

Pain Management

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Fig 8.1 | With such a devastating lesion, pain would seem obvious, but the canary did not show evidence of pain until this band was removed.

What is Pain?

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.² The IASP also includes under this definition an important note: *The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment (Fig 8.1).* This is a very important statement that gives credibility to pain experienced by non-verbal populations of species, including humans as well as all animal species.

All animals have neuroanatomical and neuropharmacological components required for nociception: transmission, perception and response to noxious stimuli. But when does nociception become pain? This is not easily determined, but for the purposes of this chapter it will be accepted that not only do birds perceive and respond to noxious stimuli, but also that birds feel pain. Pain is always subjective and the emotional component is difficult for us to translate because birds do not share a verbal language with humans. In humans, we accept that pain is what the patient says it is, but in birds as well as other animal species, it is what people think it is.

RECOGNIZING PAIN

The challenge is to recognize avian behaviors that occur with painful stimuli, both acute and chronic. Perhaps birds have evolved behaviors to minimize painful displays as a way of minimizing the attention of predators. We are not yet fully capable of recognizing when a bird is affected by pain; therefore, it may be best to err on the side of over-estimation and assume that conditions that would be painful to humans also are painful to

birds. Nonetheless, having an identified behavior or set of behaviors that correlate with pain provides a means to monitor response to pain treatment. It is difficult to say we have effectively treated something if we cannot measure it before and after therapy. But there is no reliable measurement or gold standard for the assessment of pain in animals, including birds, either for research subjects or clinical patients. Assessment of pain must give consideration to species, gender, age, strain, environment and concurrent disease. Significance must be given to the type of pain, such as acute, chronic, somatic, visceral, clinical or neuropathic.

Behaviors that occur with acute noxious stimuli are the easiest to identify. There is an immediate cause-effect relationship between activation of nociceptors (a receptor preferentially sensitive to a noxious stimulus), withdrawal reflexes and behaviors that correspond to conscious perception of the stimulus.¹² Noxious stimuli that have been used to study avian pain are similar to those used in mammalian studies, such as electrical stimulation, thermal stimulation and pressure, but other studies have employed noxious stimuli unique to birds, such as feather removal, beak amputation and comb pinching, as well as research models for chronic pain using intra-articular injection of sodium urate.^{12,18} Physiological measurements are not always consistent or specific to painful stimuli and are not useful for assessment. Respiratory rate, heart rate and blood pressure will increase during painful stimuli but also can be affected by light, sound, temperature, restraint and other external stimuli. Avian withdrawal behaviors to acute painful stimuli include escape reactions (foot lifting, wing flapping), vocalizations, decreased head movements or extreme movements (jumping). When parrots were given a mild electrical stimulus to the foot using a specially designed test perch, the expected response was foot withdrawal with a reluctance to place the foot back on the perch; but there also were several individual parrots that did not lift the foot, but began flapping their wings when a stimulus was delivered.³¹ Chickens can display a distinctive behavior termed crouching immobility, which occurs experimentally when they are exposed to repeated noxious stimulation.^{12,14,37}

How do we know when a bird is experiencing prolonged pain or chronic pain? It is generally accepted that when a bird is in pain there is a change in or absence of one or more normal behaviors. To accurately assess pain, the observer must be familiar with normal and pain-associated behavior of a given species of bird as well as that of the individual bird. Social species of birds will decrease their social interactions. This may be as subtle as a reduction in social grooming behaviors or as obvious as perching away from the flock. For social species of birds housed as single pets, there may be a reduction in inter-

actions with the owner. This is often manifested by a decrease in vocalizations or chattering that birds often do with the owner or reluctance to seek stroking or petting from the owner. Guarding behavior to protect a painful body part is seen in birds and can subtly manifest in similar antisocial behaviors. Aggression has been linked in individual birds to painful conditions because often the aggressive behaviors dissipate once the clinical problem is resolved. A behavioral change in feather grooming is common to both solitary and social birds. The change can be either an increase or decrease in grooming. Decreased self-grooming is a withdrawal behavior that occurs when a bird's focus is on pain and not daily activities. Increased grooming behavior to themselves or other birds in their environment can be an intentional distraction. Studies using chickens with induced sodium urate arthritis demonstrate that shifting attention can reduce the severe pain and potentially reduce peripheral inflammation.¹⁵ Alternatively, grooming and feather picking may increase over a specific area, often directly related to the region of discomfort or painful stimulus.

Decrease in appetite and weight loss often accompany painful conditions. In a study of rats observed postoperatively, dehydration and weight loss due to decreased food and water consumption was significantly lower in rats given adequate perioperative analgesia.⁹ Unfortunately, dehydration and weight loss can occur under numerous stressful conditions, from something as simple as changing the perches in a bird's cage to a variety of known diseases. Weight loss is not unique to pain, but because it can be quantified it is very valuable to record a bird's daily weight. If weight gain or stabilization occurs following administration of analgesia, then it was a useful gauge.

Tonic immobility is an innate fear response characterized by a profound and reversible state of motor inhibition. In chickens, crouching immobility has been associated with prolonged pain, stress and fear responses. Studies using chickens demonstrated that repeated feather plucking caused an initial agitated response, which progressed to sustained crouching immobility of the chicken.^{12,14} A later study using chickens with ulcerated oral lesions placed an irritating substance on the lesions, which caused several birds to go into a crouch-like posture, with the head held close to the body and a significant reduction in head movements.¹¹ The immobility reaction is prolonged when fear is present and reducing the fear component decreases the time of immobility. Companion birds may display similar tonic immobility postures postoperatively or under chronically painful conditions. It has been suggested that tonic immobility evolved as a response of a prey species to reduce potential damage produced brought on by struggling. In

guinea pigs, it has been demonstrated that tonic immobility induces an endogenous analgesia involving opioid synapses, which increases the animals' threshold to noxious stimuli.²¹

The correlation of elevated corticosterone has been studied in its relationship to pain. It is a hormonal indicator known to become elevated with ACTH (adrenocorticotropic hormone) release and stress in birds and other animals.²⁴ Pain can induce both acute and chronic stress. Fecal corticosterone levels may offer a measurable response that can be collected without interfering with the bird's normal activities.²² Studies are currently in progress to determine if measurable amounts of corticoids in avian feces correlate to painful stressors.

PAIN ASSESSMENT SCALES

Pain assessment scales are used in human medicine for verbal as well as non-verbal segments of the population. Pain scales can be sensitive and repeatable, and a similar process could be used to develop pain scales for birds with the understanding that each would have to be species-specific. As an example, a recent study with pigeons noted that body trembling consistently occurred for several hours after recovery from general anesthesia, orthopedic surgery and opioid analgesia, but it did not occur with controls given the same period of general anesthesia and opioid, but *without* orthopedic surgery. Additionally, all pigeons received the opioid after surgery, but the group of pigeons that also received opioids prior to surgery stopped trembling earlier in the recovery period than the other surgical group (J. Paul-Murphy, unpublished data). Body trembling may be specific to pigeons or it may be specific to orthopedic surgery, or it may be specific to some other variable not measured in this early attempt to develop a pain scale for pigeons. There are currently more than 26 published pain scales for children, each trying to manage variables that may confound pain assessment.²³ A pain scale can be a very useful assessment tool under consistent conditions, and it may be necessary to develop numerous species-specific scales until a more accurate method is found to assess pain.

PHYSIOLOGY OF PAIN

The physiology of pain in all animals involves the peripheral process of detecting a noxious stimulus (mechanical, thermal or chemical) and transmission of the impulses to the spinal cord. Here they are modulated and projected to the brain for central processing of the information, which determines the perception of the noxious stimulus. Nociceptive pain involves the activation of the pain receptors, is usually localized and transient, and usually activates a withdrawal response, both reflexive and con-

scious. All other types of pain are considered clinical or pathological, often involving tissue damage with inflammation or nerve damage. Pathological pain can originate from a gentle tactile stimulus, causing an exaggerated or prolonged pain response, or can persist in the absence of noxious stimuli.

Peripheral sensitization occurs when inflammation at the site of injury creates an increased response to a normally painful stimulus. Cell damage and leakage leads to a series of responses resulting in increased sensitivity of the peripheral receptors and may even activate "silent" nociceptors, which magnify the pain response. In addition to sensitization at the peripheral tissue and pain receptor environment, the central nervous system can be sensitized as well. Central sensitization is an increase in the excitability of spinal cord neurons and a recruitment of neurons not involved in pain perception under normal circumstances. When stimulation from the peripheral nociceptors to the spinal cord continues for an extended time period, a wide range of spinal neurons become sensitized and hyper-responsive. The response to additional noxious stimuli becomes heightened and prolonged. Stimulation from the periphery that was previously non-noxious, such as a tactile stimulus, becomes painful.

Understanding the mechanism of peripheral and central sensitization helps to explain why prevention of sensitization is critical and provides multiple places in the process that could be altered by different classes of analgesic therapy. When sufficient analgesia is provided at an early stage of tissue trauma, such as with surgery, it can greatly reduce the degree of postoperative discomfort.³³ Although this has not been experimentally demonstrated in birds, animal and human studies have demonstrated that when analgesics are given prior to a painful event rather than after the start of the stimulation, the spinal excitability can be dampened.^{35,36} The earlier pain is treated, the less total drug will be required to maintain analgesia both during and after surgery. It has been shown in mammalian species that a shorter period of analgesia is needed in the postoperative period when analgesics are given in the preoperative period.³³ A study of pigeons undergoing orthopedic surgery showed that the pigeons receiving butorphanol before and after orthopedic surgery returned to normal behaviors sooner than those pigeons receiving butorphanol only in the postoperative period (J. Paul-Murphy, unpublished data).

RELIEF OF PAIN

Pain is a combination of both peripheral inputs and neurophysiological processes within the central nervous system. Diagnosing the cause of pain can be difficult at times, but identifying the disease process or site of tissue damage will influence the choice of analgesic drugs

and supportive care. Therapy should be directed at resolving the disease process or injury as well as reducing pain signals coming from the periphery and its effects on the central neural processing of the pain. For example, immobilizing a bird's fracture maximizes bone healing, but it also reduces micromovement irritation and inflammation, thus reducing noxious stimuli projected from the site of trauma. Analgesia therapy may include an opioid plus an NSAID, but the immobilization itself greatly reduces the pain. Conversely, we may recognize the signs of pain in a patient before we actually diagnose the cause, and in these cases, treatment of the pain becomes part of the symptomatic approach to therapy. Selection of analgesic drugs should be done conservatively in situations where the cause of pain is still under investigation.

Supportive care is very important to the management of pain. This includes keeping the avian patient warm, dry and clean. Environmental stressors should be kept to a minimum by providing a quiet, soothing hospital environment away from barking dogs or strong smells of "predators," such as cats and ferrets. If the bird is a pet, provide human contact and speak in a soothing voice.

Pharmacological Approach to Pain Control

LOCAL ANESTHETICS

Local anesthetics are used to produce regional anesthesia and analgesia by blocking the transmission of noxious impulses. Local anesthetics such as lidocaine and bupivacaine block sodium channels in the nerve axon, which interferes with the conduction of action potentials (pain impulses) along the nerve. Reducing the number of pain impulses reduces the nociceptor sensitization, which has the beneficial effect of minimizing central sensitization. Local anesthetics do not need to be distributed systemically for the analgesic effect, but will slowly be absorbed by the vasculature in the region being blocked.

Regional infiltration or a local line or splash block are among the most common methods used. A 25-gauge needle is used to make several subcutaneous (SQ) injections of small volumes of dilute solution into the operative area. A line block follows the course of the intended incision by injecting a modicum of dilute anesthetic SQ, then withdrawing the needle and reinserting it at the edge of the raised area. Another modicum is delivered under the skin and the process is repeated until the length of the incision is blocked.

Lidocaine has a commercial preparation of 2% (20

mg/ml), and the formulation without epinephrine is recommended. The commercial preparation should be diluted 1:10 with sterile water or diluted further to the volume required for the block. The total dosage should not exceed 2 to 3 mg/kg. For example, a 500-g cockatoo can receive 1 mg lidocaine; 0.05 ml is diluted to 1 ml and this solution is used to block a 2-cm surgical skin incision. The commercial preparation of bupivacaine is prepared as 0.25% (2.5 mg/ml), 0.5% (5 mg/ml) or 0.75% (7.5 mg/ml) solution. No bupivacaine dosage has been established for birds, but 1 mg/kg total dose has safely been administered to large birds.

Local anesthetic dosage recommendations for birds are lower than for mammals because birds may be more sensitive to the effects of the drug. Systemic uptake of the drug may be rapid in birds, increasing the potential for onset of systemic reactions. There can be acute toxic effects if these drugs are accidentally injected intravenously. Toxic side effects can include fine tremors, ataxia, recumbency, seizures, stupor, cardiovascular effects and death. Chickens were injected with high doses of bupivacaine (2.7-3.3 mg/kg) and showed immediate signs of toxicity such as drowsiness and recumbency.¹⁸

The duration of action of local anesthetics depends on the molecular properties of each drug, especially the lipid solubility of the drug. Neither the time to effect nor duration of action has been determined for these drugs in birds. In mammals, bupivacaine lasts much longer (4-10 hours) than lidocaine (1-3 hours).

Intra-articular administration of bupivacaine (3 mg in 0.3 ml saline) was studied for its analgesic effects in chickens with experimentally produced acute arthritis. Chickens given bupivacaine were able to feed, peck and stand on the affected limb similar to birds without arthritis.¹⁸

Topical benzocaine has been used for minor wound repair in small birds.³ Topical bupivacaine has been studied when applied to the amputation site in beak-trimmed chickens and provided 4 hours of analgesia.¹⁶ In mammals, local anesthetics also are used in the form of transdermal patches and transdermal creams, but the use of these patches and creams has not been studied with birds. Local anesthetics also are used in mammalian medicine for epidural infusions, spinal blocks, intravenous blocks and peripheral nerve blocks and as an antiarrhythmic agent, but none of these applications has been reported for use in birds.

OPIOIDS

Opioids reversibly bind to specific receptors in the central and peripheral nervous systems. There are three major classes of opioid receptors associated with analge-

sia: mu, delta and kappa. Chickens have similar proportions of each receptor type as do humans.⁷ The distribution, number and type of opioid receptors are conserved across species in the brainstem and spinal cord but vary substantially in the forebrain.²⁷ In mammals, mu and kappa receptors primarily are associated with pain relief, with mu receptors being widely distributed in the forebrain, midbrain and hindbrain, whereas, delta and kappa receptors are numerous in the spinal and supra-spinal regions of the central nervous system (CNS). Autoradiography was used to identify mu, kappa and delta opioid receptors in the forebrain of rats, mice and humans, and kappa receptors represented 9, 13 and 37% of the total opioid receptor population, respectively. In contrast, the forebrain of pigeons has a relatively high proportion (76%) of kappa receptors.²⁷

All drugs in the opioid classification have morphine-like effects, which may be mediated primarily by an increase in serotonin synthesis. Given at appropriate dosages, opioids do not cause a loss of consciousness but can cause sedation and respiratory depression. Opioids vary in their receptor specificity and efficacy at different receptors, which results in a wide variety of clinical effects in different mammalian species, and is influenced by the commercial preparation of opioid, the dose and the species receiving the drug. It stands to reason that the opioid and the dose also will have a wide range of clinical effects in different avian species.

Physiological and analgesic effects of opioids have been studied in parrots using the isoflurane-sparing technique. This method anesthetizes healthy birds with isoflurane and determines the minimum anesthetic concentration (MAC) by using a noxious stimulus (toe pinch) and observing a withdrawal response with a cognitive body movement. Each bird then is injected with an analgesic and the MAC is redetermined. If the concentration of isoflurane can be lowered, then this “sparing effect” is considered due to the analgesic effects of the drug being tested. Butorphanol (1 mg/kg) was administered to three species of parrots, and the isoflurane MAC could be significantly lowered in cockatoos and African grey parrots but not Amazon parrots.^{5,6} The addition of butorphanol also caused lowering of the heart rate, tidal volume, and inspiratory and expiratory times. A similar type of study compared mu and kappa opioids in chickens, and both drugs had isoflurane-sparing effects.⁴

The effect of different opioids on conscious parrots was evaluated by studying the change in withdrawal threshold from noxious electrical and thermal stimuli before and after receiving an opioid. Butorphanol, 1 and 2 mg/kg IM, had an analgesic effect on African grey parrots, and 1 and 3 mg/kg had an analgesic effect on

Hispaniolan Amazon parrots.^{30,31} Plasma concentration of 2 mg/kg butorphanol in African grey parrots has a mean residence time of less than 2 hours (J. Paul-Murphy, unpublished data). Buprenorphine at 0.1 mg/kg IM in African grey parrots did not show an analgesic effect when tested by analgesimetry, but recent pharmacokinetic analysis suggests that this dose may not achieve effective plasma levels, and the mean plasma residence time is only 1 hour (J. Paul-Murphy, unpublished data). Higher doses of buprenorphine using different avian species may help to clarify if buprenorphine is an effective analgesic for birds. Clinical use of buprenorphine suggests it has an analgesic effect.

Fentanyl was evaluated using cockatoos and, although 0.02 mg/kg provided plasma levels similar to the concentration found to be analgesic in cats, it did not affect the withdrawal response of the cockatoos.³⁰ A ten-fold increase in the dosage of fentanyl (0.2 mg/kg SQ) did produce an analgesic response, but many birds were hyperactive for the first 15 to 30 minutes after receiving the high dose.³⁰ The duration of analgesic effect from fentanyl has not been established, but 0.02 mg/kg given IM to cockatoos maintained a plasma concentration considered analgesic in people for 2 hours.

Butorphanol (1-3 mg/kg IM) is the current recommendation for opioid analgesia in parrots. Butorphanol is a mixed agonist-antagonist with primarily kappa agonist action. This supports the one study finding of a high percentage of kappa receptors in the forebrain of pigeons. The dosage of butorphanol for effective analgesia needs to be balanced with sedation and respiratory depression, which may vary with other avian species and need further evaluation.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used classes of drugs in small animal medicine. NSAIDs interfere with eicosanoid synthesis by the inhibition of cyclooxygenase (COX) enzymes. COX enzymes initiate a cascade of reactions that results in polyunsaturated acids being converted to eicosanoids such as prostaglandins and thromboxane.³⁴ These are released at sites of tissue injury and cause inflammation and sensitization of nerve endings.

Reduction of prostaglandins and thromboxanes decreases inflammation at the site of injury and also has a modulating effect within the CNS. The physiological mechanisms involving prostaglandins, their role in inflammation and their ability to sensitize sensory neurons to physical or chemical stimuli in birds are similar to those in mammals.²⁹ The COX-1 enzyme is part of normal cell composition in numerous tissue types and the

concentrations are fairly stable, keeping prostaglandin levels at homeostatic levels. In mammals, COX-2 concentrations increase when stimulated at sites of inflammation, but both COX-1 and COX-2 are expressed in the CNS and participate in spinal pain transmission. The relative expression of COX-1 and COX-2 enzymes varies among species, and both enzymes are important in avian pain at the site of peripheral inflammation as well as in spinal pain transmission. However, more information is needed to differentiate their physiological effects in avian species.

NSAIDs can be used to relieve musculoskeletal and visceral pain, acute pain (trauma or surgical) and chronic pain such as osteoarthritis. The most common NSAIDs used in avian medicine are piroxicam, carprofen, ketoprofen and meloxicam. These compounds vary in their structure, but all inhibit COX enzymes. Generally, the current NSAIDs are safe drugs but should be monitored and evaluated in each individual patient. Increased monitoring may be indicated with high-risk patients: establishing a base-line set of hepatic enzymes and uric acid prior to NSAID administration and reevaluating these parameters at fixed intervals (see Chapter 16, Evaluating and Treating the Kidneys). NSAIDs should not be used if there is any indication of renal impairment, hepatic dysfunction or severe hypovolemia or if gastric ulceration is present. Only one NSAID should be used at a time, but in cases of chronic pain, frequently review the response to therapy and change to a different formulation NSAID if response is poor or diminishing. For treatment of mild to moderate chronic pain, NSAIDs can be given on an as-needed basis. The dose and frequency of administration has not been determined for any clinical NSAID use in birds. Ketoprofen (5 mg/kg IM) administered to ducks anesthetized with isoflurane had an analgesic effect 30 to 70 minutes after administration.²⁵ Carprofen given to rapidly growing chickens with chronic lameness improved their ability to walk and navigate a maze.²⁸ Carprofen (1 mg/kg SQ) given to chickens raised their threshold to pressure pain for at least 90 minutes.⁸ Peak plasma levels occurred at 1 to 2 hours after SQ administration of carprofen to chickens.²⁸ Plasma levels do not provide sufficient information to indicate physiological activity of the NSAID because NSAIDs tend to accumulate in areas of inflammation. In mallard ducks, 5 mg/kg flunixin and 5 mg/kg ketoprofen suppressed thromboxane B₂ levels for 12 hours, indicating a prolonged physiological effect.²⁶

MULTIMODAL THERAPY

Information specific to birds is minimal, and many current therapies for birds are extrapolated from species in a different class of vertebrates. Some drugs are handled similarly across species lines and other drugs may have very different mechanisms of action; they may be effective

in one species and range from ineffective to toxic in another species.

Combining analgesics that act by different mechanisms can maximize the analgesic effect. Administration of two or more analgesics frequently produces a synergistic effect, such as a local anesthetic at the surgical incision or site of recent trauma, a NSAID plus an opioid. This combination of drugs usually allows the dosage of each drug to be reduced, thereby reducing the side effects. Additionally, opioids such as butorphanol will reduce the concentration of inhalation anesthetic needed for a surgical plane. Adjunctive drugs, such as tranquilizers used in conjunction with analgesic drugs, can potentiate the analgesic effects by reducing anxiety. The most common sedatives used in avian medicine are the benzodiazepines, which calm the bird and may reduce anxiety.

CHRONIC PAIN

Treatment of chronic pain in birds opens more questions than there are answers. How to treat chronic pain in a non-verbal patient such as the bird is the ultimate challenge. It is difficult to evaluate response to treatment when the condition itself may be progressive, such as chronic degenerative joint disease or neoplasia. Response to analgesic therapy is based on evaluation of a set of behaviors particular for each individual bird.

NSAIDs are the first course of therapy for chronic disorders. Carprofen is the current drug of choice because of its widespread use and low incidence of reported toxicities. Carprofen is an orally administered drug and can be initiated at the low-end dosage and monitored for response to treatment. As pain gradually increases over time, the dosage of carprofen can be increased, and monitoring the renal and hepatic serum values every 2 to 4 months is recommended, especially in an older bird. If pain recurs over several months of treatment, the next set of options includes changing to another NSAID, such as meloxicam or piroxicam. There is a risk when switching NSAIDs that the side effects can be potentiated, so a no-drug period of 7 to 10 days is recommended. Piroxicam may have synergistic action with anticancer drugs and also is an effective NSAID for degenerative joint disease in birds. Piroxicam is noted for renal toxicity and gastric ulceration in mammals, but its long-term use (months of treatment) in cranes with chronic degenerative joint disease has not caused clinical problems. If pain persists or increases, especially with neoplasia, opioid therapy may be indicated. Unfortunately, most parenteral forms of opioids reach "effective" plasma levels rapidly, but these levels are maintained for only a few hours. No information is available regarding oral opioids in birds, but in mammals much higher dosages are required for oral administration to reach effective plasma levels.

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