Anesthesia and Analgesia in Research Animals

Federal guidelines, the Animal Welfare Act (AWA) and the Public Health Service Research Extension Act and the Guide for the Care and Use of Laboratory Animals (*The Guide*), require that procedures involving animals be conducted in a manner that avoids or minimizes discomfort, pain or distress. The Guide states:

"*The proper use of anesthetics and analgesics in research animals is an ethical and scientific imperative." "The selection of appropriate analgesics and anesthetics should reflect professional veterinary judgment as to which best meet clinical and humane requirements as well as the needs of the research protocol. "*

If a painful procedure must be conducted without the use of an anesthetic, analgesic, or tranquilizer – because such use would defeat the purpose of an experiment – the procedure must be approved by the IACUC.

The following sections provide detailed information regarding recommendations for the use of analgesics and anesthetics as well as recommendations for acceptable agents and dose ranges.

Overview

Animal anesthesia, analgesia and pain management are crucial components of research involving animal subjects. The standard of care at Indiana University is to prevent animal pain as far as possible and to treat animal pain whenever diagnosed. Exceptions to these principals are permitted only in the minority of protocols approved by the Institutional Animal Care and Use Committee as USDA Category E with adequate scientific justification. Animals must be acclimated to their surroundings for at least 48 hours prior to performing procedures.

Goals of anesthetic and analgesic regimen

The anesthetics and analgesics are selected to achieve the following:

- Provide precise anesthesia administration to assure that animals receive adequate anesthesia to block pain sensation, to produce unconsciousness, and

to produce immobility without creating life-threatening anesthetic overdoses.

- 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.
- Not interfere with the outcome of the study using the animal(s).
- Not result in excessive undesirable post-operative side effects.
- Not cause pain or distress on induction or recovery.

Drug Dilutions

Especially in smaller species, dilution of injected drugs allows for more precise dosing, but may shorten the shelf life of the compound. Diluted drugs must be labeled and dated, then discarded after 6 months, at the expiration date of any of the components, or as indicated by the manufacturer.

If the drug is to be diluted, the following procedures should be followed to insure sterility of the final product:

a. Aseptic technique must be observed as mixtures (cocktails) are prepared
b. All manipulations must occur in sterile vessels using sterile instruments (spatulas, syringes/needles, dosing vials, etc.…). The cover of each vial or bottle used is wiped with 70% ethanol or isopropanol prior to use.
c. Work should be carried out in a bio-safety cabinet or chemical fume hood to reduce contamination of the area.
d. The drug should be reconstituted with either Sterile Water for Injection or sterile saline for injection.
e. The solution must be placed in a sterile vial. The vial must be labeled with the drug name, concentration of the solution, the date of dilution and the expiration date. The expiration date of the diluted solution is six months from the date solution is prepared or the expiration date of the stock drug or diluent used to make the solution, whichever date is first. Any solution remaining after the expiration date must be discarded and not used in laboratory animals.
f. The solution must be handled and used in a manner to ensure continued sterility of the contents. Only new, sterile needles must be used for withdrawing aliquots from the cocktail.

Anticholinergics

Anticholinergics are often used in human and large animal surgery, but are not typically recommended for rodents. If an anticholinergic is appropriate for a specific surgery in rabbits for cardiac support or respiratory secretion reduction, glycopyrrolate is preferred because atropine is more quickly metabolized in a certain percentage of rabbits.

Pre-anesthesia fasting

Some animal species, such as monkeys, dogs and cats, are routinely fasted overnight prior to undergoing anesthesia and surgery. In these animals, feed is deprived for no more than 12 hours to prevent the occurrence of vomiting and aspiration of gastric contents when anesthesia is induced. Feed deprivation is not recommended in rodents for two reasons: First, because their gastric anatomy prevents them from being able to vomit, thus making it unnecessary to withhold food. Secondly, since mice and rats are nocturnal eaters, removing food overnight means that in effect the animal may not have eaten anything during the previous 24 hours. Rabbits and birds also do not vomit and are usually fed overnight prior to anesthesia and surgery. It is not necessary or advisable to withhold water before anesthesia and surgery in any species. Any deviations from these procedures must be stated in the protocol and approved by the IACUC.

Safe and effective animal anesthesia

Anesthesia is the loss of feeling or sensation, especially the loss of pain sensation. Muscle relaxants or paralytic drugs (e.g., succinylcholine or other curariform drugs) are not anesthetics, and thus cannot be used alone to induce anesthesia. Drugs planned to be used for anesthesia and methods of intra- and post-operative monitoring must be included in the IACUC protocol application, and then practiced as written and according to IACUC guidelines. It is not acceptable to conduct surgical procedures unless the animal is fully anesthetized. Maintenance of body temperature throughout anesthesia, surgery and recovery, and supplemental administration of warmed fluids (lactated ringers solution or isotonic saline) for longer lasting surgeries, will improve anesthetic safety for the animals.

External Temperature Support

When an animal is anesthetized, their ability to thermoregulate is lost making the animal susceptible to hypothermia. Hypothermia is an important concern as it can deepen the level of anesthesia and extend recovery time from anesthesia. Therefore, it is extremely important to supply a safe and effective external heat support to an anesthetized animal. Electric supplied heat sources are typically not recommended as they produce unpredictable heat spikes that can result in thermal burns to the animal. Acceptable heat sources include water supplied heating pads, re-useable thermal pads or rectal thermometer feedback controlled. Also heat lamps are not recommended, as they are not reliably controlled. If kept too far from the patient, they are of little use for heating, if kept too close, they can cause thermal burns to the ear tips.

Eye lubricant

When animals are anesthetized, they lose the ability to blink leaving their corneas susceptible to dryness and trauma. Sterile ophthalmic lubricating ointment must be used anytime animals are anesthetized, to prevent corneal trauma.

Anesthesia Monitoring

Anesthetic monitoring for all animals includes testing for response to a noxious stimulus, like pinching the rear foot, tail or ear, before any incision is made. Monitoring also includes frequent observation of respiratory pattern, mucous membrane color and responsiveness of the animal to manipulations throughout the procedure. It is recommended that rectal temperature and heart rate be monitored electronically. This may not be possible with fish and amphibians. Regardless, monitor the animal often, re-assessing the response to noxious stimulus at least every 15 minutes.

Toe pinch method (Withdrawal Reflex): This method is useful to evaluate depth of anesthesia but not enough in itself. One must use two fingers and give the toe/foot a good squeeze. If there is no withdrawal of the leg is noted, “withdrawal reaction,” the animal is judged deep enough to commence surgery. Remember that after this has been done the fingers are not sterile anymore. A sterile gauze pad may be used to protect the sterile gloves. Alternatively, a hemostat may be used to squeeze toe/foot. In this case, one must be careful not to squeeze too hard. Remember that after the hemostat has been used to squeeze the toe, it is not sterile anymore and must not be used for surgery.

Respiratory pattern: Anesthesia will cause a distinct slowing of respiratory rate (RR). The surgeon must evaluate if RR becomes too slow and the anesthesia needs to be lightened. Increasing RR indicates the need for supplemental anesthesia.

Skin and Mucous membranes (MM): MM's are evaluated by observing the color of the conjunctiva and gums. The skin can also be evaluated by assessing the color of the pinnae (ears) and toes. If these become bluish this is an emergency, indicating that the animal does not have enough oxygen. Pink is good and red usually indicates that the animal is too warm. Hyperthermia is not likely to occur during surgery but may occur during recovery from anesthesia, especially if an improper heat source is used to keep the animal warm.

Reaction to surgical manipulation: If the animal makes any kind of move in response to incision or manipulation of organs, surgery must be temporarily stopped and anesthesia supplemented.

Animal Recovery

Once surgery is completed, the animal is recovered from anesthesia. All animals are provided a heat source during recovery, besides amphibians and fish. Electric supplied heat sources are typically not recommended as they produce unpredictable heat spikes that can result in thermal burns to the animal. Acceptable heat sources include water supplied heating pads, re-useable thermal pads or rectal thermometer feedback controlled. All animals recovering from surgery are to be observed at least every 15 minutes until they are recovered. A recovered animal is considered recovered when able to maintain a sternal position (in the case of birds, able to perch), their body temperature is back to normal, and the animal is able to maneuver around the primary enclosure. The animal must be fully recovered before being returned to the animal holding room.

Species-specific considerations

In general, smaller animals have higher metabolic rates and frequently require higher doses of drugs at more frequent intervals to achieve the desired effect. Species, strain and age differences also contribute to differences in drug doses. 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. Also, when starting to use a new species or strain of animal, it is safer to administer the lower end of the dose range of parenteral anesthetics and analgesics. More can then be administered as needed. Safety and efficacy of a new drug regimen should be demonstrated in a pilot group of animals before a large-scale study is initiated.

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 medical grade oxygen from a precision vaporizer. See: Inhalant Anesthetics

Injectable anesthetics are typically administered by the intraperitoneal (IP) route. Injectable analgesics and reversal agents are often administered by the subcutaneous or the IP route. Intramuscular (IM) injections are not recommended because of the small muscle mass in this species. Diluting drugs in sterile saline solution will make it easier to accurately measure volume for injection.

Ketamine-xylazine and ketamine-dexmedetomidine combinations produce short-duration surgical anesthesia in larger species, but may be insufficient for major surgical procedures in many strains of mice. Reversal agents are available for xylazine and dexmedetomidine to restore cardiovascular status more quickly. See: Dissociative Anesthetics

Pain control: 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. As with all animals, pre-emptive treatment of pain before signs of pain are obvious is strongly recommended. See: Mouse Formulary

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. As in mice, intramuscular (IM) injections are not recommended because of the small muscle mass in this species. See: Inhalant Anesthetics, Dissociative Anesthetics and Rat Formulary

Hamsters

Hamster anesthesia is similar to rat and mouse anesthesia, though some anesthetic doses differ. As in other small rodents, peripheral veins are extremely difficult to access in hamsters, limiting some of the anesthetic options. As in mice, intramuscular (IM) injections are not recommended because of the small muscle mass in this species. See Hamster Formulary

Guinea Pigs

Guinea pigs can be difficult to anesthetize, especially on a survival basis. Intraperitoneal (IP) administration works well, if the large cecum can be avoided. Guinea pigs may be anesthetized by facemask with volatile/inhalant anesthetics; the soft palate is fused to the base of the tongue, with entry to the trachea only obtained through a small opening called the palatal ostium, creating a significant obstacle for endotracheal intubation. Intravenous injection is difficult. Complications from improper intramuscular injection technique often arise due to the small muscle mass present. The animals may then self-mutilate at injection sites following recovery from anesthesia. Thus, intramuscular injection is not recommended. See Guinea Pig Formulary

Chinchillas

Chinchillas and guinea pigs share many anatomic and physiologic characteristics. Thus, approaches taken towards administering anesthesia in both animals is quite similar. However, some anesthetic doses may differ. See Chinchilla Formulary

Rabbits

Long procedures are best performed using inhalant anesthesia with an endotracheal tube in place. For shorter procedures, inhalant or injectable anesthesia may be appropriate. Intramuscular injections using ketamine are not recommended in rabbits due to the resulting tissue necrosis. See: Rabbit Formulary

Birds

Small birds may be anesthetized by inhalation anesthetics (such as isoflurane) or injectable

anesthetics. As with all anesthetized animals, it is vital to maintain adequate warmth during the anesthetic period. See: Bird Formulary

Amphibians

Immersion anesthesia using tricaine methanesulfonate (also called MS-222 or Finquel) is common, especially for fully aquatic species like *Xenopus*. Because MS-222 is an acidic solution that can cause stress, discomfort, and prolonged anesthetic induction time when concentrations are above 0.5 g/L, it must be titrated to a normal pH (~7) by adding sodium bicarbonate. See: Amphibians and Fish Formulary

Fish

Immersion anesthesia using tricaine methanesulfonate (also called MS-222 or Finquel) is the most common anesthetic in use with fish, and the only anesthetic approved by the Food and Drug Administration (FDA) for the use in fish. See: Am**phibians and Fish Formulary**

Commonly used anesthetics and analgesics

Inhalant agents:

Volatile anesthetics- *Isoflurane and Sevoflurane*

Isoflurane and sevoflurane are delivered via a precision vaporizer to effect in concentrations of 1-3% in oxygen (up to 5% for initial induction). Adjusting the inhaled percentage of anesthetic gas to deepen anesthesia is far safer than repeated re-dosing of injected drugs. Volatile anesthetics are easier to decrease as well, even compared to drugs for which there are an injectable antagonist or reversal agent. A major shortcoming of the inhalant anesthetic agents is the lack of residual analgesia once the vaporizer has been turned off. If inhalant anesthetics are not possible for your study, injectable anesthetics are another option.

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, and the risk of fatal over-dosage if an open system is used instead of a precision vaporizer. In addition, once animals awaken from gas anesthesia, there is no residual analgesic activity.

Exposure to waste anesthetic gas is a serious occupational safety concern. Inhalants must be directly vented out of the room using a chemical hood, snorkel or down drafted table, or adsorbed in an appropriate charcoal canister filter. Filters must be weighed and replaced before they reach target weight (usually an increase of 50g). Office of Environmental Health and Safety Management (EHS-OH&S) can provide assistance in evaluating potential exposures.

Pre-emptive analgesia is mandatory with isoflurane and sevoflurane anesthesia. This is because the moment the animal recovers from anesthesia, which occurs rapidly with gas anesthesia, there is NO pain control, unless it has been administered BEFORE surgery.

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 and explosion hazard, and its routine use is not allowed. The use of ether must be scientifically justified and its use reviewed and approved by the IACUC. Carbon dioxide is a potent anesthetic, but concentrations are difficult to control, making the margin of safety unacceptably low.

Injectable Agents

Any solution to be injected into a live animal must be handled and used in a manner to ensure continued sterility of the contents. Only new, sterile needles must be used for withdrawing aliquots from the cocktail.

Drug dosages and frequencies of administration

Drugs doses, the route of administration (e.g. Intraperitoneal, subcutaneous, etc.) and volume to be administered must be listed within the protocol. These dosages may need to be adjusted

up or down for the different animal strains, or for the particular application (procedures conducted, animal age and health status). If recommended doses are consistently too high or too low for the particular application, the veterinarian should be informed, and a protocol modification submitted to the Institutional Animal Care and Use Committee.

Analgesic doses and frequencies are more difficult to gauge. Some analgesics are effective for only a 6-12 hour period. Caution is required for overnight pain management, as the animals need to be re-assessed before the next analgesic dose might be due. Longer lasting non-steroidal anti-inflammatory analgesics may have longer durations of action than available opioids; NSAID's are frequently co-administered with an opioid to combine potency of effect with duration of action.

Dissociative anesthetic- *Ketamine*

Ketamine is a widely used anesthetic in a variety of species. In low doses, ketamine provides chemical restraint with some somatic analgesia (no visceral 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.

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. Injections given in tissues outside of the vein sting when administered and result in tissue necrosis. If injected near the sciatic nerve in the gluteal muscles in rodents and rabbits it may cause neuronal damage evidenced by the animal losing sensation in the hind leg and self-mutilating.

Ketamine is not sufficient for anesthesia by itself. The sole use of ketamine is discouraged, as the recovery may be very stressful and agitated. Ketamine is a Class III controlled substance and subject to regulatory requirements governed by the Drug Enforcement Agency (DEA).

Ketamine combinations- *Ketamine + alpha2-agonists (Xylazine or Dexmedetomidine)*

Alpha-2 agonists are centrally acting sedatives, with excellent analgesic properties. Their most common side effects are bradycardia and cardiac arrhythmia. When combined with ketamine, these properties are minimized and the combination of ketamine with xylazine or dexmedetomidine in the same syringe produces a surgical level of anesthesia in many species, notably rodents and rabbits.

Advantages: Advantages of ketamine + alpha-2-agonist combinations are they may produce short-term surgical anesthesia with good analgesia, and that recovery can be hastened by reversing the α-2-agonist with Atipamezole or Yohimbine. Administration of reversal agents may be useful but is not routinely recommended as lingering ketamine effects may agitate the recovery.

Disadvantages: Disadvantages of ketamine + α -2-agonist combinations are that they will not reliably reach surgical anesthesia in all cases, and that they can cause profound cardiac depression.

Caution for use: If a ketamine + α -2-agonist combination is used for surgery longer than 20 minutes, animals will likely require additional anesthetic. Re-dosing with ketamine alone rather than the combination is required, as the cardiovascular and respiratory depression of α -2-agonists is often longer lasting than the sedation or analgesia produced.

Adding acepromazine to the ketamine + α -2-agonist combination will result in deeper and/or longer plane of anesthesia in small rodents, especially rats, and possibly some strains of mice.

Barbiturates- *Sodium Pentobarbital*

Barbiturates are often the anesthetic of choice when neuron-physiological 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 will provide residual pain relief following recovery from barbiturate anesthesia, and lower the required dose of barbiturate. Sodium pentobarbital (Nembutal) is the more commonly used barbiturate among rodents.

Advantages: Barbiturates do not depress cortical evoked responses to the extent that other

anesthetics might. 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. Pentobarbital has a prolonged recovery from anesthesia. Injection of barbiturates outside of the vein can be irritating and painful due to a very high pH. Barbiturates are Class II controlled substances, except for some Class III barbiturate containing euthanasia solutions. It should be noted that pentobarbital is becoming harder to obtain and when available, is very expensive due to the limited availability.

Alpha-2-agonists- *Xylazine or Dexmedetomidine*

The alpha-2-agonists (Xylazine or Dexmedetomidine) are hypnotic analgesics with significant pain relief. Combined with Ketamine they may be useful during surgery.

Advantages: α -2-agonists produce profound analgesia of short duration, can be combined with ketamine to produce deeper anesthesia, are not controlled substances, and are reversible with IP or subcutaneous atipamezole (yohimbine is sometimes used for xylazine reversal). They are not an irritant when injected via intramuscular or intraperitoneal routes.

Disadvantages: Disadvantages in most species include cardiovascular depression (decreased heart rate, decreased cardiac output, cardiac arrhythmias and hypotension), which is somewhat controlled by using with Ketamine. Alpha-2-agonists cause a transient hyperglycemia, which may have research implications, and can cause respiratory suppression especially at higher doses. Rapid IV administration of reversal agent has produced seizures in some species.

Caution for use: If a ketamine and α -2-agonist combination is used for surgery longer than 20 minutes, animals will likely require additional anesthetic. Re-dosing with ketamine rather than the combination is needed to prevent respiratory suppression. The cardiovascular and respiratory depression of alpha-2-agonists is often longer lasting than the sedation or analgesia produced.

Alpha-2-agonist Reversal agents- *Yohimbine and Atipamezole*

Advantages: Administration of a reversal agent can rescue an animal in cardiac distress due to bradycardia or cardiac arrhythmia. It will also promote quicker recovery from alpha-2-agonist agent anesthesia.

Disadvantages: If ketamine and α-2-agonist agent have been used for anesthesia, alpha-2-agonist reversal, may result in agitated recovery from anesthesia. In addition, analgesic effects of the alpha-2-agonist will be removed.

Tribromoethanol (previously known as Avertin)

Tribromoethanol produces short-term (15-20 minutes) surgical anesthesia with good muscle relaxation and moderate respiratory depression. It does not produce significant residual post-procedural analgesia. Unless strongly justified in the animal care and use protocol, use of tribromoethanol is restricted to mice only, for a single survival anesthesia plus terminal/acute use.

Advantages: Advantages of tribromoethanol are that it is easily administered via the intraperitoneal route, produces good short-term surgical anesthesia, and is not a controlled substance.

Disadvantages: Tribromoethanol is not commercially available as a pharmaceutical drug, and must be made in the laboratory from the reagents tribromoethanol and amylene hydrate. In keeping with IACUC policy, tribromoethanol must be prepared, sterilized through a 0.2-micron filter, stored and used under sterile conditions. Tribromoethanol can cause peritonitis in mice, and the risk increases with each time it is used in the same animal. Post-procedural analgesia has not been demonstrated, so use of a preemptive or postoperative analgesic is generally required. Though surgical anesthesia is short (15-20 minutes), anesthetic recovery can take 40 minutes, during which time the animal must be monitored and kept warm.

Cautions for use: Tribromoethanol must be carefully prepared in the laboratory under aseptic conditions. Working dilution of 1.25% is recommended — this is best prepared fresh for use. Tribromoethanol must be stored away from light. If stored at 4°C, tribromoethanol working solution may be used for up to 1 week. The pH must be checked before each use. If the pH of the working solution has dropped below 5, it is considered toxic and should not be used. Do not use if the solution becomes discolored or has detectable precipitate after shaking.

Tribromoethanol is used only for mice. It is not to be used twice in one animal on a survival basis (if used a second time that use should be terminal/acute).

Miscellaneous agents

Urethane, choral hydrate, equithesin, and alpha-chloralose have some specialized use in laboratory animal anesthesia. Their use should be discussed with a veterinarian.

Analgesics

Pre-emptive analgesia

Pre-emptive use enhances pain management during the immediate post-surgical period. The disadvantage of this approach is that this adds a pre-anesthetic injection, which may be distressful to the animals. To avoid this issue, it is acceptable to administer the pre-emptive analgesia as soon as the animal has been anesthetized. By the time the animal is aseptically prepared and moved to the operating table or area (in the case of rodents) and the surgeon makes the first incision, the pre-emptive analgesic will have had time to take effect. Other possible drawbacks with the administration of some pre-emptive analgesics is that anesthesia will be deepened and anesthetic doses may need to be reduced, anesthesia recovery may be delayed, and some of the drugs are Controlled Substances requiring special storage and records keeping.

The three classes of injectable drugs are:

- Opioid analgesics (such as buprenorphine or morphine);
- Non-Steroidal Anti-Inflammatory Drugs (NSAID's) (such as carprofen, meloxicam);
- Local/regional anesthetics (lidocaine, bupivacaine).

Opioids- *Buprenorphine and Butorphanol*

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. Buprenorphine and butorphanol are two commonly used opioid drugs. Butorphanol is rarely used in mice and rats as it only relieves minor pain in these small rodents, and has a short duration of action with them, only 1-2 hours. Buprenorphine is longer acting and is good for most post-operative applications. Butorphanol may be more efficacious than buprenorphine for birds as birds appear to be more receptive to kappa opioids.

There are 3 types of opioid receptors: mu, delta and kappa. Buprenorphine and butorphanol are mixed agonist/antagonists at different opioid receptors; they produce less profound respiratory depression than full agonists, but also have a "ceiling effect" in the degree of analgesia produced with higher doses. Even though the dose is increased, the level of analgesia does not increase beyond a certain point. 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.

Advantages: Opioids are potent analgesics. Concurrent use with inhalant or parenteral anesthetics for general anesthesia will lower the required dose of the anesthetic. Opioids can also be used with NSAID's for analgesia.

Disadvantages: Opioids can suppress respiration. Opioids may increase locomotor activity, and buprenorphine at high doses 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. Opioids are controlled substances. Buprenorphine is a schedule III drug. Butorphanol is a schedule IV drug.

Cautions for use: Buprenorphine has found favor as the longest-acting opioid analgesic. The duration of action for buprenorphine is from 8 to 12 hours. 12 hours is the absolute maximum dosing interval for use of buprenorphine for post-procedural pain.

Non-steroidal anti-inflammatory drugs (NSAID's)- *Carprofen and Meloxicam*

The advent of newer, more potent, more specific anti-inflammatory agents have increased their usefulness in laboratory animal use. Most reduce fever, reduce inflammation, and provide varying degrees of analgesia. The two most common NSAID's used are carprofen (Rimadyl) and meloxicam (Metacam).

Advantages: Carprofen 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 NSAID's are useful for accurate dosage and administration to small rodents.

Disadvantages: NSAID's can lead to gastric upset and even ulceration, especially with prolonged use. Prolonged use also carries the risk of kidney or liver disease.

Cautions for use: Undesired side effects are more likely with increasing duration of usage — for most situations, limit use of NSAID's 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 Bupivacaine*

Local anesthetic/analgesic drugs (lidocaine and bupivacaine) 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 (1-3 minutes), and provides only 20-40 minutes of analgesia in small rodents. Bupivacaine has a slower onset of action (~20 minutes) but provides up to 4-6 hours of analgesia. Both are administered at the surgical site, infiltrating the incision site and underlying subcutaneous tissues.

Advantages: Intra-operative use can augment the pain relief of general anesthetics, and reduce the need for frequent re-dosing. Bupivacaine 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 over-dosage (more likely to occur with smaller subjects) and with accidental intravenous injection. Lidocaine may sting when first injected.

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

Drug Formulary for Laboratory Animals

Note that all of the doses listed in the formula tables are approximations and may need adjustment due to the animal's strain, age and sex. 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. Where a dose has not been determined, it is listed as TBD (To Be Determined).