LARC FORMULARY

ANESTHESIA AND ANALGESIA FOR LABORATORY ANIMALS

Contents

I. OVERVIEW: STANDARD OF CARE IN ANIMAL PAIN MANAGEMENT

Animal anesthesia, analgesia and pain management are crucial components of the animal use protocol. The standard of care at OSU is to prevent animal pain whenever possible and to treat animal pain whenever diagnosed. Exceptions to these principles are permitted only in the minority of protocols approved by the Institutional Animal Care and Use Committee as USDA Category E.

Multi-modal anesthetic and analgesic regimens combine drugs from a variety of classes. They are designed to maximize the desired effects while minimizing unhealthy side effects that occur with reliance on a single agent.

The ideal anesthetic/analgesic regimen should:

1. Provide pre-emptive analgesia so that animal pain is already being treated as the general anesthetic is wearing off, to prevent sensitization ('ramp-up') of pain sensory mechanisms, and to lower the overall amount of general anesthetic required for the procedure.

2. Be precisely titratable to assure that animals receive adequate anesthesia to block pain sensation, to produce unconsciousness, and to produce immobility without experiencing hemodynamic instability or life-threatening anesthetic overdoses.

3. Not interfere with the animal's study.

4. Not result in unhealthy post-operative side-effects.

5. Not cause pain or distress on induction or recovery.

6. Be compatible with available equipment and available medications.

To meet number one above, LARC and IACUC advocate pre-emptive analgesia, using some combination of four drug classes 30 minutes or more prior to the start of surgery. The four classes of injectable drugs are:

- opioid analgesics (such as buprenorphine);
- non-steroidal anti-inflammatory drugs (such as carprofen, meloxicam, ibuprofen);
- dissociative anesthetic/sedatives (ketamine, tiletamine)
- local/regional anesthetics (lidocaine, bupivicaine, proparacaine)

The disadvantages of this approach are that they add pre-anesthetic injection that may be distressful to the animals, that some drugs may slow anesthesia recovery, and that some are Controlled Substances requiring special storage and recordkeeping.

Volatile anesthetics (isoflurane, sevoflurane) delivered via a precision vaporizer best meet the second goal. Adjusting the inhaled percentage of anesthetic gas to deepen anesthesia is far safer than repeated redosing of injected drugs. Volatile anesthetics are easier to decrease as well, even compared to drugs for which there is an injectable antagonist or reversal agent. A major shortcoming of the inhalant anesthetic agents is the lack of residual analgesia once the vaporizer is discontinued.

The best anesthetic plans are only as good as the skill and care with which they are applied. Training is available from the LARC veterinary staff. Veterinary consultation is encouraged when planning any potentially painful study and is required by law for USDA-covered species.

Drug dosages and frequencies of administration

Drugs should be listed in the protocol with approximate dose ranges. These are starting points which must be titrated up or down for the individual animal, or for the particular application (procedures conducted, animal age and strain differences). When laboratory experience finds that recommended dose ranges are consistently too high or too low for the particular application, the veterinarian should

be informed, and a protocol amendment submitted to the IACUC.

Anesthetics are always titrated to effect. It is not acceptable to conduct surgical procedures unless the animal is fully anesthetized.

Analgesic doses and frequencies are more difficult to gauge. Caution is required for overnight pain management. Most analgesics administered at 5 pm will not still be effective at 8 am the next morning. Newer, longer-lasting non-steroidal anti-inflammatory analgesics may have longer durations of action than available opioids; they are frequently co-administered with an opioid to combine potency of effect with duration of action.

Compounded drugs or diluted drugs may lose their efficacy more rapidly than the original bottle label indicates. Per LARC Policy the 'Beyond-Use-Date' for compounded or diluted drugs is 14 days, after which the drug can no longer be used in animals and must be discarded appropriately.

Safe and effective animal anesthesia

Plans for intra- and post-operative monitoring must be included in the ACUP, and then practiced as written and approved. Animals should be acclimated to their surroundings for 3-4 days prior to major procedures. Supplemental administration of warmed fluids (lactated ringers solution or isotonic saline) and maintenance of body temperature improve anesthetic safety for the animals.

II. SPECIES-SPECIFIC CONSIDERATIONS

In general, smaller animals have higher metabolic rates and frequently require higher doses at more frequent intervals to achieve the desired effect. Species, strain and age differences often overshadow this general principle however. It is always best to start with a drug regimen developed in the species, age and strain with which the Principal Investigator is working, rather than extrapolate from one species to another.

Mice

Isoflurane is encouraged as the first choice anesthetic in mice. It should be delivered as a known percentage (1-3% for maintenance; up to 5% for induction) in oxygen from a precision vaporizer.

Anesthetic monitoring of small rodents includes testing of rear foot reflexes *before* any incision is made, and continual observation of respiratory pattern, mucous membrane color and responsiveness to manipulations throughout the procedure. Rectal temperature and heart rate are monitored electronically during long or involved procedures.

Injectable anesthetics are typically administered by intraperitoneal route. Injectable analgesics and reversal agents are often administered by the subcutaneous or the intraperitoneal route. Intramuscular

injections must generally be avoided because of the small muscle mass. Diluting drugs in sterile saline solution will make it easier to accurately measure volume for injection. It may also make some drugs less irritating when injected. Dilution may decrease shelf-life; the LARC policy is to discard drugs within 14-days of dilution. Vials containing sterile, diluted drugs
must be labeled with the specific contents and the 14-day Beyond-Use-Date.

Ketamine-xylazine and ketamine-medetomidine combinations produce short-duration surgical anesthesia in larger species, but are frequently insufficient for major surgical procedures in many strains of mice. An excellent approach is to use a ketamine combination, but then titrate to effect with isoflurane from a precision vaporizer. Safety and efficacy should be demonstrated in a pilot group of animals before a large-scale study is initiated. It is possible to partially reverse xylazine or medetomidine using yohimbine or atipamezole, and doing so will restore cardiovascular status more quickly.

Mice are nocturnal animals, and are frequently housed in groups of nearly identical animals. These two factors make diagnosis of mild to moderate pain challenging. Weight loss is frequently monitored in animals at risk for ongoing pain. Pre-emptive treatment of pain is recommended before signs of pain are obvious.

Isoflurane provides no post-operative pain relief. If used for surgery, it will be necessary to use an analgesic during and/or after the procedure to provide pain relief. LARC veterinary staff recommend injecting the analgesic 30 minutes prior to the *start* of surgery.

Rats

Rat anesthesia and analgesia considerations are similar to mouse anesthesia considerations, though some doses vary. In rats, ketamine combinations are more likely to provide adequate surgical anesthesia than in mice, and so may not require supplemental isoflurane.

Hamsters

Hamster anesthesia is similar to rat and mouse anesthesia, though some doses differ. Peripheral veins are extremely difficult to access in hamsters, limiting some of the anesthetic options.

Rabbits

OSU works only with *Pasteurella*-negative rabbits, greatly reducing the risk of respiratory disease under anesthesia. Long procedures are best performed using inhalant anesthesia with an endotracheal tube in place. LARC staff are available to train researchers in this technique. Rabbits are easily stressed and should be pre-medicated prior to induction with inhalant anesthetics. Pre-operative fasting is unnecessary in this species and may increase the risk of gastrointestinal stasis during the recovery period.

Guinea Pigs

Guinea pigs can be difficult to anesthetize, especially on a survival basis. Intravenous injection is difficult. Intramuscular injection is acceptable for non-survival procedures, but animals may self-mutilate at injection sites if they recover from anesthesia. Intraperitoneal (IP) administration works well, if the large cecum is avoided. Guinea pigs may be anesthetized by face mask with volatile anesthetics; endotracheal intubation requires specialized training.

Cats

Cats are readily anesthetized using a variety of injectable or inhalant methods.

Initial restraint of a fractious or frightened cat can be a challenge for the researcher's safety and for the animal's welfare; choice of technique will depend on the skill level of the researchers as well as the individual cat's temperament. Intravenous injection of a fractious cat requires a very high level of skill. Chamber induction with isoflurane can be stressful to the cat, and poses occupational exposure risk to the workers. Intramuscular or subcutaneous injection of sedatives requires a moderate level of skill, and carries some risk of cat bites and scratches. Training is available through the LARC veterinary staff.

Non-steroidal anti-inflammatory drugs are useful, but must be used with caution in cats. Do not exceed recommended doses or frequencies of administration. Acetaminophen is NEVER used with cats.

Dogs

Dogs are easily anesthetized with a variety of techniques. Intramuscular injection of ketamine or ketamine combinations are to be avoided, because of the incidence of behavioral disturbances.

Pigs

Pigs are easily anesthetized with a variety of techniques. Ketamine-xylazine is a common intramuscular sedative, but requires a large volume of injection. Use of Telazol® or Telazol® combinations can significantly reduce the volume of injection for larger animals. Visualization of the larynx can be challenging in this species. Proper positioning, lidocaine spray to prevent laryngospasm, and use of an ET tube introducer will facilitate successful intubation. The ear veins provide the most convenient means of venous access.

Sheep

Sheep anesthesia is challenging because of the animals' large size and the unusual ruminant digestive physiology and anatomy. It is essential to intubate ruminants to protect their airway during general anesthesia as regurgitation of ruminal contents occurs frequently even with fasting. The benefits and duration of pre-procedural fasting in small ruminants is controversial. Adult sheep may have food

withheld for 24 hours prior to general anesthesia, though they should be allowed access to water.

Amphibians

Immersion anesthesia (buffered tricaine methanesulfonate, or MS-222) is common, especially for fully aquatic species like *Xenopus*. Post-operative pain management can include local infiltration of bupivicaine or with systemic xylazine.

Fish

Immersion anesthetics (buffered MS-222, etomidate, eugenol) are the most commonly used anesthetics for fish. Water in the induction tank should be aerated and similar to the normal tank water with regard to temperature and pH. During induction and anesthesia, fish should be monitored for voluntary locomotor activity, ability to maintain equilibrium in the water, rate of opercular movement, reflex response, and muscle tone. Sedation or light anesthesia may be sufficient for imaging, skin scrape sampling, and obtaining weights. For more invasive procedures, monitored responses should be consistent with a surgical plane of anesthesia before proceeding. During procedures care must be taken to prevent desiccation and skin damage from handling.

Birds

Birds may be anesthetized by inhalation anesthetics (such as isoflurane) or injectable anesthetics. For small birds, fasting is not generally required in advance, however fasting may be beneficial for larger birds such as commercial chicken breeds. It is vital to maintain adequate warmth during the anesthetic period.

III. COMMONLY USED ANESTHETICS AND ANALGESICS

Inhalant agents

Isoflurane and Sevoflurane

The standard inhalant anesthetics for laboratory animal use are either isoflurane or sevoflurane, delivered to effect in concentrations of 1-3% in oxygen (up to 5% for initial induction), using a precision vaporizer.

Advantages: Advantages of inhalant agents include rapid induction and recovery, with the ability to precisely titrate the level of anesthesia.

Disadvantages: Disadvantages include the cost and logistics of using precision vaporizers, occupational exposure concerns, the risk of fatal over dosage if an open system is used instead of a precision vaporizer, and depressed respiratory rate and decreased blood pressure. In addition, once animals

awaken from gas anesthesia, there is no residual analgesic activity.
Concurrent use of ketamine combinations and/or opioid and/or non-steroidal anti-inflammatory analgesics is strongly encouraged if the procedure is likely to result in any residual pain.

Several individual laboratories have their own isoflurane vaporizers, and the LARC maintains several vaporizers for laboratory use both within and outside of rodent barrier facilities
Occupational safety is a serious concern. Inhalants must be directly vented out of the room, or (less reliable), adsorbed in a charcoal canister filter. Filters must be weighed and replaced before they reach target weight (usually an increase of 50 gm).

Other inhalant agents

Other agents and techniques may be used for inhalant anesthesia, only when specifically approved by the IACUC in the animal use protocol.

Ether is an irritant and a fire hazard, and its use is discouraged at OSU.

Carbon dioxide is a potent anesthetic, but concentrations are difficult to control, making the margin of safety unacceptably low.

Injectable agents

Ketamine & Tiletamine (Dissociative anesthetics)

Ketamine is a widely used anesthetic in a variety of species. In low doses, ketamine provides chemical restraint with some analgesia. In higher doses, it may provide short-term surgical anesthesia in some species. In most instances, ketamine is used in combination with other injectable agents.

Tiletamine is similar to ketamine; it is primarily used in combination with zolazepam as the drug Telazol.

Advantages of ketamine: Advantages of ketamine are its wide margin of safety in most species and its analgesic action. In combination with other drugs, it can provide surgical plane of anesthesia for about one half hour.

Disadvantages of ketamine: Disadvantages of ketamine include some irritancy due to low pH, and insufficient anesthesia in some species and strains (especially mice) for some procedures. Ketamine is a Class III controlled substance.

Advantages of Telazol: A low volume of injection is required. Like ketamine combinations, it can occasionally produce short-term anesthesia, though rarely of sufficient depth for surgery. It is more useful as an induction agent prior to general inhalant anesthesia, or for chemical restraint for short non-

surgical procedures.

Disadvantages of Telazol: Telazol must be stored under refrigeration once reconstituted. It is not safe for use in rabbits (kidney disease). Telazol is a Class III controlled substance.

Ketamine combinations:
Ketamine-a2-agonists (Xylazine or Medetomidine)

Ketamine may be combined with the a2-agonists Xylazine or Medetomidine in the same syringe to produce a deep level of sedation. In some situations in some species and strains an adequate depth of anesthesia for surgery may be attained. In other cases, this sedation may require an inhalant agent

to achieve surgical anesthesia. It is generally safer to titrate to effect with inhalant anesthetic from a precision vaporizer than with supplemental injections of ketamine.

Advantages: Advantages of ketamine-a2-agonist combinations are that they may be combined in one syringe, that they may produce short-term surgical anesthesia with good analgesia, and that recovery can be hastened by reversing the a2-agonist with Atipamezole or Yohimbine.

Disadvantages: Disadvantages of ketamine-a2-agonist combinations are that they will not reliably reach surgical anesthesia in all cases, and that they can cause profound cardiac depression. Xylazine may cause vomiting, especially in cats. Ketamine is a Class III controlled substance**.**

Caution for use: If a ketamine a2-agonist combination is used for surgery longer than 20 minutes, animals will likely require additional anesthetic. Redosing with ketamine rather than the combination is usually safer, as the cardiovascular depression of a2-agonists is often longer-lasting than the sedation or analgesia produced.

Adding acepromazine to the ketamine-a2-agonist combination may result in deeper and/or longer plane of anesthesia in small rodents, especially rats, and possibly some mouse strains as well.

Ketamine-benzodiazepines (Midazolam or Diazepam): Ketamine may be combined with the benzodiazepines, Midazolam or Diazepam, in the same syringe to produce a deep level of sedation. In most cases, this sedation will require an inhalant agent or other anesthetic to achieve surgical anesthesia. In most applications, Midazolam is preferred, as it can be injected intramuscularly; intramuscular injection of propylene glycol (the carrier in injectable diazepam) can cause painful, sterile abscesses and is discouraged.

Advantages: Advantages of ketamine-benzodiazepine combinations are that they may be combined in one syringe and will produce deep sedation with moderate analgesia as well as amnesia.
Recovery from ketamine-midazolam is often smoother than recovery from ketamine alone.

Disadvantages: Disadvantages of ketamine- benzodiazepine combinations are that they will not reliably reach surgical anesthesia in most cases. Diazepam should be restricted to intravenous or intraperitoneal use. Ketamine is a Class III controlled substance while the benzodiazepines are in Class IV.

Pharmacologically, Telazol is a dissociate-benzodiazepine combination. *Barbiturates*
Though superseded in most applications by newer anesthetics, barbiturates still have their place in the animal laboratory. They are most frequently used in terminal or acute studies, as recovery can be prolonged and unpleasant, especially in larger animals. Barbiturates are often the anesthetic of choice when neurophysiological recordings are being conducted, such as visual or auditory evoked responses. Concurrent use of an analgesic (opioid or non-steroidal anti-inflammatory drug) is encouraged as it may improve pain relief with barbiturate use, and lower the required dose of barbiturate.

Sodium pentobarbital (Nembutal) and sodium thiopental (Pentothal) are currently the two most commonly used barbiturates. The duration of action of pentobarbital is considerably longer than that of thiopental.

Advantages: Barbiturates do not depress cortical evoked responses to the extent that other anesthetics might. Animals do not feel pain when they are at a surgical plane of anesthesia. Once stable anesthesia has been achieved, it may be longer lasting than with most other injectable agents. Barbiturates are the most common of the injected euthanasia solutions, as they reliably produce unconsciousness before respiratory depression and death.

Disadvantages: Disadvantages of barbiturates include a narrow margin of safety, primarily associated with respiratory depression. Pain sensation is only decreased at surgical planes of unconsciousness, and may even be heightened (hyperalgesia) at subanesthetic doses. Larger animals may experience a distressful anesthetic recovery. Outside of the vein (perivascular, or intraperitoneal) barbiturates can be irritating; barbiturates for IP injection should be diluted to a strength of 6 mg/kg. Barbiturates are Class II controlled substances, except for some Class III euthanasia solutions.

a2-agonists (Xylazine or Medetomidine)

The a2-agonists (Xylazine or Medetomidine) are hypnotic analgesics with significant pain relief. Used as sole agents, they do not produce sufficient depth of anesthesia for even minor surgical procedures. Combined with ketamine, and possibly supplemented with inhalants or local or topical analgesics [link to local anesthetics later in document], they may be useful during surgery. In some species, medetomidine appears to lead to greater anesthetic depth than does xylazine, and it is more reliably antagonized by atipamezole.

Advantages: a2-agonists produce profound analgesia of short duration, can be combined with ketamine (and in rodents, acepromazine) to produce deeper anesthesia, they are not controlled substances, and they are reversible with IP or subcutaneous atipamezole (yohimbine is sometimes used for xylazine reversal). They are nonirritating when injected via intramuscular or intraperitoneal routes.

Disadvantages: Disadvantages in most species include cardiovascular depression (decreased heart rate, decreased cardiac output, and hypotension), which is somewhat controlled by use of atropine or glycopyrrolate. a2-agonists cause a transient hyperglycemia which may have research implications. Xylazine often causes transient nausea and vomiting, especially in cats. Rapid IV administration of reversal agent has produced seizures in some species.

Caution for use: If a ketamine a2-agonist combination is used for surgery longer than 20 minutes, animals will likely require additional anesthetic. Redosing with ketamine rather than the combination is usually safer, as the cardiovascular depression of a2-agonists is often longer-lasting than the sedation or analgesia produced.

Propofol

Propofol can produce general anesthesia in animals, as a sole agent with continuous infusion for surgery, or as a pre-anesthetic for endotracheal intubation. It is valued for its fast recovery time, even after prolonged administration.

Advantages: Animals recover from propofol in minutes, even after prolonged administration.

Disadvantages: Propofol has minimal analgesia at sub-anesthetic doses. It can be a profound respiratory depressant, and may also cause hypotension. Because of its rapid elimination, it must be administered IV, and so is of limited use in small rodents. Unused propofol from an opened ampule should be discarded after use and not stored for future use.

Opioids

Opioid drugs are important components of many surgical anesthesia regimens, and are the most potent available post-procedural analgesics. Drugs in this group vary in their potency as well as their duration of action. Fentanyl, oxymorphone, buprenorphine and butorphanol are the most commonly used opioids in laboratory animal care, though others may be used on occasion. Fentanyl is the most potent of the three, but also the shortest acting. Buprenorphine is longer-acting and is good for most post-operative applications. Butorphanol may be more efficacious than buprenorphine for birds and for cats. Buprenorphine and butorphanol are mixed agonist/antagonists at different opioid receptors; they produce a less profound respiratory depression than full agonists, but also have a “ceiling effect” in the degree of analgesia produced with increasing doses.

Opioids are most often administered by injection. Oral use is effective, but requires much higher doses because of “first-pass” liver metabolism when absorbed from the gut.

Pre-emptive analgesic use is strongly recommended -- buprenorphine may be administered when the

general anesthetic is administered, or at any time during surgery. Respiratory depression is minimal, though sleep time may be lengthened. Pre-emptive use enhances pain management during the immediate post-surgical period. Though it increases animal handling (a stressor), administration of the analgesic 30 minutes prior to the initial surgical incision maximizes the analgesic efficacy in most situations.

Advantages: Opioids are potent analgesics. Concurrent use with inhalant or barbiturate general anesthesia will lower the required dose of the anesthetic.

Disadvantages: Opioids can suppress respiration (more marked effect in fentanyl than in buprenorphine). Opioids may increase locomotor activity, and may cause pica (abnormal ingestion of non-food items such as bedding) in rats. Alternatively, they may sometimes cause sleepiness and slower recovery from general anesthesia. Fentanyl has a very short duration of action in most animal species. Opioids are controlled substances.

Cautions for use: Buprenorphine has found favor as the longest-acting opioid analgesic. However, this duration of action is closer to 6 hours in most situations than it is to 12 hours. 12 hours is the absolute maximum dosing interval for use of buprenorphine for post-procedural pain.

Non-steroidal anti-inflammatory drugs (NSAIDs)
The advent of newer, more potent, more specific anti-inflammatory agents has increased their usefulness in laboratory animal use. Most reduce fever, reduce inflammation, and provide varying degrees of analgesia (acetaminophen does not significantly reduce inflammation).

Advantages: Carprofen, ketoprofen, ketorolac, and meloxicam may have duration of analgesic action up to 24 hours. They may be used concurrently with anesthetics, with opioid analgesics, and with local anesthetic/analgesics. Injectable NSAIDs are useful for accurate dosage and administration to small rodents. They are not controlled substances (some are by veterinary prescription only), and must be obtained through the LARC.

Disadvantages: NSAIDs may decrease clotting ability, of possible concern following surgery. Gastric upset and even ulceration may occur, especially with prolonged use. Prolonged use carries the risk of kidney or liver disease.

Cautions for use: Cats are particularly susceptible to toxic effects of NSAIDs. Acetaminophen is never administered to cats; other NSAIDs should be used only at the dose and frequency recommended.

Undesired side effects are more likely with prolonged usage -- for most situations, limit use of NSAIDs to 3-4 days per animal, except under veterinary supervision. Do not use in dehydrated animals, or in animals with kidney or liver dysfunction.

Local anesthetic/analgesic drugs (lidocaine and bupivicaine)

Local anesthetic/analgesic drugs (lidocaine and bupivicaine) may be useful both during surgery, and post-operatively. They block nerve conduction when applied locally at sufficient concentration. Lidocaine has a fast onset of action, and provides a couple of hours of analgesia. Bupivicaine has a slower onset of action (up to 30 minutes) but provides up to 12 hours of residual analgesia. Both are infiltrated subcutaneously at the surgical site, or (especially in larger animals) may be used regionally (epidural, intrathecal, intercostal). Lidocaine may also be administered as a constant rate infusion (CRI) as a component of a "balanced anesthesia" protocol, resulting in a reduced concentration of required inhalant anesthetic. A veterinarian should be consulted prior to use or inclusion in an ACUP.

Lidocaine cream (EMLA or ELAMax) is used topically on shaved, intact skin prior to venipuncture, though it requires 30-60 minutes or more of contact with skin to reach full effect.

Tricaine methanesulfonate (MS-222) is a related compound used as a general anesthetic for fish and frogs.

Advantages: Intra-operative use can augment the pain relief of general anesthetics, and reduce the need for frequent redosing. Bupivicaine can augment the post-operative analgesic action of opioids and/or NSAIDs. They are not controlled substances. At appropriate doses, they have minimal cardiovascular effect.

Disadvantages: Intramuscular and intravenous injection should both be avoided. Systemic toxicity (including seizures and death) can result from overdosage (more likely to occur with smaller subjects) and with accidental intravenous injection. Lidocaine may sting when first injected.

Miscellaneous agents

Urethane, choral hydrate, equithesin, sodium thiamylal, a-chloralose, and tribromoethanol have some specialized uses in laboratory animal anesthesia. The use of these agents should be discussed with a LARC veterinarian.

IV. Selected species-specific anesthesia-analgesia information

MICE

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

All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted. Dilution of injected drugs allows more precise dosing, but may shorten the shelf-life of the compound. (OSU standard: diluted drugs should be labeled, then discarded after 14 days.)

DRUG NAME	DOSE (mg/kg) & ROUTE	FREQUENCY	NOTES
Inhalation anesthetics			
Recommended: Isoflurane or Sevoflurane	1-3% inhalant to effect (up to 5% for induction). Up to 8% for Sevoflurane	Whenever general anesthesia is required	Survival surgery requires concurrent preemptive analgesia. Must use precision vaporizer
Carbon dioxide	To effect (cannot determine percentage)	Once, at time of euthanasia	May be used for fast terminal procedure followed by euthanasia
Ketamine combinations			
Recommended: Ketamine-Xylazine-Acepromazine	70-100 (K) + 10-20 (X) + 2-3 (A) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole or Yohimbine.
Ketamine-Medetomidine	50-75 (K) + 0.5 -1 (M) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole.
Ketamine-Xylazine	80-100 (K) + 5-10 (X) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole or Yohimbine.

Ketamine-Midazolam	80-100 (K) + 4-5 (M) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint.
Ketamine alone	100-200 IP	As needed	Deep sedation, but not surgical anesthesia. Not often used alone.
Reversal agents			
Atipamezole	0.1 - 1.0 SC or IP	Any time medetomidine or xylazine has been used	More specific for medetomidine than for xylazine (as a general rule, Atipamezole is dosed at the same *volume* as Medetomidine, though they are manufactured at different concentrations).
Yohimbine	1.0 – 2.0 SC or IP	For reversal of xylazine effects	
Other injectable anesthetics			
Sodium pento-barbital (Nembutal)	40 – 50 IP	Recommended for terminal/acute procedures only, with booster doses as needed	Consider supplemental analgesia (opioid or NSAID) for invasive procedures
Opioid analgesia			
Recommended: Buprenorphine	0.05 - 0.1 SC or IP	Used pre-operatively for preemptive analgesia and post- operatively every 4-12 hours	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.
Non-steroidal anti-inflammatory analgesia (NSAID) Note that prolonged use my cause renal, gastrointestinal, or other problems			
Recommended: Carprofen	5-10 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Recommended: Meloxicam	~ 5-10 PO or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	2 – 5 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Local anesthetic/analgesics (lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia)			
Lidocaine hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

RATS

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

All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted. Dilution of injected drugs allows more precise dosing, but may shorten the shelf-life of the compound (OSU standard: diluted drugs should be labeled, then discarded after 14 days).

DRUG NAME	DOSE (mg/kg) & ROUTE	FREQUENCY	NOTES
Inhalation anesthetics			
Recommended: Isoflurane or Sevoflurane	1-3% inhalant to effect (up to 5% for induction). Up to 8% for Sevoflurane	Whenever general anesthesia is required	Survival surgery requires concurrent preemptive analgesia. Must use precision vaporizer
Carbon dioxide	To effect (cannot determine percentage)	Once, at time of euthanasia	May be used for fast terminal procedure followed by euthanasia
Ketamine combinations			

Recommended: Ketamine-Xylazine	75-100 (K) + 5-10 (X) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures, though more reliable than in mice. If redosing, use ketamine alone. May be partially reversed with Atipamezole or Yohimbine
Ketamine-Medetomidine	75-100 (K) + ~0.5-1 (M) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole.
Ketamine-Xylazine-Acepromazine	40-50 (K) + 2.5-8 (X) + 0.75-4 (A) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole or Yohimbine
Ketamine-Midazolam	75-100 (K) + 4-5 (M) IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint.
Ketamine alone	75-100 IP	As needed	Deep sedation, but not surgical anesthesia. Not often used alone.
Reversal agents			
Atipamezole	0.1 - 1.0 SC or IP	Any time medetomidine or xylazine has been used	More specific for medetomidine than for xylazine (as a general rule, Atipamezole is dosed at the same *volume* as Medetomidine, though they are manufactured at different concentrations)
Yohimbine	1.0 – 2.0 SC or IP	For reversal of xylazine effects	
Other injectable anesthetics			
Sodium Pentobarbital (Nembutal)	40 – 50 IP	Recommended for terminal/acute procedures only, with booster doses as needed. May occasionally be appropriate for survival procedures	Consider supplemental analgesia (opioid or NSAID) for invasive procedures, especially when used on a survival basis.

Opioid analgesia			
Recommended: Buprenorphine	0.01 - 0.05 SC or IP	Used pre-operatively for preemptive analgesia and post-operatively every 4-12hrs	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.
Non-steroidal anti-inflammatory analgesia (NSAID) Note that prolonged use my cause renal, gastrointestinal, or other problems			
Recommended: Carprofen	4-5 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Recommended: Meloxicam	~ 2.0 PO, IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	2 – 5 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Local anesthetic/analgesics (lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia)			
Lidocaine hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision, or before final skin closure	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

GUINEA PIGS

Analgesia: Buprenorphine 0.05 mg/kg SQ every 8-12 hours

Guinea pigs can be difficult to anesthetize, especially on a survival basis. Intravenous injection is difficult. Intramuscular injection is acceptable for non-survival procedures, though animals may self-mutilate at injection sites if they have recovered from anesthesia. Intraperitoneal (IP) administration works well, if the large cecum can be avoided. Guinea pigs may be anesthetized by facemask with volatile anesthetics;

endotracheal intubation requires specialized training.
(Same drugs as listed for mice and rats. Contact LARC Veterinary Staff for doses.)

HAMSTERS
Analgesia: Buprenorphine 0.01-05 mg/kg SQ, every 6-12 hours

Hamster anesthesia is similar to rat and mouse anesthesia, though some anesthetic doses differ slightly. Peripheral veins are extremely difficult to access in hamsters, limiting some of the anesthetic options.
(Same drugs as listed for mice and rats. Contact LARC Veterinary Staff for doses.)

RABBITS
Rabbits can be challenging anesthetic patients due to their temperament, difficult endotracheal intubation, and propensity for developing gastrointestinal stasis post-operatively. Intravenous access is available via the marginal ear veins. Endotracheal intubation requires specialized training as their anatomy makes visualization of the larynx difficult. *(Similar drugs as listed for mice and rats. Contact LARC Veterinary Staff for doses.)*

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

All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted. *Note: Selected drug doses are listed below from the Oregon State University Veterinary Teaching Hospital Anesthesia Formulary, 2015. For a more complete swine formulary please refer to the OSU VTH Anesthesia Formulary.*

DRUG NAME	DOSE (mg/kg) & ROUTE	FREQUENCY	NOTES
Inhalation anesthetics			
Recommended: Isoflurane or Sevoflurane	1-3% inhalant to effect (up to 5% for induction). Up to 8% for Sevoflurane	Whenever general anesthesia is required	Concurrent preemptive analgesia is recommended for survival surgery Must use precision vaporizer. Mask induction is possible with very small pigs.
Dissociative (Ketamine and/or Telazol®) combinations			
Recommended: Xylazine-Ketmaine	2.2 (X) IM + 15 minutes later 10-15 (K) IM	Induction	Can result in large volumes – consider using Telazol® or Telazol® combination as alternative

Telazol® alone (a combination of tiletamine and zolazepam – when reconstituted with 5 ml sterile water, a vial contains 50 mg/ml of each drug.)	2.2 mg/kg IV if unsedated, 1.5-2 mg/kg if sedated	Induction	Note that Telazol® must be stored refrigerated once reconstituted.
Recommended: Telazol®-Ketamine-Xylazine (TKX) Add 2.5 ml xylazine and 2.5 ml ketamine to vial of Telazol	1 ml cocktail per 35-75 kg IM	For sedation or pre-anesthesia	Note that Telazol® must be stored refrigerated once reconstituted. To mix: reconstitute Telazol® with 'large animal xylazine (100mg/ml) and 100 mg/ml ketamine
Xylazine – Telazol®	2.2 mg/kg (X) IM + 6 mg/kg (T) IM	For sedation or pre-anesthesia	Note that Telazol® must be stored refrigerated once reconstituted. To mix: reconstitute Telazol® with 5 ml. of 'large animal xylazine (100mg/ml) instead of water.
Reversal agents			
Atipamezole	See comments for dosing, subcutaneous or IM	Any time medetomidine or xylazine has been used	More specific for medetomidine than for xylazine (as a general rule, Atipamezole is dosed at the same *volume* as Medetomidine, though they are manufactured at different concentrations).
Other injectable anesthetics and tranquilizers			
Propofol	4-8 mg/kg IV or 0.1-0.6 mg/kg/min IV as a CRI	As induction agent, or CRI for anesthetic maintanence	Respiratory depression upon induction is possible.

Midazolam	0.1-0.5 mg/kg IM or intranasally	Helpful for facilitating non-painful procedures and to reduce stress	
Acepromazine	0.04-0.4 mg/kg IM (maximum 15 mg)	Premedication	Usually only used in conjunction with anesthetics. Acepromazine is a tranquilizer and does not confer analgesia.
Opioid analgesia			
Recommended: Buprenorphine	0.01 - 0.05 IM	Used pre-operatively for preemptive analgesia and post-operatively every 8-12hrs	Consider multi-modal analgesia with NSAID and local analgesic.
Butorphanol	0.05-0.2 mg/kg IM	Used pre-operatively for preemptive analgesia	Consider multi- modal analgesia with a NSAID
Morphine	0.2-1.0 mg/kg IM	Post- operatively every 4-6 hrs	Consider multi- modal analgesia with a NSAID
Fentanyl	2-10 µg/kg IM	Premedication	A fentanyl patch may be used, consult a LARC vet for dosing instructions
Non-steroidal anti-inflammatory analgesia (NSAID) -- Note that prolonged use my cause renal, gastrointestinal, or other problems			
Recommended: Carprofen	2.2 mg/kg IM 2 – 3 mg/kg PO	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days.	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.
Flunixin	2.2 mg/kg IM	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.

Meloxicam	0.2 – 0.3 PO, IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days.	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.
Ketoprofen	1.0 – 2.0 PO. IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days.	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.
Local anesthetic/analgesics (lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia)			
Lidocaine hydrochloride	May dilute to 0.5 -1% (=10mg/ml). May be mixed in same syringe with bupivacaine. SC or intra- incisional	Use locally before making surgical incision	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	May dilute to 0.25 – 0.5%, May be mixed in same syringe with lidocaine. SC or intra- incisional	Use locally before making surgical incision	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

CATS

Cats may be anesthetized with a variety of techniques. Drug doses for premedication, anesthetic induction, anesthetic maintenance, and analgesia may be found in the Oregon State University Veterinary Teaching Hospital Anesthesia Formulary.

DOGS

Dogs may be anesthetized with a variety of techniques. All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted. *Note: Selected drug doses are listed below from the Oregon State University Veterinary Teaching Hospital Anesthesia Formulary, 2015. For a more complete canine formulary please refer to the OSU VTH Anesthesia Formulary.*

DRUG NAME	DOSE (mg/kg) & ROUTE	FREQUENCY	NOTES
Inhalation anesthetics			
Recommended: Isoflurane or Sevoflurane	1-3% inhalant to effect (up to 5% for induction). Up to 8% for Sevoflurane	Whenever general anesthesia is required	Survival surgery requires concurrent preemptive analgesia. Must use precision vaporizer

Dissociative combinations			
Ketamine-Midazolam	5.0 -7.5 mg/kg (K) IV + 0.2-0.4 mg/kg (M) IV	Induction	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint. Note that IM Ketamine combinations often sting upon injection.
Ketamine-Diazepam	5.0 -7.5 mg/kg (K) IV + 0.2-0.4 mg/kg (D) IV	Induction	May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint. Note that IM Ketamine combinations often sting upon injection.
Tiletamine-Zolazepam (Telazol®) when reconstituted, a vial contains 50 mg/ml of each drug.	2-5 mg/kg IV	Induction	Note that Telazol® must be stored refrigerated once reconstituted.
Reversal agents			
Atipamezole	0.1-0.3 mg/kg IM	Any time medetomidine or xylazine has been used	More specific for medetomidine than for xylazine (as a general rule, Atipamezole is dosed at the same *volume* as Medetomidine, though they are manufactured at different concentrations)
Other injectable anesthetics and tranquilizers			
Propofol	3-5 mg/kg IV (with sedation) 4-8 mg/kg IV (w/o prior sedation) 0.1-0.6 mg/kg per min IV for CRI	Induction Maintenance	May cause respiratory depression on induction Unused propofol from an opened ampule should be discarded after use and not stored for future use.
Acepromazine	0.05-0.1 mg/kg IM, SC (alone) 0.01-0.05 mg/kg IM, SC (in combination)	Used in pre-medication combinations and for sedation	Acepromazine is a tranquilizer and does not confer analgesia.

Dexmed-etomidine	5-15 µg/kg IV (alone) 3-5 µg/kg IV (in combination)	Used in pre-medication combinations and for sedation	Can be reversed with atipamezole (see above) May cause vasoconstriction and reflex bradycardia.
Midazolam	0.2-0.4 mg/kg IM	Used in pre-medication combinations and for sedation	
Opioid analgesia			
Recommended: Buprenorphine	5-20 µg/kg IM	Used pre-operatively for preemptive analgesia and post-operatively every 8-12hrs	Consider multi-modal analgesia with NSAID and local analgesic.
Butorphanol	0.1-0.4 mg/kg IM	Used in pre-medication combinations, for sedation, and post-operative analgesia (give every 1-4 hours)	Consider multi-modal analgesia with a NSAID
Hydromorphone	0.05-0.2 mg/kg IM, IV	Used in pre-medication combinations and post-operatively every 4-6 hours	More potent but shorter duration than buprenorphine
Oxymorphone	0.03-0.1 mg/kg IM	Used in pre-medication combinations and post-operatively every 4-6 hours	More potent but shorter duration than buprenorphine
Fentanyl	For CRI: 2-5 µg/kg IV followed by 0.03 – 0.4 µg/kg/min IV Transdermal patch: 2-4 µg /kg/h	Used for intraoperative and post-operative analgesia	For the fentanyl patch onset is 12-24 h duration 72 h. Available in 25, 50, 75, and 100 µg /h sizes
Tramadol	2-5 mg/kg	Used post-operatively every 8-12 hours	Consider multi-modal analgesia with a NSAID
Non-steroidal anti-inflammatory analgesia (NSAID) Note that prolonged use my cause renal, gastrointestinal, or other problems			
Recommended: Carprofen	2.2 mg/kg PO, SC, IM, IV	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.

Recommended: Meloxicam	0.2 mg/kg once followed by 0.1 mg/kg every 24 h PO, IM, SC, or IV	Used pre-operatively for preemptive analgesia and post-operatively every 24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid.
Deracoxib	1-2 mg/kg PO	Used for analgesia every 24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid
Firocoxib	5 mg/kg PO	Used for analgesia every 24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with an opioid
Local anesthetic/analgesics (lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia)			
Lidocaine hydrochloride	2-5 mg/kg SC or intraincisional Do not exceed 10 mg/kg total dose	Use locally before making surgical incision, or before final skin closure	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	2 mg/kg SC or intraincisional Do not exceed 5 mg/kg total dose	Use locally before making surgical incision, or before final skin closure	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

FISH

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

DRUG NAME	DOSE (mg/kg) & ROUTE	FREQUENCY	NOTES
Immersion anesthetics			
Recommended: Tricaine Methane-sulphonate (MS-222)	100-150 mg/L for surgical anesthesia for most small to medium-sized fish (including adult zebrafish)	Whenever general anesthesia is required Lower concentrations (20-30 mg/L) may be useful for sedation for noninvasive or brief procedures (weighting, transport, etc.)	Must be buffered before use with sodium bicarbonate. MS-222 powder can be irritating, mix with appropriate personal protective equipment Tricaine-S® (Western Chemical) is the currently available FDA-approved product

Eugenol (Clove Oil, Aqui- S®)	2-5 ppm for sedation 60-100 ppm general anesthesia	Whenever sedation or anesthesia is required	Because an FDA-approved product for fish anesthesia exists, the use of eugenol should be justified in the ACUP

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Special thanks to the University of California, San Francisco, Animal Care Program for sharing their 2011 Formulary material with Oregon State University, Laboratory Animal Resources Center.