Pharmacology: Inhalation Anesthetics

This is an edited and abridged version of:

Pharmacology: Inhalation Anesthetics by Jch Ko, DVM, MS, DACVA

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Overview

Commonly Used Inhalation Anesthetics

- Isoflurane
- Sevoflurane

Less Commonly Used Inhalation Anesthetics

- Methoxyflurane
- Halothane
- Desflurane
- Nitrous oxide

Clinical Considerations of Selecting an Inhalation Agent

Metabolism

Percentage of Anesthetic Recovered as Metabolites	
Methoxyflurane	Up to 50% is metabolized by the liver and kidneys
Halothane	Up to 20-25% is metabolized by the liver and kidneys
Sevoflurane	3.0 % is metabolized by the liver and the kidneys
Isoflurane	0.17% is metabolized by the liver and the kidneys
Desflurane	No documented metabolism
Nitrous Oxide	No documented metabolism

- **Major elimination route of inhalation anesthetics is via respiration.**
- **For a patient with hepatic dysfunction, the choice of inhalation anesthetic is isoflurane, sevoflurane or desflurane - less liver metabolism.**
- **Although nitrous oxide has almost no liver metabolism, it is not commonly used in veterinary anesthesia, see below for details**

Anesthetic Potency

- What is MAC?
  - MAC is the minimal alveolar concentration of an anesthetic (in volume %) at which 50% of the patients will not respond to painful stimuli (e.g., surgery-skin incision, tail clamp).
  - MAC is used to compare inhalation anesthetic potency. (Similar to mg/kg for injectable anesthetics).
  - Clinically, achieving a surgical plane of anesthesia usually requires 1.2 to 1.5 times MAC to ensure 99.9% of the patients will not respond to the surgical stimulation.

- The lower the MAC value, the more potent the anesthetic agent.
  - MAC values from the table below demonstrate that methoxyflurane is the most potent and nitrous oxide is the least potent inhalant anesthetics. Halothane, isoflurane and sevoflurane are somewhere in between. Sevoflurane is less potent than halothane and isoflurane.
  - The clinical implication of anesthetic potency is mainly related to the cost of the inhalant. The less potent the inhalant anesthetic, the higher the percentage of the inhalant anesthetic agent that will have to be used for anesthesia maintenance, and therefore the higher cost.

Comparison of anesthetic potency of inhalant anesthetics using MAC (volume %).

	Mouse	Rat	Dog	Human
Methoxyflurane	---	---	0.23 %	0.16 %
Halothane	---	---	0.87 %	0.74 %
Isoflurane	---	---	1.28 %	1.15 %
Sevoflurane	---	---	2.1-2.36%	1.7%
Desflurane	---	---	7.2%	
Nitrous oxide	---	---	188 %	105 %

- Nitrous oxide is not commonly used in veterinary anesthesia for the following reasons:
  - Weak analgesic property when used alone in domestic animal species (MAC is roughly 200% - it is twice as potent in humans).
  - Its use together with a primary inhalation anesthetic (such as halothane, isoflurane) only reduces the amount of primary inhalation anesthetic by 25% to 30% of the control value (using halothane or isoflurane alone) at the most. This may not significantly reduce the amount of the primary anesthetic.
  - Because nitrous oxide is a weak analgesic agent and must be used in high concentrations, the inspired oxygen concentration is proportionally reduced. This is not suitable for patients with pulmonary diseases that may require as much as 100% inspired oxygen to maintain acceptable blood oxygenation.

- The use of nitrous oxide requires a higher fresh gas flow rate than would be used with oxygen alone. Accordingly the total amount of the primary anesthetic that is vaporized is increased - more anesthetic is wasted, and therefore cost is increased.
- Nitrous oxide diffuse rapidly into closed gas cavities within body, at a faster rate than nitrogen diffuses out of the cavity, resulting in either an increase in volume or pressure. Patients with gastric or intestinal distension or pneumothorax will suffer further.
- Risk of diffusion (dilutional) hypoxia. This occurs at the time when the nitrous oxide is turned off and the patient is disconnected from the breathing circuit and starts to breathe room air (21% oxygen). Nitrous oxide is usually used in large volumes during anesthesia (> 50%), and when it is turned off its uptake is reversed and it moves from the blood to the alveoli. Thus, during the first 5 to 10 minutes after discontinuing the nitrous oxide, the volume moving into the lung is large and dilutes the oxygen in the alveoli. If breathing room air, this may result in hypoxia. To avoid dilutional hypoxia, the animal should breathe 100% oxygen for the first 5-10 minutes after discontinuing nitrous oxide.

Rate of Induction, Rate of Change in Anesthetic Depth, and Rate of Recovery

- Rate of induction, change in anesthetic depth, and rate of recovery are related to the blood/gas solubility of each inhalation anesthetic.
- The higher the blood/gas solubility, the slower the induction and recovery rates.
- The higher the blood/gas solubility, the slower rate of change in depth of anesthesia.

Comparison of solubility, vapor pressure, and use of preservatives

Anesthetic Agent Formula (Trade name)	Blood/gas solubility	Vapor Pressure at 20°C (mmHg)	Preservatives
Methoxyflurane $CHCl_2$-CF_2-O-CH_3 (Metofane®)	12	23	Required
Halothane $CBrClH$-CF_3 (Fluothane®)	2.4	243	Required
Isoflurane CF_3-$CHCl$-O-CF_3H (Forane®, Aerrane®)	1.4	240	None
Sevoflurane CFH_2-O-$(CF_3)_2$ (Ultane®, Sevoflurane®)	0.69	160	None
Desflurane CF_3-CHF-O-CF_2H (Suprane®)	0.42	664	None
Nitrous oxide N_2O	0.47	---	None

- Based on the table above, induction, recovery and changes in anesthetic depth are slowest with methoxyflurane and fastest with nitrous oxide and desflurane.

- Mask induction is impractical using methoxyflurane because of its high solubility and therefore very slow speed of induction. In addition, attempts to speed induction with high anesthetic concentration is limited by the maximum concentration achievable with methoxyflurane (approximately 3% - due to its low vapor pressure). Clinically we often use isoflurane for mask induction. With sevoflurane's lower blood/gas solubility, it may provide an advantage for mask induction.

- Because of its low solubility, nitrous oxide is used to facilitate the induction and rate of change in anesthetic depth when used together with one of the primary anesthetics such as halothane or isoflurane (this is called the 2nd gas effect).
- Because of its low blood/gas solubility, isoflurane is used extensively in avian anesthesia for rapid induction and recovery. Sevoflurane may be even better for avian species once it becomes more commonly used.

Cardiopulmonary Aspects

Overall, all inhalant anesthetics depress cardiopulmonary function in a dose-dependent manner as shown by the decreases cardiac output, blood pressure, respiratory rate and increase in partial pressure in CO_2 concentrations.

- Myocardial depression:
  Halothane > or = methoxyflurane > isoflurane = sevoflurane = desflurane > N2O
- Reduction in cardiac output:
  Halothane > or = methoxyflurane > isoflurane = sevoflurane = desflurane > N2O
- Reduction in systemic vascular resistance:
  Isoflurane = sevoflurane = desflurane > methoxyflurane > or = halothane > N2O
- Respiratory depression:
  Isoflurane = sevoflurane = desflurane > methoxyflurane > halothane > N2O

Cost

- Desflurane > sevoflurane > isoflurane > halothane
- Methoxyflurane is relatively expensive due to lack of production (it is no longer being produced by the company that produced it for many years; another smaller company may have picked up production, but availability is questionable).
- Isoflurane has lost its patent and the cost has decreased significantly in the last few years.
- Sevoflurane is a new agent and costs about four times more than isoflurane when compared on an ml/ml basis.

- Desflurane requires a special vaporizer (due to its high vapor pressure) that is only compatible with the newest human anesthetic machines - both the vaporizer and the anesthetic machines are very expensive. Desflurane itself costs about the same as sevoflurane. Because of the equipment considerations, only sevoflurane is currently making inroads into the veterinary market.

Clinical Use of Inhalant Anesthetics

Inhalant anesthetics are used for induction and maintenance of general anesthesia.

- Induction Advantages:
    - It offers the advantage of accurately controlling anesthetic depth during induction with the safety of being able to discontinue the administration of the inhalant anesthetic immediately if problems arise.
    - Furthermore, should problems arise, the inhalant anesthetic (sevoflurane, isoflurane or halothane) can be eliminated quickly through ventilation.
    - High-inspired oxygen is usually provided with inhalant anesthetic during induction.
- Induction Disadvantages:
    - The pungent smell of the isoflurane or halothane may prompt the animal to hold their breath during induction and therefore prevents the uptake of the inhalant anesthetic and slows the speed of induction. (This can be remedied through use of an induction chamber.)
    - Sevoflurane is supposed to be the best for inhalant anesthetic induction…less irritation to the airway and faster speed of induction. It has been the main inhalant anesthetic for using in human infants and children for mask induction.
    - Pollution of the work environment during induction. Waste inhalant anesthetic gas may cause headaches and other health problems. (This can be controlled by using a properly functioning waste gas evacuation system. Many choices are available.)
    - It is not suitable for healthy, unpremedicated dogs because of the relatively slow speed of induction via inhalant anesthetic. The induction is also frequently accompanied with vocalization, excitement, defecation, urination,

and vigorous struggling (if you are strong enough to hold the struggling dog and willing to clean up the mess after the induction, you may consider this induction method as suitable for your clinic).

- Maintenance Advantages:
    - Protection of the airway - since almost all patients anesthetized with inhalation anesthetic are intubated.
    - The depth of anesthesia during maintenance is easily controlled by adjusting the vaporizer output, ventilation pattern and the total flow rate.
    - High-inspired oxygen is usually provided with inhalant anesthetic during the maintenance. This will augment the oxygen content of the blood. It is especially helpful to the patient with low oxygen-carrying capacity (patients with anemia or respiratory dysfunction).
    - Rapid recovery when compared to most of the injectable combinations. (Inhalant anesthetics are mostly eliminated through ventilation, whereas injectable anesthetics rely on the liver and kidney for metabolism/elimination).

Chamber Induction

- Suitable in small intractable animals.
- Provides a "hands free" induction with minimal physical restraint to the patients. Safe to the patient as well as personnel.
- 5% isoflurane or 8% sevoflurane with high flow rates of oxygen (5+ lpm) is used until the animal losses its righting reflex. The animal is then taken out of the chamber, placed on a facemask, and anesthetic administration is continued until the patient is unconscious and ready for endotracheal intubation.

Facemask / Nosecone Induction

- Select a tight-fitting facemask and place it on the face of the animal. Use the smallest mask possible to minimize dead space ventilation. (Nosecones work best for rodents.)

- Suitable in birds, neonate ruminants or foals, debilitated dogs or cats, or in healthy dogs or cats following profound premedication (acepromazine, opioids, or alpha-2 agents).
- Facemask induction is not practical in adult large animals (equine, bovine, porcine).
- Facemask induction usually begins with 4-5% of halothane, isoflurane, or 5-8% sevoflurane and continues until the animal is unconscious and able to be intubated.
- Using facemask induction in healthy animals with isoflurane without profound premedication usually results in excitement.
- Sevoflurane is markedly better for mask inductions than isoflurane
- Debilitated patients (diseased dogs, cats, birds, other small ruminants or foals).
    - Mask induction usually begins with 2-3% of halothane, isoflurane, or sevoflurane and continues until the patient is unconscious and ready for intubation
    - Debilitated patients are already depressed by the disease and they are more sensitive to the inhalation anesthetics, therefore reducing the inhalant anesthetic % is usually a good idea.
    - Debilitated animals are less likely to become excited or struggle during induction.

Maintenance of General Anesthesia

- All major inhalant anesthetics (methoxyflurane, halothane, isoflurane and sevoflurane) are maintained with 1.2 to 1.5 times MAC for general anesthesia.
- Premedication with a tranquilizer or an opioid will reduce the maintenance concentration of inhalation anesthetics.
- In general, inhalation anesthetics are maintained with following concentrations:
    - Methoxyflurane: 0.5 - 1.5%
    - Halothane: 0.75 - 2.0%
    - Isoflurane: 1 - 2.5 %
    - Sevoflurane: 2.5 - 4.0%

Factors Affecting MAC

Although all inhalant anesthetics are maintained with 1.2 to 1.5 times MAC for general anesthesia, factors that affect MAC have to be considered during the maintenance of general anesthesia.

- **Factors that decrease MAC:**
  - Hypotension
  - Anemia (PCV < 13%).
  - Hypothermia
  - Metabolic acidosis
  - Extreme hypoxia (PaO_2 < 38 mmHg)
  - Age: older animal require less anesthetic
  - Premedication (opioids, sedatives, tranquilizers)
  - Local anesthetics
  - Pregnancy
  - Hypothyroidism

- **Factors that increase MAC:**
  - Increasing body temperature – increases cerebral metabolic rate of brain
  - Hyperthyroidism
  - Hypernatrimia

- **Factors NOT affecting MAC:**
  - Type of stimulation

- Duration of anesthesia
- Species - MAC varies by only 10-20% from species to species
- Sex
- $PaCO_2$ between range of 14-95 mmHg
- Metabolic alkalosis
- PaO_2 between range of 38-500 mmHg
- Hypertension
- Potassium – no effect