Pharmacology of Inhaled Anesthetics

Majority of Anesthetics Given USA and World Are Primarily With Inhaled Anesthetic Drugs

Definitions

Pharmacokinetics of Inhaled Anesthetics (relationship: dose, tissue concentrations, time)

Gas Man® Anesthesia Simulator
http://bwhanesthesia.org
Factor Determining Uptake and Distribution: Partial Pressure Gradients

Uptake and Distribution Step by Step: Transfer of Inhaled Anesthetic from Inspired to Alveoli
\[ P_I \rightarrow P_A \]

Transfer of Inhaled Anesthetic from Alveoli to Arterial Blood
\[ P_A \rightarrow P_a \]

Partition Coefficients at 37°C

Blood/gas

Transfer of Inhaled Anesthetic from Arterial Blood to Brain (VRG)
\[ P_a \rightarrow P_{br} \]
Elimination

Mostly, inverse of uptake, so influenced by

- \( V \)
- Solubility
- \( CO \)

Also influenced by:

- Tissue concentrations: depend on
  - Duration of anesthesia
  - Solubility of agent
- Metabolism: important for halothane

WAKEUP occurs when \( P_{br} \) reaches desired effect threshold

Determinants of Wakeup: Rarely, Fat Solubility

Agent

<table>
<thead>
<tr>
<th>Blood/gas</th>
<th>Brain/blood</th>
<th>Muscle/blood</th>
<th>Fat/Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(_2)O</td>
<td>0.47</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.4</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>2.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.42</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
<td>1.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>

(VRG)

% Cardiac Output

- 75
- 19
- 6

Drug entry into fat is limited by:

- % CO to fat

With large capacity of fat for agents (volume; sol)

Fat Solubility Rarely Determines Wakeup

Fat - A sink for anesthetic for 12 h, Des, 17 h Sevo

JH Philip, GasMan®

Pharmacodynamics

The study of drug actions, beneficial and adverse

- How the drug affects the body

Clinically, Why

Induction can be faster than Wakeup

Overpressure!

MAC

Minimum Alveolar Concentration

Alveolar partial pressure (in % atmospheric \( P_{sea\ level} \)) of an anesthetic that prevents movement in 50% of subjects in response to a standardized surgical incision.

Determined at steady state ~15 min
MAC = ED$_{50}$

Factors that Increase MAC

Factors that Decrease MAC

Factors that Do Not Change MAC

Properties of Inhaled Anesthetics:
Nitrous Oxide (N$_2$O)

Properties of Inhaled Anesthetics:
Halothane
<table>
<thead>
<tr>
<th>Properties of Inhaled Anesthetics:</th>
<th>Organ Effects:</th>
<th>Organ Effects:</th>
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</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>N\textsubscript{2}O</td>
<td>Volatile anesthetics</td>
</tr>
<tr>
<td>Structure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td></td>
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<tr>
<td>Vapor P</td>
<td></td>
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<tr>
<td>% at 20°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmHg</td>
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<tr>
<td>Contains Ether link</td>
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<td></td>
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<tr>
<td>Substitution of Fluorine for Br &amp; Cl</td>
<td></td>
<td></td>
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<tr>
<td>- Increases chemical stability</td>
<td></td>
<td></td>
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<tr>
<td>- Decreases blood solubility and anesthetic potency</td>
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<td></td>
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<tr>
<td>Similar to isoflurane: F atom substituting for iso Cl</td>
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<tr>
<td>High Vapor pressure: boils at Room T at altitude {Denver}</td>
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<tr>
<td>Requires heated (boiling-liquid) vaporizer</td>
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<tr>
<td>Vapor P permits use of conventional vaporizer</td>
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<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
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<tr>
<td>Symp NS stimulation</td>
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<tr>
<td>Contractility ↓ with net NC in CO</td>
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<tr>
<td>- Ameliorates BP drop seen with volatile anesthetics</td>
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<tr>
<td>Resp:</td>
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<tr>
<td>↓ TV, ↑ RR - NC resting PaCO2</td>
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<tr>
<td>Neuromusc:</td>
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<tr>
<td>Does not provide relaxation</td>
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<tr>
<td>Biotransformation &amp; toxicities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N\textsubscript{2}O</td>
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<tr>
<td>Not metabolized (0.004%)</td>
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<tr>
<td>Inhibits enzymes that are B12 dependent: methionine and thymidylate synthetases</td>
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<tr>
<td>Prolonged exposure: bone marrow depression, periph neuropathies - NOT at clinical exposures</td>
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<tr>
<td>? Teratogen (myelin ; DNA)</td>
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<tr>
<td><strong>Volatile anesthetics</strong></td>
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</table>
Organ Effects: **Halothane**

- Direct myocardial depressant (dose-dep)
  - ↓ HR (blunted baroreceptor reflex)
  - Net ↓ CO.
- Sensitizes heart to epinephrine-induced arrhythmias

**Biotransformation & toxicities: Halothane**

- Metabolized 20%; TriFluoroAcetic acid (TFA)
- Halothane hepatitis
  - 1:35K centrilobular necrosis
- Immune: Ab to TFA-↓ liver microsomal proteins
  - ↑ enzymes, bilirubin, encephalopathy
- Adults & children past puberty
- Sensitizes heart to catechols, esp if ↑ CO2:
  - limits use with exogenous epi; avoid > 1.5 ug/kg
- Unstable to UV: thymol preservative, amber bottle

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Organs Effects: **Isoflurane**

- Minimal myocardial depressant
  - ↑ HR, dose-dep. (preserved baroreceptor reflex)
  - NC in CO
- No sensitization to epinephrine-induced arrhythmias
- Rapid ↑ in concentration → trans ↑ HR, BP, NEpi

**Resp:**
- Mild irritant upper airway reflexes; bronchodilator

**Biotransformation & toxicities: Isoflurane**

- Metabolized 0.2%; TFA
- Rare reports of immune hepatitis
- Prolonged exposure to anesthesia or sedation → ↑ plasma F (~ 50 µmol/L)
  - no renal concentrating dysfunction seen
- Controversy re coronary steal (vasodilation)

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Organ Effects: **Desflurane**

- ↓ SVR, ↓ BP, Moderate ↑ HR
- NC in CO
- Dose-related ↑ HR, CVP, and PAP

**Biotransformation & toxicities: Desflurane**

- Minimal metabolism 0.02% TFA
- One report of immune hepatitis
- Degraded by Dried alkali in CO2 absorber (esp BaOH [n/a], KOH > NaOH):
- Delirium on emergence in children
Organ Effects: Sevoflurane

↓ contractility, ↓ SVR, ↓ BP

Biotransformation & toxicities: Sevoflurane

[] ↑ w ↑ absorber temp ~ ↓ FGF, [sevo]; dry absorbent

Inhaled Anesthetic Agents: Choices!

Based on Pharmacology

To Create a Optimal Anesthetic