Anesthetic Management of Rodents and Rabbits
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Overview

Anesthesia, the loss of feeling or sensation of pain (analgesia) in order to humanely permit surgery or other painful procedures, is a legal, moral and ethical imperative. Anesthetic agents used in rodents and rabbits are usually delivered either via inhalation or injection. Of those that are given by injection, the action may be local or general. General Anesthesia is a state of unconsciousness, produced by anesthetic agents, with absence of pain sensation over the entire body and a greater or lesser degree of muscle relaxation. Balanced anesthesia is an important concept whereby a combination of drugs or agents, each in an amount sufficient to produce its major or desired effect to the optimum degree and keep its undesirable or unnecessary effects to a minimum. Safety and cost control are driving factors.

Controlled Drugs (Policy)

Many of the drugs used for anesthesia of animals are controlled and regulated by the federal government and the State of Georgia.

Preanesthetic Medications

Preanesthetic medications, such as tranquilizers and sedatives, are not recommended, with the exception of anticholinergic drugs, because single injection anesthesia techniques have been developed that minimize the handling stress and eliminate the discomfort associated with multiple injections. Serum and tissue atropinesterases found in many rabbits and rats render atropine sulfate ineffective, therefore, subcutaneous (SC) administration of glycopyrrolate (RobinulR, A.H. Robins Company, Richmond, VA), a quaternary ammonium parasympatholytic, should be given to reduce salivary and bronchial secretions and prevent vagal bradycardia.

Pre-anestheic Agents (in mg/kg, unless otherwise noted) for Rodents and Rabbits

Agent	Guinea Pig	Mouse	Rat	Rabbit
Atropine Sulfate	0.5 SC	0.04 SC	0.05 IP, SC	Not recommended
Glycopyrrolate	0.01-0.02 SC	0.01-0.02 SC	0.5 IM	0.01 IV 0.1 SC

Injection Anesthesia

Introduction

Historically, injectable drugs have been popularly used for anesthesia of rabbits and rodents because they are inexpensive, avoid the technical demands of gas anesthesia, and have been generally safe, effective,

and easy to administer. However, disadvantages attendant to anesthesia by injection include the lack of precision in controlling anesthetic depth, prolonged recovery time, and physiologic changes such as hypotension, hypercarbemia, and hypoxemia. For uncomplicated procedures involving healthy animals, these drawbacks may not be of consequence, but their safety and predictability when used in ill animals is not known. The table below lists common anesthetics, combination regimens and doses. Users are cautioned against making broad and general assumptions about the applicability of certain regimens to species for which a regimen is not given or of concocting new combinations of drugs. For example, fentanyl-medetomidine, a very effective combination in rats, is highly lethal when used in mice. Buprenorphine, when given pre-emptively, is very effective in combination with pentobarbital in rats, but is associated with high complication rates and mortality when given with both ketamine and medetomidine.

Common Injectable Anesthetic Doses for Rodents and Rabbits
(in mg/kg, unless otherwise noted)

Agent	Guinea Pig	Mouse	Rat	Rabbit
Avertin (tribromoethanol)	----	240-375 IP	300 IP	----
Chloral hydrate	400 IP	400 IP	400 IP	----
Fentanyl + medetomidine	----	Fatal	300 g/kg IP + 300 g/kg IP	----
Ketamine + xylazine + acepromazine	-----	80 + 10 + 3 IP	40 + 8 + 4 IP	40 + 4 + 0.75 SC, IM
Medetomidine + ketamine	0.5 IP + 40 IP	1 IP + 75 IP	0.5 IP + 75 IP	0.5 IM + 25 IM
(Reverse medetomidine with atipamezole)	1 IP	1 IP	1 IP	1 IP
Pentobarbital	37 IP	40-50 IP	40-50 IP	30 IV, requires controlled ventilation

Pentobarbital + buprenorphine	----	----	36 mg/kg IP + 0.5 mg/kg SC	----
Pentobarbital + Ketamine	----	----	20 mg/kg IP + 60 mg/kg IP	----
Tiletamine/ zolazepam (Telazol)	40-60 IM	80 IP	40 IP	Not recommended
Urethane	1000-1500 IP	1000-1500 IP	1000-1500 IP	1500 IV
Xylazine + Ketamine	5-8 SC, IP + 30-60 SC, IP	10 IP + 80-100 IP	10 IP + 75-100 IP	5-8 SC, IM + 30-40 IM, SC 3 + 10 IV
(reverse xylazine with atipamezole)	1 IP	1 IP	1 IP	1 IP

Comments on Specific Agents

Avertin (tribromoethanol)

This agent is widely used in mice for embryo transfer and vasectomy and offers the advantage of not being a federally controlled drug. It can be purchased through chemical suppliers. The drawbacks to this agent are that is cumbersome to prepare, requires special storage conditions, will decompose to toxic by-products if not stored properly, sensitizes some animals to subsequent exposure, and causes idiosyncratic deaths in about 1% of naive mice. It also has arguable inflammatory properties (Zenner, 1998; Reid, 1999; Weiss, 1999). The following information on the practical use of tribromoethanol was kindly provided by Katrina Waymire.

Preparation

A stock of 100% avertin is prepared by mixing 10 gm of 2,2,2 tribromoethanol (Aldrich T4,840-2) and 10 ml of tert-amyl alcohol (Aldrich 24,048-6). Keep the mixture completely covered as it is light sensitive and stir on a stir plate or rotate in a tube at room temperature for 1-2 hours. Millipore filter and store in a covered container in the dark at 4°C. This 100% stock is stable in the cold for a year. If stored improperly, the agent will decompose to acidic by-products and cause severe peritonitis and high mortality. pH changes can be detected using Congo Red (turns purple if by-products present).

Working Solutions

or 2.5% working stock, dilute 100% avertin 1:40 (1+39) with sterile saline or PBS (1X stock). Cover with foil. Shake gently for 30 min at room temperature(oily mix takes a while to go into solution). The 1X working stock is good for only 2 months and can be stored either at 4°C or room temperature. Note: With some batches of 2,2,2-tribromoethanol, the mice may become sick and die several days after being anesthetized or if the compound is dark in color then recrystallizing the 2,2,2-tribromoethanol is necessary. To recrystallize, dissolve 50 gm of 2,2,2-tribromoethanol in 500 ml of boiling petroleum ether (NOT ethyl ether!) or hexane (boiling point 69°C) on a stirring hot plate in a fume hood. Caution: These solvents are extremely flammable; exercise extreme caution. Add a full spatula of charcoal. Filter through fluted filter paper in a glass funnel preheated to 65°C into a second beaker or flask. Cool on ice to 30° C. Pour off supernatant. Break up crystals with a glass rod or metal spatula and dry thoroughly under vacuum overnight. Store at 4°C.

Practical Dosing Tips

The proper dose of avertin may vary with different preparations and should be redetermined each time a new 100% stock is made. To test, inject several mice with doses ranging from 0.014 to 0.018 ml/gm body weight. The dose should be sufficient to give complete anesthesia, but it is also important to check the health and survival of the mice for 3-4 days afterward. For a 20 gm. mouse I usually start with 0.3cc IP injection and wait about 10 min for effect. If the mouse twitches when pinching feet then inject another 0.05 cc and wait 10 min more for complete anesthesia. After surgery, allow mice to recover undisturbed in a warm cage (»30°C). About 1% of mice are over-sensitized to this drug and will die following administration. If the agent is not stored properly, it will decompose creating products that cause toxic inflammatory peritonitis.

Chloral Hydrate (trichloracetaldehyde monohydrate), CIV

Chloral hydrate is a controlled drug with a prolonged onset of action leading to an extended state of pre-anesthetic delirium that may be unpleasant for the animal and it can cause gastric ulcers and adynamic ileus. At the traditional 300 mg/kg dose, cardiac output is stable, but analgesia is poor. Analgesia is adequate at 400 mg/kg, but there are physiologic dyscrasias such as hypotension and bradycardia that could be life-threatening for certain animals. To prevent adynamic ileus, working concentrations solutions should be 50 mg/ml or less. Chloral hydrate must be refrigerated. Administration of a pre-anesthetic anticholinergic agent is recommended to reduce the incidence of side effects. It should be purchased through chemical suppliers.

Fentanyl-Medetomidine

Fentanyl (Sublimaze, CII) is a potent, reversible opioid characterized by excellent analgesia, a short half-life, profound respiratory depression, and minimal cardiovascular depression. Its effects are pharmacologically reversible, but it is a controlled drug. It is not useful alone, but is given in combination with other agents. Fentanyl and medetomidine, each given in a combination of 300 mg/kg IP, provides 60 minutes of surgical anesthesia in the rat. This combination is highly fatal in mice and contraindicated. For best effect, give the medetomidine 30 minutes prior to fentanyl and keep animal in an oxygen-rich environment during induction. This combination is reversible with atipamezole (1 mg/kg IP), nalbuphine (2 mg/kg IP) or butorphanol (0.4 mg/kg IP). Fentanyl, nalbuphine and butorphanol should be purchased

on an interdepartmental requisition from the Emory University Hospital Pharmacy. Medetomidine and atipamezole can be ordered through the DAR.

Medetomidine-Ketamine Mixtures

Medetomidine is an alpha-2 receptor agonist with sedative and analgesic properties similar to xylazine, but with fewer undesirable side effects. It provides excellent anesthesia in combination with ketamine. It will still produce hypotension, bradycardia, respiratory depression, diuresis and glycosuria and is often fatal if re-dosed during the same procedure. However, it is completely and safely reversed with atipamezole (1 mg/kg IM, SC, IV or IP). Ketamine is a neuroleptanalgesic drug popularly used in rodents. It has little visceral analgesic properties alone. Ketamine doses, when used in combination with medetomidine, may need to be reduced for male rodents by a factor of 40-50%. Ketamine should be purchased on an interdepartmental requisition from the Emory University Hospital Pharmacy. Medetomidine and atipamezole can be ordered through the DAR.

Pentobarbital Sodium (Nembutal), CII

This sedative-hypnotic agent has little analgesic action at sub-anesthetic doses. It is a strong inducer of hepatic microsomal enzymes and a profound respiratory depressant at anesthetic dosages for many species. The veterinary formulation (100 ml) contains 65 mg/ml in 10% ethanol and the human formulation (20 ml) has 50 mg/ml in 0.678 mg/ml propylene glycol. Rapid injection of propylene glycol may cause intravascular hemolysis, hypotension, apnea, cardiac arrythmias, bradycardia. The analgesic effect of pentobarbital can be enhanced by balanced anesthesia with opioids, ketamine (pentobarbital 20 mg/kg + ketamine 60 mg/kg in rats) or narcotic agonist-antagonist drugs. Pentobarbital should be should be purchased on an interdepartmental requisition from the Emory University Hospital Pharmacy and should be diluted 1:9 with sterile water and used at a working concentration of 5.0-6.5 mg/ml to prevent chemical irritant peritonitis and to permit accurate dosing. Recovery times are often very lengthy and hypothermia, respiratory depression, and hypotension are potential complications. In guinea pigs, hamsters and rabbits, pentobarbital can be highly lethal.

Urethane

This agent is readily soluble in water and used as a 10-20% solution. It provides long-lasting anesthesia with minimal cardiovascular or respiratory depression, but urethane is mutagenic and carcinogenic. Consequently, it is considered a chemical hazard and is used only for non-survival procedures. It may be purchased through chemical suppliers.

Xylazine (Rompun)-Ketamine (Ketaset), CIII

The combination of ketamine and xylazine has been popular for the anesthesia of a wide variety of species, with the effective dose varying widely among species and between strains of the same species. While there may be genetic variability in response to anesthesia within rodent species, as a general rule, surgical anesthesia can be maintained for 45-60 minutes with a single injection of xylazine and ketamine IP. For rabbits undergoing minimally invasive diagnostic procedures requiring immobilization, surgical procedures of moderate intensity (i.e. wound suturing, tissue biopsies) lasting less than 30-45 minutes, or for induction to permit intubation prior to the administration of gas anesthesics the combination of 5 mg/kg xylazine with 35 mg/kg ketamine SC or IM is effective. However, for procedures with intense

sympathetic stimulation (i.e. laparotomy) or for anesthesia lasting 60-90 minutes, 0.1 mg/kg butorphanol tartrate (TorbutrolR, Aveco Co., Inc., Fort Dodge, IA) or 0.75 mg/kg acepromazine maleate (PromaceR, Aveco Co. Inc., Fort Dodge, IA) should be given at the time of anesthesia induction with xylazine and ketamine. If it is necessary to further extend anesthesia, incremental doses of one-fourth to one-half the original ketamine dose can be given. Xylazine can be partly reversed with 0.2 mg/kg yohimbine IV. Mixtures of ketamine and xylazine are not stable and often have changes in potency detectable within 7 days of mixing. Ketamine should be purchased on an interdepartmental requisition from the Emory University Hospital Pharmacy. Xylazine and yohimbine can be ordered through the DAR.

Administration Routes

Interscapular SC injections are preferred for both rabbits and rodents providing that the administered agent is not excessively irritating. Because of the stress of restraint, relatively low muscle mass, risk of accidental sciatic nerve injection, inflammation, and prolonged recovery times, intramuscular (IM) injection of anesthetics to rodents is not recommended. Intraperitoneal (IP) injection is better tolerated than IM and is recommended if SC injection is not feasible. Injections by the IP route should be given lateral to the umbilicus in order to avoid injection of the cecum. Properly restrained rabbits will tolerate IM injections into the semimembranosus, semitendinosus, and epaxial muscles.

Needle Sizes and Sites and Recommended Volumes for Injection

Species	Subcutaneous	Intramuscular	Intraperitoneal	Intravenous
Mouse	**Scruff, 2-3 ml, <20G**	**Not recommended. Can use quadriceps or caudal thigh, 0.05 ml, <23G**	**2-3 ml, <21G**	**Lateral tail vein, 0.2 ml, <25G**
Rat	**Scruff, back, 5-10 ml, <20G**	**Not recommended. Can use quadriceps or caudal thigh, 0.3 ml, <21G**	**5-10 ml, <21G**	**Lateral tail vein, 0.5 ml, <23G**
Hamster	**Scruff, 3-4 ml, <20G**	**Not recommended. Can use quadriceps or caudal thigh, 0.1ml, <21G**	**3-4 ml, <21G**	**Femoral or jugular vein (cut down), 0.3 ml, <25G**

Guinea Pig	**Scruff, back, 5-10 ml, <20G**	**Not recommended. Can use quadriceps or caudal thigh, 0.3 ml, <21G**	**10-15 ml, <21G**	**Ear vein, saphenous vein, 0.5 ml, <23G**
Rabbit	**Scruff, flank, 30-50 ml, <18G**	**Quadriceps, caudal thigh or lumbar muscles, 0.5-1 ml, 20G**	**50-100 ml, <20G**	**Marginal ear vein, 1-5 ml (slow bolus) or CRI, <21G**

Adapted from Flecknell, 1987 (Table 3.4)

Local Anesthesia

Specific agents can be given by various routes, topical, infiltrative, regional, retrobulbar, intra-articular, subsynovial, epidural/subarachnoid, and refrigeration/hypothermia, to block nerve depolarization and conduction. Effective use of local anesthesia is useful in MAC reduction - the outcome can be a safer, cheaper anesthetic prep. For surgical purposes, local anesthetics are generally ineffective when applied topically either pre- or post-operatively. Penetration is usually poor through intact skin, the acidic environment of inflammed tissue neutralizes the drug, and the agent may be removed from the site by the grooming patient. Infiltrative or line blocks of a surgical incision site are the most common applications in research. A 0.5% lidocaine (Xylocaine) block of a surgical site will provide < 90 min. of local anesthesia. To avoid cardiac arrhythmias, do not exceed a total dose of 7 mg/kg. For over 3 hours of analgesia, use 0.25% bupivicaine (Marcaine) in the same way, but do not exceed a total local dose of 8 mg/kg. Local anesthetic infusions can be used to facilitate anesthesia when a plane induced by injection is not quite adequate and additional injections may prove dangerous. Topical hypothermic sprays are useful for providing local anesthesia for tail snips of young rodents.

Hypothermia

Hypothermia is favored as a neonatal rodent anesthetic because of low mortality, ease of use, safety, and cost. Newborn rodents are functionally poikilothermic and, with a relatively small body mass, are amenable to rapid core cooling that causes Arefrigeration analgesia" by blockage of nerve conduction. Neural conduction is diminished by 75% when tissue is cooled below 20°C and complete neural blockage occurs at about 9°C. To induce hypothermia, pups are either (1) placed in a latex sleeve and immersed up to the neck in crushed ice and water (2°C-3°C) or (2) placed in a paper-lined tube and packed in dry ice. The former method requires a 3-4 minute induction time (2-3 minutes to unconsciousness and 3-5 minutes to complete blockage of neural transmission). The latter method may require 15 minutes to obtain a surgical plane of anesthesia. Analgesia for hypothermia induced by these methods lasts approximately 10 minutes . Simply placing conscious animals in a cold room or on an ice pack are unacceptable as induction may take 30-45 minutes. The anesthetic state may be prolonged by placing the hypothermic pup on an ice pack (3°C-4°C). Studies have shown that rodent pups will maintain a core body temperature of approximately 5°C when kept on an ice pack for a maximum of 15 minutes. Illumination of the surgical

field should be fiber optic in nature, because incandescent bulbs may cause inadvertent and uncontrollable warming. Pups should be recovered and slowly rewarmed in an incubator at 33°C or in a warm nest. Complete recovery typically requires 30-60 minutes.

Inhalation Anesthesia

Introduction

The general advantages to the use of inhalation agents are that the procedure is technically feasible and often preferred because it is precise, rapidly adjustable, safe, and effective especially for procedures lasting more than 1-2 hours. Postoperative recovery is rapid and less complicated than with injectable anesthetics. The major drawback to inhalation anesthesia in rabbits and rodents is the challenge (surmountable!) in establishing a patent airway from the anesthetic machine to the respiratory tract of the patient. Blind or direct visualization techniques are well-described for the intubation of rabbits and rodents and intubation is not as daunting as one might suspect for rabbits. Intubation of rodents usually requires either a tracheostomy (customarily a non-survival procedure) or specialized endotracheal tubes and laryngoscopic equipment. Gas anesthesia can also be delivered via a semi-closed mask system with a means of waste gas scavenging. Typically, 1-3% halothane and 2-4% isoflurane are adequate for anesthesia maintenance providing that system leaks are minimal.

For brief anesthesia, to permit IP injections, blood collection, nail and incisor trimming, or quick, uncomplicated surgical procedures, rodents can be placed in an induction chamber and exposed to inhalation agents delivered from a precision vaporizer or, alternatively, from cotton balls or gauze sponges in a chamber under a false floor (to prevent physical contact of the animal with the anesthetic liquid). The latter, a traditional method of administration, is less precise, safe and controllable than the former. The agents typically used are halothane or isoflurane. Diethyl ether is not recommended by the veterinary staff as it is explosive and flammable with a pungent, unpleasant odor and requires specific IACUC and Chemical Safety approval. Delivery using a precision vaporizer requires an anesthesia machine and considerable up front investment, but offers the advantages of precision, rapid adjustment, safety, effectiveness, and, in the long run, conserves anesthetic agent and becomes cost effective. Investigators interested in purchasing anesthesia machines for rodent use should contact the veterinary staff for advice. It is important to remember that isoflurane and halothane have high vapor pressures and, if used in an induction chamber without strict volume control, may produce rapidly lethal gas concentrations.

Anesthetic Gas Characteristics

Drug	Vapor Pressure[1]	Max. Conc.[2]	Metabolites (metabolism)	MAC[3] in Rats	Induction (%)	Maintenance (%)
Halothane	243	32%	15-20% (hepatic)	0.95%	1-4%	0.5-2%
Isoflurane	252	33%	0.2%	1.38%	2-6%	1-3%

1. Vapor Pressure at 20°C (torr/mm Hg)
2. Maximum Concentration (%) of gas at equilibrium with room air at sea level at 20°C
3. MAC = minimum alveolar concentration (minimum concentration to maintain anesthesia in 50% of patients (indicator of potency), values given are for the rat. Generally, anesthetic maintenance requires 1.5-2.0 times MAC.

Halothane (Fluothane)

This halogenated halocarbon that is a cardiac and respiratory depressant with fast induction and recovery. It is less irritating to the upper airways than other agents, but has poorer analgesia and muscle relaxation qualities and sensitizes the heart to catecholamines. Halothane has been shown to be mutagenic and hepatotoxic with other untoward effects usually related to metabolic products of the gas (including toxic by-products such as bromides and free). If halothane is used in a bell jar, gas exposure can be prevented or reduced to safe levels of exposure by using it only in a fume hood. Market availability of halothane is diminishing.

Isoflurane (Aerrane, Forane)

This agent is not metabolized into toxic by-products (but still should be used in a fume hood if administered in an induction chamber), has fast induction and recovery, does not sensitive the heart to catecholamine induced arrhythmias, and maintains good cardiac output. It is the preferred agent for inhalation anesthesia, but its major drawback is a higher cost relative to halothane.

Practical Use in An Induction Chamber

As both halothane and isoflurane have similar vapor pressures (see table above), their use is described interchangeably (as “gas” or “agent”) in the ensuing protocol. Special consideration should be given to keeping animals isolated from agent in the liquid phase which can be irritating to the skin and eyes. Owing to the high volatility of these agents, the lid should be kept on the induction chamber constantly or the volume of gas will be rapidly exhausted.

For induction, a concentration of 2-4% concentration of gas is normally adequate. To use either gas accurately, the induction chamber volume must be known precisely. After determining the chamber volume (it is recommended to record this permanently somewhere easily retrievable), add 0.1-0.2 ml of gas (in liquid form from the bottle) for each liter of chamber capacity. This can be done by applying the gas in liquid phase from its bottle to a cotton ball below the false floor of the container. For small containers, a piece of cotton can be enclosed in a histology tissue cassette and the agent may be poured or applied onto the cotton in the cassette Use of 0.2 ml liquid agent per 1000 ml chamber volume will give about a 4% concentration of gas. In the experience of the DAR veterinary staff, using nine naïve ICR mice (5 males & 4 females; 2 months of age) introduced to the chamber sequentially after the introduction of isoflurane (0.2 ml/L chamber volume), recumbency was obtained in 57 +/- 21 seconds. However, for rapid and effective induction, the agent had to be replenished in the chamber approximately every 3 mice.

Volume of liquid agent/1000 ml chamber volume	Approximate concentration ofisoflurane or halothane
0.05 ml	1%
0.1 ml	2%
0.2 ml	4%
0.3 ml	6%

Induction Chambers

Any number of apparati from simple jars with screw-top lids, dessication chambers, bell jars, or specific inhalation chambers (i.e., Inhalation Narcosis Chamber, Harvard Apparatus, #59-6717, 1-800-272-2775, $132.50) may be used for anesthesia induction.

Reversal Agents and General Drug Metabolism and Excretion

Drug	Biotransformation	Excretion	Reversal Agent
Avertin	100% Hepatic	Renal	
Chloral hydrate	100% Hepatic	Renal	
Droperidol	Hepatic	Renal	
Ether	20% Hepatic	Exhalation	
Fentanyl	90% Hepatic	Renal	Naloxone
Halothane	20% Hepatic	Exhalation	
Ketamine	None	Renal/Hepatic	
Medetomidine		Renal	Atipamezole

Midazolam	100% Hepatic	Renal	
Pentobarbital	50-75% Hepatic	Renal	
Tiletamine	None	Renal/Hepatic	
Xylazine	100% Hepatic	70% Renal + 30% Hepatobiliary	Atipamezole, Yohimbine
Zolazepam	+/- Hepatic	Renal	

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