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**Laboratory Animal Program
 Guidance Documents**

Document Title:	<i>Sedation/Tranquilization, Anesthesia and Analgesia in Laboratory Animals and Veterinarian-Recommended Formularies</i>
Date Approved:	05/15/2019
Date Reviewed:	

PURPOSE:

All procedures likely to cause pain or distress in animals must be done under appropriate sedation/tranquilization, anesthesia and/or analgesia unless specifically exempted in an approved Animal Use Protocol. Recommended drugs for management of pain and distress may be found in the formulary below. Use of any other drug(s) not on this list must be clearly justified and approved in an Animal Use Protocol. Justification not only includes an explanation of why the requested drug is appropriate, but also why one of the recommended drugs will not serve the same purpose or will interfere with the experiment.

I. Background:

Sedation and/or tranquilization, general anesthesia, and analgesia may be required for a variety of animal uses from restraint and minor procedures such as blood collection or imaging to major invasive surgery. Animal anesthesia and analgesia are crucial components of the animal use protocol, and appropriate pain management is central to the provision of adequate veterinary care, not adjunctive. It is not only a professional and ethical obligation, but also a key contributor to successful research outcomes. Managing pain successfully requires a continuum of care based on a well-thought-out plan that includes anticipation, early intervention, and evaluation of response on an individual basis.

IACUC requires that pain is prevented whenever possible and treated aggressively whenever diagnosed, unless a strong scientific justification precludes it. *The Guide* and 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 this principle are permitted only in the minority of protocols approved by IACUC as Category E and require robust scientific justification.

Balanced anesthetic and multimodal, pre-emptive analgesic regimens are the current standards of care in veterinary medicine and are required under this policy. A multimodal 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, e.g. balanced anesthesia and analgesia. It is not acceptable to conduct surgical procedures unless an animal is in a surgical plane of anesthesia. IACUC requires that preemptive analgesia be administered prior to the first incision for all surgical procedures unless otherwise scientifically justified in the protocol.

II. Procedures:

1. The ideal anesthetic/analgesic regimen must several criteria:
 - a. Minimize any pain or distress associated with handling or the induction of anesthesia
 - b. Be precisely titratable to assure that animals receive adequate anesthesia to produce

- unconsciousness and immobility and to block pain sensation without causing hemodynamic instability
- c. Provide pre-emptive analgesia so that 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
 - d. Not interfere with the research goals
 - e. Not result in undesirable intra- or post-operative side effects
 - f. Be compatible with available equipment, other medications, and staff training
2. **In planning any procedure that may cause pain or distress, a veterinarian must be consulted for advice regarding the proper use of sedatives/tranquilizers or anesthetics.** Veterinary judgment is necessary to determine the appropriate level of sedation or anesthesia required based on the species and invasiveness of the procedure. Additionally, different procedures and surgeries may require different levels of analgesic therapy for which veterinary input is required.
 3. Volatile inhaled anesthetics (such as isoflurane) 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 generally safer than repeated administration of injectable drugs; thus, **inhaled anesthetics are usually the maintenance anesthetic of choice.** However, injectable agents are often required as pre-medications to sedate or restrain the animal for anesthetic induction before a maintenance anesthetic can be used. In some cases, inhaled anesthetics may be contraindicated or unnecessary, and an injectable regimen may be more appropriate based on the invasiveness and/or length of the procedure. Additionally, inhalant anesthetics lack analgesic effects, so injectable anesthetics and/or analgesics are often given in conjunction with gas anesthetics.
 4. **Pre-emptive analgesia is implemented by administration of analgesics prior to the first incision during surgical procedures.** Use of pre-emptive analgesics significantly reduces the required concentration of anesthetic gases, resulting in minimization of cardiovascular and respiratory depression secondary to volatile anesthetics and a faster recovery from anesthesia. Additionally, pre-emptive analgesia prevents sensitization of pain receptors to reduce post-operative pain.
 5. Adjunctive, non-pharmacologic analgesic therapy should be employed whenever practical. Such methods may include providing warmth, a comfortable area for the animal to rest, use of cold and heat as appropriate to modulate inflammation, and increased ease of access to food and water. 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, and supportive care should be planned ahead of the procedure.
 6. All staff anesthetizing animals must have appropriate training. Veterinary consultation is available at all times, and investigators are required to seek veterinary input in planning of surgical or potentially painful procedures.

III. Drug Dosages and Frequencies of Administration

1. All animals experiencing a major survival surgery must be provided with systemic analgesics for no less than 3 days following the procedure, and analgesic therapy should only be discontinued at the direction of a veterinarian or based on an observation that the animal is not painful at the time the next analgesic dose is due. Furthermore, the level of invasiveness of the surgery may require a more aggressive analgesic regimen (e.g., local anesthetic for minimal invasiveness without expectation for prolonged pain, local anesthetic plus NSAID for mild to moderate pain, local anesthetic plus NSAID and opioid for moderate to severe pain) as determined by veterinary staff during protocol review.
2. Special attention must be paid to analgesic doses and frequencies. IACUC requires that investigators take into account overnight, weekend, and holiday pain management in selecting the most appropriate analgesic regimen. **It is not acceptable to give drugs at greater intervals than those prescribed and known to adequately manage pain.**
3. Note that all doses included in this formulary 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.

IV. LAP Anesthetic and Analgesic Formulary

This document contains recommendations for best practice use of sedatives/tranquilizers, anesthetics, and analgesics based on the current standard of care. While all of the drug combinations listed here are considered safe and effective, the selections shaded in gray represent best practice approach to anesthesia and analgesia in these species and should be followed whenever possible. The drugs contained within this formulary are not exhaustive of all possible anesthetics and analgesics that can be used in laboratory animals, and investigators should consult with the attending veterinarian if an alternative agent is desired to achieve the scientific goal. Veterinary staff continuously review outcomes of surgical and anesthetic procedures as well as the literature for refinements and update their recommendations and clinical practice periodically to reflect the evolving standard of care.

Abbreviations	
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
IP	Intraperitoneal
IV	Intravenous
SQ	Subcutaneous
CRI	Constant rate infusion
PO	Per os (by mouth)

1. Local Anesthetics

- a. Local anesthetics can be used in all species at similar doses, with the exception of cats. 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).
- b. In all species, a maximum of 2mg/kg bupivacaine or 6mg/kg lidocaine should be administered. Although these drugs have relatively short half-lives, a variety of studies have shown that they 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.
- c. For animals experiencing a craniotomy, a regional scalp block with 2mg/kg bupivacaine is recommended. The supraorbital nerves are blocked as they emerge from each orbit by palpating the supraorbital notch, inserting the needle along the upper orbital margin, perpendicular to the skin, just medial to the supraorbital foramen. The occipital nerve is then blocked as it exits the skull near the occipital protuberance. The occipital artery on the back of the skull is palpated, and bupivacaine is injected medially after careful aspiration to avoid intra-arterial injection. These three injections are sufficient to regionally block the scalp for the region of most head post and chamber placements.

2. Mouse Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Anesthetic Induction		
Sodium Pentobarbital (Nembutal) 30-90mg/kg (expensive)	IP	Beware of dose related deep anesthetic plane, respiratory depression, narrow margin of safety, hypothermia and prolonged recovery. (ref # 1 & 11)
Ketamine 100mg/kg + Xylazine 10mg/kg	IP	General anesthesia for surgery; only re-dose with ketamine if needed
Ketamine 100mg/kg + Diazepam OR Midazolam 5mg/kg	IP	General anesthesia for surgery; only re-dose with ketamine if needed
Ketamine 50-75mg/kg + Dexmedetomidine 0.5-1.0mg/kg	IP	
Ketamine 100mg/kg + Xylazine 20mg/kg + Acepromazine 3mg/kg	IP	Causes prolonged anesthesia, but can partially reverse xylazine with atipamezole or yohimbine

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Isoflurane	1-4%	Generally, first choice agent in rodents because it can be easily titrated to deliver dose required for anesthesia Induce rodent in a chamber at 3-4%, then reduce to 12% for procedure
Analgesics		
Meloxicam 1-2mg/kg	PO, SQ q1224h	NSAID
Flunixin Meglumine 2.5mg/kg	SQ, IM q1224h	NSAID
Carprofen (Rimadyl) 5 mg/kg	SQ q 24 hours	NSAID
Ketoprofen 5mg/kg	SQ q 24 hours	NSAID
Buprenorphine 0.1mg/kg	SQ, IP q 8- 12h	Opioid, useful in addition to an NSAID for multimodal analgesia for moderate to severe pain. DEA license required
Buprenorphine SR 0.5 – 1.0 mg/kg	SQ q 72h	Extended release formulation. DEA license required
Acetaminophen Liquid 110-305 mg/kg. Both water and gel must be used in combination and will contain 1.1 mg/ml of Acetaminophen	Oral	Used only when NSAIDs and Opiates are contraindicated due to experimental design. Direction listed on pages 12-13.

- a. Directions for Adding Acetaminophen Liquid to Water and MediGel Sucralose for Mouse Analgesia
 - i. Acetaminophen can reach a therapeutic level when given to mice in both drinking water and MediGel Sucralose together. The correct concentrations and instructions for making them up are described here.
 - ii. Materials
 - Hydropacs (420 ml) or sterile bottles of water (400 ml) for mouse MIT cage
 - Children’s’ liquid acetaminophen – cherry or grape flavored – confirm that the concentration is 160mg/5ml (1 teaspoon)
 - MediGel Sucralose (can be ordered through the LAP. If enough investigators are interested in administering acetaminophen by this method, it is recommended that you order a box (96 gels) as a group to prevent wastage.)
 - Sterile needles and syringes
 - tape

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iii. Directions:

- For Hydropacs, spray Hydropac with Rescue™: Using sterile technique, insert needle and withdraw 15 ml of water. Replace with 15 ml of liquid acetaminophen. Place tape over hole from needle.
- For water bottles, remove cap and withdraw 14 ml of water. Replace with 14 ml of liquid acetaminophen.
- For MediGel Sucralose, warm the containers in a water bath until the gel becomes liquid. Spray top of container with Rescue™. Inject 2.5 ml of the acetaminophen liquid through the lid using an 18g needle. Place tape over the hole in the lid to prevent contamination. Shake for ~10 seconds, then place in refrigerator so gel can solidify. To use, spray with Rescue™, remove lid and place in mouse cage. Replace when most of the gel has been eaten.

3. Rat Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Anesthetic Induction		
Sodium Pentobarbital (Nembutal) 3060mg/kg (expensive)	IP	Beware of dose related deep anesthetic plane, respiratory depression, narrow margin of safety, hypothermia and prolonged recovery. (ref # 1 & 11)
Ketamine 40-80mg/kg + Xylazine 510mg/kg	IP	General anesthesia for surgery; only re-dose with ketamine if needed
Ketamine 75mg/kg + Diazepam OR Midazolam 5mg/kg	IP	Light anesthesia
Ketamine 50-75mg/kg + Dexmedetomidine 0.25mg/kg	IP	
Isoflurane	1-4%	Generally, first choice agent in rodents because it can be easily titrated to deliver dose required for anesthesia Induce rodent in a chamber at 3-4%, then reduce to 12% for procedure
Analgesics		
Meloxicam 1-2mg/kg	PO, SQ q1224h	NSAID
Flunixin Meglumine 2.5mg/kg	SQ, IM q1224h	NSAID

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DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Carprofen 5mg/kg	SQ, PO SID	NSAID - Oral doses may need to be increased
Ketoprofen 5mg/kg	IM, SQ, PO SID	NSAID - Oral doses may need to be increased
Buprenorphine 0.01-0.05 mg/kg	SQ q8-12 h	Opioid, useful in addition to an NSAID for multimodal analgesia for moderate to severe pain. (ref # 9, 14) DEA License required
Buprenorphine SR 1 – 1.2 mg/kg	SQ 72h	Extended release formulation. DEA License required.

4. Anesthetics for Other Rodents

DRUG NAME and DOSE	SPECIES	ROUTE & FREQUENCY	NOTES
Isoflurane Induce 3-5%; Maintenance 2-3%	All		
Sodium Pentobarbital (Nembutal®) 45mg/kg + xylazine 7mg/kg	Guinea Pig	IP	
NOT RECOMMENDED	Hamster		
Ketamine/ xylazine 30 - 87 mg/kg ketamine + 5 -13 mg/kg xylazine	Guinea Pig	IP	Higher dose induces surgical plane of anesthesia
200mg/kg ketamine + 10 mg/kg xylazine	Hamster	IP	
50-70mg/kg ketamine + 2-3mg/kg xylazine	Gerbil	SC	
27mg/kg ketamine + 0.6mg/kg xylazine	Blind mole rat	IM	
67mg/kg ketamine + 13mg/kg xylazine	Prairie vole	SC	

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DRUG NAME and DOSE	SPECIES	ROUTE & FREQUENCY	NOTES
Ketamine/Midazolam: 5-10mg/kg ketamine + 0.5 – 1.0 mg/kg	Guinea Pig	IM	Anesthesia; only re-dose with ketamine if needed
Ketamine/Diazepam 30-100 mg/kg ketamine + 2-5 mg/kg diazepam	Guinea Pig	IM	Anesthesia; only re-dose with ketamine if needed
70mg/kg ketamine + 2mg/kg diazepam	Hamster	IP	
100mg/kg ketamine + 5mg/kg diazepam	Gerbil	SC, IP	
Ketamine/Dexmedetomidine Ketamine 50-75 mg/kg + Dexmedetomidine 0.5-1.0 mg/kg		IP	
Propofol 10mg/kg	Guinea Pig	IV	Administer to effect

5. Analgesics for Other Rodents

DRUG NAME and DOSE	SPECIES	ROUTE & FREQUENCY	NOTES
NSAIDS			
Flunixin 2.5-5mg/kg	Guinea Pig	SC; BID-SID	
2.5mg/kg	Hamster	SC; BID-SID	
Carprofen 5mg/kg	Guinea Pig	SC; BID	
1-2 mg/kg	Guinea Pig	PO; BID	
5mg/kg	Hamster	SC; SID	
Ketoprofen 1mg/kg	Guinea Pig	SC, IM; BID-SID	

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DRUG NAME and DOSE	SPECIES	ROUTE & FREQUENCY	NOTES
Meloxicam 0.1-0.3mg/kg	Guinea Pig	PO; SID	
2mg/kg loading dose, followed by 1mg/kg	Mole Rat	PO, SC; SID	
OPIOIDS			
Buprenorphine	Rodents	SC, PO; QID-BID	
Morphine	Naked Mole Rat		AVOID – causes hyperalgesia and severe aggression

6. Bird Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Anesthesia		
Isoflurane		Bird can be placed in a chamber or induced via mask. Intubation in birds is relatively easy.
Ketamine 1.5-6 mg/kg + Dexmedetomidine 40-160mcg/kg	SQ	Can be used to maintain anesthesia delivered continuously SQ diluted in LRS Reverse dexmedetomidine with atipamezole 0.5mg/kg SQ
Ketamine 10-50mg/kg + Diazepam 0.5-2mg/kg	IM	
Analgesics		
Carprofen 1mg/kg	SQ SID-BID	NSAID
Meloxicam 0.1mg/kg	IM SID	NSAID
0.5mg/kg BID	PO	
Buprenorphine 0.01-0.05mg/kg	IM TID-BID	Opioid agonist-antagonist
Butorphanol 0.5-2mg/kg	IM QID	Opioid agonist-antagonist

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7. Rabbit Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Sedation		
Acepromazine 0.75mg/kg	IM	Produces a peripheral vasodilation useful for venipuncture
Dexmedetomidine 0.05mg/kg	SQ	Produces moderate sedation, useful for minimally invasive procedures less than 30 minutes
Induction		
Ketamine 10-20mg/kg + Dexmedetomidine 0.1mg/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	
Maintenance		
Isoflurane	1-2% (MAC = 2%)	Laryngeal masks may be utilized in place of endotracheal tubes as rabbits are difficult to intubate
Analgesics		
Meloxicam 0.3-0.5mg/kg	SQ or PO SID	NSAID – useful for mild to moderate pain
Flunixin Meglumine 1-2mg/kg	SQ SID-BID	NSAID
Buprenorphine 0.02-0.05mg/kg	SQ or IV BIDQID	Opioid
Buprenorphine SR 0.12mg/kg	SQ q 72hr	Sustained release formulation that eliminates frequent dosing requirement

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8. Swine Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Pre-Medication / Induction		
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	Sufficient for intubation. 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
Maintenance		
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
Lidocaine 2-4mg/kg , then 0.3mg/kg/hr CRI	IV	Indicated for ventricular arrhythmias
Analgesics		
Carprofen 3-4mg/kg	PO BID SQ or IM SID	An NSAID, can be administered IM prior to procedure, then continued orally afterwards.
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

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9. Ruminant Formulary

DRUG NAME and DOSE	ROUTE & FREQUENCY	NOTES
Sedation		
Midazolam 0.3mg/kg + Fentanyl 0.0025mg/kg	IV	Sedation resulting in sternal recumbency for 20-30 minutes (adequate for quick minimally invasive procedures)
Pre-Medication		
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 + Glycopyrrolate 0.004mg/kg	IV	Useful for IV sedation to produce lateral recumbency for animal transport and catheter placement
Induction		
Propofol 2-4mg/kg	IV	Administer slowly to effect for intubation Causes apnea with rapid administration
Maintenance		
Isoflurane	1-2%	
Fentanyl 5-20mcg/kg/hr	IV CRI	Short-acting opioid useful for intra-operative pain management during major invasive procedures; Required as balanced anesthesia for procedures such as sternotomies that are expected to cause severe pain
Analgesics		
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 SIDBID	NSAID – generally no more than 3-5 days
Buprenorphine 0.005-0.01mg/kg	IV or IM TID	Opioid

10. Amphibian Formulary

DRUG and DOSE RANGE	ROUTE & FREQUENCY	NOTES
Anesthetics		
Isoflurane 3-5% induction to effect; 2-3% maintenance	Inhalation	
Tricaine methane sulfonate (MS222) 50-200 mg/kg ----- 0.5-2.0 g/l (frogs/salamanders)	Intracoelomic ----- Water bath to effect	Buffer to a pH of 6-7 with sodium bicarbonate
Ketamine 50-150 mg/kg	SQ, IM, IV or dorsal lymph sac	
Analgesics		
Buprenorphine 38-75 mg/kg	Dorsal lymph sac; Not less than every 4 hr	
Carprofen 2-4 mg/kg 1 st dose 1-2 mg/kg 2 nd dose	PO, SQ or IM; Every 24-72 hr	
Meloxicam 0.1-1.0 mg/kg	PO, SQ or intracoelomic; Every 24 hr	
Morphine 38-42 mg/kg	SQ; No less than every few hr	
Bupivacaine <2 mg/kg	Infiltrate or topically; Redose as needed	not to exceed a total dose of 2 mg/kg)
Lidocaine/Bupivacaine <2 mg/kg	Infiltrate or topically; Lasts 1-4 hours; Redose as needed	(not to exceed a total dose of 2 mg/kg)

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V. REFERENCES

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