Guidelines on Anesthesia and Analgesia in Rabbits

Last Updated 15 March 2016

1. Purpose
   - This document has been designed by the ULAM veterinary staff as a guideline for sedation, anesthesia, and analgesia of laboratory rabbits. This is not intended to be an inclusive tutorial on all possible drug combinations that can be used in rabbits. 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-training@umich.edu or 734-763-8039) can be contacted to provide training in these techniques at no charge.

   - More information on surgical requirements for rabbits can be found in Guidelines on the Performance of Surgery in Non-Rodent Mammals.
   - More specific information regarding monitoring procedures can be found in Anesthesia and Sedation Monitoring Guidelines.
   - More specific information regarding anesthetic, sedation and analgesic drug classes can be found in Anesthesia and Analgesia Drug Descriptions.

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

3. Definitions
   - Anesthesia: Temporarily induces loss of sensation with or without loss of consciousness.
   - Analgesia: Provides pain relief without loss of consciousness.
   - A/A: Anesthesia and analgesia.
   - CRI: Continuous rate of infusion.
   - IM: Intramuscular route of administration.
   - IV: Intravenous route of administration.
   - SC: Subcutaneous route of administration.
   - Sedation: A mild degree of central depression in which the patient is awake but calm.

4. Procedures
   - Prior to anesthetic/analgesic/sedative event
     1. Special considerations when anesthetizing rabbits
        1. Acclimation: Animals should be acclimated to their environment for a minimum of 72 hours, habituated to handling, and evaluated for obvious clinical signs of disease prior to anesthesia. Non-SPF rabbits may be infected with Pasteurella multocida; underlying lung damage from this pathogen may lead to respiratory arrest under anesthesia.
        2. Handling and Restraint: Rabbits are easily stressed by handling and induction.
           1. To avoid excessive anxiety in the pre- and post- anesthetic periods, provide an environment devoid of extraneous noise, including loud talking.
           2. The amount of restraint and its duration should be kept to the minimum required to accomplish the necessary procedure.
           3. To reduce the time of restraint, equipment and reagents should be ready to use prior to handling the animal.
           4. Pre-anesthetic doses of sedative/tranquilizer agents are often used to facilitate immobilization and to reduce anxiety.
3. **Fasting:** Rabbits cannot vomit, therefore fasting is not mandatory. They do tend to accumulate food and fluid within the oral cavity and oropharynx. For this reason, a pre-anesthetic fast of 1-4 hours is recommended. Fasting also reduces the overall volume of the gastrointestinal tract thus reducing pressure on the diaphragm while under anesthesia. Fasting for longer periods of time may predispose them to post-operative ileus and may decrease blood glucose levels. More information regarding fasting duration can be found in *Guidelines on Experimental Food or Water Restriction or Manipulation in Laboratory Animals*.

4. **Surgical Position:** Tilting the surgical table so that the rabbit's head is slightly elevated will reduce pressure on the diaphragm. Anesthetizing a rabbit on a level surface is also acceptable, however, caution should be taken to avoid inadvertently elevating the rabbit's hindquarters.

5. **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 rabbits 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 be found in *Anesthesia and Sedation Monitoring Guidelines*.

   2. The goal of monitoring should be to maintain normal cardiac function, respiratory function, and body temperature. Understanding the basic physiologic effects of the anesthetics used is paramount to correctly interpreting monitoring parameters. More information on anesthetic and sedative effects on physiologic parameters can be found in *Anesthesia and Analgesia Drug Descriptions*.

3. **Table 1: Physiologic Data of Rabbits**

<table>
<thead>
<tr>
<th></th>
<th>Temperature</th>
<th>Heart Rate</th>
<th>Respiratory Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without anesthesia</td>
<td>100.4-104 F (38.0-40 C)</td>
<td>130-325</td>
<td>30-60 in resting rabbit</td>
</tr>
<tr>
<td>With anesthesia</td>
<td>T &gt;98 F (&gt;37 C)</td>
<td></td>
<td>20-30</td>
</tr>
</tbody>
</table>

4. **Physiologic Support**

   1. **Hypothermia**

      1. An external heat source should be provided during the entire anesthetic and recovery period. For examples of approved external heat supplementation products, please refer to *Anesthesia and Sedation Monitoring Guidelines*.

   2. **Fluids**

      1. Providing fluid support during anesthesia is important particularly if a procedure lasts one-half hour or more. More information on appropriate fluid rates can be found in *Guidelines on the Performance of Surgery in Non-Rodent Mammals*.

   3. **Vascular Access**

      1. The placement of indwelling catheters are advised. The lateral (marginal) ear veins are easily accessed and the preferred site. The application of lidocaine-prilocaine EMLA® cream to the ear 30 minutes before venipuncture has been recommended to reduce pain. A tranquilizer or sedative can also be given prior to catheter placement to help decrease the rabbit's stress level. The cephalic and recurrent tarsal veins can also be utilized.

   4. **Endotracheal Intubation**

      1. Several techniques have been devised to simplify the difficult task of endotracheal intubation. The narrow mouth diameter, large tongue, limited range of jaw opening, and prominent incisors make placement of an endotracheal tube challenging. Please contact the ULAM training core to set up a time to learn how to correctly and safely perform endotracheal intubation in the rabbit.

      2. V-Gel (supraglottic airway device) Intubation: This device allows easier airway access when compared to endotracheal tubes. However, the V-Gel does not protect the airway from aspiration as effectively as endotracheal intubation. Also, there is a risk of tongue cyanosis. Please contact the ULAM training core to set up a time to learn how to correctly and safely perform endotracheal intubation in the rabbit.

5. **Recovery**

   1. More information on required monitoring parameters during post-operative recovery can be found in *Guidelines on the Performance of Surgery in Non-Rodent Mammals and Anesthesia and Sedation Monitoring Guidelines*.

   2. Recover animals in clean kennels or transport cages. Animals must be fully recovered prior to return to their home cage.

   3. If a large number of surgeries are being conducted at one time, post-surgical 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 injure non-responsive cage mates.

   4. Nutritional support should be withheld until the animal is fully recovered and ambulating normally.

6. **Sedation Protocols**

   1. Detailed information on all approved anesthetics and sedatives can be found in *Anesthesia and Analgesia Drug Descriptions*.

   2. All premedicants and sedatives should be administered 15-20 minutes prior to restraint or induction. Duration of action for sedative-analgesic combinations for use in minor procedures is generally 15-60 minutes depending upon combination used.

   3. The following drug combinations are for use with minor procedures or as premedicants prior to anesthetic induction.

      1. For dose ranges listed as IV, IM, and SC, use lower end of the range for IV administration. All dosages given in mg/kg unless otherwise indicated.
## Anesthetic Protocols

1. For dose ranges listed as IV, IM, and SC, use lower end of the range for IV administration.
2. Anticholinergics: Approximately 1/3 of all domesticated rabbits have a naturally occurring enzyme in their blood (atropinesterase, AtrE), which causes them to metabolize atropine faster. Repeated dosing of atropine every 10-15 minutes may be required if the heart rate falls below 65 beats/minute. Alternatively, glycopyrrolate may be used. Glycopyrrolate has a slightly longer duration of action compared to atropine and is less affected by circulating serum atropinase.
   1. Atropine 0.1-1 mg/kg, SQ or IM.
   2. Glycopyrrolate 0.01-0.1 mg/kg, SQ, IM or IV.
3. Injectable Anesthetic Induction Agents Used in Rabbits
   1. Supplemental oxygen should be provided for all injectable anesthetic protocols. These combinations may not provide a surgical plane of anesthesia and should be used in combination with isoflurane. If, for minor procedures, isoflurane is not utilized, in combinations involving ketamine, anesthesia can be prolonged by supplementing with 1/3 dose of ketamine only. All dosages given in mg/kg unless otherwise indicated.

<table>
<thead>
<tr>
<th>Drug or Combination</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine/Midazolam</td>
<td>10-25/0.2-3</td>
<td>IV, IM, SQ</td>
<td></td>
</tr>
<tr>
<td>Ketamine/Diazepam</td>
<td>10-40/0.2-5</td>
<td>IV, IM</td>
<td>Diazepam is not water soluble. Do not mix drugs in the same syringe. Provides approximately 20-30 minutes of anesthesia.</td>
</tr>
<tr>
<td>Ketamine/Dexmedetomidine</td>
<td>15-35/0.125-0.25</td>
<td>IM, SQ</td>
<td>Provides approximately 30-45 minutes of anesthesia.</td>
</tr>
<tr>
<td>Propofol</td>
<td>3-10</td>
<td>IV</td>
<td>For anesthesia induction only. Utilize slow bolus dosing to effect.</td>
</tr>
<tr>
<td>Ketamine/Xylazine</td>
<td>10-50/3-5</td>
<td>IM</td>
<td>Provides approximately 30-45 minutes of anesthesia.</td>
</tr>
<tr>
<td>Ketamine/Xylazine/Butorphanol</td>
<td>10-40/3-5/0.1</td>
<td>IM</td>
<td>Prolongs duration of anesthesia to 50-70 minutes.</td>
</tr>
</tbody>
</table>
4. Anesthetic Maintenance Protocols
   1. Inhalation Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane (induction)</td>
<td>To effect. Typically 3-5%</td>
<td>Calibrated vaporizer and active scavenging use required. Sedation should be used in conjunction with mask or chamber induction to avoid injury and minimize breathholding.</td>
</tr>
<tr>
<td>Isoflurane (maintenance)</td>
<td>To effect. Typically 1-3%</td>
<td>Calibrated vaporizer and active scavenging use required.</td>
</tr>
</tbody>
</table>

8. Neuromuscular Blocking Agents (NMBA)
   1. Extreme care must be taken to ensure that a proper level of anesthesia and analgesia is achieved prior to administering a neuromuscular blocking agent.
   2. Neuromuscular blocking agents require special monitoring procedures which are detailed in Anesthesia and Sedation Monitoring Guidelines.
      1. Concurrent positive pressure ventilation is required. Reversal of NMBAs with neostigmine and glycopyrrolate is possible under specific conditions. Please consult the ULAM veterinarians for instructions on NMBA reversal.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Duration of Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium</td>
<td>0.12</td>
<td>IV</td>
<td>34-46 (38 average) minutes</td>
<td>Onset in 1.5 minutes. Less variability in response than pancuronium.</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1</td>
<td>IV</td>
<td>42-70 (55 average) minutes</td>
<td>Onset in 1.5 minutes.</td>
</tr>
</tbody>
</table>

9. Local Anesthetics
   1. Appropriate for minimally invasive procedures such as skin biopsy, or as a supplement to sedation, anesthesia and analgesia.
      1. Local anesthetics are excellent analgesics for use in minor procedures or as “splash blocks” for post-operative incision pain.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Duration of Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>&lt;4 (&lt;0.4 ml/kg of a 1% solution)</td>
<td>Infiltrate</td>
<td>&lt; 1 hour (quick onset)</td>
<td>May need to dilute to achieve appropriate volume for infiltration.</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>&lt;2 (&lt;0.8 ml/kg of a 0.25% solution)</td>
<td>Infiltrate</td>
<td>4-8 hours (slow onset)</td>
<td>May need to dilute to achieve appropriate volume for infiltration.</td>
</tr>
</tbody>
</table>

10. Analgesics
    1. Signs of pain in rabbits include but are not limited to the following:
       1. Anxiety
       2. Apprehension
       3. Restlessness
       4. Decreased appetite
       5. Dullness
       6. Elevated respiratory rate
       7. Inactivity
       8. Increased aggression
       9. Immobility
      10. Hunched posture
      11. Tooth grinding
      12. Salivation
      13. Scratch/lick painful area
      14. Social isolation
      15. Vocalization
    2. Preferred opioid analgesics are buprenorphine, hydromorphone, or morphine.
       1. Buprenorphine and other narcotic agonists can be completely reversed with naloxone.
3. The preferred non-steroidal anti-inflammatory (NSAID) is carprofen because it is generally well tolerated by the gastrointestinal tract, has good duration of effect, and does not appear to adversely affect platelet function.

4. Opioids and NSAIDs can be combined for their additive or synergistic analgesic effects.

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Route</th>
<th>Duration of Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.01-0.05</td>
<td>SQ, IM, IV</td>
<td>Q6-12h</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>2-5</td>
<td>SQ, IM</td>
<td>Q2-4h</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.05-0.2</td>
<td>SQ, IM</td>
<td>Q6-8h</td>
<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.4-2</td>
<td>SQ, IM</td>
<td>Q2-4h</td>
<td></td>
</tr>
<tr>
<td>Fentanyl (transdermal patch)</td>
<td>25 mcg/hr</td>
<td>Transdermal</td>
<td>Q72 hours (from time of placement)</td>
<td>Hair should be clipped in the area of placement. Do not shave or use depilatory cream as it changes the pharmacokinetics of the drug. Analgesia onset is 12 hours. The patch should be placed 12 hours prior to the procedure or, if placed during the procedure, another opioid analgesic should be employed until efficacy.</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.05-0.2</td>
<td>SQ, IM</td>
<td>Q6-8h</td>
<td></td>
</tr>
<tr>
<td>Carprofen</td>
<td>2-4</td>
<td>SQ, IM, PO</td>
<td>Q24h</td>
<td>Use high end of dose range for PO administration</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.2-1</td>
<td>SQ, PO</td>
<td>Q24h</td>
<td>Use high end of dose range for PO administration</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>3</td>
<td>SQ, IM, PO</td>
<td>Q24h</td>
<td></td>
</tr>
<tr>
<td>Flunixin meglumine</td>
<td>0.3-2</td>
<td>SQ, IM, IV, PO</td>
<td>Q12-24h</td>
<td>Do not use for more than 3 days.</td>
</tr>
</tbody>
</table>

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.

5. Related Documents
   1. Anesthesia and Analgesia Drug Descriptions
   2. Anesthesia and Sedation Monitoring Guidelines
   4. Guidelines on Administration of Substances to Laboratory Animals
   5. Guidelines on Experimental Food or Water Restriction or Manipulation in Laboratory Animals
   6. EHS Anesthetic Gases in Animal Research

6. References