Guidelines on Administration of Substances to Laboratory Animals

Last Updated 28 June 2013

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1. Purpose
   This document is designed to provide general guidelines about administration of substances to laboratory animals. All procedures must be approved by the University Committee on the Use and Care of Animals (UCUCA). The route of administration, intervals between substance administration, dose range, and volume to be administered should be listed in the approved protocol specific to each study. 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.

2. Responsibility
   - Investigative Personnel
   - Veterinary Personnel

3. Definitions
   a. Parenteral: Administration of substances outside of the gastrointestinal tract. Routes of parenteral administration are listed below.
      - Intravenous (IV): Administration of substances into venous circulation.
      - Intraperitoneal (IP): Administration of substances into the abdominal cavity.
      - Topical (epicutaneous): The application of substances directly to the skin for topical effect.
      - Transdermal (percutaneous): The application of substances directly to the skin for systemic effect.
      - Subcutaneous (SC): Administration of substances into the subcutaneous space.
      - Intradermal (ID): Administration of substances into the dermis.
      - Intramuscular (IM): Administration of substances into the muscle
      - Intranasal (IN): Administration of substances into the nose.
      - Intratracheal (IT): Administration of substances within the trachea.
      - Intracranial: Administration of substances into the brain.
      - Epidural (ED): Administration of substances into the epidural space.
      - Intrathecal (IT): Administration of substances into the subarachnoid space (in the spinal canal but not within the spinal cord).
   b. Enteral: Administration of substances into the gastrointestinal tract. Routes of enteral administration are listed below.
      - Per os (PO): Administration of substances by mouth.
      - Gavage: Administration of substances via a tube that is passed through the nose or mouth into the esophagus or stomach.
      - Rectal: Administration of substances into the rectum.

4. Procedures
   a. Administration of substances
      - When administering substances to laboratory animals care should be taken to select an appropriate route of administration, method of restraint, dosing interval, and dose volume.
      - All personnel should be trained to safely perform the selected route of administration. Contact the ULAM training core or veterinary staff for assistance.
   b. Parenteral Administration
      - Substances administered parenterally should be:
        1. Isotonic (the same concentration of solute as the blood)
        2. Close to physiologic pH (6.8-7.2)
           - If pH is outside of physiologic range, administer the substance through a central vessel (such as the jugular or femoral vein) or buffer the solution such that pH is appropriate.
      - All substances given parenterally must be sterile and should be delivered aseptically.
      - If the preparation is not a commercially manufactured solution, it must be mixed in a laminar flow hood or biosafety cabinet and filtered through a 0.2 micron filter.
c. Routes of Parenteral Administration

i. Intravenous

1. Substances can be administered as a bolus or as an infusion (given over > 5 minutes).
   a. The maximum bolus injection volume is 1 ml/kg. If larger quantities are administered, give as an infusion.
   b. Infusions are often administered with specific equipment (precision pumps or microdrip infusion sets).

2. Site selection for venous access is species-specific. Common sites are listed below:
   a. Rodents: Lateral tail vein, saphenous vein, or retro-orbital venous sinus
   b. Rabbits: Lateral ear, jugular, or cephalic vein
   c. Larger species: Jugular, cephalic, femoral, or saphenous vein

3. Consult with veterinary staff for recommendations on refinements to improve animal comfort during repeated IV dosing.

ii. Intrapерitoneal

1. Injections are administered into lower abdominal quadrants. Aspirate before injecting to avoid inadvertent administration into the bladder or gastrointestinal tract.

2. Repeated daily intraperitoneal dosing for up to one month is well-tolerated in rodents. Doses should be administered to alternating sides of the abdomen.

3. Administration of irritating substances may cause ileus (stasis of the gastrointestinal tract) and peritonitis (inflammation of the abdominal cavity).

iii. Administration to the skin or muscle (see Figure 1)

1. Topical (epicutaneous)
   a. Avoid application of caustic or irritating substances.
   b. Apply substances to skin that is unbroken and free of hair.
   c. Avoid application of substances to sites available for grooming by the animal.

2. Transdermal (percutaneous)
   a. Transdermal dosing is typically accomplished by application of a patch impregnated with the substance of interest.
   b. Apply the patch so as to avoid inadvertent ingestion or removal by the animal.
   c. Systemic absorption is not immediate. Patches should be applied prior to the time of anticipated need according to manufacturer’s instructions.
   d. Do not cut patches to reduce dose size. If an appropriate dose of patch is not commercially available, consider an alternative route of administration.

3. Intradermal
   b. Tent the skin. Holding the syringe parallel to the animal, direct the needle into the dermis. Aspirate and inject.
   c. Inadvertent subcutaneous administration is common. Consult ULAM veterinary or training core staff for assistance.

4. Subcutaneous
   a. Tent the skin. Holding the syringe parallel to the animal, direct the needle into the subcutis. Aspirate and inject.
   b. The rate of absorption from the subcutis may be slower than with other parenteral routes.
   c. Subcutaneous infusions can be administered with the use of an oily depot or osmotic minipump. Consult veterinary staff for additional information.

5. Intramuscular
   a. IM dosing is best used in larger species with greater muscle mass.
   b. In smaller animals, use the gluteal or quadriceps muscles.
   c. In larger animals, use the gluteal, quadriceps, biceps or epaxial muscles.
   d. Take care to avoid the sciatic nerve which runs along the caudal aspect of the femur. Inadvertent injection into nerves can result in paralysis and localized muscle necrosis.

6. Intracranial
   a. Intracranial injections require anesthesia and stereotactic equipment. Injections can be administered through a surgically implanted cerebral cannula, direct injection, or an osmotic pump catheter.
   b. Animals must be heavily sedated or anesthetized for cannula or catheter placement and for direct injections.

7. Epidural or intrathecal (see Figure 2)
   a. Epidural or intrathecal administration of substances requires highly trained personnel. Consult with veterinary staff before attempting this technique.
   b. Animals must be heavily sedated or anesthetized.

8. Inhalational administration
   a. Intranasal: Use the smallest possible volume to avoid suffocation. Systemic absorption is rapid.
   b. Intratracheal: This technique requires intubation or surgical access to the trachea. Consult veterinary staff before attempting this technique.

D. Enteral Administration

i. Voluntary consumption

1. Substances are typically mixed with the daily diet, flavored water, or other palatable items to encourage consumption. Care should be taken to maintain an appropriate daily caloric intake and to habituate animals to any novel food items before adding drug.

2. Care should be taken to ensure animals consume all agent offered. Laboratory personnel are responsible for
ensuring that food and water intake is adequate.

3. Food or water containing additives should be clearly labeled and disposed of properly.

ii. Gavage

1. Gavage is often used to administer an exact PO dose.
2. Administration of gavage volumes greater than 5 ml/kg may cause distress in species that are unable to vomit such as mice.
3. The gavage tube size should be appropriate for the species being dosed. Contact veterinary staff for assistance.

iii. Rectal

1. This technique is not frequently used in laboratory animals. Substances can be administered via an enema or a suppository.

e. Recommended Dose Volumes

i. If a range is provided, the first dose is ideal. If a single value is listed, it is the maximum allowable dose.
ii. Investigators wishing to dose greater volumes than specified must consult the veterinary staff and provide justification in the UCUCA protocol.
iii. If the route or species you are considering is NOT on this list or if you have questions about your dosing material, please consult with veterinary staff.

<table>
<thead>
<tr>
<th>Species</th>
<th>PO (ml/kg)</th>
<th>IV (bolus) (ml/kg)</th>
<th>IV (ml/kg/hr)</th>
<th>IP (ml/kg)</th>
<th>SC (ml/kg)</th>
<th>ID (ml/inj)</th>
<th>IM (ml/kg/site)</th>
<th>IN (ml/inj)</th>
<th>Intrathecal (ul/inj)</th>
<th>ED** (ml/kg)</th>
<th>Intracranial (ul/inj)</th>
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<td>0.05-0.1</td>
<td>0.05</td>
<td>0.03-0.05</td>
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<td>0.15-0.2</td>
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<td>–</td>
<td>0.15-0.2</td>
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</tbody>
</table>

*Maximum single IM dose per site is 5.0 ml for animals > 10.0 kg. If the volume exceeds 5 ml, give over multiple sites.

**For epidural, no more than 6 ml total volume for animals up to 35 kg.

- Figure 1: Administration of substances into the skin or muscle (Turner et al., 2011)

- Figure 2: A comparison of epidural and intrathecal injections (Turner et al., 2011)
5. Related Documents
   a. Guidelines on the Preparation, Storage and Expiration of Injectable Medications
   b. Adjuvant Guidelines

6. References