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PAIN, NOCICEPTION AND ANALGESIA IN REPTILES: WHEN YOUR SNAKE GOES “OUCH!”

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CAN REPTILES EXPERIENCE PAIN?

In a recent survey of members of the Association of Reptile and Amphibian Veterinarians, 98% of the respondents indicated their belief that reptiles do feel pain. However, only 39% of respondents in this survey reported using analgesics in > 50% of their patients subjected to surgical interventions. The reasons for failure to use analgesics were not specifically addressed in this study. However, some possibilities include a failure to recognize painful patients, concern of adverse effects from medications or lack of dose and pharmacokinetic information. Although reptile pain and nociception have not been extensively studied, there is very strong evidence that reptiles are capable of experiencing pain. The neuroanatomic components necessary for nociception have been described in reptiles. Endogenous antinociceptive mechanisms and a demonstrable modulation of pain with pharmacological agents known to be analgesics in other species have been demonstrated in reptiles. In lizards (*Gekko gecko*), spinal projections originating in the brain stem region (nucleus raphes inferior) that project to the superficial layers of the dorsal horn have been identified. These structures suggest the presence of inhibiting nociception mediating spinal tracts, similar to those found in mammals. Neurotransmitters that are important in pain modulation in mammals have been identified in reptiles. While endogenous opioids and opioid receptors involved in reproduction and thermoregulation have been identified in reptiles, there is little known of the role of opioids in nociception. Collectively, this information suggests, at the physiological level at least, that reptiles respond to nociceptive stimuli in a manner very similar to mammals. The assumption that an animal's ability to experience pain is directly related to its position on the phylogenetic tree may be inaccurate. Rather, it may be that phylogenetic position is reflective of an animal's ability to express pain.

The benefits of providing adequate analgesia are well recognized in mammals. The consequences of untreated pain results in impaired homeostasis and this in turn can lead to alterations in numerous body systems. These alterations can result in negative energy balance, lead to immune system compromise, inhibit healing and interfere with normal behavioral process required for health. The benefits of preemptive analgesia have also been demonstrated and can not only reduce postoperative pain by decreasing central sensitization but may also facilitate healing and prevent and/or limit the actions of detrimental neurohumoral responses to pain postoperatively. In addition, many analgesics can

be used as part of a balanced anesthesia to reduce the doses of other anesthetics. This can help reduce the negative cardiopulmonary effects of general anesthesia. Overall it has been demonstrated in humans and other mammals that appropriate analgesia is an important part of complete medical care in health and disease.

ASSESSING PAIN IN REPTILES

Assessing pain in non-verbal species and human infants is an extremely challenging endeavor. Pain is defined as a sensory or emotional experience. Humans can use words to express this discomfort and the significance of this discomfort to the individual allowing assessment of an individual level of pain and response to analgesics. In non-verbal humans and animals we must rely on non-verbal signals or characteristic behavioral changes associate with pain. Behavior assessment has become the most accurate method of pain assessment in veterinary species. However, with over 8000 reptile species identified and a wide range of unique physiological and behavior adaptations among species it is exceedingly difficult to assess behavior changes in these animals. This makes the recognition of alterations in normal behavior that may be indicative of clinically significant pain and stress particularly difficult. In addition, many reptiles are prey species and hiding external signs of pain or distress is vital for survival. Recognition of abnormal behavior in reptiles requires careful observation and changes are often very subtle. It is best if the animals can be observed remotely or that the assessor is hidden from the patient's view, as simply the presence of a human can markedly alter an animal's behavior. This is also observed in more traditional veterinary species.

Ultimately successful recognition of pain in reptiles demands an intimate knowledge of normal and abnormal species-specific behaviors. In the absence of such knowledge, the delivery of appropriate analgesic therapy is based on an assessment of the anticipated level of pain associated with a given procedure or condition.

ANALGESIC THERAPY IN REPTILES

There are three primary classes of analgesic drugs used in reptiles: local anesthetics, non-steroidal anti-inflammatory drugs (NSAID's) and opioids. Local anesthetics provide complete anesthesia by interrupting nociception from the level of the nociceptor to the spinal cord. NSAID's act by modulating both peripheral and spinal nociception. Opioids act by modulating nociception in the periphery, the spinal cord and supraspinal areas of the central nervous system. Since reptiles have a more primitive central nervous system, the central actions of analgesic medications, particularly opioids, may not be as predictable as the more peripherally-acting drugs. However, it is well documented that reptiles have opioid receptors in the central nervous system. The unknown actions of opioids and NSAID's in the central nervous system of reptiles may result in variations in the duration, potency and side-effects of these drugs particularly when the doses are determined by extrapolation from mammalian doses.

Despite the unpredictable central effects of NSAID's and opioids, their administration may offer the advantage of an increased duration of effect compared to that associated with the administration of local anesthetics.

There are very few investigations that describe the assessment of analgesic efficacy in reptiles. In general, opioids administered to reptiles are not associated with significant changes in physiological parameters (heart rate, respiratory rate) or behavior (sedation or excitement). The mu-agonist morphine and meperidine have both been shown to increase latency times in response to a hot-plate test in crocodiles (*Crocodylus niloticus africana*), suggesting at least some analgesic efficacy. A dose-dependent response was observed with both of these opioids and a ceiling of effect was achieved. The latency of onset of action is approximately 30 minutes and the duration of effect is 2–2.5 hours.

Local anesthetics act by interrupting transmission of sensory and motor neurons. In reptiles, local anesthetics are commonly used to facilitate minor surgical interventions but they can also be used as analgesics. Unfortunately their duration of effect and accompanying motor paralysis limit their use primarily to the immediate post operative period or only when hospitalized. Local anesthetic toxicity can be avoided by careful attention to

total dose of local anesthetic administered to a patient. It must be kept in mind that many reptile patients are very small and large doses can accidentally be administered. In general, the toxic doses of local anesthetics in mammals (dogs) should not be exceeded; lidocaine (toxic dose 10-22 mg/kg) and bupivacaine (toxic dose 5 mg/kg). Additionally, excessive dilution of local anesthetics will decrease their efficacy. Local anesthetics should not be diluted to less than 50% of the standard bottle concentration (2% lidocaine, 0.5% bupivacaine).

The role of cyclo-oxygenase in the pathophysiology of pain and inflammation of reptiles has not been studied. However, reported clinical experience supports the efficacy of NSAID's in reptiles and they continue to be recommended. Nevertheless, until further studies in reptiles become available it is probably best to consider the possibility that side effects similar to those seen in mammals (GI irritation, renal compromise and platelet inhibition) may also occur in reptiles. Therefore hydration status, concurrent medications (steroids), presence of coagulopathy, GI disease and renal disease should all be addressed prior to administering these drugs.

References available from the author upon request.

Table 1. Dosages of Potential Analgesic Drugs in Reptiles

Drug	Route	Dosage	Comments
Butorphanol*	IM	1 mg/kg	Unable to demonstrate analgesic effect using indirect testing methods (MAC reduction)
Buprenorphine*	IM, IV, SC	0.4-1.0 mg/kg	Long duration of action in most veterinary species
Morphine	IC, IM	0.05-4.0 mg/kg	Ceiling effect seen at 0.3 mg/kg in Nile crocodiles (<i>Crocodylus niloticus africana</i>)
Meperidine	IC, IM	1-4 mg/kg	Ceiling effect seen at 2 mg/kg in Nile crocodiles (<i>Crocodylus niloticus africana</i>)
Ketamine	IM, IV, SC	10-100 mg/kg	High doses are associated with anesthesia Low doses < 5 mg/kg likely associated with analgesia with minimal sedation
Xylazine*	IM	1-1.25 mg/kg	Dose required for analgesia may be lower
Medetomidine	IM, IV, IO	50-100 µg/kg (tortoises) 150-300 µg/kg (aquatic) 150 µg/kg (snakes & lizards)	Dose required for analgesia may be lower
Meloxicam*	IM, IV, PO	0.1-0.2 mg/kg q 24 h	
Carprofen*	IM, IV, SC	2-4 mg/kg followed by 1-2 mg/kg q24-72 h	
Ketoprofen*	IM, SC	2 mg/kg q 24-48 h	
Flunixin meglumine*	IM	0.1-0.5 mg/kg q 24	
Lidocaine (2%)*	Local infiltration	Toxic dose unknown, recommend < 5 mg/kg	Dilute to 1% to increase volume
Bupivacaine (0.5%)*	Local infiltration	Toxic dose unknown, recommend < 2 mg/kg	Dilute to 0.25% to increase volume

* Doses not determined experimentally, extrapolated or anecdotal