Review Of Currently Used Inhalation Anesthetics: Part I
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Citation

Abstract

INTRODUCTION
Inhalation anesthetics are substances that are brought into the body via the lungs and are distributed with the blood into the different tissues. The main target of inhalation anesthetics (or so-called volatile anesthetics) is the brain.

Figure 1

Inhalation anesthetics act either by amplifying inhibitory function or decreasing excitatory transmission at the nerve endings in the brain. The role of inhalation agents in general anesthesia is changing. Volatile anesthetics are seldom used alone in our days. A combination of inhalation anesthetics and intravenous drugs is called balanced anesthesia. Currently used inhalation anesthetics include enflurane, halothane, isoflurane, sevoflurane, desflurane, and nitrous oxide. Older volatile anesthetics include ether, chloroform, and methoxyflurane.

Ideally, inhalation agents should provide a quick induction and emergence from anesthesia, good analgesia, muscle relaxation, quick changes and easy maintenance of anesthesia, and no side effects. Unfortunately, the real world of medicine doesn’t provide us with such an ideal agent. Relatively long and unpleasant induction times can be overcome by using an intravenous anesthetic. Neuromuscular blockers will provide muscle paralysis and adding opioids can enhance analgesia. This technique, the so-called balanced anesthesia, allows the anesthesiologist to take advantage of different beneficial effects of several drug classes.

HISTORY
Chloroform, ether, nitrous oxide and later ethyl chloride where all used during the last century. They where followed in the 1930’s and ’40s by ethylene, cyclopropane, trichloroethylene, isopropenyl vinyl ether and others until halothane was synthesized in 1951 and subsequently introduced into clinical practice in 1956. Shortly thereafter methoxyflurane appeared in the early 60’s followed by enflurane and isoflurane in the 70’s. Methoxyflurane was pulled from the market within a decade because of its nephrotoxic potential. Two other inhalation anesthetics were synthesized in the 70’s but were only released earlier this decade. The first of the two, sevoflurane, was introduced in 1990 in Japan. The other, desflurane went into practice in the U.S. in 1992. The most common used inhalation agents in our days are the good old nitrous oxide, isoflurane, and the two recently introduced inhalation anesthetics sevoflurane and desflurane.
PHARMACOKINETICS OF INHALED ANESTHETICS

Pharmacokinetics of volatile anesthetics describes their uptake, distribution, metabolism, and elimination.

UPTAKE AND DISTRIBUTION OF INHALED ANESTHETICS

A series of partial pressure gradients, beginning at the vaporizer of the anesthetic machine, continuing in the anesthetic breathing circuit, the alveolar tree, blood, and tissue will ensure the forward movement of the gas. The principal objective of that movement is to achieve equal partial pressures on both sides of each single barrier. The alveolar partial pressure governs the partial pressure of the anesthetic in all body tissues; they all will ultimately equal the alveolar partial pressure of the gas. After a short period of equilibration the alveolar partial pressure of the gas equals the brain partial pressure. It is therefore most important to understand how to influence the alveolar partial pressure. It can be raised by increasing minute ventilation, flow rates at the level of the vaporizer and by using an non-rebreathing circuit.

Two special effects increasing the amount of gas in the alveoli have to be mentioned separately. The concentration effect describes how the concentration of the gas in the remaining alveolar volume can increase after some of the gas has been transferred into the blood. The second gas effect usually refers to nitrous oxide combined with an inhalation agent. Because nitrous oxide is not soluble in blood, its rapid absorption from alveoli causes an abrupt rise in the alveolar concentration of the other inhalation anesthetic.

All the above mentioned factors influence the inflow of gas into the alveoli.

Solubility, cardiac output, and the alveolar to venous anesthetic gradient represent outflow factors. Inflow factors minus outflow factors equal alveolar partial pressure of the gas.

Solubility describes the affinity of the gas for a medium such as blood or fat tissue. The blood/gas partition coefficient describes how the gas will partition itself between the two phases after equilibrium has been reached. Isoflurane for example has a blood/gas partition coefficient of 1.4. This means that if the gas is in equilibrium the concentration in blood will be 1.4 times higher than the concentration in the alveoli. A higher blood gas partition coefficient means a higher uptake of the gas into the blood and therefore a slower induction time. It takes longer until the equilibrium with the brain partial pressure of the gas is reached.

A higher cardiac output removes more volatile anesthetic from the alveoli and lowers therefore the alveolar partial pressure of the gas. The agent might be faster distributed within the body but the partial pressure in the arterial blood is lower. It will take longer for the gas to reach an equilibrium between the alveoli and the brain. Therefore, a high cardiac output prolongs induction time.

The alveolar to venous partial pressure difference reflects tissue uptake of the inhaled anesthetic. A large difference is caused by increased uptake of the gas during the induction phase. This facilitates the diffusion of the gas from the alveoli into the blood.

Last but not least we have to discuss the transfer of the gas from the arterial blood into the tissues such as the brain. It will depend on perfusion and solubility of the gas into different tissues. The brain/blood coefficient describes how the gas will partition itself between the two phases after equilibrium has been reached. Isoflurane for example has a
brain/blood coefficient of 1.6 meaning that if the gas is in
equilibrium the concentration in the brain will be 1.6 times
higher than the concentration in the blood. All inhalation
anesthetics have high fat/blood partition coefficients. This
means that most of the gas will bind to fatty tissue as times
goes by. The partial pressure of the gas in fatty tissue will
rise very slowly. Inhalation anesthetics stored in such tissue
in obese patients may delay awakening at the end of
anesthesia.

METABOLISM AND ELIMINATION OF INHALED
ANESTHETICS

Microsomal enzymes responsible for metabolism are mainly
located in liver and kidneys. The rates of metabolism in the
human body are approximately 10 to 20 percent for
halothane, 2.5 percent for enflurane, about 0.2 percent for
isoflurane, and zero percent for nitrous oxide.

The amount of anesthetic removed from the body by
metabolism is small compared with the amount exhaled.
Induction and recovery from anesthesia with volatile
anesthetics differ somewhat from each other. On induction
all tissue partial pressures are zero. During recovery,
different tissues in the body have a different partial pressure
of the inhaled anesthetic. Therefore, recovery is not as
controllable as induction of anesthesia. In addition,
increasing minute ventilation and concentration of the
inspired anesthetic mixture can significantly accelerate
induction. Increasing minute ventilation with high
inspiratory oxygen concentration will increase the gradient
of the inhaled anesthetic between pulmonary venous blood
and the alveolar space and therefore increase the elimination
of the gas. Elimination of a volatile anesthetic depends in
summary on ventilation, cardiac output, and solubility of the
gas in blood and tissue.

MINIMUM ALVEOLAR CONCENTRATION MAC

Anesthetic potency of volatile anesthetics is measured by the
minimum alveolar concentration (MAC). This value
represents the alveolar concentration of an anesthetic (at one
atmosphere) that prevents movement in 50 percent of the
subjects in response to pain. A variety of noxious stimuli
have been used to provoke response. For determination of
MAC in humans, the usual stimulus used is surgical skin
incision. In daily practice, MAC must be exceeded by a
factor of 1.3 in order to assure sufficient surgical anesthesia
for most of our patients. 1.3 times MAC will prevent
movement in about 95 percent of the patients. The idea of
measuring MAC is that after a short period of equilibration

the alveolar concentration of the gas equals the blood
concentration and a little later equals the brain concentration.
It represents after a short time the partial pressure of the
anesthetic in the central nervous system (CNS) and it is
therefore the most useful index of anesthetic potency. MAC
is age-dependent, being lowest in newborns, reaching a peak
in infants, and then decreasing progressively with increasing
age. MAC values for inhaled anesthetics are additive, which
means that the addition of nitrous oxide will decrease the
MAC of another volatile anesthetic. The MAC can also be
altered following administration of opioids. Inhalation
anesthetics alone are not able to suppress hemodynamic
responses to painful stimuli nor does MAC for skin incision
predict the concentrations of inhalation anesthetics necessary
to avoid the motor responses to other painful stimuli such as
endotracheal intubation. As a rule of thumb, the addition of
every one percent of alveolar nitrous oxide to another
inhalation anesthetic will decrease in the MAC of that gas
about one percent. Increases in MAC result from
hyperthermia and hypernatremia. Decreases in MAC can
result from hypothermia, hyponatremia, pregnancy,
hypotension, and drugs such as lithium, lidocaine, opioids,
and a2 agonists.

Minimum alveolar concentration of inhaled anesthetics in
100% oxygen:

- Halothane 0.74 percent
- Enflurane 1.68 percent
- Isoflurane 1.15 percent
- Desflurane 6.3 percent
- Sevoflurane 2.0 percent
- Nitrous oxide 104 percent

MECHANISM OF ACTION OF INHALED
ANESTHETICS

Inhaled anesthetics act in different ways at the level of the
central nervous system. They may disrupt normal synaptic
transmission by interfering with the release of
neurotransmitters from presynaptic nerve terminal (enhance
or depress excitatory or inhibitory transmission), by altering
the re-uptake of neurotransmitters, by changing the binding
of neurotransmitters to the post-synaptic receptor sites, or by
influencing the ionic conductance change that follows
activation of the post-synaptic receptor by neurotransmitters.
Both, pre- and postsynaptic effects have been found.
Direct interaction with the neuronal plasma membrane is very likely, but indirect action via production of a second messenger also remains possible. The high correlation between lipid solubility and anesthetic potency suggests that inhalation anesthetics have a hydrophobic site of action. Inhalation agents may bind to both membrane lipids and proteins. It is at this time not clear which of the different theories are most likely to be the main mechanism of action of inhalation anesthetics.

The Meyer-Overton theory describes the correlation between lipid solubility of inhaled anesthetics and MAC and suggests that anesthesia occurs when a sufficient number of inhalation anesthetic molecules dissolve in the lipid cell membrane. The Meyer-Overton rule postulates that the number of molecules dissolved in the lipid cell membrane and not the type of inhalation agent causes anesthesia. Combinations of different inhaled anesthetics may have additive effects at the level of the cell membrane.

However, the Meyer-Overton theory does not describe why anesthesia occurs. Mullins expanded the Meyer-Overton rule by adding the so-called Critical Volume Hypothesis. He stated that the absorption of anesthetic molecules could expand the volume of a hydrophobic region within the cell membrane and subsequently distort channels necessary for sodium ion flux and the development of action potentials necessary for synaptic transmission. The fact that anesthesia occurs with significant increase in volume of hydrophobic solvents and is reversible by compressing the volume of the expanded hydrophobic region of the cell membrane supports Mullins Critical Volume Hypothesis.

The protein receptor hypothesis postulates that protein receptors in the central nervous system are responsible for the mechanism of action of inhaled anesthetics. This theory is supported by the steep dose response curve for inhaled anesthetics. However, it remains unclear if inhaled agents disrupt ion flow through membrane channels by an indirect action on the lipid membrane, via a second messenger, or by direct and specific binding to channel proteins.

Another theory describes the activation of Gamma-Aminobutyric acid (GABA) receptors by the inhalation anesthetics. Volatile agents may activate GABA channels and hyperpolarize cell membranes. In addition, they may inhibit certain calcium channels and therefore prevent release of neurotransmitters and inhibit glutamate channels. Volatile anesthetics share therefore common cellular actions with other sedative, hypnotic or analgesic drugs.

Each of the mentioned theories describes a unitary theory of narcosis. They all concentrate more or less on an unique site of action for inhaled anesthetics. The true mechanism of action of volatile anesthetics may be a combination of two or more such theories described as multisite action hypothesis.

**PHARMACOLOGICAL PROFILE OF CURRENTLY USED INHALED ANESTHETICS**

**HALOTHANE (FLUOTHANE)**

This volatile anesthetic is a nonflammable halogenated alkene. It has a vapor pressure of 244 mm Mercury at 20 degree Celsius and boils at 50.2 degree Celsius. The blood/gas coefficient is 2.3 and the MAC in 100 percent oxygen is 0.74 and in 70 percent nitrous oxide 0.29.

**Figure 3**

Halothane is susceptible to decomposition. For this reason, it is stored in amber-colored bottles and thymol is added as preservative. It is known to sensitize the myocardium to the action of epinephrine and norepinephrine and to have the potential for serious cardiac dysrhythmias. Halothane lowers airway resistance and might be used in the treatment of asthma if conventional therapy fails. It is not recommended for obstetric anesthesia except when uterine relaxation is
required. It crosses the placental barrier and can cause fetal and neonatal depression resulting in hypotension, hypoxemia, and acidosis. Halothane does not cause coronary artery vasodilation and therefore does not lead to coronary artery steal syndrome. Decrease in blood pressure is due to negative inotropic effects of halothane. Systemic vascular resistance does not change significantly. Increase in cerebral blood flow due to cerebral vasodilatation produced by halothane is greater than the one produced by isoflurane or enflurane. Halothane is able to trigger malignant hyperthermia, a potential lethal complication of anesthesia.

Fulminant hepatic necrosis and/or jaundice (halothane hepatitis) are other severe complications of halothane anesthesia. Hepatic necrosis occurs in one of 6,000 to 35,000 cases and is often fatal. Anti-trifluoroacetyl protein antibodies probably cause halothane hepatitis. These antibodies may mediate massive hepatic necrosis after re-exposure of the patient with halothane.

Halothane has excellent hypnotic but no analgesic properties. Induction of anesthesia can be achieved by using 1 to 3 percent halothane in air or in oxygen, or by using 0.8 percent halothane in 65 percent nitrous oxide. Induction occurs relatively quickly. This is one of the reasons why halothane was the drug of choice for mask induction of pediatric patients but its popularity changed in the recent years with the availability of sevoflurane. Maintenance of anesthesia can be achieved with 0.5 to 1.5 percent halothane. Emergence might be delayed in obese patients due to storage of the inhalation agent in fatty tissues.

**ISOFLURANE (FORANE)**

This volatile anesthetic is a nonflammable halogenated methyl ethyl ether. It has a vapor pressure of 239 mm Mercury at 20 degree Celsius and boils at 48.5 degree Celsius. The blood/gas coefficient is 1.4 and the MAC in 100 percent oxygen is 1.15 and in 70 percent nitrous oxide 0.50.

 Isoflurane is resistant to degradation by the absorber and can therefore be used during low flow or closed system anesthesia. Isoflurane produces a dose-dependent reduction in blood pressure due to peripheral vasodilatation. It does not sensitize the myocardium for arrhythmias. It can cause coronary artery vasodilatation that might lead to coronary artery steal syndrome. During such an event blood is diverted away from critically perfused areas because of vasodilatation in healthy parts of the heart. This might lead to myocardial ischemia or infarction. However, most clinical studies failed to prove higher incident of myocardial ischemia due to isoflurane. Isoflurane should be avoided in patients with aortic valve stenosis since they poorly tolerate a decrease in systemic vascular resistance. Like halothane, it can trigger malignant hyperthermia.

Induction of anesthesia can be achieved by using 3 to 4 percent isoflurane in air or in oxygen, or by using 1.5 to 3 percent isoflurane in 65 percent nitrous oxide. Induction with isoflurane alone can lead to coughing and apneic periods. Therefore, it should be combined with intravenous anesthetics. Maintenance of anesthesia can be achieved with 1 to 2.5 percent isoflurane. Emergence from anesthesia with
isoflurane is faster than with halothane or enflurane.

**ENFLURANE (ETHRANE)**

This volatile anesthetic is a nonflammable fluorinated ethyl methyl ether. It has a vapor pressure of 172 mm Mercury at 20 degree Celsius and boils at 56.5 degree Celsius. The blood/gas coefficient is 1.8 and the MAC in 100 percent oxygen is 1.68 and in 70 percent nitrous oxide 0.57.

**Figure 5**

Enflurane is resistant to degradation by soda lime and can be therefore used during low flow or closed system anesthesia. Its biotransformation releases fluoride ions but their concentration does not reach nephrotoxic levels. Enflurane produces a dose-dependent reduction in arterial blood pressure as consequence of negative inotropy. Like isoflurane, enflurane does not sensitize the heart for arrhythmias. In addition, it does not cause a coronary artery steal syndrome. Enflurane has been found to increase intracranial pressure and, especially in combination with hyperventilation, to increase the risk of seizure activity. It is therefore contraindicated in patients with seizure disorders. As halothane and isoflurane, it can trigger malignant hyperthermia. Enflurane enhances the action of paralyzing agents more than other inhalation anesthetics.

Induction of anesthesia can be achieved by using 3 to 4 percent enflurane in air or in oxygen, or by using 1.5 to 3 percent enflurane in 65 percent nitrous oxide. Maintenance of anesthesia can be achieved with 1 to 3 percent enflurane. Emergence from anesthesia with enflurane is a little slower than with isoflurane.

**DESFLURANE (SUPRANE)**

This volatile anesthetic is a nonflammable fluorinated methyl ethyl ether. It has a vapor pressure of 673 mm Mercury at 20 degree Celsius and boils at 23.5 degree Celsius. The blood/gas coefficient is 0.42 and the MAC in 100 percent oxygen is 6.0 and in 60 percent nitrous oxide 2.8.

**Figure 6**

Unlike other inhalation anesthetics, desflurane cannot be delivered by standard vaporizers. It requires the use of electrically heated vaporizers. Desflurane is very resistant to degradation by soda lime and can therefore be used during low flow or closed system anesthesia. Desflurane produces a dose-dependent reduction in arterial blood pressure due to peripheral vasodilatation. It might as well cause an increase
in heart rate. It should therefore not be used in patients with aortic valve stenosis. It does not sensitize the heart to arrhythmias or cause coronary artery steal syndrome. Like other inhalation anesthetics, it can trigger malignant hyperthermia.

Induction of anesthesia can be achieved by using 6 to 10 percent desflurane in air or in oxygen, or by using 5 to 8 percent desflurane in 65 percent nitrous oxide. Desflurane may cause coughing and excitation during induction and should therefore rather not be used without intravenous anesthetics. Maintenance of anesthesia can be achieved with 5 to 7 percent desflurane. The low tissue solubility of desflurane results in rapid elimination and awakening.

SEVOFLURANE (ULTANE)
This volatile anesthetic is a nonflammable fluorinated isopropyl ether. It has a vapor pressure of 162 mm Mercury at 20 degree Celsius and boils at 58.5 degree Celsius. The blood/gas coefficient is 0.59 and the MAC in 100 percent oxygen is 1.71 and in 63.5 percent nitrous oxide 0.66.

Figure 7

Sevoflurane undergoes temperature dependent degradation by baralyme and soda lime. Therefore, it cannot be used in low flow or closed systems anesthesia. Sevoflurane reacts with CO2 absorbents to form a special haloalkene, the so-called Compound A. Compound A is metabolized to nephrotoxins and can lead to kidney damage. The minimum fresh gas flow has been recommended to be at least two liters per minute. Sevoflurane produces a dose-dependent decrease in arterial blood pressure due to peripheral vasodilatation. It should therefore not be used in patients with aortic valve stenosis. It does not sensitize the heart to arrhythmias or cause coronary artery steal syndrome. Unlike desflurane, sevoflurane does not irritate the airway. Due to its low solubility in blood it can be used for rapid induction of anesthesia without intravenous anesthetics. This is one of the reasons why it is currently replacing halothane for mask induction in pediatric patients. Like all other inhalation anesthetics, sevoflurane can trigger malignant hyperthermia in susceptible patients.

Induction of anesthesia can be achieved by using 1.5 to 3 percent sevoflurane in air or in oxygen, or by using 0.7 to 2 percent sevoflurane in 65 percent nitrous oxide. Sevoflurane does not cause coughing and excitation during induction and can be used without intravenous anesthetics. Maintenance of anesthesia can be achieved with 0.4 to 2 percent sevoflurane. The low tissue solubility of sevoflurane results in rapid elimination and awakening.

NITROUS OXIDE (NITROUS OXIDE)
This is an inorganic nonflammable gas that supports combustion. It has a vapor pressure of 39,000 mm Mercury at 20 degree Celsius and boils at minus 88 degree Celsius. The blood/gas coefficient is 0.47 and the MAC in 100 percent oxygen is 104. This means that one MAC nitrous oxide can only be reached in a hyperbaric chamber.
Nitrous oxide is stored in blue cylinders (This is the case in the USA. In some parts of Europe, blue is the color for oxygen and green the color for nitrous oxide). At room temperature, nitrous oxide in the cylinder is in equilibrium between liquid and gaseous form. The pressure within the cylinder is constant as long some of the gas is in liquid form. Therefore, there is only little nitrous oxide left when the pressure in the cylinder decreases. Nitrous oxide is a weak anesthetic. It is used to supplement other inhalation agents.
Its low solubility results in rapid induction or awakening. Administration of high concentrations of nitrous oxide will facilitate the increase in alveolar concentration of a simultaneously administered second gas. This is called the second gas effect. Nitrous oxide is resistant to degradation by soda lime and can therefore be used in low flow or closed systems anesthesia. Unlike other inhalation anesthetics, nitrous oxide does not inhibit the hypoxic pulmonary vasoconstriction response in the lungs. It might produce an increase in pulmonary vascular resistance, especially in patients with pre-existing pulmonary hypertension. It is therefore contraindicated in patients with intra-cardiac right-to-left shunt. Nitrous oxide is sympathomimetic and increases systemic vascular resistance. It does not cause a decrease in blood pressure. Unlike other inhalation anesthetics, nitrous oxide does not produce skeletal muscle relaxation. It does not have any significant effect on uterine contractility. It is a weak trigger for malignant hyperthermia.

Nitrous oxide diffuses into air containing cavities 34 times faster than nitrogen can leave that space. This can cause dangerous accumulation of volume and increase in pressure in closed spaces such as bowel, middle ear, pneumothorax, pneumocranium, pneumo-peritoneum, or cuffs of endotracheal tubes. In patients with ileus, the volume of air in the bowel can double within 4 hours of nitrous oxide administration. The volume of air within a pneumothorax can double within 10 minutes if 70 percent nitrous oxide is administered. This can lead to a life-threatening tension pneumothorax. Diffusion of nitrous oxide into air bubbles will increase their size. It has therefore to be stopped immediately when air embolism is suspected.

The main danger however is the occurrence of hypoxemia. The maximum dose of nitrous oxide should not exceed 70 percent. Hypoxic inspiratory gas mixtures due to high doses of nitrous oxide or failing admixture of oxygen have lead in the past to hypoxic brain damage. A fail-safe valve in the anesthesia machine should prevent such a complication. Nitrous oxide can be used in doses of 0 to 70 percent during induction or maintenance of anesthesia. Administration of 70 percent nitrous oxide should always be accompanied by 30 percent oxygen. The combination of 70 percent nitrous oxide with 30 percent regular air results in a hypoxic air mixture.

Outpouring of large volumes of nitrous oxide during the first 5 to 10 minutes of recovery from anesthesia may displace alveolar oxygen and produce a so-called diffusion hypoxia. This can be avoided by stopping administration of nitrous oxide approximately 4 to 5 minutes prior to emerging from anesthesia and by application of 100 percent oxygen during that time.

References
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