Guidelines on Anesthesia and Analgesia in Rats

Last Updated 15 October 2013

1. Purpose
   1. This document has been designed by the ULAM veterinary staff as a guideline for sedation, anesthesia, and analgesia of laboratory rats. This is not intended to be an inclusive tutorial on all possible drug combinations that can be used in rats. The following guidelines are also general recommendations and consequently do not include reference to specific research associated concerns. If you have questions or comments about this document, please contact the ULAM veterinary staff at ulam-vets@umich.edu or 734-936-1696. The ULAM training core (ulam-trainingcore@umich.edu or 734-763-8039) can be contacted to provide training in these techniques at no charge.
   2. More information on surgical requirements for rodents can be found in Guidelines on the Performance of Surgery in Rodents.
   3. More specific information regarding monitoring procedures can be found in Anesthesia and Sedation Monitoring Guidelines.
   4. More specific information regarding anesthetic, sedation and analgesic drug classes can be found in Anesthesia and Analgesia Drug Descriptions.

2. Responsibility
   1. Principal Investigator: Responsible to ensure appropriate anesthesia and/or analgesia is provided for all rodents undergoing painful procedures including rodent survival surgery unless otherwise indicated in the relevant approved protocol.

3. Definitions
   1. Anesthesia: Temporarily induces loss of sensation with or without loss of consciousness.
   3. A/A: Anesthesia and analgesia.
   4. Sedation: A mild degree of central depression in which the patient is awake but calm.

4. Procedures
   1. Prior to anesthetic/analgesic/sedative event
      1. Newly arrived animals should be acclimated at least 3 days prior to anesthesia or sedation.
      2. Age and body weight should be considered when designing an A/A plan.
      3. Preanesthetic fasting is usually not necessary in rodents. If preanesthetic fasting is required:
         1. The fasting period must be limited to 2-3 hours and no longer due to the higher metabolism in rats.
         2. Water should NEVER be restricted.
      4. Ocular lubrication such as Paralube® must be used to prevent corneal drying during anesthesia or sedation.
   2. Routes of administration
      1. More detailed information regarding injection techniques and maximum quantities safely administered to rats can be found in Guidelines on Administration of Substances to Laboratory Animals.
   3. Normal monitoring parameters
      1. More information on anesthetic/sedation monitoring requirements can found in Anesthesia and Sedation Monitoring Guidelines.
         1. Respiratory rate should be 70 - 110 breaths/min.
         2. Respiratory pattern can be used to monitor anesthesia.
            1. Deep and slow or rapid and shallow.
      2. Pulse rate should be 260 - 500 beats/min.
      3. Normal temperature ranges while under anesthesia fall between 35.9°C and 37.5°C (96.6 - 99.5°F).
      4. Mucus membrane color should be pink. Never pale white or blue.
         1. Normal capillary refill time (CRT) is < 2 seconds.
4. Recovery

1. More information on monitoring parameters during post-operative recovery can be found in Guidelines on the Performance of Surgery in Rodents.
2. Recover animals in clean cages without bedding to limit possibility of tracheal foreign body obstruction or pneumonia.
3. Recover animals in the surgery area so they can be appropriately monitored during the recovery period.
4. Animals that have received an alpha-2 agonist (xylazine, dexmedetomidine) as part of their anesthetic protocol may receive a reversal agent to expedite recovery (see Table 3).
5. If a large number of surgeries are being conducted at one time, animals may be housed together following anesthesia and prior to full recovery if they are continually observed. This is to ensure that more alert animals do not cannibalize non-responsive cage mates.
6. Nutritional support is critical following anesthesia and should be provided as soon as the animal is recovered.
   1. Moist chow, regular chow, or diet gel should be provided on the cage floor to encourage eating as soon as possible.

5. Anesthetics

1. Detailed information on all approved anesthetics and sedatives can be found in Anesthesia and Analgesia Drug Descriptions.
2. Anticholinergics
   1. Atropine 0.05 mg/kg subcutaneously
   2. Glycopyrrolate 0.01 - 0.02 mg/kg subcutaneously

3. Table 1: Inhalant Anesthetics Used in Rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose &amp; Route a</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane RECOMMENDED</td>
<td>4 - 5% for induction 1 - 2% for maintenance</td>
<td>Requires use of calibrated vaporizer</td>
</tr>
<tr>
<td>Ether NOT recommended</td>
<td>Ambient vaporization of ether-soaked gauze</td>
<td>Use in fume hood due to its flammable and explosive nature. Notification of OSEH required.</td>
</tr>
</tbody>
</table>

4. Table 2: Injectable Anesthetics and Tranquilizers Used in Rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Route</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>40 - 50 mg/kg IP</td>
<td>80-95 min</td>
<td>Poor analgesic effects. Dose sufficient to produce surgical anesthesia may cause severe respiratory depression and death. Give diluted in saline (&lt;10 mg/ml). AVOID buprenorphine co-administration. Buprenorphine and Pentobarbital will result in cardiorespiratory depression. Administer buprenorphine after full recovery.</td>
</tr>
<tr>
<td>Dissociatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine + xylazine (Rompun®) Recommended</td>
<td>40 - 90 mg/kg ket. IP + 5 - 10 mg/kg xyl. IP</td>
<td>45 - 90 min</td>
<td>Thermal support is crucial. To prolong anesthesia, supplement with 1/3 dose of ketamine only. Xylazine can be reversed with 1 - 2 mg/kg yohimbine IP or 0.1 - 1.0 mg/kg atipamezole IP/SQ</td>
</tr>
<tr>
<td>Ketamine + acepromazine (Acepromazine®)</td>
<td>75 - 80 mg/kg ket. IM or IP + 2.5 mg/kg ace. IM or IP</td>
<td>20 - 30 min</td>
<td>Light anesthesia</td>
</tr>
<tr>
<td>Ketamine + dexmedetomidine</td>
<td>75 mg/kg ket. + 0.25 - 0.5 mg/kg, dex. IP for non-premedicated animals 75 mg/kg ket. + 0.03 - 0.1 mg/kg dex. IP for animals premedicated with buprenorphine or other opioids.</td>
<td>120 min</td>
<td>Light anesthesia Reverse dexmedetomidine with atipamezole 1.0 mg/kg IP</td>
</tr>
<tr>
<td>Ketamine + diazepam (Valium®)</td>
<td>40-80 mg/kg ket. IP + 5-10 mg/kg dia. IP</td>
<td>20 - 30 min</td>
<td><em>(Welberg et al. 2006)</em></td>
</tr>
<tr>
<td>Ketamine + xylazine + acepromazine</td>
<td>31.25 mg/kg ket. IP or IM + 6.25 mg/kg xyl. IP or IM + 1.25 mg/kg ace. IP or IM</td>
<td>Unproven</td>
<td><em>(Welberg et al. 2006)</em></td>
</tr>
</tbody>
</table>

Neuromuscular Blocking (NMB) Agents
<table>
<thead>
<tr>
<th>Drug</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>2 mg/kg IV</td>
<td>Unproven</td>
</tr>
</tbody>
</table>

Mechanical ventilation MUST be provided with NMB agents. Blood pressure and heart rate MUST be monitored every 15 min. See Anesthesia and Sedation Monitoring Guidelines for more details.

**Other**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>a- Chloralose (5% w/v concentration) Not Recommended</td>
<td>31 - 65 mg/kg IP</td>
<td>Unproven</td>
</tr>
</tbody>
</table>

Poor analgesia, possible convulsions, metabolic acidosis. Do NOT use for survival surgical procedures.

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<th>Drug</th>
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</tr>
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<tbody>
<tr>
<td>a- Chloralose + Urethane Not Recommended</td>
<td>50 - 60 mg/kg IP chl. + 500 - 800 mg/kg ure. IP (administer urethane 20-30 min. prior to a- chloralose)</td>
<td>500 min.</td>
</tr>
</tbody>
</table>

Do NOT use for survival surgical procedures. Can be used for prolonged non-recovery monitoring procedures.

<table>
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<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Chloral hydrate (5% concentration) Not recommended</td>
<td>300 - 450 mg/kg IP.</td>
<td>60 - 136 min.</td>
</tr>
</tbody>
</table>

Concentration above 5% produces peritonitis. Anesthetic dose is near the lethal dose. Do NOT use for survival surgical procedures. Can be used for sedation for monitoring procedures.

<table>
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<tbody>
<tr>
<td>Urethane (ethyl carbamate) (50% w/v concentration) Not Recommended</td>
<td>1000-1500 mg/kg IP</td>
<td>Up to 24 hr</td>
</tr>
</tbody>
</table>

Carcinogenic and mutagenic. Do NOT use for survival surgical procedures. For non-recovery use only due to progressive acidosis, hyperosmolality of body fluids, and osmotic toxicity to mesenteric vasculature.

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**Table 3: Injectable Reversal Agents Used in Rats**

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atipamezole (Antisedan)</td>
<td>0.1 - 1.0 mg/kg IP, IM or SC</td>
<td>Preferred reversal agent for alpha-2 agonists</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>1.0 - 2.0 mg/kg IP or SC</td>
<td>Less effective than atipamezole</td>
</tr>
</tbody>
</table>

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**Analgesics**

1. Signs of Pain in rats may include, but are not limited to, the following:
   1. Reluctance to move
   2. Decreased activity
   3. Unresponsive
   4. Abnormal posturing
   5. Back arching
   6. Decreased appetite
   7. Ungroomed hair coat
   8. Vocalization
   9. Piloerection
   10. Self-mutilation
   11. Social isolation

2. Prevention and Management of Pain
   1. For short-term management (less than seven days) of moderate to severe pain, the ULAM veterinary staff recommends subcutaneous injections of buprenorphine (0.01 - 0.05 mg/kg) two to three times per day. A single injection of buprenorphine will typically last eight hours, but there is considerable variation in duration. The animals should be observed carefully so that the optimum dose and frequency of administration can be determined.

**Table 4: Analgesics Used in Rats**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose &amp; Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine (Buprenex®)</td>
<td>0.01-0.05 mg/kg SQ, IP</td>
<td>8-12 hours</td>
</tr>
<tr>
<td>Carprofen (Rimadyl®)</td>
<td>5 mg/kg SQ</td>
<td>24 hours</td>
</tr>
<tr>
<td>Flunixin (Banamine®)</td>
<td>2.5 mg/kg SQ</td>
<td>12-24 hours</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>5 mg/kg SQ</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
a Subcutaneous (SQ), Intramuscular (IM), Intraperitoneal (IP), Intravenous (IV), Orally (PO).
b Preemptive analgesia, particularly opiates like buprenorphine, can reduce the dose of anesthetics required for surgical anesthesia and increase the respiratory depression associated with anesthetics. When pre-emptive analgesia is used, consider reducing the dose of anesthetic (whether inhalant or injectable) to the low end of the recommended range. Anesthetic depth must be carefully monitored and drug doses may need to be titrated to maintain appropriate levels. With new projects, sexes, strains or anesthetic analgesic combinations, assess a subset of animals before expanding to use in a larger cohort.
c Current literature (Shientag 2012) and institutional reports have identified a potential ketoprofen sensitivity in some rat stocks and strains. Therapeutic doses of ketoprofen (5mg/kg), under the right physiologic conditions, may cause gastrointestinal bleeding, erosion, ulceration, and, in extreme cases, perforation. Rats receiving ketoprofen for analgesia should be closely monitored for signs of gastrointestinal complications within 24-48 hours after administration.

7. Local Anesthetics

1. Maximum safe doses for most species including rats are:
   1. Lidocaine: 4 mg/kg (0.4 ml/kg of a 1% solution)
   2. Bupivacaine: 1-2 mg/kg (0.4-0.8 ml/kg of a 0.25% solution)

8. Neonatal Rodent Anesthesia

1. A rodent neonate is a mouse or rat <10 days of age. There are several anesthetic methods in the literature for use in neonatal rodents however, hypothermia is the primary physical method utilized in neonatal rodent anesthesia. It is believed to provide anesthesia and temporary analgesia by decreasing neural conduction and synaptic transmission. The cooling process may be painful and **direct contact with the cooling agent should be avoided**.
   1. Injectable anesthetics have been associated with a high mortality in neonatal rodents.
   2. Neonatal rodents may have a longer induction and recovery time than adult rodents with inhalant anesthetics.

2. Hypothermia - Can only be performed in neonatal rodents <6 days old and should not be used for procedures lasting longer than 30 min.
   1. Place neonates either on a latex covered bed of crushed ice, in a cut off finger of a latex glove, or in a paper lined test tube in crushed ice.
   2. Check the pup for pedal reflex indicating proper plane of anesthesia.
   3. Remove the pup from the ice bed and place on a chilled cold pack or bed of ice. Place a barrier between the pup and the ice to prevent direct damage to the tissues.
   4. Use fiber optic lighting for the surgical field as incandescent bulbs may warm the pup.
   5. Following hypothermia anesthesia, re-warm the animals slowly. Rapid warming can cause tissue damage. Use of a circulating water heating pad (40 °C) or in an incubator (33 °C) is recommended.
   6. Return pups to dam once they are able to crawl.

3. Parental cannibalism can occur with neonates after anesthesia. The following steps can be used to reduce the occurrence of cannibalism in anesthetized neonatal pups:
   1. Ensure the neonate is fully recovered before returning to the dam.
   2. Smear the pups with soiled bedding from the mother's cage.
   3. Place the pup back in the middle of the litter.

5. Related Documents

1. Guidelines on the Performance of Surgery in Rodents
2. Anesthesia and Sedation Monitoring Guidelines
3. Anesthesia and Analgesia Drug Descriptions
4. Guidelines on Administration of Substances to Laboratory Animals
5. EHS Anesthetic Gases in Animal Research

6. References


22. Other websites describing guidelines for Avertin use:

23. Other Websites regarding neonatal rodent anesthesia: