Formulary of Anesthetics and Analgesics for Laboratory Animals

Much of the material from sections I and II has been taken from the Veterinary Anesthetic and Analgesic Formulary of the University of Denver Anschutz Medical Campus.

I. Introduction and Formulary Use

Basic Definitions:

- Anesthesia: central nervous system depression that provides amnesia, unconsciousness and immobility in response to a painful stimulation. Drugs that produce anesthesia may or may not provide analgesia (1, 2).
- Analgesia: The absence of pain in response to stimulation that would normally be painful. An analgesic drug can provide analgesia by acting at the level of the central nervous system or at the site of inflammation to diminish or block pain signals (1, 2).
- Sedation: A state of mental calmness, decreased response to environmental stimuli, and muscle relaxation. This state is characterized by suppression of spontaneous movement with maintenance of spinal reflexes (1).

Anesthesia and analgesia are crucial components of an animal care and use protocol. This document is provided to aid in the design of an anesthetic and analgesic plan to prevent animal pain whenever possible. However, this document should not be perceived to replace consultation with the university's veterinary staff. As required by law, the veterinary staff should be consulted to assist in the planning of procedures where anesthetics and analgesics will be used to avoid or minimize discomfort, distress and pain in animals (3, 4). Prior to administration, all use of anesthetics and analgesic are to be approved by the Johns Hopkins Institutional Animal Care and Use Committee (IACUC).

For each species listed in the formulary, the most commonly used anesthetic and analgesic drugs have been highlighted. These drugs can be considered the "front-line" of care. However, based on the research, procedure, and need, the most common drugs may not suffice and an individual drug or a combination of drugs may be indicated to provide the most safe and effective anesthetic and analgesic plan.

Dosages or dose ranges are obtained from a variety of different laboratory animal medicine and veterinary references, thus subtle differences do exist. Where dosage ranges are provided, the effective minimum and safely administered maximum are represented. Selection of dose can be based on veterinary recommendation, literature references, or procedural experience. When listing these drugs in an animal care and use protocol, drugs should be listed with approximate dose ranges. This provides flexibility for titration up or down for the individual animal or for the particular application.

For anesthetic drugs, exact durations of action have not been provided. Duration of anesthesia is influenced by the drug combination used, strain, age, sex, body weight, procedure performed and the amount of stimulus during the procedure. As a result, any published duration of action would be a generalization. Consultation with a John Hopkins Research Animal Resources (RAR) veterinarian when developing an anesthetic regimen is therefore highly recommended. Due to all the factors that influence duration of

anesthesia, anesthetic drugs should always be titrated to effect. If anesthesia is being maintained using a gas anesthetic (i.e. isoflurane), titration of anesthetic depth can be controlled almost immediately by adjusting the percentage of anesthetic gas being delivered to the animal. In addition, anesthetic duration can be extended for as long as the anesthetic gas is administered. In contrast, injectable anesthetics do not have this flexibility; once a drug has been administered, it cannot be "removed" within seconds to minutes such that the end anesthesia coincides with the end of the procedure. Reversal drugs do exist for some, but certainly not all injectable drugs. For example, dexmedetomidine is efficiently reversed by atipamezole (see α_2 antagonists below). In addition, injectable anesthetics may need to be re-administered if the initial dose doesn't provide sufficient anesthesia or if the duration of the procedure is extended. As a generalization, it is often recommended to re-administer 25-30% of the initial dose of the injectable anesthetic to lengthen the surgical anesthesia time. Performing a surgical procedure on an incompletely anesthetized (unconscious) animal is unacceptable. Should an investigator discover a recommended dose range is consistently too high (prolonged anesthesia or long recovery) or too low (return of reflex requiring repeated administration of drugs), an RAR veterinarian should be contacted. With veterinary consultation, further flexibility can be provided to more accurately titrate dosages prior to submitting an amendment to the Institutional Animal Care and Use Committee (IACUC).

Independent of the method of anesthesia or duration of the procedure, all animals should be monitored until awake, also referred to as "recovered." An animal is considered recovered when:

- Able to remain in an upright, sternal position
- Respiration is normal (both rate and rhythm)
- Able to move spontaneously within the primary enclosure
- Responds consistently and appropriately to environmental stimulation (cage manipulation) and/or direct or indirectly conspecific interactions

Monitoring of the animal during the recovery period must be documented by the investigator or designated lab member. This is not only a legal requirement, but also ensures that the animal doesn't regress (stop breathing, become hypothermic, injure itself etc.) or take an inappropriately long time to recover. As a result, plans for intra- and post-operative monitoring must be included in the IACUC protocol, and then practiced as written. The RAR veterinarians are a valuable resource for questions related to recovery and monitoring and for assistance generating custom post-operative monitoring sheets appropriate to the research model, surgery or procedure.

Appropriate selection and dosing of analgesics (pain relieving drugs) can be difficult to gauge even when careful clinical observations are performed. Drug information and dosing regimens are therefore provided as strict guidelines supported by a wealth of laboratory animal and veterinary medical based publications. The analgesic regimen described in your animal care and use protocol must be specified and followed precisely. If an alternative regimen is desired, but not listed in the approved protocol, consultation with an RAR veterinarian is required prior to administration. Each drug has an established duration of action; this is used to determine the drug's dosing frequency. Selecting drugs and dosing

regimens to provide continuous analgesia can be difficult in a research setting. There are a limited number of single administration, "long acting" (24 hours or greater) analgesics available for use in laboratory animals. Repeated administration is often therefore necessary. This becomes problematic when administration must occur after typical business hours (10 PM, 3 AM etc.). Most opioid (buprenorphine HCl, fentanyl, oxymorphone etc.) administered at 5:00 PM will not be effective at 8:00 AM the next morning. Use of opioid analgesics therefore often necessitates after hours administration, use of extended release formulations (buprenorphine SR or meloxicam SR), and/or multimodal analgesia (shorter acting opioid + longer acting non-steroidal anti-inflammatory drugs (NSAIDS) analgesics). Appropriate drug selections and dosing regimens should be based on the species and degree of pain/distress associated with the procedure/surgery. In contrast to most opioids, the majority of NSAIDs do allow for up to 24 hours of continuous analgesia following a single administration (meloxicam, carprofen, etc.). More recently, extended release NSAIDs have become available for several laboratory animal species (meloxicam SR).

Independent of the drug(s) selected, the ideal analgesic regimen includes preemptive analgesia. Preemptive analgesia has been defined as treatment that: 1) starts before surgery; 2) prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and 3) prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period). Once pain receptors are sensitized, the threshold of pain stimulus is lowered and will require higher doses of analgesia for longer durations to control pain as compared to an animal where analgesics were provided before the procedure. Determining when to administer the preemptive analgesic will depend on the drug's duration of action and how rapidly a therapeutic concentration is reached.

Historically, analgesics such as Acetaminophen (Children's Tylenol® Elixir) and Ibuprofen (Children's Advil® Elixir) have been administered post-operatively to rodents via the drinking water. This was performed under the assumption that continuous administration of drug by consumption in the water would provide a hands-off, stress-free, continuously-administered level of analgesic therapy. With continued investigation however, it has been demonstrated that water and food consumption post-surgery and/or post-anesthesia are neither constant nor consistent (5-8). As a result, analgesics are often not appropriately consumed. "Confirmed delivery" by way of injection and/or oral administration is necessary to ensure an animal has received the appropriate dose of medication.

Irrespective of the quality of design or integration of the anesthetic and analgesic plan into a research protocol, the plan is only as good as the skill and care with which it is applied. General training is available through the ACUC by means of routinely scheduled classes or by request from individual personnel that work with laboratory animals. Advanced training and specialized protocol consultation is also available through the RAR veterinarians.

It is important to recognize that anesthesiology is an art as much as it is a science. There are a myriad of drugs that can be used to anesthetize animals, however most of them were not developed for use in laboratory animals and are therefore being used in an extra-label manner. Animal species differ in their responses to various drugs, and much of the information that we have about dosage, and especially about various drug

combinations ("cocktails") rely on empirical data. For example, ketamine hydrochloride is only approved for use in cats and nonhuman primates but does work well in other species most often in combination with other drugs including sedatives, neuroleptanalgesics and/or opioids. Even in cats and nonhuman primates, ketamine should not be used as the sole anesthetic agent for anything other than minor surgical procedures.

Anesthetizing animals is requires common sense and knowledge. Be sure that you are extremely familiar with the agent(s) that you intend to use. While many drugs will provide anesthesia (unconsciousness) or analgesia (absence of pain), they may also have profound effects on the biologic parameters that you intend to study. Drug dosages are usually based on body weight; be sure that you weigh each animal prior to drug administration. As a general rule, when a dose range is given for a particular drug, the lower end of the dose range will provide a lighter plane of anesthesia and/or for a shorter period of time. In general, drugs given intravenously (IV) require much more care than those given via other routes (SC, IM, PO). When using barbiturates intravenously, for example, approximately half of the calculated dose is administered rapidly in order to avoid a rough and potentially unsafe excitement phase of anesthesia. The rest of the dose is given slowly to effect. Unknowingly administering the total calculated dose of a barbiturate as a bolus will often result in death. Often even when inhalant anesthetics (isoflurane, sevoflurane) are used for maintenance anesthesia (intra-operatively), injectable anesthetics are still necessary to facilitate endotracheal intubation and pre-operative patient prep (IV catheter placement, aseptic prep of the surgical site etc.). An anticholinergic (atropine or glycopyrrolate) may be given as a **pre-anesthetic** to reduce oral secretions and cholinergic side effects.

Further notes about the following information:

- All doses are in mg/kg unless otherwise stated
- DEA indicates that a Drug Enforcement Agency license is needed to purchase the specific drug.
- To obtain such a license, you must register first in the State of Maryland and then with the Federal DEA. The contact numbers for doing this are:

Maryland State Department of Health and Mental Hygiene Division of Drug Control
4201 Patterson Avenue
Baltimore, Maryland, 21215-2222
Telephone 410-764-2890

United States Drug Enforcement Administration
Registration Unit - ODRR
1405 Eye St., N.W. Washington, D.C 20537
Attention: Correspondence Unit
Baltimore DEA Office 410-962-22

I. Drug Classifications

Inhalant agents: Isoflurane (Forane®, Iso, IsoFlo®)
Isoflurane is a top choice inhalant anesthetic for restraint and/or surgical procedures in laboratory animal species. Isoflurane maybe delivered via a nose-cone or an endotracheal tube. The percent of gas administered can be adjusted to effect using a volatile gas precision vaporizer and compressed O_2. Maintenance anesthesia is typically between 1-2% isoflurane however this will vary by species according the minimal alveolar concentration (MAC) and also the presence of other (injectable) drugs. Induction of anesthesia with gas is typically achieved with < 5 min exposure to 3% isoflurane. Anesthetists should always use caution when increasing the isoflurane to 4-5%; most species will become unsafely deep in a matter seconds to minutes. For this reason, many veterinary anesthesiologists avoid turning the isoflurane gas above 3 - 3.5% (unless they are anesthetizing an unique species with a particularly high MAC).

Advantages: Rapid induction and recovery. A precision vaporizer provides the ability to precisely titrate the level of anesthesia during a procedure. Purchase of volatile anesthetics (isoflurane, sevoflurane etc.) does not require a DEA controlled drug license.

Disadvantages: Upfront cost associated with a precision vaporizer and anesthetic circuitry; requires either passive or active scavenging of waste and exhaled anesthetic gas; occupational health exposure to anesthetic gas should be limited; no analgesic effect once the gas has been completely exhaled; depressed respiratory rate and decreased blood pressure.

Additional Notes: The advantages typically outweigh the disadvantages; inhalants are often a first recommendation for maintenance anesthesia as they allow for a rapid induction, recovery, and precise dose titration during the procedure. In addition, the duration of anesthesia can easily be adjusted for a variety of procedures ranging from 30 seconds up to many hours. To overcome cost and logistics, RAR provides and maintains precision vaporizers with accompanying compressed O_2 for use within the central rodent vivarium (Miller Research Building). Concurrent use of analgesics such as opioids or NSAIDs is encouraged as isoflurane has no analgesic properties once the animal has regained consciousness following the surgery/procedure. Occupational exposure is always a concern. Gas anesthesia must be vented from the room (table-top back-draft vents, biosafety cabinet [BSC] with 100% exhaust outside the building) or filtered through passive scavenging using F/Air® activated charcoal canisters. F/Air® canisters must be weighed on a regular basis and replaced according to manufacturer's instructions. Typically replacement is indicated once either the weight of the canister has increased by a specified amount (i.e. 50 grams) or the canister has been in use for a specified number of hours (i.e. 12 hours).

Cyclohexamines: Ketamine (Ketoset ®), Tiletamine
Ketamine is a commonly used injectable anesthetic across a wide variety of species. In most cases, ketamine is used in combination with other injectable agents such as α_2 agonists or

benzodiazepines to reduce or eliminate many of the less desirable side effects if used alone. In rodents, ketamine combined with xylazine or xylazine plus acepromazine are the preferred anesthetics when gas anesthesia cannot be used.

Advantages: Ketamine has a wide margin of safety in most species; residual analgesic effect following anesthetic recovery; most commonly used drug (in combination) for injectable anesthesia in rodents.

Disadvantages: Ketamine alone does not provide muscle relaxation and muscle spasms may be observed; DEA license required for use as Ketamine is a Class III controlled substance; may not be possible to achieve a surgical plane anesthesia (as a sole agent, will vary by species); prolonged recovery as compared to gas anesthetics (true of all injectable anesthetics).

Additional details about Ketamine combinations:
Ketamine + Xylazine: Both drugs can be mixed in a single syringe prior to administration. This combination is the most common injectable anesthetic used in rodent species, specifically mice and rats.
Ketamine + Xylazine + Acepromazine: All three drugs can be mixed in a single syringe prior to administration. In rodents, the addition of acepromazine to the ketamine/xylazine cocktail increases the depth of anesthesia and substantially prolongs the duration of anesthesia as well as recovery time (9). The benefit of this combination will be dependent on the procedure.
Ketamine + Diazepam (Valium ®): Both drugs can be mixed in a single syringe, however this should be done immediately prior to administration to avoid drug precipitation in the syringe. Advantages include limited cardiovascular effects including minimal hypotension as compared to ketamine/xylazine combinations. However, in rodents, ketamine/diazepam only provides light anesthesia so it may only be appropriate for chemical restraint. Furthermore, because diazepam should only be administered IV, orally or rectally (not IP, IM or SC), administration to smaller rodents (mice and rats) is not particularly practical. As a result, this is a relatively infrequently used anesthetic combination in rodents. This combination does however, facilitate rapid IV induction of anesthesia in larger animal species (cats and dogs).
Tiletamine + Zolazepam (Telazol ®): Tiletamine is a similar drug as ketamine and is available already formulated with zolazepam under the trade name Telazol®. In combination, Telazol is very similar to the anesthetic combination of ketamine and diazepam. This drug combination can also be combined with xylazine and ketamine to yield a cocktail known a TKX (specifically for swine). Telazol is primarily used with larger species such as swine. The main advantage (compared to ketamine plus an alpha-2 agonist or benzodiazepine) is that only a small injection volume is needed to provide 20 minutes or more of immobilization. Despite its relative popularity with commercial and pet swine, use of this drug on cardiovascular or pulmonary-based studies may be contraindicated due to the profound hypothermia, cardiovascular and respiratory depression possible following a single IM administration. Note: Telazol is associated with nephrotoxicity in rabbits and thus is not considered safe in this species. Once Telazol® has been reconstituted, discard after 4 days if stored at room

temperature or after 14 days if stored refrigerated.

Alpha- 2 Agonists: Dexmedetomidine (Dexdomitor ®), Xylazine (Rompun ®)
Alpha-2 agonists are used for their sedative and analgesic properties across a variety of laboratory animal species. As sole agents, however they are not general anesthetics (even minor surgical procedures). In combination with ketamine however, α2-agonists are far much more useful and effective as anesthetics for surgical procedures.

Advantages: Produces analgesia of short duration; can be combined with ketamine to produce adequate surgical anesthesia in many species; effects can be reversed with α2-antagonists; DEA license not required; not irritating when administered IM or IP; relatively safe for neonates and pregnant rabbits.

Disadvantages: Profound cardiovascular depression (decreased heart rate, cardiac output, and hypotension) possible- severity will vary by species and α2-agonist; emetic (induce vomiting) in cats, may induce premature uterine contractions in dogs and cats.

Additional Notes: If following the first injection of anesthetic, the animal does not achieve the desired level of anesthesia, it is generally recommended to re-dose with 25-30% of the initial dose of both ketamine and xylazine. When re-dosing an injectable anesthetic combination of ketamine and an α2-agonist agonists as the initial injection is wearing off, it is recommended to only re-dose ketamine as the duration of action of the α_2 agonist is much longer than the duration of effect of ketamine. Medetomidine vs. dexmedetomidine: medetomidine (Domitor®) contains two isomers of the compound, one active and one inactive. Dexmedetomidine (Dexdomitor®) is the second-generation formulation and contains only the active isomer of the drug. Thus, list dosages for medetomidine should be divided in half when using dexmedetomidine.

Alpha-2 Antagonists: Atipamezole (Antisedan ®), Yohimbine
Alpha-2 antagonists are used as reversal agents for α2-agonists. Administration at the end of a procedure can reduce unwanted sedation, cardiovascular and respiratory depression possible during the recovery period. Atipamezole is 200-300x more selective for the for α2 receptor than yohimbine. Thus, as a reversal agent, antipamezole will provide a more rapid displacement of the α2-agonst providing a more rapid reversal than yohimbine.

Advantages: Can reduce the overall duration of recovery (improved thermoregulation, mobility, alertness etc.)

Disadvantage: Reverses any analgesic benefit of α2-agonst; can cause muscle tremors, increased respiratory rate, and hyperemic mucous membranes; no use as a stand-alone drug.

Additional Notes: Reversal is not required when using an α2-agonst in an anesthetic combination but can be utilized in some situations to reduce prolonged recovery times. Atipamezole (α_2 antagonist) was developed in conjunction with medetomidine (α2-agonist) so that 5 mg of atipamezole could reverse 1 mg of medetomidine (10). Due to the high

specificity of atipamezole for the α_2 receptor as compared to xylazine, only 1 mg of atipamezole is administered to reverse every 10 mg of xylazine administered (11). Yohimbine is also an α2-antagonist and can be used to reverse xylazine at a standard dose of 0.2 mg/kg, independent of the xylazine dose administered. While both are reversal agents for α2 agonists, the onset of reversal of Yohimbine is much longer than that of atipamezole due to differences in selectivity of the α2 receptor between the two drugs.

Benzodiazepines: Diazepam (Valium ®), Midazolam, Zolazepam
This class of drug provides marked sedation and muscle relaxation across a variety of species but has minimal to no analgesic properties. Used alone, these drugs will not provide a true anesthetic state as awareness persists with relaxation even at high dosages. As a result, these drugs are primarily used as sedatives, muscle relaxants**,** pre-anesthetics and/or in combination with general anesthetics during anesthetic induction but are never used alone to provide or maintain anesthesia. Note: Because diazepam maybe adsorb to plastic, it should not be drawn up and stored in plastic syringes.

Additional Notes: Benzodiazepines are DEA Class IV controlled substances. Midazolam is favored over diazepam because pharmaceutical grade preparations of diazepam are formulated in non-water soluble compounds that should only be administered intravenously. Midazolam is however water soluble and manufactured in preparations acceptable for intramuscular injection.

Steroid Anesthetics: Alfaxolone (Alfaxan ®)
Alfaxolone is a synthetic neuroactive steroid anesthetic. Despite being an analogue of progesterone, alfaxalone does not bind to sex hormone, glucocorticoid, or mineralocorticoid receptors. The drug achieves its central effects through the enhancement GABA at the $GABA_A$ receptors (binding sites are different then benzodiazepines). Alfaxalone was first released on the veterinary market in the 1970s in combination with another neurosteroidal agent, alfadolone. At that time, the drug's *vehicle* (a castor oil surfactant known as Cremophor EL), not the drug itself was found to induce clinically significant allergic reactions lead to the drug's withdrawal from the market. Alfaxalone returned to the U.S. market in 2014 as a sole agent (dissolved in an aqueous solution and containing no preservatives). Alphaxalone is currently FDA approved for both induction and maintenance anesthesia of dogs and cats, but has safely been used extra label in laboratory animals including swine and nonhuman primates. Alphaxolone's versatility and wide margin of safety allow for use on animals that are young (12 weeks of age or older), pregnant (C-sections etc.) or have cardiovascular compromise. It can be used for initial sedation (IM), induction (IV) and/or maintenance general anesthesia (IV constant rate infusion). In general, respiratory depression and hypotension are less pronounced when inducing and maintaining anesthesia with alfaxalone compared to propofol, isoflurane and sevoflurane.

Advantages: A general anesthetic that does not act on NMDA receptors (very desirable for some research models), wide margin of safety, can be combined with sedatives, other general anesthetics, opioids and/or inhalant anesthesia, bioavailable following IM or IV administration

Disadvantages: Currently only available in 10 mg/mL concentration making the volume required

for IM administration to smaller animals (marmosets) too large to administer at one site (repeated IM injections required), Schedule IV drug (DEA license required), no significant analgesic properties

Propofol (Diprivan ®)
Propofol sedative hypnotic that acts on the central nervous system as $GABA_A$ agonist, NMDA antagonist and voltage-gated sodium channel blocker. The drug can be used as an IV sedative to facilitate a short period of restraint for non-painful or minor procedures (ultrasound, bandage change, upper airway examination etc.) or as an anesthetic induction agent to facilitate intubation before maintenance with inhaled anesthetics. Additionally because of propofol's unique pharmacokinetic profile (including a short context-sensitive half-time) it may be given by repeated injection or as a continuous infusion to maintain total IV anesthesia without significantly prolonging recovery. It has also been used concurrently with inhaled anesthetic agents (partial IV anesthesia). Analgesic drugs (opioids, α_2 agonist etc.) are recommended to reduce dose and/or provide analgesia when propofol is used for painful procedures.

Two formulations of propofol are available for veterinary use in the United States. Both are isotonic 1% (10 mg/mL) preservative free, macroemulsions with 10% soybean oil, 2.25% glycerol, and 1.2% egg-lecithin. The pH is adjusted to approximately 7.5 with sodium hydroxide. The **original preservative free formulation** should be discarded within 6 hours of initial use to minimize microbial or fungal contamination. Refrigeration is not recommended so as to prevent separation of active drug from the emulsion. The new preservative free formulation, **Propoflo™ 28** contains 2% benzyl alcohol, which extends its shelf life to 28 days following initial use. Because the 2 formulation labels differ slightly, users must be aware of which propofol formulation has been selected. For induction, PropoFlo™ 28 should be titrated against the response of the patient over 60-90 seconds or until clinical signs show the onset of anesthesia. Rapid injection of propofol (≤5 seconds) may be associated with an increased incidence of apnea. Mild hypotension may occur during propofol anesthesia. Preanesthetics may increase the anesthesia or sedative effect of propofol and result in more pronounced changes in systolic, diastolic and mean arterial blood pressure.

Advantages: Excellent for short duration procedures (ultra-short acting (< 10 min post initial bolus) and complete recovery to within 20 minutes (dogs) or 30 minutes (cats)); induction is rapid, smooth, and excitement free; no significant adverse interactions with other commonly used drugs; perivascular administration does not produce local tissue reaction

Disadvantages:
Some animals may withdraw their limb in response to administration (presumably from a burning or painful sensation), but peri-vascular administration does not cause a local inflammatory reaction; some animals exhibit focal twitches or muscle fasciculations, which do not appear harmful but can be disruptive; respiratory and/or cardiovascular depression may be observed when propofol is administered as an IV bolus. This is more likely in volume-depleted patients and those with underlying cardiovascular disease.

Barbiturates: Sodium Pentobarbital (Nembutal ®), Methohexital (Brevital ®)
Barbiturates act on the central nervous system as $GABA_A$ agonists and can therefore

produce a wide spectrum of effects, from mild sedation to total anesthesia. They are considered to be reasonably good anesthetics but provide unreliable sedation at low dosages and no analgesic effect at any dose. Pentobarbital, the most commonly used drug of this class, is considered a long acting anesthetic. Methohexital is considered a short acting anesthetic is more commonly used as induction agent in large animal species.

Advantages: Rapid anesthetic onset; prolonged durations of surgical anesthesia; decades of research has characterized its side effects; does not interact with N-methyl-D-aspartate (NMDA) receptors (as does ketamine) which may be desirable for some areas of research

Disadvantages: Prolonged recovery time; inadequate analgesic properties; extremely expensive; narrow margin of safety; produces respiratory depression at higher dosages; non-rodent species may experience a distressful anesthetic recovery; DEA license required for use as a Class II controlled substance; significant risk for human abuse.

Additional Notes: Sodium pentobarbital is the primary active ingredient in Fatal Plus®, Sleepaway®, and Euthasol® which are manufactured euthanasia solutions. In addition to pentobarbital, the euthanasia solution Euthasol® also contains the active ingredient phenytoin sodium, an antiepileptic drug that suppresses brain activity. All three products contain non-active ingredients include preservatives and coloring. The preservatives (benzyl alcohol, isopropyl or ethyl alcohol) are bacterial static, preventing bacterial growth. The added coloring (blue or pink) aids in identifying the solution while in the syringe, preventing confusion and inadvertent euthanasia of animals. Pentobarbital administration at euthanasia dosages (2-3x anesthetic dose) initiates a rapid and deep anesthesia causing a dramatic decrease in blood pressure and blocking the respiratory centers in the brain stopping respiration, followed by halting of cardiac function. While pentobarbital sodium is the active ingredient in these solutions, the intent of these solutions is euthanasia only. These solutions are not to be diluted to provide deep anesthesia for recovery procedures or prolonged anesthesia for terminal procedures. They can be used at lower dosages if the procedure that is being performed is “seamlessly” leading to death such as in transcardial perfusion with fixation solution or tissue harvest (12). No unintended consequences have been reported on research results with the use of euthanasia solutions for euthanasia of research rodents or larger species. Due to the combination of drugs within euthanasia solutions they are considered DEA Class III controlled substance where as sodium pentobarbital alone is a DEA Class II controlled drug.

Opioids: Buprenorphine (Buprenex ®), Oxymorphone, Fentanyl, Morphine, Butorphanol
Opioid drugs bind to three different receptors [mu (μ), kappa (κ), and delta (δ)] as either agonists, partial agonists or antagonists. The location of these receptors vary, but in general they reside within the brain and spinal cord.

Advantages: Potent analgesics; pre-operative or intra-operative administration can lower the dose of inhalant or injectable general anesthetic needed for surgery; long history of use in research; reversible with naloxone.
Disadvantages: DEA Controlled Class II-IV drugs (depending on opioid; high potential for human abuse and addiction; relatively short duration of action (but some sustained release

formulations do now exist for laboratory animals); repeated use may result in tolerance development; species-dependent and opioid-dependent respiratory depression and secondary gastrointestinal hypomotility.

Additional Notes: Duration of effect has continuously hampered the use of opioids in research animals. In general, opioids are short acting drugs. Buprenorphine HCl is the longest acting opioid; in some species it can provide analgesia for up to 12 hours. Over the past half-decade sustained release formulations of buprenorphine have become available(13).Dosing and duration of therapeutic efficacy will vary by species but in general one injectable dose will last 48- 72 hours. Note: At this time these injectable formulations are still quite expensive (ex. Zoopharm Bup SR [10mg/mL] is $70-80 per ml).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Carprofen (Rimadyl ®), Meloxicam (Metacam ®), Flunixin meglumine (Banamine ®), Ketoprofen (Ketofen ®),
Members of this group represent 13 different classes of drugs that share inhibitory activity of the cyclooxygenase (COX) enzyme. The COX enzyme facilitates the production of Prostaglandin G_2 (PGG_2), which in tern facilitates a variety of enzymatic processes that produce several compounds involved in normal physiological processes and production of Prostaglandin E_2 (PGE_2). PGE_2 specifically plays a role in the perception of pain in the peripheral and central nervous system. Thus, blockade of PGE_2 by COX inhibition is effective in control of discomfort at the peripheral site of insult and within the central nervous system. Two forms of the COX enzyme have been well characterized (COX-1 and COX-2). As a result, COX inhibitors are often referenced as non-selective COX inhibitors or selective COX-2 inhibitors. This distinction has been made because inhibition of COX-2 is believed to be the predominant method of NSAID function to provide analgesia and anti- inflammatory action. Over the past 10 years, several COX-2 selective NSAIDs have emerged for use in veterinary medicine. The two most commonly used carprofen and meloxicam, can be administered once every 12-24 hours (depending on the dose).

Advantages: Relatively longer duration of analgesic activity; newer drugs demonstrate analgesic quality that rivals some opioids; DEA license not required; multiple safe routes of administration for several NSAIDs; relatively safe when administered at prescribed dosages, sustained release formulations (meloxicam SR) are now available and are less expensive (~ $10-12/mL) than sustained release opioids.
http://wildpharm.com/meloxicamsr5mllab.html

Disadvantages: Inherent anti-inflammatory properties make them contraindicated across a variety of animal models including those that involve inflammatory processes, infectious diseases, and/or or coagulation; less selective COX-2 inhibitors have the potential for COX-1 related side effects including gastrointestinal complications, prolonged coagulation times, and changes in kidney function; contraindicated for pregnant animals and newborns under 6 - 8 weeks of age; can not be administered concurrently with other synthetic steroids (dexamethasone, prednisone, prednisolone etc.).

Additional Notes: Analgesic combinations that include an NSAID plus opioids are considered an ideal combination for the control and prevention of discomfort due to the

demonstrated harmony and difference in mechanism of action. In contrast, combining multiple NSAIDs or using an NSAID in combination with a steroid (Prednisone, Prednisolone, and Dexamethasone) it is strongly discouraged to as the incidence of secondary side effects will greatly increase. Oral dosing of rodents by way of drinking water results in inconsistent consumption in part due to decreased water consumption following anesthesia.

Local Anesthetics: Lidocaine, Bupivacaine (Marcaine ®), Ropivacaine (Naropin ®), Proparacaine (Alcaine ® Ophthalmic)

Local anesthetics block fast voltage-gated sodium channels in the cell membrane of postsynaptic neurons, preventing depolarization and inhibiting the generation and propagation of nerve impulses. At lower blood concentrations, sensory neurons are primarily affected while at higher concentrations the effects become generalized. Routes of administration include: topical application to the mucous membranes (nose, mouth, throat, tracheobronchial tree, esophagus, genitourinary tract), infiltration directly into tissues without taking into consideration the course of cutaneous nerves (infiltration block), infiltration directly into tissues considering the course of cutaneous nerves to produce anesthesia distally (field block), injection in the direct vicinity of individual peripheral nerves or nerve plexuses (conduction block), and IV regional anesthesia (Bier block) (1). Neuraxial anesthesia includes both epidural and intrathecal (spinal) drug administration. The spinal nerve roots are the primary site of action for local anesthetics; however, the spinal cord and paravertebral nerves may also be affected (1). These agents also have been used for immersion anesthesia of fish and amphibians, ocular topical anesthesia, and skin topical anesthesia. Administration of local anesthetics prior to the painful stimulus (i.e. incision) would be considered an adjunct analgesic to opioid and NSAID analgesics. Use as a primary analgesic for anything more than very mild local pain is strongly discouraged due to the short duration of efficacy.

Advantages: Pre-operative and intra-operative administration can provide a good adjunct pain relief to general anesthetic and systemic analgesics administered after a procedure; DEA license not required.

Disadvantages: Avoid unintentional intramuscular and intravenous administration as both routes have the potential to reach systemic circulation very rapidly. In general, topical applications (i.e. 4% lidocaine ointment) have minimal systemic absorption and hence greater clinical safety. In general higher doses will result in higher systemic absorption and peak blood levels; highly vascular areas will have faster uptake than areas with more fat (1). Generalized CNS toxicity may occur from systemic absorption or direct vascular injection. Local anesthetics readily cross the blood–brain barrier. Low doses produce CNS depression, while higher doses result in CNS excitation and seizures. Dilution of stock concentration is encouraged to provide more accurate dose administration.

Additional Notes: For rodent use, dilute 1-2% lidocaine to 0.5%, and 0.5% Bupivacaine to 0.25%. This will allow for more accurate dosing and realistic volume to infuse at the incision site. Note: 1% solution = 10 mg/mL, 50% solution = 500mg/ml. Ropivacaine requires no dilution prior to use. Lidocaine is a fast acting, shorter duration local anesthetics. Bupivacaine is a slower onset, long acting local anesthetic. When used in combination

(Lidocaine plus Bupivacaine in the same syringe) the benefits of both drugs can be achieved, namely rapid onset with long duration of local anesthesia. In addition, the duration of efficacy of local anesthetics can be extended by the addition of epinephrine to the injected solution. Epinephrine causes local vasoconstriction of blood vessels in the area of the injection resulting in decreased systemic absorption leading to prolonged duration of action. Preparations of lidocaine and bupivacaine can be purchased pre-combined with epinephrine (1:200,000).

The use of tribromoethanol (TBE, Avertin) is restricted by the JHU IACUC because a pharmaceutical grade preparation of the drug is no longer available where other pharmaceutical anesthetics do exist that can fulfill the same purpose. Please refer to the JHU ACUC policy on non-pharmaceutical grade drugs http://web.jhu.edu/animalcare/policies/index.html. This document provides guidance on establishing scientific justification for the use of a non-pharmaceutical grade drug where other pharmaceutical grade drugs exist for the same or similar purposes.

III. Species Specific Anesthetic & Analgesia Recommendations

AMPHIBIANS

Aquatic frogs such as *Xenopus laevis* or *X. tropicalis* should be handled with soft nets during unanesthetized exams and/or procedures. When indicated, physical restraint should be firm but gentle and care must be taken to preserve the integrity of the protective mucous layer. Non-powdered latex or nitrile gloves should be used when handling amphibians in order to protect their delicate skin and prevent handler contact with glandular secretions, which may be toxic.

Chemical restraint is required for prolonged or invasive procedures. Some frog species including *Xenopus* have paired lymphatic structures called dorsal lymph sacs located subcutaneously under the skin of the back. These structures communicate with the venous circulation and are an excellent site for injection. Other routes including intracoelomic, intramuscular and intravenous are also frequently used.

A light plane of anesthesia is characterized by a loss of righting reflexes, but withdrawal reflexes and gular (throat) respiratory efforts remain. As the anesthetic level deepens, abdominal respiration is lost, followed by slowing of gular (throat) movements, which stop as a surgical level is reached. The cardiac impulse (visible heartbeat) should be retained; slowing or loss indicates an anesthetic overdose.

Skin should be kept moist during recovery. Ambient recovery temperatures of 60–70◦ F are appropriate for most species; avoid unnecessary warming because cutaneous respiration cannot meet the metabolic demands of increased body temperature (1).

Immersion Anesthesia

Agent(s)	Immersion bath dosages:	Comments/Reference(s)
Tricaine methosulfonate (MS-222, tricaine, Fiquel ®)	Larvae: 200 - 500 mg/liter *more sensitive than adults Adult frogs (*Xenopus*) & salamanders: 500 mg/liter – 2 grams/ liter Toads:1-3 g/liter	Anesthetic of choice for *Xenopus*. Safest for long and/or repeated procedures- 1g/liter provides at least 30 min of surgical anesthesia in this spp. All MS-222 solutions must be buffered: NaHCO3 420-1,050 mg/liter (10-25 mEq/liter). Unbuffered solutions result in a prolonged induction time and are irritating to skin. (1)
Benzocaine	Larvae: 50 mg/liter to effect Adult frogs (*Xenopus*) & salamanders: 200-300 mg/liter to effect	Immersion anesthetic related to MS-222 but with greater potency, more rapid induction & narrower margin of safety. Less water soluble than MS-222, must be dissolved in ethanol. (1)
Eugenol (clove oil)	310-473 mg/liter * large variation by species	Not recommended. Highly variable anesthetic duration, narrow safety margin, prolonged recovery. Reversible gastric prolapse reported in 50% of leopard frogs. (1, 24)

Injectable Anesthesia

Agent(s)	Immersion bath dosages:	Comments/Reference(s)
Ketamine	50-150 mg/kg SC, IM, IV, or dorsal lymph sacs (considered same as IV)	For minor surgeries or restraint; induction time, depth of anesthesia and recovery time vary greatly with species. (1)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	Induction: 3-5% Maintenance: 1-2.5 %	Induction time can exceed 20 min. Ensure chamber is moistened. Larger amphibians with lungs can be intubated. (1)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	14 mg/kg in dorsal lymph sac	DEA required. (1, 58)
Butorphanol	25 mg/kg intracelomic	DEA required, 12 hour duration (1, 58)
Xylazine	10 mg/kg intracelomic	12-24 hour duration
Flunixin meglumine	25 mg/kg intracelomic	4 hour duration

AVIAN SPECIES

The following issues should be considered when anesthetizing avian species. Supplemental heat should always be used to protect against hypothermia. Techniques to protect against hypothermia include: minimal feather plucking, circulating warm water blankets and water bottles, heat lamps and heated IV fluids. Intravenous catheters are difficult to maintain because avian vessels are very delicate. Intraosseous (IO) catheters are placed in the distal ulna or proximal tibiotarsus are therefore recommended. Note: Pneumatic bones such as the femur or humerus should never be used for IO catheters. Birds lack a diaphragm; breathing occurs through the inward/outward movement of the sternum. Restraint must therefore be performed carefully in a manner that minimizes pressure applied to the thoracic cavity (chest).

Injectable agents may be acceptable for procedures lasting 20–30 minutes or less. Inhalant anesthetics are however, typically considered safer for procedures of even longer duration. Disadvantages of injectable agents include significant dose and response variation between species and individuals, large drug volumes may be unsafe deliver to small birds, potential for overdose by any route, severe secondary cardiopulmonary depression, and recovery periods that vary significantly according to the bird's metabolic and excretory mechanisms (1). Supplemental oxygen delivered via a facemask is recommended when injectable anesthesia is used. Birds should be fasted for roughly 4 hours to insure the crop is empty prior to anesthesia. Gentle manual manipulation of the crop may also be needed to ensure adequate clearance. The head and neck of the bird should be slightly elevated during anesthesia. Isoflurane is the anesthetic of choice in birds. Inhalation anesthetics can be administered through a facemask placed over the head (or at least the nares), an air sac breathing tube, or an endotracheal tube. A non-rebreathing system should be used when using gas to anesthesia birds < 8 kg (1,24,54).

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	Induction: 3-5% Maintenance: 1.5-2.5%	Most species. (24)

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Ketamine	60 mg/kg	The effect of ketamine may vary by species of bird; recovery is associated with ataxia and excitement; seldom used as sole agent. Restraint is recommended during the recovery period. (24)
Ketamine Acepromazine	10-25 mg/kg IM 0.5- 1.0 mg/kg IM	Most species. Used higher end of dose range for birds < 250g. (24)
Ketamine Xylazine	10-15 mg/kg IM (owl) 2 mg/kg IM (owl)	(24)
Ketamine Midazolam	10-40 mg/kg IM 0.2-2.0 mg/kg IM	Most species. (24)

Analgesia: **Note**: Birds have more kappa opioid receptors than mu opioid receptors. Thus mu agonists and partial agonists (buprenorphine, fentanyl, and morphine) do not provide adequate analgesia.

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Butorphanol	0.5 - 4mg/kg IM q 4 hr	Recommend analgesic for most species of birds. (24)
NSAID		

Carprofen (Rimadyl ®)	1 mg/kg SC q 4 hr	This dosage was shown to increase the walking ability of lame chickens. (24)
Meloxicam (Metacam ®)	0.2 - 0.3 mg/kg SC q 12-24 hr x 2-3 days PRN	Current drug of choice in addition to butorphanol for analgesia in chickens. (24)

CATS

Cats should be fasted for 6-12 hours prior to anesthesia. This will help reduce the likelihood of vomiting before induction or during recovery. Water should not be withheld. Cats typically receive a pre-medication and sedation by intramuscular or intravenous injection. If IM injections are administered, the cranial thigh muscles or lumbar muscles should be used.

Cats are prone to laryngospasm during endotracheal intubation. For this reason lidocaine spray is commonly applied to the laryngeal region. Benzocaine (Cetacaine©) spray should never be used for this purpose in cats because it can cause methemoglobinemia Gas anesthesia can be maintained with a correctly fitted nose cone for uncomplicated or short procedures. Surgeries and complicated procedures often require endotracheal intubation and inhalant anesthetic for maintenance. Cats < 10-15 pounds should be placed on a non-rebreathing system (54).

Pre-Medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.02-0.04 mg/kg IM, SC, IV	Reduces bradycardia and hypersalivation. (10)
Glycopyrrolate	0.011 mg/kg IM, IV	Reduces bradycardia and hypersalivation. (10)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance	Administer via precision vaporizer and compressed oxygen

Injectable Sedatives for Induction of Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	Dose range: 0.01-0.20 mg/kg IM, SC, IV (slowly) Commonly used: 0.01- 0.03 mg/kg IM, SC, IV	Cat max dose: 1 mg. Note: FDA labeled dose (0.55-2.2 mg/kg) is considered 10X > than necessary per most clinicians. (10)
Midazolam	0.1-0.3 mg/kg SC, IM, IV	Combined with other premeds. (10)
Dexmedetomidine	40 mcg/kg IM See dosing table in drug package	(10)
Xylazine	1.1 mg/kg IM, SC	Note: Except for its use as an antiemetic, most prefer using newer alpha-2 agonists in cats & dogs. (10)
Diazepam	0.2-0.5 mg/kg PO SID-TID	Note: Due to rare idiosyncratic hepatic failure in cats, PO diazepam is often avoided. (10)
Tiletamine Zolazepam	9.7-11.9 mg/kg IM (FDA-approved dose)	Similar to ketamine/valium. (10)
Ketamine Midazolam	10 mg/kg IM 0.2 mg/kg IM	(1)
Ketamine Medetomidine	5 mg/kg IM 15-20 mcg/kg IM	(1)

Ketamine Butorphanol Acepromazine	5 mg/kg IM 0.2 m/kg IM 0.05 mg/kg IM	(1)
Pentobarbital	1-3 mg/kg/hr IV slowly	For chemical restraint, mechanical ventilation advisable. (10)
Propofol (PropofloFlo 28 ®)	Induction: 4 -8. mg/kg IV slowly over 60 sec Maintenance:0.1- 0.5 mg/kg/min	Wide dose range for induction & maintenance. No analgesic properties alone, monitor respiration closely. Refer to (10)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01-0.03 mg/kg SC, IM, IV q 6 hr	DEA required. (10)
Buprenorphine SR™ Sustained release	0.12 mg/kg SC q 72 hr	Manufacturer: ZooPharm No longer requires refrigeration. DEA required (59) http://www.srvet.net/index.php/buprenorphine-hci-sr/companion-animals
Butorphanol	0.4 mg/kg IV, IM, SC q 2-4 hr (FDA approved analgesia dose)	DEA required. (10)
NSAID		
Carprofen (Rimadyl ®)	1-4 mg/kg SC, PO q 24 hr (extra label in USA)	(10)
Meloxicam (Metacam ®)	0.3 mg/kg SC once (only FDA approved dose as of 2014) 0.1-0.2 mg/kg SC, PO q 24 hr (extra label in USA)	See (10) for details. FDA labeled for single use only due to potential for acute renal failure with chronic admin. Extra label dosing and guidelines do however exist: http://www.icatcare.org/vets/guidelines. NOTE: Meloxicam SR is contraindicated in cats!

CHINCHILLAS

Chinchillas are normally easy to be work with provided the handler is gentle and moves slowly. Occasionally if chinchillas are startled or presented with an uncomfortable situation they may vocalize, urinate, lunge, or attempt to escape from the handler. During such instances, care must be taken to avoid "fur slip", an escape mechanism whereby a patch of hair is rapidly shed.

Gas anesthesia may be delivered via a fitted nose cone or endotracheal intubation. Intubation is however be difficult in this species so a nosecone attached to a non-rebreathing circuit is frequently used. If intubation is desired, direct visualization of the glottis using a 1.9 – 2.7 mm rigid endoscope to assist ET placement has been described (60).

Pre-operative fasting is not necessary because chinchillas cannot vomit or regurgitate (60).

Pre-medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.1-0.2 mg/kg SC, IM	Reduces oral and respiratory mucus secretions. (1)
Glycopyrrolate	0.01-0.02 mg/kg SC, IM	Reduces oral and respiratory mucus secretions (1)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen (1)

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.5 mg/kg IM	(1)
Ketamine	20-40 mg/kg IM	(1,24)
Ketamine Xylazine	35-40 mg/kg IM 4-8 mg/kg IM	(1,24)
Ketamine Acepromazine	40 mg/kg IM 0.5 mg/kg IM	(1,24)
Pentobarbital	35-40 mg/kg IP	(1,24)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.05 mg/kg SC q 8-12 hr	DEA required (1)
NSAID		
Carprofen (Rimadyl ®)	4-5 mg/kg PO, SC q 24 hr	(1)
Meloxicam (Metacam ®)	0.5-2.0 mg/kg PO, SC q 24 hr	(24)

DOGS

Prior to any anesthesia, dogs should be fasted for 10-12 hours. Water does not need to be withheld. This will help reduce the likelihood of vomiting before induction or during recovery. Dogs typically receive a pre- medication and sedation by intramuscular or intravenous injection. Intramuscular injections are commonly delivered to the thigh muscles. To avoid the sciatic nerve, which travels down the lateral aspect of the femur (thigh), IM injections should be administered within the cranial or caudal aspect of the femur (thigh) or within lumbar muscles.

Pre-medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.02-0.04 mg/kg IM, SC, IV	Reduces bradycardia and hypersalivation. (10)
Glycopyrrolate	0.01-0.02 mg/kg SC, IM	Reduces bradycardia and hypersalivation. (10)
Acepromazine	Multiples doses in Plumbs: 0.01-0.20 mg/kg IM,SC, IV (slowly); "Common dose": 0.01-0.03 mg/kg IM, SC, IV	Dog max: 3 mg. Note: FDA labeled dose (0.55-2.2 mg/kg) is considered 10X > than necessary per most clinicians. (10)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance	Administer via precision vaporizer and compressed oxygen

Injectable Sedatives and Anesthetics

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	Multiples doses in Plumb: 0.01-0.20 mg/kg IM,SC, IV (slowly); Common dose: 0.01-0.03 mg/kg IM, SC, IV	Dog max: 3 mg. Note: FDA labeled dose (0.55-2.2 mg/kg) is considered 10X > than necessary per most clinicians. (10)
Midazolam	0.1-0.3 mg/kg SC, IM, IV	Combined with other premeds. (10)
Diazepam	0.5-1 mg/kg IV bolus	(10)
Dexmedetomidine	375 mcg/m^2 body surface area (BSA) IV or 500 BSA IM	See dosing table in drug package. Mcg/kg decrease as BW increases. (10)
Xylazine	1.1-2.2 mg/kg IM, IV	(10)
Propofol (PropofloFlo ® 28)	5-6 mg/kg IV induction 0.1 mg/kg/min maintenance of sedation	(10)
Tiletamine/zolazepam	Diagnostics: 6.6-9.9 mg/kg IM; Minor procedures: 9.9-13.2 mg/kg IM (FDA -approved dose)	Similar to ketamine/valium. (10)
Acepromazine Butorphanol	0.02-0.05 mg/kg IM 0.2 mg/kg IM	(1)

Butorphanol Dexmedetomidine	0.2 mg/kg IM 5-7.5 ug/kg IM	(1)
Pentobarbital	1-3 mg/kg/hr IV slowly	For chemical restraint, mechanical ventilation advisable. (10)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.005-0.03 mg/kg IM, IV, SC q 6-12 hr	DEA required. (10)
Buprenorphine SR™ Sustained release	0.03-0.06 mg/kg SC q 72 hr	Manufacturer: ZooPharm No longer requires refrigeration. DEA required (59) http://www.srvet.net/index.php/buprenorphine-hci-sr/companion-animals
Butorphanol	0.1-0.5 mg/kg IM, IV, SC q 2-4 hr	Extra-label if used as analgesic DEA required. (10)
Tramadol	4-10 mg/kg PO q SID- TID	Synthetic opiate-like drug, DEA required. (10)
NSAID		
Carprofen (Rimadyl ®)	2.2 (q12 hr) - 4.4 (q24 hr) mg/kg PO	(10)
Meloxicam (Metacam ®)	0.2 mg/kg PO, SC q 24 hr, subsequent dosing at 0.01 mg/kg PO, SC	(10)
Meloxicam Sustained Release (SR) Zoopharm™	0.6 mg/kg SC q 72 hours (70)	Manufacturer: ZooPharm 16-18G needle is recommended to draw-up from vial (makes syringe loading easier & minimizes handling loss). Administered to dog using needles as small as 23G. http://wildpharm.com/medications/companion-animals/item/65-meloxicamsr5mldog.html

FERRETS

Ferrets, unlike rodent species, are able to vomit and should therefore be fasted for 12 hours prior to anesthesia. Animals acclimated to handling can easily be restrained for injection of anesthetic agents. Ferrets also respond well to gas anesthesia. As with the cat, a properly fitted nose cone can be used to administer gas anesthesia after sedation. Furthermore, an induction chamber can be used but some animals may become excitable during this procedure with a release of catecholamines. Ferrets are easily intubated, but may develop laryngospasm. Topical application of 0.05 mL of a 2% lidocaine solution will prevent laryngospasm. Non-cuffed endotracheal tubes ranging from 2-3.5mm should be used. A non-rebreathing anesthesia circuit is recommend for ferrets. Body temperature is rapidly lost in small mammals such as ferrets. Recirculating hot water blankets and heated recovery areas are highly recommended.

Pre-medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.04 mg/kg IM	(1)
Glycopyrrolate	0.01 mg/kg IM	(1)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance	Administer via precision vaporizer and compressed oxygen. (1)

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.1-0.3 mg/kg IM	(1)
Xylazine	2 mg/kg IM, SC	(1)
Ketamine Xylazine	30 mg/kg IM 3 mg/kg IM	(1)
Ketamine Xylazine Butorphanol	35 mg/kg IM 5 mg/kg IM 1.0 mg/kg IM	(1)
Tiletamine/zolazepam Xylazine	3 mg/kg IM 3 mg/kg IM	(1)
Tiletamine/zolazepam Xylazine Butorphanol	1.5 mg/kg IM 1.5 mg/kg IM 0.2 mg/kg IM	Profound cardiorespiratory depression (1)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01-0.02 mg/kg SC, IV, IM q 6-8 hr	DEA required (1)
NSAID		
Carprofen (Rimadyl ®)	1 mg/kg SC, PO q 24 hr	(1,24)

Meloxicam (Metacam ®)	0.2 mg/kg SC, PO, IM q 24 hr	(1,24)

FISH

Immersion is the preferred method of anesthesia. This technique is analogous to gas induction chamber use for mammals. Agents are absorbed across the gills and exert their impact centrally. It is recommended that two separate tanks of water be used: one for induction and the other for recovery. In addition, animals should be fasted for 24 hours prior to anesthesia and maintained in a calm state until induced. Fish should be handled with wet gloved hands.

Loss of the equilibrium represents the first stages of anesthesia. Surgical anesthesia is attained when there is no response to stimuli and respiration rate is very slow. Gill movements should be maintained through anesthesia. If spontaneous gill movement ceases during anesthesia, the fish should be placed in a recovery bath to increase oxygenation through the gills.

In addition to emersions, traditional routes of drug administration used for mammalian anesthesia and analgesia may also be used with fish, including oral, intramuscular (IM, given above the lateral line under the dorsal fin), intravenous (IV), and intraperitoneal (IP) injection.

Although hypothermia to immobilize fish has been well established, there little evidence to date demonstrating the process provides sufficient anesthesia or analgesia (61).

Immersion Anesthesia

Agent(s)	Immersion bath dosages:	Comments/Reference(s)
Tricaine methanesulfonate (MS-222, tricaine, Fiquel ®	Species specific variation: Induction: 100-200 mg/L Maintenance: 50-100 mg/L	Anesthetic of choice for fish. MS-222 stock solution (10g/L) can be buffered with NaHCO3 at 10g/L or to complete saturation to reach pH of 7-7.5. Aerate water to prevent hypoxemia; narrower margin of safety in younger and/or warm water fish. (1, 24)

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Ketamine	10-80 mg/kg IM	Immobilization for short procedures; complete recovery can take > 1 hour. (24)

Analgesia Note: Considerable evidence supports the presence of mu and kappa opioid receptors in teleost fish and thus endogenous opioid system that might be manipulated to provide analgesia. In general however, specific drug and dosing regimens are still lacking for most fish including zebrafish (*Danio* spp), the species those most commonly used in biomedical research, (61)

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Butorphanol	0.05-0.1 mg/kg IM	General fish dose range for post-operative analgesia. (24) DEA required

GERBILS

Initial restrain of gerbils for administration of injectable anesthetics is fairly simple. Young and/or fairly active gerbils may however need to be induced with isoflurane in an anesthetic induction chamber prior to restraint for injection.

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen or drop method

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Xylazine	5-10 mg/kg SC, IM	(24)
Diazepam	3-5 mg/kg SC, IM	(24)
Midazolam	1-2 mg/kg SC, IM	(24)
Acepromazine	0.5-1.0 mg/kg IM	(24)
Ketamine Xylazine	50-70 mg/kg IP 2-3 mg/kg IP	(24)
Ketamine Diazepam	40-150 mg/kg IP 3-5 mg/kg IP	(24)
Tiletamine/Zolazepam	50-80 mg/kg IP	(24)
Pentobarbital	50-90 mg/kg IP	(24)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.1-0.2 mg/kg SC q 8 hr	DEA required. (24)
NSAID		
Carprofen (Rimadyl ®)	5 mg/kg SC q 24 hr	(24)
Meloxicam (Metacam ®)	0.5 mg/kg SC, PO q 24hr	(24)

GUINEA PIGS

Guinea pigs are among the most challenging rodents to safely and effectively anesthetize. In general, their response to injectable anesthetics is quite variable and post-anesthetic complications (respiratory infections, GI immobility, lethargy, anorexia) periodically do occur. Gas anesthesia produces consistent and reliable results. However, breath holding when animals are first exposed to irritating gas vapors has been reported. Endotracheal intubation of guinea pigs is difficult due to the narrow oral cavity and anatomy of the larynx and upper airway. Several highly effective methods for intubation have been reported (60).

Depth of anesthesia and effectiveness of analgesia is assessed by pinching the pinna with a small hemostat and lack of a pedal withdrawal. As with other small rodents, steps should be initiated to prevent hypothermia. A large cecum can act as a reservoir for anesthetics. Depending on drug solubility, the cecum can alter the pharmacologic effect.

Pre-medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.1-0.2 mg/kg SC, IM	Reduces oral and respiratory mucus secretions; (1)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance In general GPs are particularly sensitive; consider premeds to reduce isoflurane MAC	Administer via precision vaporizer and compressed oxygen; avoid use of an anesthetic chamber for induction as this species has a tendency for extreme breath holding. (1)

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.5-1.0 mg/kg IM	Sedation. (24)
Ketamine	20-40 mg/kg IM	(24)
Ketamine Xylazine	20-40 mg/kg IM 2 mg/kg IM	Light anesthesia; (24)
Ketamine Xylazine	40-120 mg/kg IM 10 mg/kg IM	Ketamine has wide margin of safety & dose range in GPs. (1)
Ketamine Acepromazine	40 mg/kg IM 0.5 mg/kg IM	(1,24)
Ketamine Dexmedetomidine	40 mg/kg IP 0.25 mg/kg IP	(24)
Tiletamine/Zolazepam Xylazine Butorphanol	60 mg/kg IP 5 mg/kg IP 0.1 mg/kg IP	(1)
Pentobarbital	30-45 mg/kg IP	(24)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.05 mg/kg SC q 8-12 hr	DEA required. (54)
NSAID		
Carprofen (Rimadyl ®)	1-4 mg/kg SC q 24 hr	(54)
Meloxicam (Metacam ®)	0.1-0.3 mg/kg SC, PO q 24 hr	(54)
Buprenorphine SR™ Lab Sustained release buprenorphine	0.3 mg/kg SC q 48-72 hr	Manufacturer: ZooPharm Note: GP, rat and mouse dose ranges are different. No longer requires refrigeration. DEA required http://www.srvet.net/index.php/buprenorphine-hci-lab/laboratory-animals

HAMSTERS

Hamsters are easily handled and restrained. Pre-anesthetic sedation is rarely indicated. Endotracheal intubation is complicated by the small size of the oral cavity and glottis. The oral cavity, in particular the cheek pouches should be examined and cleared of any stored food prior to intubation attempts. An effective, hamster-specific intubation method has been described (60). Additional peri-operative care and procedures for laboratory hamsters can be found in the following reference (60).

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.5-1.0 mg/kg IM	(24)
Ketamine	20-40 mg/kg IM 50-100 IP	Light/moderate sedation (24) Deep sedation; 54)
Xylazine	1-5mg/kg IP, IM	(54)
Ketamine Xylazine	60-80 mg/kg IP, IM 4-5 mg/kg IP, IM	(24)
Tiletamine/ Zolazepam (Telazol ®)	50-80 mg/kg IP	(54)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01- 0.5 mg/kg SC q 8-12 hr (wide range)	DEA required. (24,54)
NSAID		
Carprofen (Rimadyl ®)	5 mg/kg SC q 24 hr	(24)
Meloxicam (Metacam ®)	1-2 mg/kg SC, PO q 24 hr	(54)

MICE

Preoperative evaluation of rodents should include careful review of the colony health history, appearance and age of the animal. Complications associated with anesthetizing mice and other small rodents are often related to their size, high surface area to body weight ratio, susceptibility to hypothermia, limited venous access (a limited number of small diameter vessels) and relatively small laryngeal region (endotracheal intubation is possible but requires considerable operator skill). Additionally, most traditional injectable anesthetics used in veterinary medicine need to be diluted (with sterile saline or water) in order to ensure accurate dosing for small rodent species (54). Volume of drug, site of administration and irritant properties of the agent should also be considered when injecting rodents.

Fasting any small rodent species prior to surgery is not necessary since vomiting and/or regurgitation is not possible. Likewise, water should never be restricted.

Gas anesthesia induction is easily accomplished by placing the mouse in a closed chamber/box with appropriate anesthetic gas scavenging attached. Once writhing reflex is lost, the rodent may be removed from the induction chamber and maintained on gas delivered via a fitted nose cone or endotracheal tube. Nose cones are more frequently used with mice; endotracheal intubation requires considerably more training and purpose built equipment. An excellent video demonstration of mouse/rat intubation is available http://www.jove.com/video/53771/an-improved-method-for-rapid-intubation-of-the-trachea-in-mice. Modification of traditional anesthesia equipment may be necessary to accommodate the small size of the rodent.

Rodent anesthesia machines equipped with isoflurane vaporizers are available through Research Animal Resources.

Note: The following are generalized anesthesia and analgesia guidelines for laboratory mice. A second, more comprehensive document with recommendations specific for various mouse models has been created by the JHU RAR veterinarians and may be found on the JHU ACUC website.

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen or drop method

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Ketamine Xylazine	80-100 mg/kg IP 5-10 mg/kg IP	Surgical anesthesia (54)
Ketamine Acepromazine	100 mg/kg IP 5 mg/kg IP	Immobilization/anesthesia.(54)
Ketamine Midazolam	100 mg/kg IP 5 mg/kg IP	Immobilization/anesthesia.(54)
Ketamine Xylazine Acepromazine	80-100 mg/kg IP 10-20 mg/kg IP 2-3 mg/kg IP	Surgical anesthesia.(54)
Pentobarbital	40-60 mg/kg IP	Considerable dose variation by strain, gender, genetic modifications etc. Starting at low end of dose range is advisable. Note: Euthanasia dose is 90-100 mg/kg or greater.(54)

Tribromoethanol (Avertin)	200-500 mg/kg IP	Non-pharmaceutical grade; special preparation and storage required; Adverse effects likely with repeat dosing. (1)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.05 - 0.1 mg/kg SC, IP q 8-12 hr	DEA required; Preferred analgesic for rodents (1)
Buprenorphine SR™ Lab Sustained release buprenorphine	0.5-1.0 mg/kg SC q 72 hr *Mouse dose rage	Manufacturer: ZooPharm Note: Rat and mouse dose ranges are different. No longer requires refrigeration. DEA required (68, 69) http://www.srvet.net/index.php/buprenorphine-hci-lab/laboratory-animals
Animalgesics ® Buprenorphine Extended Release for Mice	3.25 mg/kg SC q 72 hr	Manufacturer: Animalgesics Note: Rat and mouse doses are different. DEA required. https://vetlabel.com/lib/vet/meds/animalgesics-for-mice-and-rats/
NSAID		
Carprofen (Rimadyl ®)	4-5 mg/kg SC q 24 hr	(1, 24)
Meloxicam (Metacam ®)	1-5 mg/kg SC q 24 hr	(24)
Meloxicam SR™ Lab Sustained release meloxicam	4 mg/kg SC q 72 hours (70)	Manufacturer: ZooPharm Note: Rat and mouse doses are the same. DEA required. 16-18G needle is recommended to draw-up from vial (makes syringe loading easier & minimizes handling loss). Can be administered to rodent using needles as small as 23G. http://www.srvet.net/index.php/meloxicam-srtm/labanimals

Local Block Analgesics

Agent(s)	Dose	Comments/Reference(s)
Lidocaine (1-2%)	Local infusion; do not exceed 7mg/kg	Onset: 5-10 min, Duration: 0.5-1 hr (21) Several methods of administration (field block, infiltrative block etc.). See overview of local blocks above
Bupivacaine (0.5% Marcaine)	Local infusion; do not exceed 8 mg/kg	Onset: 15-30 min, Duration: 4-8 hr (21) Several methods of administration (field block, infiltrative block etc.). See overview of local blocks above

NEONATAL MOUSE & RAT

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen or drop method. Good first choice (1)

Hypothermia Anesthesia:

Comments: When inhalant anesthesia is not available or can't be used safety, hypothermia is a relatively safe and effective alternative to injectable anesthetics in altricial rodents up to 7 days old (1).
Induction: Place the pup in a latex/nitrile glove finger and immerse the glove finger in crushed ice and water (2-3°C or 35-37°F) up to the level of the head so that the head of the pup is visible. Anesthesia induction takes 5-8 minutes.
Procedure: Remove the pup from the ice bath and place on a re-freezable ice pack. A piece of gauze or cloth should prevent direct contact of the pup's skin with the freezable ice pack. Duration of anesthesia on an ice pack is 15 minutes maximum.

Hypothermia Recovery: Rapid warming should be avoided. Pups can be placed in a small incubator (32-35 °C or 90-95°F) for gradual warming over 20-30 minutes. Once warmed for this time, circulating warm water blankets can be used until mobile where complete recovery takes 30-60 minutes. Once mobile, pups may be mingled with the litter to aid in covering the procedure smells on the pup then the litter returned to the dam.

Injectable Anesthesia:
In general, injectable anesthetics are not as safe as hypothermia or isoflurane in neonatal rodents < 6-7 days old. Several of the injectable combinations used in adult rodents have been found to be unpredictable and associated with a greater than > 50% mortality rate in neonates (1).
If injectable combinations are used, it is important to collect an accurate rate, calculate the correct dose, begin at the low end of the recommended dose range and only use the IP route. Also note the recovery period may be prolonged and hypothermia must be avoided by keeping the neonate warm as noted above

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NONHUMAN PRIMATES

When considering pre-anesthesia, anesthesia, and analgesia for nonhuman primates, one needs to consider the diversity of species and appropriate dosage and choice of drug. There is a wide range of body size and types of primates, and extrapolation of doses from primate to primate should be avoided. There are significant differences in responses to anesthetic agents between Old World (e.g. macaques, baboons) and New World (e.g. marmosets, owl monkeys, squirrel monkeys) nonhuman primates. Generally, New World monkeys require higher doses of anesthetics per kilogram body weight compared to Old World monkeys (ketamine), although this is not the case with all agents (opioids).

Careful clinical examination should be performed prior to any anesthetic procedure. Both Old World and New World nonhuman primates may vomit upon induction so withholding food for 12-16 hours and water 2 hours (depending on procedure) is advisable (64). An exception to this are nonhuman primates < 2 kg; food should not be withheld longer than 4 hours due to their higher metabolic rate and propensity to develop hypoglycemia (64). Most sedatives and anesthetics are given IM in consideration of safety for the animal handler, After initial IM sedation, additional drugs can be administered IV and/or the monkey can be intubated and maintained under gas anesthesia.

Depending on the species and surgical procedure, adjunct pre, intra and post-operative supportive care measures may be indicated. Examples include 1) use of pre and/or post-operative gastroprotectants (famotidine, omeprazole etc.) and anti-emetic/promotility drugs (maropitant, Cerenia ®) for GI surgeries (or any long duration procedure) 2) use of 5% dextrose in lactated ringers solution as the intra-operative IV fluid of choice for marmosets (any age) or macaques (typically only infants unless otherwise indicated based on blood work).

Old World NHPs: *Macaca* species (macaques) and *Papio* species (baboons)

Old World

Pre-medications

Agent(s)	Macaque dose	Baboon dose	Comments/Reference(s)
Atropine	0.025-0.05 mg/kg IV, SC, IM	0.025-0.05 mg/kg IV, SC, IM	Prevent/treat vagal-induced bradycardia, crosses BBB. (64,2)
Glycopyrrolate	0.005-0.01 mg/kg IV, SC, IM	0.005-0.01 mg/kg IM	Same as atropine but has less side effects & may be longer acting. Doesn't cross BBB, (1,64,65)
Acepromazine	0.1-0.5 mg/kg IM, IV		Mild-moderate sedative (alone) or combined with other injectables (ketamine) to prolong deep sedation (65)

Inhalant Anesthetics

Agent(s)	Macaque dose	Baboon dose	Comments/Reference(s)
Isoflurane	1-3% maintenance	1-3% maintenance	Administer via precision vaporizer and compressed oxygen

Injectable Anesthesia

Agent(s)	Macaque dose	Baboon dose	Comments/Reference(s)
Ketamine	10-15 mg/kg IM	5-10 mg/kg IM	Moderate sedation, immobilization. (1,64)

Midazolam	0.05-0.1 mg/kg IM, IV	0.05-0.3 mg/kg IM, IV	Sedation, muscle relaxation. Not general anesthetic alone. 100% bioavailable following IM admin with no associated injection site pain (1,64)
Diazepam	0.5-1.0 mg/kg IV	0.5-1.0 mg/kg IV	Sedation, muscle relaxation. Not general anesthetic alone. Reduced bioavailability following IM admin and potential injection site pain (1,64)
Ketamine Xylazine	10 mg/kg IM (K) + 0.5 mg/kg IM (X)	5-10 mg/kg IM (K) + 0.2- 0.5 mg/kg IM (X)	Surgical anesthesia, difficult to maintain normal physiologic parameters above this dose; risk of bradycardia & AV block (64)
Ketamine Midazolam	<1 kg: 15 mg/kg IM (K) + 0.05-0.09 mg/kg IV (M) >1kg: 5-15 mg/kg IM (K) +0.05-0.15 mg/kg IV (M)	5 mg/mg IM (K) + 0.1 mg/kg IM (M)	Immobilization to light surgical anesthesia (1,64,65)
Ketamine Diazepam	15 mg/kg IM (K) + 0.3 -1 mg/kg IM (D)	10 mg/kg IM (K) + 0.2-0.35 mg/kg IM (D)	Light surgical anesthesia. (1,64)
Ketamine Medetomidine	2-5 mg/kg IM (K) + .03 -0.05 mg/kg IM (M)	5 mg/kg IM (K) 0.1 mg/kg IM (M)	Sedation to light surgical anesthesia (64)
Alphaxalone	1-3 mg/kg bolus IV followed by 0.01-0.13 mg/kg/min IV		Neuroactive steroid. IV bolus and CRI are often preceded by initial sedation with ketamine +/- midazolam IM (64)
Propofol (PropofloFlo 28)	2.5-5.0 mg/kg IV bolus to effect then 0.3-0.4 mg/kg/min CRI	2.0-4.0 mg/kg IV bolus to effect then 0.16-0.64mg/kg/min CRI	(1, 64, 65)
Pentobarbital	20-30 mg/kg IV slowly to effect	25 mg/kg IV slowly to effect	(1)
Tiletamine/ zolazepam (Telazol ®)	2-6 mg/kg IM	2-6 mg/kg IM	Immobilization to deep sedation (64)

Analgesia

Agent(s)	Macaque dose	Baboon dose	Comments/Reference(s)
OPIOID			
Buprenorphine	0.01-0.02 mg/kg IV, IM, SC q 6-8 hr or 0.03 mg/kg IV, IM, SC q 24 hr	0.01-0.02 mg/kg IV, IM, SC q 6-8 hr or 0.03 mg/kg IV, IM, SC q 24 hr	High doses may lead to sedation and/or respiratory depression. DEA required (64)

Buprenorphine SR™ Sustained Release	0.2 mg/kg SC q 48 hr	0.2 mg/kg SC q 48 hr	Manufacturer: ZooPharm DEA required. No longer requires refrigeration. Macaque dose published (66), baboon dose unpublished but appears to be efficacious at macaque dose (JHU veterinary observation)
Butorphanol	0.003–0.02 mg/kg IM, SC q 2-4 hours (or once- if part of anesthetic regimen)		Mild to moderate analgesia no sedation or muscle relaxation. Serious respiratory depression possible with macaques, works synergistically with other drugs to prolong recovery (1)
NSAID			
Carprofen (Rimadyl ®)	2-4 mg/kg SC, PO q 24 hours	2-4 mg/kg SC, PO q 24 hours	Administration longer than 3 days is likely safe as long as clinical status and blood work is routinely evaluated (1, 64, 65)
Meloxicam (Metacam ®)	Loading dose: 0.2 mg/kg SC, PO once followed by 0.1 mg/kg q 24 hr x 2-3 days	Loading dose: 0.2 mg/kg SC, PO once followed by 0.1 mg/kg q 24 hr x 2-3 days	Same criteria for prolonged admin as carprofen. NSAID of choice for mild to moderate inflammation (post laparotomy, finger amp, tooth extraction etc.). Avoid post-headcap sx if dexamethasone is used. Never admin NSAIDs to NHPs < 6-8 weeks of age. Never admin concurrently with dexamethasone or any other NSAID. (1,64, 65)
Meloxicam SR™ Lab Sustained release meloxicam	0.60 mg/kg SC once every 48-72 hours* (70)	Safety and efficacy data not currently available for baboons	Manufacturer: ZooPharm DEA required. 16-18G needle is recommended to draw-up from vial (makes syringe loading easier & minimizes handling loss). http://www.srvet.net/index.php/meloxicam-srtm/labanimals

New World NHPs: *C*ommon marmoset (*Callithrix jacchus*) and Owl monkeys (*Aotus* species)

* Note: In contrast to most NW NHPs (marmosets, squirrel monkeys), owl monkeys have a low basal metabolic rate (18–24% below the predicted value for a 1 kg mammal). Some anesthetics may therefore need to be administered at a lower than expected dose for this species.

Pre-medications

Agent(s)	Owl monkey dose	Marmoset dose	Comments/Reference(s)
Atropine	0.025-0.05 mg/kg IV, SC, IM	0.025-0.05 mg/kg IV, SC, IM	Prevent/treat vagal-induced bradycardia, crosses BBB. (1, 64,)
Glycopyrrolate	0.005-0.01 mg/kg IV, SC, IM	0.005-0.01 mg/kg IM	Same as atropine but has less side effects & may be longer acting. Doesn't cross BBB (1, 64,)
Acepromazine		0.1-0.75 mg/kg IM, IV	Mild-moderate sedative (alone) or combined with other injectables (ketamine) to prolong deep sedation (1, 64,)

Inhalant Anesthetics

Agent(s)	Owl monkey dose	Marmoset dose	Comments/Reference(s)
Isoflurane	1-2% maintenance	1-2% maintenance *Ideally 1 - 1.5%	Administer via precision vaporizer and compressed oxygen. Moderate to severe respiratory depression possible; careful monitoring is essential. Maintenance anesthetic of choice for some unconscious neuroimaging (anatomical fMRI) studies

Injectable Anesthesia

Agent(s)	Owl monkey dose	Marmoset dose	Comments/Reference(s)
Ketamine	10 mg/kg IM	15-20 mg/kg IM	Moderate sedation, immobilization (1)
Midazolam	0.03-0.09 IM, IV	0.03-0.09 mg/kg IM, IV	Sedative, muscle relaxation. Not general anesthetic alone. (1,64)
Ketamine Acepromazine	Safety and efficacy data unavailable for *Aotus* spp	20-40 mg/kg IM 0.1-0.75 mg/kg IM	Used for major marmoset surgeries, neuroimaging and ABRs at JHU (+/- isoflurane for maintenance). Ace dose most often used: 0.50 mg/kg. Alternative to ace is midazolam 0.05 mg/kg (added benefit of muscle relaxation)

Ketamine Midazolam	Safety and efficacy data unavailable for *Aotus* spp	20-40 mg/kg IM 0.03-0.09 mg/kg IM	Used for major marmoset surgeries, neuroimaging and ABRs at JHU. Midazolam dose most often used: 0.05 mg/kg. Superior to ket/ace for muscle relaxation.
Propofol (PropofloFlo ® 28)	Safety and efficacy data unavailable for *Aotus* spp	Slow IV bolus to effect over 60-90 sec followed by 0.9 mg/kg/min	Requires CRI, dose varies widely (64), Maintenance anesthetic of choice for some unconscious neuroimaging (physiological fMRI) studies in combination with agent such as fentanyl
Alphaxalone (Alfaxan ®)	Safety and efficacy data unavailable for *Aotus* spp.	PE, radiographs= 5-7 mg/kg IM (JHU dose) 20-40 min procedure or surgery=10-12 mg/kg IM (71) CRI for advanced imaging or maintenance anesthesia for major surgery= 2-5 mg/kg bolus IV followed by 0.17 mg/kg/min IV *IV bolus & CRI are often preceded by initial IM dose of ketamine or alphaxalone (64)	Neuroactive steroid labeled as an induction agent (IV delivery), but safe and effective when given IM for short to moderately long procedures. Repeated IM redosing is also safe. Minimal to no cardiovascular or respiratory depression. Does not act on NMDA receptors (desirable for some areas of research). Larger than standard volume to admin IM (intended for large anima IV admin). May need to divide & admin in two separate IM locations on marmoset Muscle fasciculation may occur as marmosets recover (also true of cats), minimal to no clinical relevance, not seizure activity
Tiletamine/ zolazepam (Telazol ®)	Safety and efficacy data unavailable for *Aotus* spp	2-5 mg/kg IM	Immobilization to deep sedation (1,64)

Analgesia

Agent(s)	Owl monkey dose	Marmoset dose	Comments/Reference(s)
OPIOID			
Buprenorphine HCl	0.01 mg/kg SC, IM q 8-12hr (1)	0.005-0.01 mg/kg SC, IM q 8-12hr (1) Full or partial reversal with naloxone (0.1 mg/kg IM, IV Repeat admin PRN based on clinical response)	In general NW spp. are very sensitive to opioids and may exhibit profound respiratory depression following admin of doses > 0.01 mg/kg. Never administer sustained release formulations to marmosets (Bup SR) DEA required (1)
NSAID			
Meloxicam (Metacam ®)	Loading dose: 0.2 mg/kg SC once followed by 0.1 mg/kg q 24 hr x 2-3 days PRN	Loading dose: 0.2 mg/kg SC once followed by 0.1 mg/kg q 24 hr x 2-3 days PRN	NSAID of choice for mild to moderate inflammation (post laparotomy, finger amp, tooth extraction etc.). Never admin post-headcap sx if dexamethasone was administered. Never admin NSAIDs to NHPs < 6-8 weeks age. Never admin concurrently with dexamethasone or any other NSAID. Never administer sustained release formulations (meloxicam SR) (1,65)

Pigs

Documented anesthetic variability exists between domestic/conventional (Yorkshire, Duroc, Landrace etc.) and miniature/micro swine (Hanford, Yucatan, Gottingen etc.). Even within one breed of pig, notable physiologic differences in response to specific anesthetic regimens have been observed. Most miniature pigs used in research weigh between 5-30 kg. This not only facilitates easier and safer handling, but also allows for the use of significantly smaller drug volumes compared to domestic pigs.

Isoflurane is often considered the default general anesthetic for survival surgery in swine unless its use is contraindicated by the protocol. Whenever injectable anesthetics are used for maintenance anesthesia, they should be continuously infused, not delivered via repeated bolus injections (46).

Because swine are very prone to laryngospasm during endotracheal intubation, the larynx is often sprayed with a topical anesthetic such as cetacaine ® (Benzocaine 14.0%, Butamben 2.0%, Tetracaine Hydrochloride 2.0%) while being visualized with a laryngoscope. All pigs anesthetized for surgery or prolonged non-surgical procedures should be intubated so as to avoid fluid accumulation within the pharyngeal region. Intubation may be performed with pigs positioned in dorsal, ventral or lateral recumbency, however typically ventral is easiest for pigs > 50 kg (46). During the late fall through early spring months (November – April), prophylactic administration of long acting antibiotics to treat the five major agents associated with swine respiratory disease (*Actinobacillus pleuropneumoniae, Bordetella bronchiseptica Mycoplasma hyopneumoniae, Pasteurella multocida and Haemophilus parasuis*) is recommended. At Johns Hopkins, all swine assigned to non-acute terminal studies must undergo a seven day acclimation period that begins with one (conventional) or two (minipigs) doses of Ceftiofur (Excede ®, 7 days protection) or tulathromycin (Draxxin ®, 9 days protection). This greatly reduces the incidence of upper and/or lower respiratory tract infections that present as clinical problems during the post-operative recovery period.

Pre-medications

Agent(s)	Dose	Comments/Reference(s)
Atropine	0.02-0.05 mg/kg SC, IM, IV	Administer 10-15 min prior to intubation. Reduces bradycardia and hypersalivation; (24)
Glycopyrrolate	0.005-0.01 mg/kg SC, IM, IV	Reduces bradycardia and hypersalivation; (24)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance	Administer via precision vaporizer and compressed oxygen

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.2-1.1 mg/kg IM, IV, SC	Sedation only. (1)
Midazolam Butorphanol	0.1- 0.5 mg/kg IM 0.1-0.3 mg/kg IM	Combined for moderate sedation for blood draw, hoof trim etc., will not produce general anesthesia. (46)
Acepromazine Midazolam Butorphanol	0.2-1.1 mg/kg IM 0.1- 0.5 mg/kg IM 0.1-0.3 mg/kg IM	Combined for heavy sedation for blood draw, hoof trim etc., will not produce general anesthesia. (46)
Ketamine	11-33 mg/kg IM,IV	Caution: IV may only require ½ - 2/3^{rds} of IM dose- admin slowly to effect (1,46)

Ketamine Xylazine	20-30 mg/kg IM,IV 2.0 mg/kg IM,IV	Caution: IV may only require ½ - 2/3rds of IM dose- admin slowly to effect (1,46)
Ketamine Acepromazine	33.0 mg/kg IM,IV 1.1 mg/kg IM,IV	Caution: IV may only require ½ - 2/3rds of IM dose- admin slowly to effect (1,46)
Ketamine Midazolam	33 mg/kg IM,IV 0.1-0.5 mg IM,IV	Caution: IV may only require ½ - 2/3rds of IM dose- admin slowly to effect (1,46)
Ketamine Dexmedetomidine	10 mg/kg IM,IV 0.1 mg/kg IM,IV	Caution: IV may only require ½ - 2/3rds of IM dose- admin slowly to effect (1,46)
Tiletamine -Zolazepam (Telazol ®)	2-8.8 mg/kg IM, SC	Cardiovascular and respiratory depressive effects last longer than anesthesia effects following single admin. (46)
Tiletamine/ Zolazepam (Telazol ®) Xylazine	4-6 mg/kg IM, SC 2.2 mg/kg IM, SC	Cardiovascular and respiratory depressive effects last longer than anesthesia effects following single admin. (46)
Tiletamine/Zolazepam (Telazol ®) Ketamine Xylazine	4.4 mg/kg IM, SC 2.2 mg/kg IM, SC 2.2 mg/kg IM, SC All combined in one syringe	Cardiovascular and respiratory depressive effects last longer than anesthesia effects following single admin; Useful in pigs > 50 kg, less volume to inject compared to ketamine. (46)
Propofol (PropofloFlo28 ®)	0.83-1.66 mg/kg IV 12-20 mg/kg/hr CRI	(46)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01- 0.05 mg/kg IM, SC q 8-12 hr	DEA required. (46, 54)
Buprenorphine SR™ Sustained release	0.12 mg/kg SC q 48 hr	Manufacturer: ZooPharm No longer requires refrigeration. DEA required (67)
Fentanyl	0.02- 0.05 mg/kg IM, SC q 2 hours 30-100 µg/kg/hour IV drip	Note: Fentanyl transdermal patch efficacy is highly variable in swine and thus are not recommended as a primary means of analgesia. Must be monitored closely if used; overdosing is possible. (46)
NSAID		
Carprofen (Rimadyl ®)	2-3 mg/kg SC, PO q 24 hr	Recommended NSAID in swine. (46)
Meloxicam (Metacam ®)	0.1-0.3 mg/kg SC, PO q24 hr	(46)

RABBITS

Rabbits should be carefully evaluated prior to all anesthetic events in particular for signs of respiratory disease i.e. stertor (heavy snoring or gasping), stridor (high-pitched musical breathing), sneezing, oculonasal discharge, ptyalism (excessive drooling), abnormal cardiopulmonary auscultation, respiratory rate and rhythm. All clinical concerns should be brought to the immediate attention of an RAR veterinarian prior to administration of anesthetics.
Pre-operative fasting of rabbits is not advisable for several reasons including the inability of this species to vomit, naturally prolonged gastric emptying times (in excess of five days), and the potential for the rapid development of a metabolic acidotic and/or hypoglycemia state. Furthermore, post-operative gastrointestinal stasis is fairly common in rabbits and should be mitigated by providing an ample amount of fresh timothy hay to the animal upon return to home cage. Ideally rabbits should regain consciousness and begin eating as soon as possible. Additional supportive care measures for rabbits exist (pro-motility drugs etc.) and may be recommended by an RAR veterinarian.

Anesthetic drug dosages for rabbits are higher than for similarly sized cats or dogs. It is recommended each rabbit be weighed prior to the administration of drugs. The significant size of the rabbit's large intestines can lead to an over estimation of lean body mass. In addition, the cecum can act as a reservoir for anesthetics and alter drug effects. It may be beneficial to calculate the drug dose based on metabolic body size (weight in $kg^{0.75}$). In addition, age, sex, breed, pregnancy status and strain and time of day may affect the response to anesthetic agents. Drugs given intravenously should be given to effect. When giving intramuscular injections start at the lower end of the dose range.

Endotracheal intubation should be used whenever possible in particular for procedure lasting more than 5-10 minutes. With proper technique and selection of the correct ET tube, rabbits are not difficult to intubate (despite urban legend suggesting otherwise). Indeed, most individuals who routinely intubate rabbis find that the "blind placement technique" works well and is easy to teach others. Investigators new to rabbit anesthesia should contact the JHU RAR veterinarians or veterinary technicians for in-person training. Recommended tube sizes range from 2.0mm to 4.0mm inner diameter, uncuffed. Prior to intubation, a few drops of lidocaine (not to exceed 2 mg total) may be applied directly to the larynx to prevent laryngospasm. A non-rebreathing circuit (e.g. Jackson Rees) should be used with rabbits receiving gas anesthesia. In addition, supplemental oxygen is recommended for animals given barbiturates or other injectable agents that reduce respiratory function. The use of a pulse oximeter is advised in rabbits because anesthesia and the large gastrointestinal tract can decrease tidal volume and compromise respiratory function.

The depth of anesthesia is best indicated by response to ear pinch. The reliability of accepted reflex tests as indicators of anesthesia level have been rated (most to least reliable) as follows: pinna, pedal, corneal, palpebral reflex (60). Rabbits have high levels of circulating catecholamines. Sudden awareness of pain can lead to breath holding, which further increase circulating catecholamines and the possibility of fatal cardiac arrhythmias.

Injectable Agents for Pre-Medication

Agent(s)	Dose	Comments/Reference(s)
Glycopyrrolate	0.01 mg/kg IV 0.1 mg/kg SC, IM	Anticholinergic of choice to use as pre-anesthetic (atropine ineffective ~ 50% of time due to potential production of atropinesterase in this species) (24,54)
Acepromazine	0.5-1.0 mg/kg IM	Moderate sedation (1, 54)
Acepromazine Butorphanol	1.0 mg/kg IM 1.0 mg/kg IM	Moderate to heavy sedation, moderate analgesia (54)
Diazepam	0.5- 2 mg/kg IV	Light to moderate sedation (54)
Midazolam	0.5- 2 mg/kg IM, IV	Light to moderate sedation (54)

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	1-3% Maintenance	Administer via precision vaporizer and compressed oxygen; Not recommended for sole agent of induction due to potential for breath holding and distress (1)

Injectable Anesthesia ***Note:** In general Dutch Belted require lower doses of injectable agents than do NZW rabbits

Agent(s)	Dose	Comments/Reference(s)
Ketamine Acepromazine	30-40 mg/kg IM 1.0 mg/kg IM	Surgical anesthesia (54)
Ketamine Xylazine	20-40 mg/kg IM 1.0-3.0 mg/kg IM	RAR vet recommended for short procedures (injectable only) or as initial anesthesia prior to isoflurane maintenance.
Ketamine Midazolam	20-40 mg/kg IM 1.0-1.5 mg/kg IM	RAR vet recommended for short procedures (injectable only) or as initial anesthesia prior to isoflurane maintenance. Note: Sedative effect of midazolam lasts 2-4 hours, may not be best selection for short surgeries, recovery periods will be long
Ketamine Dexmedetomidine (Dexdomitor ®)	20-30 mg/kg IM 25-40 mcg/kg IM	RAR vet recommended for short procedures (injectable only) or as initial anesthesia prior to isoflurane maintenance. Note: Rapid recoveries, dexmedetomidine can be reversed with antipamezole (Antisedan ®). Safe to use with newborn kits and pregnant does.
Propofol (Propoflo 28 ®)	10 mg/kg IV slowly over 60-90 seconds	Induction/light anesthesia only. Note: Propofol is less effective in rabbits compared to other species. Higher doses (15-20 mg/kg) often result in respiratory arrest (54)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01-0.05 mg/kg SC, IV q 8-12 hr	DEA required (1, 54)
NSAID		
Carprofen (Rimadyl ®)	1.5 mg/k PO q24 hr 2-4 mg/kg SC q24 hr	(54)
Meloxicam (Metacam ®)	0.2-0.3 mg/kg SC, PO q 24 hr 0.6-1 mg/kg SC, PO q24 hr	(24) (54)
Meloxicam SR™ Lab Sustained release meloxicam	0.6 mg/kg SC q 72 hr	Manufacturer: ZooPharm http://wildpharm.com/meloxicamsr5mllab.html

Local Block Analgesics

Agent(s)	Dose	Comments/Reference(s)
Lidocaine (1-2%)	2-4 mg/kg SC	Onset: 5-10 min, Duration: 0.5-1 hr (21)
Bupivacaine (0.5% Marcaine)	1-2 mg/kg SC	Onset: 15-30 min, Duration: 4-8 hr (21)

RATS

Refer to overview information under Mice (similar general principles may be applied to rats).

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen or drop method

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Ketamine Xylazine	75-100 mg/kg IP 5-10 mg/kg IP	Provides a good surgical plane of anesthesia for most procedures (32) (54)
Ketamine Acepromazine	75 mg/kg IP 1- 2.5 mg/kg IP	Best used for prolonged restraint or minor surgical procedures (32, 54)
Ketamine Xylazine Acepromazine	40 mg/kg IP 5 mg/kg IP 1 mg/kg IP	Provides a good surgical plane of anesthesia for most procedures (32)
Ketamine Midazolam	75-100 mg/kg IP 4-5 mg/kg IP	Best used for prolonged restraint or minor surgical procedures (32)
Ketamine Dexmedetomidine (Dexdomitor ®)	75-100 mg/kg IP 0.15 mg/kg IP	Provides a good surgical plane of anesthesia for most procedures (54)
Pentobarbital	40-50 mg/kg IP	May provide a surgical plane of anesthesia however there is a wide range of dose variability and often a narrow safety margin; caution should be used to avoid overdoses (54)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Buprenorphine	0.01-0.05 mg/kg SC, IP q 6-12 hr	DEA required. (54)
Buprenorphine SR™ Lab Sustained release buprenorphine	1.0 -1.2 mg/kg SC q 72 hr *Rat dose range	Manufacturer: ZooPharm Note: Rat and mouse dose ranges are different. No longer requires refrigeration. DEA required (68, 69) http://www.srvet.net/index.php/buprenorphine-hci-lab/laboratory-animals
Animalgesics ® Buprenorphine Extended Release for Mice	0.65 mg/kg SC q 72 hr	Manufacturer: Animalgesics Note: Rat and mouse doses are different. DEA required. https://vetlabel.com/lib/vet/meds/animalgesics-for-mice-and-rats/
NSAID		
Carprofen (Rimadyl ®)	5-10 mg/kg SC, PO q 24 hr	For optimal analgesia, give NSAID and buprenorphine. (1, 24)
Meloxicam (Meloxicam ®)	1-2 mg/kg SC, PO q 24 hr	(24)

Meloxicam SR™ Lab Sustained release meloxicam	4 mg/kg SC q 72 hours (70)	Manufacturer: ZooPharm Note: Rat and mouse doses are the same. 16-18G needle is recommended to draw-up from vial (makes syringe loading easier & minimizes handling loss). Can be administered to rodent using needles as small as 23G. http://www.srvet.net/index.php/meloxicam-

RUMINANTS: SHEEP & GOAT

Pre-operative fasting of ruminants for up to 48 hours is recommended to reduce rumen volume. Even appropriately fasted ruminants will however require the placement of a stomach tube to prevent bloating and to protect the airway from regurgitated rumen contents. Excessive fasting beyond 48 hours should be avoided as it often results in decreased of rumen flora, hypomotility and ketosis in severe cases.

Administration of anticholinergics (atropine, glycopyyrolate) to decrease saliva volume is not recommended in ruminants because only the water component of saliva is reduced, the viscous mucus is left behind and may interfere with intubation. In addition, these drugs may impair GI motility (1).

Ventilation is easily impaired due to both bloating and the mass of abdominal viscera. The use of positive pressure ventilation is highly recommended. During inhalation anesthesia the palpebral reflex is depressed but not lost. The eyeball is rotated medioventrally when the patient is in a light surgical plane of anesthesia and center during deep anesthesia. A dilated pupil is a sign of anesthetic overdose.

Inhalant Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Isoflurane	3-5% Induction 1-3% Maintenance	Administer via precision vaporizer and compressed oxygen

Injectable Anesthesia

Agent(s)	Dose	Comments/Reference(s)
Acepromazine	0.02 mg/kg IM	Pre-anesthetic/sedative Long duration of action. Will prolong anesthesia recovery. Not an analgesic. Minimal depression (1)
Acepromazine Buprenorphine	0.05- 0.1 mg/kg IM 0.005-0.01 mg/kg IM	Pre-anesthetic/sedative (1, 50)
Xylazine	0.05- 0.2 mg/kg IV, IM	Pre-anesthetic/sedative (1, 50)
Ketamine Diazepam	4-5 mg/kg IV 0.4-0.5 mg/kg IV	Induction; Rapid onset, duration of effect 15 to 20 min allows intubation minimum regurgitation, little cardiopulmonary dysfunction (1, 50)
Ketamine Xylazine	Sheep: 3-5 mg/kg IM 0.03-0.05 mg/kg IM Goat: 3-5 mg/kg IM, IV 0.05- 0.10 mg/kg IM, IV	Good injectable combination for short procedures, moderate muscle relaxation (1,50)
Propofol (Propoflo 28 ®)	3-5 mg/kg induction 0.4-0.5 mg/kg/min CRI	Supplementation with local anesthesia or other systemic analgesic if surgery is performed (1, 50, 54)

Analgesia

Agent(s)	Dose	Comments/Reference(s)
OPIOID		
Butorphanol	0.1-0.5 mg/kg IM q 2-4h	DEA required (1)
Buprenorphine	0.005-0.01 mg/kg IV, IM, SC q4-6h	DEA required (1)
NSAID		
Carprofen (Rimadyl ®	2-4 mg/kg SC q 24 hr	Long plasma half life 48-72 (1, 10, 50)
Flunixin (Banamine ®)	1.1-2.2 mg/kg IV, IM q 8-24 hr	(10)
Phenylbutazone	2-6 mg/kg IV, PO q 24 hr	(10)

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