

GUIDELINES FOR THE USE OF ANESTHETICS, ANALGESICS AND TRANQUILIZERS IN LABORATORY ANIMALS

(<http://www.ahc.umn.edu/rar/anesthesia.html>)

What is Anesthesia?

Anesthesia is a state of unconsciousness induced in an animal. The three components of anesthesia are *analgesia* (pain relief), *amnesia* (loss of memory) and *immobilization*. The drugs used to achieve anesthesia usually have varying effects in each of these areas. Some drugs may be used individually to achieve all three. Others have only analgesic or sedative properties and may be used individually for these purposes or in combination with other drugs to achieve full anesthesia.

Curariform skeletal muscle relaxants or neuromuscular blockers (*e.g. succinylcholine, decamethonium, curare, gallamine, pancuronium*) are not anesthetics and have no analgesic effects. They may only be used in conjunction with general anesthetics. Normally, artificial respiration must be provided. Physiologic monitoring methods must also be used to assess anesthetic depth, as normal reflex methods will not be reliable.

It is important to realize that anesthesia is not a simple thing. It has profound effects on an animal's physiology because of the generalized central nervous system effects as well as specific effects on all other body systems. Thus, while anesthesia is necessary to prevent pain or distress in research animals, it must not be ventured into lightly. It is important to learn about the drugs you will be using and about the physiology of the animal you will be monitoring. Specific [anesthetic drugs](#) and their use are detailed below. All drug dosages are listed in the [formulary](#). Click [here](#) for Standard Post-Operative Analgesic Regimens for Sheep, Pigs, and Dogs.

Intra-operative and Anesthesia Records

The Guide for the Care and Use of Laboratory Animals and the *Institutional Animal Care and Use Committee Guidebook* require that animals under anesthesia be carefully monitored to insure adequate depth of anesthesia, animal homeostasis, timely attention to problems, and support during anesthetic recovery. Monitoring includes, but is not limited to, checking anesthetic depth and physiological parameters (minimum: heart rate and respiratory rate) on a regular basis (minimum every 10 minutes).

Record keeping is an essential component of perioperative care. For major surgical procedures on non-rodent mammals, an [intra-operative anesthetic record](#) must be kept and included with the surgeon's report as part of the animal's records. In addition to the above requirements, the record should include all drugs administered to the animal, noting the dose, time, and route of administration. These records should be available to LARAC and any other personnel providing post-operative care. Although it is not required, LARAC strongly encourages the use of an intra-operative rodent anesthetic record during surgical procedures.

The required monitoring will vary according to the species and the complexity of the procedure, but should include:

- A pre-surgical assessment;
- Adequate monitoring of anesthetic depth and homeostasis
- Support such as fluid supplementation, external heat, or ventilation
- Monitoring and support during anesthetic recovery
- Post-operative monitoring

The following are suggestions from the American College of Veterinary Anesthesiology for monitoring anesthetized animals:

1. Circulation: to ensure that blood flow to the tissues is adequate.
 - a. Methods: Heart rate, Palpation of peripheral pulses, ECG, auscultation of heartbeat, non-invasive or invasive blood pressure monitoring.
2. Oxygenation: to ensure adequate oxygen concentration in the animal's arterial blood.
 - a. Methods: observation of mucous membranes color and CRT, pulse oximetry, blood gas analysis
3. Ventilation: to ensure that the animal's ventilation is adequately maintained.
 - a. Methods: respiratory rate, observation of thoracic wall movement or breathing bag movement if animal is spontaneously breathing, auscultation of breath sounds, respiratory monitor, capnography, blood gas monitoring.

What is Analgesia?

Analgesia is the relief of pain. Pain is normally defined as an unpleasant sensory and emotional experience associated with potential or actual tissue damage. Pain is difficult to assess in animals because of the inability to communicate directly about what the animal is experiencing. Instead, indirect [signs of pain](#) are often used. Because of the difficulty of determining when an animal is in pain, animal welfare regulations require that analgesia be provided whenever a procedure is being performed or a condition is present that is likely to cause pain. In the absence of evidence to the contrary, it is assumed that something that is painful in a human will also be painful in an animal. It is best if analgesia can be provided to animals *preemptively*, or prior to the painful procedure, rather than waiting until after clinical signs of pain are observed. Analgesia is normally provided using one of [several types of pharmaceutical preparations](#).

Drug Selection

Inhalation Anesthetics

General

Inhalation anesthesia is superior to most injectable forms of anesthesia in safety and efficacy. It is easy to adjust the anesthetic depth. Because the anesthetics are eliminated

from the blood by exhalation, with less reliance on drug metabolism to remove the drug from the body, there is less chance for drug-induced toxicity. Inhalation anesthetics are always administered to effect, because the dosage can vary greatly among individual animals and different animal species. The disadvantages to inhalant anesthesia are the complexity and cost of the equipment needed to administer the anesthesia, and potential hazards to personnel. All inhalant drugs are volatile liquids. They should not be stored in animal rooms because the vapors are either flammable or toxic to inhale over extended periods of time. In particular, [ether](#) must be stored in a proper hood or cabinet for flammable materials.

Inhalant Agents

Drug	MAC	Response	Toxicity	Comments
Ether	3.2	slow	liver	Pre-medication with an anticholinergic may be necessary to reduce excessive respiratory secretions. Induction and recovery can be rough. Flammable and can become explosive with prolonged storage. Ether must be used according to appropriate safety guidelines .
Chloroform				A hazardous agent (carcinogenic) and cannot be used at U of M. It has good analgesic activity, but there is significant metabolism, ++ respiratory depression and + cardiac depression. This drug is not currently being manufactured. For a replacement, consider ether or diluted isoflurane.
Methoxyflurane	0.2	slow	nephrotoxicity- is potentiated by tetracyclines	
Halothane	0.9	moderate	hepato- and nephrotoxicity if the animal is hypotensive	++ cardiopulmonary depression, and a risk of malignant hyperthermia in some breeds/strains
Isoflurane	1.5	fast	none	++ respiratory depression and + cardiovascular depression
Enflurane	2.0	fast	none	++ cardiopulmonary depression and minimal respiratory depression
Nitrous Oxide	180	very fast	hepatotoxic	Cannot be used as a sole anesthetic agent. Do not exceed a 50% mix w/ oxygen and other inhalant agent to prevent hypoxia. Moderate analgesia is provided by nitrous. In general, use of nitrous oxide in animals is

Carbon Dioxide (CO₂) 50-70 very fast cerebral anoxia

discouraged.

Can be used as an anesthetic for brief procedures and as a euthanasia agent. It has antinociceptive activity and causes unconsciousness prior to hypoxia. It is necessary to monitor carefully and work quickly, as animals die quickly (1-2 min) after losing consciousness, and likewise they wake up quickly when exposed to room air. Appropriate for quick procedures such as tail snipping, ear marking and orbital bleeding. Poses minimal hazard to personnel and can be used in laboratories or animal room

MAC: This is the % concentration of the drug needed to anesthetize 50% of animals. It does vary somewhat by species and by individual. 1.2X MAC is an approximate vaporizer setting for maintenance of anesthesia. Induction generally requires 2-3X MAC. MAC listed here is for rats (ether), mice (CO₂), goat (enflurane) and dogs (all others).

Response. This refers to how rapidly concentrations in the blood change when the lung alveolar concentration is changed. Slow anesthetics have slow induction and recovery times.

Toxicity: Drugs that are metabolized by the body can cause toxicity, especially if a pre-existing organ dysfunction exists.

Injectable Anesthetics, Analgesics and Sedatives

1. [General](#)
2. [Route of Administration](#)
3. [Local Anesthetics](#), and [Fish and Amphibian anesthesia](#)
4. [Phenothiazine and Buterophenone Sedatives](#) (Acepromazine)
5. [Benzodiazapines](#) (Diazepam, midazolam)
6. [Thiazines](#) (Xylazine and medetomidine)
7. [Opiate analgesics](#)
8. [Barbiturates](#)
9. [Dissociative Anesthetics](#) (Ketamine and Telazol)
10. Other Anesthetics ([Alpha Chloralose](#), [Tribromoethanol](#), [Urethane](#))
11. [Other Analgesics](#)
12. [Analgesia in Rats and Mice](#)
13. [Anesthetic Drug Combinations](#)

General

Some of the drugs listed here do not possess all three criteria for an anesthetic and must be used in combinations to achieve full anesthesia or may be administered individually for restraint, sedation or analgesia. Dosages for specific animals are linked from RAR's formulary. Often injectable drugs are used in [combinations](#). These drugs tend to have synergistic effects. Mixing them can significantly reduce the dosage needed for any individual drug.

As with inhalation anesthesia, injectables are given to effect. Dosages listed are guidelines. Effects may vary among individuals. If a drug is scheduled by the Controlled Substances Act of 1970, licenses are required to purchase them, and written records must be kept of their use. University [policy](#) outlines these requirements. Anesthetic drugs that have exceeded their expiration date [may not be used](#), even for terminal procedures

Injectable anesthetics are, in general, metabolized by the liver and excreted by the kidneys. Animals with liver or kidney disease should not be anesthetized with these agents. Inhalation anesthetics are safer for use in sick or debilitated animals, because there is minimal metabolism, the amount of anesthetic administered can be controlled and one can cease administration as the situation dictates. Injectable anesthetics offer the advantage of requiring less expensive equipment.

Local Anesthetics

The generic and brand names of local anesthetics often have the suffix "*caine*". Common local anesthetics are procaine (Novacaine), bupivacaine, [lidocaine](#) (Xylocaine) and proparicaine. Considerable experience and skill are necessary in the administration of local anesthetics to animals, and aseptic techniques must be employed. Some animals must be sedated before local anesthetics are injected.

Local anesthetics may be administered by several techniques. Anesthetic effects are seen within 15 minutes of administration and may last from 45 minutes to several hours, depending on the drug used.

- *Infiltration or infusion*- injection beneath the skin and other tissue layers along the site of an incision before or after a procedure
- *Field block, ring block*- injection into soft tissues distant from the actual incision in a pattern that intersects the nerve supplying the surgical site
- *Nerve conduction block*- infusion of a small amount of drug or directly adjacent to the sheath of a nerve supplying the surgical site
- *Regional or spinal anesthesia*- injection into the vertebral canal, epidurally or into the sub-arachnoid space. To avoid systemic toxicity, care must always be taken not to inject local anesthetics into blood vessels.
- Topical local anesthetics, such as lidocaine jelly, may be useful for some surgical wounds.

- Proparicaine may be used as a local anesthetic during retroorbital blood collection from mice. One drop on the eye, wait 10-15 minutes before performing the procedure.

An interesting use of local anesthetics is for **amphibian and fish anesthesia**. Tricaine and benzocaine can be added to water at a dose of from 25-100 mg/L, depending on the depth of anesthesia required. When the fish loses equilibrium (floats belly up) or an amphibian becomes inactive, it can be handled. For longer procedures, intermittent supplementation of anesthetic treated water to the gills or skin may be required. The animal is recovered in fresh water.

Phenothiazine and Buterophenone Sedatives

These sedatives include [acepromazine](#), [chlorpromazine](#), droperidol ([Innovar-Vet](#)) and [azaperone](#) (Stresnil). These drugs have excellent sedative properties, as well as muscle relaxation, antiemetic and antiarrhythmogenic effects. They have no analgesic activity, but when administered with other anesthetics can potentiate their effect. Acepromazine is the most commonly used. It is recommended as a sole sedative in dogs and as an anesthetic premedication to improve both induction and recovery (it is long acting) in all species. Droperidol is usually only available in combination with the narcotic, fentanyl (Innovar-vet) and has been associated with aggressive behavior in dogs.

Disadvantages of these sedatives are that they are alpha adrenergic blockers and cause peripheral vasodilation which can lead to hypothermia. They may have prolonged activity in sight hounds. Acepromazine and chlorpromazine decrease seizure threshold, and are contraindicated in animals with CNS lesions. Because these sedatives lack analgesic activity it is important to realize that any painful stimulation of the animal may cause it to emerge rapidly from the sedated state.

Benzodiazapines

The benzodiazapines include [diazepam](#) (Valium), [midazolam](#) (Versed) and [zolazepam](#) (Telazol). These drugs are anti-anxiety and anticonvulsant drugs with good muscle relaxation. They have minimal cardiovascular and respiratory effects. Sedation is minimal in most species, except for swine and nonhuman primates. The primary use of these drugs in anesthesia is in combination with other drugs. Ketamine-diazepam, midazolam-narcotic, and tiletamine-zolazepam (Telazol) combinations can be very useful for induction of general anesthesia and for short procedures. These drugs are regulated by the Controlled Substances Act and require special record keeping.

Thiazines

The thiazine derivatives include [xylazine](#) and [medetomidine](#). These two drugs are very similar. They are alpha-2 adrenergic agonists. They cause CNS depression

resulting in sedation, emesis and mild analgesia. They also cause hypotension, second degree atrio-ventricular block and bradycardia. Occasionally, aggressive behavior changes have been seen in dogs. They are very useful in combination with other drugs, like ketamine for anesthesia in rodents and swine. They are best avoided in dogs, cats and nonhuman primates, primarily because their significant side-effects can be avoided by using other drugs. They can be used alone for minor procedures in ruminants. *It is important to note that the dose for these drugs in ruminants is 1/10 that used in other species.* The effects of the thiazine derivatives can be reversed with [yohimbine](#) or [atapimazole](#). Use of these drugs with the reversal agent shortens anesthetic recovery and greatly expands the safety and utility of these drugs. Xylazine is a potent analgesic in frogs appropriate for relief of post-surgical pain.

Opiates

The opiates, sometimes referred to as narcotics, are a large class of drugs that exert their effects on the opiate receptors in the central nervous system. Depending on the receptors a drug is active against, and the type of action it has on the receptor, the effects of narcotics can be primarily analgesic, as with [buprenorphine](#) (Buprenex), [pentazocine](#) (Talwin) and [nalbuphine](#) (Nubain), or a mixture of analgesia and euphoria with sedation as with [butorphanol](#) (Torbugesic), fentanyl ([Innovar-Vet](#)), [morphine](#), [meperidine](#) (Demerol) or [oxymorphone](#). Opiates have little effect on the myocardium. However, there can be significant respiratory depression, as well as other side-effects such as nausea and vomiting, delayed gastric emptying, hypotension, and bradycardia. Some species may develop hyperexcitability if given certain opiates. These side-effects are seen more with the mixed effect opiates than the pure analgesics. [Naloxone](#) is a opiate antagonist that can be used to reverse the effects of other narcotics. Other opiates, like buprenorphine, nalbuphine and nalorphine, have mixed agonist-antagonist effects and may interfere with the effects of concurrently administered narcotics. All opiates are controlled substances and their use requires special record keeping. These drugs can be given alone as a post-procedural analgesic or in combination with other agents to provide balanced anesthesia, restraint with analgesia for minor procedures, or can be used to decrease the dose of an anesthetic that is needed to provide a surgical plane of anesthesia.

Don't forget to follow the University **Controlled Substances [Policy](#)**

Barbiturates

The barbiturates are an acid ring molecule with various ring substitutes that imbue the drug with different properties. Barbiturates are also considered narcotics.

- [Phenobarbital](#) is the longest-acting of the barbiturates. Its use is limited primarily to sedation or as an anticonvulsant.

- [Pentobarbital](#) is a short-acting oxybarbiturate. It is usually used as a sole anesthetic agent, or is supplemented with an analgesic. When given intravenously, about 50-75% of the calculated dose is administered. Within several minutes the animal will lose consciousness, although it may experience a brief period of excitement. When the jaw muscle tone is relaxed, the animal should be intubated. If given intraperitoneally, usually the entire dose of pentobarbital is given and surgery can be performed when the animal no longer reacts to a toe pinch. Anesthesia from pentobarbital can last from 45-120 min, depending on the dose given. Additional drug can be supplemented as needed, being careful not to overdose as described below under "Precautions".
- [Thiopental](#) and [Thiamylal](#) are thiobarbiturates that are considered ultra-short acting. Similar to these is methohexital which is an oxybarbiturate. Because of the extremely short duration of activity (up to 10 min with methohexital, up to 15-20 min with thiopental or thiamylal) of these drugs, they are usually used as an intravenous anesthetic induction agent to allow intubation prior to use of inhalant anesthesia. Use is similar to that described for pentobarbital. However, when low doses are given IV, there may only be several minutes of anesthesia before the animal begins to waken. This is desirable as an induction agent. If higher doses are give for longer effect, care must be taken not to overdose as described below under "Precautions". Longer anesthesia may be seen when these drugs are used intraperitoneally in rodents.
- **Effects and Side Effects** In general the barbiturates cause generalized central nervous system depression, which can be dosed to provide sedation or general anesthesia. The drugs also have an anticonvulsant effect. Analgesia provided by the barbiturates is poor and a relatively deep plane of anesthesia is required for surgery, unless used in combination with analgesics. The barbiturates have significant cardiopulmonary depression, with apnea and hypotension commonly seen. Anesthetic death is common in animals that are not receiving [supportive care](#). The barbiturates induce hepatic microsomal enzymes and may increase the metabolic rate of other drugs. Tolerance to the barbiturates develops with repeated use and doses may have to be adjusted accordingly.
- **Precautions**
 - Barbiturates are poorly water soluble and are only available in intravenous preparations, although they are frequently administered intraperitoneally to smaller animals with limited venous access. Because of their acidic properties, barbiturates can be irritating when administered intraperitoneal, or if any leak from the intravenous injection site. Perivascular barbiturates can result in significant tissue necrosis and skin sloughing. If any barbiturate leaks (a visible swelling is seen during injection), the best thing to do is to infuse the area with sterile saline at several times the volume of the original leak. Some people recommend mixing the

saline with 2% lidocaine to prevent pain and subsequent self-trauma.

- The barbiturates redistribute rapidly into all body tissues, including fat. Redistribution is one way that the drug is eliminated from the blood and obese animals may require higher doses of barbiturates to induce anesthesia. However, once the fat becomes saturated with the drug, metabolism becomes the primary means of elimination. Because metabolism is much slower, a common problem in administering barbiturates is overdosing with prolonged anesthetic recoveries (up to several days). Because of this problem it is best to titrate the dose carefully rather than administer large boluses. For obese animals, alternative anesthetics might be considered, although to a greater or lesser extent, most anesthetics share this problem when administered to obese animals. Prolonged anesthetic recovery can also be a problem when barbiturates are used in older animals or other animals with compromised hepatic and renal function which decreases metabolism of the drugs.
- Barbiturates are also controlled substances and their use requires special record keeping. [University **Controlled Substances Policy**]
- Despite these disadvantages, the barbiturates are perhaps the most commonly used anesthetics in laboratory animals. Overall, they are a relatively easy to use anesthetic.

Dissociative Anesthetics

The dissociative anesthetics include [ketamine](#) (Vetalar, Ketaset) and [tiletamine](#) (Telazol). These drugs are easy to use and have a wide margin of safety for most laboratory species. They are cyclohexamine compounds, chemically related to piperazine and phencyclidine (PCP). The dissociative anesthetics uncouple sensory, motor, integrative, memory and emotional activities in the brain, providing there is a functional cerebral cortex. The state induced by high doses of ketamine is best described as catalepsy and is not accompanied by central nervous system depression. There is depression of respiratory function, but cardiovascular function is maintained. Muscle relaxation is very poor.

Ketamine and Telazol are supplied in a solution of 100 mg/ml. Telazol is a 50-50 mixture of tiletamine and zolezepam, a benzodiazepine. These drugs can be injected intramuscularly, intraperitoneally or intravenously; however, the subcutaneous route is discouraged. IP and IM injections of the dissociative anesthetics can be painful, as the drug is very acidic. Induction time for IM administration is three to five minutes; peak effect lasts about 20 min in most laboratory species. IP induction times are longer than with IM administration and recovery may be prolonged. Because the volumes needed are very small, in small animals there is no real advantage to IP injection and IM injection should be used

whenever possible. Induction time following IV administration is rapid with only about 10 min of anesthesia provided. Approximately 1/2 of the dose should be given when dosing IV. The drug can be supplemented as needed.

The swallowing reflex is often preserved in animals receiving dissociative anesthetics. This may help prevent aspiration pneumonia if the animal regurgitates. However, this is not 100% and fasting and intubation are still recommended when using these anesthetics. The animal's eyes will usually remain open and the corneas should be protected with a layer of ophthalmic petrolatum or other suitable ointment. These drugs have poor analgesic activity, especially for visceral pain, and should be used in conjunction with an analgesic for abdominal, intracranial, orthopedic, ophthalmic or thoracic surgery.

Don't forget to follow the University **Controlled Substances Policy** [Policy](#)

Other Anesthetics

[Propofol](#)- is a sedative/hypnotic that can be used for induction or maintenance of general anesthesia. Analgesic effect is poor and addition of an analgesic to the anesthetic regimen is necessary for surgery. The drug comes as an emulsion that must be mixed and used within several days. The advantages of propofol are that it has rapid induction and recovery times. It can be easily titrated and given to effect for prolonged periods without resulting in prolonged recovery. The disadvantages are that it must be given intravenously, it is expensive, it may result in apnea and it can cause bradycardia and hypotension.

[Alpha Chloralose](#)- or chloral hydrate is a mild hypnotic drug that does not produce complete anesthesia because of its poor analgesic properties. Chloral hydrate is shorter acting (1-2 h) than alpha chloralose (8-10 h). The primary advantage of these drugs is the minimal cardiopulmonary depression seen at the normal doses (high doses can cause severe respiratory depression). The disadvantage is that they can only be used alone for non-painful procedures. In addition, the drugs are very irritating to the GI tract, causing adynamic ileus if given IP and ulcers if given orally. Therefore IV use is the only route recommended. These drugs should not be used if any other alternative is available.

[Tribromoethanol](#)-is a short-acting anesthetic used in rodents for surgeries. The drug has rapid induction and recovery (15 min of surgical anesthesia and up to 90 min for complete recovery). The effect on animals is reported to be quite variable. Tribromoethanol was commonly used in the past but its use is now discouraged. Abdominal adhesions caused by IP administration have been reported to cause high post-procedural mortality, however, other studies have not demonstrated this. Tribromoethanol is not available commercially and must be prepared. Sterile preparation procedures are essential. The drug must be stored in the dark at 4°C to prevent degradation. [Avertin Guidelines](#).

Urethane- is a long-acting (8-10h) anesthetic with minimal cardiopulmonary depression. The drug is used for long procedures in rodents. However, it is carcinogenic and is only allowed to be used with special justification and only for terminal (acute) procedures.

Other Analgesics

Analgesics are pain relievers most often given after a surgery. Narcotic analgesics have already been described above. Nonsteroidal antiinflammatory drugs (NSAIDs) may also be used for their analgesic effect. The NSAIDs consist of drugs like aspirin, ketoprofen, acetaminophen, flunixin and ketorolac. There are a large number of these drugs available, however, relatively few are used in animals. NSAIDs are, in general, less potent analgesics than are the narcotics. However, in specific instances they can have similar activity.

The advantages of the NSAIDs are that they do not cause sedation nor are they addictive as are the narcotic analgesics. There are no special recordkeeping requirements. In addition, they are more effective against pain caused by inflammation, such as is seen with tissue repair, orthopedic surgery, infection and injury.

One disadvantage of the NSAIDs (or any other analgesics) when given to the animal for oral self-administration (e.g. in drinking water, juice, treat food, etc) is that the physiological disturbances caused by an anesthetic episode may significantly decrease an animal's willingness to eat or drink during the immediate post-procedural period. This effect is independent of the level of invasiveness of any surgical procedure. To alleviate pain from surgical procedures, some form of parenteral analgesia should be given prior to anesthetic recovery and should be continued for a minimum of 12-24 hours after the animal has regained consciousness.

The NSAIDs have several side-effects related to their pronounced anti-prostaglandin (anti-cyclooxygenase and in some cases lipooxygenase) activity. This is peripheral with most drugs, but is primarily central with acetaminophen. These effects can alter immune function, platelet function and can cause gastrointestinal ulceration. In addition, the NSAIDs all have the potential to cause nephro- and hepatotoxicity. This is variable among species. Cats, in particular, are sensitive to the NSAIDs. Acetaminophen is contraindicated in cats due to risk of methemoglobinemia.

Acetaminophen- mild analgesic, antipyretic, no effect on platelet function/bleeding time

Aspirin- mild analgesic, antipyretic, antiinflammatory, affects platelet function/bleeding time

[Carprofen](#) is a nonsteroidal antiinflammatory drug with antiinflammatory and analgesic effects and lower risk for toxicity in animals than other NSAIDS.

[Flunixin meglumine](#) (Banamine)- potent analgesic, antiinflammatory, antipyretic. Has potential for GI ulceration, hepato- and nephrotoxicity.

[Ketoprofen](#)- moderate potency analgesic, antiinflammatory, antipyretic. Has potential for GI ulceration, hepato- and nephrotoxicity, affects platelet function/bleeding time.

[Ketorolac](#) (Toradol)- potent analgesic, antiinflammatory, antipyretic. Has potential for hepato- and nephrotoxicity, less potential for GI ulceration than other NSAIDs, affects platelet function/bleeding time.

Acetaminophen Update

[Alternatives to acetaminophen in rats and mice](#)

Anesthetic Drug Combinations

In general, by mixing anesthetic and analgesic drugs, the dose required for each individual drug is reduced, sometimes quite dramatically. Start at the low end of the dose range listed; you can always give more if needed! Drugs not listed below can be mixed using the same concepts, mix a sedative or hypnotic with an analgesic. Do not mix drugs in the syringe until you have determined that they are compatible when mixed. If in doubt administer separately.

Determining expiration dates for mixed/diluted anesthetic or pain relieving drugs: In the absence of empirical evidence, expiration dates of diluted or mixed drugs will be determined as follows:

- l. Manufacturer's dating of the drugs to be mixed together will determine the expiration date if shorter than the timelines given below.
- m. Mixed anesthetic drugs (ketamine, xylazine, acepromazine, butorphanol, telazol): Expiration date is 30 days after mixing, based on Minnesota Board of Pharmacy recommendations.
- n. Diluted drugs (buprenorphine) - Expiration date is 30 days from dilution date.
- o. Avertin - All solutions should be discarded 4 months after mixing, including stock solutions. pH should be tested prior to every use. Solution should only be used if pH is greater than 5. See <http://www.ahc.umn.edu/rar/avertin.html>
- p. Any substance which shows signs of precipitation, change of color, change in transparency or other signs of transformation should be immediately discarded.

- q. All diluted/ mixed substances must be combined into sterile containers (unless the combination is for a single acute procedure and the mixture will not be stored).

Ketamine/Diazepam: Mix drugs 1:1 by volume and administer 0.1 ml/kg IV for restraint, anesthetic induction or for non-painful procedures. This gives excellent muscle relaxation, has minimal respiratory or cardiovascular depression and the animals wake up smoothly and quickly (within 10-15 min). Visually, these drugs do not appear to mix completely. When combined and administered as described, the dose is 5 mg/kg ketamine and 0.25 mg/kg diazepam.

Ketamine/Acepromazine: Mix 10 mg acepromazine (1 ml) with 1 g (10 ml) ketamine and give 0.1-0.3 ml/kg mixture IM or IV (up to 0.6 ml/kg in rodents and rabbits). Good for restraint, but not for painful procedures. When combined and administered as described, the dose is 0.09-0.27 mg/kg acepromazine and 9-27 mg/kg ketamine.

Acepromazine/Butorphanol: Mix drugs 1:1 by volume (using 10 mg/ml butorphanol) and administer at 0.01-0.02 ml/kg IV or IM. Creates a hypnotic state that is good for restraint and minor procedures that cause some pain. When combined and administered as described, the dose is 0.05-0.1 mg/kg butorphanol and 0.05-0.1 mg/kg acepromazine.

Ketamine/Acepromazine/Butorphanol: Mix 10 mg acepromazine (1 ml), 10 mg butorphanol (1 ml) with 1 g (10 ml) ketamine and give 0.1-0.3 ml/kg of mixture IM or IV (up to 0.6-0.8 ml/kg in rodents and rabbits). Good for restraint and moderately painful procedures. More cardiac and respiratory depression will be seen with this mixture than with ketamine alone. When combined and administered as described, the dose is 8-25 mg/kg ketamine, 0.08-0.25 mg/kg acepromazine, and 0.08-0.25 mg/kg butorphanol. For rodents & rabbits, the dose is 50-67 mg/kg ketamine, 0.5-0.7 mg/kg acepromazine, and 0.5-0.7 mg/kg butorphanol.

Ketamine/Xylazine: Good for restraint and painful procedures. Administer IM, IP, or IV. More cardiac and respiratory depression will be seen with this mixture than with ketamine alone. Use 100 mg/ml ketamine and 100 mg/ml xylazine to create any of the mixtures listed below.

CAUTION: DO NOT USE this cocktail of ketamine-xylazine for cattle, sheep, goats, or other ruminants. Giving ketamine and xylazine simultaneously is not recommended for horses.

Species	Recipe by volume (ket:xyl)	Vol to give (ml/kg)	Dose (per kg body weight)	Sedation insufficient? May redose with ketamine alone...

Mouse	mix 10:1	1.1	100 mg Ket + 10 mg Xyl	At 1/3 to 1/2 original volume
Rat	mix 15:2	0.85	75 mg Ket + 10 mg Xyl	At 1/3 original volume
Rabbit	mix 20:3	0.40	34 mg Ket + 5.2 mg Xyl	At 1/3 to 1/2 original volume

Ketamine/Midazolam/Butorphanol: Mix 0.4 ml each ketamine and midazolam with 0.01 ml of 10 mg/ml butorphanol and administer 0.8 ml/kg. This provides good muscle relaxation and surgical anesthesia in rodents. When combined and administered as described, the dose is 40 mg/kg ketamine, 2 mg/kg midazolam, and 0.1 mg/kg butorphanol.

Telazol/Xylazine: For pigs: reconstitute powdered Telazol (tiletamine & zolazepam) with 5 ml of xylazine instead of saline. For pigs < 50 kg, use 20 mg/ml xylazine to make the cocktail. For pigs > 50 kg, use 100 mg/ml xylazine. Administer at 0.05-0.1 ml/kg IV or IM. When combined and administered as described, the dose is 2.5-5 mg/kg tiletamine, 2.5-5 mg/kg zolazepam, and either 1-2 mg/kg xylazine (if 20 mg/ml xylazine was used) or 5-10 mg/kg xylazine (100 mg/ml xylazine). For rats, use 20 mg/ml xylazine and administer up to 0.4 ml/kg IM. Here, the dose can be as high as 8 mg/kg xylazine, 20 mg/kg tiletamine, and 20 mg/kg zolazepam.

More cardiac and respiratory depression will be seen with this mixture than with Telazol alone.

Reversal with yohimbine 0.1-0.15 mg/kg (IM or IV) or atipamezole at 0.25 (IM) or 0.2 (IV) mg/kg is recommended to shorten recovery times.

CAUTION: DO NOT USE this cocktail of Telazol-xylazine for mice, rabbits, or ruminants such as cattle, sheep, or goats. Giving Telazol and xylazine simultaneously is not recommended for horses (contact an RAR veterinarian for more information).

Anesthetic Induction and Maintenance

Injectable Anesthesia

Anesthetic induction using injectable anesthetics is fairly simple. It involves administration of the drug and monitoring the depth of anesthesia. Supportive care may be needed. Maintenance of injectable anesthesia can be through repeated bolus doses of the drug or through a constant infusion. Infusion rates are calculated based on the clearance time of the drug. Bolus dosing is simpler. Typically, 1/2 of the original dose is given for repeat doses.

Injectable anesthetics can be administered by various routes depending upon the specific compound. The most frequently used routes of administration in laboratory animals are intraperitoneal, intramuscular and intravenous. Less frequently used routes, among

others, are intrathoracic, oral and rectal. Techniques are described below. Contact RAR at 624-9100 for training materials on handling animals and administering injections.

- Intravenous(IV)

Method- An appropriate vein must be selected. For large animals, the saphenous, cephalic or jugular veins are best. For rodents, the tail veins are best. For rabbits and swine, ear veins may be used. The vein is held off proximal to the venipuncture site. The vessel may be stroked with a finger to stimulate blood flow into it. The needle is inserted at a 30-45° angle to the vessel. Then the needle is lowered to align with the longitudinal axis of the vessel and advanced slightly. Draw back. If blood appears in the hub of the needle, the drug may be injected. If not, try redirecting the needle (before you pull it out of the skin) and repeat. You may need to try several times while learning. Using a new, sharp needle for each stick, even if it is the same animal, will improve your chances for success. Once the needle is withdrawn, it is necessary to put pressure on the vessel to prevent bleeding.

Advantages- rapid delivery of drug, ability to titrate dose, irritating substances may be given IV

Disadvantages- small veins are hard to access (i.e. small animals), restraint is critical, developing skill in venipuncture takes experience

- Intramuscular (IM)

Method- Insert the needle into a large muscle mass. Draw back slightly. If blood is aspirated, you are in a blood vessel. Redirect the needle. When the needle is placed correctly, inject the drug. The best muscle masses to use are for small animals, the caudal thigh muscles. For larger animals, the lateral dorsal spinal muscles or the cranial or caudal thigh muscles may be used. When administering into thigh muscles, inject from the lateral aspect, or if from the caudal aspect, direct the needle slightly lateral. This will help avoid injecting into the sciatic nerve.

Advantages-- Fairly rapid absorption, technique is simple

Disadvantages- IM injections are painful, small volumes are necessary, the animal may try to bite or escape

- Intraperitoneal (IP)

Method- The animal is usually restrained in dorsal recumbency. The drug may be injected anywhere in the caudal 2/3 of the abdomen. However, it is best to try to avoid the left side in rodents and rabbits because of the presence of the cecum. After the needle is inserted, draw back. If anything is aspirated, you have likely

hit the viscera. Withdraw and get a new needle before trying again. If the needle is placed correctly the drug may be injected.

Advantages- relatively large volumes may be injected (0.5 ml in mice, 2 ml in rats, etc.)

Disadvantages- technique is more difficult than IM injections, drug may be administered into the viscera resulting in no effect or in a complication.

- **Subcutaneous (SQ)**

Method- Pinch an area of loose skin. Inject into the center of the "tent" created by pinching.

Advantages- Technique is the simplest of any, large volumes may be given (basically as much as the tent of skin will hold that doesn't cause discomfort to the animal)

Disadvantages- Irritating substances cannot be given this way, absorption is slow

Inhalant Anesthesia

Induction of inhalation anesthesia can be difficult. Anesthetic gases are irritating to eyes and nasal passages. Animals may resist as they begin to lose consciousness or they may stop breathing temporarily. For this reason induction using a mask or nose cone held over the animal's nose can only be performed on smaller or non-fractious animals. In smaller animals gas can be delivered into an induction chamber large enough to contain the entire animal. Induction via a nose cone or chamber requires delivery of the anesthetic gas at 2-3x MAC. Frequently an injectable anesthetic is used to induce anesthesia and the inhalation agent is used for maintenance.

Maintenance of inhalation anesthesia is normally accomplished by delivering approximately 1.2 MAC to an animal via a mask or nose cone, or directly into the lungs via an endotracheal tube. Intubation is recommended wherever possible, particularly when a procedure will be prolonged. Endotracheal access is essential to provide ventilation support.

Gas Delivery Systems

The most complicated aspect of using inhalant anesthesia is the delivery system. A delivery system must provide the anesthetic gas to the animal at a known and constant rate. It must also ensure that animals receive adequate oxygen. There are several types of delivery systems typically used in laboratory animals.

Anesthetic Machine

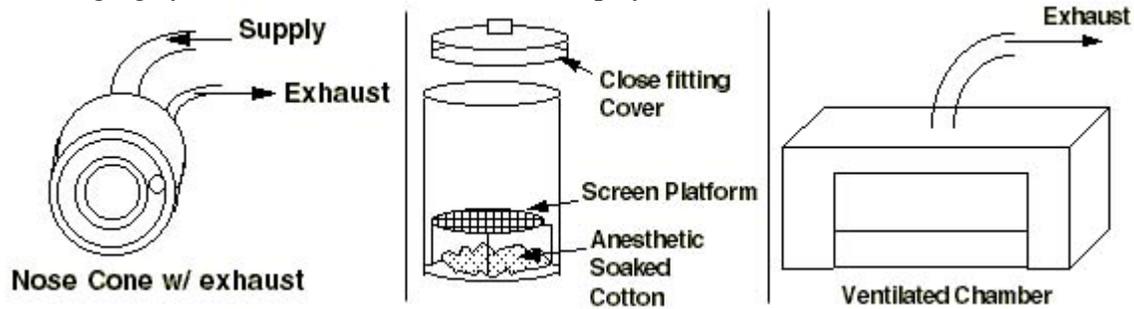
The best method of delivering an inhalant anesthetic is with an anesthetic machine. These machines precisely mix the gas with air or oxygen and can be easily adjusted. Machines can vary in construction and design. Anesthetic machines typically require more training to learn to operate.

- Anesthetic concentration is accomplished by sets of mixing valves or a precision vaporizer. Vaporizers are easier to use but are very expensive. Vaporizers are [calibrated](#) for the specific anesthetic gas to be used.
- Anesthesia circuits can be re-breathing or non-rebreathing.
 - Re-breathing circuits include typical circle systems used in large animals. The gas/oxygen mixture is delivered to the animal via a one-way valve. When the animal breathes out the gas passes out another valve attached to a y-piece. This is passed over a carbon dioxide absorbent and then back into the system. Additional gas and oxygen are continuously delivered to replace that lost.
 - Re-breathing circuits conserve anesthetic gas and the animal's body heat. The CO₂ absorbent must be replaced regularly.
 - Non-rebreathing circuits are primarily used for smaller animals that cannot cycle the valves in a re-breathing system. With newer machines non-rebreathing circuits are normally only necessary for rodents and birds. In older machines with metal valves a non-rebreathing circuit may be necessary for rabbits and cats as well. A Bain system is the most common non-rebreathing circuit available.
 - The non-rebreathing circuit is attached to the same anesthetic supply as used for a re-breathing system. However, the exhaust line is connected directly to the waste gas scavenging system.
 - Non-rebreathing circuits depend on gas and oxygen being delivered at a higher pressure than is present in the exhaust line. This tends to increase anesthetic usage and can increase body heat loss in the patient.
- Anesthesia machines must have a waste [gas scavenging system](#). Normally the exhaust line on a non-rebreathing system or the pop-off valve on a re-breathing system is connected to a vacuum line or to the building exhaust. Other scavenging systems can be used, contact RAR at 624-9100 or Environmental Health & Safety at 626-5804 for further information on anesthetic delivery systems.
- Low-flow anesthetic [techniques](#) in large animals.
- [Anesthesia breathing circuits](#).

Apparatus for Rodent Anesthesia

Left: a non-re-breathing nose cone that can be used with a large animal anesthetic machine; Middle: a typical drop system closed anesthetic chamber; Right: a gas

scavenging system that can be used with a drop system.



Preparation, Monitoring and Maintenance of Normal Physiology

A variety of things must be done to [prepare](#) for anesthesia. Once animals are under anesthesia they must be [monitored](#) closely while they are anesthetized to ensure that they do not become too deep and die, and to ensure that they do not become too light and experience pain from the surgical procedure. Normal physiologic functions such as [body temperature](#), [respiration](#) and [cardiovascular](#) function must also be monitored and supported while the animal is anesthetized. For all [major](#) surgical procedures on non-rodent mammals, an [intra-operative anesthesia record](#) must be kept and included with the surgeon's reports as part of the animal's record. The anesthetist must be prepared to handle emergencies if they occur.

Preparation

- **Withhold food and water** from large animals for 12 h prior to anesthesia and from small animals for 2 h to prevent regurgitation and aspiration. It is not necessary to withhold food and water from rodents prior to anesthesia. Prolonged food or water deprivation are distressful to animals and are rarely necessary. Please consult RAR's [policy](#) for fasting requests.
- **Have all drugs and equipment ready** before the animal is anesthetized. You may not have time to look for things once the animal is under.
- **Have an assistant.** Anesthesia takes time to perform and monitor. A person should be available to assist so the surgeon does not have to break sterility to monitor the animal or administer medications.
- **Premedication** with [atropine](#) or [glycopyrrolate](#) (anticholinergics) may reduce the respiratory tract secretions in some animals
- **Protect** the eyes from drying out using an ophthalmic ointment and protect them from being contaminated with surgical scrub solutions. Also protect pressure points, such as bony protrusions, from pressure necrosis or peripheral nerve damage by providing padding between the animal and the table.

Respiration

Most anesthetics cause direct depression of the respiratory center in the brain and reduce ventilation. This is complicated by other factors that may interfere with respiration. When an animal is in lateral recumbency the lung that is down is being compressed by the rest

of the body. Likewise, animals in dorsal recumbency may experience compression of the diaphragm by abdominal viscera. The airway may be compromised by regurgitated food or pharyngeal and tracheal secretions that normally would be removed by reflex swallowing or coughing. These reflexes are lost during anesthesia. There are several ways to monitor and support the ventilation of an anesthetized animal.

- **Intubate** the trachea whenever possible, even if injectable anesthetics are being used. Intubation can be achieved on animals as small as a rat. This will prevent aspiration pneumonia and allow you to assist respiration if the animal stops breathing. Contact RAR at 624-9100 for training materials.
- **Assist respiration** during the procedure. This can be done with a mechanical ventilator. However, mechanical ventilation is rarely needed (unless a thoracotomy or diaphragmectomy is being performed) and can be detrimental to the animal if over-done. Attaching an AMBU bag to the endotracheal tube or using an anesthetic machine's rebreathing bag will allow you to administer a deep breath every 2-5 min during the procedure. This will inflate all areas of the lungs and improve gas exchange. If the animal is not intubated, ventilation can be performed using a nose cone or face mask.
- **Monitor** respiratory function throughout the procedure and recovery.
 - Monitor respiratory rate and depth (compare to normal for your species. You can expect them to be slightly decreased). Observe chest movement, or use a stethoscope or esophageal stethoscope.
 - Monitor the color of the mucous membranes (gums, conjunctiva, vulvar mucosa). A bluish color means the animal is not getting enough oxygen-ventilate!
 - Red-tinged foam present in the airway along with dyspnea (difficulty breathing) may indicate pulmonary edema. This can result from overventilation or overhydration. A diuretic like [furosemide](#) can be administered, but prognosis is poor.
 - Sophisticated respiratory monitoring can be achieved by measuring blood gasses, or expired oxygen and carbon dioxide concentration or by use of a pulse oximeter.

Fluid Therapy/Cardiovascular Support

Many anesthetics have direct effects on the heart or vasculature, decreasing cardiac output and blood pressure. This is further complicated by increased fluid requirements during anesthesia and surgery that may result in hypovolemia. Fluid requirements are increased because: breathing dry, cold oxygen (if inhalant anesthesia is used) increases respiratory fluid loss; the animal has not received its normal fluid intake since it was fasted; fluid may be lost through hemorrhage or exposure of moist viscera to room air; many anesthetics are metabolized in the kidney (creating a slight diuresis minimizes renal toxicity).

To minimize the effects of surgery and anesthesia on hydration:

- Place an **intravenous catheter** whenever possible to provide access for fluids and medications
- **Supplement fluids**, intravenously if possible; otherwise intraperitoneally or subcutaneously
 - Fluid should be supplemented at the rate of 5-10 ml/kg/hour during anesthesia
 - **Monitor** hydration status- **Overhydration** results in frequent urination and pulmonary edema, **underhydration** results in sticky mucous membranes, loss of skin elasticity, the eyes sinking into the orbit, decrease in blood pressure and increase in heart rate
 - **To replace blood loss** with saline or lactated ringers, administer 3X the volume of blood lost by slow IV drip. Monitor the hematocrit. If it drops below 20%, whole blood replacement may be necessary.
 - Click [here](#) for clinical case studies in fluid management.
- **Monitor cardiovascular function** by monitoring one or more of the following:
 - Mucous membrane color and capillary refill time (the time it takes for the mucous membranes to regain their normal color after pressure is applied)
 - Heart rate and rhythm- stethoscope or esophageal stethoscope
 - Pulse rate and pressure- using your fingers
 - Blood pressure- arterial catheter or Doppler cuff required
 - ECG

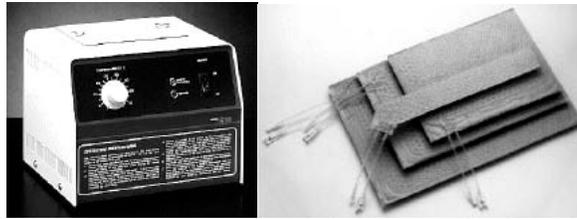
If the animal has pale mucous membranes, the capillary refill time is greater than 2 seconds, or if the other cardiovascular parameters are out of normal range (determine normal for the species you are using!) you may have a cardiovascular emergency. Increasing the rate of intravenous fluid administration will improve cardiac output temporarily. However the depth of anesthesia will need to be reduced and if there is a primary cardiac problem it will require specific treatment. Consult with an RAR veterinarian for more information on anesthetic emergencies.

Thermoregulation

Animals frequently become hypothermic during anesthesia because of inhalation of cold gases, exposure of body cavities to the room air, and loss of normal thermoregulatory mechanisms and behaviors. Hypothermia depresses all physiologic functions, including respiration and cardiac function, slows the metabolism of anesthetics and results in prolonged recoveries. All of these can contribute to anesthetic death. Hyperthermia is less common, but may occur because of excessive application of heat, hot surgery lights or malignant hyperthermia in genetically pre-disposed animals. To thermoregulate your patient:

- **Monitor the body temperature** frequently using a thermometer during the procedure and during anesthetic recovery. While animal normals vary from species- to-species, in general, when body temperature drops below 99° F, an animal is considered hypothermic. Below 95-96° F an animal cannot regain normal body temperature without supplementation.

- **Prevent heat loss** by insulating cold surfaces with a blanket
- **Prevent heat loss** during gas anesthesia by utilizing low flow techniques that conserve heat
- **Supplement heat** with a thermal blanket (keep blanket temperature below 40 C to prevent burns!) or with pre-warmed fluids
- **Treat hyperthermia** by administering intravenous fluids or applying water to foot pads or exposed skin. Only use an ice bath as a last resort, as it may cause cardiovascular shock.



Water blanket and heater

Monitoring Anesthesia

The depth of anesthesia must be monitored carefully. Animals that are too light will experience pain and may move during the procedure. Animals that are too deep run the risk of experiencing cardiopulmonary arrest. If an animal is too light the anesthesia should be supplemented, if too deep, animals on gas anesthesia can be turned down. Animals given injectable anesthetics can not be lightened directly. Instead [respiratory](#) and [cardiovascular](#) support must be administered until the anesthetic is metabolized and the animal begins to lighten on its own.

To monitor the depth of anesthesia, perform the following:

- **Reflexes**- these reflexes disappear as the animal becomes deeper in the following order:
 - *Palpebral reflex*- touching the eyelids causes blinking. The animal is light if it is blinking.
 - *Toe pinch reflex*- pinching the toe or foot web will cause a pain response. If the animal withdraws the toe it is not deep enough. If it doesn't, it is not sensing pain.
 - *Corneal reflex*- touching the cornea of the eye with a tuft of cotton results in a
 - blink. Once the animal has lost its corneal reflex, it is too deep.
- **Muscle tone** increases as the depth of anesthesia decreases, unless the animal is receiving a cataleptic drug like ketamine in the absence of a sedative. Test muscle tone by pulling on the lower jaw or a limb. Rigid tone indicates inadequate depth of anesthesia.
- **Monitor cardiopulmonary function and body temperature**- As an animal becomes too deeply anesthetized, respiration and cardiac output decrease, resulting in poor blood oxygenation and tissue perfusion and decreased blood pressure and temperature. Likewise, elevations in heart rate and blood pressure

may be indications that an animal may be feeling pain and is anesthetized too lightly. Monitor as previously described.

Anesthetic Emergency Drugs	Dose (mg/kg)	Indications
Doxopram (Dopram)	1-5 IV (10x in farm animals)	Respiratory stimulant, for complete respiratory arrest only, use with CPR
Furosemide (Lasix)	2- IV, IM	For pulmonary edema. Administer as needed
Naloxone (Narcan)	0.04 IV	For reversal of narcotic sedation or respiratory depression
Yohimbine	0.1-0.15 IV	Reversal of xylazine or detomidine sedation
Atropine	0.02-0.04 IV	For bradycardia
Epinephrine (1:1000)	0.1 ml/kg IV, IT, IC, IM	For cardiac arrest only. Administer IV, intratracheal or intracardiac and perform cardiac massage
Lidocaine	2, IV (0.5 mg/kg in cats)	For diagnosed ventricular tachycardia only. Administer to effect and monitor

Recovery

Monitoring and support must continue until the animal is completely recovered from anesthesia. Complete recovery means the animal is able to hold itself in a normal upright position, has returned to normal body temperature and all physiological indices are within normal limits. Anesthetic recovery can be rapid for gas agents and short anesthetic episodes. Recovery time can be prolonged if animals were under for a long time or if injectable agents were used.

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