PCTH 400 Systematic Pharmacology

Inhaled Anesthetics and Amnestic Agents
Dr. Peter Choi (peter.choi@ubc.ca)

Objectives
At the end of this session, you will be able to:
1. Define the components of general anesthesia;
2. Explain the pharmacology of inhaled anesthetics and propofol;
3. Describe the clinical effects of inhaled anesthetics and propofol.

Components of General Anesthesia

**General anesthesia** — “a drug-induced, reversible condition that includes specific behavioral and physiological traits — unconsciousness [hypnosis], amnesia, analgesia, and akinesia” — accompanied with autonomic depression

**Amnesia** — loss of memory

**Analgesia** — absence of sensation to pain; relief of pain without loss of consciousness

**Hypnosis** — an artificially-induced state of sleep; in anesthesiology, a drug-induced state of inability to respond to sensory stimuli

**Akinesia** — absence of movements

**Autonomic depression** — suppression of the sympathetic (“fight or flight”) response

In 1937, Arthur Guedel classified the effects observed in individuals as they went from consciousness to general anesthesia into four stages:

I “Stage of analgesia or disorientation”
   Onset of analgesia and amnesia

II “Stage of excitement”
   Onset of hypnosis

III “Stage of surgical anesthesia”
   Absence of motor response to stimulus (akinesia)
   Blunting of autonomic response to stimulus

IV “Stage of apnea and death” (i.e., anesthetic overdose)
   Respiratory arrest and circulatory collapse

With modern agents, these changes progress rapidly and are not seen usually during induction of general anesthesia.

NOTES

1. When used alone, the word anesthesia means “loss of feeling or sensation” and is sometimes used synonymously with hypnosis.


3. The components of the general anesthesia are often called the “4 A’s of general anesthesia”: amnesia, analgesia, anesthesia, and akinesia.

4. Hypnosis comes from the Greek hypnō (sleep) + οsis (state of). The term narcosis is also used in anesthesiology in a synonymous fashion. Narcosis is “a drug-induced depression of the central nervous system leading to stupor” and comes from the Greek narcō (stupor) + οsis (state of).

Pharmacology of Inhaled Anesthetics

Mechanisms of Action\(^6\)

Lipid-solubility hypotheses
- perturbation of the lipid bilayer of neuronal cell membranes
- disturbance of the lipid-protein interface

Protein hypotheses
- alteration of membrane-protein interactions

Suppression of excitation of neuronal tissues
- enhance post-synaptic ion channels’ inhibitory activity (GABA\(_A\), glycine, potassium)
- inhibit post-synaptic ion channels’ excitatory activity (nicotinic acetylcholine, serotonin, glutamate)

Measuring Uptake and Distribution\(^7\)

Concentration – amount of molecules of the drug in a given volume of liquid; measured as \(\text{mg/mL}\) or \(\text{vol}\%) and denoted by \([\_]\)

Partial pressure – amount of molecules of the drug in air at atmospheric pressure; measured as \(\text{mm Hg}\) or \(\text{kPa}\) and denoted by \(P\) or \(F\)

Dalton’s Law – The sum of the partial pressures of each gas equals the total pressure of the entire mixture

Henry’s Law – The amount of gas in a volume of liquid is directly proportional to the partial pressure of the gas in equilibrium with the liquid: \([\text{Gas}]_{\text{liquid}} = k \cdot P_{\text{atm,Gas}}\)

For inhaled anesthetics, general anesthesia is induced when the partial pressure of the anesthetic reaches a certain level in the brain. During induction, there are a number of concentration gradients:

Delivered concentration \(\equiv\) inspired concentration \((F_{i,\text{anesth}})\) \(\equiv\) alveolar concentration \((F_{A,\text{anesth}})\) \(\Rightarrow\) arterial concentration \((P_{a,\text{anesth}})\) \(\rightarrow\) brain concentration \((P_{B,\text{anesth}})\)^8

At equilibrium, \(F_{i,\text{anesth}} = F_{A,\text{anesth}} = P_{a,\text{anesth}} = P_{B,\text{anesth}}\)

---

NOTES


8. Strictly speaking, we are discussing partial pressures; however, the term concentration is often used interchangeably in the pharmacology of inhaled anesthetics.
Rate of uptake of an anesthetic – described by the alveolar-inspired concentration ratio ($F_A/F_I$) of an anesthetic over time (Figure 1)

Rate of uptake is affected by the ABCs:
- **Alveolar ventilation** (higher ventilation results in faster uptake)
- **Blood solubility** of the anesthetic
- **Concentration gradient** (partial pressure difference) of the anesthetic between the alveoli and pulmonary venous blood (larger difference results in faster uptake)

**Blood-gas partition coefficient** – a measure of solubility of an inhaled anesthetic in blood, denoted by $\lambda$ (Table 1)

High blood-gas partition coefficient = high solubility in blood, results in longer time to reach equilibrium between alveolar concentration and arterial concentration ($F_A$ anesth = $P_a$ anesth), and slower rate of induction and slower onset of anesthesia.

### Measuring Potency

**Potency** – dose of drug required to produce an effect of specific intensity; measured by the **minimum alveolar concentration** and the **oil-gas partition coefficient**

**Minimum alveolar concentration (MAC)** – minimum alveolar concentration of an inhaled anesthetic ($F_A$ anesth), measured at standard temperature and pressure (1 atm), required to prevent movement in 50% of patients undergoing a midline abdominal incision; measured by vol%

Potency is inversely correlated to MAC, which is the $EC_{50}$ for inhalational anesthetics. An anesthetic’s MAC is influenced by:

- **age** – MAC decreases as patient gets older
- **pregnancy** – MAC decreases during pregnancy
- **temperature** – MAC decreases as body temperature falls
- **other drugs** – MAC decreases if patient is receiving opioids, other anesthetics, or psychotropic agents

### Notes

9. The blood-gas partition coefficient can be derived from Henry's Law

$$[\text{Gas}]_{\text{liquid}} = k \cdot P_{\text{atm}} \cdot \text{Gas},$$

which can be rewritten as

$$[\text{anesth}]_{\text{blood}} = \lambda \cdot P_a \cdot \text{anesth}$$

Thus,

$$\lambda = \frac{[\text{anesth}]_{\text{blood}}}{P_a \cdot \text{anesth}}$$

### Table 1 Solubility of various anesthetics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood-gas coefficient (37°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>desflurane</td>
<td>0.42</td>
</tr>
<tr>
<td>sevoflurane</td>
<td>0.69</td>
</tr>
<tr>
<td>isoflurane</td>
<td>1.40</td>
</tr>
<tr>
<td>enfurane</td>
<td>1.80</td>
</tr>
<tr>
<td>halothane</td>
<td>2.30</td>
</tr>
<tr>
<td>nitrous oxide</td>
<td>0.47</td>
</tr>
</tbody>
</table>
MAC is often used to describe the clinical effects across inhaled anesthetics:

0.3 MAC – onset of analgesia
0.5 MAC – onset of amnesia
1.0 MAC – akinesia in 50% of patients \((EC_{50})\)
1.2 MAC – akinesia in 95% of patients \((EC_{95})\)
2-3 MAC – death in 50% of patients \((LD_{50})\)

Oil-gas partition coefficient – a measure of the lipid solubility of an anesthetic; defined as the ratio of concentration of anesthetic dissolved in olive oil and the anesthetic partial pressure at 1 atm: \([\text{anesth}]_{\text{olive oil}} / P_{\text{atm anesth}}\)

Potency is directly correlated to lipid solubility and the oil-gas partition coefficient. There is an inverse relationship between MAC and lipid solubility (Meyer-Overton Rule). See Table 2 and Figure 2.

Metabolism and Elimination

In general, inhaled anesthetics undergo little metabolism (Table 3) so elimination is almost entirely by ventilation. The rate of elimination is influenced in a similar fashion as the rate of uptake but is also influenced by the duration of the anesthesia, due to accumulation of the anesthetic in fat and other tissues.

Hepatotoxic metabolites – metabolites of halothane are involved in the development of post-exposure hepatotoxicity (“halothane hepatitis” – incidence 1 in 20000 to 1 in 35000). The incidence of hepatotoxicity after exposure to other inhaled anesthetics (enflurane, isoflurane, and desflurane) are extremely rare.

Nephrotoxic metabolites – metabolism of sevoflurane and enflurane result in nephrotoxic fluoride ions; however, clinically significant renal injury has only been reported with prolonged use of enflurane. Sevoflurane degrades in the carbon dioxide absorbents used in the anesthetic circuits and results in a nephrotoxic vinyl ether called “compound A”, which is nephrotoxic in rats but not in humans.

### Table 2  Potency of various anesthetics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>MAC (vol%)</th>
<th>Oil-gas coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>desflurane</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>sevoflurane</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>isoflurane</td>
<td>1.2</td>
<td>98</td>
</tr>
<tr>
<td>enflurane</td>
<td>1.6</td>
<td>98</td>
</tr>
<tr>
<td>halothane</td>
<td>0.75</td>
<td>224</td>
</tr>
<tr>
<td>nitrous oxide</td>
<td>105</td>
<td>1.4</td>
</tr>
</tbody>
</table>

### Table 3  Amount of metabolism of various anesthetics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Amount metabolized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>desflurane</td>
<td>0.02</td>
</tr>
<tr>
<td>sevoflurane</td>
<td>3</td>
</tr>
<tr>
<td>isoflurane</td>
<td>0.2</td>
</tr>
<tr>
<td>enflurane</td>
<td>2.4</td>
</tr>
<tr>
<td>halothane</td>
<td>20</td>
</tr>
<tr>
<td>nitrous oxide</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Pharmacology of Propofol

Propofol (2,6-diisopropylphenol)
Mechanism of action – GABA_A-mediated inhibition
Pharmacokinetics follow three-compartment model (Figure 3)
Route of administration – intravenous
Rapid onset – 30-45 s
Rapid awakening – t½_distr 2-4 min; duration of action 3-8 min
Volume of distribution – V_dss 2-10 L/kg
Protein binding – 97%
Clearance – 20-30 mL/kg/min
Metabolism – hepatic glucuronidation; no active metabolites
Excretion – urinary (0.004% unmetabolized)

The short context-sensitive half-time of propofol makes it ideal for continuous infusion (Figure 4).

Clinical Effects of Anesthetic Agents

Cardiovascular System

- Nitrous oxide has little overall effect on blood pressure
- Propofol and volatile anesthetics ↓ mean arterial pressure in a dose-dependent fashion by
  - ↓ myocardial contractility (propofol and halothane)
  - ↓ preload and systemic vascular resistance (other volatile anesthetics)
- Volatile anesthetics ↓ coronary blood flow
- Halothane sensitizes the myocardium to catecholamines and increases risk of ventricular dysrhythmias
- Desflurane causes transient sympathetic stimulation (↑ heart rate)

Respiratory System

- Inhaled anesthetics
  - cause bronchodilatation (useful in asthma)
  - ↓ minute ventilation (↓ tidal volume, ↑ respiratory rate)
  - ↑ apneic threshold of CO₂
  - ↓ ventilatory response to hypoxia
  - ↓ mucociliary activity in the tracheobronchial tree
- Effects are much less with nitrous oxide
- Propofol ↓ minute ventilation; ↑ apneic threshold of CO₂

NOTES

Figure 3  Redistribution of intravenous anesthetics after a single bolus

Context-sensitive half-time – “elimination half-time after a continuous infusion as a function of the duration of the infusion” (Katzung et al. Basic & Clinical Pharmacology, 12th ed.)

Figure 4  Context-sensitive half-time of various intravenous anesthetics
Central Nervous System
- All anesthetics ↓ cerebral metabolic rate
- **Inhaled anesthetics**
  - cause cerebral vasodilation
  - ↑ cerebral blood flow to varying degrees (least with isoflurane)
  - ↑ cerebral blood volume.
  - ↑ risk for elevated intracranial pressure
- **Propofol** ↓ cerebral blood flow
- Clinically significant ↓ EEG activity with some agents
  - 2.0 MAC isoflurane
  - propofol 100-400 mg bolus in presence of 0.5 MAC of other volatile anesthetics
- Small studies suggest nitrous oxide may be neurotoxic to the developing brain

Gastrointestinal System
- **Inhaled anesthetics**
  - ↓ hepatic artery blood flow and/or portal vein blood flow
  - ↓ total hepatic blood flow
  - nitrous oxide has the least effect (if used alone);
  - sevoflurane and isoflurane have the least effect amongst volatile anesthetics
- **Propofol** ↓ total hepatic blood flow, usually transiently, to a variable extent
- Nitrous oxide will expand gas-filled cavities and result in bowel distention over time.

Kidneys
- **Inhaled anesthetics** ↓ renal blood flow and ↓ glomerular filtration rate to varying degrees (least effect with desflurane)
- **Propofol** has no effect

Skeletal Muscle
- **Inhaled anesthetics**
  - cause skeletal muscle relaxation
  - potentiate the effects of non-depolarizing muscle relaxants (largest effect with isoflurane)
- **Propofol** has no effect
- **Volatile anesthetics** will trigger malignant hyperthermia in individuals with defects in the ryanodine receptor

NOTES
10. For a humourous explanation of the pathophysiology of malignant hyperthermia, see *The Malignant Hyperthermia Rap* [http://www.youtube.com/watch?v=Zs91nj-5tm0]
### Table 4 Properties of inhaled anesthetics

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Boiling Point (°C at 1 atm)</th>
<th>Vapour Pressure (mm Hg at 20°C)</th>
<th>Blood-Gas Coefficient (at 37 °C)</th>
<th>Oil-Gas Coefficient</th>
<th>MAC (vol%)</th>
<th>% Metabolized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane ((\text{C}_3\text{H}_2\text{F}_6\text{O}))</td>
<td>23.5</td>
<td>672</td>
<td>0.42</td>
<td>19</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>Sevoflurane ((\text{C}_4\text{H}_3\text{F}_7\text{O}))</td>
<td>58.5</td>
<td>157</td>
<td>0.69</td>
<td>47</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Isoflurane ((\text{C}_3\text{H}_2\text{ClF}_5\text{O}))</td>
<td>48.5</td>
<td>238</td>
<td>1.40</td>
<td>98</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Enflurane ((\text{C}_3\text{H}_2\text{ClF}_5\text{O}))</td>
<td>56.5</td>
<td>175</td>
<td>1.80</td>
<td>98</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Halothane ((\text{C}_3\text{HBrClF}_3))</td>
<td>50.2</td>
<td>244</td>
<td>2.30</td>
<td>224</td>
<td>0.75</td>
<td>20</td>
</tr>
<tr>
<td>Nitrous oxide ((\text{N}_2\text{O}))</td>
<td>-88.5</td>
<td>38628</td>
<td>0.47</td>
<td>1.4</td>
<td>105</td>
<td>0.004</td>
</tr>
</tbody>
</table>

MAC, minimum alveolar concentration