



Dartmouth College

Animal Care and Use Program

Institutional Animal Care and Use Committee

IACUC Guidelines

Title: Guidelines on Analgesia in Research Animals

Guideline: In a continuing attempt to balance judiciously the research objectives and the legal and moral obligation to alleviate pain in laboratory animals, the Dartmouth College IACUC has adopted the following position:

Unless there is a scientific or other justified reason to the contrary, investigators must administer analgesics for procedures associated with more than momentary or slight pain in animals.

Protocols for administering analgesics are better developed for some species (i.e., dogs) than others (i.e., rodents sp.), and each type of analgesic may have different efficacy in the alleviation of different kinds of pain. Therefore investigators should consult with the ARC Veterinary staff when designing an analgesia regimen for their animal care and use protocol.

If a painful procedure needs to be performed without the use of analgesic because it would defeat the purpose of an experiment, then the experimental procedure (without analgesics), justification for withholding analgesia, monitoring protocol, and endpoint(s) must be incorporated into the Animal Subjects Review Form (ASRF) and approved by the IACUC prior to implementation.

Issues:

- The evaluation of potential pain is complex because thresholds and manifestations of pain and distress vary among species and among individuals within a species.
- The determination of what constitutes pain in animals is further complicated by the fact that there are no universally agreed upon criteria for assessing or determining what is, or is not, painful to an animal.
- The alleviation of pain and distress is often a diverse task that may require drugs, adjustments to environmental enrichment, modifications in research protocols and other appropriate and human strategies.

For analgesic questions, consult the ARC Veterinary Staff at 603-650-7592. Analgesics commonly used for laboratory animal species will be listed in a separate section.

Indications for Use: Operative procedures which cause pain in humans should be expected to cause pain in animals. In determining which procedures require pre/postoperative analgesia, several factors should be considered, including:

The invasiveness of the procedure:

- Are body cavities invaded?
- Are especially sensitive tissues involved, e.g., bones or teeth?
- Is significant tissue destruction or inflammation produced?

The degree of severity of pain expected:

- How painful is a similar procedure in humans?
- This can be determined by observing the behavior of the animal during postoperative period; e.g., level of activity, appetite, dehydration, roughness of hair coat compared to sham anesthetized controls, weight loss.

Preoperative analgesia:

- The analgesic is given 30 minutes before surgical insult. Postoperative doses are given in accordance with the duration of action for the selected drug(s) vary by species. See Appendix 2. Combinations may be used.

It is important to administer the analgesic preoperatively. *Preoperative analgesia is recommended for the surgical procedures described below* because even though the animals are unconscious during anesthesia and surgery, the peripheral nerves carrying nociceptive information are still active. The nociceptive information arriving in the central nervous system produces changes that increase the perception of pain once the animal has regained consciousness. To be most effective the analgesic should prevent this noxious stimulus from reaching the central nervous system. Some anesthetic regimens contain an analgesic such as xylazine in the ketamine/xylazine mix commonly used in rodents. Other anesthetics (i.e., most inhalation anesthetics such as isoflurane) have no analgesic properties and must be used with an analgesic when a painful procedure, even a minor procedure, is performed. In addition, there are certain drugs that should not be combined. For example, *rodents should not receive preoperative buprenorphine when xylazine is used!*

Postoperative analgesia is desirable for surgical procedures involving penetration deeper than the skin and subcutaneous tissues including the invasion of bones, joints, teeth or significant destruction or inflammation in other tissues.

The following categorical examples may be useful in determining the necessity for supplementary postoperative analgesia in procedures involving experimental or instructional use of animals. **In all cases, however, analgesics should be given if signs of pain are observed.**

Category 1 – Pre-operative analgesia is required; however no postoperative analgesia is required unless signs of pain are observed. In some cases (i.e., ketamine/xylazine use in rodents) pre-operative analgesia is provided by the choice of agents used for anesthesia. Inhalation anesthetics generally have little to no analgesic properties, and analgesics must be used in conjunction with these agents. Please consult with the ARC Veterinary Staff (603-650-7592) for clarification as needed.

Procedures likely to cause mild or no postoperative pain or discomfort, e.g.:

- injections of substances of low irritation potential
- relatively non-invasive catheter or electrode placement
- skin incisions, suture or wound clip placement
- dental cleaning
- SC implant of miniosmotic pump in rodents
- embryo transfer in rodents
- Intrathecal catheter
- bone marrow aspirates
- cranial implants (canulas)
- splenectomy in mice
- vasectomy in mice
- tailing in mice

- thyroidectomy
- cutaneous mass removal
- most endoscopic surgeries with minimal tissue manipulations

Note: as more research is done, these recommendations may change!

Category 2 – Pre-operative analgesia plus 2 days of post-operative analgesics are required. Once the prescribed number of days is past, analgesics should be given as needed to control signs of pain. In some cases (i.e., ketamine/xylazine use in rodents) pre-operative analgesia is provided by the choice of agents used for anesthesia. Inhalation anesthetics generally have little to no analgesic properties, and analgesics must be used in conjunction with these agents. Please consult with the ARC Veterinary Staff (603-650-7592) for clarification as needed.

Procedures likely to cause mild to moderate pain or discomfort of short duration (12-48 hours), e.g.:

- castrations, including ovariectomies
- invasive electrode or catheter placement
- extra ocular and intra ocular surgery
- thymectomy in mice
- extensive dissection of soft tissues
- entering into pleural or peritoneal cavity with significant tissue trauma
- orthopedic or dental surgery
- dissection into joints

Pain Recognition by Species: Most of the acute or chronic clinical signs are not an absolute indication of pain as they may be associated with other problems, e.g. diseases. Experiences and professional judgment must be used, along with specific laboratory tests, to determine the cause and severity of the problem. It is imperative that research and animal care staff receive adequate training in how to recognize clinical signs of pain. If signs of pain are evident after discontinuing analgesics please consult the ARC Veterinary staff.

Signs of pain which are common for many species include anorexia with subsequent loss of weight, abnormal posture and self mutilation. Listed below are additional signs of pain for individual species and can be utilized to assist investigators and animal care staff in recognizing some degree of pain.

Bird – Birds hide signs of pain better than most other species. This, and the fact that the feathers make it difficult to visually assess the animal, means that by the time the changes are evident, the bird is quite debilitated. Clinical signs of pain in birds may include:

- decreased activity
- ruffled feathers
- not perching or perching in abnormal locations in the cage
- decreased appetite
- weight loss
- abnormal vocalization or no vocalization
- dehydration
- changes in stool appearance (color and consistency)

Cat – Cats in pain are generally silent but may howl or hiss when approached. Clinical signs of pain may include:

- tendency to hide
- still posture and may sit hunched in sternal recumbency with reluctance to stretch out
- howl and show demented behavior with desperate attempts to escape

- ungroomed appearance, with a change in normal temperament
- dilation of pupils, with increased pulse rate and panting
- behavioral changes

Dog – Dogs in pain are generally quieter and less alert with stiff body movements and an unwillingness to move. Clinical signs of pain may include:

- lying still or standing crouched
- restlessness
- shivering, increased respirations while panting
- may whimper or howl when left alone, or growl without apparent provocation and become vicious when handled
- may bite or scratch at painful regions
- behavioral changes

Ferret – Ferrets are normally very curious, inquisitive, and active in the exploration of their environment and interactions with cage mates and people. If these behaviors are absent, it may be an indicator for pain. Other clinical signs of pain may include:

- lack of interest/interaction with environment
- lethargy
- anorexia
- vocalization when handled
- rough/ungroomed appearance
- mutilation of painful area
- may become aggressive when handled

Goat and Sheep – Sheep and goats may appear dull and depressed with little interest in their surroundings. Clinical signs of pain may include:

- teeth grinding
- rapid and shallow breathing
- sudden drop in milk yield
- violent reaction to handling or rigid posture designed to immobilize the painful region
- changes in facial expression, grunting or grinding of teeth
- changes in gait or posture

Pig – Pigs normally squeal and attempt to escape when handled but these behaviors may be accentuated by pain. Clinical signs of pain may include:

- changes in gait or posture
- unwilling to move and may hide in bedding

Primate, Non-Human – Non human primates show little reaction to surgical procedures or to traumatic injury. Obvious signs of pain are not readily seen. However, signs of pain may include:

- reduced appetite and/or reduced interest in food treats
- huddling in a crouched posture, head pressing, touching or pushing or scratching affected areas, favoring limbs, reduced movement, increased or decreased aggressiveness toward care givers, and other changes in behavior
- avoid companions
- poor or absent grooming
- increased attention from cage mates
- facial contortions, clenching of teeth
- restlessness and shaking accompanied by grunts or groans
- self mutilation

Rabbit – Rabbits in pain may be apprehensive, and assume a hunched posture or unwillingness to move. Other clinical signs of pain include:

- exaggerated reactions to handling, sometimes with vocalization
- excessive scratching or licking
- teeth grinding
- increased respiratory rate
- dilation of pupils
- anorexia

Rodentⁱ - Rodents in pain usually exhibit decreased exploratory behavior, piloerection, hunched posture, rough and ungroomed hair coat and ungroomed appearance. It must be emphasized that these signs are also associated with illness. Consult Veterinary Services for evaluation. Other clinical signs of pain may include:

- excessive scratching and licking
- more aggressive when handled
- vocalization when handled
- weight loss
- porphyrin tearing (rats)
- twitching of the back and flank (following laparotomy)
- mutilation of painful area

ⁱ Roughan and Flecknell (2001) identified the following as useful (more specific) indexes of pain in Wistar rats: twitching of the back and flank, a momentary loss of, or compromised, balance (fall), a cat-like arching of the back, and a squirming of the flank...twitching and arching back were shown to be of particular value...in assessing analgesic efficacy.