Center for Biomedical Research / IACUC
Standard Operating Procedure - Guidelines

Analgesia Guidelines for Laboratory Animals

Analgesia is the relief of pain without loss of consciousness. Pain is difficult to assess in animals, so indirect signs are often used to identify pain, including abnormal posturing, vocalization, decreased appetite, and self-mutilation. Because of the difficulty in determining when an animal is in pain, animal welfare regulations require that analgesia be provided whenever a procedure is being performed or a condition is present that is likely to cause pain. **In the absence of evidence to the contrary, it is assumed that something that is painful in humans will also be painful in animals.** It is best if analgesia can be provided pre-emptively, or prior to the painful procedure, rather than after clinical signs of pain are observed. Systemic and/or local analgesics may also reduce anesthetic requirements. Several viable options exist for relief of pain in laboratory animals.

Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. The CBR Attending Veterinarian and the IACUC review animal procedures to ensure that proposed anesthetics and analgesics are appropriate for the species and research objectives.

The CBR Attending Veterinarian must be consulted in the planning of procedures or practices that cause pain to animals and is available to provide assistance with or training in the proper administration and use of anesthetics.

Opioids (Buprenorphine)
Opioids exert their effects on the opiate receptors in the central nervous system. Opioids are effective for acute, deep, or visceral pain. The most commonly used opioid in laboratory animal medicine is buprenorphine, which manages mild to moderate pain. Potential side effects include respiratory depression, nausea, vomiting, pica (rats) and constipation. Sustained-release buprenorphine has been associated with dermatitis and ulceration at the site of administration in rats and mice. All opiates are controlled substances, and their use requires special record keeping.

Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Carprofen, Meloxicam, Ketoprofen) Generally, the classification NSAID is applied to drugs that inhibit one or more steps in the metabolism of arachidonic acid (AA). NSAIDs act primarily to reduce the biosynthesis of prostaglandins by inhibiting cyclooxygenase (COX). NSAIDs are effective for pain associated with inflammation. On their own, NSAIDs are effective against pain of mild to moderate intensity. Potential side effects include gastric or intestinal ulceration, disturbance of platelet function, and changes in renal function.

Local Analgesia (Lidocaine, Bupivacaine)
Local analgesics may be administered by several techniques. Anesthetic effects are

seen within 15 minutes of administration and may last from 45 minutes to several hours, depending on the drug used.

1. Infiltration or infusion- injection beneath the skin and other tissue layers along the site of an incision before or after a procedure.
2. Field block, ring block- injection into soft tissues distant from the actual incision in a pattern that intersects the nerve supplying the surgical site.
3. Nerve conduction block- infusion of a small amount of drug or directly adjacent to the sheath of a nerve supplying the surgical site.
4. Topical local anesthetics, such as lidocaine jelly, may be useful for some surgical wounds.

Note that the doses provided **DO NOT** apply for epidural administration.

Abbreviations used in this document:
SQ = Subcutaneous
IP = Intraperitoneal
IM = Intramuscular
IV = Intravenous
PO = Orally (Per Os)
Q = Every

Administration Routes for Rodents

- Direct routes of administration (e.g. oral gavage or parenteral) are strongly recommended for accurate dosing.
- For procedures that cause mild or momentary pain or discomfort, analgesics *may* be given in the water. For procedures that cause a **mild persistent pain or discomfort**, analgesics in the water may be utilized post-operatively**, provided that an initial analgesic dose is administered via a direct route during or immediately after the procedure**. Please see Table 1 below for examples of these types of procedures.
- For procedures that cause **moderate to severe pain**, post-operative **analgesics should be administered directly** via parenteral injection or oral gavage. In most cases, a multi- modal regimen should be considered. Please see Table 1 below for examples of these types of procedures.
- Sustained release (SR) formulations of opioid or non-steroidal anti-inflammatory drugs (NSAIDs) are available and may represent excellent options for decreasing stress associated with multiple injections.
  Principal Investigators must provide a plan for the use of analgesics to manage pain. If PIs are unsure of what may be appropriate, they must consult with the Attending Veterinarian to develop an appropriate analgesic plan. PIs may also consult with the Attending Veterinarian if they would like more information on acquiring sustained release products.

Analgesics may be administered via the drinking water for procedures causing more than mild momentary pain/discomfort if the following are provided as part of the Animal Care and Use Protocol:

The IACUC protocol must include:

- A clearly stated scientific justification indicating why direct administration cannot be used for the study.
- A description of the methods used to ensure animals are consuming the appropriate amount of analgesic water and an outline of how clinical assessments of pain will be performed. It is the investigator's responsibility, in consultation with the Attending Veterinarian, to determine the best methods to accomplish these tasks.
  - Examples for monitoring fluid intake include but are not limited to: measuring the volume or weight of the water bottle to ensure that an acceptable amount of fluid displacement has occurred within the daily time period. This should also be accompanied by daily weighing of each animal to ensure appropriate fluid and food consumption.
  - Examples for clinical assessment of pain include identifying signs such as: hunched posture, decreased or hyper-activity, dehydration determined by a prolonged skin tent when scruffed, ruffled hair coat or lack of grooming, self-mutilation, altered mobility, decreased hind limb rearing behavior, decreased fecal output, or poor nest incorporation.
- A description of criteria for provision of rescue analgesics (additional doses or routes of analgesia given) or euthanasia for any animals identified as having unexpected or unrelieved pain.
- An outline of procedures for replacing analgesic water when an empty water bottle is identified on weekends, nights, and holidays.

Lab personnel must:

- Provide water bottles containing analgesics at least 12-24 hours before the painful procedure. Rodents are neophobic, and they may initially decline to consume water that contains new substances.
- **Include documentation in post-operative records that a daily assessment for the presence or absence of signs of pain was performed**
- Maintain appropriate identification of the cages receiving medicated water by properly labelling bottles and provide signage on the cage stating the analgesic used, the date the bottle was made, and the dose of the drug.

Table 1: Examples of Potentially Painful Procedures in Rodents

Mild Momentary Pain/Discomfort	Mild Persistent Pain/Discomfort	Moderate Pain	Severe Pain
Percutaneous vascular catheter implantation	Tail snipping (adult rodents)	Embryo transfer (surgical)	Orthopedic procedures
Ear notch	Subcutaneous pump or pellet implantation	Ovariectomy/Orchidectomy	Thoracotomy
Superficial tumor inoculation (SQ or similar)		Tail amputation	Organ transplant
Multiple injections		Craniotomy	Major laparotomy with organ manipulation
Tail snipping (neonatal rodents)		Minor laparotomy with minimal organ manipulation	Burns
Embryo transfer (transvaginal)			Trauma models

Table 2: Recommended Analgesic Protocols for Rodents

Mild Momentary Pain/Discomfort	Mild Persistent Pain/Discomfort	Moderate Pain	Severe Pain
Analgesia may not be indicated.	Use any one of the three types of analgesia (local, opioid, or NSAID). *Single dose of injectable analgesia on day of procedure. Analgesia may be given in the water following the initial injection. Additional doses as needed based on pain evaluation.	Use a combination of at least two of the three types of analgesia. For example: NSAID + opioid NSAID + local *Single dose of injectable analgesia on day of procedure. Additional doses provided via injection or analgesia in drinking water for at least 1-2 days following procedure. Additional or rescue analgesia doses provided as needed based on clinical pain evaluation.	Use all three types of analgesia. Where possible, pre-empt the painful event by starting NSAIDs and/or opioids in advance. *At least 3-5 days of **injectable** analgesia. Analgesia in the drinking water is not a reliable source.

Table 3a: Recommended Analgesics for Mice

	DRU	DOSE	ROUTE	FREQUENCY
Opioids	Buprenorphine-HCL	0.05-0.1 mg/kg	SQ, IP	Q 4-6 hrs for first 12 hrs, Q 8-12 hours afterward. Frequency of dosing may be decreased if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia.
	BuprenorphineSR™ (Sustained Release)	2 mg/kg	SQ	Q 72 hrs. Administer first dose 2-4 hours prior to painful procedure to ensure effective analgesia.
NSAIDS	Carprofen	5 mg/kg	SQ, IP	Q 24 hrs
	Meloxicam	1-2 mg/kg	SQ, PO	Q 24 hrs
	Ibuprofen*	50-60 mg/kg/day—10 ml Children's Motrin in 500 ml water**	PO	Continuously in the water (change water every 3 days).
	Ketoprofen	5 mg/kg	SQ	Q 24 hrs, for 3 days maximum.
Local Analgesia	Lidocaine	4 mg/kg (0.4 mL/kg of a 1% solution)	Local infiltration	Do not exceed 7 mg/kg total dose
	Bupivacaine	1-2 mg/kg (0.4-0.8 mL/kg of a 0.25% solution)	Local infiltration	Do not exceed 6 mg/kg total dose

***** All drinking water doses are approximations based on NORMAL daily water consumption for a given species. A neophobic response has been documented when adding drugs to water of rodents, which can cause weight loss, but is usually temporary. The drug should be added to the water several days prior to the painful procedure, to allow rodents the opportunity to acclimate. Drugs delivered via drinking water should not be used as the sole source of analgesia for the first 24 hours after a painful procedure.

Table 3b: Recommended Analgesics for Rats

	DRUG	DOSE	ROUTE	FREQUENCY
Opioids	Buprenorphine-HCL	0.01-0.05 mg/kg	SQ, IP	Q 4-6 hrs for first 12 hrs, Q 8-12 hours afterward. Frequency of dosing may be decreased if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia.
	BuprenorphineSR™ (Sustained Release)	1.0-1.2 mg/kg	SQ	Q 48-72 hrs
NSAIDS	Carprofen	5 mg/kg	SQ, IP	Q 24 hrs
	Meloxicam	1-2 mg/kg	SQ, PO	Q 24 hrs
	Ibuprofen*	60-150 mg/kg/day—25 ml Children's Motrin in 475 ml water**	PO	Continuously in the water (change water every 3 days).
	Ketoprofen**	2.5-5 mg/kg	SQ	Q 24 hrs, for 3 days maximum.
Local Analgesia	Lidocaine	4 mg/kg (0.4 mL/kg of a 1% solution)	Local infiltration	Do not exceed 7 mg/kg total dose
	Bupivacaine	1-2 mg/kg (0.4-0.8 mL/kg of a 0.25% solution)	Local infiltration	Do not exceed 6 mg/kg total dose

***** All drinking water doses are approximations based on NORMAL daily water consumption for a given species. A neophobic response has been documented when adding drugs to water of rodents, which can cause weight loss, but is usually temporary. The drug should be added to the water several days prior to the painful procedure, to allow rodents the opportunity to acclimate. Drugs delivered via drinking water should not be used as the sole source of analgesia for the first 24 hours after a painful procedure.

****** Ketoprofen should be used with caution in rats. Rats given ketoprofen may develop severe gastric ulcers. If used, provide moist food, and watch for side effects such as firm dark feces or a rat that is pale in color indicating possible ulcers. If seen, contact the Attending Veterinarian.
Alternative NSAIDs such as carprofen or meloxicam are preferred.

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