Anesthesia Considerations in Rodent Biomedical Research

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Anesthesia Types in Rodents
- Injectable (e.g. ketamine cocktails)
- Volatile gas (e.g. isoflurane, sevoflurane)
- Physical (e.g. hypothermia)

Why Anesthetize an Animal
1 or more reasons:
- Avoid pain (loss of sensation)
- Immobilize (muscle relaxation)
- Avoid distress (loss of consciousness)

Injectable or Inhalation Anesthesia?

Injectable Anesthetics - Advantages
- Simple
- Cheap
- Minimal equipment

Injectable Anesthetics - Disadvantages
- Higher morbidity & mortality when compared to inhalants
- Easier to overdose
- Slow and variable absorption
- Longer recovery times
- Variable effects from a single dose
- Strain and gender differences
Inhalant Anesthetics - Advantages

- Usually suitable as sole agents to reach ‘balanced’ anesthesia
  - Loss of sensation
  - Loss of consciousness
  - Muscle relaxation

Inhalant Anesthetics - Disadvantages

- Anesthetic delivery system - $???
- Requires a scavenging system
- Requires yearly calibration (unless otherwise specified by manufacturer)

Volatile Anesthetics

- Ether
- Halothane
- Methoxyflurane
- Enflurane
- Isoflurane
- Desflurane
- Sevoflurane
**Isoflurane - Advantages**
- Rapid induction & recovery
- Can manipulate depth of anesthesia easily & rapidly
- Non-irritant, non-explosive & non-flammable
- Nearly 100% eliminated in exhaled air... minimal interference in drug metabolism
- Minimal cardiovascular depression
- Inexpensive... eventually!!!

**Isoflurane - Disadvantages**
- Some respiratory depression
- Pungent odor may lead to breath holding in rabbits, but does not appear to be a problem in other spp

**Sevoflurane - Advantages**
- Faster induction & recovery than isoflurane
- Nonirritating to airways and well accepted, lending itself to mask or chamber inductions
- Becoming increasingly more popular in rodents

**Sevoflurane - Disadvantages**
- Undergoes slightly greater hepatic metabolism than isoflurane

**Anesthetic Gas Recovery as Metabolite**
- Methoxyflurane: 50%
- Halothane: 20-25%
- Sevoflurane: 2-5%
- Enflurane: 2.4%
- Isoflurane: 0.17%
- Desflurane: 0.02-0.2%

1Humans

Recovery times (min) in rats after 1 hour of anesthesia - Eger and Johnson, 1987
**Somnosuite (Kent Scientific)**

- Integrated digital vaporizer
- Pre-warmed isoflurane gas
- Tissue oxygen-hemoglobin concentration (SpO₂)
- Temperature control
- Heart rate
- Respiration rate
- Ventilator

**The Savings**

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**Physiosuite (Kent Scientific)**

- Temperature control: Homeothermic (warms rodent at exact temp by far infrared warming that goes beyond cutaneous warming by heating deep into rodent’s body with temp feedback)
- Pulse oximeter and heart rate
- Automatic ventilator (ventilate animals as small as 3g - simple enter weight and press run)
- End tidal CO₂ monitor
Open Drop
Method of Isoflurane & Sevoflurane Administration

Open Drop

- Quite useful & easy to apply, but...
  - Prolonged use = deaths
  - Used for short term anesthesia (minutes)

Injectable Anesthetics

Pentobarbital - Advantages

- Placental transfer of barbiturates occurs rapidly. However, when used in proper induction doses, excessive depression of the fetus does not occur
- Administered IV or IP
- Neither hepato- or nephrotoxic

Pentobarbital - Disadvantages

- Pharmaceutical grade very pricey
  - High cost renders it “unavailable in pharm grade” ***
- Chemical grade use must be addressed & justified
  *** NIH statement 2013
Pentobarbital - Disadvantages

- Prolonged recovery esp. if additional doses administered
- Severe cardiovascular & respiratory depression
  - Anesthetic & lethal doses close to each other... high mortality possible

Ketamine

- Thought to be a specific antagonist of N-methyl-D-aspartate glutamate receptors (NMDA)
- "Cocaine-like" effect in that it inhibits uptake of catecholamines into postganglionic sympathetic nerves
- Cleared by hepatic metabolism
- Alone it is a poor anesthetic and analgesic in rodents (when used alone)... must be used with other tranquilizers &/or sedatives ('cocktail')

Ketamine

- CV effects resemble sympathetic nervous stimulation - i.e. increased arterial BP, HR, CO, cardiac workload & myocardial oxygen consumption
- Such effects obtunded by prior or co-administration of tranquilizers or sedatives ('cocktail')
- Transient increase of norepinephrine & epinephrine in plasma

Ketamine - Advantages

- In hypovolemic patients, arterial BP is maintained with ketamine because of peripheral vasoconstriction
- No significant effect on hepatic or renal function
- Increases myocardial contractility

Ketamine - Disadvantages

- Increased airway & salivary secretions in some species (mild in mice & rats)
- Induces epileptiform bursts in thalamus & limbic system, but w/o spread to cortical areas - may increase seizure threshold in rats & mice
- Some respiratory depression following anesthetic doses in rodents

Ketamine ‘Cocktails’

- Safer, more ‘balanced’ anesthesia than pentobarbital or ketamine alone
  - Ketamine/xylazine
  - Ketamine/dexmedetomidine
  - Ketamine/xylazine/acepromazine
  - Other combinations
Ketamine ‘Cocktail’ Reversal

- **Antagonist atipamezole** shortens recovery of ketamine/xylazine & ketamine/dexmedetomidine
- Atipamezole (0.5-1 mg/kg SC, IP, IM, IV) partially reverses xylazine & dexmedetomidine (not ketamine)
- Early reversal (10–20 minutes after induction) associated with undesirable behavioral disturbances due to effects of ketamine

Ketamine/Medetomidine Reversal with Atipamezole

Courtesy of Dr. Paul Flecknell

Video Mouse - Anesthetic recovery w Atipamezole reversal.

Ketamine ‘Cocktails’

- Use of yohimbine for reversal of ketamine/xylazine no longer recommended due to yohimbine’s reported side effects
- For cocktail doses refer to [http://research.utsa.edu/research-funding/laboratory-animal-resources-center/training/](http://research.utsa.edu/research-funding/laboratory-animal-resources-center/training/)

Tribromoethanol (Avertin)

- Adequate anesthesia up to 30 min
- Repeat doses not recommended due to abdominal irritation & peritonitis reports
- Degrades in presence of heat or light - refrigerate, wrap in foil
- Non-pharmaceutical grade compound

Urethane
**Urethane - Advantages**

- IP Administration results in long-lasting unconsciousness of 6-10 hr
- Cardiopulmonary functions minimally affected, including blood pressure due to effects on catecholamine release
- Good analgesia for surgery in rodents

**Urethane - Disadvantages**

- Peritoneal effusion & hemolysis
- Mutagen/carcinogen
- Readily absorbed through skin
  - pre-neoplastic changes in skin
  - targets multiple organs
  - suppresses bone marrow
  - readily crosses the placenta
  - fetal tumor formation (*in utero*)

**Urethane**

- Strict guidelines (gloves, mask, prepare in fume hood)
- Non-pharmaceutical grade compound
- Not used for survival surgeries

**Resources**

Presentations, References & Useful Notes
http://research.utsa.edu/research-funding/laboratory-animal-resources-center/training/

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