IACUC POLICY ON RODENT AND RABBIT ANESTHESIA AND ANALGESIA

11/17/15 MW

IACUC Approved: 12/3/15	Other Approvals:
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This Policy describes the recommended methods for analgesia in rodents and rabbits. The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training state "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." and "Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia." The University of Hawaii IACUC requires that analgesia must be utilized in all protocols that involve more than a mild and momentary perception of pain (such as a single injection). Any research that prohibits the use of analgesia for painful procedures must be scientifically justified and be included in IACUC protocol that has been reviewed and approved by UH IACUC.

Analgesia: type and timing

The choice of analgesic must take into consideration the estimated level and duration of pain or discomfort associated with the procedure. Investigators are encouraged to consult with Animal & Veterinary Services Veterinary staff for direction in the choice of appropriate analgesia.

Analgesics are generally considered to be most effective when provided as early as possible with respect to the pain producing stimulus. Pre-emptive analgesia refers to analgesia administered prior to the pain stimulus and is considered to be the best method for analgesia. Whenever possible pre-emptive analgesia techniques should be utilized and provision of analgesia during the procedure (of an anesthetised animal) is considered to be the minimal standard.

Some animals may have an aversion to water that contains a novel substance, and may not consume sufficient amounts of water. This may lead to dehydration and other confounding variables that may affect the study. In addition, mice and rats do not drink water throughout the day and may not receive the therapeutic dose for certain analgesics that are metabolized rapidly in these species. If analgesics are given in water (via water bottles), the bottles must be weighed daily to determine the amount of water consumed. Mice should consume approximately 1.5ml per 10g of body weight per day. Rats consume approximately 10-12ml per 100g of body weight per day. Rabbits consume approximately 50-100ml per 1 kg of body weight per day. For conversion purposes for water consumed 1 ml~1 g. If the animals are not drinking their daily requirements for water after the first 24 hours, the veterinary staff should be consulted and animal assessed prior to use. In lieu of giving analgesics via the water, the veterinary staff may recommend an alternate method of analgesia be used instead.

Acetaminophen and ibuprofen are metabolized rapidly in mice and rats. Acetaminophen should not be used in mice and rats. Ibuprofen may only be gavaged.

For procedures considered to generate moderate to severe pain, analgesia should be continued for 48-72 hours post-operatively.

Routes of Administration:

Route Abbreviation	Route Description
SQ/SC	Subcutaneous
IM	Intramuscularly
IP	Intraperitoneally

IV	Intravenous
PO	Per Os (orally, by mouth)

Mouse Anesthetics and Analgesics[1]

Inhaled Anesthetics			
Agent	**Dosage**	**Route**	**Comments (*Ref.*)**
Isoflurane	Induction: 3-5% Maintenance: 1.5-3%	Inhaled Nose Cone	Administer via precision vaporizer & compressed O_2. Open-drop method with IACUC approval.
Injectable Anesthetic Drug Combinations			
Agent(s)	**Dosage**	**Route**	**Comments**
Ketamine | Xylazine	80-100 | 7.5-16 mg/kg	IP or IM	Requires DEA and state NED license
Ketamine | Xylazine |Acepromazine	100 | 2.5 | 2.5 mg/kg	IP or IM	Requires DEA and state NED license
Ketamine | Medetomidine	75 | 1.0 mg/kg	SQ or IP	Requires DEA and state NED license
Pentobarbital (Nembutal)	50-90 mg/kg,	IP	Requires DEA and state NED license
Telazol®	7.5-45 mg/kg	IP or IM	Requires DEA and state NED license
Tribromoethanol[2]	125-300 mg/kg	IP	Non-pharmaceutical, requires IACUC justification, one time use only
Alpha 2 Agonist Reversal (Xylazine and Medetomidine)			
Agent	**Dosage**	**Route**	**Comments**
Yohimbine	0.2 mg/kg	IM, SQ	Xylazine reversal
Atipamezole	5 mg for every 1 mg of Medetomidine	IM, SQ	Medetomidine reversal
Atipamezole	1 mg for every 10 mg of Xylazine	IM, SQ	Xylazine reversal
Local Anesthetics			
Agent	**Dosage**	**Route**	**Comments**
Lidocaine (1-2%)	2-4 mg/kg (max 7 mg/kg)	SQ used as a local block	Onset 5-10 min, Duration 0.5-1 hr
Bupivacaine (0.5% Marcaine®)	1-2 mg/kg (max 8 mg/kg)	SQ used as a local block	Onset 15-30 min, Duration 4-8 hrs
Ropivacaine (0.2% Naropin®)	1-2 mg/kg (max 8 mg/kg)	SQ used as a local block	Onset 15-30 min, Duration 4-8 hrs
Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%	1 drop into eye 5 minutes prior to procedure	Topical	15 min duration
Tetracaine Hydrochloride Ophthalmic Solution (0.5%)	1 drop into eye immediately before procedure	Topical	10 min duration
Analgesics			
Opioids			
Agent	**Dosage**	**Route**	**Comments**
Buprenorphine (Buprenex®)	0.05-0.2 mg/kg	SQ or IP	Requires DEA and State NED license 6-12 hrs duration
Buprenorphine LAB SR™	0.5-1.0 mg/kg	SQ	Requires DEA and State NED license 72 hrs duration
Oxymorphone	0.2-0.5 mg/kg	SQ or IP	Requires DEA and State NED license 4-6 hrs
Fentanyl	0.05 mg/kg	IP	Requires DEA and State NED license 4-6 hrs
Non-Steroidal Anti-Inflammatory Drug (NSAID)			
Agent	**Dosage**	**Route**	**Comments**
**Carprofen (Rimadyl®)	5 mg/kg	SQ, IP, or PO	Duration 24 hrs
*Meloxicam (Metacam®) or	1-2 mg/kg	SQ, IP, or	Duration 24 hrs *Meloxicam SR has the

Meloxicam oral suspension (Meloxidyl)		PO	same effect as Meloxicam in mice.
Flunixin (Banamine®)	1-2.5 mg/kg	SQ	Duration 12-24 hrs
Ketoprofen (Ketofen®)	5 mg/kg	SQ	Duration 12-24 hrs
Ibuprofen (Children's Advil® or Advil® liquid Gel)	40 mg/kg	PO	Gavage

Rat Anesthetics and Analgesics[1]

Inhaled Anesthetics			
Agent	**Dosage**	**Route**	**Comments (*Ref.*)**
Isoflurane	Induction: 3-5% Maintenance: 1.5-3%	Inhaled Nose Cone	Administer via precision vaporizer & compressed O_2. Open-drop method with IACUC approval.
Injectable Anesthetic Drug Combinations			
Agent(s)	**Dosage**	**Route**	**Comments**
Ketamine | Xylazine	40-80 | 5-10 mg/kg	IP or IM	Requires DEA and state NED license
Ketamine | Medetomidine	60-90 | 0.5 mg/kg	IP	Requires DEA and state NED license
Pentobarbital (Nembutal)	50-90 mg/kg,	IP	Requires DEA and state NED license
Telazol®	7.5-45 mg/kg	IP or IM	Requires DEA and state NED license
Alpha 2 Agonist Reversal (Xylazine and Medetomidine)			
Agent	**Dosage**	**Route**	**Comments**
Yohimbine	0.2 mg/kg	IM, SQ	Xylazine reversal
Atipamezole	5 mg for every 1 mg of Medetomidine	IM, SQ	Medetomidine reversal
Atipamezole	1 mg for every 10 mg of Xylazine	IM, SQ	Xylazine reversal
Local Anesthetics			
Agent	**Dosage**	**Route**	**Comments**
Lidocaine (1-2%)	2-4 mg/kg (max 7 mg/kg)	SQ used as a local block	Onset 5-10 min, Duration 0.5-1 hr
Bupivacaine (0.5% Marcaine®)	1-2 mg/kg (max 8 mg/kg)	SQ used as a local block	Onset 15-30 min, Duration 4-8 hrs
Ropivacaine (0.2% Naropin®)	1-2 mg/kg (max 8 mg/kg)	SQ used as a local block	Onset 15-30 min, Duration 4-8 hrs
Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%	1 drop into eye 5 minutes prior to procedure	Topical	15 min duration
Tetracaine Hydrochloride Ophthalmic Solution (0.5%)	1 drop into eye immediately before procedure	Topical	10 min duration
Analgesics			
Opioids			
Agent	**Dosage**	**Route**	**Comments**
Buprenorphine (Buprenex®)	0.05-0.2 mg/kg	SQ, IP, IV	Requires DEA and State NED license 6-12 hrs duration
Buprenorphine-LAB SR™	1.2 mg/kg	SQ	Requires DEA and State NED license 72 hrs duration
Oxymorphone	0.2-0.5 mg/kg	SQ or IM	Requires DEA and State NED license 4-6 hrs duration
Fentanyl	0.05 mg/kg	IP or IM	Requires DEA and State NED license 4-6 hrs duration
Non-Steroidal Anti-Inflammatory Drug (NSAID)			

Agent	Dosage	Route	Comments
Carprofen (Rimadyl®)	5 mg/kg	SQ, IP, or PO	Duration 24 hrs
Meloxicam (Metacam®) or Meloxicam oral suspension (Meloxidyl)	1-2 mg/kg	PO or SQ	Duration 24 hrs
Meloxicam SR (Zoopharm)	4mg/kg	SQ	Duration 48-72 hrs
Flunixin (Banamine®)	1.1-2.5 mg/kg	SQ	Duration 12-24 hrs
Ketoprofen (Ketofen®)	5 mg/kg	SQ	Duration 12-24 hrs
Ibuprofen (Children's Advil® or Advil® liquid Gel)	40 mg/kg	PO	Gavage

Rodent Neonate (less than 10 days of age)[1,3,4]

Inhaled Anesthetics			
Agent	**Dosage**	**Route**	**Comments**
Isoflurane	Induction: 3-5% Maintenance: 1.5-3%	Inhaled Nose Cone	Administer via precision vaporizer & compressed O_2. Open-drop method with IACUC approval.

Hypothermia

- Mouse and rat pups up to 6 days of age may be anesthetized by hypothermia when inhalant anesthetic is not feasible.
- Place the neonate on a bed of crushed ice with a barrier between ice and neonate until anesthesia can be confirmed by immobility. Useful barriers are: layer of latex, plastic wrap, clean gauze, or a petri dish
- Monitor the readiness of the animal for a procedure by noting lethargy and immobility. Expect the neonate to remain immobile for up to 10 minutes. If additional time is needed for the procedure, maintain immobility by keeping the neonate covered cold pack with a barrier separating cold pack from the neonate.
- If necessary illuminate the surgical field by use of a fiber optic light source, as incandescent bulbs may cause inadvertent and uncontrollable warming.
- Recover pups and slowly rewarm them in an incubator at 33° C or in a warm nest. Complete recovery typically requires 30 to 60 minutes.

Rabbit Anesthetics and Analgesics[1]

Inhaled Anesthetic Drugs			
Agent	**Dosage**	**Route**	**Comments**
Isoflurane	Induction: 3-5% Maintenance: 1.5-3%	Inhaled ±Nose Cone ±Intubation	Administer via precision vaporizer & compressed O_2.
Injectable Sedation for Induction Drugs/Combinations			
Agent	**Dosage**	**Route**	**Comments**
Acepromazine	0.25-1.0 mg/kg	IM	Pre-med
Xylazine	1-5 mg/kg	IM or SQ	Pre-med
Medetomidine	0.25 mg/kg	IM	Pre-med
Diazepam	1-5 mg/kg	IM	Pre-med
Midazolam	1-2 mg/kg	IM	Pre-med
Propofol	5-8 mg/kg	IV	Induction
Injectable Anesthetics Combinations			
Agent(s)	**Dosage**	**Route**	**Comments**
Ketamine | Xylazine	25-35 | 5 mg/kg	IM or SQ	Requires DEA and state NED license
Ketamine | Medetomidine	15-35 | 0.25-0.5 mg/kg	IM or SQ	Requires DEA and state NED license
Ketamine | Diazepam	20-40 | 1-5 mg/kg	IM or SQ	Requires DEA and state NED license
Pentobarbital	20-40 mg/kg	IV	Requires DEA and state NED license
Alpha 2 Agonist Reversal (Xylazine and Medetomidine)			
Agent	**Dosage**	**Route**	**Comments**
Yohimbine	0.2 mg/kg	IM, SQ	Xylazine reversal
Atipamezole	5 mg for every 1 mg	IM, SQ	Medetomidine reversal

	of Medetomidine		
Atipamezole	1 mg for every 10 mg of Xylazine	IM, SQ	Xylazine reversal
Local Anesthetics			
Agent	**Dosage**	**Route**	**Comments**
Lidocaine (1-2%)	2-4 mg/kg	SQ	Onset 5-10 min, Duration 0.5-1 hr
Bupivacaine (0.5% Marcaine)	1-2 mg/kg	SQ	Onset 15-30 min, Duration 4-8 hrs
Ropivacaine (0.2% Naropin)	1-2 mg/kg	SQ	Onset 15-30 min, Duration 4-8 hrs
Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%	1 drop into eye 5 minutes prior to procedure	Topical	15 min duration
Tetracaine Hydrochloride Ophthalmic Solution (0.5%)	1 drop into eye immediately before procedure	Topical	10 min duration
Analgesics			
Opioids			
Agent	**Dosage**	**Route**	**Comments**
Oxymorphone	0.05-0.2 mg/kg	SQ or IM	Requires DEA and state NED license 8-12 hrs duration
Fentanyl	0.005-0.02 mg/kg	IV	Requires DEA and state NED license 0.5-1 hrs duration
Buprenorphine (Buprenex®)	0.01-0.05 mg/kg	SQ, IM, or IV	Requires DEA and state NED license 8-12 hrs duration
Butorphanol	0.1-0.5 mg/kg	SQ, IM, or IV	Requires DEA and state NED license 4-6 hrs duration
Non-Steroidal Anti-Inflammatory Drug (NSAID)			
Agent	**Dosage**	**Route**	**Comments**
Meloxicam (Metacam®)	0.3 mg/kg	PO or SQ	24 hrs duration
Meloxicam SR (Zoopharm)	0.6-0.9 mg/kg	SQ	48-72 hrs duration
Carprofen (Rimadyl®)	4 mg/kg SC 1-2.2 mg/kg PO	PO or SQ	24 hrs duration 12 hrs duration
Flunixin (Banamine®)	1.0 mg/kg	SQ or IM	12-24 hrs duration. Do not administer for longer than 3 days
Ketoprofen (Ketofen®)	1-3 mg/kg	SQ or IM	12-24 hrs duration
NSAID Agent (Water Dosing)			
Ibuprofen (Children's Advil® Elixir)	7.5 mg/kg	PO	Given in water bottle

Notes:

***Meloxicam (5 mg/ml) added to water: 2.34 ml meloxicam injectable to 87.66 ml of water yields a final solution concentration of 0.130 mg/ml. Dextrose solution should be added to the water to improve palatability. Stable for 7 days in ambient light, ambient dark, and 4 degrees C conditions.**

****Carprofen (50 mg/ml) added to water: 0.12 ml Rimadyl injectable added to 89.88 ml of water to yield a final solution concentration of 0.067 mg/ml. Stable for 7 days in ambient light, ambient dark, and 4 degrees C conditions. To achieve peak blood drug levels similar to those obtained by oral gavage, carprofen-containing water bottles should be place on mouse cages at least 12 h prior to painful procedures.**

References:

1. University of Colorado Denver IACUC. Veterinary Anesthetic and Analgesic Formulary. Edition 3.10: University of Colorado Denver; 2015.
2. Fish R.E., Brown M.J., Danneman P.J., Karas A.Z., editors. Anesthesia and Analgesia in Laboratory Animals. 2nd Ed. New York: Academic Press; 2008.
3. University of Colorado Boulder IACUC. Hypothermia as an anesthetic in neonatal rodents. University of Colorado Boulder; 2014.
4. Cornell University IACUC. Rodent Anesthesia. Cornell University 2014.

5. Aqueous Stability and Oral Pharmacokinetics of Meloxicam and Carprofen in Male C57BL/6 Mice. J. Ingrao, R. Johnson, E. Tor, et. al. JAALAS: 52(5), September 2013, pp. 553-559.