

Anne Martin Scholarship Winner

Avian Analgesia: Which Opioid Works Best?

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Initial stabilisation and pain relief are important considerations in any species presented to a veterinary clinic. It is commonly held that butorphanol is a 'better' analgesic agent in birds than morphine - that is, kappa receptor agonists are better at inducing analgesia than mu receptor agonists. However, what evidence do we have that this is truly so?

WHAT WE KNOW

Mammals

Endogenous opioid peptides are shown to be distributed widely in the brain, spinal cord, and long descending pathways from the midbrain to the dorsal horn; their important role in nociception is widely accepted. Nociception is defined as 'the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system'. Endogenous opioids are also produced in the endocrine and exocrine systems, immune system, and have properties relating to the regulation of many other physiologic systems.¹

Opioid receptors are divided into mu, delta and kappa receptors, which are thought to all have slightly different actions. Stimulation of mu receptors is thought to provide the most analgesia, and be responsible for major side-effects such as respiratory depression, sedation, dependence and euphoria. Delta receptors are located peripherally and may also contribute to analgesia. Although these may still cause sedation and dysphoria, stimulation of kappa receptors results in less side-effects than mu receptors and contribute towards analgesia at the spinal level.¹

Opioids act on different receptors to different degrees – a pure agonist (like morphine) acts mainly on mu receptors, with a lower affinity for kappa and delta receptors, but these agonists may also bind to mu receptors with different strengths. Butorphanol is an agonist-antagonist drug that binds strongly and stimulates kappa receptors, but weakly antagonises mu receptors.

Birds

In the past, researchers have had difficulties in stating efficacies of analgesic medication in pet birds because of a lack of a standardised, objective method to measuring a noxious stimulus. A 1999 study using African Grey parrots showed that a withdrawal response could be repeatedly demonstrated using an electrical stimulus to the foot, giving scientists a way to measure the effect of opiates in birds.²

Peripherally, there are three types of nociceptors (high-threshold mechanothermal, mechanical and thermal nociceptors). These serve to detect and transmit information about actual or potential tissue damage. Like mammals, birds seem to have endogenous opioids that modulate central responses to nociceptor stimulation, via mu, kappa and delta receptors.³ Although the receptors seem similar in distribution and concentration across the brainstem and spinal cord, pigeons have been shown to have a higher amount of kappa receptors in the forebrain compared to rats, mice, and humans (76% vs 9, 13, and 37% respectively).⁴ Hence, it has been suggested that kappa-receptors play a greater role in avian analgesia than that of their

mammalian counterparts. It should be noted that the forebrain is thought to be responsible for higher thought processes. As such, does increased stimulation of opioid receptors in the forebrain contribute directly to analgesia or just modulate the birds' perceived response to pain?⁵

Morphine has been shown to have a significant analgesic effect at a dose of 5 – 30mg/kg in chickens.³ However, there is little matching data in other avian species (pet birds, raptors etc), nor on variance in effect seen between routes of administration - intramuscular, intravenous, or per os.

A study of the effect of 0.1 mg/kg (intramuscular) buprenorphine (a partial mu-agonist) in African Grey parrots suggested that mu-agonists might not have as much an analgesic response in these parrots than other animals - though this buprenorphine dose maintained mean plasma concentrations at or above those needed for analgesia in humans, this dose is not known to demonstrate a comparable effect. It was hypothesised that at higher plasma concentrations than recommended in mammals, buprenorphine might 'crossover' to act at different opioid receptors (as demonstrated in other species), and hence appear in birds to provide sufficient analgesia (due to increased kappa-receptor stimulation).⁶

A canine dose of 0.02mg/kg buprenorphine every 6 hours allometrically scales to 0.02mg/kg buprenorphine every 2.4 hours in a 400g bird.⁷ From this, we can see that the amount of buprenorphine given to the birds in this study was five times above that recommended for analgesia in canines. This could be interpreted to give weight to the theory that the greater analgesic effect in birds comes from kappa-receptor stimulation.

In anaesthetised cockatoos and African Grey parrots – but not blue-fronted Amazon parrots - butorphanol at 1mg/kg has been shown to decrease the amount of isoflurane required to prevent response to an applied painful stimulus. It has not been determined if this decrease is due to the analgesic or sedative properties of butorphanol.³

Studies have shown that some larger parrots have had significant levels of analgesia when given butorphanol doses between 2 – 6mg/kg, with the dose required varying between species (2mg/kg in African Grey Parrots, and 3mg-6mg/kg in Hispaniolan Amazon Parrots had similar effects).^{8,9} A canine dose of 0.2mg/kg butorphanol every 4 hours allometrically scales to 0.2mg/kg butorphanol every 1.6 hours in a 400g bird⁷ - like the above study, the relative dose of opioid administered is much higher than that used to achieve effect in other animals.

In birds butorphanol seems to provide effective analgesia with fewer side effects, such as initial transient hyperactivity recorded in cockatoos given increased doses of mu-agonists required for significant pain relief (0.2mg/kg fentanyl subcutaneously). Butorphanol, buprenorphine and fentanyl have all been shown to have a rapid absorption and elimination times. The current recommendation for opioid analgesia in parrots is butorphanol at 1 – 3 mg/kg administered via intramuscular injection every 2 – 3 hours. There have been no published studies on oral opioids in birds. As mammalian doses need to be increased to reach effective plasma levels via oral route, it is hypothesised that so too do bird doses.⁸

What does this show?

There is still a lot of speculation surrounding opioid use in birds. Although there seems to be some scientific support to anecdotal evidence of butorphanol providing increased analgesia over mu-agonists in a clinical setting, this has not been definitively shown to be the case. It has not been determined what effect the increased ratio of kappa to mu receptors in the pigeon forebrain has on pain perception or analgesia – nor if this phenomenon is repeated in all avian species – yet it seems as though this is the basis for the commonly upheld idea of there being an 'increased number of kappa receptors' in birds. Further research is needed in determining opioid effect from differing routes of administration, and in comparing oral opioid absorption across gastrointestinal mucosa in birds to mammals.

Currently we are using information gathered from one species of bird (eg African Grey parrots) to speculate about opioid effects on all the other species. This does not take into account vast differences in anatomical

structure of major drug clearance organs (such as the liver and kidney), physiology and behaviour in these animals.

As they do not usually demonstrate overt signs, it is difficult to clinically assess the 'painful' bird and make an accurate assessment of the analgesia we provide. No conclusions about the more effective analgesic agent (kappa versus mu agonists) in birds can be drawn from the current studies available. Factors that need to be considered in these studies include allometric scaling of drugs given, a consistent and measurable pain response, number of subjects (most studies relied on only a few birds of the same species) and – most importantly – species differences.

References

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