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Inhalational Anesthetic Agents

Agent	Notes	Side Effects
Halothane	- Volatile liquid, easily vaporizes, stable, and nonflammable. - Most potent inhalational anesthetic. - Efficacious in depressing consciousness. - Very soluble in blood and adipose. - Emergence takes time. **Contraindications** - Liver dysfunction. - An intracranial mass lesion, hypovolemia, and myocardial depression. - Malignant hyperthermia **Drug interactions** - Myocardial depression is exacerbated by β-blockers and CCB. - With aminophylline = serious ventricular arrhythmia. **Biotransformation and Toxicity** - Oxidized in the liver by cytochrome P-450	**Hepatitis** - Oxidized in the liver to trifluoracetic acid. - Causes fever, jaundice, hepatic necrosis, or even death. - Immunologically mediated assault. - Exposure-time dependent. **Hyperthermia** - Sx: rapid rise in body temperature, muscle rigidity, tachycardia, rhabdomyolysis, acidosis, DIC, and hyperkalemia. - Physiology: hypermetabolic state caused by inhibition of calcium reuptake in the sarcoplasmic reticulum. - Diagnosis: previous symptoms, increased CO2, rise in CPK levels, myoglobinuria. - Autosomal dominant inheritance. - Treatment: early detection, d/c agents, hyperventilate, bicarb, IV dantrolene (2.5 mg/kg), ice packs/cooling blankets, Lasix / mannitol / fluids. - Requires ICU monitoring.
Enflurane	- Stable, nonflammable liquid. - Halogenated methyl ethyl ether.	- Metabolism is one-tenth that of halothane → does not release quantity of hepatotoxic metabolites - Metabolism releases fluoride ion → renal toxicity - Epileptiform EEG patterns
Isoflurane	- Nonflammable, pungent (having a sharply strong smell) - Halogenated methyl ethyl ether - A chemical isomer of enflurane	-
Desflurane	- The structure is similar to isoflurane - High vapor pressure; requires a special vaporizer - Low solubility → ultrashort duration of action - Moderate potency	- Degraded by desiccated CO2 absorbent into carbon monoxide **Contraindications** - Severe hypovolemia, malignant hyperthermia, intracranial hypertension

Agent	Notes	Side Effects
Sevoflurane	- Non-pungent. - Rapid increase in alveolar anesthetic concentration. - Smooth and rapid inhalation inductions in pediatric and adult patients	**Contraindications** - Severe hypovolemia, malignant hyperthermia, intracranial hypertension **Biotransformation and Toxicity** - Degraded by alkali (barium hydroxide lime, soda lime), producing nephrotoxic end products (compound A)
Nitrous Oxide	- The only inorganic anesthetic gas in clinical use. - Characterized by inert nature with minimal metabolism. - Colorless, odorless, tasteless, and does not burn. - Weak Anesthetic, but good analgesic agent → Needs other agents for surgical anesthesia - Low potency and blood solubility	- Inhibits vitamin B-12 metabolism - Diffusion into closed spaces - Postoperative nausea and vomiting - Pneumothorax, air embolism, acute intestinal obstruction, intracranial air, pulmonary air cysts, intraocular air bubbles, tympanic membrane grafting **Contraindications** - Avoided in pulmonary hypertension. - It (principally N2) diffuse into the cavity more rapidly than air diffuse out, thus it is contraindicated in the cases of Pneumothorax, air embolism, acute intestinal obstruction, intracranial air, pulmonary air cysts, intraocular air bubbles, and tympanic membrane grafting.
Xenon	- Nonexplosive, non-pungent, odorless, and chemically inert - No metabolism and low toxicity, but high cost - It has some analgesic effect. - Reduces anesthesia-emergent nausea and vomiting	- Very close to the 'ideal agent' - Minimal hemodynamic effects. - Seems not to trigger malignant hyperthermia.

Note:

"Inhaled nitrous oxide may produce the second-gas effect. This is a consequence of the large fraction of inspired gas that nitrous oxide constitutes and the fact that nitrous oxide diffuses more rapidly across alveolar basement membranes than does nitrogen (because it is 30 times more water-soluble). The rapid exit of nitrous oxide from the alveoli causes remaining alveolar gases to be concentrated, thus accelerating the uptake of the volatile agent into the blood and speeding the onset of anesthesia. Additionally, the large net movement of gas from alveoli to blood during the rapid absorption of nitrous oxide causes fresh gas to be drawn into gas-exchanging regions of the lung (i.e. alveoli and respiratory bronchioles), further accelerating uptake of companion gases.

The reverse may occur at the end of anesthesia when the administration of nitrous oxide ceases. Nitrous oxide enters the alveoli far more rapidly than nitrogen leaves, causing dilution of the gaseous contents of the alveolus. This results in the dilution of oxygen within the alveoli of patients breathing air and may cause 'diffusion hypoxia'. The dilution of the alveolar contents by the egress of nitrous oxide from the blood may also dilute the concentration of volatile agents, enhancing their elimination, and speeding wakening".

Inhalational Anesthetic Agents Systemic Effects in Summary:

Cardiovascular

- All Inhalational Anesthetic Agents decrease BP, however, Isoflurane and desflurane cause increased heart rate which may mask depression.
- Isoflurane decreases vascular resistance the most. Halothane and nitrous oxide do not affect it.
- Nitric oxide causes no or little increase in MAP. Halothane decreases it through cardiac depression, while others decrease it through reducing SVR.

Respiratory

- All cause respiratory depression, increased respiratory rate, decreased tidal volume, CO_2 retention, decreased alveolar minute ventilation, abolish the hypoxic response (ventilatory response to hypoxia) at less than half MAC concentrations. They are fantastic bronchodilators by direct action on smooth muscle.

CNS

- They cause an increase in CBF (dose-dependent) and ICP.
- All decrease CNS O_2 requirement except N_2O

Renal

- All decrease arterial pressure and cause a dose-related decrease in renal blood flow, GFR and urine output.
- Enflurane is nephrotoxic

Hepatic

- Hepatic blood flow is maintained or decreased, and they cause a transient increase in liver enzymes.
- Halothane induces hepatitis

Skeletal muscles

- They cause dose-dependent potentiation of neuromuscular blocking drugs (except for N_2O)
- They trigger malignant hyperthermia (except for N_2O and Xenon)

Obstetric

- They produce a dose-dependent decrease in uterine contractility and blood flow and may cause uterine atony and postpartum hemorrhage.
- They rapidly cross the placenta and reach the fetus

	Inhalational Anesthetic Agents Systemic Effects					
	Cardiac	*Respiratory*	*Cerebral*	*Neuromuscular*	*Hepatic*	*Renal*
Halothane	- Direct myocardial depression (dose-dependent reduction of arterial BP). - Does not affect systemic vascular resistance - Coronary artery vasodilator, but coronary blood flow↓ due to systemic BP↓ - Low BP inhibits baroreceptors in the aortic arch and carotid bifurcation → vagal stimulation↓ → compensatory rise in HR - Sensitizes the heart to the arrhythmogenic effects of epinephrine	- Rapid, shallow breathing. - ↓ Alveolar ventilation - ↑ Resting PaCO2 - Severely depresses the hypoxic drive - Potent bronchodilator reverses asthma-induced bronchospasm	- Dilating cerebral vessels → cerebral vascular resistance ↓ → CBF ↑ → ICP ↑ - Reduces autoregulation (the maintenance of constant CBF during changes in arterial BP) - ↓ Metabolic oxygen requirement	- Relaxes skeletal muscle - Triggers malignant hyperthermia	- ↓ Hepatic blood flow	- ↓ Renal blood flow, GFR, and urine output. Part of this can be explained by a fall in arterial BP and CO. Pre-operative hydration limits these changes.
Enflurane	- Inhibits sympathetic baroreflex response - Sensitizes myocardium to effects of exogenous catecholamines → arrhythmias - Potent inotropic and chronotropic depressant + ↓ systemic vascular resistance → lowers BP and conduction dramatically.	- Depresses central and peripheral responses - Increases dead space - Widens A-a gradient - Produces hypercarbia in spontaneously breathing patient - Bronchodilator	-	-	-	-
Isoflurane	- Minimal cardiac depression. - ↓ Systemic vascular resistance (Produces most significant reduction in systemic vascular resistance) → ↓ BP - Sensitizes myocardium to catecholamines, but less than halothane or enflurane	- Respiratory depression, ↓ minute ventilation - Blunts the normal ventilatory response to hypoxia. - A good bronchodilator	- ↑ CBF, ICP. Reversed by hyperventilation - ↓ Cerebral metabolic oxygen requirement	- Relaxes skeletal muscle - Triggers malignant hyperthermia	- ↓ Total hepatic blood flow	- ↓ Renal blood flow, GFR, and U/O

	Inhalational Anesthetic Agents Systemic Effects					
	Cardiac	*Respiratory*	*Cerebral*	*Neuromuscular*	*Hepatic*	*Renal*
Desflurane	- ↓ Systemic vascular resistance → ↓ BP - CO does not change or is slightly depressed - Rapid increases in concentration lead to a transient elevation in HR, BP, catecholamine levels	- ↓ Tidal volume, ↑ Respiratory rate - ↓ Alveolar ventilation ↑ Resting PaCO2 - ↓ The respiratory response to ↑ PaCO2 - Pungency and airway irritation	- Vasodilate cerebral vasculature → ↑ CBF, ICP. Lowered by hyperventilation - ↓ Cerebral metabolic rate of oxygen	- A trigger of malignant hyperthermia	-	- ↓ U/O
Sevoflurane	- Mildly depresses myocardial contractility - ↓ Systemic vascular resistance, arterial BP - CO is not maintained well due to little rise in HR	- Rapid shallow breathing - Depress respiration - Reverses bronchospasm	- Slight ↑ in CBF, ICP - ↓ Cerebral metabolic ~~oxygen requirement~~	- Adequate muscle relaxation for intubation of children	- ↓ Portal vein blood flow	- Slightly ↓ renal blood flow - Associated with impaired renal tubule function
Nitrous Oxide	- Depress myocardial contractility. - Arterial BP, CO, and HR remain unchanged or slightly ↑ due to stimulation of catecholamines. - Constriction of pulmonary vascular smooth muscle → increase pulmonary vascular resistance → PHTN - Peripheral vascular resistance is not altered	- ↓ Tidal volume, ↑ Respiratory rate - Minimal change in minute ventilation and resting arterial CO_2 - ↓ Hypoxic drive (ventilatory response to arterial hypoxia).	- ↑ CBF, cerebral blood volume, ICP - ↑ Cerebral oxygen consumption ($CMRO_2$)	- Does not provide significant muscle relaxation. - Not a triggering agent of malignant hyperthermia	- ↓ Hepatic blood flow	- ↑ Increase renal vascular resistance - ↓ Renal blood flow, GFR, U/O

Minimal alveolar concentrations (MAC): it is the minimal alveolar concentration of inhalational agents that prevent movement in 50% of the patients in response to surgical stimulation (skin incision). MAC is important to compare the potencies of various inhalational anesthetic agents.

Halothane	0.75%
Isoflurane	1.2%
Enflurane	1.68%
Sevoflurane	2%
Desflurane	6%
Xenon	71%
Nitrous Oxide	104%

TABLE 8–6 Clinical pharmacology of inhalational anesthetics.

	Nitrous Oxide	Halothane	Isoflurane	Desflurane	Sevoflurane
Cardiovascular					
Blood pressure	N/C[1]	↓↓	↓↓	↓↓	↓
Heart rate	N/C	↓	↑	N/C or ↑	N/C
Systemic vascular resistance	N/C	N/C	↓↓	↓↓	↓
Cardiac output[2]	N/C	↓	N/C	N/C or ↓	↓
Respiratory					
Tidal volume	↓	↓↓	↓↓	↓	↓
Respiratory rate	↑	↑↑	↑	↑	↑
$Paco_2$					
Resting	N/C	↑	↑	↑↑	↑
Challenge	↑	↑	↑	↑↑	↑
Cerebral					
Blood flow	↑	↑↑	↑	↑	↑
Intracranial pressure	↑	↑↑	↑	↑	↑
Cerebral metabolic rate	↑	↓	↓↓	↓↓	↓↓
Seizures	↓	↓	↓	↓	↓
Neuromuscular					
Nondepolarizing blockade[3]	↑	↑↑	↑↑↑	↑↑↑	↑↑
Renal					
Renal blood flow	↓↓	↓↓	↓↓	↓	↓
Glomerular filtration rate	↓↓	↓↓	↓↓	↓	↓
Urinary output	↓↓	↓↓	↓↓	↓	↓
Hepatic					
Blood flow	↓	↓↓	↓	↓	↓
Metabolism[4]	0.004%	15% to 20%	0.2%	<0.1%	5%

Figure 29.5 Ranking of clinical properties of volatile agents. D = desflurane, H = halothane, I = isoflurane, S = sevoflurane

	Worst	Worse	Better	Best
Induction	D	I	H	S
Cardiovascular stability	H	I	D	S
Respiratory irritation	D	I		H & S
Ease of titration	H	I	S	D
Emergence	H	I	S	D
Metabolism/toxicity	H	S	I	D

Figure 29.6 Grading of clinical properties of volatile agents. ○○○○ = least effect, ●●●● = maximum effect

	Halothane	Isoflurane	Desflurane	Sevoflurane
Pungency	●○○○	●●●○	●●○○	○○○○
Respiratory irritation	○○○○	●●○○	●●●○	○○○○
Respiratory depression	●●○○	●●●○	●●●●	●●○○
Cardiovascular depression	●●●○	●●○○	●○○○	●○○○
Coronary vasodilatation	●○○○	●●○○	●○○○	●●○○
Muscle relaxation	●●○○	●●●○	●●●○	●●●○
Intracranial pressure elevation	●●●●	●●○○	●●●○	●●○○