B. 5 Intravenous anaesthetic agents

a. List the ideal properties of an intravenous induction agent.

Definition
A drug or combination of drugs which will induce anaesthesia safely and reversibly when injected in sufficient doses and which could also be used intermittently or by infusion for maintenance of anaesthesia.

Classification
- rapid acting
  - barbiturates, imidazoles, phenols, steroids, eugenols
- slower acting
  - phencyclidines, benzodiazepines, opioids, neurolept combinations

Ideal properties
- simple preparation
- compatible with other agents and IV fluids
- painless on administration
- high potency and efficacy
- predictable action within one circulation time
- minimal cardiovascular effects or other toxicity
- depression of airway reflexes for intubation
- rapid and predictable offset of effect
- rapid metabolism for minimal hangover

b. Describe the structure-activity relationship of the barbiturates.

Barbituric acid is formed by the condensation of urea and malonic acid:

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{O=C} & \quad \text{C=O} \\
\text{NH}_2 & \quad \text{HOOC} \\
\text{NH}_2 & \quad \text{HOOC} \\
\text{+} & \quad \text{CH}_2 \\
\text{O=C} & \quad \text{C=O} \\
\text{HN} & \quad \text{C=O} \\
\end{align*}
\]

It is insoluble in water and has no activity in vivo. Barbiturates have two structural isomers which are in equilibrium, keto and enol forms:

\[
\begin{align*}
\text{HN} & \quad \text{C=O} \\
\text{O=C} & \quad \text{CH}_2 \quad \text{HO} & \quad \text{C} & \quad \text{CH}_2 \\
\text{HN} & \quad \text{C=O} & \quad \text{HN} & \quad \text{C=O} \\
\end{align*}
\]

The barbiturates have substitutions of functional groups of barbituric acid:

\[
\begin{align*}
\text{R}_3 & \quad \text{N} & \quad \text{C=O} \\
\text{X=O} & \quad \text{C} & \quad \text{R}_1 \\
\text{HN} & \quad \text{C=O} & \quad \text{R}_2 \\
\end{align*}
\]

X is oxygen (oxybarbiturates) or sulfur (thiobarbiturates). The thiobarbiturates such as thiopentone are generally more lipid-soluble and so have a more rapid onset of action. \(R_3\) is usually hydrogen, but in the case of methohexitone a methyl group is substituted which increases convulsive effect and shortens elimination half-life. The \(R_1\) and \(R_2\) groups can be short alkyl or aryl chains in the hypnotic barbiturates or longer (more than 5 carbon) chains in the anticonvulsants. Branched chains give greater hypnotic than anticonvulsant effect. Phenobarbitone has phenol and ethyl groups at \(R_1\) and \(R_2\) and is an anticonvulsant.
c. Describe the pharmacology of propofol, thiopentone and methohexitone and the factors which influence their effects.

thiopentone

pharmaceutics
presented as the Na⁺ salt of the enol form
0.5 g in 20 ml ampoule with Na₂, Na₂CO₃ 30 mg to pH 11
prepared with water or saline to 25 mg/ml solution
pH 11-12 precipitates in neutral or acid solution
stable (<7% loss of potency) for 5 days at 25°C or 45 days at 5°C

pharmacokinetics
distribution
pKa 7.6
85% protein bound
V₁ 1-2 l/kg
metabolism
t¹/α fast 8 min, slow 60 min, t¹/β 11 h
clearance 3 ml/min/kg
rapid redistribution from VRG into muscle (30 min peak) and fat
slow hepatic metabolism, easily saturated in infusion
pentobarbitone is one metabolite

pharmacodynamics
CNS
potentiates GABAA transmission, prolongs channel opening
may depress excitatory transmission by inhibiting Ca²⁺ transport
acts at reticular formation, hypothalamus and limbus
brief stimulatory phase before sleep
anticonvulsant at hypnotic doses
↓ CMRO₂, CBF, vasoconstrictor (may cause inverse steal)
not analgesic

CVS
effects depend on dose and rate of administration and filling
venodilator: ↓ LVEDV
myocardial depressant at high doses: ↓ SV, CO, MAP
but ↑ myocardial O₂ demand in anaesthetic doses
not an arterial vasodilator: baroreceptor reflex ↑ SVR

respiratory
central depressant
↓ rate, ↑ V₆ followed by apnoea
↓ CO₂ sensitivity
↓ upper airway reflexes when deep

renal, hepatic
minimal ↓ function

uterine
crosses placenta readily, no effect on tone

local
thrombophlebitis, pain, thrombosis
intraarterial injection causes vasoconstriction
due to endogenous vasoconstrictor release
treat with local anaesthetic, vasodilator, heparin, regional

adverse effects
above plus anaphylaxis (1/14000), anaphylactoid

clinical use
induction of general anaesthesia around 4 mg/kg
cerebral protection (5 mg/kg + 5 mg/kg/h)
contraindicated
no IV access, no airway support equipment
respiratory obstruction (croup, epiglottitis)
allergy
porphyria
relative contraindications
cardiac disease
septicaemia, acidosis
adrenocortical insufficiency

methohexitone

pharmaceutics
500 mg in 50 ml glass ampoule
white/yellow powder, sodium salt
stabilized with anhydrous sodium carbonate
mostly αL and αD isomers. β isomers increase involuntary movement.
prepared with water or saline
pH 10.6-11.6

pharmacokinetics
pKa 7.2
70% protein bound
Vdss 1l/kg
t1/2α fast 6 min, slow 60 min, t1/2β 2-4 h
clearance 11 ml/min/kg

pharmacodynamics
excitatory phenomena
more irritant to vessels
dose 1-1.5 mg/kg

propofol

pharmaceutics
10 mg/ml in 20, 50 and 100 ml ampoules
white aqueous isotonic emulsion
solubilized with 2.25% glycerol, 10% soybean oil, 1.2% purified egg phospholipid
previously solubilized in Cremaphor EL → anaphylaxis
pH 6.0 to 8.5

pharmacokinetics
weak organic acid, pKa 11
98% protein bound
Vdss 10 l/kg
metabolism by conjugation in liver
three compartment model
t1/2α 2 min, t1/2β 45 min, t1/2γ 4 h

pharmacodynamics
similar to thiopentone
GABA_α transmission effect may be its mechanism of action
CNS
excitatory effect, but anticonvulsant
? analgesic
little psychomotor effect after awakening
PNS: potentiates effect of NMJ blockers
respiratory: greater incidence of apnoea
CVS: ↓ SVR, SV, MAP

clinical use
induction 2-2.5 mg/kg (less in elderly or hypovolaemic)
maintenance 0.1-0.2 mg/kg/min

levels (µg/ml)
0.3 psychomotor effects
1.0 sleep
3 minor surgery
4 major surgery

ketamine

pharmaceutics
500 mg/10 ml, 100 mg/ml 10 ml, 2 ml vials
benzethonium chloride preservative
pH 3.5-5.5
(+ ) isomer 3-5 times more potent

pharmacokinetics
V, 3 l/kg
hepatic metabolism hydroxylation or N-demethylation, conjugation
norketamine has 20% potency
clearance 18 ml/kg/min
t'α 10 min, t'β 3 h

pharmacodynamics
NMDA antagonist
CNS
dissociative anaesthesia
inhibits thalamic transmission to cortex
↑ CBF, ICP, IOP
hallucinations on emergence
CVS
↑ sympathetic tone (central and ↓ NA uptake)
↑ HR, MAP, PVR
direct cardiac depressant
respiratory
retention of airway reflexes in low dose
↑ secretions, bronchodilation
muscle: ↑ tone, movements, inhibits PIChE

clinical use
induction 1-2 mg/kg IV (4-6 mg/kg IM)
maintenance 5-30 µg/kg/min
analgesia 150 ng/ml
anaesthesia 1000 ng/ml

Althesin
alphaxolone and alphadolone (3α-hydroxy steroids)
not available

pharmaceutics
alphaxolone 9 mg/ml, alphadolone 3 mg/ml in Cremaphor EL

pharmacokinetics
rapid induction of anaesthesia in one circulation time

pharmacodynamics
alphaxolone is twice as potent as alphadolone
high therapeutic index (30.6)
excitatory movements common
cardiodepressant → hypotension
propanidid
pharmaceutics
eugenol derivative
50 mg/ml in Cremaphor EL
pharmacokinetics
rapidly metabolized by pseudocholinesterase
competes with suxamethonium
pharmacodynamics
excitatory movements common
marked hyperventilation in induction
hypotension, tachycardia

d. Describe the formulation of thiopentone, methohexitone, propofol, diazepam and midazolam.

Diazepam
- Diazemuls
  1 ml of 5 mg/ml glass ampoule
  solubilized in soybean oil
- Diazepam USP
  2 ml of 5 mg/ml brown glass ampoule
  clear yellow solution
  dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate
  pH 6.6-6.9

Midazolam
- 5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules
- clear aqueous solution
- buffered to pH 3.3
- precipitates in strongly alkaline solutions

e. Compare the pharmacokinetic and pharmacodynamic differences between thiopentone, methohexitone, midazolam, diazepam, ketamine, etomidate and the steroid anaesthetics.

Thiopentone and methohexitone are barbiturate induction agents used intravenously. Their brief duration of action results from rapid distribution from the vessel-rich group into skeletal muscle and then fat. Methohexitone is slightly less dependent on redistribution for its duration of action as its rate of hepatic metabolism and renal clearance is significantly higher.

<table>
<thead>
<tr>
<th></th>
<th>Rapid Distribution</th>
<th>Slow Distribution</th>
<th>Elimination</th>
<th>Clearance</th>
<th>V_{dist}</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiopentone</td>
<td>8.5 min</td>
<td>62.7 min</td>
<td>11.6 h</td>
<td>3.4</td>
<td>2.5</td>
</tr>
<tr>
<td>methohexitone</td>
<td>5.6 min</td>
<td>58.3 min</td>
<td>3.9 h</td>
<td>10.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Both are highly protein-bound, lipid soluble and metabolized by hepatic oxidation (and desulfuration in the case of thiopentone) to inactive and less lipid-soluble metabolites which are renally cleared. Elimination half-life is shortened in children and patients with induced liver enzymes.

Barbiturates act by depressing the reticular activating system, possibly by inhibiting the dissociation of GABA from its receptors. Tolerance develops rapidly with continuous use.

Diazepam and midazolam are benzodiazepines which are active orally, transmucosally, intravenously, and in the case of midazolam, epidurally. Midazolam is used
as a sedative and coinduction agent. They are both highly lipid soluble and 96–98% protein bound. They have similar volumes of distribution but differ in metabolism.

<table>
<thead>
<tr>
<th></th>
<th>Elimination $t_{1/2}$ (h)</th>
<th>Clearance (ml/min/kg)</th>
<th>$V_{\text{dist}}$ (l/kg)</th>
<th>Oral bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>diazepam</td>
<td>21-37</td>
<td>0.2-0.5</td>
<td>1-1.5</td>
<td>94%</td>
</tr>
<tr>
<td>midazolam 50%</td>
<td>1-4</td>
<td>6-8</td>
<td>1-1.5</td>
<td></td>
</tr>
</tbody>
</table>

Diazepam is oxidized in the liver to desmethyldiazepam, oxazepam and temazepam all of which are active. Desmethyldiazepam has an elimination half-time of 48-96 hours, greatly prolonging the clinical effect of diazepam. The elimination half-time of diazepam increases with age and hepatic impairment to over 100 h in the elderly. The effective duration of action depends on both metabolism and initially on redistribution into fat.

Midazolam spontaneously converts to a water-soluble form at acidic pH due to a reversible ring-opening reaction and possibly due to ionization of the imidazole nitrogen. This allows preparation of a buffered (pH 3.5) water-based solution for intravenous use.

Midazolam is metabolized by hepatic microsomal enzymes to 1–hydroxymidazolam and 4–hydroxymidazolam both of which are excreted renally as glucuronide conjugates.

Benzodiazepines act by binding to a specific receptor site on GABA receptors, facilitating GABAergic transmission. In the CNS, it acts predominantly in the cortex; the concentration of GABA receptors being less in the more primitive parts of the CNS. There are GABA receptors on spinal motor interneurones, which may account for the activity of diazepam in reducing muscle tone.

Ketamine is a phencyclidine derivative used to induce dissociative anaesthesia.

<table>
<thead>
<tr>
<th></th>
<th>Elimination $t_{1/2}$ (h)</th>
<th>Clearance (ml/min/kg)</th>
<th>$V_{\text{dist}}$ (l/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketamine</td>
<td>1-2</td>
<td>16-18</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>etomidate</td>
<td>2-5</td>
<td>10-20</td>
<td>2.2-4.5</td>
</tr>
<tr>
<td>propofol</td>
<td>4</td>
<td>30-60</td>
<td>10</td>
</tr>
</tbody>
</table>

Ketamine is active intravenously, intramuscularly, epidurally and intrathecally. It is not significantly protein-bound. It is extremely lipid soluble and when administered IV is rapidly redistributed into the vessel-rich group including the brain, with slower redistribution to muscle and fat. It is demethylated by cytochrome p450 enzymes to
norketamine (active) and hydroxylated and excreted renally as a glucuronide conjugate. Its metabolism is slowed by the administration of halothane or diazepam. Ketamine induces the enzymes responsible for its metabolism so tolerance and dependence are seen.

Ketamine is thought to interact with opioid receptors in the CNS. Its analgesic effects exhibit cross-tolerance with opiates. It inhibits reuptake of catecholamines, causing an indirect sympathomimetic effect. It blocks glutamic acid NMDA transmission in the CNS. Its direct effect on the heart is depressant, intact sympathetic activity is required for its effect in increasing cardiac output. It enhances the activity of non-depolarizing muscle relaxants and inhibits plasma cholinesterase, prolonging the effect of suxamethonium.

Etomidate is an imidazole containing compound which can be used as an induction agent. It is water-soluble at acidic pH and is used intravenously. Its brief duration of action is a result of redistribution as with thiopentone. It is moderately lipid-soluble at physiological pH. It is 76% protein bound.

Etomidate is metabolized by hydrolysis by hepatic microsomal enzymes and plasma esterases. Its metabolism is more rapid than thiopentone. Metabolites are inactive and renally cleared.

Etomidate probably acts to increase GABA transmission. Like methohexitone lowers the seizure threshold and causes myoclonic movements. It acts to inhibit 11-ß-hydroxylase in the adrenal, reducing synthesis of cortisol and inhibiting the normal stress response. It is not used in Australia.

gamma-hydroxybutyrate
- water soluble hydrocarbon
- high dose (50 mg/kg for induction)
- slow onset (3 min)
- long duration
- bradycardia, emesis and hallucinations

pregnanolone
- steroid
- solubilized in intralipid
- rapid onset, short duration
- $t^{1/2}_\alpha$ 10 min, $t^{1/2}_\beta$ 1 h
- $V_{dss}$ 4 l/kg
- clearance 30-60 ml/kg/min
- dose 0.6 mg/kg
- may produce “steroid pyrogen fever”
- similar thrombophlebitis to barbiturates

f. Describe the undesirable systemic effects of individual agents.

g. Describe the toxic and adverse reactions to intravenous agents.