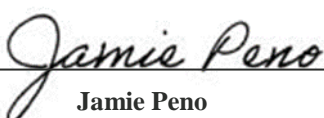
 <div> <div>DIVISION OF RESEARCH &amp; INNOVATION</div> <div>Research Integrity &amp; Compliance</div> </div>		<b>Institutional Animal Care and Use Committee</b>  <b>Standard Operating Procedures</b>	
<b>Title:</b> Standards for Analgesia			
<b>Effective Date:</b>	December 22, 2020	<b>Document Number:</b>	IACUC-SOP-02-16.00
<b>Approval/Date:</b>  <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">             _____            Jamie Peno            Director, Research Integrity and Compliance         </div> <div style="text-align: center;">           12/22/2020            _____            Date         </div> </div>			
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<b>Date</b>	<b>Section</b>	<b>Author</b>	

## PURPOSE

Appropriate analgesics must be used for procedures which cause pain unless withholding such agents is scientifically required and justified in a UNT approved animal use protocol.

## SCOPE

It is the responsibility of the Principal Investigator to ensure use of appropriate analgesics when performing potentially painful procedures on animals. The PI should consult with the UNT AV (Attending Veterinarian) for information on which analgesic(s) to use if the PI is unsure.

Some analgesics are controlled substances and will require a DEA license. It is the responsibility of the PI to have this license or include an approved collaborator with such.

## DEFINITIONS AND ABBREVIATIONS

UNT- University of North Texas, Denton

IACUC- Institutional Animal Care and Use Committee

SOP/SOP's- Standard Operating Procedure(s)

PI- Principal Investigator

USDA- United States Department of Agriculture

LAF- Laboratory Animal Facility

AV- Attending Veterinarian

DEA- Drug Enforcement Administration which monitors use and issues licenses for use of Controlled Substances to researchers.

## **PROCEDURES**

- I.** When determining which procedures require analgesia and which analgesics may be useful, several factors should be considered:
  - A.** The invasiveness of the procedure that was performed:
    - 1. Are body cavities invaded?
    - 2. Are especially sensitive tissues involved (e.g. bones or teeth)?
    - 3. Is significant tissue destruction or inflammation produced?
  - B.** The degree or severity of pain that is expected:
    - 1. Comparison to similar procedures in people: would a reasonably stoic human be able to tolerate the postoperative period without analgesics?
  - C.** Behavior of the animal during postoperative period; e.g., level of activity, appetite, etc. when compared to sham (anesthetized) control animals.
  - D.** Duration of the postoperative pain or discomfort expected:
    - 1. Postoperative analgesia is desirable for most surgical procedures involving penetration deeper than the skin and subcutaneous tissues.
- II.** For procedures involving invasion of bones, joints, teeth or significant destruction or inflammation in other tissues, it is the responsibility of the PI to make sufficient justification in their animal use protocol if postoperative analgesics cannot be used.
  - A.** No post-operative analgesia required:
    - 1. Injections that will cause mild or no pain or discomfort. Examples such as injections of low irritation potential substances, non-invasive catheter or electrode placement, skin incisions, or sutures.
    - 2. Short-term postoperative analgesia desired:
    - 3. Procedures likely to cause mild to moderate pain or discomfort of short duration (12-24 hours). Examples include:
    - 4. Castrations, including ovariectomies
    - 5. Invasive electrode or catheter placement
    - 6. Adrenalectomy and hypophysectomy in rodents
    - 7. Extraocular surgery
  - B.** Prolonged postoperative analgesia required:
    - 1. Procedures likely to result in severe or prolonged pain or discomfort. Examples include:
    - 2. Extensive dissection of soft tissues
    - 3. Major entry into the pleural or peritoneal cavity
    - 4. Intraocular surgery
    - 5. Orthopedic or dental surgery
- III.** Types of analgesics:
  - A.** Opioids - These are controlled substances. The Principal Investigator or an approved collaborator must have a DEA license for use of opioids.
  - B.** NSAIDs - Non-steroidal anti-inflammatory drugs.
  - C.** Local analgesics – act only at the site of application
- IV.** Points to remember when using analgesics:
  - A.** Always use the analgesic that is listed in protocol.
  - B.** Calculate the dose by recent or current body weight.
  - C.** Drugs under the control of the Drug Enforcement Agency (DEA) must be stored in a locked cabinet in a secure area. (see IACUC Procedure 02-18 Controlled Substances)
    - 1. A written record is required when controlled drugs under the control of the DEA are used (how much of the drug you have, how much was used and for what purpose).
  - D.** An inventory list of analgesics should be kept.

- V. The following listings of analgesics and the corresponding doses for each species must be considered for use by the Principal Investigator. If another drug or dosage not on this list is to be used, the Attending Veterinarian must be consulted.

## Mice

### Opiod Analgesics

Drug Name	Dose and Route	Frequency	Notes
Buprenorphine (Recommended)	0.05-0.1 mg/kg SC or IP	Pre-operatively for preemptive analgesia and post-operatively every 4 – 12 hours	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8- 12 hrs as needed. Consider multi- modal analgesia with NSAID and local analgesic.
Buprenorphine SR LAB	0.5-1.0 mg/kg SC	Give once for 72 hours	
Buprenorphine ER	3.25 mg/kg SC	Give once for 72 hours	
Oxymorphone	0.2-0.5 mg/kg SC	Give every 4 hours	
Morphine	1-2.5 mg/kg SC	Give every 2-6 hours	

### Non-steroidal anti-inflammatory (NSAID) analgesia

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Carprofen (Recommended)	2-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Carprofen (50mg/ml) in Drinking Water	10 mg/kg - 0.12 ml carprofen in 89.88 ml of drinking water (0.067 mg/ml) stable x 7d. Start treatment 12-24 h prior to surgery		
Meloxicam	1-2 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.

Meloxicam	4 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 72 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Ketoprofen	2-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Ketorolac	5-7.5 mg/kg ORAL or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Flunixin Meglumine	~2 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.

### Local anesthetic/analgesics

Lidocaine and Bupivacaine may be combined in one syringe for rapid onset and long duration analgesia

Drug Name	Dose and Route	Frequency	Notes
Lidocaine hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose SC or Intra- Incisional	Use locally before making surgical incision, or before final skin closure	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose SC or Intra- Incisional	Use locally before making surgical incision, or before final skin closure	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

### Mice/ Rat

#### Lidocaine/Bupivacaine Pre-Operative Infiltration

Incision site and underlying tissues

1-2 % lidocaine/0.25-0.5% bupivacaine (50/50) mix by volume. May need to dilute, especially for mice (e.g. 1/10 dilution). Epinephrine prolongs action.

Local Anesthetic	Onset	Duration	Do not exceed (toxic dose)
Lidocaine (xylocaine)	1-3 minutes	20-40 minutes	10 mg/kg
Bupivacaine	~20 minutes	4-6 hours	6 mg/kg

## Recommended Peri-Operative Analgesic Protocols for Mice and Rats

### Mild Pain

<b>Preemptive<sup>1</sup> (once)</b>		Lidocaine/bupivacaine as local infiltration
<b>Post-surgical</b>	<b>Drug</b>	Buprenorphine, morphine or oxymorphone
	<b>Frequency</b>	Once

<sup>1</sup>Administration of analgesics prior to induction of pain.

### Mild to Moderate Pain – OPTION 1

<b>Preemptive (once)</b>		Lidocaine/bupivacaine as local infiltration
		<i>AND</i>
		Buprenorphine, morphine or oxymorphone
<b>Post-surgical</b>	<b>Drug</b>	Buprenorphine
	<b>Duration</b>	1-2 days

### Mild to Moderate Pain – OPTION 2

<b>Preemptive (once)</b>		Lidocaine/bupivacaine as local infiltration
		<i>AND</i>
		Buprenorphine, morphine or oxymorphone
<b>Post-surgical</b>	<b>Drug</b>	Carprofen, ketoprofen or meloxicam
	<b>Duration</b>	1-2 days

### Moderate to Severe Pain

<b>Preemptive (once)</b>		Lidocaine/bupivacaine as local infiltration
		<i>AND</i>
		Buprenorphine, morphine or oxymorphone
<b>Post-surgical</b>	<b>Drug</b>	Buprenorphine
	<b>Duration</b>	2 days
		<i>AND</i>
	<b>Drug</b>	Meloxicam (use highest dose)
	<b>Duration</b>	2-3 days
		<i>AND</i>
	<b>Drug</b>	Morphine for severe pain
	<b>Duration</b>	As needed

## Rat

### Opioid Analgesia

<b>Drug</b>	<b>Dose and Route</b>	<b>Frequency</b>	<b>Notes</b>
Buprenorphine	0.01-0.05 mg/kg IM or SC	Pre-operatively for preemptive analgesia and post-operatively every 8-12 hours	Takes 1 h to be effective so should be given pre-emptively. Duration of effect is 4-6 h. NSAID is recommended for continued pain relief.
Buprenorphine SR LAB	1-1.2 mg/kg SC	Give once for 72 hours	

Buprenorphine ER	0.65 mg/kg SC	Give once for 72 hours	
Oxymorphone	0.2-0.5 mg/kg SC	Give every 4 hours	
Morphine	1-2.5 mg/kg SC	Give every 2-6 hours	

### Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Ketoprofen	2-5 mg/kg SC	Give once every 24 hour	
Carprofen	2-5 mg/kg SC	Give once every 12-24 hour	
Meloxicam	1-2 mg/kg SC, PO	Give once every 12 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Rimadyl ®	Tablet	Give once every 24 hour	

### Non-steroidal anti-inflammatory analgesia (NSAID) continued

Drug Name	Dose and Route	Frequency	Notes
Meloxicam	4 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 72 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.

### Local anesthetic/analgesics

Lidocaine and Bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug Name	Dose and Route	Frequency	Notes
Lidocaine	Dilute to 0.5%, should not exceed 7 mg/kg. SC or intra-incisional.	Use locally before making surgical incision, or before final skin closure	Use as local anesthetic, fast onset but duration of action is less than 1 h.
Bupivacaine	Dilute to 0.25%, should not exceed a total dose of 8 mg/kg. SC or intra-incisional.	Use locally before making surgical incision, or before final skin closure	Use as a local anesthetic, slow onset but duration of action is 4-8 h. Do not give IV.

## Hamster

### Opioid analgesia

Drug Name	Dose and Route	Frequency	Notes
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Buprenorphine	0.05-0.1 mg/kg SC	Every 8-12 hours	
Butorphanol	1-5 mg/kg SC	Every 2-4 hours	

#### Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Aspirin	240 mg/kg PO	Every 24 hours	
Flunixin	2.5 mg/kg SC	Every 12 – 24 hours	Consult with Vet regarding repeated administration

#### Local anesthetic/analgesics

Lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug Name	Dose and Route	Frequency	Notes
Bupivacaine	1-2mg/kg max dose, mixed with Lidocaine at 1-4 mg/kg Lidocaine	Before incision is made	Use as a local anesthetic, slow onset but duration of action is 4-8 h. Do not give IV.
Lidocaine	1-4 mg/kg max dose, mixed with bupivacaine at 1-2 mg/kg bupivacaine	Before incision is made	Use as local anesthetic, fast onset but duration of action is less than 1 h.

### Rabbit

#### Opioid analgesia

Drug	Dose and Route	Frequency	Notes
Recommended: Buprenorphine	0.05 – 0.1 mg/kg SC or IP	Used pre-operatively for preemptive analgesia and post-operatively every 4-12 hrs	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8- 12 hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.
Buprenorphine SR	1.0-2.0 mg/kg SC	Give once for 72 hours	

#### Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug	Dose and Route	Frequency	Notes
Recommended: Carprofen	4-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.

Meloxicam	0.1-0.3 mg/kg PO, IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
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#### Non-steroidal anti-inflammatory analgesia (NSAID) continued

Drug	Dose and Route	Frequency	Notes
Ketorolac	0.3-0.5 mg/kg PO or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.
Ketoprofen	2-5 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour (4-8 hour) duration of action	Depending on the procedure, may be used as sole analgesic, or as multi- modal analgesia with buprenorphine.

#### Local anesthetic/analgesics

Lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug	Dose and Route	Frequency	Notes
Lidocaine Hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision	Faster onset than bupivacaine but short (< 1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision	Slower onset than Lidocaine but longer (~ 4/8 hour) duration of action

## REFERENCES

1. The Guide for the Care and Use of Laboratory Animals.
2. Animal Welfare Act
3. UNT HSC Procedures for Analgesia

## APPENDICES

IACUC Standard Operating Procedures