Guidelines on Veterinary Anesthesia and Analgesia

CONTENTS

BACKGROUND

It is the responsibility of investigators and instructors to mitigate pain and distress in animals used in research and instruction. Unfortunately, objectively measuring pain and distress in the wide variety of animals used in research and teaching is very difficult. Therefore, the National Research Council Committee on Recognition and Alleviation of Pain in Laboratory Animals concluded that **all vertebrates should be considered capable of experiencing pain**.[1] Adequate and consistent alleviation of pain results in reduced variability in experimental data, and improved scientific outcomes. Appropriate pain management and humane endpoints, can prevent or reduce animal pain in most experimental designs without compromising the scientific validity of the research.

Specific Guidance Documents (emphasis by authors):

- Office of Laboratory Animal Welfare PHS Policy on Humane Care and Use of Laboratory Animals Principle #4 states: Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. **Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals**.
- United States Department of Agriculture Animal Care Policy #11 defines a painful procedure as "**any procedure that would reasonably be expected to cause more than slight or momentary pain or distress in a human being** to which that procedure is applied, that is, pain in excess of that caused by injections or other minor procedures."

Key Points

- OLAW PHS policy #4 and USDA Animal Care policy #11 indicate that investigators should assume that a procedure that is painful to a human would be painful to an animal.
- Assessing for pain in animals can be difficult. *Any* changes in posture or behavior should be considered as signs of pain and ought to be addressed.
- Pain management should start prior to initiation of a painful procedure and should continue for a *minimum* of several days following a painful procedure.
- Multi-modal analgesia, as opposed to a single analgesic, should be considered for any painful procedure or situation that is moderate to severe.
- Local anesthesia should be considered for all surgical procedures as a part of a multi-modal analgesic plan.
- General anesthetics cause physiologic changes (hypothermia and hypotension) that need to be considered and addressed.
- Recording the use of analgesics and anesthetics and monitoring their effectiveness are important for improving surgical outcomes and animal welfare.

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The determination of whether animals are likely to experience stress, distress, or pain should be determined during the protocol veterinary review process through discussion between the investigator and a veterinarian in the Office of the University Veterinarian - https://www.research.vt.edu/university-vet/. An appropriate pain/distress management plan, including anesthesia, should be determined on a case-by-case basis. If a study must tolerate a level of pain or distress to obtain valuable data, scientific justification must be provided in the IACUC protocol. For detailed descriptions of the USDA pain categories, please refer to https://www.researchcompliance.vt.edu/iacuc/sites/researchcompliance.vt.edu.iacuc/files/guideline_-_usda_pain_categories.pdf.

ANESTHESIA

Anesthesia eliminates the animal's conscious perception of pain during a painful procedure. There are two main types of anesthesia: local anesthesia and general anesthesia. In most laboratory animal species, general anesthesia is the predominant means of effective pain management. However, these two types of anesthesia can be used concurrently to provide significant pain relief by means of preventing post-procedural wind-up pain.

LOCAL ANESTHESIA

Local anesthetics (lidocaine, mepivacaine, proparacaine) are effective in awake, sedated, and anesthetized animals. Their effect is due to reversible inhibition of neural conduction. Multiple techniques for delivery of local anesthesia are available:

- Epidural anesthesia
- Regional nerve blocks
- Local administration at site of painful procedure
    - Subcutaneous infiltration at the site of surgical incision prior to surgery
    - Ophthalmic drops for retro-orbital blood collection

Advantages of using local anesthetics include:

- Possible reduction of required dose of general anesthetics
- Anti-inflammatory properties which can allow for an earlier return to function
- Comfortable awakening from surgery
- Excellent post-operative analgesia without sedation

Disadvantages of using local anesthetics include:

- Certain techniques require technical expertise
- Relatively short duration (4-6 hours for long-acting drugs)

GENERAL ANESTHESIA

Animals should be anesthetized for procedures that are painful and require unconsciousness (i.e. surgical procedures). There are multiple drug combinations for providing general anesthesia including injectable drug combinations (i.e. xylazine/ketamine) and inhalant anesthesia (isoflurane). Anesthetic choice will depend on species, procedure, duration of procedure, age of animal, amongst others. **In general, inhalation anesthesia is superior to most injectable forms in regards to safety and efficacy**. In addition, it should be noted that not all anesthetic drugs provide pain relief.

Hypothermia can be used as **anesthesia in neonatal rodents** during the first week of life for short, minor surgical procedures (less than 15 minutes). Neonatal rodents are placed on top of a bed of well-packed crushed ice with a

nitrile or latex glove between to protect the skin from thermal injury. Mice should be appropriately anesthetized after 2-4 minutes of contact time with the ice. Recovery from hypothermia is facilitated by gentle external warming.

Anesthetic Depth

It is important to maintain an appropriate depth of anesthesia to ensure adequate analgesia while preventing inadvertent overdose and death. The most useful means of ensuring adequate depth is suppression of withdrawal responses secondary to noxious stimuli (very hard toe pinch). Anesthetic depth is easier to adjust when using inhalant anesthetics compared to injectable drugs.

Physiologic Support

Unwanted side effects of general anesthesia include loss of thermoregulation, dehydration, decreased blood pressure and respiratory drive. Therefore, **animals under general anesthesia must be monitored and supported as needed**. Some physiologic changes can be anticipated and the animal supported from the initiation of anesthesia and throughout the procedure.

- **Hypothermia** alters the animal's ability to metabolize the drugs used to cause general anesthesia, slowing down drug metabolism and elimination. Thus, animals that experience hypothermia will also experience prolonged recovery and even inadvertent overdose. In addition, hypothermia has been shown to increase the incidence of post-operative infection, increase cardiac morbidity, and increase blood loss during surgery.[3]

  The degree of hypothermia is dependent upon:
  - Size of the animal → small animals, such as rodent, have a higher body surface area to body mass ratio compared to large animals, such as horses and cows. Therefore, there is relatively more skin available in small animals to release heat from the body's core which causes body temperatures to drop much more quickly than in larger animals.
  - Duration of anesthesia → General anesthesia impairs an animal's ability to thermoregulate. Therefore, the longer an anesthetic procedure is, the longer the animal will lose body heat.
  - Surgical exposure of a major body cavity → any surgery that exposes the thoracic or abdominal cavities compounds the effect of small body size by creating a direct outlet for core body warmth escape.

  Prevention of hypothermia during general anesthesia is recommended to prevent the adverse effects. All small animals, all animals that have a long procedure, and all animals that have a procedure that exposes a body cavity should have external warmth supplied starting at the initiation of general anesthesia. Products available include:

Rodents	**Larger Animals**
Circulating warm water blankets	Circulating warm water blankets
Warm subcutaneous fluids	Warm intravenous fluids
Warm intraperitoneal fluids	Bair Huggers®
Homeothermic blanket (Harvard Apparatus)	Warmed blankets
Heat lamps	

- **Hypotension** decreases the delivery of oxygen to tissues and can lead to organ damage. For lengthy procedures, the provision of isotonic fluids should be considered to **prevent significant hypotension**. In

rodents, the fluids can be administered subcutaneously or intraperitoneally. In larger animals, the fluids should be administered by continuous intravenous infusion through a catheter.

SEDATION/ANXIOLYSIS

Sedation and anxiolysis are often adjuncts to general anesthesia, but can be used in isolation. Sedatives (alpha-2 adrenoreceptor agonists, barbiturates) produce dose-dependent states of CNS depression, which can range from mild somnolence to general anesthesia to death. Anxiolytics (phenothiazines and benzodiazepines) are drugs that reduce anxiety or fear. These drugs can produce a state of relaxation and indifference to external stimuli. **Of all the aforementioned drugs, only the alpha-2 adrenoreceptor agonists (xylazine, detomidine, metdetomidine, and romifidine) have analgesic properties.**

ANALGESIA

For most laboratory animal species, pain is assessed based on the animal's clinical appearance and overall behavior. In all cases, **pain must be assumed to be present if the animal underwent a procedure, or an illness was induced that would normally cause pain or discomfort in humans.** Below is a table delineating generalized signs of pain in laboratory animals (adapted from NRC Committee on Recognition and Alleviation of Pain in Laboratory Animals 2009):

Behavioral Signs of Persistent Pain	
Guarding	The animal alters its posture to avoid moving or causing contact to a body part, or to avoid the handling of that body part.
Abnormal appearance	Different species show different changes in their external appearance, but obvious lack of grooming, changed posture, and a changed profile of the body are all observable signs. In species capable of some degree of facial expression, the normal expression may be altered.
Altered behavior	Behavior may be depressed; animals may remain immobile, or be reluctant to stand or move even when disturbed. They may also exhibit restlessness (e.g., lying down and getting up, shifting weight, circling, or pacing) or disturbed sleeping patterns. Large animal species may grunt, grind their teeth, flag their tail, stomp, or curl their lips (especially sheep and goats). Animals in pain may also show altered social interactions with others in their groups.
Vocalization	An animal may vocalize when approached or handled or when a specific body area is touched or palpated. It may also vocalize when moving to avoid being handled.
Mutilation	Animals may lick, scratch, shake, or rub a painful area.
Sweating	In species that sweat (horses), excessive sweating is often associated with some types of pain (e.g., colic).
Inappetence	Animals in pain frequently stop eating and drinking, or markedly reduce their intake, resulting in rapid weight loss.

For more species specific signs of pain please refer to http://www.nap.edu/catalog/12526/recognition-and-alleviation-of-pain-in-laboratory-animals.

Conventional analgesic drugs include opioids and non-steroidal anti-inflammatory drugs (NSAIDs). In addition there are non-pharmacologic options that may augment pharmacologic pain relief. The goal of analgesic drug intervention is to achieve a balanced state during which an animal is neither substantially hindered by pain nor adversely affected by the side effects of analgesics. Often the use of a single analgesic drug is sufficient, but multimodal analgesia (using more than one type of analgesic (and/or anesthetic) may have added benefits. **Optimal usage of analgesics includes their administration prior to the painful procedure (i.e. pre-operative administration) and continuation of therapy for several days after the procedure.**

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OPIOIDS

Opioids are the most efficacious analgesics available. Opioids can also cause behavioral changes in healthy, pain-free animals, which can confound attempts to assess pain. For example, opioid side effects include: sedation or hyperactivity, constipation, cough suppression, respiratory depression, and urinary retention. As a result, behavioral changes after the use of this class of drugs could be due to the provision of effective pain relief or a nonspecific drug effect. These side effects are most often noted at the higher end of the dose scale or during extended therapy.

Opioids can be delivered systemically via a variety of routes (IV, IM, SQ, IP, oral) dependent on the specific drug and formulation. Additionally, several sustained release formulations of opioids are available providing up to 72 hours of analgesia. Fentanyl patches (transcutaneous administration) are available for dogs, cats, and horses and sustained buprenorphine SR (injectable) is available for dogs, cats and rodents (ZooPharm Pharmaceuticals, Fort Collins, CO). In larger animals, opioids can also be administered intraarticularly (within a joint) to provide specific analgesia to that joint while minimizing the total dose administered to the patient.

NSAIDs

NSAIDs can be used as anti-inflammatory agents and/or analgesic agents. The therapeutic index varies widely for NSAIDs where a safe dose for one species can be toxic for another. In addition, side effects of NSAIDs include: liver injury, kidney injury, decreased coagulation, and gastrointestinal mucosal ulceration, which can lead to inappetence or hemorrhage. Despite and increased cardiovascular risk in adult human populations, adverse cardiovascular effects of NSAIDs have not been reported in veterinary species.

NSAIDs can be delivered systemically via a variety of routes (IV, IM, SQ, IP, oral) dependent on the specific drug and formulation**. Combinational use of NSAIDs with opioids should strongly be considered for procedures that are moderately painful.**

Pain Intensity	Analgesic Approach
Low	**Single agent therapy acceptable** NSAIDs, local anesthetic infiltration, opioids
Moderate	**Multimodal analgesia to be considered** NSAIDs in combination with adjuncts such as local anesthetics, opioids, alpha-2 agonists, other
High	**Multimodal analgesia recommended** Opioids plus one of the following: NSAIDs, local anesthetics, alpha-2 agonists
General anesthesia to be used in addition if necessary.	

NON-PHARMACOLOGIC METHODS OF PAIN RELIEF

Non-pharmacologic methods should be utilized to complement drug therapy or when pharmacologic methods are contraindicated. These methods include:

- Minimizing tissue handling and trauma during surgery
- Proper positioning during anesthesia to prevent undue pressure on joints, nerves, or soft tissues
- Provision of adequate and comfortable bedding
- Temporary single housing to lessen the impact of cage mates on a painful condition
- External warmth or bandaging if possible

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Monitoring

General anesthesia carries the risk of compromising the animal's health and can cause death. Animals should be closely monitored and anesthetic records kept during induction, maintenance, and recovery from general anesthesia. Close, regular monitoring allows early detection of anesthetic complications and timely adjustments, improving outcomes. Trouble shooting complications is impossible without accurate records of anesthetic administration and animal responses. It is ideal for one member of the research team to be dedicated to anesthetic monitoring and documentation**. For more details, please refer to the Guidelines on Perioperative Monitoring and Record Keeping (Rodent and Non-Mammalian, Non-Rodent Mammalian) [LINK].**

CONCLUSION

It is vitally important that adequate analgesia and anesthesia is delivered to laboratory animals. There are numerous methods and techniques to choose from. The Office of the University Veterinarian is poised to help in developing an appropriate therapeutic plan individualized to the project's needs.

References

[1] National Research Council (US) Committee on Recognition and Alleviation of Pain in Laboratory Animals. Recognition and Alleviation of Pain in Laboratory Animals. Washington (DC): National Academies Press (US); 2009. 1, Pain in Research Animals: General Principles and Considerations. Available from: http://www.ncbi.nlm.nih.gov/books/NBK32655/

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