SIDES EFFECTS OF INHALED ANESTHETICS

CARDIOVASCULAR SYSTEM

Blood pressure: All volatile anesthetics with the exception of nitrous oxide produce a dose-dependent decrease in blood pressure. Nitrous oxide produces either no change or only a slight increase in blood pressure. The decrease in blood pressure produced by halothane and enflurane results mainly from negative inotropy (decrease in myocardial contractility), whereas hypotension produced by desflurane, isoflurane, and sevoflurane mainly result from a decrease in systemic vascular resistance.

Heart rate: Isoflurane and desflurane produce a dose-dependent increase in heart rate. This increase occurs at low doses of isoflurane or high doses of desflurane. It might be blunted by simultaneous use of opioids during balanced anesthesia. Nitrous oxide, halothane and sevoflurane are not associated with substantial changes in heart rate.

Cardiac performance: As mentioned earlier, halothane and enflurane produce a dose dependent decrease in cardiac output due to decrease in myocardial contractility. Administration of nitrous oxide can modestly increase cardiac output because its sympathomimetic effect. High doses may cause myocardial depression. Isoflurane, desflurane and sevoflurane do not significantly alter cardiac output.

Systemic vascular resistance: Isoflurane, desflurane, and sevoflurane produce dose dependent decreases in systemic vascular resistance.

Pulmonary vascular resistance: Nitrous oxide is known to increase pulmonary vascular resistance, especially in patients with pre-existing pulmonary hypertension. All other inhalation agents may decrease pulmonary vascular resistance and blunt the Hypoxic Pulmonary Vasoconstriction Reflex (HPV).

Coronary blood flow: Isoflurane is known to be a potent coronary artery vasodilator. Isoflurane induced coronary artery vasodilatation can lead to redistribution of coronary blood flow away from diseased areas to areas with normal responsive coronary arteries. This phenomenon is called the coronary steal syndrome. However, most clinical studies failed to prove a higher incident of myocardial ischemia due to isoflurane. Enflurane, halothane, desflurane, and sevoflurane are all weaker coronary artery vasodilator than isoflurane.

Cardiac dysrhythmias: Especially halothane is known for its dysrhythmic effect in combination with catecholamines such as epinephrine.

All cardiac depressant effects of volatile anesthetics are able to recover. Cardiac output, heart rate, and systemic vascular resistance usually return to base value if these agents are administered for five hours or longer.

PULMONARY SYSTEM

Respiratory rate: All inhaled anesthetics produce a dose-dependent increase in respiratory rate. This is associated with a decrease in tidal volume. The net effect results in a decrease of minute ventilation and therefore in increase of PaCO2. Central response to higher CO2 levels is decreased during administration of inhalation anesthetics. This is probably due to a direct depressant effect of these drugs on the medullary ventilatory center. In addition, all inhaled anesthetics depress the ventilatory response to arterial hypoxemia. This reflex is usually mediated by the carotid bodies. In summary, inhaled anesthetics blunt synergistic effects of arterial hypoxemia and hypercapnia on simulation of ventilation.

Airway resistance: Enflurane, isoflurane, sevoflurane, nitrous oxide, and especially halothane produce a dose-dependent decrease in airway resistance. Halothane was
successfully used in the past to treat status asthmaticus unresponsive to conventional treatment. Administration of desflurane during induction in unmedicated patients results in coughing and laryngospasm. Desflurane is therefore known to be an airway irritant.

Functional residual capacity: All inhaled anesthetics including nitrous oxide decrease functional residual capacity.

**RENAral System**

All volatile anesthetics produce a dose-dependent decrease in renal blood flow, urine output, and glomerular filtration rate. Potential nephrotoxic effects of inhalation agents will be discussed at a later time point in this review.

**HEPATIC SYSTEM**

All inhalation agents produce a dose-dependent decrease in hepatic blood flow. They might interfere with hepatic clearance of other drugs. Changes in liver function tests resulting from inhalation anesthetics are usually not clinically important. Potential hepatotoxic effects of volatile agents will be discussed at a later time point in this review.

**CENTRAL NERVOUS SYSTEM**

All inhalation agents produce cerebral vasodilatation and therefore an increase in cerebral blood flow and cerebral blood volume. This might lead to an increase in intracranial pressures. The elevation of intracranial pressure parallels the increase in cerebral blood flow. Enflurane is known to have the potential to cause seizures.

**UTERINE SYSTEM**

Inhalation anesthetics produce a dose-dependent uterine vasodilatation and decrease in uterine contractility. Uterine relaxation produced by inhalation agents may be helpful for removal of a retained placenta. However, uterine vasodilatation might lead to increased blood loss during obstetric surgery or delivery. Nitrous oxide does not change uterine contractility in doses provided during vaginal delivery. Inhaled anesthetics delivered to the mother can cross the placenta and potentially affect the fetus.

**SKELETAL MUSCLE SYSTEM**

Volatile anesthetics do not only potentiate the action of neuromuscular blocking agents but also have muscle relaxants properties of their own. Enflurane, isoflurane, desflurane, and sevoflurane produce skeletal muscle relaxation that is about twice as high than that associated with halothane. Nitrous oxide does not relax skeletal muscle and may, especially in combination with opioids cause muscle rigidity. Halothane and to a lesser extent nitrous oxide can trigger malignant hyperthermia, a potentially fatal disease.

**TOXICITY OF INHALED ANESTHETICS**

The three target organs for toxicity of inhalation agents are the liver, the kidney, and the blood cell.

**LIVER**

Fulminant hepatic necrosis following halothane anesthesia (halothane hepatitis) occurs in one of 6,000 to 35,000 cases and is often fatal. Halothane hepatitis is probably caused by trifluoroacetetyl-containing metabolites binding to protein and subsequently forming anti-trifluoroaceetyl protein antibodies. During re-exposure of the patient with halothane these antibodies may mediate massive hepatic necrosis. Other agents such as enflurane, isoflurane and desflurane has been associated with immune based hepatitis. Because the metabolism of enflurane, isoflurane or desflurane is much less than the one of halothane, fulminant hepatic necrosis occurs to a much lesser extent. Sevoflurane does not form such proteins and does therefore not cause hepatic toxicity.

**KIDNEY**

Nephrotoxicity in the earlier years was mainly caused by methoxyflurane. It caused high output renal failure with elevation of serum creatinine and BUN. It was related to the metabolism of methoxyflurane possibly releasing inorganic fluorides. Toxicity started to occur at peak fluoride levels of 50 to 80 mM and was evident at levels of 80 to 175 mM. The threshold of 50 mM was subsequently selected to be the magic number for renal toxicity. Despite levels higher than 50 mM, other agents such as enflurane, isoflurane and sevoflurane did not cause nephrotoxicity. Methoxyflurane is metabolized to a significant degree in the kidney whereas the other inhalation agents undergo mainly hepatic biotransformation. It seems that the site of biotransformation is crucial for the occurrence of renal toxicity. Furthermore, newer agents such as enflurane, isoflurane and sevoflurane are far more insoluble in body tissues than methoxyflurane and are therefore less available for renal and hepatic biotransformation to fluorides. The slower elimination of methoxyflurane might as well play a role in its renal toxicity.

Another kind of renal toxicity is caused by haloalkenes produced in a reaction with the carbon dioxide absorbents. Halothane, enflurane, isoflurane and sevoflurane are all known to react with the CO2 absorbents. Halothane
nephrotoxicity caused by haloalkenes occurred in rats but was never reported to be a problem in humans.

A much bigger interest in the recent years has been attracted towards sevoflurane. Sevoflurane reacts with CO2 absorbents to form a special haloalkene, the so-called compound A. This compound A is formed in increased concentrations when using sevoflurane in high concentrations, with low fresh gas flow, with baralyme (instead of soda lime), drier absorbents, increased CO2 production, and higher CO2 absorbents temperatures. However, low flow sevoflurane anesthesia seems to be as safe as low flow anesthesia with other inhalation agents. The term low flow is used to describe the administration of inhalation anesthetics with lower flows of fresh gas such as air or oxygen. Using lower flows of fresh gas can save a significant amount of inhalation agents and therefore money. Compound A is metabolized in the liver to cystein conjugates which are themselves metabolized by renal b-lyase to nephrotoxins. Sevoflurane was recommended to be used at the gas flow rates equal or bigger than two liters a minute.

**RED BLOOD CELLS**

Carbon monoxide production from inhalation anesthetic degradation in anesthesia circuits can cause carbon monoxide toxicity. Carbon monoxide formation occurs when relatively dry baralyme or soda lime degrades inhalation agents such as enflurane, desflurane and isoflurane. This occurs usually on Monday mornings after the anesthesia machine had been idle with fresh gas flow all weekend resulting in dry CO2 absorbents. Sevoflurane and halothane are not or only minimally degraded to CO. Desflurane produces the highest CO concentration, followed by enflurane and isoflurane. Fully hydrated absorbents do not degrade volatile agents to CO. Factors known to produce high carbon monoxide concentrations are dry absorbents, high CO2 absorbent temperature, Baralyme versus soda lime, higher concentrations of volatile anesthetics, and as mentioned desflurane more than enfurane and enfurane more than isoflurane. Fresh gas flows through the anesthesia machines should be reduced at the end of each case and should be turned off overnight and over the weekend. The recommendation has been made that the absorbents should be changed on Monday mornings.

Carbon monoxide toxicity is dependent on the amount of inhaled carbon monoxide and the duration of exposure. Once in the anesthesia circuits, the carbon monoxide diffuses easily from the alveoli into the blood. Its affinity for hemoglobin is approximately 220 times greater than that of oxygen. CO will therefore displace oxygen from hemoglobin and form carboxyhemoglobin. In addition, carboxyhemoglobin causes a left-shift in the oxygen hemoglobin dissociation curve, thereby decreasing oxygen release and delivery to the tissues. Clinical signs of carbon monoxide toxicity include nausea, headache, vomiting, dizziness, diminished consciousness, coma, syncope, seizures, cardiac and respiratory failure, and death. Late clinical signs can occur 3 to 21 days after carbon monoxide exposure in prior asymptomatic patients and occurs in two third of the patients. The symptoms include personality changes, cognitive deficits, dementia, incontinence, and gait disturbances. The treatment of carbon monoxide poisoning is oxygen administration, either at atmospheric pressure or in hyperbaric environment.

Intraoperative detection of carbon monoxide toxicity is difficult. Dual wavelength pulse oximetry can not distinguish between carboxyhemoglobin and oxyhemoglobin. Trifluoromethane, a breakdown product of desflurane and isoflurane can react with the absorbents to produce carbon monoxide and enfurane. Presence of enfurane on the gas analysis screen during isoflurane or desflurane anesthesia can therefore indicate the presence of carbon monoxide.

**FILLING OF VAPORIZERS**

The vaporizers are mounted to the fresh gas flow piping of the anesthesia machine. They have to be periodically filled. Different systems to fill vaporizers are available. It is important to understand their mechanisms in order to avoid human errors.
FILLING WITH A KEY SYSTEM

All vaporizers can be equipped with special key systems. A connection tubing with special adapters for the bottle containing the inhaled anesthetic and the filling part of the vaporizer was designed to decrease human error. The connector is placed on the bottle and connected to the special filling part of the vaporizer. It will only fit to the appropriate vaporizer. Once the key has been inserted and properly locked, the bottle can be raised in order to start filling.
The desflurane bottle has been specially designed to only fit into the desflurane vaporizer. No other agent can be filled into this vaporizer. The bottle has to be inserted into the specially designed entry of the vaporizer in order to raise the bottle together with the filling mechanism. After filling, the
bottle is lowered again and pulled back from the adapter.

Figure 7

Figure 8
FILLING WITHOUT SPECIAL SAFETY MECHANISM

Unfortunately, many of the vaporizers are not equipped with any safety mechanisms. A screw has to be removed in order to access the filling part of the vaporizer. The liquid inhalation agent is then filled by hand into the vaporizer. It is absolutely possible to fill the wrong agent into the vaporizer. This is dangerous since all volatile anesthetics require specially designed vaporizers. Human errors during filling may result in potentially fatal concentrations of volatile anesthetics during anesthesia. Another problem is the spilling of liquid volatile agents during the filling process.
SUMMARY

Inhalation anesthetics are used in our days in combination with other drugs such as opioids and intravenous hypnotics. The technique of combining several classes of drugs is called balanced anesthesia.

Halothane is used in patients with airway disease and was for many years the inhalation agent of choice for mask induction of pediatric patients. Repeated administration can cause halothane hepatitis. Halothane is known to sensitize the myocardium for arrhythmias, especially in combination with catecholamines. It is not recommended for obstetric anesthesia unless uterine relaxation is required. Emergence from anesthesia is slower compared to other inhaled anesthetics.

Isoflurane is currently one of the most used inhalation anesthetics. It may cause coronary artery steal syndrome. Decrease in blood pressure is due to peripheral vasodilatation.
Enflurane is similar to isoflurane. Decrease in blood pressure however is caused by negative inotropy. Enflurane has been found to increased intracranial pressure and, especially in combination with hyperventilation to increase the risk of seizure activity. It is therefore contraindicated in patients with seizure disorders.

Desflurane is one of the newer agents. It requires a specially designed electrically heated vaporizer. Desflurane may cause coughing during induction and should therefore be combined with intravenous anesthetics. Increase of heart rate might be a disadvantage in patients with coronary artery disease. Rapid elimination results in quick awakening.
Sevoflurane, another newer inhalation agent, is known for rapid induction and awakening. It might react with the CO2 absorbents to form the nephrotoxic compound A. Therefore, it should not be used in low flow systems. A minimal fresh gas flow of two liters per minute is required. Due to its low solubility in blood and therefore rapid induction of anesthesia it is often used for mask induction especially of pediatric patients. It replaces in many hospitals halothane for this purpose. Rapid elimination results in quick awakening.

Nitrous oxide is a week anesthetic. It is used to supplement inhalation agents. It is the only inhalation anesthetic with sympathomimetic activity. It should not be used in doses higher than 70 percent combined with 30 percent oxygen. It is known to diffuse into air containing spaces and to increase the pressure in such cavities. 100 percent oxygen should be administered during awakening in order to avoid diffusion hypoxia.

And last but not least one should be aware that all inhalation anesthetics are able to trigger malignant hyperthermia in susceptible patients.

References
Author Information

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