

# **Anesthesia and Analgesia in USDA Regulated Laboratory Animals at UR**

## **OVERVIEW**

Animal anesthesia, analgesia and pain management are crucial components of the animal use protocol. The standard of care at UR is to prevent animal pain whenever possible and to treat pain aggressively whenever diagnosed. US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training, and thus PHS Policy, require that “unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.” Exceptions to these principles are permitted only in the minority of protocols approved by UCAR as USDA Category E and require robust scientific justification.

Multi-modal anesthetic and analgesic regimens are the standard of care in veterinary medicine. This document contains veterinary recommendations for best practices based on the current standard of care. This approach combines drugs from a variety of classes to maximize the desired effects while minimizing potential undesirable side effects that occur with over-reliance on a single agent. Special considerations are required in some species, ages, or types of procedures. These considerations may include administration of additional drugs, fluid therapy, or handling of the animal. The Animal Welfare Act requires that a veterinarian be consulted in the planning stages of all proposed surgical procedures. Veterinary staff continuously review outcomes of surgical and anesthetic procedures as well as the literature for refinements, and update these recommendations periodically to reflect the evolving standard of care.

### **The Ideal Anesthetic/Analgesic Regimen**

The ideal anesthetic/analgesic regimen must balance several goals:

1. It should provide pre-emptive analgesia so that animal pain is already being treated as the general anesthetic is wearing off to prevent sensitization of pain sensory mechanisms, and to lower the overall amount of general anesthetic required for the procedure
2. It should be precisely titratable to assure that animals receive adequate anesthesia to block pain sensation, to produce unconsciousness, and to produce immobility without causing hemodynamic instability
3. It should not interfere with the research goals of the protocol
4. It should not result in undesirable post-operative side effects
5. It should not cause pain or distress during induction or recovery
6. It should be compatible with available equipment and medications

Pre-emptive analgesia is implemented by administration of analgesics prior to the first incision during surgical procedures. Volatile inhaled anesthetics (such as isoflurane and sevoflurane) delivered via a precision vaporizer allow titration of anesthetic delivery to the needs of the individual animal for the procedure. Adjusting the percentage of anesthetic gas to modify depth of anesthesia is safer than repeated administration of injectable drugs. However, inhalant anesthetics lack residual analgesic effects after the procedure. Use of pre-emptive analgesics significantly reduces the required concentration of anesthetic gases

All staff anesthetizing animals must complete training as prescribed by UCAR and DLAM. Veterinary consultation is available at all times.

### **Drug Dosages and Frequencies of Administration**

The DLAM standard anesthetic procedures are continually updated by veterinarians to reflect the current best practices in veterinary anesthesia and pain management and reviewed at least annually by UCAR.

UCAR requires that pre-emptive analgesia be administered prior to the first incision for all surgical procedures unless otherwise scientifically justified in the protocol. It is not acceptable to conduct surgical procedures unless an animal is in a surgical plane of anesthesia.

Special attention must be paid to analgesic doses and frequencies. UCAR requires that investigators take into account overnight pain management. It is not acceptable to give drugs at greater intervals than those prescribed and known to adequately manage pain.

### **DLAM Anesthetic and Analgesic Formulary for Regulated Species**

While all of the drug combinations listed here are considered safe, appropriate, and within current veterinary standards, the selections shaded in gray represent the DLAM best practice approach to anesthesia and analgesia in these species and should be followed whenever possible.

Note that all of these doses are approximations and must be titrated to the animal's strain, age, sex, and individual responses. Significant departures from these doses should be discussed with a veterinarian. Doses will also vary depending on what other drugs are being administered concurrently.

All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted.

<b>Abbreviations</b>	
SID	Once daily (every 24 hours)
BID	Twice daily (every 12 hours)
TID	Three times daily (every 8 hours)
QID	Four times daily (every 6 hours)
IM	Intramuscular
IV	Intravenous
SQ	Subcutaneous
CRI	Constant rate infusion
PO	Per os (by mouth)

## LOCAL ANESTHETICS

Local anesthetics can be used in all species except cats at similar doses. Nerve blocks should be considered prior to surgery whenever possible. Alternatively, infiltration of the surgical site with a local anesthetic at closing can significantly reduce pain in the post-operative period. Bupivacaine is the local anesthetic of choice due to its relatively long duration of action (6-8hrs compared to 2-4 hours of analgesia from lidocaine). In all species, a maximum of 2mg/kg bupivacaine should be administered. Although these drugs have relatively short half-lives, a variety of studies have shown that reduce post-operative pain long after the drug has been metabolized and eliminated, demonstrating the power of prevention of nociceptor wind-up in controlling pain.

## DOG FORMULARY

DRUG NAME and DOSE	ROUTE AND FREQUENCY	NOTES
<b>Pre-Medication / Sedation</b>		
Ketamine 2mg/kg + Dexmedetomidine 0.01mg/kg	IM	Dexmedetomidine may cause bradycardia that should not be treated with atropine unless patient is hypotensive. This combination results in moderate to profound sedation Dexmedetomidine is an alpha-2 agonist that is reversible with atipamezole IM at an equal volume Can be mixed and given in the same syringe
Dexmedetomidine 0.01- 0.03mg/kg	IM or IV	Useful for quick procedures (~30 minutes) requiring mild to moderate sedation Choose the lower end of the dose range for larger dogs Reversible with atipamezole at an equal volume (IM)
<b>Induction</b>		
Ketamine 5mg/kg + Diazepam 0.2mg/kg	IV	Give half as a bolus and the remaining to effect for intubation
Propofol 4-6mg/kg	IV	Administer to effect via intravenous catheter May cause apnea with rapid administration
<b>Maintenance</b>		
Isoflurane	1-2%	
<b>Analgesics</b>		
Meloxicam 0.2mg/kg	IM or PO SID	A COX-2 specific NSAID with fewer side effects than other NSAIDs

		Generally given for no more than 3-5 days
Buprenorphine 0.01mg/kg	IM BID-TID	Opioid useful as an adjunctive analgesic
Buprenorphine SR 0.03-0.06mg/kg	SQ q3days	Sustained release formulation that provides 3 days of analgesia May be associated with sedation and inappetence Choose the lower end of the dose range for larger dogs
<b>Emergency Drugs</b>		
Dopram 5mg/kg	IV	Indicated to stimulate respirations
Epinephrine 0.01-0.02mg/kg	IV	Indicated for cardiac arrest

## References

1. Papich MG. 2007. Saunders Handbook of Veterinary Drugs. 2<sup>nd</sup> ed. Elsevier: St. Louis, MO.
2. Plumb DC. 2005. Plumb's Veterinary Drug Handbook. 5<sup>th</sup> ed. Blackwell: Ames, IA.

## CAT FORMULARY

DRUG NAME and DOSE	ROUTE AND FREQUENCY	NOTES
<b>Pre-Medication / Sedation</b>		
Ketamine 10mg/kg + Diazepam 0.3mg/kg	IM	Deep sedation with minimal cardiovascular and respiratory effects
<b>Induction</b>		
Ketamine 5mg/kg + Dexmedetomidine 0.04mg/kg	IM	May require isoflurane mask for intubation Dexmedetomidine reversible with same volume of atipamezole (Antisedan) IM Dexmedetomidine may cause significant bradycardia that should not be treated with atropine unless patient is hypotensive
Diazepam 0.5mg/kg + Ketamine 10mg/kg	IV	Useful for calm cats – no pre-medication required for intubation Give half as a bolus and the remaining to effect
<b>Maintenance</b>		
Isoflurane	1-2%	
<b>Analgesics</b>		
Banamine 0.25mg/kg	IM SID	Use extreme caution with NSAIDs in cats due to potential for renal toxicity Can repeat once 12-24hrs later
Meloxicam 0.1mg/kg	PO or SQ SID	Use extreme caution with NSAIDs in cats due to potential for renal toxicity – only a single dose

Buprenorphine 0.01mg/kg	IV or IM or Buccal BID-TID	
Buprenorphine SR 0.12mg/kg	SQ	Sustained release formulation that provides 3 days of analgesia
<b>Emergency Drugs</b>		
Dopram 5mg/kg	IV	Indicated to stimulate respirations
Epinephrine 0.01- 0.02mg/kg	IV	Indicated for cardiac arrest
Lidocaine 2-4mg/kg followed by 0.05mg/kg/min CRI	IV	Indicated for ventricular arrhythmias

## References

1. Papich MG. 2007. Saunders Handbook of Veterinary Drugs. 2<sup>nd</sup> ed. Elsevier: St. Louis, MO.
2. Plumb DC. 2005. Plumb's Veterinary Drug Handbook. 5<sup>th</sup> ed. Blackwell: Ames, IA.

## RABBIT FORMULARY

<b>DRUG NAME and DOSE</b>	<b>ROUTE AND FREQUENCY</b>	<b>NOTES</b>
<b>Sedation</b>		
Acepromazine 0.75mg/kg	IM	Produces a peripheral vasodilation useful for venipuncture
<b>Induction</b>		
Ketamine 10-20mg/kg + Dexmedetomidine 0.1- 0.2mg/kg	SQ	IM administration of ketamine may cause myonecrosis, vasculitis, and axonal degeneration with resultant self-trauma Dermal ulcers may occur even with SQ administration, so 1ml saline can be injected at the same site following administration
Ketamine 44mg/kg + Xylazine 5mg/kg	SQ	
<b>Maintenance</b>		
Isoflurane	1-2% (MAC = 2%)	Laryngeal masks may be utilized in place of endotracheal tubes as rabbits are difficult to intubate
<b>Analgesics</b>		
Meloxicam 0.3-0.5mg/kg	SQ or PO SID	Generally no more than 3-5 days
Flunixin Meglumine 1- 2mg/kg	SQ SID-BID	Generally no more than 3 days
Buprenorphine 0.01- 0.05mg/kg	SQ or IV BID-QID	Clinically insignificant respiratory depression
Buprenorphine SR	SQ q 72hr	Sustained release formulation that eliminates

0.12mg/kg		frequent dosing requirement
<b>Emergency Drugs</b>		
Dopram 5mg/kg	IV	Indicated to stimulate respirations
Epinephrine 0.01-0.02mg/kg	IV	Indicated for cardiac arrest
Atipamezole 0.2mg/kg	IV	Indicated to reverse alpha-agonists

## References

1. Lipman NS, Marini RP, Flecknell PA. 2008. Anesthesia and Analgesia in Rabbits. In: Anesthesia and Analgesia in Laboratory Animals. 2<sup>nd</sup> ed. Academic Press: San Diego, CA.
2. Williams A, Wyatt J. 2007. Comparison of Subcutaneous and Intramuscular Ketamine-Medetomidine With and Without Reversal by Atipamezole in Dutch Belted Rabbit (*Oryctolagus cuniculus*). J Am Assoc Lab Anim Sci 46(6):16-20.
3. Wyatt JD, Scott RA, Richardson ME. 1989. The effects of prolonged ketamine-xylazine intravenous infusion on arterial blood pH, blood gases, mean arterial pressure, heart and respiratory rates, rectal temperature and reflexes in the rabbit. Lab Anim Sci 39(5): 411-416.
4. DiVincenti L, Westcott R, Meirelles L. 2015. Safety and clinical efficacy of sustained release buprenorphine for post-operative analgesia in New Zealand white rabbits. J Am Assoc Vet Med: in press.

## NONHUMAN PRIMATE FORMULARY

DRUG NAME and DOSE	ROUTE AND FREQUENCY	NOTES
<b>Induction</b>		
Ketamine 10mg/kg + Diazepam 0.5mg/kg + Atropine 0.04mg/kg	IM	May require isoflurane via mask for intubation
Ketamine 3mg/kg + Medetomidine 0.15mg/kg	IM	Medetomidine is alpha-2 agonists that are associated with bradycardia that should not be treated with atropine <ul style="list-style-type: none"> <li>• Reversible with atipamezole at 0.22mg/kg IM</li> </ul>
Ketamine 8-10mg/kg + Midazolam 0.25mg/kg	IM	Diazepam may cause pain on intramuscular injection, so midazolam is an alternative benzodiazepine to diazepam
<b>Maintenance</b>		
Isoflurane	1-3% (MAC = 1.3%)	Dose-dependent hypotension due to a reduction systemic vascular resistance especially pronounced when >2%
<b>Analgesics</b>		
Meloxicam 0.2mg/kg followed by 0.1mg/kg	PO or IM SID	A COX-2 specific NSAID with fewer side effects than other less specific NSAIDs and has an oral formulation Generally no more than 3-5 days
Buprenorphine 0.02-0.04 mg/kg	IM or SC BID	An opioid useful as an adjunctive agent to NSAIDs; required for major invasive surgeries
Buprenorphine SR 0.06-0.12mg/kg	SQ q 72hrs	Sustained release formulation of buprenorphine that lasts for 72hrs
Flunixin (Banamine) 1mg/kg	IV or IM SID	NSAID – generally no more than 3-5 days
<b>Emergency Drugs</b>		
Dopram 1-4mg/kg	IV	Indicated to stimulate respirations
Epinephrine 0.1mg/kg	IV	Indicated for asystole
Lidocaine 1-4mg/kg	IV	Indicated for pre-ventricular contractions
Mannitol 0.25-2g/kg	IV	Indicated for brain swelling; give slowly over 30 minutes

### References

1. Association of Primate Veterinarians. Nonhuman Primate Formulary. Available at: [http://www.primatetvets.org/pub\\_downloads.aspx](http://www.primatetvets.org/pub_downloads.aspx). [Accessed 12/1/11].
2. Authier S, Chaurand F, Legaspi M, Breault C, Troncy E. 2006. Comparison of three anesthetic protocols for intraduodenal drug administration using endoscopy in rhesus monkeys (*Macaca mulatta*). J Am Assoc Lab Anim Sci 45(6): 73-79.

3. Plumb DC. 2005. Plumb's Veterinary Drug Handbook. 5<sup>th</sup> ed. Blackwell: Ames, IA.
4. Popilskis SJ, Lee DR, Elmore DB. 2008. Anesthesia and Analgesia in Nonhuman Primates. In: Anesthesia and Analgesia in Laboratory Animals. 2<sup>nd</sup> ed. Academic Press: San Diego, CA.

## SWINE FORMULARY

DRUG NAME and DOSE	ROUTE AND FREQUENCY	NOTES
<b>Pre-Medication / Induction</b>		
Ketamine 33mg/kg + Acepromazine 1.1mg/kg + Atropine 0.05mg/kg	SQ	A butterfly catheter attached to a syringe can be used to avoid stress associated with restraining pigs. Behind the ears is the most easily accessible site for SQ injections in swine. This combination will not be adequate for intubation
Ketamine 10mg/kg + Medetomidine 0.2mg/kg	SQ	Medetomidine reversible with same volume of atipamezole (Antisedan) IM
Propofol 2-4mg/kg	IV	Used to induce general anesthesia for intubation; administer slowly to effect
<b>Maintenance</b>		
Isoflurane	1-2%	
Amiodarone 10mg/kg + 0.5mg/kg/hr	IV	Amiodarone is an anti-arrhythmic drug useful to prevent arrhythmias common in anesthetized swine especially during cardiac manipulation
<b>Analgesics</b>		
Carprofen 3-4mg/kg	PO BID SQ or IM SID	An NSAID
Meloxicam 0.4mg/kg	PO or SQ SID	Can increase bleeding time in swine
Buprenorphine 0.02-0.05 mg/kg	IV, IM or SC BID-TID	Useful for breakthrough pain
Buprenorphine SR 0.18mg/kg	SQ q72hrs	Sustained release formulation eliminates need for frequent dosing
<b>Emergency Drugs</b>		
Dopram 5-10mg/kg	IV	Indicated to stimulate respirations
Epinephrine 0.02mg/kg	IV	Indicated for asystole
Lidocaine 2-4mg/kg , then 0.3mg/kg/hr CRI	IV	Indicated for ventricular arrhythmias

## References

1. Swindle MM. 2007. Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques. 2<sup>nd</sup> ed. CRC Press: Boca Raton, FL.

2. Thiede AJ, Garcia KD, Stolarik DF, Ma J, Jenkins GJ, Nunamaker EA. 2014. Pharmacokinetics of sustained-release and transdermal buprenorphine in Gottingen minipigs (*Sus scrofa domestica*). J Am Assoc Lab Anim Sci 53:692-699.

## RUMINANT FORMULARY

DRUG NAME and DOSE	ROUTE AND FREQUENCY	NOTES
<b>Sedation</b>		
Midazolam 0.3mg/kg + Fentanyl 0.0025mg/kg	IV	Sedation resulting in sternal recumbency for 20-30 minutes (adequate for quick minimally invasive procedures)
<b>Pre-Medication</b>		
Midazolam 0.5mg/kg + Fentanyl 0.005mg/kg	IV	Excellent sedation resulting in lateral recumbency for 30-45 minutes
Ketamine 7.5mg/kg + Midazolam 0.4mg/kg + Glycopyrolate 0.004mg/kg	IV	Useful for IV sedation to produce lateral recumbency for animal transport and catheter placement
<b>Induction</b>		
Propofol 2-4mg/kg	IV	Administer slowly to effect for intubation Causes apnea with rapid administration
<b>Maintenance</b>		
Isoflurane	1-2%	
Fentanyl 5-20mcg/kg/hr	IV CRI	Short-acting opioid useful for intra-operative pain management during major invasive procedures
<b>Analgesics</b>		
Meloxicam 1mg/kg	IM or PO	NSAID – generally no more than 3-5 days, may provide analgesia for up to 72hrs
Flunixin (Banamine) 1.1mg/kg	IM or IV SID-BID	NSAID – generally no more than 3-5 days
Buprenorphine 0.005-0.01mg/kg	IV or IM TID	Opioid
<b>Emergency Drugs</b>		
Amiodarone 10mg/kg, then 0.05mg/kg/hr	IV	Indicated for treatment of arrhythmias
Epinephrine 0.02mg/kg	IV	Indicated for asystole
Lidocaine 4mg/kg, then	IV	Indicated for ventricular tachycardia / fibrillation
Dopram 5-10mg/kg	IV	Indicated for stimulation of respiration

## References

1. Carney EL, Clark JB, Myers JL, Peterson R, Wilson RP, Weiss WJ. 2009. Animal Model Development for the Penn State Pediatric Ventricular Assist Device. *Artif Organs* 33(11):953-957.
2. Valverde A, Doherty TJ. 2008. Anesthesia and Analgesia of Ruminants. In: *Anesthesia and Analgesia in Laboratory Animals*. 2<sup>nd</sup> ed. Academic Press: San Diego, CA.