ANIMAL CARE AND USE UPDATE

Institutional Animal Care and Use Committee

The University of Texas at Austin

November 2019
Volume 12, Issue 4

The next IACUC Full Committee Review (FCR) is **December 9, 2019.**

See column in this newsletter about submission deadlines.

Thank You for Your Participation in the Semiannual Evaluations!

The IACUC would like to thank animal researchers and animal care personnel for your time spent preparing for inspections, meeting with IACUC representatives, and making appropriate corrections.

Per federal guidance, the IACUC is obligated to perform these semiannual evaluations twice per year. Your assistance in helping them run smoothly is greatly appreciated.

IACUC FCR Submission Deadline Dates

The IACUC may choose to review any submission at a convened meeting. These submissions are designated as Full Committee Review (FCR). Submissions of increased complexity and concern have a higher likelihood of going to the FCR.

Protocols must undergo a pre-review procedure that includes an assessment for inaccuracies and confirmation of content prior to being sent to the Committee. Therefore, investigators must allow sufficient time for ORSC staff to complete pre-review when submitting an application. **It is recommended that complex protocols such as those with invasive procedures, multiple procedures, and novel procedures be submitted at least 4 weeks prior to the meeting.** Researchers should not expect complete protocols submitted less than 3 weeks prior to the meeting to be placed on the upcoming agenda.

Rather than focusing on a deadline to submit a protocol, researchers should focus on ensuring complete submissions.

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ORSC Closed for Thanksgiving Break

November 28-29, 2019

The Office of Research Support and Compliance (ORSC) will be closed Thursday, November 28 and Friday, November 29. No protocol processing will occur during this time.

For all animal-related emergencies, contact the on-call veterinarian at the Animal Resources Center (ARC).

Protocol Review and Winter Break

December 23, 2019- January 3, 2020

As the semester draws to a close, ORSC wants to share information that may be useful in planning your IACUC protocol submissions. The RSC office will be closed between Monday, December 23, 2019 and Friday, January 3, 2020.

Amendments or continuing reviews containing significant revisions submitted after Tuesday, December 10, 2019 are unlikely to have approval finalized before winter break. Please note that if the protocol is returned or requires substantial revision, we may not be able to complete the review of those changes before the University closes. No new submissions will be processed during the break.

See the column "**IACUC FCR Submission Deadline Dates**" in this newsletter about what the IACUC considers to be a *complete* submission: Compete new or third-year resubmissions submitted before December 10, 2019 will be reviewed at the January 13, 2020 IACUC meeting.

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voice: (512) 471-8871 | web: http://www.utexas.edu/iacuc | email: IACUC@austin.utexas.edu

MSI's Hurricane Recovery Update

In August 2017, Hurricane Harvey, a Category 4 hurricane, devastated the Marine Science Institute (MSI) in Port Aransas. Since then, MSI has worked diligently to recover. Research has picked back up since then, but the institute still has not completely recovered from this catastrophe.

MSI staff have been working hard improving their facilities, and were recently awarded $11.7 million from the National Oceanic and Atmospheric Administration (NOAA) for their continued recovery efforts. According to Robert Dickey, MSI's director and a professor of marine science, "This final piece of the puzzle will help us get over the finish line."

For more information about this story:
https://cns.utexas.edu/news/noaa-helps-ut-marine-science-institute-rebound-from-hurricane-harvey

To learn about the exciting research occurring at MSI: https://utmsi.utexas.edu/research

Training Update for Macaques Users

At the October 7, 2019 IACUC Full Committee Review, the committee voted to require the AN0055: Working Safely with Macaques in Research class to be repeated every 3 years. This is the requirement for all other species-specific training at UT Austin. The IACUC determined that a refresher must be taken every 3 years in order to update researchers on the latest procedures, such as current OHP requirements (i.e. new prescription card protocols, updated prophylactic requirements for anti-virals), updated training materials, and evolving best practices for exposures. If you have not completed the AN0055: Working Safely with Macaques in Research class in the last 3 years, you must schedule a refresher. *Remember: expired training prevents protocol submission, so users must take the refresher training ASAP.*

For more information about the course or for scheduling, contact the ARC Training and Compliance Manager at jencassaday@austin.utexas.edu.

Original notice sent to macaque users on October 22, 2019.

NEW IACUC Guideline

The IACUC has recently approved a new guideline to assist rodent users with proper analgesia for their animals. Approved October 7, 2019. The guideline is attached.

- #22- Guidelines for Analgesia Use in Rodents

Laboratory Assistance Program

The Animal Resource Center (ARC) developed an outreach program in 2012 that has been well received by the research community. This outreach program is called Laboratory Assistance Program. The ARC will schedule a visit with laboratories performing animal research to assist with interpretation of guidelines and expectations in regards to animal care and use practices, policies and procedures. The LAP manager often discusses with the lab how surgeries are done, post-operative records, and aseptic technique. Common areas of non-compliance are also discussed, which can help labs to avoid such issues. The intent of these visits is to get ARC staff and research staff together in the context of actual work being performed, because that is the best way to have meaningful discussions of the specific techniques performed.

Since these visits are not part of an official inspection and are voluntary, there can be a more informal interaction. The goal is not to identify problems to be reported but instead to make sure everyone is aware of the appropriate expectations so adjustments can be made if needed. The collaboration also helps ARC personnel to better understand the practical issues that affect research projects and procedures, which allows them to better represent the research community as policies and guidelines are discussed and formulated by the IACUC.

Participation by research groups is optional; however, PIs and their research personnel are strongly encouraged to participate in the program. For more information about the LAP or for scheduling, contact the ARC Training and Compliance Manager at jencassaday@austin.utexas.edu.

Need Help?

ORSC is here to assist. Please call or email us with any questions, comments, or concerns!

http://www.utexas.edu/iacuc
512-471-8871 | IACUC@austin.utexas.edu

The University of Texas at Austin
Office of Research Support and Compliance
Office of the Vice President for Research

Guidelines for Analgesia Use in Rodents
The University of Texas at Austin Institutional Animal Care and Use

These guidelines have been written to assist faculty, staff, and students in performing vertebrate animal procedures in a humane manner and complying with pertinent regulatory requirements. Under some circumstances deviations from these procedures may be indicated but such variances must be approved in advance by the IACUC.

This document provides analgesia information to researchers who use rodents in research, teaching, or other purposes at the University of Texas at Austin. It is organized into six sections:

Section A – Background
Section B – Types of Analgesia and Recommendations
Section C – Administration Routes
Section D – Administering Analgesia in Drinking Water
Section E – Examples of Potentially Painful Procedures and Recommended Analgesic Protocols
Section F – References and Acknowledgements

Section A – Background

According to The Guide for the Care and Use of Laboratory Animals, "Pain is a stressor and, if not relieved, can lead to unacceptable levels of stress and distress in animals." To optimize animal well-being and decrease scientific variability associated with distress, analgesics and anesthetics are used to alleviate pain resulting from spontaneous illness or experimental manipulation. The proper dosing strategy for analgesics is imperative for the humane use of animals and scientific integrity.

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 providing analgesia 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. **If analgesia cannot be provided due to scientific reasons, the rationale should be described and approved by the IACUC in the Animal Use Protocol.**

The current guiding principles of pain management include preemptive (preventative) analgesia, multimodal analgesia (using different classes of drugs simultaneously to interrupt the pain pathway at various points), and appropriate follow-up analgesia. Administration of pain-relieving drugs BEFORE pain circuits begin to activate due to surgical trauma has been shown to prevent "wind- up" pain and provide better analgesic outcomes in both human and animal surgery. As such, analgesia is best provided prior to the painful procedure, rather than after observing clinical signs of pain. Advantages of pre-emptive use of analgesics include 1) Reduces the intensity of painful stimulation, 2) Improves the animal's comfort level after surgery, 3) Decreases the amount of anesthesia required to maintain a surgical plane, 4) Results in a smoother recovery.

The Animal Resource Center's (ARC) Rodent Anesthesia Record template contains a Post-Procedural Recovery / Analgesic Administration Log. The template may be adapted for your laboratory's use or the information contained in this template should be recorded in your study records.

Section B – Types of Analgesia and Recommendations

This section describes three types of analgesia: opioids, NSAIDS, and local analgesia. Section E of this guideline describes recommended analgesic protocols based on the pain or discomfort an animal is expected to feel with various procedures.

Opioids

- Examples include buprenorphine HCL and SR
- 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.

	Mice	**Rats**	**Hamsters**	**Gerbils**
Buprenorphine-HCL	Dose: 0.05-0.1 mg/kg Recommended dose*: 0.1 when used alone; 0.075 when used in combination** Frequency: Every 6-12 hours. Dosing frequency may be decreased if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ), intraperitoneal (IP)	Dose: 0.01-0.05 mg/kg Recommended dose*: 0.05 when used alone; 0.03 when used in combination*** Frequency: Every 6-12 hours. Frequency of dosing may be decreased if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ), intraperitoneal (IP)	Dose: 0.1-0.5 mg/kg Recommended dose*: 0.5 when used alone; 0.3 when used in combination Frequency: Every 6-12 hours Route: Subcutaneous (SQ)	Dose: 0.05-0.2 mg/kg Recommended dose*: 0.5 when used alone; 0.3 when used in combination Frequency: Every 6-12 hours Route: Subcutaneous (SQ), intraperitoneal (IP)
Buprenorphine SR (sustained release)	Dose: 1.0-2.0 mg/kg Frequency: Every 72 hours. Administer the first dose 2-4 hours prior to the painful procedure to ensure effective analgesia. Route: SQ	Dose: 1.0-1.2 mg/kg Frequency: Every 48-72 hours. Administer the first dose 2-4 hours prior to the painful procedure to ensure effective analgesia. Route: SQ		

*Recommended doses are a good starting point and may differ for procedures that are expected to elicit more/less pain than others

** One study suggests that 0.05 mg/kg may be more appropriate for analgesia specifically in female mice

*** One study suggests that 0.03 mg/kg may be more appropriate for analgesia specifically in female rats

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Examples include carprofen, meloxicam
- Generally, the NSAID classification applies 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.

	Mice	Rats	Hamsters	Gerbils
Carprofen	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ, IP	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ, IP	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ
Meloxicam	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ

Local analgesia

- Examples include lidocaine, bupivacaine, or 50:50 lidocaine bupivacaine block
- 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.
  i. Infiltration or infusion: Injection beneath the skin and other tissue layers along the site of an incision before or after a procedure.
  ii. Field block, ring block: Injection into soft tissues distant from the actual incision in a pattern that intersects the nerve supplying the surgical site.
  iii. Nerve conduction block: Infusion of a small amount of drug or directly adjacent to the sheath of a nerve supplying the surgical site.
  iv. Topical local anesthetics, such as lidocaine jelly, may be useful for some surgical wounds.

	Mice	Rats	Hamsters	Gerbils
Lidocaine*	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose Route: Local infiltration	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose Route: Local infiltration	Dilute to 0.5%, do not exceed 4 mg/kg (0.8 ml/kg) total dose Route: Local infiltration	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose Route: Local infiltration
Bupivacaine*	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 6 mg/kg (2.4 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration
0.5% Lidocaine/ 0.25% Bupivacaine mixture **	Dose: Dilute as described below, do not exceed 7 mg/kg (0.9 ml/kg) total dose	Dose: Dilute as described below, do not exceed 7 mg/kg (0.9 ml/kg) total dose	Dose: Dilute as described below, do not exceed 4 mg/kg (0.5 ml/kg) total	Dose: Dilute as described below, do not exceed 7 mg/kg (0.9 ml/kg) total dose

	Route: Local infiltration	Route: Local infiltration	Route: Local infiltration	Route: Local infiltration

* Lidocaine has a quick onset (1-2 minutes), but is short-acting (1-2 hours). Bupivacaine has a slow onset (10-15 minutes), but is long-acting (4-8 hours). When used in combination (lidocaine plus bupivacaine in the same syringe), local anesthesia can have a fast onset with a relatively long duration of action.

*For rodent use, dilute 1-2% lidocaine to 0.5% and 0.5% bupivacaine to 0.25% to allow for feasible volumes to infuse at the incision site (1% solution is equal to 10 mg/mL).

** Dilute 2% (20 mg/ml) Lidocaine 1:4 and 0.5% (5mg/mL) Bupivacaine 1:2 in the same vial (Example: 0.5 mL 2% lidocaine + 1 mL 0.5% bupivacaine + 0.5 mL sterile saline)

Section C – Administration Routes

Direct routes of administration (e.g., parenteral) are strongly recommended for accurate dosing.

Mild pain or discomfort: 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. Animals in pain may not adequately self-medicate using water administration because fluid intake is often decreased, so observation and assessment are important.

Moderate to severe pain: 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.

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. Animals requiring SR formulations of opioid or NSAIDs should be dosed 3-4 hours before the start of surgery to be effective. Consult with a UT Austin veterinarian to develop an appropriate analgesic plan or for more information on acquiring sustained release products. Note that many of the analgesic formulations are new and the optimal dosing regimens are still being developed for some species.

Section D – Administering Analgesia in Drinking Water

If analgesics will be administered via drinking water for procedures causing more than mild pain or distress, the Animal Use 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 consume 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 area veterinarian, to determine the best methods to accomplish these tasks. Examples include:
    i. Monitoring fluid intake: Measure the volume or weight of the water bottle to ensure an acceptable amount of fluid displacement has occurred within the daily time period. In addition, weigh each animal every day to ensure appropriate fluid and food consumption.
    ii. Clinical assessment of pain: Include identifying signs such as hunched posture, decreased activity or hyperactivity, dehydration determined by a prolonged skin tent when scruffed, ruffled hair coat or lack of grooming, self-mutilation, altered mobility, decreased hindlimb-rearing behavior, decreased fecal output, or poor nest incorporation.
- A description of criteria for providing 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 do the following if analgesics will be administered via drinking water for procedures causing more than mild momentary pain or distress:

- 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.
- Document in post-operative records that a daily assessment for the presence or absence of signs of pain was performed.
- Maintain appropriate identification of cages receiving medicated water by properly labeling bottles and provide signage on the cage stating the analgesic used, the date the bottle was made, and the dose of the drug.

Section E – Examples of Potentially Painful Procedures and Recommended Analgesic Protocols

The tables below describe examples of potentially painful procedures and recommended analgesic protocols for each. Contact a UT Austin veterinarian for assistance in developing an appropriate analgesia plan for rodents on your studies.

Mild and Momentary Pain or Discomfort

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Percutaneous blood draw	Analgesia may not be indicated.
Ear notch	
Superficial tumor inoculation (SQ or similar)	
Multiple injections	
Tail snipping (neonatal rodents) – see IACUC Guidelines for Tail and Toe Clipping Rodents	

Mild and Persistent Pain or Discomfort

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Tail snipping (adult rodents) – see IACUC Guidelines for Tail and Toe Clipping Rodents	Use any one of the three types of analgesia in Section B. Give a single dose of injectable analgesia on the day of the procedure.
Subcutaneous pump or pellet implantation	
Enucleation	

Moderate Pain

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Embryo transfer (surgical)	Use a combination of at least 2 of the 3 types of analgesia in Section B. For example: • NSAID + opioid • NSAID + local Give a single dose of injectable analgesia on the day of the procedure. Additional doses to be provided via injection for at least 1-2 days following the procedure.
Ovariectomy/ Orchidectomy	
Tail amputation	
Craniotomy	
Minor laparotomy with minimal organ manipulation	

	Additional or rescue analgesia doses to be provided as needed based on clinical pain evaluation.

Severe Pain

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Orthopedic procedures	Use all 3 types of analgesia in Section B. Where possible, preempt the painful event by starting NSAIDs and/or opioids in advance. At least 3-5 days of injectable analgesia to be given. *Analgesia in the drinking water is not a reliable source.*
Thoracotomy	
Organ transplant	
Major laparotomy with organ manipulation	
Burns	
Trauma models	

Section F – References and Acknowledgements

This document contains content that was adapted from

- University of Colorado Denver Veterinary Anesthetic and Analgesic Formulary: https://www.colorado.edu/researchinnovation/sites/default/files/attached-files/CU%20Denver%20Analgesic%20%26%20Anesthetic%20Drug%20Formulary.pdf
- University of Iowa Analgesia Guideline: https://animal.research.uiowa.edu/iacuc-guidelines-analgesia
- University of Minnesota Analgesia Guidelines: https://www.researchservices.umn.edu/services-name/research-animal-resources/research-support/guidelines/analgesia
- Recognition and Alleviation of Pain and Distress in laboratory animals https://www.nap.edu/read/12526/chapter/1
- Guidelines for the assessment and management of pain in rodents and rabbits https://www.aclam.org/media/0472274f-1d17-4957-b01b-4076d73e6d5a/qimOxQ/ACLAM/About%20Us/Position%20Statements/position_pain-rodent-rabbit.pdf
- Ramirez et al., J Am Assoc Lab Anim Sci. 2015 Jul;54(4):426-32