What do you need to know about volatile anaesthetics?

• Basic principles
• Need to know class actions
• Individual pharmacological properties and
• Individual physiochemical properties
• Structures
• You will be asked this:
  – MCQ
  – Common Viva question in pharmacology section
• Examiners expect high quality responses
How do volatiles work?
Meyer-Overton Hypothesis

- Over 100 years old
- Recognized link between potency and lipid solubility
- Sufficient drug dissolves into neuronal lipid layer anaesthesia occurs
- Critical Volume hypothesis
- But
  - $\text{MAC} \times \text{oil/gas coefficient} = \text{same constant for all}$
  - In fact newer agents = 100 and older agents = 200
  - Isomers same oil/gas coefficient but different potencies
Lipid Solubility vs. MAC %

Key:
- N2O
- Xenon
- Desflurane
- Sevoflurane
- Isoflurane
- Halothane
Protein receptor hypothesis

- Specific volatile anaesthetic binding sites have been found on membrane proteins

- In particular GABA\textsubscript{A} Receptor
  - Also binding sites for barbiturates, bdz, propofol and ethanol.
  - Binding facilitates opening of channel with GABA
  - Inflow Cl- hyperpolarises
  - Potent agents directly open channels without GABA (not BDZ)
• Many other receptors and ion channels share common subunits with GABA

• So others may be affected e.g:
  – Ach, NMDA and other ligand gated receptors
  – voltage gated channels
Multi-site theories of narcosis

- Volatile anaesthetics impair memory, learning and produce unconsciousness at different concentrations

- Effect on different receptor subtypes (isoforms) found in different areas
  - Alpha5 GABA_A subtype and memory
  - Hypocampus

- An indirect then direct effect on ion channels at high concentrations

- No unitary hypothesis can account for all their actions
Pharmacokinetics/
Pharmacodynamics
What is MAC?

• Minimum Alveolar Concentration
  – At equilibrium (15 minutes of inhalation)
  – At sea level, in 100% Oxygen

• 50% of unpremedicated animals (ED50)
  – consistent within and between species

• Fail to respond to standard noxious stimuli

• MAC 90, MAC awake, MAC Bar
What factors modify MAC?

### Factors increasing MAC
- Hyperthermia
- Hypernatremia
- Increased CNS transmitters
  - MAOI
  - Amphetamine
  - Cocaine
  - Ephedrine
  - L-DOPA
  - Chronic ETOH abuse

### Factors with no influence on MAC
- Duration of anesthesia
- Sex
- Alkalosis
- PCO$_2$
- Hypertension
- Anaemia
- Potassium
- Magnesium
- And others
What factors modify MAC?

Factors decreasing MAC

- Increasing age
- Hypothermia
- Hyponatremia
- Hypotension (MAP<50mmHg)
- Pregnancy
- Hypoxemia (<38 mmHg)
- O₂ content (<4.3 ml O₂/dl)
- Metabolic acidosis
- Narcotics
- Ketamine
- Benzodiazepines
- α₂ agonists
- LiCO₃
- Local anesthetics
- ETOH (acute)
- And many more...
What is the Oil-Gas Partition Coefficient?

- Partition Coefficients:
  - ratio of the amount of substance in one phase to the amount in another phase
  - at a stated temperature, with the two phases being of equal volume and at equilibrium with each other
  - Olive oil

- Index of potency
- Related to MAC - Inversely
- Measure of Lipid solubility
[Oil/gas partition coefficient (37°C)]

- MAC %
- Oil/gas partition coefficient (37°C)

- N2O
- Xenon
- Desflurane
- Sevoflurane
- Isoflurane
- Halothane
What is the blood/gas partition coefficient?

- Measure of solubility in blood
- Paradox
  - Low B/G solubility - rapid onset/offset
  - High B/G solubility - slow onset/offset

- Why do agents which rapidly dissolve into blood have slow onset of action?
  - Effects on CNS relates to Partial Pressure in Blood not amount dissolved in blood
  - Highly soluble agents have low partial pressures
  - More molecules of a soluble gas are required to saturate liquid phase before increasing partial pressure
<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Blood:Gas PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>0.42</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.46</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.46</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.91</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.50</td>
</tr>
</tbody>
</table>

![Graph](image-url)
What is the main factor to affect speed of onset \((\text{and more importantly offset})\)?

- Anaesthesia depends on partial pressure of agent in the brain \(P_b\)
- \(P_b\) itself depends on \(P_A\) (\(P_A\) Partial pressure in Alveolus)
- This is CRUCIAL to understanding this.
  - Because almost instantaneous equilibration of \(P_A = P_a = P_b\)
  - (where \(P_a\) = Partial pressure in arterial blood)
Speed of Onset

• Faster the rise in $P_A$ ($\uparrow$ in $P_A$) then faster the rise in $P_b$ and therefore faster speed of onset.

• $\uparrow$ in $P_A = \text{balance between delivery of drug to alveolus and the loss from alveolus into arterial blood}$

• This is Input minus Uptake
What is Uptake?

- Loss from alveolus into arterial blood
- Depends on:
  1. Alveolar blood flow equal to CO ($Q$)
  2. Blood solubility (blood gas coefficient) ($\lambda$)
  3. Partial pressure difference between alveolar gas and venous blood ($P_A-P_v$)
     - The gradient depends on tissue uptake
     - Determined by Tissue solubility and Tissue blood flow

$$\text{Uptake} = Q \times \lambda \times P_A - P_v$$
Inspired Concentration
Alveolar Ventilation

P_A Agent

INPUT

UPTAKE

P_A Agent

INPUT

UPTAKE
What is the concentration effect?

- Occurs with N₂O because:
  1. N₂O is given in high concentration
     - An order of magnitude greater than volatiles
  2. N₂O is more soluble than N₂ or O₂
     - 35 times more soluble than N₂
     - 20 times more soluble than O₂

- Other agents are more soluble but not given at 70% end-tidal concentration
- Volume of N₂O in alveolus decreases rapidly
- N₂ cannot diffuse back into alveolus at equal volume
- Therefore Partial Pressures (concentrations) of other gases increases:
  - O₂ and volatile agents
What is the Second Gas Effect?

- Consequence of the concentration effect
- Volatile agents (2nd Gas) used alongside high concentrations of N₂O (1st Gas) are concentrated.
- Leads more rapid rise in $P_A$
- Faster onset of action
What is diffusion hypoxia?

• Occurs:
  – At the end of anaesthesia
  – when no oxygen given pt breathing air
  – Because of N₂O greater solubility

• The volume of N₂O diffusing back out of blood into alveolus > volume of N₂ entering blood stream from alveolus.

• This results in dilution of other Alveolar gases including partial pressure of O₂
Metabolism
Do inhaled anaesthetic agents undergo metabolism?

- Yes
- In liver
- Hepatic cytochrome P450 metabolizes C-Halogen bond
- Releases halogens (F, Cl, Br) which can cause hepatic or renal damage

Increasingly difficult to metabolise

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Metabolized</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂O</td>
<td>&lt;0.01</td>
<td>N₂</td>
</tr>
<tr>
<td>Halothane</td>
<td>20</td>
<td>Trifluoracetic acid Cl⁻ and Br⁻</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>3.5</td>
<td>Inorganic and Organic fluorides</td>
</tr>
<tr>
<td>Enflurane</td>
<td>2</td>
<td>Inorganic and Organic fluorides</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0.2</td>
<td>Trifluoracetic acid F⁻</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.02</td>
<td>Trifluoracetic acid</td>
</tr>
</tbody>
</table>

Trifluoroacetic acid causes hapten (covalently bonds with hepatic proteins) - hepatitis
Degradation products of sevoflurane in circle systems.

- Sevoflurane is absorbed and degraded by carbon dioxide absorbers
- At temperatures of 65°C 5 products are formed
- Compounds A to E (vinyl ethers)
- In clinical practice Compound A and lesser Compound B
- Concentrations higher with baralyme (attains higher temp) than soda lime
- Concentrations produced at 0.25lmin⁻¹ for 5 hours peaks at 20 ppm
- Toxic effects:
  - Renal, hepatic and brain
  - Concentrations produced are lower than toxic thresholds (200 ppm) in animal studies
  - New zeolite coated soda lime may absorb these compounds.
Side effects
What effects do inhaled anesthetics have on the CV system?

• ↓ Blood pressure
  – except N₂O

• Heart rate
  – Effects variable and agent-specific
  – Halothane decreases HR
  – Sevoflurane and enflurane neutral
  – Desflurane associated with transient tachycardia
    • occurs with rapid increases in MAC
    • associated with increases in serum catecholamines
What effects do inhaled anesthetics have on the CV system?

• ↓ Myocardial contractility
  – at 1 MAC anesthetics depress contractility in the following order
    • H = E > I = D = S.
  – Preconditioning
  – CO often preserved

• ↓ Systemic vascular resistance
  – All are direct vasodilators, except N$_2$O
  – relax vascular smooth muscle
What effects do inhaled anesthetics have on the CV system?

- **Dysrhythmias**
  - Halothane

- **Coronary blood flow - Coronary Steal**
  - Isoflurane
  - Potent coronary vasodilator
  - In practice, doesn’t seem to be a problem
  - Volatiles myocardial protection
What effects do inhaled anesthetics have on Respiratory pattern?

- Increased frequency
- Decreased tidal volume
- Decreased minute ventilation
What effects do inhaled anesthetics have on Chemoreceptors?

- Apnoeic threshold raised
- Response to PCO₂ blunted
  - dose dependent
  - PCO2 increased while spontaneously ventilating
  - E>D=I>S=H
- Hypoxic drive abolished by 0.1 MAC
What effects do inhaled anesthetics have on Bronchial musculature?

- Reduce vagal tone
- Direct relaxation
  - increased cAMP (but not adrenoreceptor mediated)
- When bronchospastic, a dose dependent reduction in $P_{aw}$ occurs with most agents
What effects do inhaled anesthetics have on the renal system?

- Fluoride nephrotoxicity at serum conc 50 μmol/l
- F⁻ opposes ADH leading to polyuria
- Methoxyflurane 2.5 MAC-hours
  - Methoxyflurane metabolised also in kidneys to produce local F⁻ release
- Sevoflurane renal toxicity not observed even though levels can reach 50μmol/l
What effects do inhaled anesthetics have on the Central nervous system?

• ↑ cerebral blood flow
• ↑ ICP

• Decreased CMRO$_2$

• 2 MAC enflurane increases seizure activity

• Skeletal muscle relaxation
• Potentiate non depolarising muscle relaxants

• Trigger MH
• \(N_2O\) has no effect
• Halogenated volatiles lead to dose-dependent
  – uterine relaxation
  – reductions in uterine blood flow
Discuss the complications of N2O use?

- N₂O-related myelosupression if >12 hr exposure
  - inhibition of methionine-synthetase
  - Homocystein levels up
  - megaloblastic anemia
- Inhaled anesthetics, N₂O in particular, decrease leukocyte function
- Teratogenesis with prolonged exposure in rats
- Increased risk (RR = 1.3) of spontaneous abortion with chronic exposure to N₂O
- ENIGMA trials
- Enigma 1 - increased length of stay, wound infection
- Enigma 2 - ongoing, Cardiac Morbidity