

Perioperative Analgesia in Rodents

The Public Health Service Policy on Humane Care and Use of Laboratory Animals states that procedures on animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia or anesthesia. Procedures that cause pain or distress in human beings are now considered to cause pain or distress in animals. While NCI at Frederick fully recognizes the difficulties in objectively assessing perioperative pain in rodents, the NCI at Frederick Animal Care and Use Committee [ACUC] has taken the position that rodents undergoing major surgical procedures must routinely receive the benefit of perioperative analgesic administration unless justified. In general, **major surgery** includes any surgery that penetrates and exposes a body cavity, produces substantial impairment of physical or physiologic functions [such as laparotomy, thoracotomy and craniotomy], or involves extensive tissue dissection or transection. **Minor surgery** does not expose a body cavity, causes little or no physical impairment and includes procedures such as skin biopsy, castration, etc. Signs of pain and distress include: decreased movement, aggression when handled, failure to groom, ruffled coat, and abnormal posture.

In adopting this position, the NCI at Frederick ACUC recognizes that there may be occasions when analgesic use would interfere with the scientific objectives of a study. In such cases, the Principal Investigator can request an exception to the ACUC guideline by including a written scientific justification [e.g., study involves the liver and analgesic is metabolized by the liver] in the animal study proposal for review and approval by the NCI at Frederick ACUC. ***For major surgeries and tumor resection, an injectable analgesic must be used unless an exemption to this guideline, which provides scientific justification, is submitted to and approved by the ACUC.***

The analgesic agents listed below have been used successfully in rodents. The selected analgesic should be administered before the animal recovers from anesthesia, depending on the compound. While a single dose of a relatively long-acting analgesic is expected to alleviate the pain and distress associated with the immediate post-operative period, this initial dosing should be followed by an evaluation of the animal at the expected end of the analgesic's duration, to see if subsequent dosing is required. If you have any questions regarding appropriate analgesia, contact the Laboratory Animal Medicine veterinary staff at 301-846-5577.

Agent	Species	Recommended Administration	Notes
Bupivacaine [Marcaine]	Mouse and Rat	1-3 drops [appx one drop for each centimeter of the incision size] of 0.25% bupivacaine placed on the incision site at the time of closure. 8mg/kg dose should NOT be exceeded.	<p>Related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.</p> <p>Systemic absorption of local anesthetics produces affects on the cardiovascular and central nervous systems. At normal therapeutic doses, changes on the heart are minimal. The onset of action with bupivacaine is ~15 minutes and there is a 4-8 hour period of analgesia following administration. Depending on the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart and brain. Metabolism occurs in the liver and the kidney is the main excretory organ. When administered in recommended doses and concentrations, bupivacaine does not ordinarily produce irritation or tissue damage.</p>

Agent	Species	Recommended Administration	Notes
Buprenorphine* § [Buprenex]	Mouse Rat	0.05-0.1 mg/kg, SC q8-12 hours 0.05 mg/kg, SC q8-12 hours	<p>A thebaine derivative, buprenorphine is a synthetic partial opiate agonist. It has partial agonist activity at the mu receptor and is considered to be 30 times as potent as morphine and exhibits many of the same actions as the opiate agonists. The cardiovascular effects of buprenorphine may cause a decrease in both blood pressure and cardiac rate. It concentrates in the liver, but is also found in the brain, GI tract and placenta. It is metabolized in the liver by N-dealkylation and glucuronidation. These metabolites are then eliminated by biliary excretion into the feces [70%] and urinary excretion [27%]. It has been reported that use of buprenorphine can cause a decrease in IL2 and IL18 production. **Note: Please consider the use of other analgesics for rats due to the fact that the use of buprenorphine can lead to pica in this species.</p> <p>Dosage will depend on the type of procedure. High dose (0.1mg/kg) – if using a solution of buprenorphine diluted to 1:20 a 30g mouse would receive 0.2mL (E.g. – orthopedic, major laparotomy procedures, organ transplantation, thoracotomy) Low dose (0.05mg/kg) – If using a solution of buprenorphine diluted to 1:20 a 30 gram mouse would received 0.1mL (E.g. – punch biopsy, skin incision with tissue manipulation, minor laparotomy procedures, subcutaneous implant)</p>
Buprenorphine SR* [Zoopharm, Buprenorphine Sustained Released (SR)-LAB (1mg/ml)]	Mouse Rat	0.1-1.0mg/kg SC once 1.0-1.2mg/kg SC once	<p>This is a sustained release formula which provides analgesia for up to 72 hours. This solution should NOT be diluted. Due to the small volume necessary the use of tuberculin or Hamilton Syringe is recommended for accurate dosing. Buprenorphine SR may be stored at room temperature in accordance to DEA regulation.</p>

NOTES: *All drugs given PO [Per OS] can be administered in water bottles or in nutritional Jell-O supplements. 1-2 cc of warm sterile NaCL [0.9%] or Lactated Ringer's Solution [SQ or IP] will speed recovery and help prevent post-operative complications.*

*Expired, unwanted, or unneeded controlled drugs must be accounted for and disposed of in accordance with application State and Federal Regulations (21 CFR Title 1317 Subpart A and Subpart C).

- Expired controlled drugs must be clearly labeled as expired (e.g., “expired – do not use”) and kept in a separate place from non-expired drugs within the securely locked cabinet until they can be disposed of properly.
- Expired, unwanted, or unneeded controlled drugs may be disposed of by contacting Biological Safety at NCI-Frederick: 301-836-151
 - <https://ncrifrederick.cancer.gov/ehs/Safety/Biosaety.aspx>

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§Buprenorphine (Buprenex) should be diluted 1:20 (0.015mg/ml) for ease of use in rodents

- One vial (1mL) of buprenorphine (0.3mg) is drawn into a sterile syringe with a 0.2 millipore filter needle [optional] and added to 19mL of sterile 5% dextrose or sterile 0.9% NaCl and dispensed into a sterile vial
- Expiration date is not to exceed 30 days following preparation, unless it is precluded by the original vial's expiration date
- Protect solution from light and store according to DEA regulations

The chart below is an overview of the common surgical procedures conducted at the NCI at Frederick with the LAM veterinary staff's recommendations for analgesics. Please contact the LAM veterinary staff for additional analgesia guidance as it pertains to your specific research requirements.

Procedure	Recommendations
Tumor Excision	Bupivacaine [Marcaine] and Buprenorphine
Skin Incision or Biopsy	Bupivacaine [Marcaine]
Embryo Transfer*	Bupivacaine [Marcaine] and Buprenorphine [Buprenex]
Laparotomy*	Bupivacaine [Marcaine] and Buprenorphine
	Bupivacaine [Marcaine] and Carprofen Tabs
Mammary Transplant or Fat Pad Removal	Bupivacaine [Marcaine] and Buprenorphine or Carprofen Tabs
Intracranial Injections*	Bupivacaine [Marcaine] and Buprenorphine [Buprenex]

**A longer-acting analgesic, such as buprenorphine [Buprenex], must be used in conjunction with bupivacaine [Marcaine]*

Reference: NCI-Bethesda Postoperative Analgesic Recommendations for Mice

Note: Post-operative analgesia should be noted on the cage card with the following minimum information: Date, drug name, dose and route, and initials.