

research a-z

Guidelines on Anesthesia and Analgesia in Swine

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This set of guidelines was prepared by the ULAM veterinary staff to provide general recommendations for <u>anesthesia</u> and <u>analgesia</u> in laboratory pigs. This is not intended to be an all-inclusive tutorial, and does not factor in specific research-related concerns.

The primary reference for these guidelines is Swindle MM. Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques, 3rd edition. CRC Press; 2015.

PROCEDURES

1. Specific Concerns in Swine Anesthesia

- a. Pigs have a marked variation in body size; however, most research animals are less than 50 kg. Therefore, most of the following guidelines apply to smaller (miniature or juvenile) pigs. Body conformation and anatomy make manual restraint difficult, necessitating use of mechanical restraint (e.g. slings, "pig board") and/or chemical agents.
 - i. **Vascular Access:** Pigs have very few superficial veins making the intramuscular route (IM) the most common route of drug administration. When venous access is necessary, the auricular, lateral saphenous, or cephalic veins are the most common locations for catheterization or IV injections. The central ear vein is the most consistently used site. This vein can accept a 22 gauge or larger catheter depending on the size of the animal. If repeated vascular access is required, implantation of a vascular access port (VAP) is recommended. Swindle, et al. provides an excellent resource for VAP.
 - ii. Endotracheal Intubation: Swine are one of the more difficult species to intubate and improper technique can result in significant trauma. Trauma can result in laryngeal rupture or passage of the ET tube in the subcutaneous space. To facilitate proper intubation, the animal should be at a deeper anesthetic level and premedication/induction agent with sedatives, anxiolytics, dissociatives, or one of their combinations, is highly recommended. For a complete description of proper intubation technique, the reader is referred to the discussion by Swindle, 2015 (pg. 41-48).

- iii. Cautions: Swine are also very susceptible to vasospasm and ventricular arrhythmias. They have very fragile pulmonary tissue, which is likely to be damaged by hyperinflation; maintain ventilator pressure between 18-22 cm H2O.
- iv. Malignant Hyperthermia: Perhaps their most significant idiosyncrasy is the susceptibility of some breeds of swine to malignant hyperthermia with certain anesthetic protocols. Malignant hyperthermia (MH) affects mainly Landrace, Pietrain, and Poland China breeds and is described as a "fulminant and hypermetabolic state of skeletal muscle" induced by volatile inhalational anesthetics, succinylcholine, and stress and exercise (Kaplan, 1991). Early signs of MH include decreases in pH and pO2, and increases in lactate, PCO2, potassium, and temperature. The onset of MH is usually during induction.
 - MH is best prevented by avoiding those breeds of pigs known to be susceptible. Perioperative stress and exercise should be avoided by use of appropriate preanesthetic regimes (ketamine, opiates, benzodiazepines have been used successfully). Agents that have been associated with MH include succinylcholine, halothane, isoflurane, enflurane, and desflurane (halothane seems to be most potent (Kaplan, 1991)). Dantrolene can be used both in the treatment and prevention of MH. A chart for managing MH is attached as an appendix.
 - There is another postoperative condition in swine that resembles MH but is considered a distinct condition. It is characterized by critically-elevated body temperature and hyperlactatemia (>2.5 mmol/L) during the recovery period (Swindle, 2015). It can be treated with cooling interventions (ice, cold IV solution, fan).
- v. Pre-anesthetic Fasting:
 - i. Healthy swine should receive no food for 6-12 hours prior to sedation or anesthesia in order to reduce the risk of regurgitation or aspiration.
 - ii. Overnight fasting is recommended for procedures scheduled earlier in the day.
 - iii. Remove any bedding or enrichment items that may be ingested.
 - iv. Pigs should be allowed free access to water until sedatives or pre-anesthetic medications are administered.
 - v. Special care is required for neonnatal piglets. Consult a ULAM faculty veterinarian prior to fasting these animals.
- b. Apply sterile non-medicated ophthalmic ointment to the eyes to prevent corneal drying during anesthesia or sedation.

2. Monitoring & Recovery

- a. Standard mammalian monitoring techniques are applicable to swine the goal of monitoring should be to maintain cardiovascular homeostasis and core body temperature. Understanding the basic physiologic effects of the anesthetics used is paramount to correctly interpreting monitoring parameters. For uncomplicated, brief surgeries, monitoring vital signs (e.g. temperature, HR, RR), and pulse oximetry may be adequate. For more invasive procedures, blood pressure monitoring and blood gas analysis may be indicated. Monitoring body temperature is critical especially in those breeds prone to MH.
- b. **Jaw tone** most reliably reflects depth of anesthesia and should be assessed throughout the procedure. If the jaw is inaccessible, use ocular and other muscular reflexes.
- c. Anesthetic Adjuncts:

- i. Premedication and induction with anesthetic adjuncts, such as the sedatives, helps facilitate animal handling for intubation and surgical preparation.
- ii. Acepromazine (0.11 1.1 mg/kg IM, IV, SC) is commonly used alone for sedation or as an anesthetic premed. High doses can cause alpha- adrenergic blockade (resulting in low blood pressure, peripheral vasodilation, etc.), which may be a contraindication for their use in cardiovascular studies.
- iii. Diazepam (0.5-10 mg/kg SQ; 0.44-2 mg/kg IV SLOWLY) or midazolam (0.1-0.5 mg/kg IM, SQ or IV) have successfully been used as pre-anesthetic tranquilizers. Diazepam infusion at 1 mg/kg/hr can cause profound hypothermia with prolonged use (>6 hr). Midazolam is preferred over diazepam for IM use because it has more consistent absorption from muscle. Benzodiazepines can increase the recovery period, especially if used intraoperatively. Flumazenil (0.02 mg/kg IV), a selective benzodiazepine antagonist, can be used as a reversal agent for midazolam or diazepam.
- iv. The anticholinergic glycopyrrolate (0.004-0.01 mg/kg IM) may be used to dry oral and respiratory secretions and for its vagolytic (ability to block vagal nerve stimulation and consequent bradycardia) effects during endotracheal intubation. This may be used intraoperatively if mean arterial pressure (MAP) decreases below 60 mmHg and fluid boluses are insufficient to correct hypotension. Sinus tachycardia can result from indiscriminate use of these agents.

3. Preferred General Anesthetics

- a. **Inhalant** anesthetics are the preferred agents used in research settings. Anesthesia may be induced with many of the injectable anesthetic agents, after which the pigs are intubated endotracheally and maintained on gas anesthetics safely for prolonged periods.
 - i. **Isoflurane** has a low blood gas solubility resulting in more rapid anesthetic recoveries and the ability to rapidly alter depth of anesthesia. Although isoflurane also produces a dose-dependent depression of the cardiovascular system, it has the greatest margin of safety of all the inhalation anesthetics currently in use and is considered to be the inhalation agent of choice in swine.
 - ii. Sevoflurane has similar physiologic effects and may be used instead of isoflurane.
- b. Injectable anesthetic agents are encouraged as an adjunct to inhalant anesthetics for some experimental procedures. Dissociative anesthetic agents like ketamine are the most commonly used anesthetic agents in swine. Ketamine produces rapid and safe immobilization with minimal cardiovascular depression. Ketamine does not provide good visceral analgesia and provides very little muscle relaxation; therefore, it is usually used in combination with another agent like xylazine. Doses of ketamine alone and combined with other agents are listed in the table that follows.
 - i. ULAM recommends the combination of **Telazol**® (tiletamine/zolazepam, 4.4 mg/kg) and **xylazine** (2.2 mg/kg). This is an excellent combination for induction IM, it provides rapid sedation for intubation and catheter placement.
 - 1. Large dose volumes may need to be split into multiple doses. See <u>Guidelines on Administration of Substances</u> <u>to Laboratory Animals (/animalcare/guidelines/guidelines-administration-substances-laboratory-animals)</u>.
 - 2. Ketamine volume may be reduced by half using Zoopharm's 200 mg/mL formulation.
 - ii. Atipamezole is recommended as a reversal agent for xylazine. However, we do not recommend reversing this agent to facilitate recovery after painful procedures as it continues to provide some level of analgesia

postoperatively. Reversal should be reserved for emergencies or for nonsurgical procedures (e.g. chemical restraint for noninvasive procedures).

4. Other General Anesthetics

a. Inhalant

- i. Nitrous Oxide may reduce the concentration of isoflurane required by 50% and may be useful for some cardiovascular studies. It cannot be used as a sole anesthetic agent and must be delivered in a 1:1 or 2:1 mixture of nitrous oxide to oxygen combined with other inhalant anesthetics. Additionally, nitrous oxide is not absorbed by charcoal canisters and can only be used with vacuum scavenging anesthetic systems.
- b. Injectable
 - i. Opioids may be used as continuous IV infusions with other anesthetics because they enhance analgesia, produce minimal cardiovascular depression, and protect against cardiac arrhythmias. **Fentanyl**, **sufentanil**, and combinations of fentanyl are the most common opiates used with pigs. Fentanyl causes dose-dependent NMDA-receptor activation, so combination with ketamine or dextromethorphan is recommended.
 - ii. A variation of the telazol/xylazine combination is TKX: telazol, ketamine, and xylazine. The advantage to this preparation is that it increases the dissociative component of anesthesia, which reduces posterior weakness that may be seen with TK.
 - Preparation: reconstitute an unused vial of Telazol with 2.5 mL ketamine (100 mg/mL) and 2.5 mL xylazine (100 mg/mL). This results in 100 mg/mL dissociative (tiletamine and ketamine), and 50 mg/mL each of xylazine and zolazepam. The benzodiazepine component is reduced to 25% of the total drug dose compared to the TX mixture.
 - iii. GKX (Guaifenesin-Ketamine-Xylazine; "Triple Drip"): the major advantage to this drug combination is that recovery is very rapid (30 to 45 min). The disadvantage is that, as an induction agent, it must be given I.V. It is prepared by adding 2 mg ketamine and 1 mg xylazine to each milliliter of 5% guaifenesin prepared in 5% dextrose in water.

5. Swine Anesthetics & Combinations (Smith, 2008; Swindle, 2015; Plumb, 2015)

Anesthetic	Route	Dose	CRI Dosing	Notes
Fentanyl	IV	50 ug/kg	30-100 ug/kg/hr	 Minimal cardiodepression Protect from arrhythmias NMDA receptor activation Nalaxone reversal @ 0.5-2 mg/kg IV
GKX (Guaifenesin+ Ketamine+Xylazine; "Triple Drip")	IV	0.67 to 1.0 mL/kg (induction)	2.2 mL/kg/hr	 Rapid recovery from anesthesia

Isoflurane	Inhaled	2-4% induction 1.2-2% maintenance	N/A	 Anesthetic gas of choice
Ketamine	IM	11-33 mg/kg	3-33 mg/kg/hr	Poor muscle relaxationPoor visceral analgesia
Ketamine / Acepromazine	IM	33/1.1 mg/kg	N/A	 Slightly cardiodepressant Muscle relaxation for ~30'
Ketamine / Xylazine (Rompun®)	IM	20/2 mg/kg	N/A	 Good intubation mix Short term analgesia (~5 min) but prolonged cardiodepression and heart block
Pentobarbital	IV	20-40 mg/kg	5-40 mg/kg/hr	 Cardiodepressant Prolonged recovery Good for non-recovery surgery
Propofol	IV	0.83-1.66 mg/kg	14-20 mg/kg/hr	 Can cause severe apnea if administered too rapidly. Use to effect for as an induction agent
Tiletamine / Zolazepam (Telazol®)	IM	2-8.8 mg/kg	N/A	 Acceptable for minor surgery Hypothermia Cardiodepression Lasts 20-30 mins
TKX (Telazol®+ Ketamine+ Xylazine)	IM	4.4 mg/kg T+ 2.2 mg/kg K+ 2.2 mg/kg X	N/A	 Less posterior weakness than telazol/zylazine
TX (Telazol®+ Xylazine; RECOMMENDED)	IM	2-8 mg/kg T+ 1-3 mg/kg X	N/A	 Recommended by ULAM for premedication/induction.

6. Local Anesthetics

a. If used as the only form of <u>anesthesia</u>, regional anesthetics should be combined with sedatives and manual restraint in a sling. The most commonly used regional anesthetic is **lidocaine**. The onset of action is rapid and duration of action of lidocaine is 90-180 minutes. Longer acting <u>local anesthetics</u>, like **bupivacaine**, can provide 180-300 minutes of analgesia,

but onset is slow. Local anesthetics are only appropriate for minimally invasive procedures with the exception of epidural analgesia. Epidural anesthesia can be helpful for abdominal surgeries - for a more complete description, the reader is referred to the discussion by R.T. Skarda, 1987 and Swindle, 2015.

- b. Wound infusion catheters, aka "soaker catheters," can be used to deliver continuous infusions of local anesthetics to the surgical site. Contact your ULAM veterinarian for more information.
- c. Lidocaine and bupivacaine can be mixed 1:1 prior to administration to maximize their kinetics. Total dosages should not exceed 8 mg/kg for lidocaine and 2 mg/kg for bupivacaine.

7. Analgesics

- a. Signs of Pain: Signs of pain in swine may include, but are not limited to, the following:
 - i. Abnormal gait
 - ii. Abnormal posture
 - iii. Reluctance to move
 - iv. Social isolation
 - v. Abnormal vocalizations
 - vi. Abnormal aggression
 - vii. Decreased appetite
 - viii. "Tucked up" abdomen
 - ix. Elevated respiratory rate
 - x. *Contact a ULAM veterinarian to develop a pain scale for your specific studies.
- b. Prevention and Management of Pain: Most analgesics used in swine have a relatively short half-life. Buprenorphine is considered the analgesic of choice because it is effective for 8-12 hours at higher dosages.
 - i. It is good practice to administer analgesics prior to surgery (preemptive analgesia **D**) to diminish the afferent nerve impulses involved in the nociceptive process. For procedures and surgeries that are likely to cause only minor pain and discomfort, this may be the only analgesic dose necessary.
 - ii. Consideration of continuous intravenous infusion (Continuous Rate Infusion or CRI) or alternative delivery systems is appropriate for procedures likely to cause significant post-operative pain.
 - iii. Lidocaine and bupivacaine are encouraged because they provide local anesthesia and <u>analgesia</u> that decrease post-operative pain association with incision sites.
 - iv. Preemptive analgesia, particularly <u>opiates</u> like buprenorphine, can reduce the dose of anesthetics required for surgical anesthesia and increase the respiratory depression associated with anesthetics. When preemptive 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 and analgesic combinations, assess a subset of animals before expanding to use in a larger cohort.

8. Analgesics in Swine

Analgesic	Route	Dose	Notes
Buprenorphine (RECOMMENDED)	IM, SC	0.01-0.05 mg/kg q 8-12 hrs	 Can cause significant respiratory depression.
Buprenorphine patch (Buprenex®)	Trans-dermal patch	30 mcg/hour for up to 72 hours in pigs weighing 20-30 kg. Absorption is variable (Lujan et al. 2017; Thiede et al. 2014)	 Absorption can vary greatly, so animals must be monitored closely for signs of pain.
Butorphanol	IM	0.1-0.3 mg/kg q 4-6 hrs	 Safe, but short duration
Cerenia® (maropitant)	SC	1 mg/kg q 24 hr for up to 5 days	 Counteracts appetite suppression from buprenorphine SR. Evidence for visceral analgesia. Dosage based on dog formulary and other institutions.
Fentanyl	CRI Trans-dermal patch	30-50 μg/kg/hr 5 μg/kg/hr (highly variable)	 Causes dose-dependent NMDA receptor stimulation. It is difficult to titrate dose with the transdermal patch.
Morphine epidural	epidural	0.1 mg/kg	 Use preservative-free for epidural use
Oxymorphone	IM / SC	0.15 mg/kg q 8-12 hrs	
Sufentanil	CRI	5-10 μg/kg q 2 hrs	 15-30 μg/kg/hr IV CRI

For musculoskeletal pain, non-steroidal anti-inflammatory drugs (<u>NSAIDs</u>) like phenylbutazone, aspirin, ketoralac, and ketoprophen have all been used in swine. Enteric-coated products are recommended because of this species' susceptibility to gastric ulcers. Oral medications are readily accepted if placed in canned dog food or chocolate syrup. Carprofen (Rimadyl®) comes in a convenient chewable tablet form.

NSAID	Route	Dose
Aspirin	РО	10-20 mg/kg q 6 hrs
Ketoprofen	PO / IM / SC	1-3 mg/kg q 12 hrs

Ketoralac	PO / IM / SC	1 mg/kg q 12 hrs
Phenylbutazone	PO	5-20 mg/kg q 12 hrs
Carprofen (RECOMMENDED)	PO / SC	2-3 mg/kg q 12 hrs 2 mg/kg q 24 hrs
Flunixin Meglumine	IV	1-4 mg/kg q 24 hours

ADDITIONAL RESOURCES

- 1. Sinclair Research (http://www.sinclairresearch.com/) (external link)
- 2. Zoopharm: Compounds drug formulations for special circumstances (http://wildpharm.com/medications/labanimals.html) (external link)

APPENDIX A: EMERGENCY RESUSCITATION BASICS

- 1. For a thorough discussion of cardiopulmonary resuscitation procedures, the reader is referred to other sources. A brief reminder of the "ABCs" of CPR follows:
 - a. A Airway: If the pig is not already intubated, a cuffed endotracheal tube should be placed.
 - b. **B Breathing:** Ventilation with pure oxygen should be initiated (anesthetic should be off). Usually hyperventilation is indicated to "blow off" carbon dioxide, which will help correct acidosis and decrease cerebral pressure.
 - c. C Cardiovascular Support: Strong rapid chest compressions should begin immediately after establishing ventilation. It is not necessary to coordinate cardiac massage with respiration, but keep in mind that swine have relatively fragile pulmonary tissue (high ventilation pressures should be avoided). Abdominal counter pressure may be helpful. For pigs over 10 kg, thoracotomy and open-chest massage is often necessary. Volume expansion with rapid infusion of crystalloid fluids is also necessary to establish adequate perfusion.
 - d. D Drugs: Drugs used and dosages are similar to those used in other species. An emergency drug dosage table is included below for quick reference.
 - e. E EKG/Monitoring: Heart rate and rhythm, blood gases, electrolytes, lactate, blood pressure, and urinary output are useful monitoring parameters for preventing/treating consequences of cardiopulmonary arrest.

APPENDIX B: EMERGENCY DRUGS

Swine Emergency Drug Dose Volumes in Milliliters

Drug	Dosage	Route	Notes
Amiodarone ^a	10 - 12 mg/kg followed by 0.5 - 3.5 mg/kg/h i.v.	IV	 Antiarrhythmic
Atipamezole	0.24 - 1 mg/kg	IM, IV, SC	 Reverse alpha-2 agonists
Atropine	0.02 - 0.05 mg/kg	IM, IV, SC	Counteract bradycardiaHeart block
Dexamethasone	0.1 mg/kg	IM, IV	 Anti-inflammation (laryngeal edema) Shock
Diazepam	0.5 – 1 mg/kg	IV	 Muscular tremors Sedation Anticonvulsant
Dopamine	2.0-20.0 μg/kg/min CRI	IV	Counteract hypotensionCardiogenic shock
Dobutamine	2.5-10.0 μg/kg/min CRI	IV	Counteract hypotensionCardiogenic shock
Doxapram	0.5 mg/kg	IV	 Stimulates breathing
Epinephrine	0.5 - 2.0 mL of 1:10,000 solution	IV	Counteract asystoleDecreased contractility
Furosemide	250 mg per animal	IM, IV	 Treat pulmonary edema due to fluid overload
Glycopyrrolate	0.004 - 0.01 mg/kg	IM, IV, SQ	 Counteract bradycardia Heart block Recommended over atropine
Lidocaine ^b	2 - 4 mg/kg	IV	AntiarrythmicAntiectopic
Naloxone	0.5 - 2 mg/kg	IV	 Reversal for opiates

Phenylephrine	1 - 3 mcg/kg/min CRI	IV	 Treat hypotension
Yohimbine	1 mg/kg	IV	Reversal agent for xylazineNot as reliable as atipamezole

^a Give I.V. bolus slow, as rapid administration can cause hypotension. Follow with 0.5-3.5 mg/kg/hr I.V. CRI.

^b Follow with 50ug/kg/min CRI.

APPENDIX C: MALIGNANT HYPERTHERMIA CRISIS MANAGEMENT

- 1. Once the animal is stabilized, call a veterinarian:
 - a. Normal business hours (M-F, 08:00-17:00): 734-764-0277
 - b. After hours and holidays: 734-763-1131

2. Step by Step Procedures

- a. Stop use of all triggering agents continue with "safe agents" if surgery cannot be stopped.
- b. Hyperventilate with 100% oxygen. Use new anesthetic circuit and soda lime.
- c. Administer 2.5 mg/kg dantrolene IV immediately. Continue doing up to 10-20 mg/kg until all signs normalize. Maintain IV dantrolene at 1 mg/kg/hr.
- d. Correct metabolic acidosis. Give 1-2 mEq/kg of HCO3 STAT and continue treatment based on arterial blood gas analysis.
- e. Treat hyperkalemia with HCO3 or 0.5 g/kg glucose with 0.15 U/kg regular insulin.
- f. Treat hyperthermia. Administer cooled fluids, body cavity lavage, cooling blanket, extracorporeal circulation.
- g. If arrhythmias are persistent, administer 3 mg/kg procainamide and repeat up to a total of 15 mg/kg.
- h. Monitor blood gases, venous and arterial pressures, urine output, end-tidal CO2, electrolytes, lactate, CK, urine myoglobin, PT, PTT, and platelets.
- i. Maintain urine output of greater than 1 ml/kg/hr with parenteral fluids, mannitol, and furosemide.
- j. Transfer to ICU when stable. While in ICU monitor for 24-48 hours for recrudescence and late complications.
- k. Convert to oral dantrolene when extubated and stable. Dose is 1 mg/kg PO q 6 hr for 24-48 hours.

APPENDIX D: NON-MH HYPERTHERMIA MANAGEMENT

1. Once the animal is stabilized, call a veterinarian at 734-936-1696.

2. Step by Step Procedures

- a. Discontinue gas anesthetic and provide the animal with 100% oxygen.
- b. Cool the animal by administering cold I.V. fluids and/or submerging the animal in an ice bath.
- c. Administer methylprednisolone 1-5 mg/kg I.V. for shock.

d. Administer diazepam 0.5-1 mg/kg I.V. for muscular tremors.

3. Request unrelated swine from the same or different breeder to prevent this from recurring

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Species: <u>Swine</u> Topic: <u>Anesthesia and Analgesia</u>

QUESTIONS?

If you have questions or comments about this document, contact ULAM Veterinary Staff (<u>ULAM-vets@umich.edu (mailto:ULAM-vets@umich.edu)</u> or **734-936-1696**).

The **ULAM Training Core** (<u>ULAM-trainingcore@umich.edu (mailto:ULAM-trainingcore@umich.edu)</u> or **734-763-8039**) can be contacted to provide training in techniques at no charge.

For any concerns regarding animal health after work hours or on holidays/weekends, contact **DPS** (3-1131) who will contact the oncall veterinarian.

Related Documents

Anesthesia and Sedation Monitoring Guidelines (/animalcare/guidelines/anesthesia-and-sedation-monitoring-guidelines)

<u>Guidelines on Administration of Substances to Laboratory Animals (/animalcare/guidelines/guidelines-administration-substances-laboratory-animals)</u>

EHS Anesthetic Gases in Animal Research (/animalcare/informational/ehs-anesthetic-gases-animal-research)

Anesthesia and Analgesia in Swine (Chapter 15 of Anesthesia and Analgesia in Laboratory Animals). (/animalcare/informational/anesthesia-and-analgesia-swine-chapter-15-anesthesia-and-analgesia)