Pharmacology of Inhaled Anesthetics

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The original version of this chapter was revised. The abbreviation "MAP mean arterial pressure" was additionally present in the footnote of Table 10.2. This has now been removed. The correction to this chapter can be found at https://doi.org/10.1007/978-3-319-62067-1_39

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Key Points

1. Inhalational agents are chemical compounds that possess general anesthetic properties and can be administered via inhalation. The contemporary agents available for clinical use include nitrous oxide and the volatile agents: halothane, isoflurane, desflurane, and sevoflurane.
2. Currently, the mechanics of inhaled volatile anesthetics are believed to occur through a combined effect by prolongation of inhibitory effects ($GABA_A$ and glycine receptors) and inhibition of excitatory effects. This has minimized the belief in the Meyer and Overton theory that proposed the lipid membrane was the primary site of anesthetic action.
3. Volatile anesthetics decrease mean arterial pressure in a dose-dependent manner, which varies with the type of agent used. All volatile agents depress ventilation and blunt responses to changes in $PaCO_2$.
4. The minimum alveolar concentration (MAC) of an inhaled anesthetic is the alveolar concentration at which 50% of patients will not show a motor response to a standardized surgical incision.
5. Inhalational anesthetics undergo biotransformation to many different degrees and locations depending primarily on their lipophilicity and clinical stability. The major organs involved in biotransformation, the liver and kidneys, are exposed to the highest metabolite concentrations; and therefore, are the primary sites of toxicity
6. The single most important factor in determining the speed of induction and recovery for inhalational agents is the blood:gas coefficient, which expresses the agent's distribution between the blood and gas at the same partial pressure. The higher the agent's solubility in the blood, the slower its induction rate.

10.1 Introduction

Inhalational agents are used in anesthesia primarily to produce a loss of consciousness, but may have other effects such as muscle relaxation and analgesia. Inhalational anesthetics have been in use since the 1840s, when agents such as ether, chloroform, and nitrous oxide were introduced. Due to safety issues, the search for better inhalational agents was begun and fluorinated ethers and hydrocarbons were introduced. Halothane was introduced into clinical practice in 1956 and revolutionized anesthetic practices. However, secondary to its arrhythmogenic effects with epinephrine and possible postoperative liver failure, alternative agents were developed to minimize negative effects. Enflurane, a methyl ether derivative, was not arrhythmogenic or hepatotoxic, but had side effects including lowering the seizure threshold. With further research, the modern inhalational agents of fluorinated ethers including isoflurane, sevoflurane, and desflurane were introduced by the 1980s. These drugs resist metabolism and make organ toxicity unlikely. As research continues, the noble gas, xenon, has a potential for future development. These agents have improved safety and reliability.

10.2 Physical and Chemical Properties of Inhaled Anesthetics

10.2.1 Nitrous Oxide

Nitrous oxide (Fig. 10.1) is a low-molecular weight inorganic gas that is odorless and colorless. Although it is nonexplosive, it does support combustion [1]. Because of its low potency and poor blood solubility (Table 10.1), it is commonly administered in conjunction with volatile anesthetics or narcotics to produce general anesthesia. Nitrous oxide has

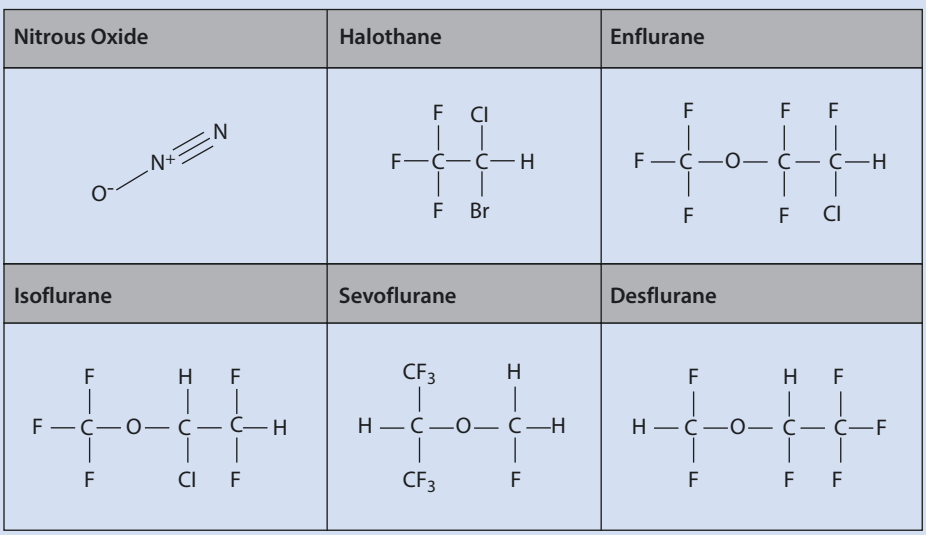

Fig. 10.1 Molecular structure of inhalational anesthetics

Table 10.1 Physical and chemical properties of inhaled anesthetics

	Nitrous Oxide	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Molecular weight	44	197	165	184	184	200	168
Boiling point (°C)	−89	51	105	57	48	23	59
Blood:gas coefficient @ 37 °C	0.47	2.5	12	1.9	1.4	0.45	0.65
Oil: gas coefficient @ 37 °C	1.3	197	950	99	97	19	53
Vapor pressure (mmHG @ 20 °C)	Gas	244	22.5	172	240	669	170
MAC % (30–55 year old at 1 atm)	104	0.75	0.2	1.63	1.17	6.0	2.0
Stable in soda lime	Yes	No	Yes	Yes	Yes	Yes	No

Sources: Bovill [2] and Yasuda et al. [3]

the lowest potency of the inhalational agents, with a minimum alveolar concentration (MAC) value of 104%, which is clinically not achievable and thus cannot provide general anesthesia when administered solely. Nitrous oxide is a gas at room temperature, but can be stored as a liquid under pressure as its critical temperature lies above room temperature. Although it does have amnestic and analgesic properties, it does not provide muscle relaxation as other inhalational agents do. Controversy exists over the role of nitrous oxide in postoperative nausea and vomiting (PONV), which may occur through activation of the chemoreceptor trigger zone and vomiting center in the medulla [4].

10.2.2 Halothane

Halothane is a halogenated alkane (Fig. 10.1) that remains a clear liquid at room temperature. Carbon-fluoride bonds make it nonflammable and non-explosive. It is well tolerated for inhalational inductions with a notable sweet, nonpungent odor. It has a high potency and intermediate solubility, which allows for an intermediate onset and recovery from anesthesia (Table 10.1). Thymol must be added to halothane which also must be stored in amber bottles to prevent spontaneous oxidative decomposition [5, 6].

10.2.3 Enflurane

Enflurane is a halogenated ether (Fig. 10.1) with an ethereal odor that remains a liquid at room temperature. It has an intermediate solubility and high potency allowing for intermediate onset and recovery times from anesthesia (Table 10.1). Enflurane is oxidized in the liver and can produce nephrotoxic fluoride ions [7, 8].

10.2.4 Isoflurane

Isoflurane is a fluorinated methyl ethyl ether (Fig. 10.1) that is a nonflammable liquid at room temperature. Although it is an isomer of enflurane, it has different physiochemical properties and different manufacturing methods. Like enflurane and halothane, it has an intermediate solubility and high potency allowing for intermediate onset and recovery times from anesthesia (Table 10.1). It has a pungent ethereal odor [8].

10.2.5 Sevoflurane

Sevoflurane is a fluorinated methyl isopropyl ether (Fig. 10.1). It has a potency similar to enflurane. However, it has a significantly lower solubility in blood (Table 10.1). This property allows for a rapid increase in alveolar concentration and a rapid on and offset of anesthesia. Combined with its nonpungent odor, these attributes make sevoflurane an ideal inhalational induction agent. Its vapor pressures allow for the use of a conventional vaporizer. Sevoflurane is susceptible to metabolism, with 3–5% undergoing biodegradation. Unlike other volatile agents, sevoflurane is not metabolized to acyl halide intermediates (as with halothane, enflurane, isoflurane, and desflurane), which can potentially cause hepatotoxicity or cross-sensitivity between drugs.

10.2.6 Desflurane

Desflurane is also a fluorinated methyl ethyl ether (Fig. 10.1) that differs from isoflurane only by a substitution of a fluoride for the chlorine atom. The "minor change" of fluorination increases the vapor pressure, enhances molecular stability,

and decreases the potency of the drug [9]. Because of its vapor pressure (Table 10.1), desflurane will boil at room temperature at high altitudes. This requires a vaporizer (Tec 6, GE Healthcare, Chicago, IL) designed specifically to handle this inhalational agent. The vaporizer is heated to 39°C and pressurized to 2 atm. No fresh gas flows through the vaporizer pump; rather pure desflurane vapor joins the fresh gas flows before exiting the vaporizer [10]. Low solubility and potency allow for a rapid on and offset of anesthesia. Its lower blood-gas solubility creates precise control and the ability for more rapid recovery times from anesthesia [8]. Desflurane has a pungent odor, which limits its utility for inhalational inductions.

10.2.7 Xenon

Xenon is a noble gas found in the atmosphere; and was recognized as an anesthetic in 1951. It has a MAC value of 71% and can be combined with oxygen to deliver anesthesia. The blood:gas partition coefficient is 0.12, which results in rapid onset and recovery. Xenon depresses post-sympathetic excitatory transmission through N-methyl-D-aspartate (NMDA) receptor blocks. There are minimal cardiovascular side effects, even in the setting of severely limited myocardial reserve. Xenon affects anesthetic-induced preconditioning of the heart and brain against ischemic damage in the same way as volatile agents. Xenon may have neuroprotective action, but it may be offset by an increase in cerebral blood flow. It is a non-irritant to the airway for easy induction. Although a mild respiratory depressant, it decreases respiratory rate and increases tidal volume, in contrast to the volatile agents. Xenon has a high relative density, which causes an increase in pulmonary resistance. Caution is advised in patients who have severe chronic obstructive pulmonary disease (COPD) or in premature infants. It is not metabolized in the liver or kidneys and it does not trigger malignant hyperpyrexia. Xenon is also a potent intraoperative analgesic, attenuating responses to surgical stimuli to a greater extent than sevoflurane.

Xenon anesthesia provides more stable intraoperative blood pressure, lower heart rate, and faster recovery from anesthesia than volatile agents. However, it is associated with higher postoperative nausea and vomiting. The main limitations for wider use are lack of studies, need for hyperbaric conditions, impracticality in surgery, and inefficiency of conventional anesthesia equipment. These limitations make xenon cost prohibitive.

10.3 Mechanism of Action

The exact mechanism of action for volatile anesthetics is complex and still unknown. Currently, the mechanics of inhaled volatile anesthetics is believed to occur through a combined effect by prolongation of inhibitory effects ($GABA_A$ and glycine receptors) and inhibition of excitatory effects (nicotinic acetylcholine and glutamate receptors). Typical anesthetic agents produce anesthesia, amnesia, analgesia, and immobilization.

Initially, Meyer and Overton proposed a lipid theory and believed the lipid membrane was the primary site of anesthetic action by correlating inhaled anesthetics potency with their solubility in lipids. They observed a strong correlation between the potency of inhalational anesthetics and their solubility in oil, theorizing they had a nonspecific lipid membrane mechanism of action [11]. Later, researchers demonstrated that proteins may also be the site of action for inhaled anesthetics [12, 13]. Additional research on the mechanism of action for inhaled anesthetics explained ligand gated ion channels proteins are mostly likely the targets of inhaled anesthetics [14].

Electrical activity in human cells is generated through influx and efflux of ions (mostly Na+, Ca2+, Cl− and K+) through a variety of ion channels. Some receptor-mediated ion channels are targets of inhaled anesthetics at clinical anesthetic concentrations, such as serotonin receptors, $GABA_A$ receptors, glycine receptors, and NMDA or AMPA (α[alpha]-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (glutamate neurotransmitter) [15–18].

$GABA_A$-related anesthetic action is common for all volatile anesthetics due to its abundancy in the brain. Normal physiologic function of $GABA_A$ and glycine receptors (Cl− ion channels) is to inhibit the excitation of postsynaptic neurons. At effective clinical concentrations, volatile anesthetics enhance the $GABA_A$ receptor-mediated activity by increasing its sensitivity to gamma-aminobutyric acid (GABA) and the sensitized receptors prolong the inhibition of excitatory neurons. Gaseous anesthetics, such as nitrous oxide, have a minimal effect on GABA-related mechanisms [19–23]. Normally K+ channels maintain a polarized state of neurons and are targeted sites for isoflurane. Isoflurane activates the K+ channel and leads to a decrease of neuronal excitation [24].

Inhibition of excitatory neurotransmission can be achieved either by inhibition of a neurotransmitter release from presynaptic nerve endings or a postsynaptic receptor blockade. Halothane and isoflurane at clinical concentrations inhibit the NMDA receptor (Na+ ion channel) associated excitation by postsynaptic blockades or decreasing presynaptic glutamate release. The volatile anesthetics also can inhibit the presynaptic release of an excitatory neurotransmitter by blocking presynaptic voltage-gated Na+ channels at clinical concentrations [25]. Excitatory postsynaptic nicotinic acetylcholine receptors and NMDA-sensitive glutamate channels are inhibited by gaseous anesthetics to inhibit the excitation of excitatory neurons [26].

The mechanism of action for immobilization and amnesia occurs at distinct sites. Studies have proven that immobilization to surgical stimulus can be achieved at the spinal cord level without brain involvement. Immobility to surgical stimuli occurs by inhibiting ascending transmission of pain stimuli to the brain from the spinal cord. At the spinal cord level, volatile anesthetics prolong the inhibitory effects of glycine receptors and inhibit the postsynaptic excitatory effects

of NMDA and AMPA receptors [27–29]. Amnesia can be induced without immobilization at lower clinical concentrations. Specific loci in the brain are responsible for this amnesic effect. Inhaled anesthetics act on nicotinic acetylcholine receptors in the brain and impair the memory process leading to amnesia [30–33].

GABA receptors function differently between the growing brain in children and the brain in adults. In the growing brain, GABA receptors function as stimulators and in the adult brain they act as inhibitors; therefore, a neurotoxic effect from anesthetics can be seen in the growing brain. In contrast to its inhibitory action in the adult brain, GABA receptors act as an excitatory neurotransmitter in the growing brain of the child. These GABA receptors generate action potentials directly opening voltage-dependent calcium channels and increase the calcium concentration in the brain. This increase in intracellular calcium can lead to apoptosis. In addition, the mitochondrion appears to be the mediator between anesthesia-induced increased calcium levels and cell apoptosis, leading to mitochondrial damage. Every year, millions of children are treated with anesthetic agents. There is evidence that suggests that exposure to anesthetics may be neurotoxic to the developing brain and lead to long-term neurological effects.

Lithium protects against anesthesia-induced developmental neuroapoptosis along with melatonin. Coadministration of hydrogen gas acts as part of the carrier gas mixture and may suppress neuronal apoptosis. Therefore, there may not be a safe anesthetic, but only safe anesthetic concentrations and exposure durations.

10.4 Systemic Effects of Inhaled Anesthetics

Inhaled anesthetics have several effects on systemic organs. Anesthetics effects on the central nervous system, cardiovascular system, pulmonary function, neuromuscular junction, renal and liver function, and hematology and immune systems have been described in sub-sections and are summarized in Table 10.2.

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Table 10.2 Systemic effects of inhaled anesthetics

	Nitrous oxide	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular	↔	↓	↓	↓	↓	↓	↓
HR	↔	↓	↑	↑	↑	↑[b]	↔
SVR	↔	↔	↔	↓	↓	↓	↓
CO	↑[a]	↓	↓	↓	↔	↔	↓
Myocardial contractility	↔	↓	↔	↓	↔	↔	↔
Respiratory	↓	↓	↓	↓	↓	↓	↓
TV	↑	↑	↑	↑	↑	↑	↑
RR	↔	↑	↑	↑	↑	↑	↑
$PaCO_2$	↑	↔	↔	↔	↔	↔	↔
PVR	↓	↓↓	↓	↓	↓	Irritant	↓
Airway resistance							
Cerebral	↑	↑↑	↑	↑	↑	↑	↑
Blood flow	↑	↑	↑	↑	↑	↑	↑
ICP	↑	↑[a]	↓	↓	↓	↓	↓
$CMRO_2$	↓	↓	↓	↑	↓	↓	↓/↑
Seizures							
Nondepolarizing blockade	↑	↑	↑	↑	↑	↑	↑
Renal	↓	↓	↓	↓	↓	↓	↓
Blood flow	↓	↓	↓	↓	↓	Unknown	Unknown
GFR	↓	↓	↓	↓	↓	Unknown	Unknown
Urine							
Hepatic	↓	↓	↓	↓	↓	↓	↓
Blood flow							

Abbreviations: HR heart rate, *SVR* systemic vascular resistance, *CO* cardiac output, *TV* tidal volume, *RR* respiratory rate, $PaCO_2$ partial pressure of carbon dioxide, *PVR* pulmonary vascular resistance, *ICP* intracranial pressure, $CMRO_2$ cerebral metabolic rate of oxygen, *GFR* glomerular filtration rate

[a]Minimal

[b]With rapid change in inhaled concentration

10.4.1 Effects on Central Nervous System

The changes in an electroencephalogram (EEG) are noticed after the induction of inhaled anesthetics. At lower clinical concentrations (low MAC), the volatile anesthetics and gaseous anesthetics produce high frequency and low amplitude (Beta waves) waves in the EEG, and are transformed to low frequency and high amplitude waves (Delta waves) at clinical anesthetic concentrations [33]. Some volatile anesthetics, such as isoflurane and desflurane at 1.5–2 MAC anesthetic concentration, cause electrical silence in the EEG [34].

Enflurane has the tendency to induce convulsions (seizures) to decreased $PaCO_2$, MAC >2, and repetitive auditory stimuli [35]. Isoflurane has anti-convulsive properties, and desflurane does not produce seizures [36, 37]. There are case reports that support that sevoflurane can produce seizure activity [38, 39].

Typically, cerebral blood flow is autoregulated and depends on the cerebral oxygen consumption ($CMRO_2$), and $PaCO_2$. All inhaled anesthetics increase cerebral blood flow in a dose-dependent manner despite a decrease in cerebral oxygen consumption. Inhalation agents also partially preserve the autoregulation of CBF to changes in $PaCO_2$. Desflurane and isoflurane preserve the responsiveness of CBF to changes in $PaCO_2$ [40]. Cerebral metabolic oxygen requirements are dose-dependent and are decreased with volatile anesthetics [41]. Increased intracranial pressure is seen with halothane use due to significant increases in cerebral blood flow compared to other inhaled anesthetics [42].

Preconditioning and postconditioning is a mechanism for inhaled anesthetics for neuroprotective effects. Inhalational anesthetics provide neuroprotective effects against brain ischemia by pre-, pro- and post-conditionings. Preconditioning is a process where a relatively small amount of inhalational agent is administered prior to the ischemic insult. Postconditioning is applied after the cerebral ischemic event has developed. Many studies have confirmed the protection of pre- and post-conditioning of inhalational anesthetics in their neuroprotection against cerebral ischemia. Sevoflurane preconditioning and early postconditioning reduced both cerebral infract size and neurological defect score at 24 h of reperfusion. Pretreatment with sevoflurane or its early administration at reperfusion provided neuroprotection via mitoKATP in a rat model for focal cerebral ischemia.

Although sevoflurane and isoflurane are similar in their systemic effects, they appear to differ in cerebral circulation. Sevoflurane can maintain cerebral autoregulation up to 1.5 MAC; whereas, isoflurane results in loss of autoregulation. Thus, cerebral autroregulation is better preserved during 1.5 MAC sevoflurane than isoflurane and is a better neuroanesthetic agent.

10.4.2 Effects on Cardiovascular System

Volatile anesthetics decrease mean arterial pressure in a dose-dependent manner, which varies with the type of agent used. At clinical anesthetic concentration, halothane decreases the mean arterial pressure by decreasing myocardial contractility and cardiac output; whereas, isoflurane, sevoflurane, and desflurane decrease systemic vascular resistance. Enflurane decreases both systemic vascular resistance and cardiac output. The change in heart rate is variable with type of agent used and the type of pharmacological agent administrated during surgery. The decrease in heart rate is observed with halothane use due to suppression of the carotid sinus to changes in systemic blood pressure and rate of sinus node depolarization. At anesthetic concentrations, the heart rate is increased with desflurane, enflurane, sevoflurane (>1 MAC) and isoflurane use [41, 43]. Nitrous oxide has very little effect in mean arterial pressure and heart rate changes [44, 45]. Significant decrease in cardiac output is noticed with halothane and enflurane, and sevoflurane can decrease cardiac output at MAC between 1 and 1.5. Sevoflurane can prolong the QT interval and should be cautiously used in patients with prolonged QT interval syndrome or patients susceptible to QT interval changes [46]. Volatile agents can induce arrhythmias. Halothane and isoflurane sensitize the heart to epinephrine, compared to desflurane and sevoflurane, and cause cardiac arrhythmias [47, 48]. Coronary steal syndrome, wherein normally responsive coronary anenoles are dilated "stealing" blood from vessels supplying ischemic zones, may be associated with isoflurane [49]. 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, which have decreased ability to vasodilate. Thereby, blood is redistributed in greater amounts to areas with normally responsive coronary arteries. However, most clinical studies failed to prove a higher incident of myocardial ischemia due to isoflurane. Sevoflurane and desflurane do not cause coronary steal syndrome.

10.4.3 Effects on Respiration

All volatile agents depress ventilation and blunt responses to changes in $PaCO_2$. Volatile agents cause rapid, shallow breathing. There is a reduction in the tidal volumes and minute ventilation. The increase in respiratory rate does not adequately compensate for the amount of tidal volume decrease and hence causes an increase in $PaCO_2$.

Volatile agents reduce minute ventilation by reducing tidal volumes. Reduced tidal volume causes a slight increase in $PaCO_2$. The agents minimally suppress the responsiveness to increased $PaCO_2$ (hypercapnia) from decreased tidal volume at central medullary respiratory centers [50, 51]. Nitrous oxide has very little effect in ventilation depression, bronchial muscle tone, and in hypoxic drive [52]. Increases in respiratory rate are associated with all volatile anesthetics. Halothane, isoflurane and sevoflurane decrease airway resistance in COPD and asthmatic patients [53]. Due to low airway irritant effects, nitrous oxide, halothane and sevoflurane can be used for induction of anesthesia. Isoflurane and desflurane can irritate the airways during induction with MAC greater than 1.5 and 1, respectively, but have little or no effect during the maintenance of anesthesia. Desflurane is a pungent gas that

can cause airway irritability during induction, manifested as breath-holding, salivation, coughing, and possibly laryngospasm. Small doses of opioid administration and humidification help to reduce irritant properties [54–56].

10.4.4 Effects on Neuromuscular Junction

Volatile anesthetics enhance the effects of neuromuscular blocking drugs by inhibiting nicotinic acetylcholine receptors [57]. Volatile anesthetics produce dose-dependent muscle relaxation; whereas, nitrous oxide can cause skeletal muscle rigidity (>1 MAC) [58]. One potential complication of volatile agents is malignant hyperthermia (MH). Succinylcholine administration with a volatile agent potentiates a patient susceptible to MH. Malignant hyperthermia can occur even without succinylcholine administration in genetically susceptible patients [59–61]. Halothane has a higher tendency to produce MH than other volatile agents. MH can appear hours after uneventful anesthesia with desflurane [62] and sevoflurane [63, 64]. Nitrous oxide does not manifest this complication [11].

10.4.5 Effects on Renal Function

Volatile agents have little effect on renal physiology. The decrease in renal blood flow that is clinically observed is a product of their glomerular filtration rate and urine output is systemic vascular effects. There is no direct effect of inhalational agents on renal blood flow. Inorganic fluorides and metabolites, such as compound A, produced from the metabolism of volatile anesthetics can be nephrotoxic; and these effects are further discussed in the next section (Biotransformation and Toxicity of Inhaled Anesthetics).

10.4.6 Effects on Hepatic Function

All inhaled anesthetics reduce the hepatic blood flow. Severe hepatic injury following volatile anesthetics administration is very rare, with a ratio of 1:10,000,000 [65]. Anesthetics agents interfere with hepatic metabolism of other pharmacological agents that are administrated during the anesthesia [66, 67]. Hepatotoxicity can occur with inhaled anesthetics due to inadequate hepatic oxygenation from reduced hepatic blood flow. Hepatotoxicity incidences are higher with halothane induction compared with other inhaled anesthetics. These effects are further discussed in the next section (Biotransformation and Toxicity of Inhaled Anesthetics).

10.4.7 Effects on Hematologic and Immune Systems

Prolonged exposure to nitrous oxide can interfere with bone marrow function. Nitrous oxide affects DNA synthesis by inhibiting vitamin B_{12} dependent enzymes (methionine synthetase) [68, 69]. Megaloblastic changes are noticed in patients who receive nitrous oxide for a duration of 24 h. Agranulocytosis occurs in patients with 4 days or longer exposure to nitrous oxide. Volatile anesthetics have an immunosuppressive effect on both innate immunity (neutrophils, NK cells, and macrophages) and cell-mediated immunity (T-cells and B-cells), and are dose-dependent. Volatile agents impair neutrophil, macrophage, dendritic, and T-cell function. The suppressive action on immunity is from a combined exposure of the patient to surgery and anesthesia. Surgery releases stress hormones (catecholamines and corticosteroids) [70]. Inhaled anesthetics inhibit the actions of polymorphonuclear cells such as chemotaxis and phagocytosis. Sevoflurane and isoflurane can induce dose-dependent apoptosis in lymphocytes. Isoflurane and sevoflurane also reduce the expression of adhesion molecules on lymphocytes and macrophages; and thus, decreases the recruitment and accumulation of immune cells at inflammatory sites [71].

10.5 Biotransformation and Toxicity of Inhaled Anesthetics

Inhalational anesthetics undergo biotransformation to many different degrees and locations depending primarily on their lipophilicity and clinical stability. The major organs involved in biotransformation, the liver and kidneys, are exposed to the highest metabolite concentrations, and therefore, are the primary sites of toxicity (see Table 10.3).

10.5.1 Nitrous Oxide

Nitrous oxide undergoes very little biotransformation (0.004%) and is almost solely eliminated by exhalation during emergence [8]. Anaerobic bacteria in the gastrointestinal (GI) tract are responsible for the minimal amount of metabolism. Nitrous oxide irreversibly oxidizes the cobalt atom in vitamin B_{12}, including methionine synthetase and thymidylate synthetase. These enzymes are responsible for myelin formation and DNA synthesis; and thus, nitrous oxide has been questioned to cause bone marrow suppression and neurologic deficiencies in prolonged usage.

10.5.2 Halothane

The liver is the primary site of biotransformation and metabolism for most drugs, particularly lipophilic drugs such as halothane [74, 75]. Approximately 25% of administered halothane is oxidized by an isoenzyme of P450 (CYP2E1) into its principal metabolite trifluoroacetic acid (TFA), as well as lesser amounts of bromide and chloride [76]. The TFA metabolites react with tissue proteins to form trifluoroacetylated protein adducts. Clinical exposure to halothane results in 2 distinct types of hepatitis [77–79]. Type I hepatotoxicity is benign and self-limiting and occurs in 25–30% of patients

Table 10.3 Biotransformation and toxicity of inhaled anesthetics

	Nitrous oxide	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Tissue metabolism (%)	0.004	25	70	2.5	0.2	0.02	5
Oxidating enzymes	Anaerobic bacteria in gastrointestinal tract	CYP2E1, CYP2A6	CYP2E1, CYP1A2, CYP2C9/10, CYP2D6	CYP2E1	CYP2E1	CYP2E1	CYP2E1
Principal metabolite	Inactivation of methionine synthetase	TFA, bromine, chloride	Oxalic acid, free fluoride	TFA, small fluoride level rise	TFA, small fluoride level rise	TFA (fluoride levels unchanged from pre-anesthetic levels)	Fluoride
Trifluoroacetylated hepatocellular protein degree of modification	None	++++++	None	++	+	+	None
CO_2 stability	Yes	CO from desiccated carbon dioxide absorbent	CO from desiccated carbon dioxide absorbent	CO from desiccated carbon dioxide absorbent	CO from desiccated carbon dioxide absorbent	CO from desiccated carbon dioxide absorbent	Compound A from desiccated carbon dioxide absorbent, heat production
Possibly toxicities	DNA synthesis, Bone marrow suppression, Vitamin B12 deficiency	**Hepatic** (1:20,000 fulminant hepatitis)	**Renal**, hepatic	Hepatic (1:300,000 fulminant hepatitis)	Hepatic (rare fulminant hepatitis)	Hepatic (rare fulminant hepatitis)	Hepatic (few case reports fulminant hepatitis)

Sources: Yasuda et al. [72, 73]
Abbreviations: TFA trifluoroacetic acid, *CO_2* carbon dioxide, *CO* carbon monoxide

receiving halothane. Symptoms include transient nausea, fever, and serum transaminase levels. "Halothane hepatitis," or type II hepatotoxicity, has been reported in 1:5000 to 1:35,000 cases of halothane administration. This immune-mediated reaction is believed to result from the trifluoroacetylated protein adducts in the liver. Clinical symptoms of halothane hepatitis include fever, eosinophilia, and jaundice. Laboratory findings include elevated serum alanine and aspartate transferase and elevated bilirubin. Patients also have a positive IgG against TFA. Severe cases are associated with centrilobular necrosis that may lead to fulminant liver failure with a mortality rate of 50% [80]. Higher rates of halothane hepatitis are found in patients exposed to multiple halothane anesthetics in a short period of time, obese patients, patients >50 years old, female patients, and patients with a history of postanesthetic fever or jaundice.

10.5.3 Methoxyflurane

As the most lipophilic inhaled anesthetic, methoxyflurane undergoes the most biotransformation at an estimated 70% of the drug administered [81]. Only a small amount of the drug, taken into body tissue, is exhaled and respiratory clearance from muscle and fat can extend over a period of several days. Methoxyflurane is metabolized in both the kidneys and the liver, and inorganic fluoride (F-) is produced during its metabolism in clinically significant quantities [82, 83]. Many studies have demonstrated direct links between methoxyflurane dosages, metabolism, and fluoride production. Inorganic fluoride likely causes renal injury with a nephrotoxic threshold of 50 μ(mu)mol/L [84]. Methoxyflurane, the first modern halogenated ether anesthetic, is no longer in clinical use because it is now known to produce polyuric renal insufficiency. More recent anesthetics have been cautiously studied for their renal impairment and fluoride production abilities [85].

10.5.4 Isoflurane

The minimal metabolism (0.2%) of isoflurane results in extremely low rates of hepatic or renal impairment. TFA is the primary metabolite, but serum fluoride levels have not been shown to cause renal dysfunction [86].

10.5.5 Desflurane

Desflurane undergoes extremely low metabolism rates in humans (0.02%); and thus, the serum and urine fluoride levels are essentially unchanged from pre-anesthetic levels. More than the other volatile agents (desflurane > enflurane > isoflurane), desflurane is susceptible to degradation in dessicated carbon dioxide absorbancy to carbon monoxide, when water content falls below 1.4% for soda lime and 5% for baralyme. This carbon monoxide can lead to increased levels of blood carboxyhemoglobin [87–89].

10.5.6 Sevoflurane

Inorganic fluoride ions in plasma concentrations greater than enflurane and hexafluoroisopropanol are produced during the metabolism of sevoflurane in humans. The overall rate of sevoflurane metabolism is more than 10 times that of isoflurane (5%), clinically producing higher serum fluoride levels. Despite this, clinical studies have demonstrated no clinical nephrotoxicity with sevoflurane administration, even with peak concentrations of 50 μ(mu)mol/L. Production of fluoride ions of sevoflurane is mainly in the liver and, therefore, has minimal effect on the kidney function. The liver metabolizes 2–5% of the sevoflurane. Typical fluoride levels after 2–3 MAC hours are 20–30 μ(mu)mol/L [90]. Because of sevoflurane's low blood:gas solubility and rapid elimination, fluoride concentrations fall quickly and renal toxicity is not clinically present. In the presence of a strong alkali, such as those in carbon dioxide absorbents, sevoflurane has been shown to degrade to compounds toxic to animals, particularly compound A (fluoromethyl-1, 1-difluro-1(trimethyl) vinyl-ether) [91–93]. Larger amounts of compound A are produced with lower gas flows, increased respiratory temperatures, high sevoflurane concentrations, anesthetics of long duration and dessicated soda lime. Amsorb® (Armstrong Ltd., Coleraine, Northern Ireland) is a newer absorbent that does not contain strong base and does not form CO or compound A in vitro. It is clinically recommended to maintain fresh gas flows greater than 2 L/min to limit possible compound A production. Despite proven nephrotoxicity in rats, no postoperative renal impairment or injury has been seen in humans. This difference may be secondary to the lower β(beta)-lyase activity in humans [94]. Degradation of sevoflurane to hydrogen fluoride in the presence of metal and environmental impurities can also occur. Hydrogen fluoride can cause respiratory mucosal burns. Degradation is inhibited through the addition of water in manufacturing and packaging in plastic containers [90]. The US Food and Drug Administration (FDA) recommends the use of sevoflurane with fresh gas flow rates at least 1 L/min for exposure up to 1 h and at least 2 L/min for exposures greater than 1 h.

10.5.7 Possible Neurotoxicity of Inhaled Anesthetics

The possibility of neurotoxic effects of inhaled and other general anesthetics does exist in patients of extreme ages [95, 96]. The greatest concern is the use of general anesthetics in the youngest patients, where rapid brain development is occurring. Widespread neuronal apoptosis in 7-day-old rats after exposure to midazolam, isoflurane, and nitrous oxide caused lasting deficits in behavior, learning, and memory centers [97, 98]. Continued research has demonstrated, in nonhuman species including primates, sensitive periods of early brain development when anesthetics can accelerate apoptosis [99]. Clinical studies in humans have demonstrated mixed results. Although a possible association with multiple anesthetic exposure and impaired neurocognitive development was demonstrated in one study, others have found no cognitive outcome differences [100–102]. Ongoing clinical trials will provide more information on this important issue and additional information is available at smarttots.org.

10.6 Minimum Alveolar Concentration and Its Affecting Factors

Minimal alveolar concentration of an inhaled anesthetic is defined as the alveolar concentration at which 50% of the patients are immobile to a standard surgical incision at 1 atmospheric pressure [62, 103]. The immobility is achieved in 99% of patients with 1.3 MAC. This is the state where somatic responses are lost. The potency of the anesthetics is measured by MAC. Anesthetics with higher MAC have a lower potency (eg, N_2O) and vice versa. As the MAC of nitrous oxide exceeds 100%, it cannot be used alone to provide general anesthesia. It is typically combined in a 70% concentration with 30% oxygen and in concert with more potent agents. The MAC values are additive when used in combinations. The MACs of different inhalational anesthetics are summarized in Table 10.1. Numerous factors are involved in affecting MAC values and they are described in Table 10.4 [104, 105].

"MAC-awake" is defined as the concentration at which response to the vertebral commands are lost in 50% of the patients. This is the state where amnesia occurs. Amnesia is observed before the immobility occurs. The MAC-awake values are significantly lower than the MAC values.

Many studies have demonstrated an age-related MAC value for the volatile agents. MAC is highest at 6 months of age, after which it begins to decline. After age 40, MAC declines ~6% per decade such that by 80 years of age, MAC is about 0.75 that of a 40-year-old.

Table 10.4 Factors affecting minimum alveolar concentrations (MAC)

Factors decreasing MAC requirements	Factors increasing MAC requirements
Decreased catecholamine levels in CNS	Increased catecholamine levels in CNS
Hyponatremia	Hypernatremia
Hypothermia	Hyperthermia
Older age (elderly)	Infants (greatest MAC at 6 months)
Acute alcohol intoxication	Chronic alcohol usage
Anemia (hematocrit <10%)	Red hair (20% increase)
Hypercarbia ($PaCO_2$ >95 mmHg)	Hyperthyroidism
Hypoxia (PaO_2 <40 mmHg)	
Pregnancy (decreased by 30% at 8 weeks)	
Drugs	Drugs
Opioids	Cocaine
Ketamine	Ephedrine
Benzodiazepines	MAO inhibitors
Clonidine, Dexmetetomidine, Methydopa	Amphetamine (acute)
Local Anesthetics	
Lithium	
Amphetamines (chronic)	

CNS central nervous system, *$PaCO_2$* partial pressure of carbon dioxide, *PaO_2* partial pressure of oxygen, *MAO* monoamine oxidase

10.7 Trace Concentrations, Operating Room Pollution, and Personnel Hazards

Health care workers, surgeons, and anesthesiologists in operating theaters or anesthetizing locations are at risk of exposure to trace concentrations of anesthetics. Spontaneous abortions and congenital defects were observed in rats that were exposed to nitrous oxide for longer times [106, 107]. Even in humans, potential occupational associated risks are noticed after prolonged exposure to nitrous oxide. Spontaneous abortions and decreases in fertility occurred in female workers who were exposed to nitrous oxide in the absence of scavenging systems during nitrous oxide administration [108, 109]. Halogenated agents in vitro are embryolethal and produced teratogenic effects in animals [110–112]. In humans, halogenated agents can cause spontaneous abortions and there is some evidence they might produce congenital defects in the offspring of exposed pregnant women [112–114]. Appropriate safety measures, such as scavenging systems and proper ventilation systems, must be taken in hospital operating rooms and anesthetizing locations to prevent occupational-related hazards, especially in females.

Nitrous oxide enhances the greenhouse effect just as carbon dioxide does, but is 300 times more potent, accounting for 6% of the heating effect and causing ozone depletion. In addition, inhaled anesthetics also contribute to global climate change. Isoflurane, sevoflurane, and deslurane undergo very little in vivo metabolism in clinical use, and upon exhalation these agents remain in a form that may pollute the environment. Whenever N_2O or a volatile anesthetic is administered, a continuous flow fresh air ventilation system or scavenger must be used to prevent waste gas accumulation (WGA). Health care facilities are accountable for ensuring that all anesthesia equipment, including the scavenging system, is properly maintained to promote a safe and healthy environment.

10.8 Comparative Pharmacokinetics of Inhaled Anesthetics

The pharmacokinetics of inhaled anesthetics describes their uptake from the alveoli into the systemic circulation, distribution in the body, and primary elimination by the lungs or liver metabolism. Although the mechanism of action of these agents remains hypothetical, their therapeutic effect ultimately depends on their tissue concentration in the central nervous system. The goal of delivering the inhaled anesthetic is to obtain an optimal brain partial pressure (P_{br}) of the anesthetic. The alveolar partial pressure (P_A), in equilibrium, mirrors the P_{br} and is used as an index of anesthetic depth. The pharmacokinetics can be influenced by aging and increases in body fat [115].

10.8.1 Uptake and Partial Pressure Equilib rium

There are many steps involved between the administration of the inhaled anesthetic from a vaporizer and its distribution into the central nervous system (see Fig. 10.2).

A series of partial pressure gradients drives the forward movement and systemic absorption of the gas. The principal objective is to achieve equal partial pressures on both sides of each single barrier in the gas flow.

P_A (alveolar partial pressure) ↔ P_a (arterial partial pressure) ↔ P_{br} (brain partial pressure):

The alveolar partial pressure is dependent on the inspired pressure, ventilation, and breathing system components. This gradient begins with the inspiratory concentration of the gas leaving the anesthesia machine. This content depends on the concentration set by the vaporizer as well as the fresh gas flow, the volume of the breathing circuit, and the possible absorption of the gas by the circuit. Increasing ventilation promotes the input of anesthetics to offset the tissue uptake. The effect is a more rapid rate of increased in the P_A [117].

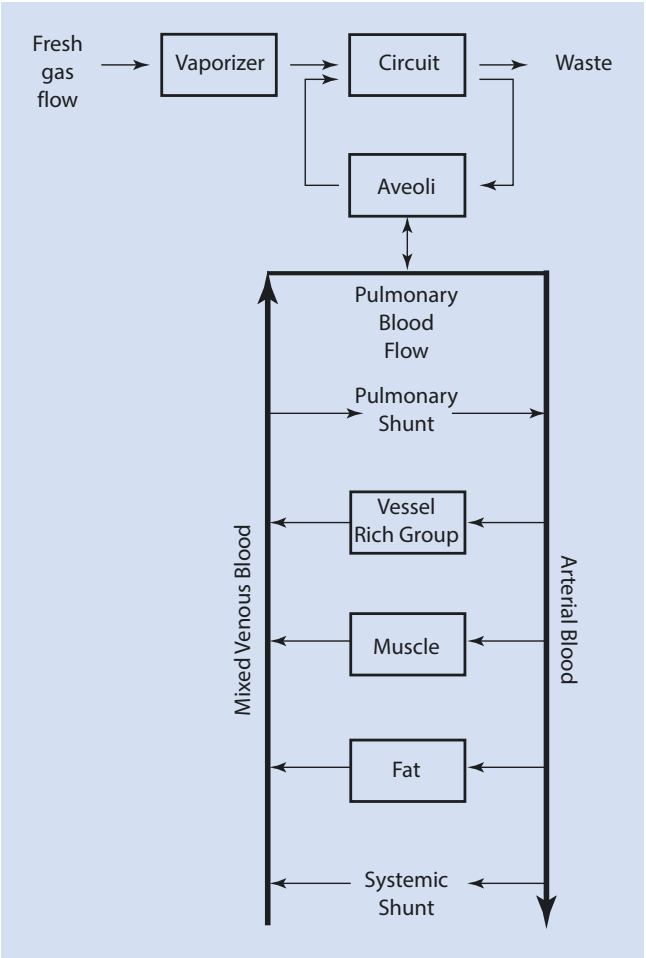

Fig. 10.2 The uptake and distribution of inhaled anesthetics in the body (Adapted from Miller and Pardo [116])

The second component in the uptake of inhaled anesthetics is the alveolar gas concentration that is achieved in lung tissues during anesthesia. As the agent is taken up in the pulmonary blood stream during induction, the alveolar tissue concentrations remain less than in inspired concentrations. When the blood uptake of the agent is greater, its rate of rise in the alveolar gas is slower. Increasing the inspired concentration of an agent not only increases its alveolar concentration, but also its rate of rise (F_A/F_I). This phenomenon is known as the concentration effect. The alveolar partial pressure of an agent is important because it determines the partial pressure of the anesthetic in the blood and ultimately in the brain. Hence, the partial pressure in the brain is directly proportional to its brain tissue concentration and therefore its clinical effect.

The impact of a right-to-left shunt on the rate of increase in the P_a depends on the solubility of the anesthetic. A right-to-left shunt slows the rate of increase of the P_a of a poorly soluble anesthetic more than that of a soluble anesthetic. It appears unlikely that a right-to-left shunt alone will alter the speed of induction of anesthesia significantly. Left-to-right shunts result in delivery to the lungs of blood containing a higher partial pressure of anesthetic than that present in blood that has passed through tissues. As a result, left-to-right shunts offset the dilutional effects of a right-to-left shunt on the P_a.

P_A (alveolar partial pressure) ↔ **P_a (arterial partial pressure)** ↔ P_{br} (brain partial pressure):

The uptake of the inhaled anesthetics from the alveoli into the pulmonary capillary blood depends on its solubility in body tissue (the partition coefficients), the cardiac output, and the alveolar-venous partial pressure difference [3, 118]. A slower rate of induction occurs if there is a greater uptake of the agent and a greater difference between the inspired and alveolar concentrations. The blood:gas partition coefficient is the single most important factor in determining the speed of induction and recovery (Table 10.5). A partition coefficient is a property of a chemical that describes its relative distribution at equilibrium given the same temperature, pressure, and volume. For anesthetics, the blood:gas coefficient is an important measure describing an inhalational agent's distribution between the blood and gas at the same partial pressure. A higher blood:gas coefficient correlates with higher blood solubility and thus a slower induction rate. A lower blood:gas coefficient transiently corresponds with a faster induction rate; for instance, nitrous, desflurane, and sevoflurane have faster induction rates than isoflurane and halothane (see Table 10.5). The second-gas effect states that a high volume of uptake of one gas will accelerate the rate of increase of the P_A of a simultaneously administered second gas. For instance, a high uptake of nitrous oxide will accelerate the uptake of a second gas, such as a volatile anesthetic [119, 120].

The cardiac output, in the absence of pulmonary shunting, directly affects the uptake of the inhaled agent into the

Table 10.5 Partition coefficients of inhaled anesthetics

Partition coefficient @ 37 °C	Nitrous Oxide	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Blood: gas	0.47	2.5	12	1.9	1.4	0.45	0.65
Brain: blood	1.1	2.9	2	1.5	2.6	1.3	1.7
Fat: blood	2.3	60	49	36	45	27	48

blood stream. As the cardiac output increases, a more rapid uptake will occur, which causes the rate of rise in the P_A to slow and the induction rate to decrease. Insoluble anesthetics display less effect from the cardiac output since little is taken up in the alveolar blood flow.

The final factor in determining the alveolar blood anesthetic uptake is the alveolar to venous partial pressure difference. A larger gradient slows the rise in P_A. These factors are determined by the tissue uptake of the anesthetic, primarily in vessel-rich groups that receive 75% of the cardiac output. The vessel rich groups—including the brain, heart, and kidneys—equilibrate rapidly with the P_a. In approximately 3 time constants, 75% of the returning venous blood has the same partial pressure as the P_A.

P_A (alveolar partial pressure) ↔ P_a (arterial partial pressure) ↔ **P_{br} (brain partial pressure)**:

The anesthetic partial pressure in the brain is the final component, and the clinically significant end result of drug administration. It is affected by the blood:brain partition coefficient, the cerebral blood low and the arterial to venous partial pressure difference (Table 10.4).

10.8.2 Elimination

Recovery from anesthesia is represented as the lowering of the anesthetic concentration in the brain tissue. A majority of modern anesthetic elimination is through exhalation; however, a small percentage is elimination in biotransformation or transcutaneous loss. The most important route of elimination is through ventilation and the alveolus. As such, many of the same factors that determine induction speed account for the speed of recovery: elimination of rebreathing, high fresh gas flows, low circuit absorption, decreased agent solubility, high cerebral blood flow, and increased ventilation [72, 73]. The main difference in recovery from anesthetics is that, in recovery, different tissues in the body have different partial pressures of the inhaled anesthetic. Therefore, recovery is not as controllable as induction [121]. Because nitrous oxide is eliminated so quickly, it can dilute alveolar oxygen and carbon dioxide, causing diffusion hypoxia. Clinically, this hypoxia is avoided by administering 100% oxygen for 5–10 min after discontinuing nitrous oxide [122].

10.9 Questions and Answers

Questions (Choose the most Appropriate Answer)

1. The rate of uptake of an anesthetic gas from the lungs and hence the rate of induction with an inhalational anesthetic:
   A. Increases when a premedication has been administered prior to induction
   B. Is proportional to the solubility of the inhalational agent in the blood
   C. Is increased if tidal volumes are decreased
   D. Is dependent only on the MAC of the inhalational agent
   E. Correlates with the vapor pressure of the inhalational agent
2. A pediatric patient presents for an inhalational induction. The reason desflurane is not the most appropriate agent in this scenario is:
   A. Desflurane has a low blood:gas partition coefficient
   B. Desflurane has a high vapor pressure
   C. Desflurane may produce hepatitis postoperatively
   D. Desflurane may produce airway irritability
   E. Desflurane cannot attain adequate potency due to its higher MAC value
3. The anesthetic agent that should be avoided in patients with a history of seizure activity is:
   A. Halothane
   B. Isoflurane
   C. Desflurane
   D. Enflurane
   E. All of the above
4. While administering only an inhalational agent, you notice that the cardiac output of your patient has decreased. The agent that you are most likely using is:
   A. Halothane
   B. Isoflurane
   C. Desflurane
   D. Nitrous Oxide
   E. Sevoflurane
5. The recommended fresh gas flows when using sevoflurane is 2 L/min because:
   A. Sevoflurane biodegrades into peak concentrations of 50 μ(mu)mol/L of fluoride, which may cause nephrotoxicity.
   B. Metal degrades sevoflurane into hydrogen fluoride.
   C. Alkali, such as soda lime, can degrade sevoflurane compound A.
   D. Nitrous oxide remaining in the circuit can cause degradation of sevoflurane.
   E. Sevoflurane is less pungent to airways with higher gas flows.
6. A patient presents to the operating room for a knee arthroscopy. She is a 65-year-old woman with obesity. Postoperatively, she develops fever, eosinophilia, jaundice, and elevated serum transaminase levels. Which is the most likely inhalational agent he received during his case?
   A. Halothane
   B. Isoflurane
   C. Desflurane
   D. Nitrous Oxide
   E. Sevoflurane

7. A patient undergoes a 25-h anesthetic for hand reconstruction after a crush injury with sevoflurane, nitrous oxide, fentanyl, and rocuronium. He is observed on postoperative day one to have megaloblastic anemia. What is the most likely source?:
   A. Sevoflurane
   B. Nitrous Oxide
   C. Fentanyl
   D. Inadequate Ventilation
   E. Rocuronium
8. The anesthetic agent that most can produce regional myocardial ischemia during tachycardia due to a preferential dilation of the normal coronary arteries is:
   A. Halothane
   B. Isoflurane
   C. Desflurane
   D. Nitrous Oxide
   E. Sevoflurane
9. The resting $PaCO_2$ is elevated in patients undergoing a general anesthetic with volatile agents primarily because:
   A. The respiratory rate is decreased.
   B. Central ventilator depression occurs.
   C. Bronchodilation causes an elevated $PaCO_2$.
   D. The patient becomes apneic.
   E. The tidal volumes are decreased.
10. Metabolism plays an important role in the emergence from anesthesia with which of the following agents:
   A. Halothane
   B. Methoxyflurane
   C. Desflurane
   D. Nitrous Oxide
   E. None of the above

Answers

1. **B**. Inhalational agents with high solubility in the blood are taken up very rapidly from the alveoli. This rapid uptake lowers their partial pressure in the lung and increases the latency for induction of anesthesia. Therefore, the higher the agent's solubility in the blood, the slower its induction rate. A low blood solubility of an agent is desirable as induction and recovery times are faster.
2. **D**. Desflurane is a pungent gas that can cause airway irritability during induction, manifested as breath-holding, salivation, coughing, and possibly laryngospasm. Although its low blood:gas partition coefficient would allow for a rapid induction, this agent is not well suited for pediatric inductions due to its airway irritability.
3. **D**. Enflurane has the tendency to induce convulsions (seizures) to decreased $PaCO_2$, MAC >2, and repetitive auditory stimuli. Isoflurane has anti-convulsive properties, and desflurane does not produce seizures. There are case reports that support sevoflurane can produce seizure activity.
4. **A**. At clinical anesthetic concentration, halothane decreases the mean arterial pressure by decreasing myocardial contractility and cardiac output; whereas, isoflurane, sevoflurane, and desflurane decrease systemic vascular resistance. Nitrous oxide increases cardiac output due to a mild increase in sympathetic tone.
5. **C**. Alkali, such as soda lime, can degrade sevoflurane into another proven nephritic product in animal models, compound A. Larger amounts of compound A are produced with lower gas flows, increased respiratory temperatures, high sevoflurane concentrations, anesthetics of long duration, and dessicated soda lime. It is clinically recommended to maintain fresh gas flows greater than 2 L/min to limit possible compound A production. Despite proven nephrotoxicity in rats, it has never shown postoperative renal impairment to indicate injury or toxicity in humans.
6. **A**. "Halothane hepatitis," or type II hepatotoxicity, has been reported in 1:5000 to 1:35,000 cases of halothane administration. This immune-mediated reaction is believed to result from the trifluoroacetylated protein adducts in the liver. Clinical symptoms of halothane hepatitis include fever, eosinophilia, and jaundice. Severe cases are associated with centrilobular necrosis that may lead to fulminant liver failure with a mortality rate of 50%.
7. **B**. Nitrous oxide irreversibly oxidizes the cobalt atom in vitamin B_{12}, including methionine synthetase and thymidylate synthetase. These enzymes are responsible for myelin formation and DNA synthesis; and thus, nitrous oxide has been questioned to cause bone marrow suppression. Megaloblastic changes are noticed in patients who receive nitrous oxide for duration of over 24 h.
8. **B**. Coronary steal syndrome may be associated with isoflurane. Sevoflurane and desflurane do not cause coronary steal syndrome. When the perfusion pressure of a coronary artery is reduced, only the vessels that are capable of dilation can effectively compensate. Atherosclerotic coronary vessels cannot effectively dilate and blood is diverted further from these areas to those with the dilation, "stealing" the blood and causing ischemia.
9. **E**. Volatile agents cause rapid, shallow breathing. There is a reduction in the tidal volumes and minute ventilation. The increase in respiratory rate does not compensate for the amount of tidal volume decrease and hence causes an increase in $PaCO_2$.
10. **B**. As the most lipophilic inhaled anesthetic, methoxyflurane undergoes the most biotransformation at an estimated 70% of the drug administered.

Only a small amount of the drug, taken into body tissue, is exhaled and respiratory clearance from muscle and fat can extend over a period of several days. Methoxyflurane is metabolized in both the kidneys and the liver and inorganic fluoride (F-) is produced during its metabolism in clinically significant quantities.

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