



Veterinary Guidance: Analgesic Plans for Rodents

GOAL: Ensure proper pain relief to rodents undergoing surgical manipulations. Considerations for pain management must include **both non-pharmacologic support as well as the provision of pharmacologic agents**. The veterinary staff can provide guidance on recognition of signs of pain and distress and further consultation during the project design phase is highly encouraged. Regardless of the pain management strategy used, **animals must be evaluated at sufficient frequencies** to determine the appropriateness of the analgesia plan. Assessing pain in rodents can be difficult as they typically minimize pain-associated behaviors unless the pain is incapacitating. The animal may show “normal” behavior as an inherent response to avoid predation. Clinical signs suggestive of pain in rodents include but are not limited to lethargy, rough coat, lack of grooming, and isolation. The rodent grimace scale²⁰, which considers assessment of orbit tightening, nose bulge and ear position, is an additional way to evaluate pain in rodents.

DEFINITIONS:

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Unless the contrary is established, procedures that may cause pain or distress in human beings should be considered to cause pain or distress in animals³

Analgesia: absence of pain in response to stimulation, which would normally be painful.

Analgesic: drug utilized to induce analgesia

Pre-emptive analgesic: analgesic interventions used prior to a painful event such as a surgery. The use of pre-emptive analgesia prevents sensitization of the pain pathways, and therefore is more effective in improving animal comfort than post-inductive analgesia.

Post-inductive analgesic: analgesic interventions used once signs of pain are recognized. Once pain is present, the pain receptors have already been stimulated and hyper-sensitized, thereby requiring more intervention (analgesics) than pre-emptive treatment.

Standard of care guidance for alleviation of pain in rodents:

Non-pharmaceutical interventions should include:

- Gentle handling of the awake rodent as well as gentle manipulation of the tissues intraoperatively to minimize tissue trauma
- Appropriate wound closure including sufficiently spaced wound clips or suture with knots that are secure but not overly tight
- A **warm** dry environment during recovery from anesthesia to prevent hypothermia
- Maintaining a quiet environment during recovery to minimize external stress
- Ensuring the animal has easy access to food/water (rearing up to food bin may be difficult depending on the location of the surgical incision)
 - Mash (3 food pellets + water in a petri dish) or other nutrient based support such as boost or diet gel (Clear H₂O products) placed on the cage floor in a dish and/or
 - Hydrogel (Clear H₂O product) or water bottle with a long sipper tube
- Group housing for socially compatible animals following recovery from anesthesia
- Ensuring enrichment such as a nestlet is present, and utilizing a soft bedding material if a ventral incision is present

Pharmaceutical Interventions should include:

- Appropriate analgesic use as described in the IACUC protocol based on the anticipated level of pain that might be induced by the experimental procedure.
- Ongoing **evaluation of the effectiveness of the analgesic plan to ensure pain/distress is effectively alleviated**. The veterinary staff should be consulted if the animal exhibits signs of pain/distress which are not alleviated by the pre-approved plan as described in the IACUC protocol. Alternatively, if pain cannot be relieved, humane euthanasia may be warranted



TABLE 1: Analgesic guidance based on anticipated pain level

Level of Pain or Distress	Mild	Moderate	Severe
Suggested pharmacologic analgesia plan		Perioperative opioid (1-2 doses) and 3 days of NSAID analgesia	Opioid + NSAID for 3 days +/- local analgesia
Examples of procedures in each category	Tail clipping at 21 days of age or greater, trocar implantation of tumor cells	Ovariectomy, intracerebral implantation, osmotic minipump implantation	Thoracotomy/MI creation, abdominal surgery with organ manipulation (i.e. cannulation of bile duct)

NSAIDS (Non-Steroidal Anti-Inflammatory)

Function by inhibiting inflammation and the production of kinins and prostaglandins. They have varying degrees of effectiveness as antipyretics, analgesics and anti-inflammatory agents. More selective NSAIDS such as (carprofen and meloxicam) can alleviate acute pain, such as that produced by surgery.⁸ In addition, such agents have minimal side effects caused by COX-2 specific inhibiting agents and provide a longer duration of effect thereby minimizing dosing requirements. In a research setting, consideration should be made when evaluating inflammatory, infectious disease or coagulation models.^{16,23} Inhibition of tumor production has been documented for xenograft models, and chemically induced tumors of the mouse skin and rat colon.^{18, 19, 21}

Drug (Brand name)	Dose	Duration	Route	Recommendations
Ibuprofen (Children's Motrin®)	40 mg/kg (Mouse) 20 mg/kg (rat)		PO (in water bottle)	Must be placed 24-48 hours in advance of surgical procedure to ensure therapeutic levels have been reached.
Meloxicam (Metacam® 1.5mg/ml)	5mg/kg (mouse,rat)	Every 24 h	PO	Syringe without needle should be placed in the cheek of a manually restrained rodent
Meloxicam (Metacam® 5mg/ml)	2mg/kg (mouse,rat)	Every 24 h	SQ	Mice: Recommend 0.1ml of meloxicam (5mg/ml) to 1.9ml of sterile saline to create a 0.25mg/ml solution for SQ injection
Meloxicam (Metacam® 5mg/ml)	2mg/kg (mouse,rat)	Every 24 h	Oral	Mice: Bacon Flavored Tablets 0.05mg/tablet (Bio-Serve) Rats: Bacon Flavored Tablets 0.25mg/tablet (Bio-Serve)
Carprofen (Rimadyl® 50mg/ml)	5 mg/kg (mouse,rat)	Every 24 h	SQ	Stock solution is very viscous and requires refrigeration, recommend using a 22g needle when drawing up Mice: 0.1mL of carprofen to 8 ML of sterile saline to make a 0.6mg/mL solution Rats: 0.2mL carprofen to 3.8mL sterile saline to make a 2.5 mg/mL solution
Carprofen (Rimadyl® 50mg/ml)	5 mg/kg (mouse,rat)	Replace as needed (2-3 days)	oral	Mice: Gel formulation (available by Clear H2O) 2oz cup/5 mice Rats: Gel formulation (available by Clear H2O) 2oz cup/ 2 rats



NARCOTICS (OPIOIDS)

Bind to mu, delta and kappa receptors to produce analgesia by blocking nociception and also affect the limbic system, which makes pain more tolerable. Opioids may be classified as agonists (morphine), agonist-antagonists (butorphanol) or partial agonists (buprenorphine) in their activity on these receptors. They are generally indicated for moderate to severe acute pain. Adverse effects have been observed when high doses of opioids are given to pain-free animals including gastrointestinal issues, bradycardia, hypotension, dizziness.^{4,5,6,15} At clinical doses, respiratory depression and sedation are minimal with buprenorphine^{6,14, 22} but elevation of both biliary tract and CSF (cerebral spinal fluid) pressure has been noted.⁷ Potential impacts on fetuses should be considered as opioids do cross the placental barrier.^{6, 10, 22}

Drug (Brand name)	Dose	Duration	Route	Recommendations
Buprenorphine (Buprenex® 0.3mg/ml)	0.1mg/kg	Every 8-12 h	SC	Mice: 0.1mL buprenorphine + 0.9 mL sterile saline to make a 0.03 mg/ml solution
	0.05mg/kg	Every 8-12 h	SC	Rat: 0.1mL buprenorphine + 0.9 mL sterile saline to make a 0.03 mg/ml solution

LOCAL ANALGESIA

Local anesthetic agents can be utilized for topical, local, regional and spinal anesthesia to prevent or alleviate pain. They should be used locally before making surgical incision, or before final skin closure. Lipid solubility and protein binding in the axons determine the potency of these agents, which generally are secondary or tertiary amines that are ester or amide linked. Most of the agents are metabolized by the liver and excreted by the kidneys. CNS and cardiovascular toxicities are possible in cases of overdose or inadvertent intravascular administration^{4, 5,6,15} Research impacts include a potential for modulation of the inflammatory response.^{7,12,17} Protective effects on post-ischemia reperfusion injury and a cecal ligation and puncture model have been documented.^{9,12}

Drug (Brand name)	Dose	Duration	Route	Recommendations
Bupivacaine (Mercaine®)	0.25%, do not exceed 8 mg/kg total dose,	once	SC or intra-incisional	Use locally before making surgical incision, or before final skin closure. Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

Abbreviations used: PO= *per os* or by mouth SC = Sub-cutaneous

Unrelieved Pain and Distress

Unrelieved pain/distress associated with surgery can contribute to immunosuppression of the patient through effects on the hypothalamic pituitary adrenal axis (HPAA), lymphocyte proliferation, and natural killer (NK) cell activity.¹¹ Such impacts can confound research results as well as impact the welfare of the animal. **Unless the IACUC has approved withholding of analgesics based on documented interference with the specific model of interest, analgesics must be used to alleviate pain.** In some cases, the IACUC may require a pilot study be performed to determine the effect of analgesics on the specific model if there is no published information on which to make the determination, keeping in mind that **unrelieved pain or distress can also have a significant effect on data collection.**

PLEASE NOTE: Researchers and the IACUC need to consider not just the factual question of whether anesthesia or analgesics would invalidate the study, but also the ethical judgement whether the potential benefits of the study outweigh the unrelieved pain or distress.²



RESOURCES

ULAR Veterinary Best Practices <http://ular.osu.edu/resources/veterinary-best-practices/>

Rodent Surgical Incisions - Closure Guidelines and Recommendations
Approved Anesthesia Plans for Rodent Survival Surgery
Best Practices for Rodent Survival Surgery

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