B. 6 Inhalational anaesthetic agents

a. Describe the properties of an ideal inhalational anaesthetic agent.

preparation
   easily administered
      boiling point above ambient temperature
      low latent heat of vaporization
      simple apparatus
      chemically stable
      long shelf-life, compatible with soda-lime, metals and plastics
      not flammable
      cheap
pharmacokinetic
   low solubility
      rapid onset, rapid offset, adjustable depth
   minimal metabolism
   predictable in all age groups
pharmacodynamic
   high potency
      allows high FiO₂
   high therapeutic index
   analgesic
adverse actions
   minimal toxicity
   minimal unwanted effects
      nausea, vomiting, cardiac arrhythmogenicity
   no toxicity with chronic low-level exposure of staff

b. Describe the structure-activity relationships of the volatile agents.

\[
\begin{align*}
\text{Desflurane} & : \quad \text{F–} \quad \text{C–} \quad \text{C–} \quad \text{O–} \quad \text{C–} \quad \text{H} \\
\text{Isoflurane} & : \quad \text{F–} \quad \text{C–} \quad \text{C–} \quad \text{O–} \quad \text{C–} \quad \text{H} \\
\text{Enflurane} & : \quad \text{F–} \quad \text{C–} \quad \text{C–} \quad \text{H} \\
\text{Halothane} & : \quad \text{Cl–} \quad \text{F–} \quad \text{C–} \quad \text{C–} \quad \text{O–} \quad \text{C–} \quad \text{H} \\
\text{Ether} & : \quad \text{F–} \quad \text{Br} \quad \text{H} \\
\text{Trichloroethylene} & : \quad \text{F–} \quad \text{Cl} \quad \text{H} \\
\text{Methoxyflurane} & : \quad \text{F–} \quad \text{F–} \quad \text{C–} \quad \text{F} \quad \text{H} \\
\end{align*}
\]

Structure-activity relationships for the volatile anaesthetic agents apply to their physical and chemical properties and to their metabolism.

physical
   low molecular weight and non-polar structure produce low boiling point, high vapour pressure
chemical
   large number of hydrogen atoms increases flammability
   high fluorine content minimizes flammability
   CF₂H moiety can liberate CO in reaction with dry soda-lime
pharmacokinetics
fluorine content reduces solubility in blood and fat
hydrolysis of ethers is most rapid when the adjacent carbon atoms are not halogenated
hydrolysis produces a halogenated acetic acid and halogenated methanol which can release some halides
fluorine on the 1-carbon of methyl-ethyl-ethers can be liberated as F

pharmacodynamics
chlorine and hydrogen content increases potency
fluorine content reduces potency

c. Provide a brief overview of the history of nitrous oxide, cyclopropane, ether and chloroform.

1772 N₂O first prepared by Priestly
1779 Humphrey Davy suggested N₂O had anaesthetic and analgesic properties
1844 N₂O demonstrated by Horace Wells for dental extraction
1846 ether demonstrated by Morton at Massachusetts General
1847 chloroform introduced, used by Queen Victoria
1880s ethyl chloride introduced
1930s cyclopropane and trichloroethylene introduced
cyclopropane used for single-breath gas inductions (MAC 9%)
trichloroethylene (Trilene) blue coloured agent with good analgesic properties
1951 halothane synthesized
fluroxene enters clinical use
1956 halothane enters clinical use
1960 methoxyflurane enters clinical use
1963 enfurane synthesized
1965 isofoflurane, desflurane synthesized
1966 enfurane enters clinical use
1968 sevoflurane synthesized
1971 isofoflurane enters clinical use
1990 sevoflurane enters clinical use
1992 desflurane enters clinical use

d. Describe the preparation of nitrous oxide and Entonox and outline their physical properties.

nitrous oxide
physical properties
MW 44.02
BP -88.5°C
SG 1.53 kg/l
prepared by heating NH₄NO₃ at 245-270°C
NH₄NO₃ → N₂O + 2H₂O
small amounts of NH₃ and HNO₃ produced recombine to NH₄NO₃ on cooling
small amounts of NO and NO₂ are also produced
can cause methaemoglobinemia, pulmonary oedema if inspired
N₂O must be purified to remove these contaminants

Entonox™
50% O₂, 50% N₂O supplied in cylinders at 138 bar
maximum pseudo-critical temperature -5.5°C at 117 bar
separation of constituents occurs below pseudo-critical temperature
analgesic for labour and brief procedures
e. Describe the undesirable effects of nitrous oxide.

pharmaceutic contamination in manufacture
\[ \text{NO}_2, \text{NO}, \text{HNO}_3 \]

physiological cardiovascular haematological
\[ \uparrow P_{50} \text{ by } 1.6 \text{ mmHg} \]
inhibition of thymidylate synthetase and methionine synthetase by oxidation of cobalt ion on B_{12}

- megaloblastic anaemia
- neuropathy
- teratogenicity

CNS
\[ \uparrow \text{ muscle tone, rigidity especially with opiates} \]

physical flammability
not flammable, but will support combustion
gas spaces
partition into physiological spaces
middle ear, gut \( \rightarrow \) nausea
other spaces
- expansion of pneumothorax, gas emboli, tube cuffs

hypoxia
low potency requires high Fi, potential for hypoxic gas mix
rapid flow of \( \text{N}_2\text{O} \) into alveoli on ceasing administration causes diffusional hypoxia unless supplemental oxygen is inhaled

f. Describe the comparative pharmacology of halothane, enflurane, isoflurane, methoxyflurane, desflurane and sevoflurane.

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<th></th>
<th>BP</th>
<th>MW</th>
<th>SVP</th>
<th>blood:</th>
<th>blood:</th>
<th>MAC</th>
<th>metabol.</th>
<th>vapor/liquid</th>
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<tr>
<td></td>
<td>(˚C)</td>
<td></td>
<td>(mmHg)</td>
<td>gas</td>
<td>brain</td>
<td>(%)</td>
<td>(%)</td>
<td>(v/v)</td>
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<tr>
<td>( \text{N}_2\text{O} )</td>
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<td>44</td>
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<tr>
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<td></td>
<td></td>
<td>9.2</td>
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</tr>
</tbody>
</table>

oil:gas partition \( \approx \frac{150}{\text{MAC}} \)

\[ [\text{Inhalational anaesthetics}] \quad 2.B.6.3 \quad \text{James Mitchell (December 24, 2003)} \]

\[ 2.B.6.3 \quad \text{James Mitchell (December 24, 2003)} \]

g. Describe the physiological effects of the volatile agents.

CNS

- anaesthesia facts
  - anaesthetics act at millimolar concentrations (high)
  - lipid solubility increases potency for most agents
    (Meyer-Overton relationship)
  - some stereospecificity is displayed by chiral agents
lipid fluidity changes induced by agents are very small
inhibition of intracellular Ca\textsuperscript{2+} release occurs
several theories
unitary vs degenerate
agents act at a single site or at multiple sites
lipid vs protein
agents act by altering lipid fluidity or binding lipophilic regions of proteins
likely explanation
binding to lipophilic protein regions (differing slightly for different agents) alters ligand-gated ion channel activity, altering some or all of ACh, GABA, NMDA, AMPA and KA transmission
analgesia
uncertain mechanism of action, probably related to anaesthetic actions
EEG ↓ frequency ↑ voltage from 0.4MAC (asleep)
I, S, D burst suppression at 1.5MAC, silence at 2MAC
H silence at 3.5MAC (impractical)
E seizure activity (↑ by low PCO\textsubscript{2})
evoked potentials ↓ amplitude ↑ latency
CSF volume E↑ I↓
CBF loss of autoregulation → vasodilation
H from 0.6MAC
E > I from 1.0MAC
CVS
↓ contractility H, E > I, S, D
↑ RAP H, E > I
↓ SVR I, S, D > E > H (I can cause coronary steal, no tachycardia with S)
catecholamine sensitization H > I, S, D > E
respiratory
↓ hypoxic response markedly from 0.1MAC
↓ hypercarbic response: E, S > I > H
↓ TV
↑ RR up to 1MAC, then I↓ H, E↑
bronchodilation (↓ vagal tone, smooth muscle relaxation)
GIT
hepatotoxicity
all ↓ portal flow
hepatic artery flow H↓ I↑
renal
F\textsuperscript{-} ion toxicity (below)
E ↓ RBF and GFR
I, H, D maintain RBF and GFR
muscle
relaxant due to
↓ central outflow, ↑ blood flow, ↓ post junctional sensitivity, ↓ Ca\textsuperscript{2+} flux
E, I > H
trigger for malignant hyperpyrexia
H > E > I
obstetric
↓ contractility, vasodilation (↑ blood loss), depression in fetus
immune, haematological
H ↓ platelet aggregation
impair neutrophil activity
N\textsubscript{2}O > volatiles
teratogenic

Inhalational anaesthetics

2.B.6.4

James Mitchell (December 24, 2003)
no proven toxicity from volatiles

h. Describe the metabolism of the volatile agents and the role of their metabolites in toxicity.

halothane
  oxidation (most metabolism if hepatic oxygen delivery is adequate)
  \[ \rightarrow \text{trifluoroacetic acid, Br}^{-}, \text{Cl}^{-} \rightarrow \text{conjugates of TFA} \]
  inhibited by cimetidine, isoflurane, ischaemia
  reduction (0.1-0.5%)
  \[ \rightarrow \text{Br}^{-} + \text{CF}_3\text{CH}_2\text{Cl} \rightarrow \text{HF} + \text{F}_2\text{C}==\text{CHCl} \rightarrow \text{conjugates} \]
  toxicity
  alkane volatiles are more arrhythmogenic than ethers
  Br$^{-}$ direct sedative
  F$^{-}$ nephrotoxicity (but very little liberated)
  dose- and hepatic blood flow-related hepatotoxicity
  mild ↑ ALT, AST
  incidence ≈20%
  associated with increased reductive metabolism
  autoimmune fulminant hepatic necrosis
  1:30000
  accompanied by eosinophilia, rash
  associated with oxidative metabolites modifying hepatic proteins
  may also be associated with other volatiles more rarely

fluoride ion liberation
  most severe with α-carbon fluorinated ethers
  \[ M >> S > E >> I > D \]
  systemic [F$^{-}$] > 50µmol/l associated with high output renal failure
  sevoflurane is metabolized by cytochrome p450 E1 in liver
  methoxyflurane and enfurane are metabolized by p450 in kidney, producing higher
  local F$^{-}$ concentrations
  sevoflurane may also alter renal handling of amino-acids and glucose

i. Describe the interaction of soda-lime with trichloroethylene, halothane and sevoflurane.

sevoflurane
  forms compound A (PIFE) on reaction with warm soda-lime
  \[ \text{sevoflurane} \rightarrow \text{HF} + \text{FH}_2\text{C-O-C(CF}_3)\text{=CF}_2 \] (a vinyl ether)
  other compounds formed in very small quantities
  compound A causes nephrotoxicity in rats at 150-200 ppm (LD$_{50}$ 1000 ppm)
  normal levels in human anaesthesia don't exceed 30 ppm
  reduced by gas flow (>2 l/min recommended)

halothane
  forms a vinyl compound in soda-lime
  \[ \text{halothane} \rightarrow \text{HF} + \text{F}_2\text{C}=\text{CBrCl} \]
  greater toxicity in rats than compound A (LD$_{50}$ 250 ppm)
  normal levels in high flow anaesthesia 4-6 ppm

trichloroethylene
  forms toxic compounds with soda-lime
  \[ \text{trichloroethylene} \rightarrow \text{dichloroacetylene} \rightarrow \text{phosgene (Cl}_2\text{C}=\text{O} + \text{CO} \]
  dichloroacetylene causes neurotoxicity
  esp. cranial nerves V, VII, VIII
  phosgene causes pulmonary toxicity
  \[ \text{phosgene} + \text{H}_2\text{O} \rightarrow 2\text{HCl} + \text{CO}_2 \]
  (never to be used with soda-lime; rarely used anyway)