

Pain and its management in Flying-foxes and microbats

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Abstract

Analgesia in flying-foxes and microbats is an essential aspect of treatment and rehabilitation. The unique physiology of both flying-foxes and microbats as well as the most common injuries with which they present to wildlife hospitals and carers at rescue means that the use of analgesia needs to be carefully chosen and balanced with the current physiological status of the animal at the time. The potential adverse affects of certain modalities need to be balanced with their benefit, however, when correctly used, will greatly increase welfare as well as rehabilitation and release outcomes for injured flying-foxes and microbats.

Keywords: pain; analgesia and pharmacology; flying-fox and microbat analgesic modalities; physiology of pain

Introduction

Flying-foxes and microbats often present to wildlife hospitals and carers with injuries involving significant trauma. Fractures, electrocution, netting injuries and barbed wire all cause significant trauma and pain.

The unique physiology of flying-foxes as well as microbats and these afflictions means that animals presented often have underlying physiological conditions which complicate the routine use of many analgesic modalities commonly utilised in other species.

Analgesia is an extremely important modality in the acute and ongoing care in these species, however special consideration and an understanding of the pharmacology of drugs utilised and the timing of these is important to avoid adverse reactions which may compromise the ultimate survival and releasability of patients during and after the rehabilitation phase.

Discussion

Flying foxes and microbats each create challenges as patients due to their unique physiologies and fast metabolic rates.

Being heavy flighted mammals, flying-foxes have metabolic rates twice that of their non-flighted mammals. Flying-foxes are also mainly frugivorous, and nectivorous in nature and have very little ability to concentrate urine. (Lee McMichael et al 2016) Due to this, rescued flying-foxes are often very dehydrated and potentially in a state of shock. Due to their unique physiology and the nature of the most common afflictions of flying-foxes in care, shock, dehydration and heat stroke are common conditions, which need to be considered when creating a treatment plan post rescue.

For microbats, hypoglycaemia, hypothermia and dehydration due to their fast metabolic rates are the most common physiological conditions that need to be addressed when creating a therapeutic plan post rescue.

The use of analgesia in rescued flying-foxes and microbats is not just an animal welfare consideration. The extreme cortisol output seen with acute pain causes immunosuppression and delayed healing as well as a catabolic state and extreme stimulation of the sympathetic nervous system, a problem augmented in patients with high metabolic rates. It can also potentially lead to magnification of pain perception, shock and death.

The use of analgesia, however, does need to be balanced with the potential adverse affects of the drugs used. Hence the need to understand the pharmacokinetics and choose analgesic modalities that do not further compromise the physiological state of the patient at the appropriate stage of care.

Due to the nature of the injuries with which the majority of flying-foxes and microbats present, good analgesia is not only an animal welfare necessity, it is also key to good healing and increased rates of successful rehabilitation and release.

The Physiology of Pain

Pain in animals has been defined as “an aversive sensory and emotional experience representing an awareness by the animal of damage or threat to the integrity of its tissues; it changes the animal’s physiology and behavior to reduce or avoid damage, to reduce the likelihood of recurrence, and to promote recovery” (Molony & Kent, 1997).

The experience of pain is always subjective, which makes the determination of levels of pain, especially in wild and often prey species, which naturally mask pain very difficult.

It can be measured by loss of normal behaviours, abnormal behaviours, reactions to handling and physiological parameters such as increased heart rate, changes in respiratory rates, pupil dilatation and increased or decreased body temperatures.

Pain experience is usually proportional to increasing levels of circulating cytokines from damaged tissues. (Hunton et al 2005) Thus injuries with extensive tissue damage will by nature be more painful.

The experience of pain involves initial detection of a noxious stimulus (mechanical, chemical or thermal) from transduction in nociceptors. These then transmit that stimulus via sensory nerves to the dorsal horn of the spinal cord where the sensation is modulated in the dorsal horn of the grey matter of the spinal cord. A reflex arc will often send a motor signal to move the body part away from the noxious stimulus.

That pain signal is then projected to the brain via the spinal cord where it is perceived by the brain. This is the final step where conscious perception of a stimulus as pain occurs.

The relief of pain is far more complex than solely inhibiting the conscious perception and reaction to pain. A good analgesic plan should aim to block all stages of the body’s perception of pain from nociception through to transduction, transmission, modulation and finally the conscious perception of pain.

This is important as the body starts to react physiologically to pain before pain is perceived consciously. Sensory cell bodies in the dorsal horn of the spinal cord become more sensitive to pain the longer they are exposed to a pain stimulus making pain relief harder to control the longer the sensory inputs from painful stimuli continue, a phenomenon known as “dorsal horn windup”. (Egger & Doherty, 2014)

Severe trauma often involving amputation, which is common especially in flying-foxes post barbed wire and netting injuries, can sometimes develop neuromas (the overgrowth of sensory nerves at a stump) or phantom limb pain. Monitoring and careful management of pain after injury or prior, during and after surgeries can help reduce the incidences of these phenomena.

Good analgesia will also increase anaesthetic stability and recovery of flying-foxes and microbats as many commonly used anaesthetics only render the patient unconscious meaning that they are not consciously perceiving pain, however unconscious perception, sensitization of the nervous system to pain and its physiological consequences are still occurring in the absence of administered adequate analgesia.

PAIN MANAGEMENT

A good analgesic plan should involve good pre-emptive (preventative) analgesia, multimodal analgesia (using differing classes of drugs to simultaneously interrupt the pain pathways at differing points), and good follow up (post-op or discharge medication)

Combinations of drugs often act synergistically reducing doses needed as well as adverse effects of each drug individually.

It must be stressed that all of the drugs mentioned below are off-label use as no official studies have been carried out specifically for registration of drugs in flying-foxes and microbats, which is the case in almost all wildlife. All medications mentioned below are prescription only medications or are restricted or S8 drugs, which must be prescribed by a veterinarian. The exceptions are Panadol® and Aspirin®, which are available over the counter. Doses have been extrapolated and adjusted over years of use, reviewing blood and post mortem results and discussion between veterinarians. A few mentioned drugs have not been registered at all for use in animals to date, however they have been added due to their common use in flying-foxes and microbats.

NSAIDs – Non-Steroidal Anti-inflammatory Drugs

Some NSAIDs offer good relief of orthopaedic pain and aid in the reduction of intraoperative and postoperative pain. They also have a synergistic effect when used in conjunction with opioids, as each mediate anti-nociception via a different mechanism. (Hellyer et al., 2007) Non-steroidal drugs alone are good for mild pain and where anti-inflammatory action is required. NSAIDs are divided into COX-2 specific and the older non-COX-2 specific groups.

Whilst NSAIDs are very useful therapeutically, the adverse effects associated with their use can be serious. There is a narrow therapeutic index for most NSAIDs; therefore, a thorough knowledge of the current physiological status of the organ systems of the patient is required

before their use is considered. The use of NSAIDs in the immediate rescue period can also delay or increase the risk of use of other essential medications once veterinary treatment is sought.

Non-steroidal anti-inflammatory drugs generally block cyclooxygenase (COX) pathways responsible for the production of various prostaglandins. Prostaglandins involved in the COX-1 pathway maintain renal, platelet and gastrointestinal function. Prostaglandins involved in the COX-2 pathway are mainly responsible for the initiation of inflammatory responses giving rise to pain, however they also have some role in the protection of gut mucosa (Halter et al., 2001), meaning that COX-2 specific NSAIDs can also affect gastric mucosa under some circumstances.

Non-COX-2 specific NSAID's, such as aspirin, inhibit both pathways giving rise to common side effects involving gastrointestinal ulceration and renal function damage. These side effects are augmented when blood pressure is low or the flying-fox or microbat is dehydrated. Flying-foxes are particularly susceptible to the effects of non-COX-2 specific anti-inflammatory drugs due to their reduced ability to concentrate urine leading to dehydration in most rescued flying foxes. Non-COX-2 specific NSAIDs are associated with renal damage and failure if used in dehydrated or shocked flying foxes.

COX-2 specific NSAID's such as meloxicam preferentially inhibit the COX-2 pathway responsible for inflammatory responses more so than the COX-1 pathway significantly reducing the adverse effects associated with the use of Non-COX 2 specific NSAIDs.

These are far safer NSAIDs and due to this, the use of non-COX-2 specific NSAIDs is now minimal. Despite this, the susceptibility of especially flying-foxes to GI and renal damage under conditions of shock, heat stroke and dehydration means that all NSAIDs should be used with caution in the first 24-48 hours post rescue until the flying-fox is well hydrated. Microbats do not exhibit the same degree of sensitivity; however, these drugs should always be used in well-hydrated animals to avoid potential side effects.

Acetaminophen (Panadol®)

Although classified as an NSAID, acetaminophen or Panadol® does not appear to work by either COX-1 or COX-2 inhibition. It is believed that Panadol® acts on a variant of COX-1 now called COX-3 that has minimal to no anti-inflammatory action. It is believed that Panadol® achieves analgesia via non-COX pathways. Panadol® is not approved for use in animals with toxicity common in many species. Panadol® can be toxic to the liver.

Despite this, Panadol® has been used @ 15mg/kg every 6-8 hours in many mammalian wildlife species with no known toxic effects, however the analgesia achieved by Panadol would only relieve very mild pain and would be unlikely to be effective for many of the injuries with which flying-foxes and microbats present. The variant including codeine Pain stop® also used @ 15mg/kg of the paracetamol component every 6-8 hours would also only relieve mild pain and would not sufficiently relieve the pain of most injuries with which microbats and flying-foxes present. The Author does not use either of these medications in flying-foxes and microbats due to the availability in veterinary hospitals of safer and more

efficacious options, however the availability over the counter does make these medications attractive for use by carers.

Out of any of the available over-the-counter medications, Panadol® and Pain Stop® (now discontinued) would be the safest to administer to most flying-foxes and microbats directly post rescue, however it must be stressed that these medications only offer very mild analgesia at best and do not replace the need to seek veterinary attention and administer adequate alternative analgesic options as soon as possible.

Aspirin®

Whilst the Author does not use Aspirin® in flying-foxes or microbats, it has been included due to its use post netting and barbed wire injuries mainly in flying-foxes where membrane damage is involved. Its use under these circumstances has mainly been to avoid platelet aggregation with a view to minimise membrane damage associated with these injuries. Aspirin should be used with caution as therapeutic concentrations are very close to toxic concentrations in most species. (Morton & Knottenbelt 1989) Compared to other NSAIDs the analgesic properties of aspirin are also very weak. Aspirin has also been associated with irreversible cartilaginous destruction, irreversible platelet dysfunction, renal impairment and gastrointestinal bleeding and ulceration. (Fox, 2010) The anti-clotting effects on platelets also increases the likelihood of catastrophic bleeds during surgeries if required post administration of Aspirin®. Considering the physiological state of most flying-foxes rescued off barbed wire and netting, (dehydration, heatstroke, shock), the benefits of Aspirin® use do not outweigh the short and long-term risks of its use. Topical medications mentioned below achieve the same function without the systemic side effects seen with Aspirin.

Meloxicam (Metacam®)

Meloxicam is considered a COX-2 specific nonsteroidal anti-inflammatory drug. It offers moderate analgesia for musculoskeletal pain and acts synergistically with opioids. It is the most commonly used NSAID in flying-foxes and microbats @ 0.2 mg/kg SC once daily or 0.2mg/kg PO once daily. Despite Metacam® being a very effective drug, this drug should only be used in well-hydrated animals with good blood pressure. Due to flying-foxes having poor concentrating abilities of their kidneys as well as sensitive GI tracts and usually presenting with hyperthermia, GI and renal compromise, the Author rarely uses Metacam in the first 24-48 hours post rescue until adequate hydration is achieved. In microbats, Meloxicam is safe to use once hydration is adequate. Due to their small size, oral Meloxicam can be diluted with methylcellulose to achieve concentrations able to safely treat microbats whilst the injectable Meloxicam can be diluted with water for injection.

TOPICAL MEDICATIONS

Topical creams and solutions containing local anaesthetics, cortisone and anti-fungals or antiseptic agents are also effective adjuncts for the relief of painful conditions in flying-foxes and microbats.

Neotopic H® – a cream containing Hydrocortisone, neomycin and Lignocaine is absorbed readily into skin and membranes of flying-foxes and microbats and is particularly useful in

post-barbed wire, netting and some electrocution lesions where the cortisone both reduces unwanted micro clotting and infection without the systemic side effects of aspirin as well as offering effective direct pain relief via the lignocaine.

Dermotic® or Surolan® - are both topical solutions that contain cortisone and an antifungal and anti-septic agent useful for treating slimy wing or dermatitis of the wing membranes in flying-foxes and microbats.

Acular Eye drops® - (Keratolac tromethamine) – Topical NSAID – reduces inflammation of the eyes associated with eye lesions – safe to use in ulcerated eyes from exposure ulcers.

LOCAL AND REGIONAL ANAESTHETICS

Applying analgesia directly to affected nerve endings provides excellent pain control by disrupting the nerve transmission by axons at the treatment site directly providing true analgesia. It also results in reduced need for systemic drugs.

Local anaesthetics completely block the sensory nerves and are readily absorbed by mucosal, pleural, joint spaces, the periosteum and peritoneal surfaces. Local infiltration or nerve blocks can be used.

Lignocaine is the most commonly used topical analgesic, takes about 3-5 minutes to take effect and last for approximately 60-90 minutes. Topical local anaesthetics or nerve blocks are useful for painful mouth conditions post barbed wire injuries in flying-foxes.

Infiltration of lignocaine 20% 1:10 in saline over a fracture site also offers good adjunctive pain relief in orthopaedic cases.

OPIOIDS

Opioids are by far the most commonly used analgesics in hospitalised critical flying-foxes and microbats due to their rapid onset of action and safety. Different opioids will offer differing levels of pain relief and side effects depending on which receptors in the brain or spinal cord that they affect.

Despite the fast metabolic rate of flying-foxes and microbats, it is the author's observation that flying-foxes and microbats seem to be particularly sensitive to the affects of opioids in general needing smaller doses of opioids to achieve good analgesia and sedation than other wildlife or dogs and cats. Flying-foxes and microbats also don't seem to experience opioid-induced ileus to the same degree as other wildlife species, most likely related to their naturally faster gastric transit time. It must also be noted that all opioids have the potential to increase intracranial pressure, therefore it is important to always use medications to reduce intracranial pressure when treating head injuries. Pain relief must not be withheld due to this side effect as unmanaged pain can also contribute to increased blood pressure and therefore increased intracranial pressure.

Methadone – potent μ agonist – Methadone or Methone ® 10 mg/ml is a potent analgesic. Methadone is effective against moderate severe pain and its effect is dose dependent. In the

author's experience doses of 0.1 - 0.3 mg/kg IM every 4 hours are effective. For microbats dosing may need to vary from 3-4 hours due to variable metabolic rates associated with injuries and current physiological states. The Author utilized monitoring of heart rate and behavior to titrate the need for repeated doses in various microbat species. Higher doses cause narcosis. Higher doses are usually used as a pre-operative dose for orthopaedic surgery, fractures or for severe extensive burns. Lower doses are good for tissue laceration and peritonitis and severe extensive tissue damage associated with netting. Whilst repeat doses are effective, methadone can achieve a rollercoaster effect in analgesia between dosing meaning that if continued opioid pain relief is required, a CRI of opioid achieves a good constant plane of analgesia and achieves good post op return to normal behavior and eating indicating adequate analgesia has been achieved.

Fentanyl – Fentanyl® 50 µg/ml – also a potent μ agonist 75-125 times more potent than morphine but is quite short acting. Fentanyl is mainly used as a constant rate infusion of CRI after an initial bolus to control severe acute pain is administered. Fentanyl is then used to maintain a constant plane of analgesia, which can be titrated down as recovered before finally weaning off onto alternative analgesia in recovery. In the author's experience the use of fentanyl and methadone are safe when used in pregnant and lactating females.

Fentanyl can be titrated easily based on degree of analgesia required with 1-3 µg/kg/hr. The highest dose is usually used in the 1st 24 hr immediately post op for orthopaedic procedures and 1-2 µg/kg/hr for severe netting, peritonitis and severe barbed wire injuries. Due to size, Fentanyl is rarely used in microbats with yellow-bellied sheath tails being an exception, as the most common use for Fentanyl is as a CRI, requiring IV placement.

Whilst Fentanyl is available as transdermal patches commonly used in small animal practice, the doses that the patches are available in as well as the varied vasculature and uptake of medications via the membranes of flying-foxes and microbats would make uptake quite variable and the degree of analgesia achieved by these patches could not be controlled or guaranteed adequately enough to make them a useful tool for analgesia in these species.

Buprenorphine (Temgesic® - 324 µg/ml)

Buprenorphine is a partial μ opioid agonist meaning that it has a ceiling effect. Increased dosing past a certain point does not increase analgesia achieved unlike the pure μ agonists, methadone and fentanyl mentioned previously. Buprenorphine also has a longer duration of action, around 8-12 hours when used SC. Buprenorphine is mainly used for mild-moderate pain in flying-foxes and microbats. Minor lacerations, minor burns and when weaning off stronger opioids in the post op period after orthopaedic procedures.

BENZODIAZEPINES

The Benzodiazepine class of drugs, whilst not directly analgesic in action, potentiates analgesics via their anxiolytic (reduction of distress) and muscle relaxant properties. They also facilitate the efficacy of lower doses of other drugs thus reducing associated side effects. As myopathy and concurrent muscle spasm is a common physiological complicating factor in

many flying-fox and microbat injuries, the use of Benzodiazepines in a treatment regime is beneficial.

Diazepam (Valium®)

The most commonly used Benzodiazepine used in flying-foxes and microbats. It is of most benefit in the immediate post rescue period for the reduction of stress, facilitation of action and analgesic medications. The Author uses Valium in pregnant females to reduce stress and relax muscles to avoid premature labour. In most cases, combined with effective analgesia and supportive treatment, this has been used with good results.

Dose – 0.5-1 mg/kg IM every 4 hours as required. Note that the dose required can vary depending on the degree of stress and metabolic rate of the bat. It is best to start with the lower dose and repeat if not effective in 5-10 minutes.

NON-PHARMACOLOGICAL ANALGESIC MODALITIES

Stress plays a major role in perpetuating pain and distress associated with injuries. Once in care, the reduction of stressors, cannot be underestimated in their effectiveness and ability to facilitate the effectiveness of analgesic regimes. Warmth, Quiet, immobilising fractures and “slinging” or “hammocking” within the hospital cage can significantly reduce stress and aid in the efficacy of an analgesic regime.

CASE STUDIES

Pregnant little red flying fox

Compound fracture of L humerus – Initially Methadone (Methone®) 0.3 mg/kg I.M once then on Fentanyl 3 µg/kg/hr perioperatively and for the 1st 24 hr post op. Lignocaine® 20% 1:10 infused over fracture site at reduction. Fentanyl® reduced to 2 µg/kg/hr then 1µg/kg/hr over the next 48 hr. Diazepam (Pamlin®) was used @ 0.5 mg/kg I.M. as needed initially to reduce stress and facilitate opioid efficacy, muscle relaxation and stress reduction.

Meloxicam® is started post op once blood pressure is normalized @ 0.2 mg/kg once daily. Around 48 hr post op, Buprenorphine (Temgesic 324 µg/ml®) is started @ 10 µg/kg or 1 ml/30 kg SC every 8-12 hr as needed for pain. Meloxicam is continued orally for 2 weeks. Baby was monitored throughout treatment and birth was normal and released back to wild.

Yellow-Bellied Sheath tail bat – head injured.

The head injury was addressed medically, an IV was placed. Methone® @ 0.2 mg/kg I.M was given initially. Fentanyl was used @ 1 µg/kg/hr for 24 hr and then weaned off to Buprenorphine (Temgesic®) @ 10 µg/kg every 12 hr for a further 24 hr. Meloxicam was then started @ 0.2 mg/kg orally at this point for 1 week.

Large Forest bat female – 8g

Compound fractured L radioulna - Methone® given @ 0.3 mg/kg – diluted 1:100 with water for injection IM (0.03 ml) every 3 hr as needed for pain peri and post operatively for IM pin placement. Lignocaine 20%® diluted 1:10 with saline infused over fracture site prior to

reduction. Meloxicam started post op once blood pressure and hydration good @ 0.2 mg/kg IM - (diluted 1:100 – 0.04 ml SC) once daily – changed to meloxicam cat oral 0.5 mg/ml – diluted 1:10 with methylcellulose – 0.04 ml once daily once oral resumed.

Older Male Flying Fox – Barbed wire entrapment

Oral lesions from barbed wire as well as extensive soft tissue and membrane damage. Had heat stroke on presentation with GI sloughing, severe dehydration and ocular exposure ulcers.

Methone® @ 0.2 mg/kg I.M. initially for acute pain. Fentanyl® @ 1 µg/kg/hr used for 1st 24 hr then Buprenorphine or Temgesic® 324 µg/ml @ 10 µg/kg or 1 ml/30kg every 8-12 hours for pain over next 48-72 hours. Topical Neotopic H® cream was used on membrane lesions for 7 days twice daily. Xylocaine spray® was used topically on an ulcerated area of the gums to facilitate eating. No NSAIDs were used due to heat stroke and gastric mucosal sloughing from heat stroke from struggling on the barbed wire.

Acular eye drops® were used in the eyes twice daily to reduce the pain and inflammation from exposure ulcers due to dehydration without systemic side effects.

Conclusions

Ultimately, more work needs to be done on the delivery of slow release analgesics transdermally, especially in patients too small for IV delivery for these modalities to be available and safe for use in care.

As most people who care for Flying-foxes and microbats would know, pain can be difficult to quantify in patients who instinctively hide injury as a survival mechanism.

These patients can go from being very aggravated and distressed to almost becoming catatonic. Physiological parameters such as breath holding, heart rate and the absence of normal behaviour associated with injuries can assist. The degree of visible tissue damage can assist however many injuries such as peritonitis associated with raptor attack or heat stroke and gut lining sloughing may be very painful and show very little external damage.

A good relationship with a wildlife veterinarian with the help of diagnostic equipment will facilitate the development of an effective analgesic regime.

Normal eating, physiological parameters, behaviour and ultimately the start of healing will return rapidly once adequate analgesia has been administered, which greatly improves animal welfare, treatment outcomes and ultimately successful releases.

Acknowledgements

Thank you to all the carers over the years who have taken my patients and done the hard yards to achieve the releases and helped me learn all of the new things I now use everyday.

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