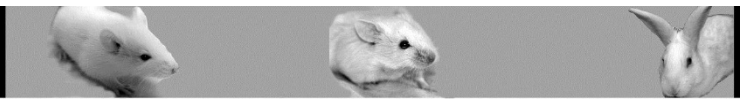
Forsyth  IACUC

Animal Program Policy

Title: **Administration of Analgesia in Rats and Mice**
Date Created: 12/5/2011
Date Reviewed: 7/25/2018

Some research protocols involving the use of animals, especially those involving surgery, are likely to result in pain and/or distress for the animals. It is the policy of the IACUC that such pain and/or distress be identified, minimized or eliminated wherever possible. Administration of analgesics is encouraged as a means to reduce or eliminate pain and distress.

Specific analgesia should be specified in the protocol, but modification of dose, duration, route of administration, or substitution of a different drug from the list below may be enacted **upon approval by the Consulting Veterinarian** without submission of a protocol amendment.

General Considerations:

A procedure which would be expected to be painful if it was done on a human must be considered painful to the animal. When there is a question of whether or not a procedure is painful, the animal should receive the benefit of analgesia. Analgesia should be provided at an appropriate dose, duration and frequency to control pain. Any deviation from this procedure must be justified by the investigator and approved by the IACUC.

Assessment of Pain

Some research protocols, particularly those involving the study of inflammation, may be anticipated to produce pain. In these cases, the IACUC may request the investigator to document the extent of pain experienced by experimental animals. Animals should be observed at appropriate frequencies for signs of pain and distress. The IACUC suggests implementation of the following pain scoring system. In each case, a normal healthy animal would receive a score of 0.

1. Activity (Score 1, relatively distressed; score 2, significantly distressed): hypo activity (huddled, lethargic), hyperactivity, restlessness, lack of inquisitiveness, and reduced food intake
   a. Spontaneous Behavior: These observations are made without disturbing the animal, e.g., vocalization, self-trauma, (isolation from cage mates).
   b. Provoked Behavior: These observations are made when the animal is disturbed or even prodded, e.g., vocalization, hiding, aggressiveness, and minimal response.
2. Fur and skin (score 1, relatively distressed; score 2, significantly distressed) - e.g., unkempt, greasy or dull fur; porphyrin staining around eyes and nostrils; pale or congested mucous membranes or skin (ears, feet, tail); soiled anogenital area.

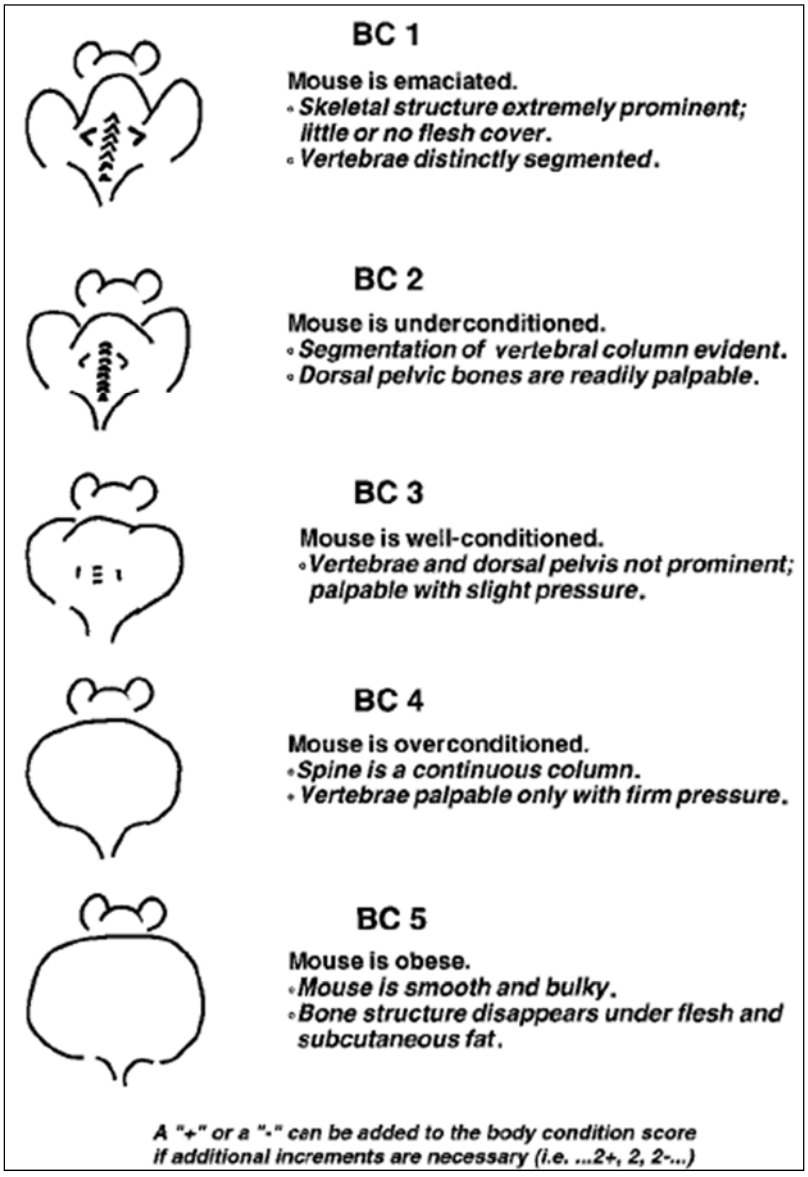
3. Posture and locomotion (score 1, relatively distressed; score 2, significantly distressed)
    a. Posture: hunched back (a sign of abdominal pain, score 2, tucked abdomen, head tucked down.
    b. Locomotion: gait, ataxia, lameness, action of each limb, position of tail when ambulating.

When any animals under experimentation show a total of pain score more than 2, analgesia should be administered. In addition, endpoints should be specified in the case of unrelieved pain.

An alternative method of assessing pain and distress is the Body Condition Score. Scoring the body condition of rodents is a non-invasive method for assessing health and establishing endpoints for adults where body weight is not a viable monitoring tool, such as with tumor models, ascites production and pregnancy, or for young growing animals.

Body condition scores (BCS) range from 1 (emaciation) to 5 (obesity). An anticipated BCS of 2 – under conditioned – or lower, requires justification in the protocol.

Scores are determined by frequent visual and hands-on examination of each animal. The hands-on evaluation is done by gently holding the mouse by the base of the tail and passing a finger over the sacroiliac bones. The findings are matched to the descriptions and diagrams below to determine a score.


BC 1
Mouse is emaciated.
◦ Skeletal structure extremely prominent; little or no flesh cover.
◦ Vertebrae distinctly segmented.
BC 2
Mouse is underconditioned.
◦ Segmentation of vertebral column evident.
◦ Dorsal pelvic bones are readily palpable.
BC 3
Mouse is well-conditioned.
◦ Vertebrae and dorsal pelvis not prominent; palpable with slight pressure.
BC 4
Mouse is overconditioned.
◦ Spine is a continuous column.
◦ Vertebrae palpable only with firm pressure.
BC 5
Mouse is obese.
◦ Mouse is smooth and bulky.
◦ Bone structure disappears under flesh and subcutaneous fat.
A "+" or a "-" can be added to the body condition score if additional increments are necessary (i.e. ...2+, 2, 2-...)

Current IACUC recommendations for analgesia in rats and mice

Oral (in alphabetical order):

Drug name*	**Species**	**Dose**	**Administered Dose**	**Source**
Aspirin	Rodents	100-400 mg/kg	*1-2x per day* for 3-5 days	
Meloxicam	Rats	1.0 mg/kg	.00625 mg/ml 2 ml of 1.5 mg/ml per 500 ml water For 3-5 days	Metacam Anti-Inflammatory Oral Suspension For Dogs 1.5 mg/ml
Carprofen	Rodents	5-10 mg/kg in water	For 3-5 days	
Ibuprofen	Mice	40 mg/kg	4.7 ml Children's Motrin in 500 ml water or 1mg/ml Liqui-gel Caps in water For 3-5 days	Children's Motrin or Advil Liqui-gel
Ibuprofen	Rats	15 mg/kg—2.35 ml Children's Motrin in 500 ml water	4.7 ml Children's Motrin in 500 ml water or 1mg/ml Liqui-gel Caps in water For 3-5 days	Children's Motrin Advil Liqui-gel
Acetaminophen (Tylenol)	Rats	100-300 mg/kg	Orally using dispenser 2 to 3 times a day For 3-5 days. 6mg/ml in drinking water for 3-5 days.	Baby Tylenol Cherry flavored

Normal Daily Water Consumption

Rat 8-11 ml/100 gm body weight/day	Mouse: 15 ml/100 gm body weight/day

Considerations for oral administration of analgesia:

A neophobic response has been documented when adding drugs to water of rats which can cause weight loss but is usually temporary. ("Regarding the Inadvisability of administering postoperative analgesics in the drinking water of rats (Rattus norvegicus)" Speth, Robert C., Smith, Susan, Brogan, Rebecca S. Contemporary Topics In Laboratory Animal Science, 40 (6), 15., Nov. 2001).

Administration of analgesia in the drinking water should take into account circumstances when animals may not drink much, such as in the immediate post-surgical period, and provide alternative routes of administration.

Injectable analgesic options:

Drug	Species	Dose	Route	Source	Frequency
Buprenorphine **	Rodents	0.05-0.1 mg/kg	IM, SC, IP	See Yoga Henry Schein	Daily – 2X for 3 days
Buprenorphine ** (sustained release) Bup-SR 1mg/ml in 5 ml vial	Mice Rats	0.15 -1.0 mg/kg 1.0 – 1.2 mg/kg	SC	Buprenorphine HCl SR, ZooPharm, Fort Collins, CO See Yoga	Once in 72 hours. **Recommended**
Flunixin meglumine (Banamine)	Rodents	2.5 mg/kg	SC	See Yoga	1-2X per day
Ketoprofen	Rodent	5 mg/kg	SC	See Yoga	Daily for 3-5 days
Carprofen	Rodents	5-10 mg/kg	SC	See Yoga	Daily for 3-5 days
Meloxicam	Rats	1.0 mg/kg	SC	See Yoga	Daily for 3-5 days

**** Buprenorphine is a controlled substance. Contact the Director of Animal Care for information on use.**

Surgical Analgesia

Even with general anesthesia, the topical, subcutaneous (at surgical incision site), intra-articular, etc. administration of a local anesthetic is recommended in order to provide additional post-surgical analgesia. Local anesthetics should not be used alone to provide post-surgical/post-procedural analgesia.

Buprenex Use: Consideration should be given for use as pre-emptive analgesia just before the surgery, to assure adequate analgesia post-operatively.

Agent	Potency Procaine=1	Onset	Duration*	Topical Use	Infiltration Use	Nerve Block Use
Lidocaine (Xylocaine)	2:1	Fast	2 hours	2-4%	0.5-2%	0.5-2%
Bupivicaine (Marcaine)	8:1	Int	24 -48 hours	-	0.25%	0.5%

* Duration is given for larger species. Duration in rodents (with their higher metabolic rate) should be considered to be less than indicated above.

IACUC recommendations

Ibuprofen has been recommended for use as a pain reliever with a wide ranging dose of 7.5 to 30 mg/kg (Liles, JH and Flecknell, P, 1992 "Use of NSAID for Relief of Pain in Rodents and Rabbits" Lab Animal 26: p. 241-255). Thus, this compound can be used as an additive to water to treat mild to moderately painful conditions. Liqui-gel caps are suggested to be superior to Children's motrin, but are more difficult to dilute in water (Ezell et al).
Carprofen is also recommended for use in water as an alternative.
Buprenorphine is recommended following major surgery. The long-acting form of the drug is provides longer duration analgesia than standard forms and is recommended.

Acetaminophen

Acetaminophen (Tylenol) has been used in the past for easily administered pain relief through the drinking water for rats and mice. However, it is not conclusive whether this drug has been proven to be an effective pain reliever when administered in this manner. Using acetaminophen in the drinking water for pain relief in rodents has to be carefully considered.

In certain instances, oral acetaminophen is the only drug of choice. Eg: In spinal cord injury studies, it is recommended as a suitable pain relieving agent. It is reported that Tylenol use is an effective treatment for neuropathic pain and also to avoid autophagia. (Dose: 100-300 mg/kg orally for 3-5 days).

Additional characteristics of analgesic drugs

Ibuprofen

Ibuprofen has anti-inflammatory, analgesic and an anti-pyretic (fever) activity. Ibuprofen is a non-specific COX inhibitor resulting in decreased prostaglandin formation. It is well absorbed orally and the majority is excreted in the urine within 24 hours with a small amount also excreted through the stool. Excretion is virtually 100% within 24 hours of the last dose. Possible side effects include GI ulceration, blood thinning effects (avoid use with blood thinning drugs), decrease in efficacy of blood pressure lowering drugs, and an interference with secretion of lithium and aminoglycosides that can result in increased blood levels of those drugs. At higher doses, some renal effects may be seen as well. No studies of effects in pregnancy have been completed (pregnant humans only use it on advice from their doctors) and it is excreted in small amounts into milk. Ibuprofen is available as an oral suspension (100mg in 5 ml) from Henry Schein.

Carprofen

Carprofen (Rimadyl) is a relatively new drug which has been used in water but has not been scientifically proven to be effective in this route. (It has, however, been shown to be effective when delivered in jello – Flexnell, 1999 "Comparison of the Effects of Oral or Subcutaneous Carprofen or Ketoprofen in Rats Undergoing Laparotomy" Veterinary Record 144(3): 65-7). Carprofen is a NSAID and has a much more selective effect than Ibuprofen (inhibits COX 2 while allowing COX 1 activity) which protects the GI system while still being effective in lowering pain. In normal dogs, doses up to 10X the recommended dose resulted in little adversity. Animals with chronic disease appear to be most at risk for developing toxicity with this drug. Effects such as GI problems, hepatocellular damage, renal disease, blood thinning effects on platelets activity, and hypoalbuminemia have been reported. Recommended dose is 5-10 mg/kg orally (Plumb Veterinary Drug Handbook, 4th Edition, 2002).

Meloxicam

Another new NSAID that is available for oral use is Meloxicam. It is expensive and thus may not be practical for everyday use but it also shows a more selective inhibition of COX 2. A dose of 1.0 mg/kg orally or subcutaneously once a day for rats has been given.

Other resources:

1. National Institute of Health, Office of Animal Care and Use: "Guidelines for Pain and Distress in Laboratory Animals: Responsibilities, Recognition and Alleviation", Revised 11/14/12. (PDF Document, 7 pages)" http://oacu.od.nih.gov/ARAC/documents/Pain_and_Distress.pdf
2. Mook, Deborah M., "The Use of Analgesic in Rodents and Rabbits" Emory University, website, updated 8/2009. http://www.dar.emory.edu/vetcare/analgesic_drugs.php
3. Flecknell P.A. 1996. Anaesthesia and analgesia for rodents and rabbits. In: Handbook of Rodent and Rabbit Medicine, Laber-Laird K, Swindle MM and Flecknell PA, eds., Pergammon Press, Butterworth-Heineman, Newton, MA, pp. 219-37.
4. Anesthesia and analgesia 2008. ACLAM text.
5. Laboratory Animal Medicine James Fox, Editor in Chief Academic Press 2015 Chapter 24, section II, pages 1137-1138.

Adapted from:
http://www.research.cornell.edu/care/sops.html#anesthesia
http://www.ahc.umn.edu/rar/AcetaminophenUpdate.doc

Recent references:
J Am Assoc Lab Anim Sci. 2012;51(5):609-15.
Palatability and treatment efficacy of various ibuprofen formulations in C57BL/6 mice with ulcerative dermatitis.
Ezell PC, Papa L, Lawson GW. PMID: 23312090

Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats.
Foley PL, Liang H, Crichlow AR.
J Am Assoc Lab Anim Sci. 2011 Mar;50(2):198-204.
PMID: 21439213

Pharmacokinetic Comparison of Sustained-Release and Standard Buprenorphine in Mice
Tannia S Clark, David D Clark, Robert F Hoyt Jr
J Am Assoc Lab Anim Sci. 2014 July; 53(4): 387–391.
PMCID: PMC4113239

Body condition scoring: a rapid and accurate method for assessing health status in mice.
Ullman-Culleré MH, Foltz CJ. Lab Anim Sci. 1999 Jun;49(3):319-23. PMID: 10403450

Sustained-Release Buprenorphine Improves Postsurgical Clinical Condition but Does Not Alter Survival or Cytokine Levels in a Murine Model of Polymicrobial Sepsis. Herndon NL, Bandyopadhyay S, Hod EA, Prestia KA. Comp Med. 2016 Dec 1;66(6):455-462. PMID: 28304248 Free PMC Article

Efficacy of Sustained-Release Buprenorphine in an Experimental Laparotomy Model in Female Mice. Kendall LV, Wegenast DJ, Smith BJ, Dorsey KM, Kang S, Lee NY, Hess AM.
J Am Assoc Lab Anim Sci. 2016 Jan;55(1):66-73. PMID: 26817982 Free PMC Article