General Anesthetics

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General Anesthetics

- **General anesthesia is typically a state of analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes, and skeletal muscle relaxation.**
- **This is achieved by a combination of intravenous and inhaled drugs.**

General Anesthetics

Types of General Anesthesia:

A. Intravenous agents used alone, or in combination with other anesthetic agents, to achieve an anesthetic state or sedation. These drugs include:

1. Barbiturates: Thiopental, methohexital.
2. Benzodiazepines: Midazolam, diazepam.
3. Propofol.

General Anesthetics

4. **Ketamine.**
5. **Opioid analgesics:** Morphine, fentanyl, sufentanil, alfentanil, remifentanil.
6. **Miscellaneous sedative-hypnotics:** Etomidate, dexmedetomidine.

B. Inhaled anesthetics which include:

1. **Volatile liquids:** Halothane, isoflurane, desflurane, enflurane, methoxyflurane, and sevoflurane.
2. **Gases:** Nitrous oxide.

General Anesthetics

- **No anesthetic agent can produce the five desired effects without adverse effects.**
- **Balanced anesthesia employs multiple drugs (inhaled anesthetics, sedative-hypnotics, opioids, neuromuscular blocking drugs) to minimize unwanted effects.**

General Anesthetics

Although general anesthesia can be produced by only intravenous or only inhaled anesthetic agents, modern anesthesia typically involves a combination of:

1. **IV agents for induction of anesthesia.**
2. **Inhaled agents for maintenance of anesthesia.**
3. **Muscle relaxants.**
4. **Analgesics.**
5. **Cardiovascular drugs to control autonomic responses.**

Intravenous Anesthetics

- **Are commonly used for induction of general anesthesia because of more rapid onset than inhaled agents.**
- **They are also used to provide sedation for patients in ICU settings.**
- **Rapid onset is due to their lipophilicity and preferentially partition into highly perfused lipophilic tissues (brain, spinal cord).**

Intravenous Anesthetics

- **Recovery is rapid and permits their use for short procedures.**
- **Termination of the effect of a single bolus is determined by redistribution of the drug into less perfused and inactive tissues such as skeletal muscle and fat, and is not related to their metabolism.**

Propofol

- **It interacts with $GABA_A$ receptor-chloride channel. It also potentiate glycine-gated currents.**
- **Propofol acts as hypnotic but does not have analgesic properties.**
- **It is the most popular IV anesthetic, and has replaced barbiturates.**
- **Its rate of onset of action is similar to IV barbiturates but recovery is more rapid and patient ambulation is earlier.**
- **The patient subjectively feel better in the**

Propofol

- **It is the agent of choice for ambulatory surgery.**
- **It can be used for both induction and maintenance of anesthesia.**
- **It reduces the required concentration of inhaled anesthetics.**
- **When used during maintenance of anesthesia, propofol infusion can be combined with IV opioids and neuromuscular blockers to completely avoid the use of inhaled anesthetics.**

Propofol

- **It is effective in producing prolonged sedation in patients in critical care setting, but cumulative effect can lead to delayed arousal.**
- **The recovery from propofol is more complete, with less "hangover" than that observed with thiopental.**
- **Prolonged administration of conventional emulsion formulation can raise serum lipids.**

Propofol

- **When used in critically ill young children for sedation, it has caused severe acidosis in the presence of respiratory infection and to possible neurologic sequelae upon withdrawal.**
- **It produces depression of central ventilatory drive and apnea.**

Propofol

- **Excitatory effects such as twitching or spontaneous movement are occasionally observed during induction of anesthesia.**
- **These effects can be confused with seizures.**
- **It produces a marked decrease in blood pressure during induction of anesthesia through arterial and veno dilation.**

Propofol

- **It has the greatest direct negative inotropic effect than other IV anesthetics.**
- **Profound bradycardia and asystole have been reported.**
- **Pain at the site of injection is the most common adverse effect after IV bolus administration (reduced by admixture with lidocaine).**

Propofol

- **Muscle movements, hypotonus and rarely tremors have been reported after prolonged use.**
- **Propofol decreases cerebral blood flow, which decreases intracranial pressure (ICP) and intraocular pressure, but may lead to decrease in cerebral perfusion pressure.**

Fospropofol

- **Fospropofol is a water-soluble prodrug of propofol.**
- **The effects of fospropofol are similar to that of propofol, but onset and recovery are prolonged compared with propofol because the prodrug must first be converted into an active form.**
- **No injection site pain**
- **Can produce paresthesia in the perianal region.**

Etomidate

- It has hypnotic but no analgesic effects.
- It acts primarily through potentiation of $GABA_A$-mediated chloride current.
- It is used for induction of anesthesia in patients with limited cardiovascular reserve, because it causes minimal cardiovascular and respiratory depression and minimal hypotension.
- It produces rapid loss of consciousness.
- Recovery is less rapid than that of propofol.

Etomidate

- **Distribution of etomidate is rapid.**
- **Redistribution of the drug from the brain to highly perfused tissues is responsible for the short duration of action.**
- **It is a potent cerebral vasoconstrictor, leading to decreased cerebral blood flow and ICP, like thiopental.**

Etomidate

Adverse effects:

1. **Pain upon injection.**
2. **Myoclonic activity.**
3. **Postoperative nausea and vomiting.**
4. **It may activate seizure foci.**

Etomidate

5. **Inhibition of steroidogenesis (inhibition of 11β-hydroxylase) with decreased plasma levels of cortisol and hypoadrenalism → hypotension, electrolyte imbalance and oliguria.**

- **Not used as continuous infusion.**

Ketamine

- It produces a "dissociative anesthetic state" characterized by catatonia (muscular rigidity and mental stupor, sometimes alternating with great excitement and confusion, eyes remain open with a slow nystagmic gaze), amnesia and analgesia, with or without loss of consciousness.
- It is chemically related to phencyclidine, a psychoactive drug with high abuse potential.

Ketamine

Mechanism of Action:

- **It blocks glutamic acid NMDA receptor subtype.**

Pharmacokinetics:

- **It is highly lipid soluble and rapidly distributed into well-perfused organs, including brain, then it redistributes to less well perfused tissues.**

Ketamine

Pharmacodynamics:

- **It is the only IV anesthetic that have both analgesic properties and the ability to produce dose-related cardiovascular stimulation.**
- **It can be administered by multiple routes (intravenous, intramuscular, oral, rectal, epidural)**

Ketamine

- **It stimulates the central sympathetic nervous system and, to a lesser extent, inhibits the reuptake of norepinephrine at sympathetic nerve terminals.**
- **It increases heart rate, cardiac output and arterial blood pressure (transient).**
- **It increases cerebral blood flow, oxygen consumption, and intracranial pressure (ICP).**
- **It is dangerous in patients with elevated ICP.**

Ketamine

- **It decreases respiratory rate but upper airway muscle tone is well maintained and airway reflexes are usually preserved.**
- **It relaxes bronchial smooth muscle.**
- **Lacrimation and salivation are increased. This effect can be limited by premedication with an anticholinergic drug.**
- **May cause laryngospasm especially in children.**

Ketamine

- **Its use has been associated with postoperative disorientation, sensory and perceptual illusions, and vivid colorful dreams, out-of body experiences and increased and distorted visual, tactile, and auditory sensitivity. (This is called emergence phenomena).**
- **These reactions can be associated with fear and confusion**

Ketamine

- **A euphoric state may be induced explaining the potential for its abuse.**
- **These effects can be reduced by premedication with a benzodiazepine (diazepam, midazolam).**
- **It is specially useful in patients undergoing painful procedures such as burn dressing.**
- **It reduces opioid tolerance and opioid-induced hyperalgesia.**

Dexmedetomidine

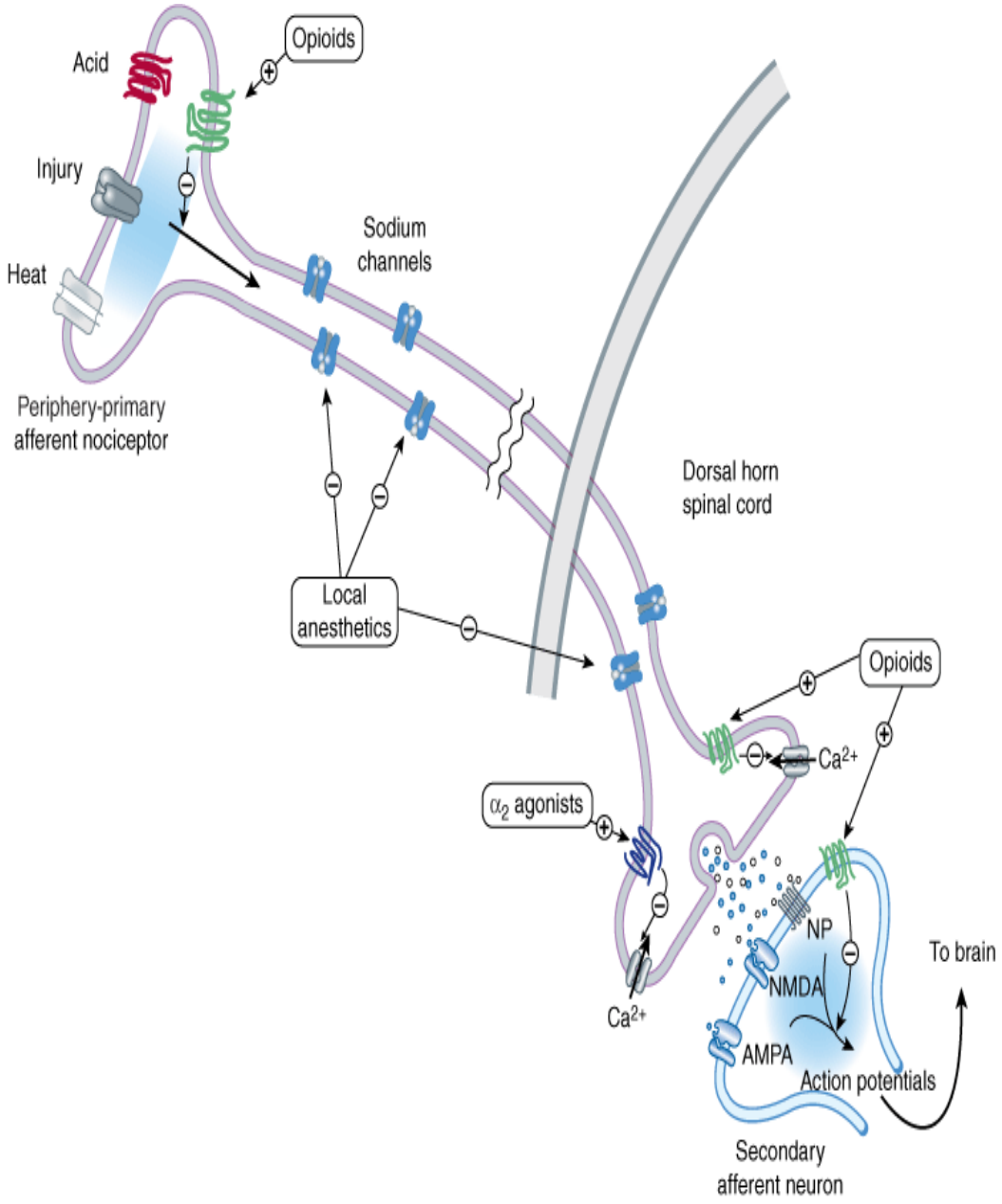
- **Dexmedetomidine is a highly selective α_2-adrenergic agonist.**
- **Recognition of the usefulness of α_2 agonists is based on observations of decreased anesthetic requirements in patients receiving chronic clonidine therapy.**

Dexmedetomidine

- **Hypnotic effects of the intravenous anesthetic dexmedetomidine are produced *via* actions in the locus ceruleus.**
- **It stimulates α_2-adrenergic receptors at this site and reduces central sympathetic output, resulting in increased firing of inhibitory neurons.**

Dexmedetomidine

- **In the dorsal horn of the spinal cord it modulates release of substance P → analgesic effects.**
- **Its sedative effect resembles a physiologic sleep state through activation of endogenous sleep pathways.**



Schematic diagram of a primary afferent neuron mediating pain, its synapse with a secondary afferent in the spinal cord, and the targets for local pain control. The primary afferent neuron cell body is not shown. At least three nociceptors are recognized: acid, injury, and heat receptors. The nerve ending also bears opioid receptors, which can inhibit action potential generation. The axon bears sodium channels and potassium channels (not shown), which are essential for action potential propagation. Synaptic transmission involves release of substance P, a neuropeptide (NP) and glutamate and activation of their receptors on the secondary neuron. Alpha2 adrenoceptors and opioid receptors modulate the transmission process.

Dexmedetomidine

- **Tolerance and dependence may develop.**
- **Its infusion results in moderate decreases in heart rate, systemic vascular resistance, and blood pressure.**
- **Heart block, severe bradycardia, and asystole have been observed and may result from unopposed vagal stimulation.**

Dexmedetomidine

- **It is used for the short-term sedation of intubated and ventilated patients in an ICU setting.**
- **It is used as an adjunct to general anesthesia or to provide sedation, during awake fiberoptic tracheal intubation or regional anesthesia.**
- **It decreases the dose requirements for inhaled and injected anesthetics.**

Inhaled Anesthetics

1. **Volatile anesthetics: halothane, enflurane, isoflurane, desflurane, sevoflurane.**
2. **Gaseous anesthetics: nitrous oxide, xenon.**

Inhaled Anesthetics

Pharmacokinetics:

- **An adequate depth of anesthesia depends on achieving therapeutic concentrations in the central nervous system.**
- **The rate at which an effective brain concentration is achieved (time to induction of anesthesia) depends on multiple pharmacokinetic factors that influence brain uptake and tissue distribution of the anesthetic agent:**

Inhaled Anesthetics

1. Uptake and distribution of inhaled anesthetics:

- **The driving force for uptake of an inhaled anesthetic into the body is the ratio between inspired and alveolar concentration.**
- **Achievement of a brain concentration of an inhaled anesthetic to provide adequate anesthesia requires transfer of the anesthetic from the alveolar air to the blood, and from the blood to the brain.**

Inhaled Anesthetics

2. Elimination of inhaled anesthetics:

- **The time of recovery from inhalation anesthesia depends on the rate of elimination of the anesthetic from the brain.**
- **Many of the processes of anesthetic transfer during recovery are simply the reverse of those that occur during induction of anesthesia.**

Inhaled Anesthetics

- **Inhaled anesthetics that are relatively insoluble in blood and brain (possess low blood:gas partition coefficients) are eliminated faster than the more soluble anesthetics.**
- **The washout of nitrous oxide, desflurane, and sevoflurane occurs at a rapid rate, leading to a more rapid recovery from their anesthetic effects compared with halothane and isoflurane.**

Inhaled Anesthetics

- **Halothane is much more soluble in brain tissue and in blood than nitrous oxide and desflurane; its elimination therefore takes place more slowly, and recovery from halothane- and isoflurane-based anesthesia is predictably less rapid.**

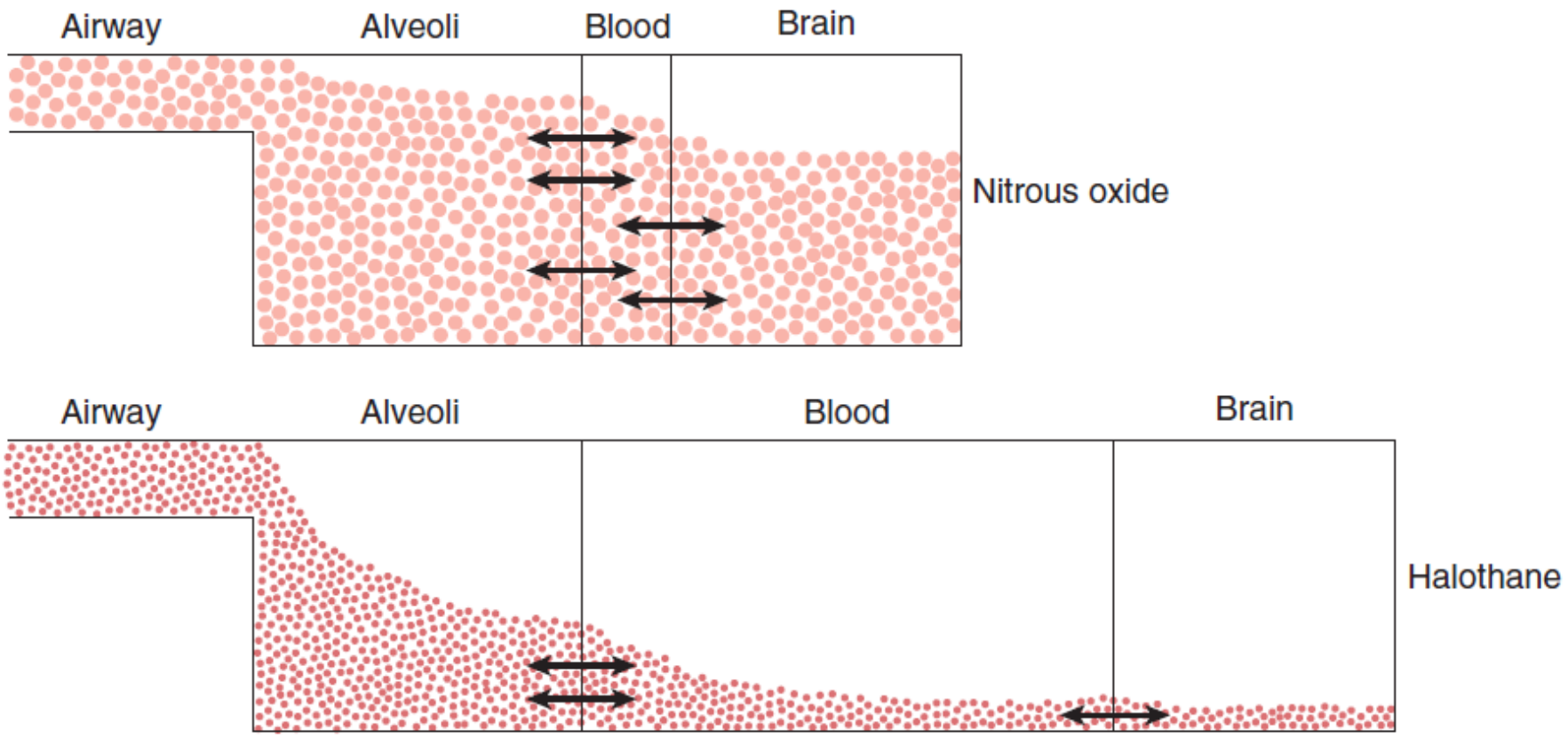


FIGURE 25–5 Why induction of anesthesia is slower with more soluble anesthetic gases. In this schematic diagram, solubility in blood is represented by the relative size of the blood compartment (the more soluble, the larger the compartment). Relative partial pressures of the agents in the compartments are indicated by the degree of filling of each compartment. For a given concentration or partial pressure of the two anesthetic gases in the inspired air, it will take much longer for the blood partial pressure of the more soluble gas (halothane) to rise to the same partial pressure as in the alveoli. Since the concentration of the anesthetic agent in the brain can rise no faster than the concentration in the blood, the onset of anesthesia will be slower with halothane than with nitrous oxide.

Inhaled Anesthetics

- **Clearance of the inhaled anesthetics by the lungs is the major route of elimination from the body.**
- **Hepatic metabolism may also contribute to the elimination of halothane (~ 40% during an average anesthetic procedure).**

Inhaled Anesthetics

- **Oxidative metabolism (CYP2E1) of halothane results in formation of trifluoroacetic acid and release of chloride and bromide ions.**
- **Under conditions of low oxygen tension, halothane is metabolized to the chlorotrifluoroethyl free radical which is capable of reacting with hepatic cell membrane and producing halothane hepatitis.**

Inhaled Anesthetics

- **< 10% of enflurane is metabolized.**
- **Isoflurane and desflurane are the least metabolized of fluorinated anesthetics.**
- **The metabolism of methoxyflurane (70%) results in elevation of renal fluoride levels → nephrotoxicity.**

Inhaled Anesthetics

- **Nitrous oxide is not metabolized by human tissues, but can be metabolized by bacteria in the GIT.**
- **Sevoflurane is degraded by contact with the carbon dioxide absorbent [soda lime = Ca(OH)2 (about 75%), H_2O (about 20%), NaOH (about 3%), KOH (about 1%)] in anesthesia machines yielding a vinyl ether which can cause renal damage if high concentrations are absorbed.**

Inhaled Anesthetics

Pharmacodynamics:

- **Interaction of the anesthetics with specific nerve membrane components results in modification of ion currents.**
- **A primary molecular target of halogenated inhalational agents is the $GABA_A$ receptor-chloride channel, a major mediators of inhibitory synaptic transmission. Either it is directly activated or facilitated.**

Inhaled Anesthetics

- **Glycine receptor is another target for inhaled anesthetics, which enhance the capacity of glycine to activate glycine-gated chloride channels → inhibitory neurotransmission in spinal cord and brain stem.**
- **The only general anesthetics that do not have significant effects on $GABA_A$ or glycine receptors are nitrous oxide and ketamine, which act on calcium selective NMDA glutamate receptor.**

Inhaled Anesthetics

- **Neuronal nicotinic acetylcholine receptors inhibition by inhalational agents do not mediate anesthetic effect but mediate analgesia and amnesia.**
- **Certain inhalational anesthetics may cause membrane hyperpolarization by activation of potassium channels.**

Inhaled Anesthetics

- **Inhalational agents can produce presynaptic inhibition of neurotransmitter release in the hippocampus contributing to the amnesic effect of these agents.**

Inhaled Anesthetics

Organ System Effects of Inhaled Anesthetics:

A. Effects on the Cardiovascular System:

- **Halothane and enflurane reduce arterial pressure by reduction of cardiac output.**
- **Isoflurane, desflurane, and sevoflurane reduce arterial blood pressure by decreasing systemic vascular resistance.**

Inhaled Anesthetics

- **Halothane may cause bradycardia probably because of direct vagal stimulation.**
- **Desflurane and isoflurane increase heart rate.**
- **All depress myocardial function, including nitrous oxide.**
- **Halothane, and to a lesser extent isoflurane sensitize the myocardium to circulating catecholamines → ventricular arrhythmias.**

Inhaled Anesthetics

B. Effects on the Respiratory System:

- **All except nitrous oxide decrease tidal volume and increase respiratory rate**
- **All volatile anesthetics are respiratory depressants and reduce the response to increased levels of carbon dioxide.**
- **All volatile anesthetics increase the resting levels of $PaCO_2$.**

Inhaled Anesthetics

- **The respiratory depressant effect is overcome by assisted or controlled ventilation.**
- **Inhaled anesthetics depress mucociliary function of airways → pooling of mucus → atelectasis and postoperative respiratory infection.**
- **All volatile anesthetics have some degree of bronchodilating action (of value in patients with asthma!?).**
- **Airway irritation with desflurane.**

Inhaled Anesthetics

C. Effects on the Brain:

- **Decrease metabolic rate of the brain.**
- **Increase cerebral blood flow by decreasing cerebrovascular resistance (not desirable in patients with increased intracranial pressure). Nitrous oxide is the least likely to do so.**
- **If the patient is hyperventilated before the volatile agent is administered, the increase in ICP can be minimized (by inducing hypocapnoeic vasoconstriction).**

Inhaled Anesthetics

- **Nitrous oxide has analgesic and amnesic properties.**

D. Effects on the Kidney:

- **Decrease GFR and urine flow.**
- **Impair autoregulation of RBF.**

E. Effects on the Liver:

- **Reduce portal blood flow.**

Inhaled Anesthetics

F. Effects on Uterine Smooth Muscle:

- **Nitrous oxide has little effect.**
- **Halogenated anesthetics are potent uterine muscle relaxants.**

Inhaled Anesthetics

Toxicity:

1. **Hepatotoxicity:**

- **Potentially life-threatening in subjects previously exposed to halothane.**
- **Incidence is 1:20,000 – 35,000.**
- **Obese patients are most susceptible.**
- **Mechanism is unclear, but may be due to:**

  a. Direct hepatocellular damage by reactive metabolites (free radicals).

Inhaled Anesthetics

b. Initiation of immune-mediated responses by reactive metabolites. Serum of patients with halothane hepatitis contain a variety of autoantibodies against hepatic proteins.

Trifluoroacetylated proteins in the liver could be formed in hepatocytes during halothane biotransformation.

- **They are also found in the sera of patients who did NOT develop hepatitis after halothane anesthesia.**

Inhaled Anesthetics

2. **Nephrotoxicity:**

- **Prolonged exposure to methoxyflurane (and ? enflurane) leads to formation of fluoride ions intrarenally by the renal enzyme β-lyase → changes in renal concentrating ability (and may be proximal tubular necrosis).**

Inhaled Anesthetics

3. **Malignant hyperthermia:**

- **Is an autosomal dominant genetic disorder of skeletal muscle that occurs in individuals undergoing general anesthesia with volatile agents + succinylcholine.**
- **It consists of rapid onset of tachycardia and hypertension, severe muscle rigidity, hyperthermia, hyperkalemia, and acidosis.**
- **It is rare but is an important cause of anesthetic morbidity and mortality.**

Inhaled Anesthetics

- **Associated with increased calcium concentration in skeletal muscle cells (from the sarcoplasmic reticulum). Reduced by dantrolene.**

4. Prolonged exposure to nitrous oxide decrease methionine synthase activity and can potentially cause megaloblastic anemia in inadequately ventilated operating room personnel.