



Florida State University Post-Operative Analgesia For Rodents

Adherence to federal guidelines and regulations as well as Burch and Russell's 3Rs necessitate the use of drugs to alleviate or ameliorate pain and distress associated with research procedures. The basic assumption is that, if a procedure would be likely to cause pain or distress in a human, then it is likely to also do so in animals.

Published literature indicates that providing adequate post-operative pain relief enhances recovery to normal behavior (food and water intake, movement) in almost all species studied to date. Certainly in humans it has repeatedly been shown that successful analgesia has reduced the post-operative recovery period. Research over several decades has demonstrated that surgery and anesthesia both have effects on the hypothalamo-pituitary axis which can be altered with the type of surgery or choice of anesthetic. Analgesia should be provided post-operatively not only to larger mammals, but to rodents as well. The FSU ACUC has determined that post-operative analgesia must be provided in all cases unless non-administration has been scientifically justified in the animal use protocol and approved by the FSU ACUC.

It is important to note that the level, type and duration of analgesia will depend upon the procedure performed. Minimally invasive procedures need less potent or shorter-acting analgesics and may respond to a single dose of analgesic. More invasive procedures (e.g. laparotomy, orthopedic surgery) may require multiple doses of analgesic for up to 72 hours post-operatively. Following are some general recommendations for analgesia in rodents. Remember that analgesia will vary with the individual animal. It is the responsibility of the investigator and staff to evaluate the animal on a routine basis and determine whether additional treatment is needed. It is recommended that investigators consult an LAR veterinarian for the final selection of an analgesic regime as well as with questions as to whether additional treatment is needed.

Local Anesthetics: These agents (e.g. lidocaine, bupivacaine) have been shown to provide effective analgesia by blocking nerve impulse conduction. They can be used topically (e.g. bathe exposed nerves or cut tissues) or injected locally using a fine needle. For thoracic and abdominal surgery they can be instilled post-operatively. Local anesthetics have not been shown to significantly delay tissue healing. These agents can be cardiotoxic, so it is important that a maximum safe dose should not be exceeded (4 mg/kg lidocaine; 1-2 mg/kg bupivacaine). Bupivacaine has a longer duration of action (4-12 hours) than lidocaine (1-2 hours) but takes slightly longer to take effect (5-10 minutes vs. 1-2 minutes). These agents can be diluted in a balanced electrolyte solution to provide more volume for injection or instillation. LAR recommends the use of bupivacaine (0.25-0.5%) over lidocaine due to its longer duration of action. Local anesthetics should not be used as sole analgesic agents except in minor procedures.

Non-steroidal Anti-inflammatory Drugs (NSAIDs):

NSAIDs are an alternative class of compounds for pain management. These drugs act by reducing prostaglandin synthesis by inhibiting one or both of the

COX isoenzymes. These compounds have analgesic activity both locally and centrally and are synergistic with opioids. In addition to aspirin and acetaminophen, newer compounds used extensively for managing pain include carprofen, ketoprofen, ketorolac and meloxicam. The advantage of the newer compounds is that they are not controlled substances and can be dosed once daily. With the exception of carprofen, these drugs should be given in the post-operative period rather than pre-operatively or intra-op to avoid renal problems. There is a delay in the onset of action, so the drug should be given immediately after the procedure is completed and before anesthesia wears off. Combinations of NSAIDs should not be used, as adverse side effects of GI ulceration or renal failure can occur. These compounds may be used as sole analgesic agents in both minor and some major procedures. For rats, LAR is currently recommending the use ketoprofen at a dose of 5 mg/kg subcutaneously once daily (for no longer than 5 days) or meloxicam (0.3-1.0 mg/kg IM, IP, SQ every 24 hours, if repeated injections required or in drinking water dose, Mice: 1.7 ug/ml [0.3 mg/kg/day], Rats: 10.89 ug/ml [1.0 mg/kg/day]).

For significantly invasive procedures or procedures which are expected to have severe pain, these agents should be combined with an opioid for maximum effectiveness. For these types of procedures, LAR recommends at least one dose of opioid (either butorphanol or buprenorphine, see below) and 1-5 days of ketoprofen.

Opioids:

Long known for their potent analgesic activity, opioids remain the gold standard for analgesic therapy. Opioids are the drug of choice for treatment of moderate to severe pain. Side effects such as respiratory depression and bradycardia are dose-dependent and are reduced with the new mixed agonists and agonist-antagonist compounds (buprenorphine, butorphanol). Pica may be seen with buprenorphine, but again is dose dependent and transient. Metabolic rates for opioids are high for rodents, making several of the opioids (morphine, meperidine and pentazocine) impractical for use, however buprenorphine is effective for 8-12 hours after administration. Opioids are ideal for using pre-operatively, which reduces the overall amount of anesthetic needed and allows analgesia to be available when the animal wakes up. The exception to this would be neuroleptanalgesia (e.g. xylazine/ketamine) where buprenorphine or butorphanol may reverse the anesthetic state. While analgesia is excellent with these compounds, there are disadvantages. The primary disadvantage is that all of these drugs are controlled substances and subject to federal regulations for acquisition, record keeping and disposal. Of the opioids, LAR recommends buprenorphine due to its long duration of effectiveness and few side effects. Buprenorphine, however, only comes in 1 ml glass ampules and there are problems with proper storage of the drug after opening an ampule. On average, one - 1ml ampule will dose 6 - 250 gram rats once each. The dose for buprenorphine is 0.01-0.5 mg/kg subcutaneously every 8-12 hours (mice -

0.5-2.5 mg/kg every 6-12 hours). If combining an opioid with an NSAID, a good combination is butorphanol (1-2 mg/kg subcutaneously every 4-6 hours for rats and mice) + either ketoprofen or flunixin (2.5 mg/kg subcutaneous for both rats and mice). For a multiple dosing alternative, buprenorphine can be mixed with Jello (strawberry, grape or cherry appear to be preferred flavors) and dosed by giving 3 of a 4 ml cube per rat twice daily. Contact an LAR veterinarian for specifics on this mixture.