Evaluating the Analgesic Effects of Opioids in Birds (3-Dec-2002)

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Background
It is easily accepted that birds are able to feel pain. Studies with chickens suggest that pain perception is mediated by neural pathways and neurotransmitters similar to mammals [1-3]. Yet research for the avian patient is still needed to identify effective techniques to evaluate pain in these species and the reduction of pain through the use of analgesic agents.

The analgesic effect of opioids varies widely among vertebrate species. This may be due to the distribution, number and type of opioid receptors within the brain. In general, distribution of opioid receptor types is conserved across species in brainstem and spinal cord areas but varies significantly in the forebrain [2]. In the pigeon forebrain 76% of the total opioid receptors are kappa [2]. Early discrimination trials concluded that pigeons may not be able to discriminate mu and kappa agonists and the opioid receptors may share a common mechanism of action [4].

Reduction of inhalant anesthetic concentration following administration of an opioid is an accepted method to assess analgesic effects of opioids in mammalian species [6-8]. The first application of this technique to birds was done at the University of Wisconsin using parrots [9,10] and has since been applied to turkeys [11] and chickens [5]. Butorphanol (1 mg/kg) was tested in 3 species of parrots and was effective at reducing the isoflurane levels in Cockatoos and African gray parrots but NOT Amazon parrots. Using a similar inhalation anesthesia-sparing model, butorphanol was evaluated in turkeys using 0.1 mg/kg [11]. This low dosage did NOT have any significant effect on the halothane levels needed for analgesia in turkeys.

Early studies with conscious birds
Conducting experiments in anesthetized animals is easily performed, but a general anesthetic is a confounding variable in the assessment of analgesic action. The earliest published avian opioid study described the effects of morphine administered to conscious chicks and determined that dosages greater than 10X a mammalian dose were needed to produce analgesia [12]. Subsequent studies using different testing modalities as well as different strains and ages of chickens have yielded conflicting results, concluding that opioid effects are variable depending on the species, strain and route of administration.

Recent studies with conscious parrots
Electrical and thermal stimulation have been used to evaluate the response to pain in both mammals and birds. Utilizing two different stimuli to assess pain increases effective evaluation of withdrawal threshold and response to analgesics. At University of Wisconsin, the effects of electrical current and thermal gradients on nociception thresholds were evaluated in conscious parrots [13]. Birds were fitted with a surface electrode on the medial surface of one leg and an electrical stimulus was delivered to the bird’s foot through one side of the perch. The alternate side of the perch delivered a progressive thermal stimulus, and lifting the foot resulted in reversing the thermoelectric modules to return to resting temperature. A withdrawal response to either stimulus was recorded when the bird lifted its foot off the perch or vigorously flinched its wings. Responses to thermal stimuli were extremely variable. Birds lifted their feet over a wide range of temperatures during baseline testing thus significant differences were not detected after treatments. In contrast, the birds responses to an electrical stimulus was predictable and less variable. Response to noxious stimuli was compared before and after administration of butorphanol or saline [14]. In the African gray parrot, 1.0mg/kg butorphanol significantly decreased the response to a noxious electrical stimulus. The same testing protocol was used to evaluate different dosages of butorphanol in the Hispanolian parrot. This species of bird also had a reliable response to the electrical stimulus and required a higher dosage of butorphanol (3 and 6 mg/kg) to increase withdrawal threshold.
Electrical stimulation has qualities that differ from those of thermal stimulation of the somatosensory system. Thermal nociception has been used extensively in many forms to experimentally evaluate pain response in mammals, but a wide range of environmental factors influence the results [15]. Thermal stimulation is difficult to use, because the exact time of nociceptor activation by heat is problematic and crucial to latency measurement [16]. The skin warms gradually, and warmth receptors are excited before nociceptors [16]. The analgesiometry experiments were not designed to identify discharge from nociceptors. Some birds tolerated the heat for long periods, so it is questionable as to how noxious the thermal stimulus actually was. Tail flick tests in rodents use 55ºC as a common painful stimulus, but the actual temperature of the tail can vary from 38 to 45ºC [16]. In an effort to avoid tissue damage, the upper limit set for our study was 75ºC, as determined on the basis of studies with chickens [17-19]. Most parrots lifted their foot before the upper set point was reached. When Cockatoos were used in a similar analgesiometry study, the thermal stimulus provided a reliable withdrawal response and correlated well to the withdrawal thresholds using the electrical stimulus [20].

Ongoing studies
Although the term pain is used to define all sensations that hurt or are unpleasant, nociceptive pain is very different than clinical pain. We combined an analgesia study with an ongoing orthopedic study creating bilateral ulnar osteotomies in pigeons (n=16). Butorphanol was given to 8 birds in the pre and post-operative period and another 8 birds received butorphanol 4 hours following anesthesia and surgery. Subjective measures included a numerical rating scale (NRS) and objective measurements included heart rate, level of activity, and body temperature using remote telemetry techniques. Subjective criteria included evaluation of behaviors, responsiveness, postures and whether the bird was eating and drinking. The NRS was the only measurement that differed between the two treatment groups. Birds given butorphanol prior to and immediately following surgery returned to a low NRS earlier than those birds given analgesia after recovery from anesthesia. Body temperatures were similar in both treatment groups. Heart rates and activity patterns were influenced by environmental events so that no pattern could be attributed to the treatment itself. It was surprising how sensitive the birds were such that heart rates would increase 5 - 10 times to events such as turning on the room lights, opening the door to the room, or operating a computer.

Future studies and dilemmas
The study currently underway is measurement of fecal cortisone concentration to evaluate post-operative pain in birds. Plasma corticosterone is a reliable indicator of stress in birds [21] but it has yet to be established as a reliable indicator of stressful response to pain. It is documented to increase in response to ACTH psychological stress, extremes of temperature and restraint procedures [22-25]. Measurement of plasma corticosterone is limited because birds must be handled, restrained and bled, all of which are stressors that significantly cause corticosterone levels to increase two to six fold above baseline concentrations [25]. Two hours following ACTH administration to pigeons, fecal cortisone concentrations are significantly elevated. The question still unanswered is if corticoids are a reliable indicator of the response to pain and the modulation of the response to pain by using analgesic agents.

References

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