

Rodent Anesthesia and Analgesia

Mouse Anesthetics and Analgesics

Inhaled Anesthetic Drugs

<i>Agent</i>	Dosage	Route	Comments (Ref.)
<i>Isoflurane</i>	Induction: 3-5% Maintenance: 1.5-3%	Inhaled w/nose cone	Administer via precision vaporizer or open-drop method with IACUC approval (5,6)

Injectable Anesthetic Drugs/Combinations

<i>Agent(s)</i>	Dosage	Use	Comments (Ref.)
<i>Ketamine/Xylazine</i>	80-100/ +6-10mg/kg IP	Anesthesia	Anesthesia duration of 20-40 minutes (1)
<i>Ketamine/Xylazine Acepromazine</i>	65/13/2 mg/kg, IP	Anesthesia	About 30% longer anesthesia duration and recovery than the above
<i>Pentobarbital (Nembutal)</i>	40-85 mg/kg, IP	Anesthesia	Anesthesia duration of 20-40 minutes (1,9)
<i>Ketamine/Dexmedetomidine</i>	50-75 mg/kg +0.5-1.0 mg.kg IP 100 mg/kg + 0.5 mg/kg IP		

Local Anesthetics

<i>Agent</i>	Dosage	Use	Comments (Ref.)
<i>Lidocaine (1-2%)</i>	2-4 mg/kg (max 7 mg/kg), SQ	Local Anesthetic	Onset 5-10 min Anesthetic duration 0.5-1 hr (10)
<i>Bupivacaine (.5% Marcaine®)</i>	1-2 mg/kg (max 8 mg/kg), SQ	Local Anesthetic	Onset 15-30 mins Anesthetic duration 4-8 hrs (10,11)

Analgesics (Pain Relief)

<i>Opioid</i>	Dosage	DEA License	Comments/Dosage Frequency (Ref.)
<i>Buprenorphine (Buprenex®)</i>	0.05-0.1 mg/kg, SC	Yes	Every 8-hrs

<i>Buprenorphine SR</i> [®]	1.5 mg/kg, SC	Yes	Every 72 hrs
<i>Buprenorphine ER</i> (<i>Animalgesics Zoopharm</i> or <i>Ethica</i>)	3.25 mg/kg (A and E) SC 1 mg/kg (Z)	Yes	Every 72 hrs
NSAID Anti-inflammatory Drug			
<i>Carprofen (Rimadyl)</i> [®]	5 mg/kg, SC	No	Every 12 hrs (1,13)
<i>Carprofen (Clear H₂ Medigel)</i>	1-2oz cup of MediGel on the floor with the animals 48 hours prior to surgery. Animals will readily consume the gel providing them an oral dose of carprofen equivalent to 5 mg/kg/day Bioserv tablet: 2 mg (1/4 to 1 5 gram tablet)	No	1-2oz cup for up to 5 mice
<i>Meloxicam (Metacam)</i> [®]	2-5 mg/kg, SC	No	Every 24 hrs
<i>Meloxicam SR (Zoopharm)</i>	4 mg/kg, SC	No	Every 72 hrs
NSAID (Water Dosing)			
<i>Ibuprofen (Children's Motrin)</i> [*]	30 mg/kg *	No	PO in water bottle
*Add 2.25 ml Children's Motrin (100gm/5ml) to 250 ml water = .18 mg/ml solution. This solution provides a dose of 30 mg/kg assuming a 30 gram mouse drinks 5 ml/day. The solution should be changed twice a week.			

SPECIAL NOTE:

In rodent species, historically, the use of analgesics such as Ibuprofen (Children's Motrin) have been administered in the drinking water for post-surgical procedures. This was performed based on the assumption that continuous administration of the drug by consumption in the water would provide a hands-off, stress-free, continuously-administered level of analgesic therapy. With continued investigation, it has been demonstrated that water and food consumption post-surgically and/or post-anesthesia are neither constant nor consistent (2,23). As a result, analgesics may not be consumed by the patient. "Confirmed administration" is encouraged by routes such as injection or oral/gastric gavage to insure that the patient received the appropriate dose of medication to better manage discomfort.

For analgesic drugs that are administered via the drinking water:

- if administered via the drinking water, the drug must be placed in the drinking water starting a minimum of 7 days prior to the surgery/painful procedure in order for the animal to be "exposed", and, presumably, adapted to the altered taste of the water at the time of the

surgery/procedure. This preparatory step is necessary to overcome ‘neophobia,’ a behavioral adaptation of rodents (especially rats) whereby they may not consume adequate quantities of fluids when a new taste sensation is recognized. Placing a flavored analgesic in the water post procedure may allow for association of the ‘pain’ with the new flavor and thereby rejection of the flavored water resulting in inadequate analgesia.

For purposes of administering a drug via the drinking water:

	MOUSE	RAT
Normal* Daily Water Consumption	15 ml/100 gm body weight/day	8-11 ml/100 gm body weight/day

*Animals that have been subjected to a painful procedure/surgery will not drink the “normal” amount of water for a minimum of 24 hours post-surgery/post-procedure. It is estimated that normal water consumption will be reduced by at least 50%.

Rat Anesthetics and Analgesics

Inhaled Anesthetic Drugs

<i>Agent</i>	Dosage	Route	Comments (Ref.)
<i>Isoflurane</i>	Induction: 3-5% Maintenance: 1.5-3%	Inhaled w/nose cone	Administer via precision vaporizer or open-drop method with IACUC approval (5,6)

Injectable Anesthetic Drugs/Combinations

<i>Agent(s)</i>	Dosage	Use	Comments (Ref.)
<i>Ketamine/Xylazine</i>	75/+10 mg/kg IP 60-90 mg/kg +5-15 mg.kg IP	Anesthesia	Anesthesia duration of 20-40 minutes (1, 13)
<i>Ketamine/Xylazine Acepromazine</i>	75/5/1 mg/kg, IP	Anesthesia	About 30% longer anesthesia duration and recovery than the above
<i>Pentobarbital (Nembutal)</i>	30-50 mg/kg, IP	Anesthesia	Anesthesia duration of 20-40 minutes (1,13)
<i>Ketamine/Dexmedetomidine</i>	50-75 mg/kg + 0.25 mg/kg IP 75-100 mg/kg + 0.15 mg/kg IP		

Local Anesthetics

<i>Agent</i>	Dosage	Use	Comments (Ref.)
<i>Lidocaine (1-2%)</i>	2-4 mg/kg (max 7 mg/kg), SQ	Local Anesthetic	Onset 5-10 min Anesthetic duration 0.5-1 hr (10)
<i>Bupivacaine (.5% Marcaine®)</i>	1-2 mg/kg (max 8 mg/kg), SQ	Local Anesthetic	Onset 15-30 mins Anesthetic duration 4-8 hrs (10,11)

Analgesics (Pain Relief)

Opioid			
	Dosage	DEA License	Comments/Dosage Frequency (Ref.)
<i>Buprenorphine (Buprenex®)</i>	0.01-0.05 mg/kg, SC, IV 0.5 mg/kg PO Q 12 hrs	Yes	Every 8 hrs (1,12,13,14,16)
<i>Buprenorphine SR®</i>	0.5 mg/kg, SC	Yes	Every 48-72 hrs
<i>Buprenorphine ER (Animalgesics®)</i>	0.65 mg/kg SC	Yes	Every 48-72 hrs
NSAID Anti-inflammatory Drug			
<i>Carprofen (Rimadyl®)</i>	5 mg/kg, SC	No	Every 12 hrs(1,13)
<i>Carprofen (Clear H₂ Medigel)</i>	1-2oz cup of MediGel on the floor with the animals 48 hours prior to surgery. Animals will readily consume the gel providing them an oral dose of carprofen equivalent to 5 mg/kg/day Bioserv tablet: 2 mg once a day (one 5 gram tablet)	No	1-2oz cup for up to 2 rats
<i>Meloxicam (Metacam®)</i>	1-2 mg/kg, SC	No	Every 24 hrs
<i>Meloxicam SR (Zoopharm)</i>	4 mg/kg, SC	No	Every 72 hrs
NSAID (Water Dosing)			
<i>Ibuprofen (Children's Motrin)</i>	15 mg/kg*	No	PO in water bottle (2,13)
*Add 3.75 ml Children's Motrin (100mg/5ml) to 500 ml water = .15mg/ml solution. This solution provides a dose of 15 mg/kg assuming a 300 gram rat drinks 30 ml/day. The solution should be changed twice a week.			

SPECIAL NOTE:

In rodent species, historically, the use of analgesics such as Ibuprofen (Children's Advil® Exlixir) have been administered in the drinking water for post-surgical procedures. This was performed based on the assumption that continuous administration of the drug by consumption in the water would provide a hands-off, stress-free, continuously-administered level of analgesic therapy. With continued investigation, it has been demonstrated that water and food consumption post-surgically and/or post-anesthesia are neither constant nor consistent (2,23). As a result, analgesics may not be consumed by the patient. "Confirmed administration" is encouraged by routes such as injection or oral/gastric gavage to insure that the patient received the appropriate dose of medication to better manage discomfort.

For analgesic drugs that are administered via the drinking water:

- if administered via the drinking water, the drug must be placed in the drinking water starting a minimum of 7 days prior to the surgery/painful procedure in order for the animal to be “exposed”, and, presumably, adapted to the altered taste of the water at the time of the surgery/procedure. This preparatory step is necessary to overcome ‘neophobia,’ a behavioral adaptation of rodents (especially rats) whereby they may not consume adequate quantities of fluids when a new taste sensation is recognized. Placing a flavored analgesic in the water post procedure may allow for association of the ‘pain’ with the new flavor and thereby rejection of the flavored water resulting in inadequate analgesia.

For purposes of administering a drug via the drinking water:

	MOUSE	RAT
Normal* Daily Water Consumption	15 ml/100 gm body weight/day	8-11 ml/100 gm body weight/day

*Animals that have been subjected to a painful procedure/surgery will not drink the “normal” amount of water for a minimum of 24 hours post-surgery/post-procedure. It is estimated that normal water consumption will be reduced by at least 50%.

Neonatal Rodent Anesthetics and Analgesics

Inhaled Anesthetic Drugs

<i>Agent</i>	<i>Dosage</i>	<i>Route</i>	<i>Comments (Ref.)</i>
<i>Isoflurane</i>	Induction: 3-5% Maintenance: 1.5-3%	Inhaled w/nose cone	Administer via precision vaporizer or open-drop method with IACUC approval (5,6)

Neonatal Hypothermia Anesthesia

<i>Comments (Ref.)</i>
<p><i>Hypothermia Method: Mouse and rats pups up to 6 days of age may be anesthetized by hypothermia when inhalant anesthetic is not feasible.</i></p> <ol style="list-style-type: none"> <i>Hypothermia induction: Place the pup in a latex/nitrile glove finger and immerse the glove finger in crushed ice and water (2-3°C or 35-37°F) up to the level of the head so that the head of the pup is visible. Anesthesia induction takes 5-8 minutes.</i> <i>Procedure: Remove the pup from the ice bath and place on a re-freezable ice pack. A piece of gauze or cloth should prevent direct contact of the pup's skin with the freezable ice pack. Duration of anesthesia on an ice pack is 15 minutes maximum.</i> <i>Hypothermia Recovery: Rapid warming should be avoided. Pups can be placed in a small incubator (32-35 °C or 90-95°F) for gradual warming over 20-30 minutes. Once warmed for this time, circulating warm water blankets can be used until mobile where complete recovery takes 30-60 minutes.</i> <p><i>Once mobile, pups may be mingled with the litter to aid in covering the procedure smells on the pup then the litter returned to the dam.</i></p>

Comments (Ref.)
(1,17-21)

Injectable Anesthetic Drugs/Combinations

<i>Agent(s)</i>	Dosage	Use	Comments (Ref.)
<i>Ketamine/Xylazine</i>	40-80 / 5-10 mg/kg IP	Anesthesia	(21)
<i>Pentobarbital</i>	30-40 mg/kg, IP	Anesthesia	(18)

Comments: *Injectable anesthetics in neonatal rodents is unpredictable and has a great than 50% rate of mortality (18). Use of injectable anesthetics should only be considered in neonates greater than 6 days of age and where gas anesthesia is not feasible.*

Analgesics (Pain Relief)

	Dosage	DEA License	Comments/Dosage Frequency (Ref.)	<i>Opioid</i>
<i>Buprenorphine (Buprenex®)</i>	0.05-0.2 mg/kg, SC, IP	Yes	Every 6-8 hrs (21)	

Drug Considerations

Inhalant agents: Isoflurane (Forane®, Iso, IsoFlo®)

Isoflurane is the first choice of anesthetic used for animal restraint or surgical procedures in laboratory animal species. Isoflurane is delivered via a nose-cone and inhaled in rodents or provided through an intra-tracheal tube. The concentration of drug can be administered to effect by adjusting the percent of displacement of O₂ with a precision vaporizer. Maintenance anesthesia is typically between 1.5-3% Isoflurane. Induction of anesthesia with gas is typically achieved with < 2 min exposure to 3-5% Isoflurane.

Advantages: Rapid induction and recovery. A precision vaporizer provides the ability to precisely titrate the level of anesthesia during a procedure. Liquid Isoflurane is not a DEA controlled drug

Disadvantages: Upfront cost associated with a precision vaporizer; requires either passive or active scavenging of waste and exhaled anesthetic gas; occupational health exposure to anesthetic gases should be limited; prolonged analgesic effect is not achieved after the animal is awake; depressed respiratory rate and decreased blood pressure.

Additional Notes: Advantages typically outweigh disadvantages as gas anesthesia is the first recommendation for anesthetic administration due to rapid induction, recovery, and precise dose titration during the procedure. In addition, the duration of anesthesia can be easily adjusted for a variety of procedures ranging from 30 seconds up to many hours. Concurrent use of analgesics such as opioids or NSAIDs is encouraged as Isoflurane has no analgesic properties once the animal is awake from the procedure. Occupational exposure is always a concern. Gas anesthesia must be vented from the room (table-top back-draft vents, biosafety cabinet [BSC] with 100% exhaust outside the building) or filtered through passive scavenging using F/Air® activated

charcoal canisters. F/Air® canisters must be weighed on a very regular basis and replaced before the canister gains 50 grams of weight during use.

Cyclohexamines: Ketamine (Ketaset®)

Ketamine is the most commonly used injectable anesthetic used in a variety of species. However, Ketamine used as the sole anesthetic is not recommended. In most cases, Ketamine is used in combination with other injectable agents such as α_2 agonists or benzodiazepines to reduce or eliminate many of the less desirable side effects if used alone. In rodents, Ketamine combined with Xylazine or Xylazine plus Acepromazine are the preferred anesthetics when gas anesthesia cannot be used.

Advantages: Ketamine has a wide margin of safety in most species; residual analgesic effect following anesthetic recovery, most commonly used drug (in combination) for injectable anesthesia in rodents.

Disadvantages: Ketamine alone does not provide muscle relaxation and muscle spasms may be observed; DEA license required for use as Ketamine is a Class III controlled substance; surgical anesthesia may be limited depending on the species; prolonged recovery as compared to gas anesthetics (true for any injectable anesthesia).

Additional details about Ketamine combinations:

- **Ketamine + Xylazine:** Both drugs can be mixed in a single syringe prior to administration. This combination is the most common injectable anesthetic used in rodent species.
- **Ketamine + Xylazine + Acepromazine:** All three drugs can be mixed in a single syringe prior to administration. In rodents, the addition of Acepromazine to the Ketamine/Xylazine cocktail increases the depth of anesthesia and substantially prolongs the duration of anesthesia as well as recovery time. The benefit of this combination will be dependent on the procedure.

Alpha-2 Agonists: Xylazine (Rompun®) Alpha-2 agonists are used for their sedative and analgesic properties in a variety of species. Used as the sole agent, they do not produce an adequate level of anesthesia for even minor surgical procedures. However, in combination with Ketamine, α_2 -agonists become much more useful and effective as anesthetics for surgical procedures.

Advantages: Produces analgesia of short duration; can be combined with Ketamine to produce adequate surgical anesthesia in many species; effects can be reversed with a subcutaneous α_2 antagonists

Disadvantages: Cardiovascular depression (decreased heart rate, cardiac output, and hypotension); transient hyperglycemia following administration which may have research significance

Additional Notes: When re-dosing an injectable anesthetic combination of Ketamine and an α_2 agonists as the initial injection is wearing off, it is recommended to only re-dose Ketamine as the duration of action of the α_2 agonist is much longer than the duration of effect of Ketamine.

Barbiturates: Sodium Pentobarbital (Nembutal®)

Barbiturates function as GABA_A agonists and are considered to be good anesthetic agents but provide unreliable sedation at low dosages and inadequate analgesic effect at any dose. Pentobarbital, the most commonly used drug of this class, is considered a long acting anesthetic.

Advantages: Rapid anesthetic onset; provides a prolonged duration of surgical anesthesia; decades of use has characterized many research side effects.

Disadvantages: Prolonged recovery time; inadequate analgesic properties; extremely expensive; narrow margin of safety; produces respiratory depression at higher dosages; DEA License required for use as a Class II controlled substance.

Opioids: Buprenorphine (Buprenex®)

Opioid drugs produce their effect by binding three different receptors [μ (μ), κ (κ), and δ (δ)] as either agonists, partial agonists or antagonists. The location of these receptors vary, but in general, reside within the brain and spinal cord.

Advantages: Provide potent analgesia; concurrent administration can lower the dose of inhalant or barbiturate general anesthetic for surgery; mechanism mediated by receptor binding in the brain and spinal cord; long history of use in research.

Disadvantages: DEA Controlled Class II-IV drugs; high potential for human abuse and addiction; relatively short duration of action; repeated use may result in tolerance development.

Additional Notes: Duration of effect has continuously hampered the use of opioids in research animals. In general, opioids are short acting drugs.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs): Carprofen (Rimadyl®), Meloxicam (Metacam®), Ibuprofen (Children's Motrin)

Members of this group represent 13 different classes of drugs which share inhibitory activity of the cyclooxygenase (COX) enzyme. The COX enzyme facilitates the production of Prostaglandin G₂ (PGG₂) which then follows a variety of enzymatic processes in the production

of several compounds that are involved in normal physiological processes and production of Prostaglandin E2 (PGE2). PGE2 specifically plays a role in the perception of pain in the periphery and within the central nervous system. Thus, blockade of PGE2 by COX inhibition is effective in control of discomfort at the site of insult and within the central nervous system. Two forms of the COX enzyme have been well characterized (COX-1 and COX-2). As a result, COX inhibitors are often referenced as non-selective COX inhibitors or selective COX-2 inhibitors. This distinction has been made because inhibition of COX-2 is believed to be the predominant method of NSAID function to provide analgesia and anti-inflammatory action even though this “consensus” is still under debate. Over the past 10 years, several NSAIDs have emerged for veterinary use that are COX-2 selective, such as Carprofen and Meloxicam which can be administered once every 12-24 hours in most species.

Advantages: New drugs (Carprofen, Meloxicam) including a long duration of analgesic activity; newer drugs demonstrate analgesic quality that rivals some opioids; not a DEA controlled substance; there are multi-route administration methods for several NSAIDs; relative safety when administered at prescribed dosages.

Disadvantages: Contraindicated for inflammation models, infectious disease, or coagulation research due to anti-inflammatory properties; COX-1 side effects such as: gastrointestinal complications, prolonged coagulation times, and changes in kidney function with non-COX-2 selective forms.

Additional Notes: Analgesic combinations that include NSAIDs plus opioids would be considered an ideal combination for the control and prevention of discomfort due to the demonstrated harmony and difference in mechanism of action. In contrast, it is discouraged to combine multiple NSAIDs in combination or use NSAIDs in combination with steroids (Prednisone, Prednisolone, and Dexamethasone) as the incidence of complications increase.

Local Anesthetics: Lidocaine, Bupivacaine (Marcaine®)

Local anesthetics block nerve impulses by specifically binding the voltage-gated Na⁺ channel in the nerve cell membrane. Reversible drug binding stabilizes the ion channel preventing the transmission of action potentials, thus preventing nerve information transmission to the spine and brain. Local anesthetic routes of administration include topical to mucus membranes (nose, eye, etc.) or injected directly into tissues and around nerve bundles. Administration of local anesthetics prior to the painful stimulus (e.g. incision) would be considered an adjunct analgesic to opioid and NSAID analgesics. Use as the primary analgesic is discouraged due to the short duration of effect (hours).

Advantages: Pre-operative and intra-operative administration can provide a good adjunct in pain relief to general anesthesia and systemic analgesics administered after a procedure. Drugs of this class are not controlled substances.

Disadvantages: Avoid administering by intramuscular and intravenous injections as both routes reach systemic circulation very rapidly. Signs of overdose or systemic toxicity include seizures and death.

Dilution of stock concentration is encouraged to provide more accurate dose administration.

Additional Notes: For rodent use, dilute 1-2% Lidocaine to 0.5%, and 0.5% Bupivacaine to 0.25%, to allow for more accurate dosing and realistic volume to infuse at the incision site. [Note: 1% solution is equal to 10 mg/mL]. Lidocaine is a fast acting, short duration local anesthetics. Bupivacaine is a slow onset, long acting local anesthetic. When used in combination (Lidocaine plus Bupivacaine in the same syringe) the benefits of both drugs can be achieved, namely rapid onset with long duration of local anesthesia. In addition, the duration of efficacy of local anesthetics can be extended by the addition of epinephrine to the injected solution. Epinephrine causes local vasoconstriction of blood vessels in the area of the injection resulting in decreased systemic absorption leading to prolonged duration of action. Preparations of Lidocaine and Bupivacaine can be purchased pre-combined with epinephrine (1:200,000).

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