Pharmacology- Inhalant Anesthetics

Lyon Lee DVM PhD DACVA

Introduction

- Maintenance of general anesthesia is primarily carried out using inhalation anesthetics, although intravenous anesthetics may be used for short procedures.
- Inhalation anesthetics provide quicker changes of anesthetic depth than injectable anesthetics, and reversal of central nervous depression is more readily achieved, explaining for its popularity in prolonged anesthesia (less risk of overdosing, less accumulation and quicker recovery) (see table 1)

Table 1. Comparison of inhalant and injectable anesthetics

Inhalant Technique	Injectable Technique
Expensive Equipment	Cheap (needles, syringes)
Patent Airway and high O_2	Not necessarily
Better control of anesthetic depth	Once given, suffer the consequences
Ease of elimination (ventilation)	Only through metabolism & Excretion
Pollution	No

- Commonly administered inhalant anesthetics include volatile liquids such as isoflurane, halothane, sevoflurane and desflurane, and inorganic gas, nitrous oxide (N_2O). Except N_2O, these volatile anesthetics are chemically 'halogenated hydrocarbons' and all are closely related.
- Physical characteristics of volatile anesthetics govern their clinical effects and practicality associated with their use.

Table 2. Physical characteristics of some volatile anesthetic agents.
(MAC is for man)

Name	partition coefficient.		boiling point	MAC %
	blood /gas	oil/gas	(deg=C)	
Nitrous oxide	0.47	1.4	-89	105
Cyclopropane	0.55	11.5	-34	9.2
Halothane	2.4	220	50.2	0.75
Methoxyflurane	11.0	950	104.7	0.2
Enflurane	1.9	98	56.5	1.68
Isoflurane	1.4	97	48.5	1.15
Sevoflurane	0.6	53	58.5	2.5
Desflurane	0.42	18.7	25	5.72
Diethyl ether	12	65	34.6	1.92
Chloroform	8	400	61.2	0.77
Trichloroethylene	9	714	86.7	0.23

- The volatile anesthetics are administered as vapors after their evaporization in devices known as vaporizers.
- Ideal properties of an inhalant anesthetic
  - Non-explosive

- Non-flammable
- Non-toxic
- Safe with CO_2 absorbent
- Potent
- Pleasant to inhale
- Minimal metabolism
- Low blood gas solubility
- Good analgesia
- Good shelf life
- Minimal organ depression
- Inexpensive

- The mechanism by which inhaled anesthetics produce the CNS depression is not clearly understood, and a single theory to explain it is unlikely. Most evidence is consistent, however, with inhibition of synaptic transmission through multineuronal polysynaptic pathways, particularly in the reticular activating system (see CNS & Anesthesia lecture)

Practical aspects of the use of inhalational (volatile) anesthetic agents

Anesthetic potency: The minimum alveolar concentration (MAC)

- The term 'potency' refers to the quantity of an inhalational anesthetic that must be administered to cause a desired effect such as general anesthesia, and the standard index of inhalation anesthetics is the **minimum alveolar concentration (MAC)** which was proposed by Merkel and Eger in 1963.
- MAC is defined as the alveolar concentration of anesthetic that prevents muscular movement in half the test subjects in response to a painful stimulus.
- It is usually expressed as a % but this assumes a normal sea level atmospheric pressure.
- As blood anesthetic gas levels are difficult to measure, end tidal levels of inhalant anesthetics are usually accepted as approximating to alveolar and therefore to blood gas tensions. The anesthetic potency of an inhaled agent is inversely related to MAC.
- MAC is also inversely related to the oil/gas partition coefficient (PC).
- The partition coefficient is defined as the ratio of the amount of substance (e.g., inhalant) present in one phase (oil, blood etc.) compared with another (gas), the two phases being of equal volume and in equilibrium.
    - A blood:gas PC of 0.5 means that the concentration of inhalant in the blood is half that present in the alveolar gas when the partial pressure of the anesthetic is identical at both sites.
    - PC in an inhalation anesthetic is most commonly used to refer to its solubility in a given solvent (e.g., oil, blood etc.).
    - A very potent anesthetic (e.g., methoxyflurane) has a low MAC value and a high oil/gas PC, whereas a low potency agent (e.g., N_2O) has a high MAC and low oil/gas PC.
    - In other words, an anesthetic with a high oil solubility (i.e., high oil/gas PC) is effective at a low alveolar concentration and has a high potency.

- The anesthetic dose is commonly defined in terms of multiples of MAC (i.e., 1.5 times MAC or 1.5 MAC).
- Surgical depth is usually achieved at 1.2 to 1.5 times of MAC values.
- In a single species the variation in MAC values is generally small.
- Even between species the variation is not usually large.
- One exception is N_2O where MAC in man is 104 %, whereas in most animals close to 200%, making the agent far less effective in domestic animals.
- In man, MAC is greatly influenced by age in inverse relationship.
- MAC is also reduced by any sedative, analgesic or parental anesthetic agents which has been used.
- Factors to decrease MAC
  - hypotension
  - anemia (PCV<13%)
  - hypothermia
  - metabolic acidosis
  - hypoxia
  - premedicants
  - pregnancy
  - aging
  - hypothyroidism
  - concurrent use of analgesics.
- Factors to increase MAC
  - increased body temperature
  - hyperthyroidism
  - hypernatremia
  - concurrent use of central nervous stimulant (e.g., doxapram).
- Factors known not to affect MAC
  - type of stimulation to test
  - duration of anesthesia
  - sex
  - $PaCO_2$ (between 15-95 mmHg)
  - hypertension
  - potassium

Table 3. Comparison of anesthetic potency of inhalant anesthetics using MAC (volume %).

Name	Dogs	Cats	Horses	Human
Methoxyflurane	0.23 %	0.23 %	0.28 %	0.16 %
Halothane	0.87 %	0.82 %	0.88 %	0.74 %
Isoflurane	1.28 %	1.63 %	1.31 %	1.15 %
Sevoflurane	2.1-2.36%	2.58%	2.36%	1.7%
Desflurane	7.2%	9.8%	7.6%	5.72 %

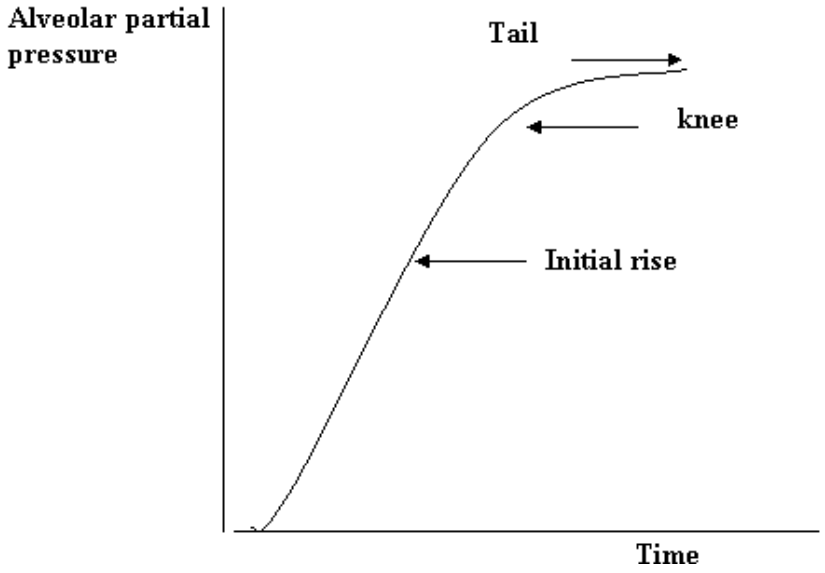
Nitrous oxide	188 %	255 %	205%	105 %

Uptake and elimination of volatile agents.

- Understanding of the uptake and elimination of an inhalational anesthetic is necessary for the proper use and subsequently improved safety for the patient.

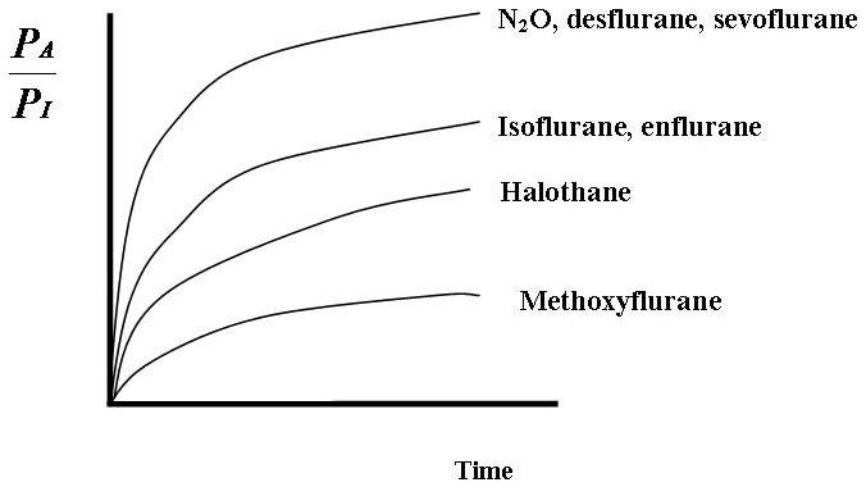
Alveolar partial pressure curve

- The alveolar partial pressure (P_A) of an inhaled anesthetic is in equilibrium with the arterial blood (Pa) and brain (Pbr). As a result the P_A is an indirect measurement of anesthetic partial pressure in the brain; $P_A \approx Pa \approx Pbr$.
- Kety described alveolar partial pressure curves for all inert gases have the same characteristics (inhalant anesthetics are considered to behave in the body as inert gases).
- *Figure 1. Kety's alveolar partial pressure curve of inhalant during uptake*



- The curve as depicted in the figure 1 above has three distinctive stages; initial rise, knee and tail. Initial rise represents a steep slope where the ventilation moves the agent rapidly into the lungs. Following this, the knee stage arrives where the rate of the agent start to slow down.
- Slopes of knee are determined by rate of uptake by vessel rich tissues (heart, brain, liver etc.) which receives greater than 70 % of cardiac output.
- The slopes of tail are determined by the rate of uptake of gas by muscles and fat (have relatively poor blood supply) which continues for a long time especially if the anesthetic has high oil/gas PC.
- The overall slopes differ between inhalants, principally affected by its solubilities in the tissue and blood (see figure 2 and 3).
- For example, the curve for methoxyflurane will be less steep than N_2O which has a very low blood or tissue solubility.

Figure 2. The rise of alveolar partial pressure (P_A) toward the inspired partial pressure (P_I) in different volatile anesthetics.



- Anesthetic elimination or recovery from inhalation anesthesia results from the elimination of anesthetic from the brain.
- This process is simply the reversal (wash-out) of the anesthetic uptake so the prominent factors affecting the recovery are the same as those for anesthetic induction.
- Alveolar concentration of inhalant reflects the amount in the brain

Factors governing the alveolar concentration of inhalants

- Alveolar anesthetic concentration primarily depends on (see table 4)
  a. Inspired concentration
  b. Alveolar ventilation
  c. Solubility of inhalant in blood and tissues
  d. Cardiac output
  e. Tissue capacity and blood flow to the tissues

Table 4. Factors influencing alveolar concentration

FACTORS (WITH INCREASE)	ALVEOLAR CONCENTRATION
Inspired concentration	↑
Alveolar ventilation	↑
Solubility	↓
Cardiac output	↓
Tissue capacity and blood flow	↓

Inspired concentration

- The higher the vaporizer setting, the higher the inspired concentration (or partial pressure, P_I) of the inhalant by the patient, which results in the higher alveolar concentration

- Volatility (boiling point).
  - Induction can be speeded by increasing the concentration of anesthetic gas inspired.
  - However, the concentration that can be obtained is governed by the volatility of the agent. (NB, with very volatile agents, it may not be safe to use maximal possible concentrations for other reasons).

Alveolar ventilation

- The inspired gases reach the alveoli, where gas exchange takes place.
- Initially there should be a rapid rise in alveolar concentration, but this is contra-balanced by the solubility of the inhalant anesthetics.
- The better a patient breathes in, the better the gas exchanges, and the faster the patient gets anesthetized.
- Increased alveolar ventilation, like P_I, promotes input of anesthetic to offset uptake. The net result is a more rapid rate of increase in P_A toward the P_I (i.e., the faster the alveolar concentration (P_A) will achieve the inspired concentration (P_I)), and thus induction of anesthesia.

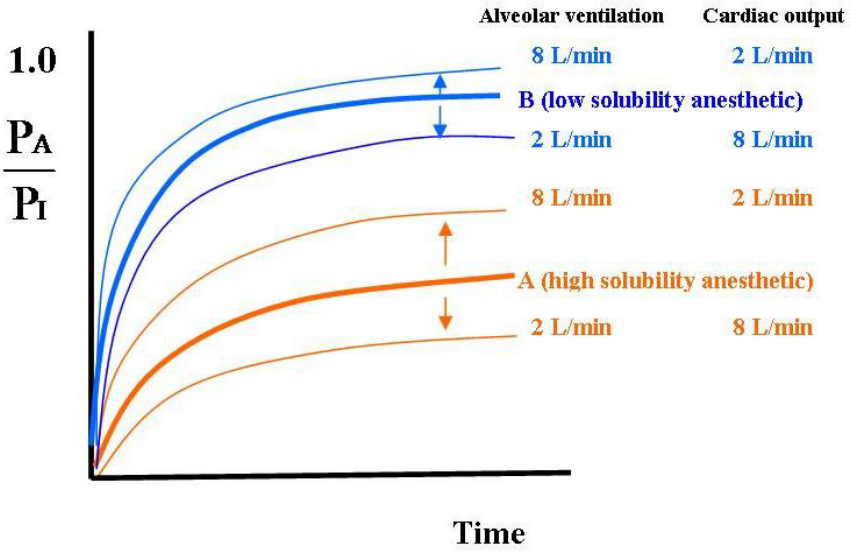
Solubility

- Uptake of inhalant by blood (wash-in) is determined by
  - blood/gas solubility (**S**)
  - cardiac output (blood flow; **CO**)
  - the **pressure gradient** of the partial pressure of anesthetics between the alveolus and venous blood returning to the lung (P_A-P_V; expressed in millimeters of mercury, mmHg), where, P_{bar} equals the barometric pressure in mmHg.

$$\text{Uptake} = S \times CO \times \frac{P_A - P_V}{Pbar}$$

- Note that if any of these three factors equals zero, there is no further uptake of anesthetic by the blood.
- Blood/gas solubility
  - The lower the solubility of the anesthetic agents, the faster the equilibration of gas in the blood, and the faster the speed of induction and recovery.
  - Figure 3 below shows, for uptake, how the magnitude of change for B –low solubility agent, is less than that for A-high solubility agent.

Figure 3. influence of alveolar ventilation and cardiac output on alveolar partial pressure and P_A/P_I in inhalants with different blood:gas solubility.



- Blood/tissue (fat) solubility
  - The less soluble the anesthetic gas in fat, the lower the uptake in fat tissue.
  - In short anesthetics this factor is not important, but for long anesthetics, it affects recovery.
  - If the blood/fat solubility of the anesthetic gas is high, then in a fat animal, recovery from a long anesthetic will be slow, even with agents with a low blood/gas solubility.

Cardiac output

- The higher the CO, the higher the uptake.
- This result in slower rate of rise in PA/PI
- It mainly affects drugs with a high solubility (see figure 3)
- A positive feedback (danger!):
  - The deeper the patient gets, the further decrease of CO (while PA approaches PI more quickly, as there is less uptake of the anesthetic by the blood), which further deepens the patient.
  - In sick animals with reduced cardiac output, anesthetics have more profound cardiopulmonary effects because of increased Pbr (vicious cycle in a way).

Tissue capacity and the blood flow

- With the higher blood flow to the tissue and its capacity, the greater the uptake of the anesthetic by the tissue.
- When the tissue gets saturated with the anesthetic, the alveolar concentration would remain constant, and P_A would approach P_I through equilibration.

Agents in current use

Isoflurane (Forane®, Isoflo®, Generics).

- This agent was the first which really appeared to be as good, if not better than halothane.

- For years, the significant difference in pricing (10 times) has been the primary deterrent for veterinarians to use it over halothane, but more recently due to the generic product competition, the pricing of isoflurane has come down substantially making it more affordable for veterinarians as well as for physicians.
- MAC is about 1.3%, so surgical anesthesia is produced with end tidal concentrations of about 1.5-1.7% in oxygen (2 – 2.4 % at vaporizer). This will be further reduced with premedicants and induction agents.
- It is very insoluble in blood and a lot less soluble than halothane in fat. Thus induction and recovery is faster
- Signs of anesthesia are identical to those seen with halothane.
- Analgesia is poor and muscle relaxation moderate (i.e., as halothane).
- Dose dependent depression of respiratory and cardiovascular system is seen. These changes are similar to those occurring with equipotent doses of halothane, but the myocardial depression with isoflurane is less, whilst respiratory depression is greater (to the extent that in horses isoflurane should only be used with IPPV).
- Liver metabolism is very low, decreasing the risk of hepatitis. Nevertheless, there has been at least one report of a human patient previously sensitized by exposure from halothane suffering hepatitis after an isoflurane anesthetic.
- If administered by rebreathing circuits (especially those with in circle vaporizers) the quantities used are reduced, therefore cost can be reduced.

Sevoflurane (Ultane®)

- A halogenated ether which underwent trials some years ago, then was “dropped” as it is metabolized, is unstable in the presence of soda lime (compound A formation) which has been shown to be nephrotoxic in rats.
- However, it was licensed in Japan for human usage over a decade, and has now been used safely on over 8 millions of people. As a result the potential toxicity has been re-investigated and is now clinically used in the USA and Europe.
- It has low blood/gas solubility even lower than isoflurane, so induction and recovery is quick.
- In a horse this quick recovery may cause emergence excitement, so a low dose of sedative (usually xylazine) is given to slow the recovery and avoid the adverse reaction at the time of recovery.
- Unlike isoflurane it does not cause mucous membrane irritation so it is considered that it will totally displace the last remaining reasons for using halothane (e.g., neonatal mask induction by pediatricians).
- MAC in horses has been shown to be 2.36%.
- Cardio respiratory effects were similar to those induced by other agents.
- Similar results have been obtained in the goat (although MAC is slightly higher).
- Has taken on well recently both in human and veterinary market due to market push by the pharmaceutical company.
- Just as isoflurane, when the patent expires (soon), the price is expected to drop substantially due to generic product competition.

Agents no longer in regular current use

Nitrous oxide

- Presented in blue cylinders filled with liquid N_2O.
- Boiling point low, so vaporizes in cylinder, and obtained from cylinder as a gas.
- MAC above 100%, so cannot be used on its own.
- Much more wide spread use in human medicine than in veterinary medicine.
- Ensure at least 30% O_2 is given.
- Advantages:
  - Very insoluble in blood and in fat, so rapid uptake and elimination.
  - May also speed up induction with other agents by the "second gas effect".
  - Excellent analgesia and its use reduces the concentration of halothane required.
  - Little cardiovascular or respiratory depression and very safe as long as sufficient oxygen (30%+) is given.
- Disadvantages:
  - Limited potency.
  - Tends to diffuse into all gas-filled cavities such as gut, so some authorities. DO NOT use in horses or ruminants.
  - Danger of hypoxia.
  - Diffusion hypoxia during recovery. A 5-10 minutes of 100 % oxygen supplementation should prevent the diffusion hypoxia.
  - Increase environment pollution.
  - Drug abuse by personnel.
- Practical use
  - Do not use unless the anesthetic machine has an oxygen deficit alarm!
  - In fit animals, can be used in a non-rebreathing circuit at 50% N_2O with 50% O_2.
  - In rebreathing circuits accumulation of N_2O and of Nitrogen increases the danger of hypoxia.
  - This danger can be avoided by emptying rebreathing bag several times in early stages to remove nitrogen, however not recommended to deliver N_2O using such system, and use of nonrebreathing system is recommended if N_2O is used.
  - 100% O_2 should be given at the end of the procedure approximately 5-10 minutes to prevent diffusion hypoxia.
  - Higher concentrations of O_2 must be used in pulmonary disease.
  - It should not be used in ruminants or horse unless blood gas oxygen analysis is available.
  - Probably not very practical for private veterinary practice setting as disadvantages outshadow the real useful advantages.

Halothane (Fluothane®, generics).

- Once the most widely used volatile anesthetic agent in veterinary practice, but taken over more recently by isoflurane and to lesser extent by sevoflurane.
- Moderately insoluble in blood, and adequate volatility, therefore fast induction.
- Fairly fat soluble, so recovery from long anesthetic in fat animals may be prolonged.

- Halothane has been very widely used in human and veterinary anesthesia for around 50 years. However, it is no longer marketed in the US.
- Some equine practices will still carry it in their inventory, and preferably use it over isoflurane due to advocated superior recovery quality.
- It is a very effective, but potent and dangerous agent, as are most halogenated inhalation anesthetics. The following properties must be considered.
- A potent respiratory depressant. However, depressed respiration often consists of shallow rapid panting respiration, which being inefficient causes CO2 retention, and subsequent muscle tension and twitching.
- This makes judging the depth of anesthesia by older conventional reflex signs difficult.
- A marked hypotensive agent, which is dose dependent (and can be used to assess the depth of anesthesia). It has a particularly marked myocardial depressant action, as well as causing peripheral vasodilation.
- It is not a good analgesic, and is not good at suppressing reflex movements, Analgesics (e.g. N_2O) may have to be given to avoid the need for deep anesthesia.
- Muscle relaxation is moderate.
- Shivering is frequently seen in the recovery period, reason unknown (? calcium imbalance).
- Halothane is significantly metabolized in the liver (~20%). Some people who have received a halothane anesthetic become sensitized to the metabolites, and respond to a second challenge with a severe (sometimes fatal) hepatitis. It must be emphasized that this reaction is very rare and halothane is NOT directly hepatotoxic. However, for legal reasons, in human anesthesia another agent would be chosen for a second anesthetic (main danger period is 3-6 weeks after first exposure). It has not been conclusively proven to occur in animals. The significance to the veterinarian is that of preventing pollution, and exposure of staff to the agent.
- Sensitizes the heart to epinephrine induced arrhythmias. This is rarely a practical consideration unless the animal is very frightened at induction or in some animals where stress induced epinephrine release is expected such as with conditions of GDV and severe trauma.
- MAC in animals for halothane is about 0.9 % - this gives, for stable anesthesia in practical situations, an end-tidal value of about 1- 1.2 % when oxygen alone is used as the carrier gas, and about 0.9 -1% when nitrous oxide /oxygen mixtures are used. This will be further reduced by premedicants and induction agents.
- N.B. Remember the normal distribution curve, and the fact that the MAC value only relates to 50% of the subjects. Thus, after acepromazine premedication and induction of anesthesia using 7-15mg/kg thiopental sodium, an end tidal concentration (as delivered via a non-rebreathing circuit) of about 0.6-1.0 % (1-2 % at vaporizer) halothane should be adequate for most surgical procedures.

Methoxyflurane (Penthrane®, Metofan®).

- Soluble agent with a very low saturated vapor pressure so that induction and recovery are very slow.
- Analgesia is excellent, and some post operative analgesia remains.

- Nephrotoxic if used for very prolonged periods, and for this reason now no longer used in man. This meant the flow of the product into the veterinary market also was influenced, and this product is no longer available in the US.
- Good for use in small animals, but its low saturated vapor pressure prevents its use in horses.
- Very obvious smell gives some people very severe headaches, so good scavenging essential.
- High liver metabolism (~50%), so best to avoid in liver diseased patient.

Enflurane

- This is much less soluble than halothane so that induction and recovery are faster.
- MAC is about 2% and, clinically, following intravenous induction, end-tidal concentrations of about 2.3% in oxygen appear to produce satisfactory anesthesia.
- However, in dogs the anesthetic dose is close to the convulsant dose, making it very difficult to obtain smooth anesthesia.
- Signs of anesthesia differ from usual, the dog's eye becoming central at much lighter levels of anesthesia than for other agents.
- In the horse the rapid recovery is associated with emergence excitement.
- In man it is primarily used with neuromuscular blocking agents.
- Liver metabolism is low, but does occur.

Cyclopropane

- A very good agent in that it is very insoluble so that induction and recovery are rapid, but explosive.
- So now rarely used (if still available?)

Chloroform

- The earliest agent used dating back mid 19^{th} century.
- Fairly fast and quiet induction and recovery.
- Good analgesia and fair muscle relaxation.
- Dose related respiratory and cardiovascular depression.
- However, sensitizes heart to epinephrine-induced arrhythmias (far worse than halothane in this respect).
- Liver toxic.
- Not used now except in the horse usually by those who feel comfortable with this agent through their previous exposure and experiences, where 'Standing' chloroform can still be useful.
- Premed with acepromazine to reduce the chance of epinephrine induced fibrillation.

Trichlorethylene

- Excellent analgesic, but causes rapid jerking respiration, which makes stabilization of anesthesia difficult unless neuromuscular blocking agents are employed.
- Must not be used with soda lime!, as breaks down to toxic compounds.
- ? if still available but was still used in human cardiac work in the 1980's.

Ether

- This is still a useful agent. It gives excellent analgesia and muscle relaxation (has a direct effect on the neuromuscular junction).
- It is respiratory depressant, but cardiovascular function is well maintained at clinically suitable levels of anesthesia.
- Induction and recovery are fairly slow.
- Ether has a pungent smell and is irritant to mucous membranes.
- It causes copious salivation and bronchial secretion, so that atropine (or similar drugs) must be used for premedication.
- The use of ether is mainly limited by the fact that it is inflammable.
- It is inexpensive so still used in developing countries.

New agent. (limited veterinary experience to date).

Desflurane (Suprane®).

- This is one of the latest of the volatile agents. It is very insoluble, and has a very rapid induction/recovery (note, also fat insoluble).
- Its boiling point is close to room temperature, so a complicated heated vaporizer is required.
- Experience in animals has shown it to be an excellent anesthetic agent, with most cardiovascular effects similar to those of isoflurane.
- However in contrast to most other halogenated volatile anesthetics, desflurane causes a tachycardia.
- In the horse, the rapid changes in depth which can be achieved result in particularly 'controlable' anesthesia, and recovery is exceptionally rapid, and, if coupled with some post-operative sedation, is of outstanding quality. It would seem that desflurane might be particularly useful in this species.
- Currently its high cost limits its widespread use in veterinary practice.

Xenon

- Since 1994, research on the evaluation of the possible use of xenon as an anesthetic in inhalation narcosis has been conducted throughout the world.
- Xenon (Xe), an inert gas, is present in the atmosphere in extremely low concentration. Xenon produces inhalation anesthesia similar to Nitrous Oxide, however there is not enough xenon in the earth atmosphere to be used for this purpose.
- Xenon has minimal hemodynamic effects, and the lowest blood/gas partition coefficient among the known anesthetic agents.
- With a minimum alveolar concentration of 71%, it is more potent than nitrous oxide (105% MAC). It is an inhaled agent with analgesic and anesthetic effects.
- Not metabolized in the body and is eliminated via the lungs. Low flow and closed breathing systems are recommended.

- Experiments conducted over the last several years in Germany, Russia, Sweden and Japan have proven that Xenon, which possesses more pronounced narcotic properties than nitrous oxide due to its higher inertness, is in fact safer for patients.
- Due to its lower solubility in blood, xenon is quickly eliminated from the body: upon stopping the gas supply, patient recovery is immediate.
- So far, no hazardous side effects from the use of xenon have been reported. However, despite all of the advantages of Xenon over the anesthetics in current use, the use of this inert gas is limited by its high price (the average retail price in Europe is about U$ 10 per liter) and the small volume of world production.
- By the beginning of the 1990s, several medical centers (both in Russia and abroad) almost simultaneously approached a solution of this problem by developing equipment in which Xenon is trapped during and after surgery and recycled for repeated use.
- Such a method would decrease the price of Xenon anesthesia to a level equal to or only marginally higher than that of the currently available anesthetics.
- Many advantages such as analgesia, hemodynamic stability, quick induction and recovery make this gas a very promising inhaled anesthetic agent in the future.
- However, its routine use both in human and veterinary anesthesia is unlikely for considerable time to come.

Clinical Notes

- The use of inhalational anesthetics better enables prolonged surgery and diagnostic procedures in a safe and efficient manner.
- Inhalational anesthetics are used in combination with injectable premedicants, induction agents and ancillary analgesics (best know as balanced anesthetic technique)
- Cardiopulmonary depression is invariably anticipated with modern potent inhalant anesthetics.
- The degree of cardiopulmonary depression depends on the dose and patient health status, and careful administration will ensure safe anesthesia.