ANESTHESIA AND ANALGESIA FOR THE CRITICAL PATIENT

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Pain is present with many diseases as well as in association with surgical and traumatic conditions. The demonstration of pain is not always obvious; therefore, an animal should be assumed to be experiencing pain in any condition expected to produce pain in humans. The assessment and control of pain is an art as well as a science. Clinicians should keep in mind that the art of pain management is a continual learning experience requiring assessment and therapeutic adjustment for individual animals even when they are undergoing similar surgical procedures. Therefore, standard or rule-of-thumb analgesic and anesthetic protocols are not always appropriate.

If we accept that animals can experience pain, then how do we determine if a ferret or rabbit is or is not painful? It is likely that the tolerance of pain by ferrets and rabbits varies greatly between individuals, as it does in other species. This coupled with ferrets' innate ability to mask significant disease, and probably pain, make it difficult to assess pain. Compared with dogs and cats, very few investigations have been carried out on the assessment and alleviation of pain in ferrets and rabbits. Most likely, as in cats, the mainstay of pain assessment in ferrets, rabbits, and birds appears to be behavioral.

There are certain behaviors that are commonly seen in ferrets and rabbits suffering acute trauma or postoperative pain. Such ferrets and rabbits are often depressed, immobile, silent, and appear and distanced from their environment. They do not respond normally to petting or attention; ferrets and rabbits tend to hide when experiencing pain. They may also hyperventilate. In the my clinic, I have found that ferrets and rabbits have a very similar response to pain as is seen in cats.

MULTIMODAL APPROACH

The process of nociception and pain involves many steps and pathways, so one analgesic agent is unlikely to alleviate pain completely. An effective management plan includes drugs of different classes, each acting at a different part of the pathway; this is termed multimodal analgesia. For example, a ferret can be premedicated with an opioid, which will modulate pain; ketamine can be used as a part of the induction protocol to reduce wind-up; a local anesthetic block could be incorporated to inhibit transmission; and a nonsteroidal anti-inflammatory drug (NSAID) can be added pre- or postoperatively to alter transduction. This approach also allows smaller doses of each drug to be used as the effects are additive and may reduce any undesirable side effects from larger doses of individual drugs.

Constant rate infusions (CRIs) are delivered intravenously at a constant rate, frequently over a long period of time. Constant rate infusions have several advantages. They allow the drug to be titrated to effect resulting in a reduction in the total amount of drug used, frequently resulting in fewer side effects, less "rollercoaster" analgesia, fewer hemodynamic effects, and more cost effectiveness. Disadvantages include a slow rise in plasma concentrations to therapeutic levels, which is why a loading dose of the drug is frequently given prior to starting the CRI.

The easiest way to administer a CRI is via an automated mechanical pump system. In veterinary medicine, syringe pump systems are the most common delivery system and are mandatory for the small volumes used for rabbits and ferrets. These are small pumps that can utilize a 1 cc to 60 cc syringe for delivery of the drug through an intravenous extension line. The syringe pump is advantageous because it allows very small volumes of drug to be delivered at a constant rate infusion.

PAIN MANAGEMENT OPTIONS IN THE RABBIT AND FERRET

There is no doubt that pain management for rabbits and ferrets in clinical practice is presently inadequate. The ferret and rabbit have an undeserved reputation for adverse respiratory depression after opiate treatment. In the author's opinion, the ferret and rabbit become very comfortable and sleep normally after administration of opioids postoperatively. Birds have mainly kappa pain receptors and therefore respond to kappa agonist drugs for pain relief. Rabbits are very sensitive to the side effects of most drugs. Ferrets are deficient in the glucuronidation pathway as are cats, and inappropriate dosing of NSAIDs can lead to toxicity. Fear of these adverse effects has resulted in many ferrets and rabbits not receiving analgesics after surgery or trauma. Drugs used in rabbits and ferrets are discussed in the next section.

ANESTHETIC/ANALGESIC DRUGS USED IN FERRETS AND RABBITS

The five major classes of analgesics employed for acute pain management are considered in this section. Drugs and dosages used by the author in ferrets and rabbits are discussed.

Opioids

Ferrets and rabbits continue to have an undeserved reputation of having "respiratory depression" after administration of opioid drugs. Resting very quietly without pain is being interpreted as respiratory depression. When used appropriately, opioids can be administered to ferrets and rabbits and are safe and effective for alleviating pain. Opioids in general have a very wide margin of safety and excellent analgesic properties. In veterinary medicine, the most commonly used opioid CRIs are fentanyl, hydromorphone, morphine, and butorphanol. Some animals may respond better to one opioid over another depending on individual variability, breed, species, and source of pain.

Butorphanol continues to be the most commonly used opioid in ferrets despite recent questioning of its analgesic properties. Described as an agonist-antagonist
agent, its agonist activity is exerted at the kappa receptors and its antagonist actions are demonstrated at the mu receptors. Opioid drugs in this class exert a ceiling effect, after which increasing doses do not produce any further analgesia. Butorphanol appears to be an effective visceral, but a poor somatic, analgesic. Butorphanol is a poor analgesic choice for surgery patients where there will be somatic and visceral pain, however. Its ceiling effects limits its use to minor procedures, and the frequent dosing required is inconvenient and expensive. When used in the author’s clinic for treatment of pain in the ferret and rabbit we prefer to use it as a CRI, instead of repeated dosing. Higher doses repeated throughout the day are used in avian medicine for pain relief.

Hydromorphone and fentanyl are mu receptor agonists. They are excellent analgesics for visceral and somatic pain. Intuitively, CRIs are necessary when using rapidly metabolized opioids, such as fentanyl, for operative and postoperative analgesia.

Tramadol (opioid-type drug) is another possible drug to be used orally for postoperative pain control. No studies have been done on use of this drug in the ferret. Tramadol binds to opiate receptors and also inhibits reuptake of norepinephrine and serotonin. The agent thus stimulates two endogenous, antinociceptive mechanisms in the spinal cord and the brain stem.

**Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

NSAIDs are excellent agents for alleviation of acute postoperative and traumatic pain. As in other species there are concerns about preoperative use of NSAIDs in ferrets. The main concern relate to inhibition of prostaglandin synthesis, which may lead to gastrointestinal erosion, impaired renal function, and bleeding. The limited ability for glucuronide conjugation in ferrets can prolong the duration of action of the NSAIDs, but with appropriate changes in dose and dosing intervals they can be used safely. The advantages of this category of drugs are their long duration of action and that no Drug Enforcement Administration (DEA) paperwork is required. In young ferrets with no evidence of renal disease, this group of drugs is a good choice.

Injectable carprofen has become available in the United States, but it is unlikely to be labeled for use in ferrets. Carprofen is a potent inhibitor of prostaglandin synthetase and has proved to be a safe agent in ferrets. Ketoprofen (Ketofen®, Fort Dodge Animal Health) is available as an injectible agent, but because of its COX-1 inhibition, should be reserved for postoperative administration. Meloxicam (Metacam®, Boehringer Ingelheim Vetmedica) is recently available as an injectible and oral form, and is the most commonly used NSAID in the ferret. It has primary COX-2 inhibition. NSAIDs should not be used in animals with preexisting renal disease, hypovolemia, or bleeding disorders or if severe surgical hemorrhage is anticipated. Flunixin meglumine is an NSAID and is a very potent inhibitor of cyclo-oxygenase. Recommendations for its use in rabbits and ferrets with gastric stasis and septic shock are common in literature. This is most likely due to its use in horses in colic. The author warns against its use with preexisting renal disease, hypovolemia, or bleeding disorders as with only NSAIDs. Newer NSAIDs that are specifically COX-2 inhibitors may be safer to use in ferret and rabbits than use of flunixin.

**Local Anesthetics**

Local anesthetic agents can be employed successfully in ferrets. The two most commonly used agents are lidocaine (Lidocaine HCl oral topical solution, USP 2%, Hi-Tech Pharmacal Co.) and bupivacaine. An advantage of this group of drugs is their low cost and uncontrolled status. A complete sensory block prevents nerve transmission, making use of these agents one of the most potentially practical pre-emptive techniques. Local anesthetics can be infiltrated into the surgical skin site, or discrete nerve blocks can be preformed.

**Alpha-2 Agonists**

Alpha-2 agonists as medetomidine (Domitor®, Pfizer Animal Health) possess analgesic, sedation, and muscle-relaxant properties. These drugs are usually reserved for healthy animals because of the cardiopulmonary depression that accompanies their use. Microdose medetomidine preserves the blood pressure effects in healthy animals with good cardiac output, and provides good analgesic, sedation and muscle relaxation when used with a tranquilizer and opioid. These drugs have not been used by the author in ferrets.

**NMDA Antagonists (Ketamine)**

The NMDA receptor plays an important role in the central sensitization, and there is much interest in developing drugs that can inhibit this receptor. In veterinary medicine a commonly used NMDA antagonist is ketamine (Vetake®, Lloyd Laboratories), which may be effective at preventing, or at least lessening, wind-up at subanesthetic doses. When used with gas anesthesia and opioids there is a reported opioid-sparing and gas anesthetic-sparing effect seen. The interesting thing about ketamine is that minute amounts of it need to be used via a CRI to have analgesic effects. Therefore, the cardiovascular effects that commonly occur with the anesthetic doses of ketamine do not occur at the analgesic dose. Ketamine is an excellent adjunct to opioid therapy and frequently allows reduction in the opioid dose being administered.

The author uses micro-dose ketamine continuous rate infusions (CRIs) with opioid CRIs during surgery in the ferret. When the CRIs are combined there is a overall gas anesthetic-sparing affect. The common side effects of gas anesthesia are hypotension and are avoided when combined with ketamine/opioid CRIs.

**ANESTHESIA INDUCTION AGENTS IN RABBITS AND FERRETS**

**Etomidate/Propofol**

Etomidate (Amidate®, BenVenue Laboratories) is an imidazole derivative that undergoes rapid redistribution and hepatic metabolism, resulting in rapid recovery
following a single bolus. Etomidate induces minimal cardiovascular and respiratory depression and has a wide margin of safety. Etomidate is frequently used in the author’s clinic in patients that have poor cardiovascular function. We routinely combine diazepam with etomidate induction in compromised patients. The recommended dose of etomidate after a benzodiazepine premix (ie, diazepam 0.5 mg/kg intravenously) is 1.0 mg/kg.

Propofol (Rapinovet®, Abbott Laboratories) is chemically unrelated to other anesthetic drugs. It has a fast onset and short duration of action. Apnea following administration of propofol is common and is more pronounced with rapid injection of the drug. The author uses propofol as an induction agent in the stable ferret patients at a dose of 4 to 6 mg/kg intravenously.

**Epidural Anesthesia/Analgesia in Rabbits and Ferrets**

Epidural drugs achieve pain relief with less to no systemic effects as compared with drugs administered intramuscularly or intravenously. This factor is important in small mammals when the administered drug has negative side effects, such as cardiac and respiratory depression. Epidural drugs may decrease recovery time, which is always an advantage when working with ferrets and rabbits. The improvement in recovery time occurs because of the decreased percentage of gas anesthesia needed when used in conjunction with an epidural anesthetic.

In most small mammals, after epidural injection of lidocaine, analgesia develops within 10 to 15 minutes and lasts 60 to 90 minutes. Bupivacaine can provide up to 6 to 8 hours of surgical analgesia. Ferrets have been treated with lidocaine 1.5% at 0.4 mL/kg. Bupivacaine can provide up to 5 to 6 hours of surgical analgesia. Morphine at 0.22 mg/kg that is administered into the epidural space provides prolonged postoperative analgesia for up to 24 hours.

**Intubation Techniques for Inhalation Anesthesia**

- Ferrets
  - Endotracheal intubation in the ferret is done in the same way as is described in cats and dogs.

- Rabbits
  - Use of a semi-flexible fiberoptic endoscope (Focuscope) inserted into the endotracheal tube (2.0–2.5 mm ID) from its adapter end, and the tip of the scope is positioned to within 1 to 2 mm of the beveled end of the tube. The semi-flexible endoscope has a portable handheld light source. The endoscope and ET tube is advanced over the base of the tongue until the tip of the epiglottis is visible through the soft palate. The tip of the scope is advanced in a dorso-caudal direction, lifting the soft palate and thus allowing the epiglottis to fall forward. The tube is advanced into the laryngeal opening and the ET (endotracheal tube) tube is advanced over the scope into the trachea. The endoscope is removed.
  - Nasotracheal Intubation. The rabbit is held in extreme extension. An 8 French (small rabbits <1 kg) or 2-mm ET tube is passed medially and ventrally into the nose. The ventral meatus is entered while the ET tube is passed into the larynx and trachea.

- Small Mammals
  - Small mammals may be intubated using the same technique described above for rabbits. When a flexible endoscope is not available, most small mammals are anesthetized and maintained with inhalant anesthesia using a mask.

- Dental Nerve Blocks
  - This is a local block procedure that is used along with opioids and NSAIDs for dental procedures. Anesthesia used is lidocaine 2% is mixed with bupivicaine 0.5% in a ½ cc syringe with a 25-auge needle. For each kilogram body weight mix 0.05 mL of lidocaine with 0.18 mL of bupivicaine and 0.27 mL of sterile water (can increase amount of sterile water to increase the total volume to be given). The total volume will be divided into the number of sites to block. The 5 dental blocks will be described in the lecture and consist of the infraorbital, palatine, mandibular, maxillary, and mental nerve blocks.

**References** are available from the author upon request.