg), and methylprednisolone (2 mg/kg) all decrease pain-related behaviors.

Corticosteroids can alter responses to endogenous or parenterally administered opioids. In the rat, administration of a potent synthetic corticosteroid, dexamethasone, can reduce antinociceptive properties of µ agonists and potentiate antinociception of κ agonists. Administration of corticosteroids may therefore potentially reverse stress-induced analgesia (analgesia brought about by repeated stress-
ful or painful stimuli) by its antagonistic action at the μ receptor. Thus, caution should be used when considering administration of corticosteroids to birds either demonstrating, or presumed to be experiencing, high levels of stress. This, in combination with the risk of possible immunosuppression and other complications associated with corticosteroid administration, make NSAIDs preferable in many situations.

**NSAIDs**

Prostaglandins (PGs) are important local mediators of inflammation that are known to lower the threshold of activation of thermal, mechanical, and chemical nociceptors. NSAIDs control pain by inhibiting the cyclooxygenase enzyme, which prevents production of PGs. Drugs that inhibit PG biosynthesis in mammals produce analgesia by decreasing inflammation at the site of injury and also through transmitter mechanisms in the spinal cord. PGs are involved in modulation of avian responses to painful stimuli, and physiologic mechanisms involving PGs are similar to those described in mammalian models.

Orally administered NSAIDs in birds demonstrate a shorter half-life and lower bioavailability than in mammals. Unfortunately, pharmacokinetic data cannot be extrapolated between species, and pharmacokinetic studies of NSAIDs are poor predictors of analgesic efficacy. Plasma levels do not reflect physiologic or pharmacologic activity, particularly because NSAIDs are weak acids, highly protein bound, and tend to accumulate in areas of inflammation. The pharmacologic effects of the drugs can be used to gain information about how NSAIDs function within the animal. For example, NSAIDs block access to arachidonic acid to its binding site on the cyclooxygenase enzyme, thus preventing conversion of arachidonic acid to thromboxane B2 (TBX). Consequently, TBX may be used to estimate the length of NSAID action. In mallard ducks, flunixin meglumine (5 mg/kg) and ketoprofen (5 mg/kg) suppress TBX levels for up to 12 hours, suggesting that their physiologic action may be at least that long. Further investigations are required to adequately assess analgesia associated with these observations.

Preemptive use of NSAIDs may decrease nociceptor sensitization caused by surgical trauma and may reduce postoperative opioid requirements. NSAIDs can also be used effectively in the postoperative period in both birds and mammals. Both sodium salicylate and acetaminophen have analgesic properties in pigeons. Indomethacin has anti-inflammatory effects in the chicken and analgesic effects in pigeons. Unlike untreated birds, chickens undergoing a partial beak amputation given phenylbutazone topically are able to maintain their pretrimming feed intake levels over the first 24 hours after the procedure. Chickens given carprofen (1 mg/kg subcutaneously) demonstrate peak plasma concentrations 1 to 2 hours after injection and an elevated threshold of response to pressure for at least 90 minutes. Lame chickens preferentially select food with carprofen compared with food without analgesics, and the amount of carprofen consumed increases with the severity of lameness. Carprofen increases speed and walking ability of rapidly growing broiler chickens with chronic lameness. Carprofen (30 mg/kg), flunixin (5 mg/kg), and ketoprofen (12 mg/kg) all produce significant analgesia for sodium urate–induced synovitis in chickens.

Administration of ketoprofen (5 mg/kg) reduces increases in heart and respiratory rates associated with the application of a noxious stimulus in spontaneously breathing adult female mallard ducks anesthetized with isoflurane. In addition, mean time a noxious stimulus can be applied before gross purposeful movements are observed (up to a maximum of 5 seconds) is significantly longer when ducks are treated with ketoprofen. The administration of ketoprofen at a dose of 5 mg/kg to mallard ducks results in clinically detectable analgesia. NSAIDs are capable of producing gastrointestinal ulceration and bleeding because of inhibition of PG synthesis. Flunixin meglumine appears to produce more adverse effects in birds than other NSAIDs. Regurgitation and tenesmus have also been noted in budgerigars after administration of a high dosage of flunixin (10 mg/kg). Nephrotoxicity has been reported with the use of flunixin in northern bobwhite and in some mammalian species. Renal ischemia and necrosis have been documented in Siberian cranes, and anecdotal reports also suggest that the repetitive use of flunixin can cause lesions of renal gout in a variety of avian species. Muscular necrosis at the site of injection has been documented in mallard ducks and northern bobwhite.

A combination of bupivacaine and ketoprofen during propofol anesthesia results in increased mortality rates of male spectacled and king eiders. Deaths of the male eiders are likely due to ketoprofen-mediated renal damage. Male eiders may be more susceptible to the nephrotoxic effects of ketoprofen because of unique behavioral and physiologic characteristics. The potential interaction of the 3 drugs in male eiders is not clear. More recently, meloxicam (0.1 mg/kg) has been used in birds, but there are no published reports of...
its safety or efficacy as an analgesic. Interspecies variation in pharmacokinetics does not allow cross-species dose extrapolation. For example, the elimination half-life of meloxicam in dogs is 24 hours, compared with 4 hours in the minipig and 11 hours in the rat. Meloxicam (0.5 mg/kg) has a significantly shorter half-life of elimination in ostriches than in ducks, pigeons, and chickens. The half-life of the drug seems inversely proportional to the bird’s weight, with smaller birds needing longer dosing intervals and larger birds needing shorter dosing intervals. Although no adverse effects are reported after the administration of meloxicam (0.5 mg/kg), the analgesic efficacy of this dose in birds has not been established.

**Alpha2-Adrenergic Agonists**

Alpha2-agonists produce sedation, anxiolysis, analgesia, and a reduction in minimum alveolar concentration of inhalant anesthetics. Although α2-agonists such as xylazine or medetomidine can be useful as premedicants in a balanced anesthesia protocol, they are not usually administered to birds in the postoperative period because of undesirable side effects. They can produce muscle tremors, respiratory depression, and a sensitivity to auditory stimulation. Other disadvantages of α2-agonists include hypertension after intravenous bolus injections, hypotension, bradycardia with partial arterioventricular block, dose-dependent hypothermia, increased postoperative fluid requirements, and sedation. To ameliorate these negative side effects, α2-agonists are often administered in combination with other drugs, most commonly ketamine. Atipamezole is a highly potent, specific, competitive α2-antagonist that is active at both central and peripheral α2-adrenoceptors. The administration of atipamezole in the face of unwanted α2-agonist-mediated side effects will reverse these side effects, but analgesia is also reversed.

**Ketamine**

Ketamine is a dissociative anesthetic and is an N-methyl-D-aspartate glutamate receptor antagonist. Ketamine is often combined with sedatives such as α2-agonists and benzodiazepines for premedication or general anesthesia for minor procedures. Lower doses of ketamine can be useful for preemptive analgesia in major surgeries and also for postoperative analgesia, because it can enhance analgesia by preventing or abolishing N-methyl-D-aspartate receptor-mediated sensitization of nociceptive pathways in the CNS. Although ketamine prevents sharp, superficial pain effectively, it does not control visceral, dull pain, so ketamine alone is not adequate for laparotomies or orthopedic surgery.

**Local Anesthetics**

Local anesthetics (such as lidocaine and bupivacaine) function by blocking sodium ion channels that prevent the generation and conduction of nociceptive impulses. Local anesthesia before tissue trauma can reduce postoperative pain significantly, because it prevents nociceptor sensitization and reduces the CNS changes that occur as a result of activation of nociceptive pathways. Local nerve blockade before nerve transaction in amputation can decrease the incidence of “phantom limb” pain in humans. Chickens that receive topical bupivacaine on the beak stump after amputation are able to maintain their pretrimming feed intake levels during the first 4 hours after the procedure. In uric acid–induced synovitis in chickens, intra-articular bupivacaine (2 mg/kg) increases feeding, pecking, activity levels, and standing time.

The duration of action of local anesthetics in birds is unknown. In mammals, lidocaine is shorter acting (60-120 min) compared with bupivacaine (240-360 min). A pharmacokinetic study of a single dose (2 mg/kg) of bupivacaine in mallard ducks suggests that it may be shorter acting than in mammals.

Birds may be more sensitive to local anesthetics than mammals, because lower doses in birds (2.7-3.3 mg/kg) produce toxic effects compared with higher doses (3.5-4.5 mg/kg) in dogs. It is recommended that the dosage of lidocaine not exceed 4 mg/kg in birds, because seizures and cardiac arrest can be produced with overdose. Chickens show signs of toxicity (recumbency with outstretched legs, drowsiness, and distress immediately after injection) with the administration of higher doses of bupivacaine (2.7-3.3 mg/kg). Pharmocokinetic data suggest that rapid absorption of bupivacaine may, in part, be responsible for the apparent sensitivity of birds to the toxic effects of this local anesthetic. In addition, the appearance of high plasma concentrations of bupivacaine 6 to 12 hours after administration may also contribute to any observed sensitivity. However, other mechanisms may be involved, because the avian blood brain barrier is not as highly structured as that of mammals. This may allow for higher concentrations of local anesthetic in the brain. Local anesthetic toxicity may also be associated with ataxia, nystagmus, muscle tremors, and hypotension. Dosages of bupivacaine should not exceed 2 mg/kg.
Although local anesthesia is sufficient for pain relief it does not reduce stress that may be induced by physical restraint and handling of an awake bird. Sedation or general anesthesia should also be considered during stressful or prolonged procedures.

**Summary**

Pain perception in birds is believed to be analogous to that of mammals. Thus, invasive and painful procedures should always be accompanied by appropriate analgesia and anesthesia. A balanced approach to anesthesia and treating postsurgical or injury pain is not only ethical but also promotes healing, reduces hospitalization times, and provides for greater client satisfaction. Providing appropriate pain relief for birds involves a consideration of the type and severity of pain along with management of physical, environmental, and behavioral factors that may contribute to the experience of pain. Although pain management in birds is in its infancy, research and clinical studies demonstrate the benefits associated with the use of opioids, steroidal drugs and NSAIDs, as well as other analgesics such as α-agonists, ketamine, and local anesthetics. Ongoing assessment of pain and analgesic efficacy is extremely important, because the dosage and choice of analgesic may vary widely between species. Clearly, there is a paucity of information in the scientific literature addressing pain and its treatment in the bird. Further clinical investigations and communication of clinical successes and failures in treatment should be reported in the veterinary literature to expand the very limited body of knowledge.

**References**

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