INHALATIONAL ANAESTHETIC AGENTS

(a) ***To describe the principles of vaporisation of inhalational agents.***

Overview of inhaled anaesthetic agents:

- Volatile anaesthetic agents (Eg. desflurane, isoflurane, sevoflurane, Etc.) are volatile liquids that require vaporisation into vapours to achieve GA
- N_2O and Xe are true gases (Ie. do not need vaporisation) to achieve GA

> Note – Gas and vapour are defined based upon a substance in gaseous state with respect to its "critical temperature" (temperature above which a gas cannot be liquefied by pressure alone):
> - Gas → defined as a substance in a gaseous state when ambient temperature is ABOVE its critical temperature
> - Vapour → defined as a substance in a gaseous state when ambient temperature is AT or BELOW its critical temperature

Physical principles in process of vaporisation:

- "Latent heat of vaporisation"
  - Defined as energy required to convert a substance from a liquid to gaseous phase
  - With liquid cooling (Ie. liquid evaporation in a vaporiser) → latent heat of vaporisation ↑↑↑ → this means more energy is needed to vapourise a liquid → this poses an issue with vaporisers
  - This is issue is circumvented by constructing vaporisers from metals with a high thermal conductivity (Ie. heat is able to flow through substance easily) → allows heat flow form atmosphere into liquid volatile agent to supply external energy for "latent heat of vaporisaiton"
- "Saturated vapour pressure" (SVP) of a volatile anaesthetic:
  - Defined as the partial pressure exerted by the vapour phase when in equilibrium with the liquid phase (Ie. when equal # molecules is leaving and entering each phase per unit time)
  - It is dependent on:
    - (i) Temperature (usually measured at 20°C) → SVP ↑ with ↑ temperature (Ie. more molecules enter vapour state)
    - (ii) Nature of liquid
  - It is a measure of volatility of a volatile agent (Ie. it determines the concentration of vapour molecules above the liquid volatile anaesthetic) → agents with a high SVP (Eg. desflurane) require a smaller proportion of total gas flow through the vaporiser to pass through vaporising chamber to produce a given concentration than an agent with a low SVP (Eg. sevoflurane)

> Note – "Vapour pressure" is defined as the partial pressure of vapour in a gas mixture (such that "Boiling point" occurs when vapour pressure = atmospheric pressure)

Overview of vaporisers:

- Fresh gas leaving the flowmeters enters the vaporiser downstream:
  - Within the vaporiser, the fresh gas is split into two streams:
    - (1) Bypass flow – Majority of fresh gas enters this stream and is NOT exposed to the volatile agent
    - (2) Vapouriser flow – Smaller amounts of fresh gas enters the vapourising chamber and is passed over the volatile agent. The gas then becomes 100% saturated with the agent
  - These two streams are later combined via the Common gas outlet
- "Concentration dial setting" of a volatile agent:
  - This influences the proportion of gas flow that enters each of the two streams, which then determines the concentration of inhaled agent in the fresh gas leaving vaporiser

    - This is calibrated to using 100% O_2 as fresh gas, such that using other gases (Eg. N_2O) will decrease vaporiser output and cause the concentration of the inhaled agent in the fresh gas leaving the vapouriser to be lower than the concentration dial setting
- Vaporisers are specific to a volatile agent as each agent will have a different SVP at a given temperature:
    - Using an agent in the wrong vapouriser will give an incorrect agent output (Ie. if SVP of agent is higher than that handled by the vaporiser, then agent output will be excessive; if SVP of agent is lower than that handled by the vaporiser, then agent output will be reduced)
    - Desflurane requires a special vaporiser (TEC6 vaporiser) – This is because the boiling point of the agent is at room temperature (22.8 °C) and the SVP is 681 mmHg (at 20 °C). As a result, passive vaporisation of desflurane will cause large temperature variations that must be compensated for. To overcome this, desflurane is actively heated using a special vaporiser to 39°C where SVP is ~ 2 atmospheres
- Effect of altitude on the concentration of inhaled agent:

$$C' = C \times (P/P')$$

C' = [Inhaled agent] in fresh gas at a given altitude
C = [Inhaled agent] in fresh gas where the vaporiser is calibrated
P' = $P_{BAROMETRIC}$ at given altitude
P = $P_{BAROMETRIC}$ where vaporiser is calibrated

    - Increased altitude (Ie. lower $P_{BAROMETRIC}$) causes vapourisers to produce a higher output concentration of volatile agents
    - This actually overcompensates for a rise in MAC (or fall in potency) of the agent with increased altitude!
- "Temperature compensation":
    - During vaporisation, the liquid volatile agent will cool causing heat to be drawn from the metal of the vaporiser, which draws heat from the OT
    - As this happens, SVP decreases (Ie. less volatility of the agent) causing vaporiser output to decrease
    - "Temperature compensation" is a way the vaporiser adjusts volatile output to compensate for changes in temperature

(b) ***To explain the concepts of partition coefficients, concentration effect and second gas effect.***

Concept of "Partition coefficient":

- "Partition coefficient" is defined as the ratio of gas concentrations in each of the two phases at equilibrium, which occurs when the partial pressures and volumes are equal between the two phases at a stated temperature

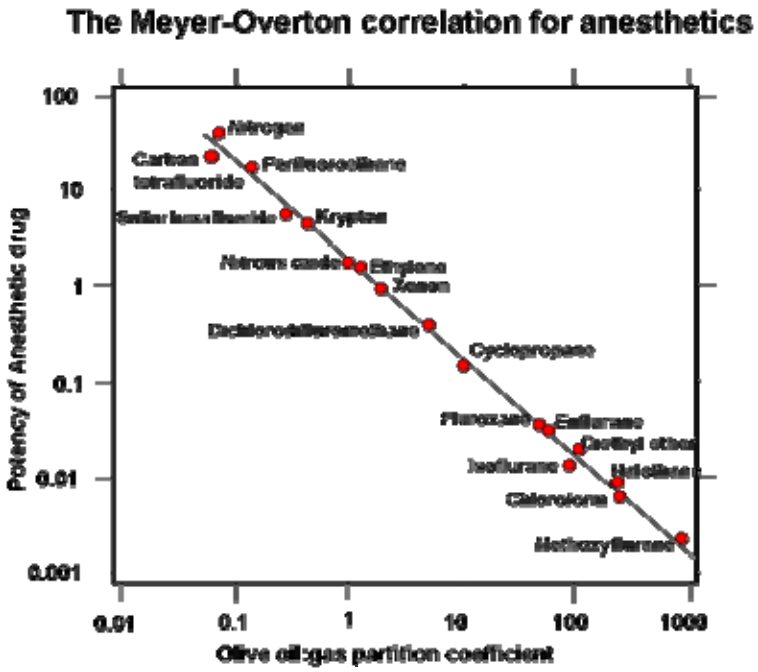
> For example, a blood-gas partition coefficient of 0.47 for N_2O means that at equilibrium, an volume of blood will contain 0.47 as much as an equal volume of alveolar gas when partial pressures are the same at 37°C

- There are three relevant partition coefficients:
  - (1) Blood: gas partition coefficient (BGPC):
    - BGPC is defined as the ratio of gas concentration in blood to alveolar gas at equilibrium, which occurs when the partial pressures and volumes are equal between the two phases at 37 °C
    - It is a measure of the solubility of an inhaled agent in blood
    - It is the MAIN determinant of uptake of the agent by pulmonary blood (Ie. influences F_A and F_A/F_I ratio) and thus the MAIN factor affecting induction/emergence rate of an inhaled agent:
      - Agents with a lower BGPC (Eg. N_2O, desflurane) are less soluble in pulmonary blood and thus have less uptake in pulmonary blood. This leads to a higher F_A (with F_A/F_I ratio → 1), which results in faster induction/emergence
      - Agents with a higher BGPC (Eg. halothane, ether) are more soluble in pulmonary blood and thus have more uptake in pulmonary blood. This leads to a lower F_A (with F_A/F_I ratio → 0), which results in slower induction/emergence

Agent	BGPC at 37 °C
Xenon	0.12
Desflurane	0.42
N_2O	0.47
Sevoflurane	0.69
Isoflurane	1.4
Enflurane	1.8
Halothane	2.4
Diethyl ether	12

    - BGPC for an agent can be altered by certain factors:
      - Age – BGPC increases with age
      - Body habitus – Obesity decreases BGPC
      - Haematocrit – BGPC decreases with haemodilution (Ie. 20% less when Hcrt 21%)
      - Albumin – BGPC decreases with hypoalbuminaemia
      - Temperature – Hypothermia causes increased BGPC
      - Fasting status – BGPC increases post-prandially
  - (2) Oil: gas partition coefficient (OGPC):
    - OGPC is defined as the ratio of gas concentration in adipose tissue to alveolar gas at equilibrium, which occurs when partial pressures and volumes are equal between the two phases at 37 °C
    - OGPC determines:
      - (i) Anaesthetic potency

- As per Meyer-Overton plot, there is a direct relationship between OGPC and potency



- MAC and OGPC are inversely related, whereby:

MAC x OGPC = ~ 150

- (ii) Uptake into adipose stores
- (iii) Degree of metabolism of inhaled agent by the body

Agent	OGPC at 37 °C
N_2O	1.4
Xenon	1.9
Desflurane	18.7
Sevoflurane	53
Isoflurane	93.7
Enflurane	98.5
Diethyl ether	~100
Halothane	220

- (3) Tissue: blood partition coefficient (TBPC):
  - TBPC is defined as the ratio of gas concentration in tissue (Eg. brain, fat, skin, muscle, Etc.) to blood at equilibrium, which occurs when the partial pressures and volumes are equal between the two phases at 37 °C
  - It describes the capacity for tissues to hold an inhaled anaesthetic agent, and thus determines the time for equilibrium of the agent between tissue and blood
  - Types of tissue groups:
    - (i) Vessel-rich groups (Eg. brain, heart, liver, kidney), muscle and skin – TBPC is ~ 1. Thus, the rate of rise in partial pressure (and concentration) in these tissues is directly proportional to the arterial-tissue tension gradient
    - (ii) Fat – TBPC is ~ 20. Thus, the partial pressure (and concentration) in lipid tissues is much higher than in blood, even before equilibrium is reached

- (iii) Vessel-poor group – TBPC ~ 0, hence at equilibrium a negligible amount of inhaled agent is stored

Agent	Brain-blood PC	Muscle-blood PC	Fat-blood PC
N_2O	1.1	1.2	2.3
Halothane	2.9	3.5	60
Isoflurane	2.6	4	45
Desflurane	1.3	2	27
Sevoflurane	1.7	3.1	48

Concepts of "Concentration Effect" and "Second Gas Effect":

- "Concentration Effect":
  - Increased F_I of an inhaled anaesthetic gas leads to a disproportionate increase in the rate of rise in F_A relative to F_I, thereby leading to an increased F_A/F_I ratio (Ie. attenuates uptake of agent by pulmonary blood) and faster induction times of that agent
  - This effect applies MAINLY to N_2O as it is the only inhaled agent that can be used at a sufficiently high F_I (due to its low potency/MAC)
  - Mechanism of how high F_I of N_2O impacts the uptake of itself:
    - (a) Concentrating effect – As gas is taken up by pulmonary blood, the gas remaining is in a smaller alveolar volume, thereby diminishing the change in F_A that might otherwise be expected. At a higher F_I, this effect is more pronounced resulting in an increased rise in F_A relative to the rise in F_I

      For example, ~ 50% of N_2O is taken up by the pulmonary circulation (as it has a B:G partition coefficient of 0.47)
      - At a *F_I of 20%* (20 parts N_2O per 100 parts of gas total) will result in an uptake of 10 parts of N_2O, resulting in a *F_A of 11%* (10 parts N_2O remaining per 90 parts of gas total)
      - A *F_I of 80%* (80 parts N_2O per 100 parts of gas total) will result in an uptake of 40 parts of N_2O, resulting in a *F_A of 67%* (40 parts of N_2O remaining per 60 parts of gas total)

    - (b) Augmented inflow effect – As gas is taken up by pulmonary blood, more gas is brought into the lungs to replace the lost volume and prevent alveolar collapse. This increases alveolar ventilation, which retards the effect of uptake on lowering F_A

      Using the above example with N_2O
      - At a *F_I of 20%*, an extra 10 parts of total gas is required to prevent alveolar collapse – This is accomplished by filling the alveoli with 2 parts of N_2O per 10 parts of gas total, thus making a *F_A of 12%* (10 + 2 parts of N_2O per 100 parts of gas total)
      - At a *F_I of 80%*, an extra 40 parts of total gas is needed to prevent alveolar collapse – This is accomplished by filling the alveoli with 32 parts of N_2O per 40 parts of gas total, thus making a *F_A of 72%* (40 + 32 parts of N_2O per 100 parts of gas total)

    - More simplistically – N_2O it is 20X more soluble than air (N_2/O_2) in blood. As a result, the volume of N_2O entering blood is much greater than the volume of air entering the alveolus. This causes:
      - (i) Alveolar volume to decreases, which leads to and thereby causing F_A of alveolar gases to increase
      - (ii) Augmentation of $V_{ALVEOLAR}$ to compensate of loss of alveolar volume, which leads to increased F_A of alveolar gases
  - "Diffusion Hypoxia"

        - Can occur with any inhaled agent, but generally occurs with an insoluble agent (esp N_2O) that has been inhaled for some time
        - Mechanism – Reverse process of concentration effect, whereby elimination of the agent from the alveoli proceeds as high as its uptake. This dilutes alveolar gases and effectively reduces PAO_2, thus resulting in alveolar hypoxia
        - Mild and rarely clinically significant. It can be easily managed by increasing the FIO_2 to 100% for 5-10 minutes after cessation of the inhaled agent
- "Second Gas Effect"
    - When two inhaled gases are given simultaneously (one of which includes N_2O), rapid uptake of large volumes of the first gas (N_2O) leads to a rapid rise in F_A of the second gas (either a different inhaled anaesthetic agent or O_2), thereby leading to faster induction of anaesthesia
    - Mechanism of how high F_I of N_2O impacts the uptake of a second gas:
        - (a) Concentrating effect – Rapid uptake of first gas (N_2O) in significant volumes causes a decrease of alveolar volume. This causes the second gas in the alveoli (O_2/volatile agent) to be concentrated, thereby increasing the F_A (and F_A/F_I ratio) of the second gas
        - (b) Augmented inflow effect – As the first gas is taken up, more of the second gas is brought into the lungs to replace the lost volume and prevent alveolar collapse. This increases alveolar ventilation, which retards the effect of uptake on lowering F_A (and the F_A/F_I ratio) of the second gas

Note: Both the "Concentrating effect" and "Second gas effect" have minor effects on increasing the rate of onset of inhaled anaesthetic agents – This is because the body is saturated with N_2O within minutes

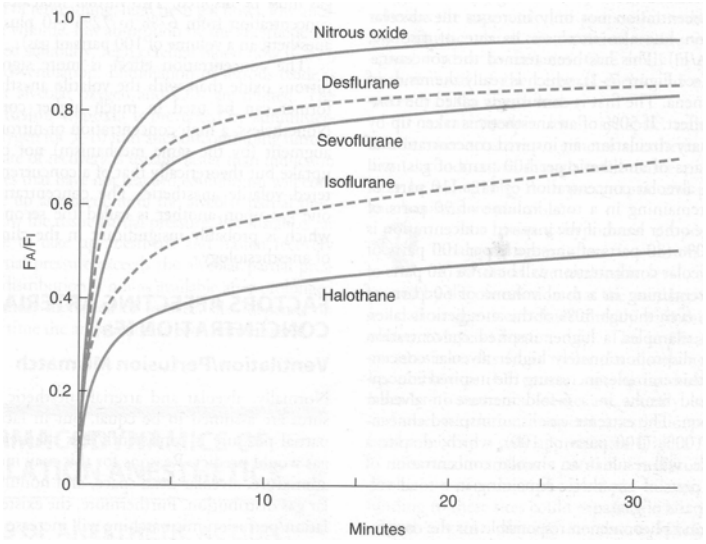
(c) ***To describe the relationships between inhaled and alveolar concentration. To describe the factors that affect this and their clinical importance.***
(d) ***To explain the significance of the distribution of cardiac output and tissue partition coefficients on uptake and distribution of volatile agents.***

Fractional concentration of an inhaled agent:

- Inspired gas fractional concentration (F_I) – Fractional concentration of inhaled agent leaving the anaesthetic circuit
- Alveolar gas fractional concentration (F_A) – Fractional concentration of inhaled agent present in the alveoli

$$\text{Fractional volume (\% volume)} = P_{\text{INHALED AGENT}} / P_{\text{BAROMETRIC}}$$

Inhaled anaesthetic agent uptake (or F_A/F_I) curve:

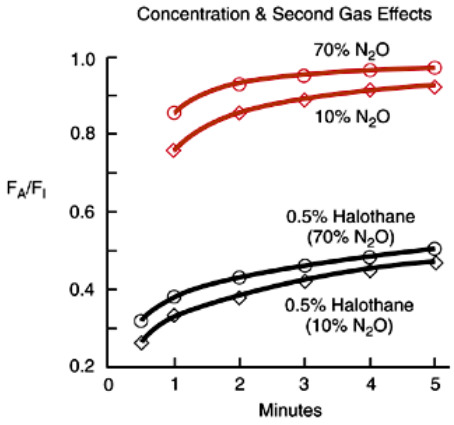


- For any inhaled anaesthetic agent, the F_A/F_I ratio will always be < 1.0 as the agent is continuously being taken up by pulmonary blood flow (Ie. ongoing uptake causes F_A to always lag behind F_I) – Note that $F_A = F_I$ (Ie. $F_A/F_I = 1$) only IF there was no uptake of the agent by the body (Ie. no cardiac output)
- The F_A/F_I ratio and the shape of the uptake curve of a particular inhaled anaesthetic agent are dictated by its phases of uptake and distribution:
    - Phase I: Initial rate of uptake is due to transfer of agent from inspired air to alveoli. This is determined by:
        - (i) Inspired gas concentration of the agent (F_I)
        - (ii) Alveolar ventilation
        - Note: Initial steep rate of uptake curve is due to unopposed filling of alveoli by ventilation
    - Phase II: Rate of uptake is then due to transfer of agent from alveoli to arterial blood. This is determined by:
        - (i) Blood-gas partition coefficient
        - (ii) Alveolar blood flow (or cardiac output)
        - (iii) Alveoli-venous pressure difference
    - Phase III: Finally, the rate of uptake is then due to transfer of agent from arterial blood to tissues. This is determined by:
        - (i) Tissue-blood partition coefficient
        - (ii) Tissue blood flow
        - (iii) Arterial-tissue pressure difference

        - Note: Rate of rise in uptake curve gradually slows as vessel-rich group (and then muscle and fat) reach their capacity for the agent

Phase I: Transfer of inhaled anaesthetic agent from inspired air to alveoli

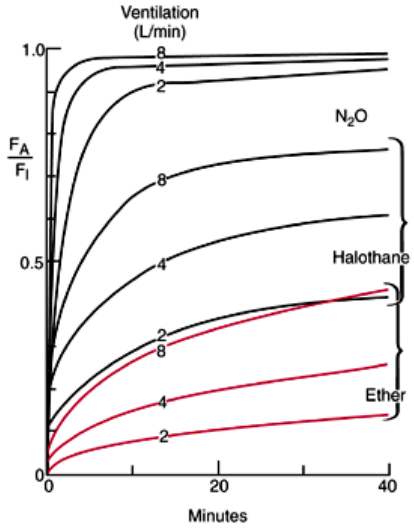
(1) Inspired gas concentration (F_I)
- "Concentration Effect"
    - Increased F_I leads to a disproportionate increase in the rate of rise in F_A relative to F_I, thereby leading to an increased F_A/F_I ratio (Ie. attenuates uptake of agent by pulmonary blood) and faster induction times



    - Mechanism of how a high F_I of an inhaled agent impacts its own uptake:
        - (a) Concentrating effect – As gas is taken up by pulmonary blood, the gas remaining is in a smaller alveolar volume, thereby diminishing the change in F_A that might otherwise be expected. At a higher F_I, this effect is more pronounced resulting in an increased rise in F_A relative to the rise in F_I
        - (b) Augmented inflow effect – As gas is taken up by pulmonary blood, more gas is brought into the lungs to replace the lost volume and prevent alveolar collapse. This increases alveolar ventilation, which retards the effect of uptake on lowering F_A
    - This effect applies MAINLY to N_2O as it is the only inhaled agent that can be used at a sufficiently high F_I (due to its low potency/MAC)
- Factors that affect inspired gas concentration (F_I):
    - F_I is NOT the same as the "fresh gas concentration" set on the vapouriser as the inhaled anaesthetic gas is mixed with other gases in the breathing circuit before being delivered to the patient
    - Therefore, F_I depends on:
        - (a) Fresh gas flow rate, which is determined by:
            - (i) Fresh gas concentration set on the vapouriser
            - (ii) Flow meter setting of other gases (Eg. O_2, air, N_2O)
        - (b) Characteristics of the anaesthetic circuit:
            - (i) Volume of the circuit
            - (ii) Absorption of inhaled agent by the circuit (Eg. methoxyflurane is absorbed by rubber tubing; sevoflurane is absorbed by soda lime CO_2 absorber)
    - F_I approximates "fresh gas concentration" (and thus resulting in faster induction/emergence times) with:
        - (a) Higher FGF rates
        - (b) Smaller breathing system volumes
        - (c) Minimal absorption by the machine/circuit (Eg. keeping CO_2 absorbers moist and cold, using agents not absorbed by rubber tubing)

(2) Alveolar ventilation (V_{ALV})

- (a) Increasing V_{ALV} increases F_A and the F_A/F_I ratio (Ie. attenuates uptake of agent by pulmonary blood), thereby leading to more rapid induction/emergence
    - This has more prominent effects for soluble agents (Eg. halothane, ether) than for insoluble agents (Eg. N_2O). This is because:
        - (i) Soluble agents have a lower F_A/F_I ratio than insoluble agents, and thus have a greater ability to increase their F_A and F_A/F_I ratio
        - (ii) The effects of hyperventilation at reducing CBF is matched or exceeded by the rises in F_A and F_A/F_I ratio for soluble agents (Nb. the rise in F_A and F_A/F_I ratio for insoluble agents are so small such that the effects of reduced CBF by hyperventilation actually causes a slower induction time)



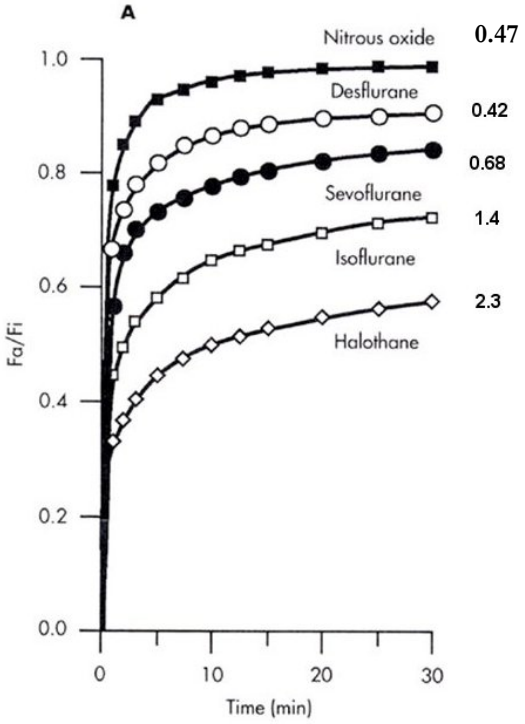
    - In a spontaneously ventilating patient, inhaled anaesthetic agents have a –ve feedback effect on ventilatory drive:
        - As the patient is breathing in an inhaled agent, the rate of rise in F_A and F_A/F_I ratio slows down because agent depresses ventilatory drive and decreases V_{ALV}, such that the patient becomes apnoeic when F_A approaches F_I (F_A/F_I ratio ~ 1.0)
        - Apnoea causes F_A and F_A/F_I ratio to fall, thus resulting in loss of the inhibition on ventilatory drive by the inhaled agent. This causes resumption of spontaneous ventilation and a return to a rise in F_A and F_A/F_I ratio again as the agent is breathed in
- (b) A smaller FRC will result in a larger F_A (and F_A/F_I ratio) than a larger FRC due to a smaller dilutional effect by alveolar/airway gases at FRC. This leads to more rapid induction/emergence

Phase II: Transfer of inhaled anaesthetic agent from alveoli to pulmonary blood

(1) Blood-gas partition coefficient (BGPC)

- BGPC is defined as the ratio of gas concentration in blood to alveolar gas at equilibrium, which occurs when the partial pressures and volumes are equal between the two phases at 37 °C
- It is a measure of the solubility of an inhaled agent in blood
- It is the MAIN determinant of uptake of the agent by pulmonary blood (Ie. influences F_A and F_A/F_I ratio) and thus the MAIN factor affecting induction/emergence rate of an inhaled agent:
    - Agents with a lower BGPC (Eg. N_2O, desflurane) are less soluble in pulmonary blood and thus have less uptake in pulmonary blood. This leads to a higher F_A (with F_A/F_I ratio → 1), which results in faster induction/emergence

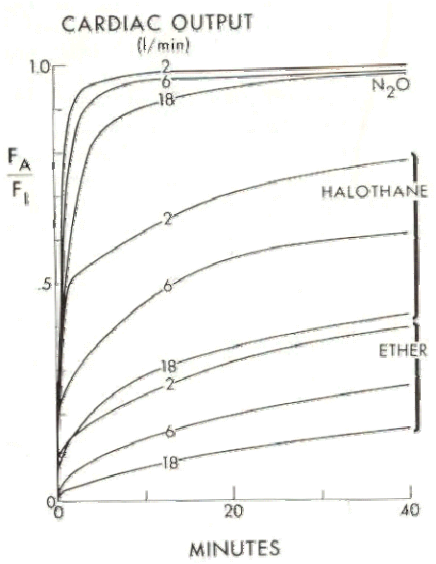
- Agents with a higher BGPC (Eg. halothane, ether) are more soluble in pulmonary blood and thus have more uptake in pulmonary blood. This leads to a lower F_A (with F_A/F_I ratio → 0), which results in slower induction/emergence
- Note: Regarding the uptake curves for N_2O and desflurane – Despite its low BGPC, F_A for desflurane does not approach F_I as quickly as N_2O because of (i) Concentration effect with N_2O, and (ii) Relative lack of tissue uptake of N_2O



- BGPC for an agent can be altered by certain factors:
  - Age – BGPC increases with age
  - Body habitus – Obesity decreases BGPC
  - Haematocrit – BGPC decreases with haemodilution (Ie. 20% less when Hcrt 21%)
  - Albumin – BGPC decreases with hypoalbuminaemia
  - Temperature – Hypothermia causes increased BGPC
  - Fasting status – BGPC increases post-prandially

(2) Pulmonary blood flow

- Pulmonary blood flow influences the rate at which an inhaled agent is removed from the alveoli. As a result, as pulmonary blood flow EQUALS cardiac output (assuming there is no pulmonary shunting), then:
  - High C.O. results in increased uptake of the agent by pulmonary blood, thereby causing in a fall in F_A and F_A/F_I ratio. This produces slower rates of induction/emergence
  - Low C.O. results in decreased uptake of the agent by pulmonary blood, thereby causing a rise in F_A and F_A/F_I ratio. This produces faster rates of induction/emergence
- The effect of C.O. on uptake is influenced by two factors:
  - (a) BGPC of the inhaled agent – The effect of C.O. on uptake is more significant with soluble agents (Ie. high BGPC) because of the larger amounts of soluble agents can be taken up by alveolar blood flow
  - (b) Distribution of C.O. – If cerebral perfusion is reduced during a low C.O. state, then the induction/emergence rate will remain slow despite reduced uptake (Ie. high F_A and F_A/F_I ratio). If cerebral perfusion is maintained, however, then a low C.O. state will translate into faster induction/emergence rates



- Inhaled anaesthetic agents have a <u>+ve feedback effect on low C.O. states</u>:
    - Low C.O. leads to increased F_A and F_A/F_I of inhaled agents (esp soluble agents) and more rapid onset of the CVS-depressant effect of the agent
    - This inhaled agent-induced CVS depression further attenuates C.O. and feedbacks +vely on the uptake of the agent

(3) <u>Alveoli-venous partial pressure difference</u>

- <u>$P_{GRADIENT}$ of the inhaled agent between alveoli and MVB</u> will affect the rate of uptake (and rate of induction):
    - At the <u>start of induction</u>, $P_{INHALED\ AGENT}$ in MVB is zero but rises rapidly with uptake due to the large $P_{GRADIENT}$ – This causes the $P_{GRADIENT}$ to fall rapidly, resulting in <u>rapid rises in F_A and F_A/F_I (Ie. faster induction)</u>
    - <u>Later in induction</u>, $P_{INHALED\ AGENT}$ in MVB approaches that in alveoli – $P_{GRADIENT}$ approaches zero, resulting in <u>slower rises in F_A and F_A/F_I</u>
- The $P_{INHALED\ AGENT}$ in MVB (and the $P_{GRADIENT}$ between MVB and alveoli) is influenced by the <u>rate of tissue uptake of the inhaled agent from arterial blood</u> (Eg. by brain, muscle, fat, Etc.)

<u>Phase III: Transfer of inhaled anaesthetic agent from arterial blood to tissues</u>

(1) <u>Tissue-blood partition coefficient (TBPC)</u>

- TBPC is defined as the ratio of gas concentration in tissue (Eg. brain, fat, skin, muscle, Etc.) to blood at equilibrium, which occurs when the partial pressures and volumes are equal between the two phases at 37 °C
- It describes the <u>capacity for tissues to hold an inhaled anaesthetic agent</u>, and thus determines the <u>time for equilibrium of the agent between tissue and blood</u>
- Types of tissue groups:
    - (i) <u>Vessel-rich groups</u> (Eg. brain, heart, liver, kidney), <u>muscle and skin</u> – <u>TBPC is ~ 1</u>. Thus, the rate of rise in partial pressure (and concentration) in these tissues is directly proportional to the arterial-tissue tension gradient
    - (ii) Fat – <u>TBPC is ~ 20</u>. Thus, the partial pressure (and concentration) in lipid tissues is much higher than in blood, even before equilibrium is reached
    - (iii) <u>Vessel-poor group</u> – <u>TBPC ~ 0</u>, hence at equilibrium a negligible amount of inhaled agent is stored in this group

(2) <u>Tissue-blood flow</u>

- (i) <u>Vessel-rich group</u> (heart, brain, kidney, liver) – Well-perfused (75 mL/min/100 g) and receives large % of C.O. (75%)

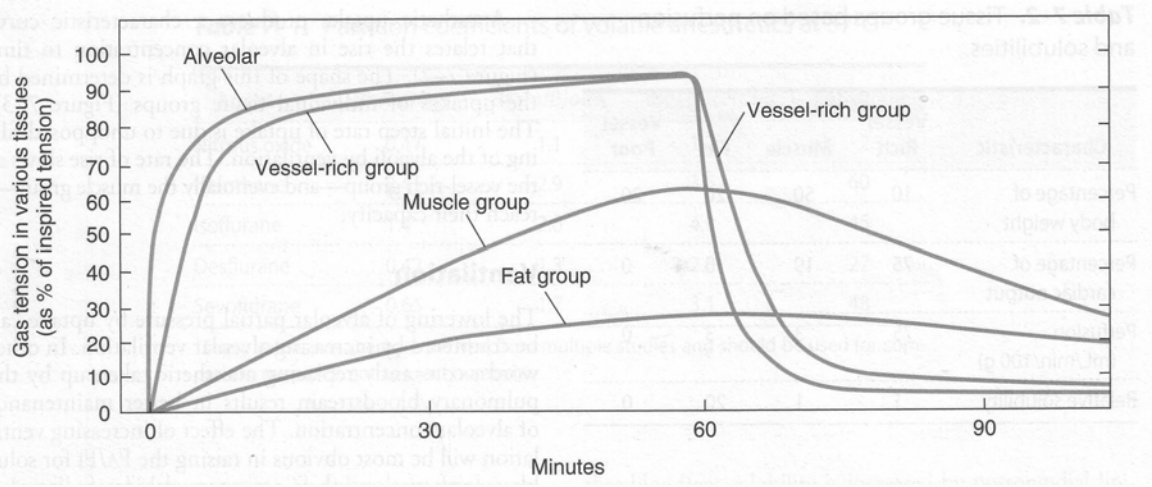
- (ii) Muscle and skin – Not as well perfused as VRG (3 mL/min/100 g) but receives a sizeable % of C.O. (19%)
- (iii) Fat – Equally perfused as muscle (3 mL/min/100 g) but receives less % of C.O. (6%)
- (iv) Vessel-poor group – Receives negligible perfusion and % of C.O.

(3) Arterial-tissue partial pressure difference

As a result of these factors, the uptake and distribution of inhaled agents will be influenced by the types of tissues found in the body:

- (i) Highly perfused vessel-rich group (Eg. brain, heart, liver, kidney),
    - First to take up inhaled agents on induction (and first to release agents on emergence) due to their high perfusion and % C.O. received
    - First to fill up on inhaled agents on induction (and first to be depleted of agent on emergence) due to the low % body weight (Ie. low capacity volume) and moderate TBPC (Ie. average solubility)
    - It takes 3-10 minutes to fill up (and empty) VRG with an agent
- (ii) Muscle, fat and skin
    - Delay in taking up inhaled agents on induction (and delay on releasing agents during emergence) due to lower perfusion and % C.O. received
    - Very slow to fill up on inhaled agents on induction (and very slow to be depleted of agent on emergence) due to large capacity volume of muscle and fat (70% body weight combined) and high TBPC of fat
    - It takes 1-4 hours to fill up (and empty) muscle with an agent, but < 5 days to fill up (and empty) fat with an agent – This is why **absorption of agent into muscle/fat plays a MAJOR role in delaying emergence**
- (iii) Vessel-poor group (Eg. bones, ligament, teeth, Etc.) have insignificant uptake

Characteristics	Vessel rich	Muscle	Fat	Vessel poor
% body weight	10	50	20	20
% C.O.	75	19	6	0
Perfusion (mL/min/100g)	75	3	3	0
Relative solubility (combination of blood-brain, -muscle, fat- PC)	1	1	20	0
Equilibrium time	3-10 min	1-4 hrs	< 5 days	0



Factors affecting arterial concentration (F_a) of inhaled agent:

- Effect of dead space:

    - Produces an increased arterial-end tidal partial pressure gradient for the inhaled agent
    - However, assuming that perfused alveoli have a normal level of ventilation, then the rate of rise in F_A of the agent (and hence the rate of induction) should remain unchanged
- Effect of shunt:
    - Produces a delayed increase in arterial partial pressures of the agent
    - This effect is more prominent for insoluble anaesthetic gases (cf. soluble gases):
        - For insoluble gases, increased ventilation of ventilated alveoli can only deliver slightly more of the insoluble agent to the lungs, and is thus not enough to compensate for unventilated alveoli
        - For soluble gases, increased ventilation of ventilated alveoli is adequate to compensate for lack of gas transport in the shunted blood

(e) ***To describe factors that affect recovery from inhalational anaesthesia. To compare induction and recovery.***

Factors that determine the rate of induction of anaesthesia with an inhaled agent:

- With induction during inhalational anaesthesia, there is a diffusion gradient in partial pressure of the inhaled anaesthetic gas from the alveolus to the brain

$$P_{ALVEOLAR} \rightarrow P_{ARTERIAL\ BLOOD} \rightarrow P_{BRAIN}$$

- The rate of induction of anaesthesia is determined by the size of this $P_{GRADIENT}$ between the alveolus and the brain:
    - A large $P_{GRADIENT}$ between alveolus and brain results in a more rapid induction rate of anaesthesia – This is achieved MAINLY by rapidly increasing the $P_{ALVEOLAR}$ of the agent
    - An increase in $P_{ALVEOLAR}$ of the agent occurs as a result of rapid rises in F_A of the agent towards F_I (as F_A is proportional to $P_{ALVEOLAR}$ of an agent), and an increased F_A/F_I ratio of the agent (which indicates less uptake by pulmonary blood)
- As a result, the factors that increase the rate of induction include:
    - (1) Low BGPC (MAIN factor)
    - (2) Low C.O. (esp for soluble agents), although this is influenced by the effect of low C.O. on distribution of blood to CBF
    - (3) High alveolar ventilation (esp for soluble agents), although this is influenced by the attenuating effects of hyperventilation on cerebral blood flow
    - (4) Small FRC
    - (5) High F_I of anaesthetic gas
        - Concentration effect/second gas effect with N_2O
        - Increasing FGF rates, fresh gas concentration, low volume circuit, low absorption by the circuit/machine, eliminating rebreathing of mixed gases
    - (6) High cerebral blood flow
    - (7) High brain:blood partition coefficient

> Note that factors anaesthetists can alter include:
> - (i) Alveolar ventilation
> - (ii) Choice of inhaled agent (influences BGPC and BBPC)
> - (iii) F_I (by fresh gas conc, FGF rates, use of N_2O for concentration/second gas effect)

Factors that determine the rate of recovery from anaesthesia with an inhaled agent:

- With recovery from inhalational anaesthesia, there is a lowering of the [inhaled agent] from the brain by three mechanisms:
    - (1) Biotransformation
        - All inhalational agents (EXCEPT N_2O and Xe) undergo biotransformation by CYP450 enzymes
            - Predominantly by hepatic CYP450 (especially 2E1 isoform), but also some renal CYP450
            - Involves oxidation and dehalogenation – Metabolise C-halogen bonds to release the halogen (F^-, Cl^-, Br^-)
            - Lead to production of toxic agents:
                - Trifluoroacetic acid (hepatotoxic) – Halothane >> Isoflurane, Desflurane (none with sevoflurane)
                - Inorganic fluoride (nephrotoxic and hepatotoxic) – All volatile agents (esp with methoxyflurane)
        - The extent of this biotransformation process is influenced by:

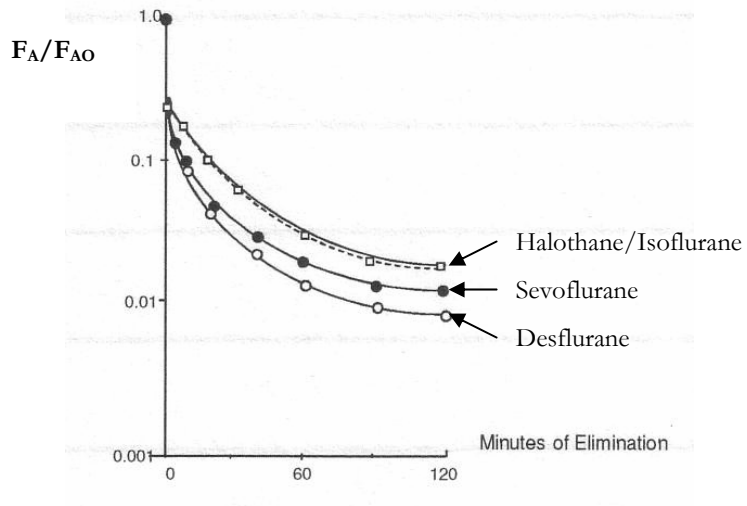
- (i) Agent's lipid solubility (or OGPC) – Degree of biotransformation is proportional to the agent's solubility
- (ii) Chemical structure of the agent
  - Type of C-halogen bonds – C-F > C-Cl > C-Br in terms of stability
  - Number and position of C-halogen bonds

Agent	% biotransformation
Methoxyflurane	50%
Halothane	20%
Sevoflurane	5%
Enflurane	2%
Isoflurane	0.2%
Desflurane	0.02%
Xenon, N_2O, Ether	0%

- (2) Transcutaneous loss (insignificant)
- (3) Exhalation of agent from the lung (MOST important route)
  - The diffusion gradient in partial pressure is reversed such that gradient goes from the brain to the alveolus

$$P_{BRAIN} \rightarrow P_{ARTERIAL\ BLOOD} \rightarrow P_{ALVEOLAR}$$

  - The rate of recovery is determined by the size of this $P_{GRADIENT}$ between the brain and the alveolus:
    - A large $P_{GRADIENT}$ between the brain and alveolus results in a more rapid emergence rate from anaesthesia – This occurs MAINLY by rapidly decreasing the $P_{ALVEOLAR}$ of the agent
    - This occurs as a result of rapid falls in "expired fractional concentration of agent" (F_A) from "expired concentration at time zero" (F_{AO}) – Ie. small F_A/F_{AO} ratio



  - As a result, the factors that increase the rate of emergence through elimination of the inhaled agent via the lungs are the SIMILAR as for the factors that increase induction rate. The differences, however, are as follows:
    - (a) Length of administration and lipid solubility of the agent
      - With brief use of an inhalational agent, the recovery rate is FASTER than induction – This is due to redistribution of the agent from the alveoli and saturated/well-perfused

organs (Eg. VRG) to other high capacity tissues (Eg. muscle and fat)
    - With prolonged use of an inhalational agent, the recovery rate may be SLOWER than induction, ESPECIALLY if the agent's OGPC is high (Ie. very lipid soluble) – This is due to delayed redistribution of the agent from high capacity tissues (Eg. muscle, fat, skin) back into blood at subanaesthetic doses
- (b) Lack of concentration effect – This is because the high [N_2O] is not being drawn from an infinite reservoir as it was on induction

(f) ***To describe the properties of an ideal inhalational anaesthetic agent.***

The properties of an ideal inhaled anaesthetic agent are as follows:

- (1) Preparation:
    - Easily administered by standard vapouriser
    - Boiling point above ambient temperature (Ie. liquid at room temperature to permit easy storage)
    - Low latent heat of vapourisation and specific heat
- (2) Physico-chemical properties:
    - Stable to heat and light (thus allowing long shelf-life)
    - Inert when in contact with metal, rubber and soda lime
    - Preservative free
    - Not flammable or explosive
    - Pleasant odour and non-irritating to airways
    - Atmospherically friendly
    - Cheap and easily manufactured
- (3) Pharmacokinetic properties:
    - High oil-gas partition coefficient (high lipid solubility causes a low MAC, which means higher potency)
    - Low blood-gas partition coefficient (means more rapid onset/offset)
    - Not metabolised in the body (especially by liver/kidney)
    - Eliminated completely and rapidly by the lungs
- (4) Pharmacodynamic properties:
    - High therapeutic index
    - Predominantly affects the CNS (causing unconsciousness/anaesthesia) and has minimal depressive effects on CVS and respiratory systems
    - Not epileptogenic and does not raise ICP
    - Possesses some analgesia properties and skeletal muscle relaxant properties
    - Non-toxic (esp with chronic low-level exposure to theatre staff)
    - Minimal unwanted side-effects (Eg. PONV, cardiac arrhythmogenicity, renal toxicity)
    - Does not interact with other commonly used anaesthetic agents (Eg. pressor agents)
    - Sufficiently potent to allow the use of high FIO_2 (as necessary)

Unfortunately, no inhaled anaesthetic agent has all these properties.

However, the need for an ideal inhaled agent has been eliminated because:

- IV drugs are available, such as ultrashort-acting IV anaesthetic agents, potent opioid analgesics with short duration of action and specific muscle relaxants
- Concurrent use of IV anaesthetic agents allows a lower concentration of an inhaled agent to be used, thus making the safety margin of an inhaled agent less of an issue

Minimum Alveolar Concentration:

Definition of Minimum Alveolar Concentration (MAC):

- Defined as the minimum alveolar concentration of an inhaled agent at equilibrium at 1 atmosphere and FIO_2 of 100% that prevents movement in response to a surgical stimulus (Eg. 1 cm deep x 1 cm wide skin incision on ventral aspect of forearm) in 50% of patients
- It is measured by its end-tidal [ ] as a "fractional volume":

$$\% \text{ volume of inhaled agent} = (P_{ALVEOLAR} \text{ of inhaled agent}) / (P_{BAROMETRIC})$$

MAC of commonly used inhalational agents:

Agent	MAC (%)
N_2O	105
Xenon	71
Desflurane	6
Sevoflurane	2.05
Diethyl ether	1.9
Enflurane	1.68
Isoflurane	1.15
Halothane	0.75

Implications of MAC:

- (1) Individual variability of MAC is small, and MAC is invariant with a variety of noxious stimuli
- (2) MAC (and alveolar concentration) is an indirect measure of the anaesthetic effect of an inhaled agent:
    - Anaesthetic effect of inhaled agents (Ie. unconsciousness) is determined by the concentration of the inhaled agent at the brain, which is proportional to the brain partial pressure of the agent
    - Alveolar concentration (as end-tidal [ ] in % volume) is easily measured, and is proportional to the alveolar partial pressures of the inhaled agent
    - A diffusion gradient in partial pressure of an inhaled agent exists between the alveolus and the brain ($P_{ALV} > P_{ARTERIAL} > P_{BRAIN}$). But at steady-state, the alveolar partial pressures of the inhaled agent will equilibrate with and closely mirror the partial pressure of the agent at the brain ($P_{ALV} \approx P_{ARTERIAL} \approx P_{BRAIN}$)
    - Thus, MAC (and alveolar concentration) is indirectly used as a measure of anaesthetic effect for an inhaled agent
- (3) MAC is a measure of potency:
    - MAC value of an inhaled agent is inversely related to its potency (Eg. lower value of 1 MAC means more potent inhaled agent)
- (4) MAC allows comparison of potency between inhalational agents:
    - 1.0 MAC of one agent is equipotent in its anaesthetic effects (Ie. CNS depression) to 1.0 MAC of another agent
    - MAC multiples can be used to compare the dose-response curves of various inhalational agents ASSUMING the curves are parallel, straight and continuous for the physiological effect being measured
    - Levels of physiological effects other than CNS depression (Eg. myocardial depression, respiratory depression, Etc.) may differ between equal MAC values of different agents
- (5) Multiples of MAC represent points on a dose-response curve, whereby each multiple has clinical significance in anaesthesia:
    - 1.5 MAC (MAC_{BAR}) – Alveolar concentration whereby 50% of patients will have a blunted ANS response (such as a rise in HR/BP) to surgical stimulus. Anaesthesia

at MAC_{BAR} attenuates the stress response to surgery, which is useful in reducing the incidence of certain complications (Eg. AMI, arrhythmias, CVA, Etc.)
    - 1.3 MAC (MAC_{SUPER})– Alveolar concentration whereby movement is prevented in 95% of patient in response to a surgical stimulus (= ED_{95})
    - 1.0 MAC – Alveolar concentration whereby movement is prevented in 50% of patients in response to a surgical stimulus (= ED_{50})
    - 0.6-0.8 MAC – Alveolar concentration whereby most patients will have a loss of awareness
    - 0.3-0.4 MAC (MAC_{AWAKE}) – Alveolar concentration whereby 50% of patients will be awaken from anaesthesia (Ie. open eyes to verbal sitmulus). This MAC level has a role in performing extubation safely (Nb. although airway reflexes resume at 0.1 MAC), and to reduce incidence of intraoperative awareness
- (6) MAC values of different agents are additive (Eg. 0.5 MAC of N_2O (53%) + 0.5 MAC of halothane (0.37%) = 1 MAC)
- (7) Other relevant MAC values:
    - MAC-Hour – Determined by "MAC x duration of anaesthesia (in hrs)". This allows assessment of cumulative toxicity of inorganic fluoride, and to be able to compare this with other agents
    - MAC-N_2O – Using 70% N_2O will reduce the MAC of volatile agents by ~ 60%

Variability of MAC values:

Factor	Decreases MAC	Increases MAC
Age	(1) Increasing age (6% decrease in MAC per decade) (2) Neonatal period	Infancy (peaks at 6 months, then declines thereafter)
Temperature	(1) Hypothermia (2) Hyperthermia (T < 42 °C)	Hyperthermia (T > 42 °C)
Blood pressure	Hypotension (MAP < 40 mmHg)	
PaO_2	PaO_2 < 40 mmHg	
$PaCO_2$	$PaCO_2$ > 95 mmHg	
Patient state	(1) Pregnancy (decreases MAC by 33% at 8/40; normalises 3 days post-partum) (2) Anaemia (Hcrt < 10%) (3) Hyponatraemia (4) Hypercalcaemia (5) Cardiopulmonary bypass	Hypernatraemia
Drugs and alcohol	(1) Acute EtOH intoxication (2) Acute opioid use (3) Chronic amphetamine use (4) Induction agents/sedatives (barbiturates, benzodiazepines, ketamine) (5) Pancuronium (6) Local anaesthetics (7) Sympatholytics (clonidine, methyldopa, dexmedetomidine) (8) Verapamil (9) Lithium	(1) Chronic EtOH abuse (2) Chronic opioid use (3) Acute amphetamine use (4) Sympathomimetics (ephedrine, cocaine, L-DOPA) (5) Catecholamines (NAd, Adr)
Atmospheric pressure	High atmospheric pressures	Low atmospheric pressures

MAC is NOT affected by:
- Thyroid gland dysfunction (Eg. hyper- or hypothyroidism)
- Gender

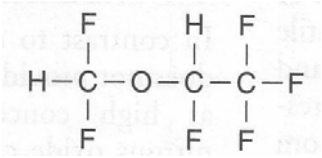
- Body surface area
- Duration of anaesthesia
- Potassium levels

(g) ***To describe the structure-activity relationships of inhalational agents.***
(h) ***To describe the pharmacology of nitrous oxide. To give a detailed account of its potential adverse effects.***
(i) ***To describe the comparative pharmacology of nitrous oxide, halothane, enflurane, isoflurane, desflurane, sevoflurane, xenon and ether.***
(j) ***To describe the cardiovascular effects of the inhalational agents.***
(k) ***To describe the central nervous system effects of the inhalational agents.***
(l) ***To describe the respiratory effects of the inhalational agents.***
(m) ***To describe the toxicity of the inhalational agents.***

Desflurane:

Use: Generally used for the maintenance of GA

Structure: Fluorinated ethyl methyl ether



Nb. Similar to isoflurane – Substitution of fluorine atom for chlorine atom

Physical properties:

Property		Value	Significance
Molecular weight		168	
MAC		6.0	Less potent than most other volatile agents
Induction dose		4-11%	
Maintenance dose		2-6%	
Partition coefficient	BGPC	0.42	Lowest B-G solubility coefficient – Rapid induction and recovery
	OGPC	18.7	Lower than most volatile agents, meaning lower potency, lower hepatic metabolism, and lower distribution to fat
	Brain	1.3	
	Muscle	2.0	
	Fat	27	
Vapour pressure at 20°C		88.5 kPa (681 mmHg)	Requires a special vapouriser that heats the agent up to 39 °C at 2 atm. At high altitudes, it boils at room temperature.
Boiling point		22.8 °C	

Pharmacodynamic effects:

Cardiovascular effects		
HR	- At 1.0 MAC, mild rise in HR due to ANS reflex (preserved BRR) 2° to fall in MAP/C.O. - With rapid increases in F_I or MAC > 1.25, transient tachycardia with catecholamine release	↑/nc
C.O.	At 1.0 MAC, unchanged to slightly depressed – Myocardial contractility decreased, but compensated by mild rise in HR (due to BRR)	↓/nc
MAP	- Dose-dependent fall in MAP due to (i) Fall in SVR and (ii) Slight depression in C.O. - With rapid increases in F_I or MAC > 1.25, transient hypertension with catecholamine release	↓↓
SVR	Dose-dependent decrease in SVR due to peripheral	↓↓

	vasodilation	
Pulmonary vascular resistance	Decreased due to attenuation of hypoxic induced pulmonary vasoconstriction	↓
CVP	Increased	↑
Arrhythmogenic effects	- Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome) - Myocardium not sensitised to arrhythmogenic effects of Adr	Nil
Coronary blood flow	Unchanged	n/c
Cardiac metabolic rate of O_2 consumption	Decreased	↓
Presence of "ischaemic preconditioning"	Present	
Respiratory effects		
RR	Dose-dependent increase	↑
TV	Dose-dependent decrease	↓
MV	Dose-dependent decrease	↓
Resting $PaCO_2$	Increased	↑
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Depressed (increased apnoeic threshold)	↓
Ventilatory response to PaO_2	Ventilatory responses to hypoxia are blunted at 0.1 MAC (by 50%), but especially > 1 MAC (by 100%)	↓↓↓
Effect on airways	- AW irritant and pungeant odour causes salivation, breath-holding, coughing, and broncho- and laryngospasms (esp in smokers), esp at high concentrations (> 6%) – Thus, not ideal for gaseous induction - UAW responses impaired - Impaired mucociliary response - Increased mucous secretions	
Pulmonary vasculature	Impaired hypoxic pulmonary vasoconstriction (leads to V/Q mismatching)	
CNS effects		
General anaesthesia and analgesia	- Dose-dependent CNS depression from amnesia, to sedation, to hypnosis then GA - Minimal analgesia	
CBF	- At < 0.5 MAC, CBF autoregulation is preserved - At > 0.5 MAC, dose-dependent rise in CBF due to cerebral vasodilation that can be reversed by hyperventilation	↑↑
ICP	- At > 0.5 MAC, dose-dependent rise in ICP due to increases in CBF (Nb. this can be reversed by hyperventilation) - Thus, desflurane is NOT ideal for neurosurgical patients or those with raised ICP	↑↑
Cerebrovascular responsiveness to $PaCO_2$	Intact (so CBF and ICP can be lowered by hyperventilation)	Ok

$CMRO_2$	- Dose-dependent decline in $CMRO_2$ (similar to isoflurane) - Uncoupling of $CMRO_2$ from CBF causes "luxury perfusion" (Ie. neuroprotection form potential ischaemic insult)	↓↓↓
EEG/seizure activity	- EEG activity shows an initial increase in frequency (α waves), then a dose-dependent decrease in frequency (θ → δ waves), with eventual burst suppression and electrical silence (esp at > 2 MAC) - Nb. electrical silence is useful during cerebral ischaemia - Not epileptogenic. It increases seizure threshold	↓↓↓
CSF production	Nil	n/c
Skeletal muscle effects		
- Skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)		↑↑↑
Renal effects		
- Dose-dependent decreases renal blood flow, GFR and urine output (due to fall in C.O. and renal afferent arteriolar VC)		↓
Hepatic effects		
- Total HBF and hepatic O_2 delivery are maintained due to "hepatic arterial buffer mechanism (Ie. PV flow decreases but is compensated for by increased HA flow due to dilation of HA)		n/c
Uterine effects		
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow		↓↓
Toxicities		

- (1) With rapid increases in F_I or MAC > 1.25, causes transient rises in HR, BP and catecholamine release
  - An issue in patients with CVS disease (Eg. IHD)
  - Avoiding desflurane as an induction agent in these patients
  - Following IV induction, give desflurane at 4-6% with fresh gas flows of 3-5 L/min. Then gradually increase it by < 1% every few breaths until desired anaesthetic depth reached. Then FGF can be decreased to 1 L/min
  - Fentanyl, Esmolol or Clonidine can be used to attenuate these CVS effects
- (2) AW irritant and pungeant odour causes salivation, breath-holding, coughing, and broncho- and laryngospasms (esp in smokers), esp at high concentrations (> 6%)
- (3) Carbon monoxide poisoning
  - Desflurane is most likely than other volatile agents to be degraded by desiccated alkali CO_2 absorbents (esp baralime > sodalime) into CO
  - Factors increasing CO production (apart from agent used):
  - (i) High absorber temperature
  - (ii) Desiccated baralyme absorbent – There is ~ 13-15% water content in CO_2 absorbent. Up to 90% of this water must be removed before any CO is produced (Nb. Baralyme produces more CO for a given water content than soda-lime)
- (4) Potential to cause autoimmune hepatic injury as trifluoroacetic acid is produced
- (5) No renal toxicity due to relative absent production of inorganic fluoride
- (6) Risk of malignant hyperthermia		

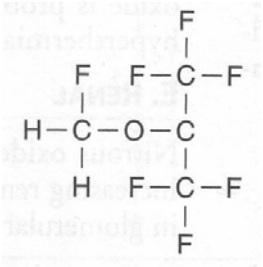
- (7) Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome)
- (8) PONV

Metabolism and Elimination:
- Minimal metabolism (0.02%) by hepatic CYP 450 2E1 to trifluoroacetic acid (mainly) and inorganic fluoride (minor)
- Mainly eliminated via the lungs

Sevoflurane:

Use: Induction and/or maintenance of GA

Structure: Polyfluorinated isopropyl methyl ether



Physical properties:

Property		Value
Molecular weight		200
MAC		2.05
Induction dose		5-7%
Maintenance dose		0.5-3%
Partition coefficient	BGPC	0.69
	OGPC	53
	Brain	1.7
	Muscle	3.1
	Fat	48
Vapour pressure at 20°C		21.3 kPa (160 mmHg)
Boiling point		58.6 °C

Pharmacodynamic effects:

Cardiovascular effects		
HR	Unchanged (or very mild rise) due to blunting of BRR	n/c
C.O.	Fall in C.O. (unlike isoflurane/desflurane) due to (i) Mild depression in myocardial contractility, and (ii) No change in HR	↓
MAP	Dose-dependent fall in MAP due to fall in (i) SVR and (ii) C.O. (less than isoflurane/desflurane)	↓
SVR	Dose-dependent fall due to vasodilation (less than isoflurane/desflurane)	↓
Pulmonary vascular resistance	Decreased due to attenuation of hypoxic induced pulmonary vasoconstriction	↓
CVP	Increased	↑

Arrhythmogenic effects	- Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome) - Myocardium not sensitised to arrhythmogenic effects of Adr (unlike halothane)	Nil
Coronary blood flow	Unchanged	n/c
Cardiac metabolic rate of O_2 consumption	Decreased	↓
Presence of "ischaemic preconditioning"	Present	
Respiratory effects		
RR	Dose-dependent increase	↑
TV	Dose-dependent decrease	↓
MV	Dose-dependent decrease	↓
Resting $PaCO_2$	Increased	↑
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Depressed (increased apnoeic threshold)	↓
Ventilatory response to PaO_2	Ventilatory responses to hypoxia are blunted at 0.1 MAC (by 50%), but especially > 1 MAC (by 100%)	↓↓↓
Effect on airways	- Relaxes bronchial SM (causes bronchodilation, and thus useful for bronchospasms) - Non-pungent and non-irritable – Given its decent MAC and low BGPC, it is commonly used as an inhalational induction agent (given at 5-7% in 50% mixture of N_2O and O_2. Induction takes 1-3 minutes) - UAW responses impaired - Impaired mucociliary response - Increased mucous secretions	
Pulmonary vasculature	Impaired hypoxic pulmonary vasoconstriction (leads to V/Q mismatching)	
CNS effects		
General anaesthesia and analgesia	- Dose-dependent CNS depression from amnesia, to sedation, to hypnosis then GA - Minimal analgesia	
CBF	- At < 1.5 MAC, CBF autoregulation is preserved - At > 1.5 MAC, dose-dependent rise in CBF due to cerebral vasodilation that can be reversed by hyperventilation (Ie. fall in $PaCO_2$)	↑
ICP	- At > 1.5 MAC, dose-dependent rise in ICP due to increases in CBF (Nb. this can be reversed by hyperventilation) - Suitable for neurosurgical patients and those with raised ICP	↑
Cerebrovascular responsiveness to $PaCO_2$	Intact (so CBF and ICP can be lowered by hyperventilation)	Ok
$CMRO_2$	- Dose-dependent decline in $CMRO_2$ similar to isoflurane - Uncoupling of $CMRO_2$ from CBF causes "luxury	↓↓↓

	perfusion" (Ie. neuroprotection form potential ischaemic insult)	
EEG/seizure activity	- EEG activity shows an initial increase in frequency (α waves), then a dose-dependent decrease in frequency (θ → δ waves), with eventual burst suppression and electrical silence (esp at > 2 MAC) - Nb. electrical silence is useful during cerebral ischaemia - Not epileptogenic. It increases seizure threshold	↓↓↓
CSF production	Nil	n/c
Skeletal muscle effects		
- Skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)		↑↑↑
Renal effects		
- Dose-dependent decreases renal blood flow, GFR and urine output (due to fall in C.O. and renal afferent arteriolar VC)		↓
Hepatic effects		
- Total HBF and hepatic O_2 delivery are maintained due to "hepatic arterial buffer mechanism (Ie. PV flow decreases but is compensated for by increased HA flow due to dilation of HA)		n/c
Uterine effects		
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow		↓↓
Toxicities		

- (1) Renal toxicity
  - Inorganic fluoride (F^-)
    - 5% of sevoflurane is metabolised by hepatic CYP450, which produces nephrotoxic inorganic fluoride (F^-). However, peak levels of F^- are generally < 50 umol/L (unlike methoxyflurane), thus renal toxicity is unlikely
    - Of note, sevoflurane use can be associated with peak plasma [F^-] > 50 umol/L, BUT this still does not produce renal toxicity (unlike with methoxyflurane) – This is because sevoflurane is less soluble and chemically stable cf. methoxyflurane, and thus does not last long enough in the body to undergo renal CYP450 metabolism. As a result, intrarenal [F^-] remains low
  - Compound A (and compounds B to E)
    - Alkali-based CO_2 absorbers (sodalime/baralyme) degrade sevoflurane into Compound A (and B to E), which is a nephrotoxin found to be produced mainly in lab rat
    - Production of compound A is enhanced in the presence of:
      - (i) Low FGF (due to increased absorber temperature and desiccation)
      - (ii) Increased absorber temperature (due to low FGF or high CO_2 output)
      - (iii) Prolonged and/or high concentration use of sevoflurane
      - (iv) Type of absorbent and level of desiccation
        - Dehydration of sodalime and baralime increases both production and degradation of compound A

        - Dry baralyme produces MORE compound A than dry sodalime – This is because production of compound A exceeds degradation with dry baralyme, while degradation exceeds its production with dry sodalime
        - Nb. Compound A can be made even when the absorbent is not dry!
    - In humans, there is no evidence of nephrotoxicity with sevoflurane:
        - (i) Prolonged low flow sevoflurane (0.25 mL/min x 5 hrs) produces < 20 ppm (Nb. nephrotoxic dose of compound A is 150-200 ppm)
        - (ii) Toxicity in rats is due to β-lyase activity (forms thiol from compound A) – Humans have < 10% enzyme activity cf. rats
    - Despite this (and to minimise renal toxicity):
        - (i) Avoid using sevoflurane in patients with renal disease
        - (ii) Avoid use of baralyme with sevoflurane
        - (iii) If sevoflurane is to be used for prolonged periods, use FGF > 2 L/min
- (2) Production of HF, which causes acid burns of respiratory mucosa:
    - The presence of metal, glass and impurities can cause sevoflurane to release HF – This is because these impurities act like Lewis acids (substances that accept electron pairs) and attack the ether and halogen bonds of sevoflurane to release HF
    - This is why sevoflurane is packed in (i) Water (as water is a Lewis acid inhibitor), and (ii) Plastic containers (plastic is not a Lewis acid)
- (3) Minimal risk of hepatic injury due to absence of TFA production (although inorganic F^- can cause transient and reversible hepatic impairment)
- (4) Higher incidence of post-operative agitation and delirium (cf. other agents)
- (5) Risk of malignant hyperthermia
- (6) Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome)
- (7) PONV

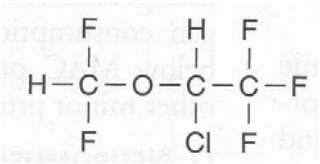
Metabolism and Elimination:

- Moderate metabolism (5%) by hepatic CYP 450 2E1 (2nd highest before halothane) to inorganic fluoride only (No TFA is produced)
- Mainly eliminated via the lungs

Isoflurane:

Use: Mainly for maintenance of GA

Structure: Halogenated ethyl methyl ether (structural isomer of enflurane)



Physical properties:

Property		Value
Molecular weight		184.5
MAC		1.15
Induction dose		1-4%
Maintenance dose		0.5-3%
Partition coefficient	BGPC	1.4
	OGPC	93.7
	Brain	2.6
	Muscle	4
	Fat	45
Vapour pressure at 20°C		32 kPa (239 mmHg)
Boiling point		48.5 °C

Pharmacodynamic effects:

Cardiovascular effects		
HR	- At 1.0 MAC, rise in HR due to ANS reflex (preserved BRR) to fall in MAP/CO - Rapid rise in F_I of isoflurane leading to transient tachycardia and catecholamine release (less than desflurane)	↑↑
C.O.	At 1.0 MAC, maintained due to reflex rise in HR (due to BRR), which offsets depression of myocardial contractility	n/c
MAP	- Dose-dependent fall in MAP due to fall in SVR - Rapid rise in F_I of isoflurane leads to transient hypertension and catecholamine release (less than desflurane)	↓↓
SVR	Dose-dependent decrease in SVR due to peripheral vasodilation	↓↓
Pulmonary vascular resistance	Decreased due to attenuation of hypoxic induced pulmonary vasoconstriction	↓
CVP	Increased	↑
Arrhythmogenic effects	- Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome) - Myocardium not sensitised to arrhythmogenic effects of Adr	Nil
Coronary blood flow	- Dilates coronary arteries, which can produce a "Coronary steal effect" (Ie. normal arteries dilate and steal blood away from arteries with fixed stenotic lesions) - Thus, isoflurane should be avoided in patients with IHD due to risk of regional myocardial ischaemia during hypotensive or tachycardia events	↑
Cardiac metabolic rate of O_2 consumption	Decreased	↓
Presence of "ischaemic preconditioning"	Present	
Respiratory effects		
RR	Dose-dependent increase (less pronounced than other	↑

	agents) – Ceiling effect at 1 MAC	
TV	Dose-dependent decrease (more pronounced than other agents, except for halothane/enflurane)	↓↓
MV	Dose-dependent decrease	↓
Resting $PaCO_2$	Increased	↑
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Depressed (increased apnoeic threshold), especially at very LOW doses (0.1 MAC)	↓↓
Ventilatory response to PaO_2	Ventilatory responses to hypoxia are blunted at 0.1 MAC (by 50%), but especially > 1 MAC (by 100%)	↓↓↓
Effect on airways	- Pungeant and irritating to UAWs (causes coughing, sneezing, breath holding) – This prevents its use as a gaseous induction agent - Bronchodilator (relaxes bronchial SM) - UAW responses impaired - Impaired mucociliary response - Increased mucous secretions	
Pulmonary vasculature	Impaired hypoxic pulmonary vasoconstriction (leads to V/Q mismatching)	
CNS effects		
General anaesthesia and analgesia	- Dose-dependent CNS depression from amnesia, to sedation, to hypnosis then GA - Minimal analgesia	
CBF	- At < 1 MAC, CBF autoregulation is preserved - At > 1 MAC, there is a dose-dependent rise in CBF that can be reversed by hyperventilation (Ie. fall in $PaCO_2$) whilst administering isoflurane	↑
ICP	- At > 1 MAC, dose-dependent rise in ICP due to increases in CBF (Nb. this can be reversed by hyperventilation) - The rise in ICP is the lowest amongst volatile agents – Thus, isoflurane is most ideal for neurosurgery	↑
Cerebrovascular responsiveness to $PaCO_2$	Intact (so CBF and ICP can be lowered by hyperventilation, which decreases $PaCO_2$)	Ok
$CMRO_2$	- Dose-dependent decline in $CMRO_2$ (most marked decline of all volatile agents) - Uncoupling of $CMRO_2$ from CBF causes "luxury perfusion" (Ie. neuroprotection form potential ischaemic insult)	↓↓↓
EEG/seizure activity	- EEG activity shows an initial increase in frequency (α waves), then a dose-dependent decrease in frequency (θ → δ waves), with eventual burst suppression and electrical silence (esp at > 2 MAC) - Nb. electrical silence is useful during cerebral ischaemia - Not epileptogenic. It increases seizure threshold	↓↓↓
CSF production	Nil	n/c
Skeletal muscle effects		
- Skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)		↑↑↑

Renal effects	
- Dose-dependent decreases renal blood flow, GFR and urine output (more than desflurane and sevoflurane) – Due to renal afferent arteriolar VC	↓↓
Hepatic effects	
- Total HBF and hepatic O_2 delivery are maintained (best of all agents) due to "hepatic arterial buffer mechanism (Ie. PV flow decreases but is compensated for by increased HA flow due to dilation of HA)	n/c
Uterine effects	
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow	↓↓
Toxicities	

- (1) Rapid rise in concentration can produce transient increases in HR, MAP and plasma NAd release
- (2) Carbon monoxide poisoning
  o Isoflurane is the 2nd most likely agent to be degraded by desiccated alkali CO_2 absorbents (esp baralime > sodalime) into CO
  o Factors increasing CO production (apart from agent used):
  ▪ (i) High absorber temperature
  ▪ (ii) Desiccated baralyme absorbent – There is ~ 13-15% water content in CO_2 absorbent. Up to 90% of this water must be removed before any CO is produced (Nb. Baralyme produces more CO for a given water content than soda-lime)
- (3) Minimal hepatic dysfunction – Due to minimal production rate of TFA as a result of low hepatic metabolism of isoflurane. TFA causes hepatotoxicity via an autoimmune mechanism similar to halothane
- (4) Minimal renal toxicity – Peak inorganic fluoride levels can exceed 15-50 umol/L with prolonged use as a result of hepatic metabolism. However, there is no demonstrable renal impairment because renal CYP450 metabolism of isoflurane is minimal (due to its lower solubility and chemical stability cf. methoxyflurane)
- (5) Risk of malignant hyperthermia
- (6) Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome)
- (7) PONV	

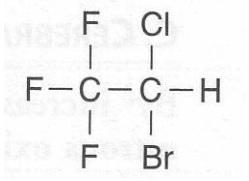
Metabolism and Elimination:

- Minimally metabolised (0.2%) by hepatic CYP 450 2E1 to trifluoroacetic acid and inorganic fluoride
- Mainly eliminated via the lungs

Halothane:

Use: Induction and/or maintenance of GA

Structure: Halogenated ethane with Br, Cl and F



Physical properties:

Property		Value	Significance
Molecular weight		197.4	
MAC		0.75	Most potent of volatile agents
Induction dose		2-4%	
Maintenance dose		0.5-2%	
Partition coefficient	BGPC	2.3	Highest BGPC of all volatile agents (delayed induction and recovery times)
	OGPC	220	High OGPC means high potency, high hepatic metabolism and high distribution to adipose tissues
	Brain	2.9	
	Muscle	3.5	
	Fat	60	
Vapour pressure at 20°C		32 kPa (244 mmHg)	
Boiling point		50.2 °C	

Note:

- Halothane is stored in 0.01% thymol (which interferes with vapouriser function) and amber-coloured bottle – This prevents spontaneous oxidative and photo decomposition that liberalises bromide
- Halothane is readily soluble in rubber – It easily leaches out of circuit tubing
- Halothane attacks aluminium, brass and lead in the presence of water vapour

Pharmacodynamic effects:

Cardiovascular effects		
HR	Junctional rhythm or bradycardia due to (i) Increased vagal tone, (ii) Depression of SA and AV nodes (due to decreased phase 4 depolarisation and increased threshold for depolarisation), and (iii) Impaired baroreceptor response in view of hypotension	↓↓
C.O.	Dose-dependent fall in C.O. (> 50% fall at 2 MAC) due to direct myocardial depression	↓↓↓
MAP	Dose-dependent fall in MAP (> 50% fall at 2 MAC) due to fall in C.O.	↓↓↓
SVR	Unchanged as there is balance of vasodilation and vasoconstriction in certain vascular beds	n/c
Pulmonary vascular resistance	Decreased due to attenuation of hypoxic induced pulmonary vasoconstriction	↓
CVP	Increased	↑
Arrhythmogenic effects	- Halothane sensitises the myocardium to the arrhythmogenic effects of catecholamines – This is an issue in response to exogenous catecholamines (Adrenaline doses > 1.5 ug/kg) and endogenous catecholamines (hypoxia, hypercapnoea, phaechromocytoma, Etc.) - Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome)	↑↑↑
Coronary blood flow	Decreased due to hypotension (despite coronary vasodilation)	↓

Cardiac metabolic rate of O_2 consumption	Decreased	↓
Presence of "ischaemic preconditioning"	Present	
Respiratory effects		
RR	Dose-dependent increase (most pronounced of all agents)	↑↑
TV	Dose-dependent decrease (2nd most pronounced before enflurane)	↓↓
MV	Dose-dependent decrease	↓
Resting $PaCO_2$	Increased	↑
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Depressed (increased apnoeic threshold) especially at > 1 MAC	↓↓
Ventilatory response to PaO_2	Ventilatory responses to hypoxia are blunted at 0.1 MAC (by 50%), but especially > 1 MAC (by 100%)	↓↓↓
Effect on airways	- Most potent bronchodilator (relaxes bronchial SM directly, and indirectly via inhibiting histamine-induced bronchoconstriction) - Non-irritating and sweet smelling – Can be used as inhalational induction agent - UAW responses impaired - Impaired mucociliary response - DECREASED mucous secretions (unlike other agents)	
Pulmonary vasculature	Impaired hypoxic pulmonary vasoconstriction (leads to V/Q mismatching)	
CNS effects		
General anaesthesia and analgesia	- Dose-dependent CNS depression from amnesia, to sedation, to hypnosis then GA - Minimal analgesia	
CBF	- At < 0.5 MAC, CBF autoregulation is preserved - At > 0.5 MAC, there is a dose-dependent rise in CBF. At 1 MAC, CBF increases by 200% (highest of all volatile agents) - Rise in CBF can be reversed by hyperventilation PRIOR to administering halothane	↑↑↑
ICP	- At > 0.5 MAC, dose-dependent rise in ICP due to increases in CBF (rises the most of all volatile agents) – Nb. this can be reversed by hyperventilation PRIOR to administering halothane) - The rise in ICP makes it not ideal of neurosurgery or patients with raised ICP	↑↑↑
Cerebrovascular responsiveness to $PaCO_2$	Intact (so CBF and ICP can be lowered by hyperventilation)	ok
$CMRO_2$	- Moderate decline (not as much as isoflurane) - Uncoupling of $CMRO_2$ from CBF causes "luxury perfusion" (Ie. neuroprotection form potential ischaemic insult)	↓
EEG/seizure activity	- Reduced EEG activity with burst suppression (electrically silent only at 3 MAC)	↓

	- Increased seizure threshold	
CSF production	Nil	n/c
Skeletal muscle effects		
- Skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) – Not as much as other volatile agents - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)		↑
Renal effects		
- Dose-dependent falls in RBF, GFR and urine output (due to fall in C.O. and renal afferent arteriolar VC) - Increased filtration fraction (as GFR falls more than RBF)		↓↓
Hepatic effects		
- Decreased total HBF and O_2 delivery (MOST of all agents) due to ↓ C.O./MAP and obtundation of "hepatic arterial buffer" mechanism		↓↓
Uterine effects		
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow		↓↓
Toxicities		

- (1) Liver damage:
  - (a) Reversible liver damage (Hepatic hypoxia)
    - Subclinical in nature. Associated with rise in hepatic transaminases
    - Due to hepatic hypoxia
  - (b) Fulminant hepatic necrosis (Halothane hepatitis)
    - Very rare condition (1:35,000) with mortality of 50-75%
    - Associated with deranged LFTs (bilirubin, ALT, AST) and encephalopathy following exposure to halothane. It is diagnosed on basis of exclusion of other causes of liver disease
    - Usually occurs in middle-aged obese women, patients with repeated halothane exposure within short intervals, or those with a family history of halothane toxicity
    - Caused by – (a) Immune mechanism (antibody response to trifluoroacetylation of liver microsomal proteins), (b) Reductive metabolites of halothane (during liver hypoxia)
    - Thus – (a) Halothane should NOT be used in patients with previous halothane hepatitis (or if there is unexplained liver dysfunction following halothane exposure), and (b) Repeated exposure to halothane (Ie. within 6 months of each other) should be avoided
    - Note – There is no evidence that it worsens preexisting liver disease
- (2) Arrhythmogenic effects of halothane:
  - (a) Halothane sensitises the myocardium to the arrhythmogenic effects of catecholamines – This is an issue in response to exogenous catecholamines (Adrenaline doses > 1.5 ug/kg) and endogenous catecholamines (hypoxia, hypercapnoea, phaechromocytoma, Etc.)
  - (b) Prolongs QTc (risk of polymorphic VT in patients with Long QTc syndrome)
  - (c) Causes junctional rhythm or bradycardia
- (3) Post-operative shivering ("Halothane shakes")
- (4) Risk of malignant hyperthermia
- (5) PONV

Metabolism and Elimination:

- Heavily metabolised (20%) by hepatic CYP 450 2E1, which produces trifluoroacetic acid and inorganic fluoride, bromide and chloride
- In the presence of hypoxia, reductive metabolism occurs – This produces reductive metabolites and inorganic fluorides
- Mainly eliminated via the lungs

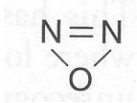
Nitrous oxide:

Uses:

- (1) Supplement other volatile agents in providing GA at a concentration of 70%:
  - Reduces the concentration requirements (or MAC) of other volatile agents by 60%, thus attenuating the adverse cardio-respiratory effects of those agents
  - Accelerates the uptake of other agents via the "Second gas effect"
  - Reduces the risk of awareness during GA
  - Note – N_2O is rarely used alone as a GA due to its high MAC
- (2) Potent analgesia (at < 1.0 MAC) for labour and painful procedures
  - Used as a 50:50 gas mixture (N_2O and O_2) as Entonox – Given the Poynting effect, Entonox is pressurized at room temperature to keep both N_2O and O_2 in their gaseous states. At a temperature < -7 °C, N_2O liquefies while O_2 remains in its gaseous state
- (3) Facilitate laparoscopic surgery by providing pneumoperitoneum
- (4) Used in patients who are MH-sensitive

Structure:

- A colourless and odourless inorganic anaesthetic gas



- Produced from thermal decomposition (170-240 °C) of ammonium nitrate (low cost and easy to produce); however, impurities (Eg. NH_3, NO, N_2, HNO_3) can arise if temperature is not well-controlled. Scrubbers, caustic soda and water are used to filter out these impurities

Physical properties:

Property		Value	Significance
Molecular weight		44	
MAC		105	Least potent of inhaled agents
Induction and maintenance dose for GA		70%	Rarely used alone. Usually supplement a second volatile agent at 70%
Partition coefficient	BGPC	0.47	Very low BGPC (rapid induction and recovery times)
	OGPC	1.4	Low OGPC means low potency, low metabolism and low distribution to adipose tissues
	Brain	1.1	
	Muscle	1.2	
	Fat	2.3	
Critical pressure and temperature		71.7 atm / 36.5 °C	- Stored as liquid at room temperature and pressure - To prevent an explosion, it

		requires special tubing and storage under pressure
Boiling point	- 88 °C	

Pharmacodynamic effects:

Cardiovascular effects		
HR	- MAP, CO, HR and TPR remain unchanged - N_2O depresses myocardial contractility, but the fall in CO is offset by SNS stimulation – However, in the event of severe hypovolaemia or IHD, myocardial depression can be unmasked, leading to fall in MAP and CO	n/c
C.O.		n/c
MAP		n/c
SVR	Unchanged	n/c
Pulmonary vascular resistance	Causes pulmonary vasoconstriction – Thus, contraindicated in pulmonary HT and RSHF	↑
CVP	Increased	↑
Arrhythmogenic effects	Catecholamine-induced arrhythmias due to SNS stimulation (in response to myocardial depression)	↑
Coronary blood flow	Unchanged	
Cardiac metabolic rate of O_2 consumption		
Presence of "ischaemic preconditioning"	Absent	
Respiratory effects		
RR	Increased	↑
TV	Decreased	↓
MV	Unchanged	n/c
Resting $PaCO_2$	Unchanged	n/c
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Decreased (increased apnoeic threshold)	↓
Ventilatory response to PaO_2	Hypoxic-ventilatory drive is markedly depressed	↓↓
Effect on airways	Odourless and non-irritating and does not induce bronchospasms	
Pulmonary vasculature	Increased pulmonary vasoconstriction	
CNS effects		
General anaesthesia and analgesia	- Supplements other volatile agents in providing GA (reduces risk of awareness, MAC-sparing of other volatile agents, second gas effect) - Given high MAC, it is NOT given as sole anaesthetic agent - Potent analgesic effect (even at < 1 MAC) – Used at 50:50 mixture in Entonox	
CBF	Mildly elevated	↑
ICP	Mildly elevated	↑
Cerebrovascular responsiveness to		

$PaCO_2$		
$CMRO_2$	Increased	↑
EEG/seizure activity	Increased seizure threshold	↓
CSF production	Nil	n/c

Skeletal muscle effects

- Does not cause muscle relaxation alone; it does potential effects of muscle relaxants (but not as much as volatile agents)
- Can cause muscle rigidity at high concentrations
- NOT a trigger for MH (can be used safely in MH-sensitive patients)

Renal effects

- Dose-dependent decreases renal blood flow, GFR and urine output (due to fall in C.O. and renal afferent arteriolar VC) ↓↓

Hepatic effects

- Decreases total HBF (less so than volatile agents) ↓

Uterine effects

- No effect on uterine tone n/c

Toxicities

- (1) Highly emetogenic with risk of PONV (NNT 4) due to central stimulation of CTZ/VC
- (2) Can cause muscle rigidity at high concentrations
- (3) With prolonged use it irreversibly oxidses Cobalt in Vitamin B12, thus inhibiting enzymes that are dependent on Vitamin B12:
    - Methionine synthetase (used for myelin) – Risk of peripheral neuropathy
    - Thymidylate synthetase (used for DNA synthesis) – Risk of BM suppression and megaloblastic anaemia
- (4) Potential teratogenic effects (thus avoid in pregnancy)
- (5) Impairs chemotaxis and motility of PMNL
- (6) N_2O diffuses into air-containing cavities more rapidly from blood than air (or N_2) – This is because N_2O is 35X more soluble than air (or N_2) in blood. This raises two issues:
    - (a) Diffusion hypoxia – N_2O is eliminated into alveoli rapidly during emergence, such that alveolar O_2 is diluted. Hypoxia is prevented by giving 100% O_2 for 5-10 minutes after ceasing N_2O
    - (b) Expand air-containing cavities such as air emboli, pneumothorax, intestinal obstruction, intracranial air (causing tension pneumocephalus), intraocular air bubbles (following ocular surgery), TM grafting, pulmonary air cyst, and ETT cuff (causing mucosal ischaemia)
- (7) Contraindicated in patients with pulmonary HT and/or RSHF (due to pulmonary vasoconstriction)
- (8) Risk of arrhythmia (due to SNS stimulation in response to myocardial depression)
- (9) Greenhouse gas causing ozone destruction
- (10) Non explosive and non-inflammable BUT still capable of supporting combustion

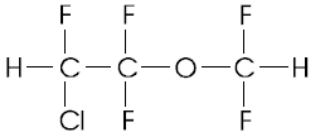
<u>Metabolism and Elimination</u>:

- Only inhalational anaesthetic agent that is NOT biotransformed by hepatic CYP450
- Small amounts diffuse from the skin and undergo reductive metabolism by GIT anaerobic bacteria (< 0.01%)
- Largely eliminated by exhalation

Enflurane:

Uses: For induction and maintenance of GA

Structure: Halogenated ethyl methyl ether (geometric isomer of isoflurane)



Physical properties:

Property		Value
Molecular weight		184.5
MAC		1.68
Partition coefficient	BGPC	1.80
	OGPC	98
Vapour pressure at 20°C		23 kPa (175 mmHg)
Boiling point		56.5 °C

Pharmacodynamic effects:

Cardiovascular effects		
HR	Mild reflex tachycardia (intact BRR) due to fall in BP	↑
C.O.	Dose-dependent fall due to myocardial depression	↓↓
MAP	Dose-dependent decrease due to fall in C.O. and SVR	↓↓
SVR	Mild dose-dependent decrease due to vasodilation	↓
Pulmonary vascular resistance	Decreased due to attenuation of hypoxic induced pulmonary vasoconstriction	↓
CVP	Increased	↑
Arrhythmogenic effects	Not marked as halothane, but myocardium still sensitized to catecholamines	↑
Coronary blood flow	Coronary vasodilation occurs	↑
Cardiac metabolic rate of O_2 consumption	Decreased	↓
Presence of "ischaemic preconditioning"	Present	
Respiratory effects		
RR	Mild dose-dependent increase	↑
TV	Dose-dependent decreased (most marked of all volatile agents)	↓↓↓
MV	Dose-dependent decreased (most of all volatile agents)	↓↓↓
Resting $PaCO_2$	Increased (most of all volatile agents)	↑↑↑
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Decreased (increased apnoeic threshold)	↓

Ventilatory response to PaO_2	Ventilatory responses to hypoxia are blunted at 0.1 MAC (by 50%), but especially > 1 MAC (by 100%)	↓↓↓
Effect on airways	- Bronchodilation - Non-irritant, non-pungent odour - UAW responses impaired - Impaired mucociliary response - Increased mucous secretions	
Pulmonary vasculature	Impaired hypoxic pulmonary vasoconstriction (leads to V/Q mismatching)	
CNS effects		
General anaesthesia and analgesia	- Dose-dependent CNS depression from amnesia, to sedation, to hypnosis then GA - Minimal analgesia	
CBF	Increased due to cerebral vasodilation (less than halothane, but more than isoflurane)	↑
ICP	Increased due to rise in CBF (less than halothane, but more than isoflurane)	↑
Cerebrovascular responsiveness to $PaCO_2$		
$CMRO_2$	Decreased	↓
EEG/seizure activity	Epileptiform EEG (esp with hypocapnoea) – High voltage, high frequency EEG changes that progress to 3 Hz spike-and-wave and tonic-clonic seizures	↑↑↑
CSF production	Net increase in CSF volume due to increased production and decreased reabsorption	↑↑
Skeletal muscle effects		
- Marked skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) – Not as much as other volatile agents - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)		↑↑↑
Renal effects		
- Dose-dependent falls in RBF, GFR and urine output (due to fall in C.O. and renal afferent arteriolar VC)		↓↓
Hepatic effects		
- Decreased total HBF (and O_2 delivery) due to ↓ C.O./MAP and obtundation of "hepatic arterial buffer" mechanism		↓
Uterine effects		
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow		↓↓
Toxicities		
- (1) Risk of malignant hyperthermia - (2) Post-operative shivering - (3) Risk of PONV - (4) Risk of cardiac arrhythmia due to catecholamines (Eg. Adr, SNS stimulation due to hypoxia, hypercapnoea, Etc.) - (5) Risk of hepatotoxicity - (6) Potential risk of inorganic fluoride renal toxicity (although plasma levels rarely reach toxic levels of > 50 umol/L) - (7) EEG-like seizure activity (thus avoided in patients with epilepsy)		

<u>Metabolism and Elimination</u>:

- Metabolised (2%) by hepatic CYP 450 2E1, which produces inorganic fluoride
- Mainly eliminated via the lungs

Xenon:

Uses: For induction and maintenance of GA

Physical properties:

Property	*Value*
Molecular weight	138
MAC	71
Blood-gas solubility coefficient	0.115
Oil-gas solubility coefficient	1.9
Boiling point	-107 °C

Benefits of Xe:

- (i) An inert and odourless noble gas that is NOT explosive
- (ii) Non-toxic, non-teratogenic and environmentally-friendly
- (iii) Does NOT undergo any metabolism by the body (entirely eliminated by the lungs)
- (iv) Very low BGPC, which means very quick wash in and washout of gas (Ie. rapid induction and recovery)
- (v) Minimal CVS effects (Ie. can be used if patients with limited CVS reserve) – No effect on myocardial contractility and small decrease in HR
- (vi) Minimal respiratory effects – TV increases but RR slows down, thus causing MV to remain constant. Does not cause diffusion hypoxia
- (vi) Has analgesia properties
- (vii) Does NOT cause malignant hypethermia

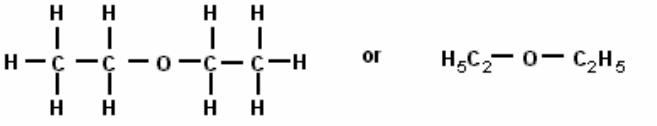
Disadvantages of Xe:

- (i) High MAC value implies a low potency, which means – (a) Large amounts of this gas must be used, and (b) N_2 washout from the lungs (Ie. breathe 100% O_2 for 3-5 minutes) is required to maximise its effect
- (ii) Very expensive to produce – It is made by fractional distillation of air (as Xe is 8.7 x 10^{-6}% of air)
- (iii) No commercially available anaesthesia equipment
- (iv) Cannot be used for neurosurgery (as it has variable increase in CBF)
- (v) Increases AW resistance at high concentrations (due to higher viscosity and density than N_2O)

Diethyl ether:

Uses: For induction and maintenance of GA

Structure:



Physical properties:

Property		Value
Molecular weight		74
MAC		1.9
Partition	BGPC	12

coefficient	OGPC	~100
Vapour pressure at 20°C		57 kPa
Boiling point		35 °C

Note: Inert gas but decomposes in air, heat and light into acetaldehyde and ether peroxide

Pharmacodynamic effects:

Cardiovascular effects	
HR	Increased due to ANS reflex and vagolytic effects
C.O.	Increased due to SNS stimulation (despite myocardial depression)
MAP	Unchanged due to rise in C.O.
SVR	Increased at low doses due to vasoconstriction; Decreased at high doses due to vasodilation
Arrhythmogenic effects	Myocardium not sensitized to arrhythmogenic effects of catecholamines
Coronary blood flow	Coronary vasodilation occurs
Respiratory effects	
RR	Increased
TV	Decreased
MV	Unchanged
Resting $PaCO_2$	Unchanged
Ventilatory response to $PaCO_2$ (Apnoeic threshold)	Unchanged
Effect on UAW/bronchial tone	- Bronchodilation - Sweet smell - Irritant to UAW (causes coughing and breath holding)
Others	- Decreased ventilatory response to hypoxia - Decreased mucociliary clearance
CNS effects	
General anaesthesia	Causes GA
CBF	Increased due to cerebral vasodilation
ICP	Increased due to rise in CBF
Cerebrovascular responsiveness to $PaCO_2$	
$CMRO_2$	Decreased
EEG/seizure activity	Increased causing convulsions
CSF production	Unchanged
Analgesic effects	Present
Skeletal muscle effects	
- Marked skeletal muscle relaxation (dose-dependent decrease in TOF and tetany) – Not as much as other volatile agents - Potentiates effects of muscle relaxants (both depolarising and non-depolarising)	
Renal effects	
- Dose-dependent falls in RBF, GFR and urine output - ADH-resistant diabetes insipidus	

Hepatic effects
- Decreased total HBF
Uterine effects
- Dose-dependent fall in uterine muscle tone (issue with PPH) and blood flow
Toxicities
- (1) Inflammable and explosive (caution with diathermy) - (2) High risk of PONV (> 50%) - (3) Increased salivation - (4) Convulsions - (5) Post-op shivering

Metabolism and Elimination:

- Metabolised (2%) in the liver into acetaldehyde, alcohol, acetic acid and CO_2 (which are then excreted in the urine)
- 90% eliminated via the lungs

CO_2 Absorbers:

Overview of CO_2 absorbents:

- "CO_2 absorbents" absorb CO_2 in exhaled alveolar gas, thereby preventing the rebreathing of CO_2 in anaesthetic machines that use rebreathing circuits
- There are two types of absorbents:
    - (1) Soda lime
        - Contains $Ca(OH)_2$ (94%), NaOH (5%), KOH, H_2O, silica and pH indicator

$$\mathbf{CO_2} + \mathbf{H_2O} \rightarrow H_2CO_3$$

$$H_2CO_3 + \mathbf{2\ NaOH} \rightarrow Na_2CO_3 + 2\ H_2O + \mathbf{Heat} \quad (\textit{FAST})$$

$$Na_2CO_3 + \mathbf{Ca(OH)_2} \rightarrow CaCO_3 + 2\ NaOH \quad (\textit{SLOW})$$

    - (2) Baralyme
        - Contains $Ca(OH)_2$ (80%), $Ba(OH)_2$ (20%), KOH, H_2O and pH indicator

$$\mathbf{Ba(OH)_2} + \mathbf{CO_2} + \mathbf{H_2O} \rightarrow BaCO_3 + 9\ H_2O + \mathbf{Heat}$$

$$\mathbf{CO_2} + \mathbf{H_2O} \rightarrow H_2CO_3$$

$$H_2CO_3 + \mathbf{Ca(OH)_2} \rightarrow CaCO_3 + 2\ H_2O + \mathbf{Heat}$$

- Both types of absorbents
    - (i) Contain strong bases/alkali
    - (ii) Require H_2O for efficient CO_2 absorption
    - (iii) Produce heat with CO_2 absorption
    - (iv) Can degrade volatile agents into potentially toxic by-products

Potential interactions between volatile agents and CO_2 absorbents:

(1) Carbon monoxide production with desflurane, enflurane and isoflurane

- All volatile agents containing difluormethyl groups can be degraded by the alkali in CO_2 absorbents to produce carbon monoxide (CO)
- Factors that increase the production of CO:
    - (i) Volatile agent used – Desflurane > Enflurane > Isoflurane (BUT not Halothane or Sevoflurane as they lack difluoromethyl groups)
    - (ii) Warm CO_2 absorbent (Eg. high temperature from increased CO_2 absorption or low FGF)
    - (iii) Desiccated CO_2 absorbent (especially baralyme)
        - There is ~ 13-15% water content in CO_2 absorbent
        - CO_2 absorbents absorb more volatile agent when they are desiccated (Ie. prolonged low FGF, such as leaving O_2 on over the weekend)
        - Up to 90% of water in CO_2 absorbent must be removed before any CO is produced
        - Baralyme produces more CO for a given water content than soda-lime

(2) Compound A-E production from sevoflurane

- Alkali found in CO_2 absorber degrade sevoflurane into Compound A-E, especially in lab rats (Nb. only compounds A and B are produced in levels detectable for analysis)
- This occurs especially in the presence of:
    - (i) Low FGF

        - This leads to increased absorber temperature and dehydration, and thus increased compound A production
    - (ii) Increased absorber temperature
        - Temperature of the absorber will increase with decreased FGF and with increased CO_2 output, thereby leading to increased compound A production
        - If the absorber canister is immersed in an ice bath, compound A production is significantly reduced
    - (iii) Prolonged and/or high concentration use of sevoflurane
    - (iv) Type of absorbent and level of desiccation
        - Dehydration of sodalime and baralyme increases both production and degradation of compound A
        - Dry baralyme produces MORE compound A than dry sodalime – This is because production of compound A exceeds degradation with dry baralyme, while degradation exceeds its production with dry sodalime
        - Nb. Compound A can be made even when the absorbent is not dry
- In humans, there is no evidence of nephrotoxicity when sevoflurane due to compound A – Of note, prolonged low flow sevoflurane (0.25 mL/min x 5 hrs) produces < 20 ppm (Nb. nephrotoxic dose of compound A is 150-200 ppm)
- Despite this finding, to prevent risk of renal toxicity:
    - (i) Avoid using sevoflurane in patients with renal disease
    - (ii) Avoid use of baralyme with sevoflurane
    - (iii) If sevoflurane is to be used for prolonged periods, use FGF > 2 L/min

(3) Bromochlorodifluoroethylene from halothane
- Although this is nephrotoxic to rats, it has no clinical impact in humans

(4) Various toxic substances from trichloroethylene (TCE)
- At high temperatures, TCE is degraded by CO_2 absorbent into toxic substances:
    - Phosphogene (sarin gas – respiratory toxin)
    - Dichloroacetylene (neurotoxin)
    - HCl
    - CO
- Thus, TCE should NEVER be used with sodalime or baralyme

(5) Risk of malignant hyperthermia from all volatile agents
- Volatile agents can leach out of CO_2 absorbers at a later stage (Ie. beginning of another case), and this poses an issue to patients who are MH-susceptible

(6) Slower rates of induction and emergence
- Because CO_2 absorbers also absorb volatile agents, this reduces the amount of volatile agents rebreathed in the circuit. Thus, induction times of GA and recovery times are delayed
-

INTRAVENOUS ANAESTHETIC AGENTS

(a) ***To describe the properties of an ideal intravenous induction agent.***

The properties of an ideal intravenous anaesthetic agent are as follows:

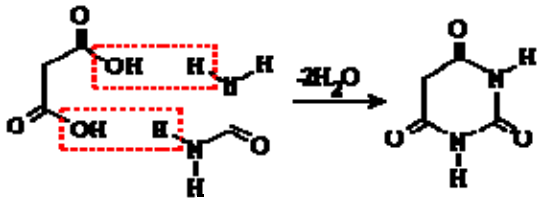
- (1) Preparation and physico-chemical properties:
  - Simple preparation with a water-soluble formulation
  - Stable in solution
  - Long shelf-life at room temperature
  - Inexpensive to produce
  - Compatible with other agents and fluids
- (2) Pharmacokinetic properties:
  - With administration:
    - Can be used IM (if needed)
    - Safe following inadvertent intra-arterial injection
    - No pain or irritation on injection
    - Lack of local tissue damage with extravasation
  - Rapid and smooth onset of induction within one arm-brain circulation time (< 30 secs). This is aided when the agent is:
    - Mainly unionised at physiological pH (pH 7.35-7.45)
    - Highly lipid soluble
    - Small $V_{DISTRIBUTION}$
    - Small degree of protein-binding
  - Rapid and smooth recovery of consciousness and cognitive skills. This is aided when the agent:
    - Rapidly redistributes from the brain into other well-perfused tissues (Eg. muscle) – Short distribution half-life (t ½ α)
    - Is rapidly cleared (metabolised and excreted) – Short elimination half-life (t ½ β)
    - Metabolites should be inactive
    - Does not accumulate during prolonged infusion – Short context-sensitive half-time
  - Metabolism is independent of renal and hepatic function
- (3) Pharmacodynamic properties:
  - Agent should have high potency and efficacy at causing anaesthesia, with predictable dose-effect response
  - Depression of AW reflexes for intubation
  - Analgesic at sub-anaesthetic concentrations
  - Minimal CVS and respiratory depression
  - No excitation phenomena (Eg. coughing, hiccoughing, involuntary movements) or emergence phenomena (Eg. nightmares)
  - Should not raise ICP, increase $CMRO_2$ or be epileptogenic
  - Should not have any emetic effects
  - Should not have any amnesic and/or psychomimetic effects
  - Agent should be non-toxic and not teratogenic
  - Agent should not cause histamine release (Eg. itching, bronchospasm) or hypersensitivity reactions
  - Agent should lack interaction with muscle relaxants

(b) ***To describe the formulations of thiopentone, propofol, midazolam and ketamine.***
(c) ***To describe the central nervous system effects and proposed mechanism of action of the intravenous anaesthetic agents.***
(d) ***To describe the pharmacokinetics and the clinical implications of these differences.***
(f) ***To describe the factors which affect recovery from intravenous anaesthesia.***
(g) ***To describe the pharmacodynamics of propofol, thiopentone, midazolam, ketamine and etomidate. Provide a detailed account of the cardiovascular and respiratory effect of these agents.***
(h) ***To describe the adverse effects of individual agents.***
(i) ***To outline how physiological and pathological disturbances can alter the pharmacology of the intravenous anaesthetic agents.***

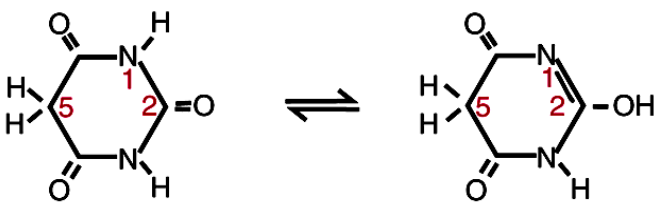
(I) **Thiopentone**

Chemical structure of thiopentone:

- Barbiturates are derivatives of barbituric acid:
    - Barbituric acid is a cyclic compound formed by the condensation of urea and malonic acid

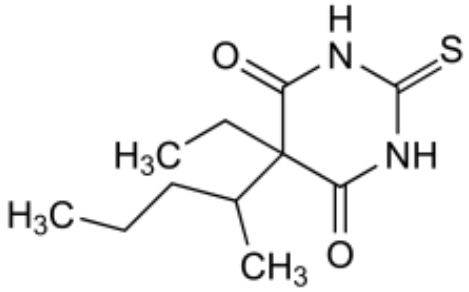


    - Barbituric acid in itself lacks CNS activity – Its pharmacological properties (Eg. sedation, hypnosis, anticonvulsant) are derived by substitutions at its:
        - C2 atom:
            - Oxybarbiturates (Eg. pheno- and pentobarbitone) – Possess "oxygen" on C2 atom, which makes it less lipid-soluble. This attenuates its potency as a sedative-hypnotic and retards onset, BUT enhances it duration of action
            - Thiobarbiturates (Eg. thiopentone, methohexitone) – Posses "sulphur" on C2 atom, which makes it more lipid-soluble. This increases its potency as a sedative-hypnotic and rate of onset, BUT attenuates its duration of action
        - C5 atom:
            - Long-branched chains confer greater sedative-hypnotic properties than short-straight chains
            - Phenyl group (Eg. phenobarbitone) confers anticonvulsant activity
    - Solubility of barbiturates depends on its keto-enol transformation (Tautomerism):
        - Keto-form – Lipid-soluble; present in neutral-acidic pH
        - Enol-form – Water-soluble; present in alkaline pH



KETO FORM ENOL FORM

- Thiopentone (STP) is a thiobarbiturate – in fact, it is a sulphur analogue of pentobarbitone (an oxybarbiturate). It has two isomers (S- and R+), of which the S-isomer is 2x more potent



Formulation of thiopentone:

- A vial of STP contains a hygroscopic pale yellow water-soluble power that contains:
  - (1) Na^+ salt of STP as a racemic mixture – Generally diluted to 2.5% in N/S or H_2O (higher concentrations, such as 5%, not recommended due to risk of venous thrombosis and pain on injection
  - (2) Sodium carbonate (Na_2CO_3; 6%) – This reacts with H_2O to produce $NaHCO_3$ and NaOH, which produces an alkaline solution (pH 10.5) that:
    - (i) Solubilises STP in water – Alkaline pH favours the water-soluble "enol form" of STP
    - (ii) Improves stability of STP in solution – Alkaline pH keeps STP stable and sterile (bacteriostatic function) for up to 1-2 weeks (Nb. STP power is stable at room temperature indefinitely!)
    - (iii) Impairs compatibility with acidic drugs (Eg. opioids, non-depolarising muscle relaxants, ketamine, catecholamines, Etc.)
  - (3) N_2 – This is because the trace levels of CO_2 in air can react with H_2O to form HCO_3^- and H^+, which reduces the alkalinity of the solution and make STP less soluble (Ie. less "enol form" of STP)

Mechanism of action of thiopentone:

- (1) Barbiturates (including STP) potentiate the inhibitory effects of GABA on GABA-A receptor in the brain (esp at the reticular activation system, which is important in wakefulness):
  - GABA is the main inhibitory neurotransmitter in the CNS (esp the brain). It acts on a pentameric (2α, 2β, γ) ligand-gated GABA-A receptor associated with a central Cl^- channel pore. This receptor is found widespread in the CNS and is mainly postsynaptic in location
  - GABA (and high dose barbiturates) binds to the α-subunit and directly activate the receptor – This causes Cl^- channel opening and Cl^- influx, which hyperpolarises the neuron and inhibits action potential propagation
  - Barbiturates bind to the β-subunit and increases the duration of GABA-A receptor-activated Cl^- channel opening by reducing the dissociation rate of GABA from the receptor
- (2) Barbiturates also suppress transmission of excitatory neurotransmitters – Inhibits nACh (esp at SNS ganglia), Glutamate and Adenosine receptors

Pharmacokinetics of thiopentone:

- Overview:
  - IV bolus of STP has a rapid onset of LOC (within 30 seconds) due to a rapid increase in effect-site concentration of STP. This is caused by its:
    - (i) High lipid-solubility

        - (ii) Rapid effect-site equilibrium
        - (iii) Large fraction of unionised STP at physiological pH (despite the high degree of protein-binding)
    - IV bolus of STP has a rapid offset and emergence (within 5-15 minutes) due to a rapid decrease in effect-site concentration of STP (decreases by 50% within 5 minutes such that only 10% remain at 30 minutes). This is caused by:
        - (i) Mainly by rapid redistribution of STP from the brain into peripheral tissues:
            - (a) STP first redistributes to other VRG (heart, liver, kidneys) as they have higher blood flows; however, they saturate quickly (Ie. low capacity)
            - (b) STP then redistributes to skeletal muscle – This is the major site for redistribution (and contributor to offset) of STP due to its relatively high blood flow and capacity to store. It saturates in 15 minutes. Thus, STP dose needs to be adjusted with decreased muscle mass (Eg. elderly) and low muscle perfusion states (Eg. shock, hypovolaemia)
            - (c) STP will redistribute to fat – This plays a minor role in offset of an IV bolus of STP. This is because fat takes 2.5 hours to saturate with STP due to its low blood flow (despite its high capacity as STP is very lipid-soluble)
        - (ii) Clearance of STP by hepatic metabolism and renal excretion plays minimal role in offset of an IV bolus of STP
    - When given as an IV infusion, offset of STP is significantly delayed:
        - Peripheral compartments (esp fat and muscle) are saturated with STP, such that with cessation of the infusion, STP redistributes back into plasma and maintains the plasma and effect-site concentrations
        - Clearance of STP (hepatic metabolism, and renal excretion) plays a more important role now in reducing plasma concentrations and causing offset
        - The CSHT of STP is high and increases with prolonged infusions (Ie. accumulates in the body) – This is because:
            - (a) Clearance of STP is very low – This is because hepatic CYP450 are saturated and metabolism becomes linear (zero-order)
            - (b) Peripheral compartments (esp fat and muscle) are highly saturated with STP

Absorption	Only given as IV bolus (NOT as an infusion)
Distribution	- Highly lipid-soluble (due to the "sulphur" on the C-2 atom) - Short effect-site equilibrium time - Protein binding is determined by the lipid solubility of the unionised molecule: - Thiobarbiturates (esp STP) are highly protein bound cf. oxybarbiturates they are highly lipid-soluble - STP is 80% protein-bound (cf. 40% for pentobarbitone) - Reduced protein binding (Ie. more unionised fraction) occurs with – Hypoalbuminaemic states, uraemia (N_2-byproducts bind protein), drugs (esp NSAID, aspirin), neonates (50% protein-bound) - Degree of ionisation – STP has a pKa ~ 7.6 (60% unionised at physiological pH). Thus, acidosis increases the proportion of unionised STP (Ie. lower dose of STP needed) - Tissue perfusion – Low perfusion states (Eg. low CO states or hypovolaemia) increase the fraction of STP delivered to the CNS (Ie. less dose of STP needed) - $V_{DISTRIBUTION}$ ~ 2.5 L/kg

	- Short "Distribution half life" (t ½ α) ~ 8.5-60 minutes

Metabolism and Excretion	- Low clearance rate (3.4 mL/kg/min)
	- Metabolism of STP:
	  - Hepatic CYP450 (main)
	  o Oxidative metabolism by hydroxylation of C5-atom side chain to form inactive water-soluble metabolites that are renally-excreted (hydroxy-STP and COOH derivatives)
	  o At high-doses, it can be desulphated at C2-atom to form pentobarbitone. Cleavage of barbituric acid ring into urea and 3-C fragment can also occur
	  - Extrahepatic CYP450 (minor) – CNS and kidneys
	  - CYP450 enzyme induction generally occurs after 2-7 days of sustained drug administration (esp for Phenobarbital – 20-40% increase in enzymes) – This can lead to drug interaction (Eg. increased metabolism of other drugs) and altered drug response (Eg. tolerance)
	- Excretion of STP – < 1% of STP is excreted unchanged renally (due to high protein-binding [prevents glomerular filtration] and high lipid solubility [increases tubular reabsorption])
	- CSHT of STP is long and increases with duration of infusion (Ie. accumulates in body) – 4 mins at 10 mins; 85 mins at 3 hrs
	- "Elimination half-life" (t ½ β) ~ 3-12 hrs

<u>Clinical uses of thiopentone</u>:

- (1) Induction of anaesthesia
  - Onset occurs in one arm-brain circulation time (30 seconds), which is signified by loss of eye-lash reflex. Awakening occurs after 5-15 minutes with residual CNS effects lasting hours ("hangover")
  - IV dose of 3-7 mg/kg
  - Repeated doses or infusion of STP cannot be used to maintain anaesthesia due to its long CSHT and accumulation in the body (and thus prolonged recovery)
- (2) Treat increased ICP
  - ICP falls due to decreased cerebral blood volume associated with a fall in CBF
  - CPP is usually increased because the fall in ICP is generally greater than the fall in MAP (since CPP = MAP – ICP) – However, CPP may actually decrease when significant hypotension occurs with high doses of STP
  - High doses used to treat raised ICP can be associated with – (i) Hypotension (which can compromise CPP), (ii) Increased use of inotropic support to maintain BP (and CPP), and (iii) Prolonged awakening and delayed extubation
- (3) Cerebral protection:
  - Despite a fall in CBF, a HIGH perfusion-to-metabolism ratio is maintained due to the greater falls in $CMRO_2$ (up to 55%) and increased CPP (especially at STP doses that give an isoelectric EEG):
    - This is why silent (isoelectric) EEG with STP conveys cerebral protection against focal cerebral ischaemia (Eg. cerebral emboli) – Nb. It is NOT useful against global ischaemia (Eg. cardiac arrest)
    - However, the high doses used for this can be associated with – (i) Hypotension (which can compromise CPP), (ii) Increased use of inotropic support to maintain BP (and CPP), and (iii) Prolonged awakening and delayed extubation
- (4) Anticonvulsant (used to treat grand-mal seizures and status epilepticus)

<u>Pharmacodynamics effects of thiopentone</u>:

CNS effects	
General effects	- Sedative-hypnotic effect to full general anaesthesia – Smooth and rapid induction with rapid recovery, BUT with residual CNS effects lasting hours ("hangover") - Antanalgesic (lowers pain threshold) at low doses
CBF	Falls due to cerebral vasoconstriction as a result of a decrease in cerebral metabolism (or fall in $CMRO_2$)
ICP (and IOP and CPP)	- ICP falls due to decreased cerebral blood volume associated with a fall in CBF (hence, thiopentone is used to treat raised ICP) - CPP is usually increased because the fall in ICP is generally greater than the fall in MAP (since CPP = MAP – ICP) – However, CPP may actually decrease when significant hypotension occurs with very high doses of thiopentone - Decreased IOP
$CMRO_2$	Dose-dependent fall (such that at isoelectric EEG, it decreases by a maximum of 55%)
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage), then to burst suppression, and finally silent (isoelectric) EEG at very high doses - Since thiopentone can suppress EEG activity to an isoelectric EEG, it is effective as an anticonvulsant (Eg. treat grand-mal seizures and status epilepticus)
CVS effects	
HR	Compensatory increase due to intact BRR and SNS output (BRR is blunted at high doses of STP)
CO	- Dose-dependent fall (20%) due to direct myocardial depression (–ve inotrope) - At induction doses, fall in CO is MINIMAL due to SNS outflow from an intact BRR (Ie. BBR causes compensatory rise in HR and blunts the –ve inotropic effect) - BRR ineffective at unmasking –ve inotropic effects (Ie. causing a fall in CO and BP) with – (i) Hypovolaemia, (ii) Beta-blockade, (iii) Underlying IHD/CCF, and (iv) Large or rapid IV doses of STP
BP	- Dose-dependent fall mainly due to drop in SVR (and also a fall in CO at higher doses only) - At induction doses, the fall in BP is only mild and transient as CO is minimally affected (due to masking of –ve inotropy by an intact BRR) - At higher doses, BP fall significant due to loss of BRR and unmasking of –ve intropic effects
SVR	Dose-dependent fall due to peripheral vasodilation
Haemodynamic sequelae of AW instrumentation	- Mild fall in BP does not blunt the haemodynamic sequelae of AW instrumentation - Fall in BP can be reversed by hypetensive effects of AW instrumentation
Arrhythmogenicity	Nil. Also QTC not prolonged
Coronary BF and CMRO2	↑ myocardial O_2 consumption; consequent ↑ coronary blood flow
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Dose-dependent ventilatory depression (due to decreases in both TV and RR). Usually causes apnoea when used with other CNS depressants - Increased resting $PaCO_2$
Ventilatory response to $PaCO_2$ and PaO_2	Decreased ventilatory response with increased apnoeic threshold

Effect on AW	- Depresses UAW reflexes ONLY at high doses - Laryngospasm and bronchospasm occur in response to AW instrumentation or presence of secretions as UAW reflex may be inadequately depressed at induction doses (Ie. higher doses needed)
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact

GI, GU, metabolic and other effects

- Reduced HBF (but normal LFTs)
- Reduced GFR, RBF and U/O due to fall in CO and increased ADH release (due to CNS depression)
- No effects on the uterus
- No suppression of adrenal steroidogenesis
- Does not trigger MH

Issues with injection

- Pain on injection (esp if concentrations of STP > 2.5% are used)
- Extravascular injection is very painful and can cause serious tissue necrosis
- Intra-arterial injection:
    - STP crystals precipitate at physiological pH as it converts to the less water-soluble "keto form"
    - When injected intra-arterially, these crystals form microemboli that block small vessels and cause arteritis – This leads to severe pain and tissue ischaemia distally
    - Treatment of intra-arterial STP – (i) Dilute STP intra-arterially with saline, (ii) Give vasodilators (lignocaine, papaverine, phenoxybenzamine), (iii) Anticoagulate artery with hepain, (iv) Sympathetectomy of affected limb (Eg. Block SNS using brachial plexus block), (v) Adequate analgesia
- Venous thrombosis:
    - Due to deposition of STP crystals in the vein – Note that this is less of an issue (cf. intra-arterial STP crystals) as veins are larger diameter and can easily dilute the crystals
    - Increased incidence of venous thrombosis if higher concentrations of STP are used (Eg. 5%)

Relevant adverse or undesired effects

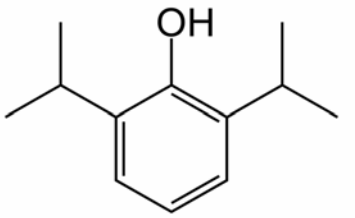
- Porphyria (acute porphyric crisis)
    - Barbiturate-induced enzyme induction leads to increased activity of mitochondrial D-aminolevulinic (ALA) synthetase – This leads to increased haeme production, which increases the risk of an acute porphyric crisis
- Allergic reactions
    - Anaphylaxis and anaphylactoid reactions (1:20,000-30,000)
    - Thiobarbiturates do not induce mast cell histamine release as much as oxybarbiturates – But this is still an issue with atopic/asthmatic patients
- Tolerance
    - Acute tolerance to barbiturates occurs EARLIER than barbiturate-induced induction of microsomal enzyme (which occurs after 2-7 days of continuous administration)
    - When maximal tolerance to barbiturates is achieved, the dose of barbiturates needed can increase 6X (Nb. this is at > 2X MORE than due to enzyme induction alone)
    - Tolerance to sedation occurs earlier and to a greater effect than that for its anticonvulsant and toxic effects – Thus, the "Therapeutic index" of barbiturates decrease as higher doses are required for desired effect
- Abusive potential
    - Dependence and withdrawal occur with prolonged barbiturate use
- Immunosuppression
    - Long-term high dose STP (Ie. used to treat raised ICP) can cause immune function impairment, thus increasing the risk of infection

Drug interactions
- Hepatic CYP450 enzyme induction generally occurs after 2-7 days of sustained drug administration - This can lead to drug interactions (esp increased metabolism of other drugs, such as anticoagulants, TCA, phenytoin, endogenous steroids, bile salts, vitamin K)

(II) **Propofol**

Chemical structure of propofol:

- Propofol is an alkyl phenol derivative (2,6-diisopropylphenol)



Formulation of propofol:

- Propofol is highly lipid soluble, and thus requires a lipid vehicle for emulsification in solution
- As a result, it is prepared as a white "oil-in-water" emulsion:
    - (1) Propofol (1 or 2%)
    - (2) Oil phase – Soybean oil (10%)
    - (3) Emulsifying agents – Glycerol (2.25%), purified egg phosphatide or egg lecithin (1.2%), and LC TGs
    - (4) Preservative/anti-microbial – Either Sodium metabisulfite (pH 4.5-6.5) with generic propofol, OR Disodium edenate and NaOH (pH 7-8.5) with Diprivan
    - (5) Water
- Alternate emulsifying agents can be used – Liposomes, cyclodextrins, or MC TGs

Mechanism of action of propofol:

- Propofol potentiates the inhibitory effects of GABA on GABA-A receptor in the CNS (esp the brain):
    - GABA-A receptor is a pentameric ligand-gated receptor (2α, 2β, γ) that is associated with a central Cl^- channel pore. It is found widespread in the CNS and is mainly postsynaptic in location
    - Propofol acts at a specific subunit of the receptor SEPARATE from the binding site of GABA on the α-subunit
    - It causes decreased rate of dissociation of GABA from the receptor, which effectively results in prolonged GABA-A receptor activation and opening of the central Cl^- channel – This leads to increased Cl^- influx, which causes hyperpolarisation and inhibition of the postsynaptic neuron

Pharmacokinetics of propofol:

- Overview:
    - When given as an IV bolus, propofol causes a rapid onset of LOC as high effect-site (Eg. brain) concentrations of propofol is achieved due to its:
        - (i) High lipid solubility (Ie. easily crosses the BBB)
        - (ii) Short effect-site equilibrium time
        - (iii) Entirely unionised fraction at physiological pH (despite large proportions being protein bound)

- When given as an IV bolus, propofol is associated with a rapid offset:
  - This is caused by rapid distribution of propofol (Ie. short "distribution half-life" or t ½ α) from the central compartment to peripheral tissues (esp the lungs), which causes the effect-site and plasma concentrations to fall rapidly
  - Clearance (metabolism and excretion) plays a negligible role
- When given as an IV infusion, offset of propofol is slightly prolonged:
  - Peripheral compartments are saturated with propofol, such that with cessation of the infusion, propofol redistributes back into plasma and maintains the plasma and effect-site concentrations
  - Clearance of propofol (hepatic and extrahepatic metabolism, and renal excretion) plays a more important role now in reducing plasma concentrations and causing offset
  - Of note, the rapid clearance of propofol prevents excess accumulation of the drug with prolonged infusions:
    - CSHT of propofol is only slightly increased with prolonged infusions (5 mins at 10 mins; 9 mins at 3 hrs; < 40 mins at 8 hrs)
    - This is because the rate of redistribution of propofol to the central compartment (distribution half-life; t ½ α) is only moderately faster than the rate at which it is eliminated from the central compartment by redistribution and clearance (metabolism and excretion) (elimination half life; t ½ β)

Absorption	Only given as IV bolus or infusion
Distribution	- $V_{DISTRIBUTION}$ ~ 3.5-4.5 L/kg (Nb. largest of IV induction agents) - pKa ~ 11 (weak organic acid; Nb. entirely unionised at physiological pH) - 98% protein-bound - Short effect-site equilibrium time - Short "Distribution half life" (t ½ α) ~ 1-4 minutes (Nb. significant amounts of propofol are taken up into the LUNGS)
Metabolism and Excretion	- Very high clearance rate (30-60 mL/kg/min), which vastly exceeds HBF. This implies propofol is cleared two ways: - (1) Hepatic clearance o Propofol is undergoes oxidative metabolism by CYP450 to 4-hydroxypropofol (33% active) via hydroxylation o This active metabolite is then transformed via glucuronidation and/or sulphation into an inactive and water-soluble metabolite - (2) Extrahepatic clearance o (a) Pulmonary first-pass metabolism (some propofol distributed to the lung is metabolised by CYP450 into 4-hydroxypropofol) o (b) Renal metabolism of propofol via glucuronidation - 99.7% of inactive metabolites are renally-excreted (such that < 0.3% is renally-excreted unchanged) - Note: Despite its clearance via hepatic and renal routes, renal and hepatic dysfunction does NOT impair clearance of propofol! - CSHT of 5 mins (at 10 mins), 9 mins (at 3 hrs), < 40 mins (at 8 hrs) - Slightly longer "Elimination half-life" (t ½ β) ~ 0.5-1.5 hrs

<u>Clinical uses of propofol</u>:

- (1) Induction of GA:

- Propofol is an ideal induction drug due to its:
  - (i) Rapid onset (one arm-brain circulation time; 30 seconds)
  - (ii) Relatively rapid offset (~10 minutes after IV bolus) with minimal PONV, complete awakening and lack of residual CNS effects
- Doses:
  - IV bolus of 1.5-2.5 mg/kg (Nb. 50% higher doses for children due to large V_D and clearance rates; 25-50% smaller doses for elderly due to smaller V_D and clearance rates)
  - TCI – Set target [ ] at 4-8 μg/mL (less if premedicated with midazolam 2 mg and fentanyl 100 μg). If sick or old, set target [ ] at 3-4 μg/mL, and increase by 0.5-1 μg/mL every minute to effect. This takes 60-120 seconds
  - Infusion pump – Start with 12 mg/kg/hr for 10 mins (unless already premedicated), then 10 mg/kg/hr for 10 mins, then 8 mg/kg/hr for 10 mins, then 6 mg/kg/hr for 10 mins
- Co-administration of midazolam and/or fentanyl prior to induction with propofol has synergistic effects – This leads to faster onset of induction and lower total dose requirements

- (2) Maintenance of GA:
  - Propofol is an ideal maintenance drug because:
    - (i) Rapidly titratable due to its short effect-site equilibrium
    - (ii) Relatively rapid offset (even with prolonged infusions) as it has a short CSHT (that is minimally influenced by duration of infusion) and does not accumulate in the body with an infusion
    - (iii) Minimal PONV and complete awakening with lack of residual CNS effects following offset
  - Doses:
    - TCI – Target [ ] ~ 3-6 μg/mL (titrate to effect based upon patient factors, surgical factors and anaesthetic factors)
    - Infusion pump – Rate of 6-12 mg/kg/hr (titrate rate to effect)
- (3) IV sedation for use in regional anaesthesia or ICU:
  - Propofol is an ideal sedation drug for all the reasons listed above, but in the ICU setting it can be used to:
    - (i) Block haemodynamic responses (Eg. post-cardiac surgery)
    - (ii) Manage raised ICP (Eg. post-head trauma)
    - (iii) Permit mechanical ventilation
  - Doses:
    - TCI – Target [ ] ~0.5-2 μg/mL
    - Infusion pump – Rate of 1-4 mg/kg/hr + midazolam or opioid
- (4) Non-hypnotic uses:
  - (a) Anticonvulsant
    - Increases seizure threshold via GABA-mediated neuronal inhibition
    - Used to treat status epilepticus; when used for ECT it shortens the duration of seizures
  - (b) Antiemetic agent
    - Ideal for PONV and chemotherapy-induced N/V
    - Unknown mechanism of action (?D2-receptor antagonism)
    - Given at subhypnotic bolus doses (which means no sedation, lack of side-effects and rapid onset)
  - (c) Antipruitic effect (esp for neuraxial opioids or cholestasis)

<u>Pharmacodynamic effects of propofol</u>:

CNS effects	
General effects	- Conscious sedation to full general anaesthesia

	- Smooth and rapid induction with clear and rapid recovery - Amnesic effect - No analgesia
CBF	Decreased due to cerebral vasoconstriction from decreased metabolism
ICP (and IOP and CPP)	- Decreased ICP due to fall in CBF - CPP may decrease – Due to significant hypotensive effects of propofol (Ie. fall in MAP may be greater than that for ICP) - Decreased IOP
$CMRO_2$	Decreased
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage), then to burst suppression, and finally silent (isoelectric) EEG at very high doses - Anticonvulsant used to treat grand-mal seizures and status epilepticus - Reduces seizure duration during ECT
CVS effects	
HR	- Generally unchanged (due to depression of BRR and SNS outflow) - Significant bradycardia and asystole can occur - Due to disinhibited vagally-mediated outflow (due to loss of BRR and SNS outflow) - Significant bradycardia can compromise preload, which can lead asystole – This tends to occur at extreme ages, patients taking -ve chronotropic agents, premedication with fentanyl, or surgery associated with oculocardiac reflex - Can be resistant to anticholinergics, thus treat with beta-agonist (isoprenaline)
CO	Dose-dependent decrease by up to 20% (due to direct –ve inotropy and myocardial depression – Caused by attenuated IC levels of Ca^{2+} as a result of inhibition of transsarcolemmal Ca^{2+} influx)
BP	- Dose-dependent decrease by 15-25% due to fall in SVR and C.O. - Exacerbated by – (i) Larger doses and more rapid rate of injection, (ii) Older age (due to smaller clearance and V_D), (iii) Hypovolaemia (smaller V_D), and (iv) LV dysfunction (IHD/CCF)
SVR	Dose-dependent decrease (due to impaired sympathetic vasoconstrictor activity, which results in vasodilation)
Haemodynamic sequelae of AW instrumentation	- Fall in BP can be reversed by hypertensive sequelae of AW instrumentation - Fall in BP can blunt the hypertensive response to AW instrumentation
Arrhythmogenicity	Nil. Also QTC not prolonged
Coronary BF and CMRO2	Decrease in myocardial O_2 consumption and myocardial perfusion, BUT myocardial ischaemia can occur due to regional mismatch in myocardial O_2 supply and demand
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Dose-dependent ventilatory depression (due to decreases in both TV and RR), which can lead to apnoea - Increased resting $PaCO_2$
Ventilatory response to $PaCO_2$ and PaO_2	- Decreased - Increased apnoeic threshold
Effect on AW	- Bronchodilation (although sodium metabisulfite can cause bronchoconstriction!) - Depresses UAW reflexes (good for AW instrumentation but risk of aspiration and AW obstruction)
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact

GI, GU, metabolic and other effects

- Does not adversely impact renal/hepatic function
- Anti-emetic effect
- Anti-pruritic effect
- Does not trigger MH
- Does not trigger acute porphyric crisis
- Inhibits platelet aggregation

Issues with injection

- Pain on injection (as a result of the emulsifying agents) is the MOST common side-effect (30%) – Minimise this by injecting into large vein (cf. dorsum of hand), mixing propofol with 1% lignocaine (BUT risk of PE due to formation of oil droplets), or premedicating with a potent short-acting opioid
- Venous thrombosis and phlebitis (< 1%)
- Intra-arterial injection causes severe pain but NO vascular compromise!

Relevant adverse or undesired effects

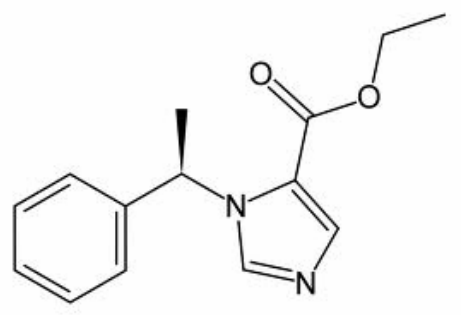
- Low risk of allergic reactions and anaphylaxis:
    - Mainly due to propofol – Reactions occur on first exposure to propofol due to previous sensitisation to phenol and diisopropyl groups on other drugs
    - Rarely due to additives – (i) Egg allergies often to albumin/protein (NOT egg lecithin or phosphatide), (ii) Soybean allergies are due to protein in soybeans (which are REMOVED from soybean oil)
- Propofol infusion syndrome:
    - Long-term sedation (> 24 hrs) with propofol as an IV infusion can lead to:
        - (i) Fat overload (hyperlipidaemia and fat infiltration of heart, lungs, liver, kidneys)
        - (ii) Rhabdomyolysis
        - (iii) Metabolic acidosis
        - (iv) Cardiac arrhythmia and death
    - Due to emulsifying agents (glycerol, egg lecithin/phosphatide, TGs), which disrupt FA metabolism (esp disrupting the ETC), leading to cytopathic hypoxia and muscle necrosis (esp cardiac and skeletal muscle)
    - Thus, propofol should NOT be used for sedation in patients < 16 y.o., and used > 48 hours or > 5 mg/kg/hr in adults
- "Excitatory phenomenon":
    - Propofol can mimic "seizures" on induction or emergence (Eg. muscle twitching, dystonic and choreiform movements, hiccupping) but WITHOUT EEG seizure activity
    - Due to spontaneous excitatory movements of subcortical origin (Ie. not true cortical seizure activity)
    - Nb. Does NOT induce seizures in epileptic patients!
- Addictive and abusive potential (Eg. due to amorous hallucinations, esp on recovery)
- Bacterial growth and risk of sepsis:
    - Emulsifying agents used in the formulation promotes bacterial growth (esp E. coli and P. aeruginosa). This risk is decreased with use of:
        - (i) Preservatives/antimicrobial agents (Eg. sodium metabisulfite)
        - (ii) Aseptic technique – Draw propofol into sterile syringe and administer ASAP. Discard propofol if not used within 6 hrs of opening an ampoule
- Excretion of green urine and production of green hair with prolonged infusions (due to accumulation of phenols)

Drug interactions

(III) **<u>Etomidate</u>**:

Chemical structure of etomidate:

- Etomidate is a carboxylated imidazole-containing compound
- The imidazole group allows it to be – (i) Water-soluble at acidic pH, and (ii) Lipid-soluble at physiological pH
- It has two isomers – R+ and S- (R+ is 5X more potent!)



Formulation of etomidate:

- Etomidate is available as a clear and colourless aqueous solution at a pH of 6.9. It contains:
    - (1) Etomidate (0.2%) – Racemic mixture
    - (2) Either – (a) Propylene glycol (35%), which causes more pain on injection, or (b) Fat emulsion (less pain on injection)
    - (3) Water

Mechanism of action of etomidate:

- Etomidate potentiates the inhibitory effects of GABA on GABA-A receptor in the CNS (esp the brain):
    - GABA-A receptor is a pentameric ligand-gated receptor (2α, 2β, γ) that is associated with a central Cl^- channel pore. It is found widespread in the CNS and is mainly postsynaptic in location
    - Propofol acts at a specific subunit of the receptor SEPARATE from the binding site of GABA on the α-subunit
    - It causes decreased rate of dissociation of GABA from the receptor, which effectively results in prolonged GABA-A receptor activation and opening of the central Cl^- channel – This leads to increased Cl^- influx, which causes hyperpolarisation and inhibition of the postsynaptic neuron
- Although etomidate is prepared as a racemic mixture, the R+ isomer has pharmacological activity (5X more than S- isomer)

Pharmacokinetics of etomidate:

- Overview:
    - When given as an IV bolus, etomidate causes a rapid onset of LOC as high effect-site (Eg. brain) concentrations of it is achieved due to its:
        - (i) Moderate lipid solubility (Ie. crosses the BBB)
        - (ii) Moderate effect-site equilibrium time
        - (iii) Entirely unionised fraction at physiological pH (despite large proportions being protein bound)
    - When given as an IV bolus, etomidate is associated with a rapid offset:
        - This is caused by rapid distribution of etomidate (Ie. short "distribution half-life" or t ½ α) from the central compartment to peripheral tissues (esp VRG, muscle and fat), which causes the effect-site and plasma concentrations to fall rapidly
        - Clearance (metabolism and excretion) plays a negligible role

- When given as an IV infusion, offset of etomidate is slightly prolonged:
  - Peripheral compartments are saturated with etomidate, such that with cessation of the infusion, it redistributes back into plasma and maintains the plasma and effect-site concentrations
  - Clearance of etomidate (hepatic and plasma metabolism, and biliary and renal excretion) plays a more important role now in reducing plasma concentrations and causing offset
  - Of note, the rapid clearance of etomidate prevents excess accumulation of the drug with prolonged infusions – CSHT of etomidate is only slightly increased with prolonged infusions. This is because the rate of its redistribution to the central compartment (distribution half-life; t ½ α) is only moderately faster than the rate at which it is eliminated from the central compartment by redistribution and clearance (metabolism and excretion) (elimination half life; t ½ β)

Absorption	Given as an IV bolus (can also be given as an infusion)
Distribution	- $V_{DISTRIBUTION}$ ~ 2.2-4.5 L/kg (Nb. 2nd largest of IV induction agents) - pKa ~ 4.2 (weak base; Nb. 99% unionised at physiological pH) - 75% protein-bound - Moderate effect-site equilibrium time - Short "Distribution half life" (t ½ α) ~ 1-4 minutes (Nb. etomidate is redistributed to VRG, muscle and fat)
Metabolism and Excretion	-Clearance rate (10-20 mL/kg/min): - Metabolism – Hydrolysis of ethyl ester side chains by hepatic and plasma esterases into an inactive water-soluble metabolite - Excretion – 97% excreted as inactive metabolites (85% in urine; 12% in bile). Only 3% excreted renally unchanged - Slightly longer "Elimination half-life" (t ½ β) ~ 2-5 hrs - CSHT is more likely to be increased with a continuous infusion (cf. propofol)

Clinical uses of etomidate:

- Etomidate is used an alternate thiopentone and propofol for the induction and/or maintenance of GA in a patient with an unstable CVS
- The induction dose is 0.2-0.4 mg/kg
- Benefits of etomidate include:
  - (1) Being CVS stable
  - (2) Rapid onset within one arm-brain circulation time (30-60 secs)
  - (3) Rapid awakening (IV bolus lasts 5-10 minutes) without hangover or significant psychomotor dysfunction (Nb. more than propofol though)
  - (4) Relatively rapid offset (even with prolonged infusion or repeated boluses) as it has a relatively short CSHT (Nb. but longer than propofol) and does not accumulate in the body with an infusion
- Major drawbacks of etomidate are its side-effects (especially transient depression of adrenocortical function, but also increased PONV, proconvulsant tendency and risk of porphyric crisis)

Pharmacodynamic effects of etomidate:

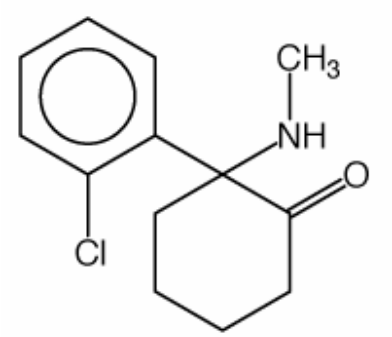
CNS effects	
General effects	- Conscious sedation and amnesia to full general anaesthesia - Smooth and rapid induction with rapid recovery (however, mild psychomotor dysfunction) - No analgesia
CBF	Decreased due to cerebral vasoconstriction from decreased metabolism

ICP (and IOP and CPP)	- Decreased ICP due to fall in CBF - CPP maintained due to minimal fall in MAP - Decreased IOP
$CMRO_2$	Decreased
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage), then to burst suppression, and finally silent (isoelectric) EEG at very high doses - Anticonvulsant used to treat grand-mal seizures and status epilepticus - Ideal for ECT as it has minimal effects on duration of seizures
CVS effects	
HR	Minimal change at induction doses (compensatory increase in HR occurs at higher doses due to BRR)
CO	Minimal change at induction doses (-ve inotropic effects and fall in CO occur at higher doses
BP	- Dose-dependent decrease mainly due to fall in SVR (and at higher doses, fall in CO/-ve inotropy also contributes to fall in BP) - At induction doses, BP falls by 15% (less prominent cf. other IV agents)
SVR	Decreased due to peripheral vasodilation
Haemodynamic sequelae of AW instrumentation	Hypertensive response to AW instrumentation cannot be blunted by the fall in BP caused by etomidate – Thus, opioids must be given concurrently
Arrhythmogenicity	Nil. QTc not prolonged
Coronary BF and CMRO2	Cardiac MRO2 and O2 delivery stable as –ve inotropic effects minimal at induction doses
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Dose-dependent ventilatory depression (due to decreases in both TV and RR), which can lead to apnoea at high doses - At induction doses, significant respiratory depression and apnoea are unlikely if given alone (cf. propofol and barbiturates) - Mildly increased resting $PaCO_2$
Ventilatory response to $PaCO_2$ and PaO_2	- Mild depression of ventilatory response - Slight increase in apnoeic threshold
Effect on AW	- No effect on AW smooth muscle - Depresses UAW reflexes (good for AW instrumentation but risk of aspiration and AW obstruction)
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact
GI, GU, metabolic and other effects	
- No effect on hepatic or renal function - Decreased antiplatelet activity	
Issues with injection	
- Pain on injection (only with propylene glycol; not with lipid solution) - Risk of venous thrombosis - No issues with intra-arterial injection	
Relevant adverse or undesired effects	
- Adrenocortical suppression o Dose-dependent inhibition of 11-β-hydroxylase and 17-α-hydroylase, which blocks the cholesterol conversion to cortisol and aldosterone o A single IV dose has little effect in a fit/healthy patient, but this poses an issue if unwell with suppressed cortisol function (Ie. septic, haemorrhagic shock), or with repeated dosing or long-term infusion - Risk of inducing porphyric crisis - Increased PONV	

- Excitatory phenomenon and proconvulsant activity: o Etomidate can mimic "seizures" on induction or emergence (Eg. muscle twitching, dystonic and choreiform movements, hiccupping) – This is due to spontaneous excitatory movements of subcortical origin (Ie. not true cortical seizure activity) o 20% of patients demonstrate generalised epileptiform EEG activity (caution in patients with focal epilepsy as it could trigger seizures) - Histamine release and allergic reactions rare
Drug interactions

(IV) **Ketamine**:

Chemical structure of ketamine:
- Ketamine is a arylcyclohexylamine, which is a derivative of phencyclidine
- It has two isomers (S+ and R-), of which the S+ isomer of ketamine is:
  - (i) Is 2-3X more potent
  - (ii) Provides more intense analgesia
  - (iii) Has more rapid metabolism (and hence, recovery)
  - (iv) Has fewer side-effects (esp cardiac depression, salivation, emergence reactions, cognitive impairment)
  - (v) Possess ischaemic preconditioning



Formulation of ketamine:
- Ketamine is available as a clear and colourless aqueous solution at a pH of 3.5-5.5. It contains:
  - (1) Ketamine (10, 50 and 100 mg/mL) – Either racemic preparation or S+ isomer only preparation. Highly water-soluble
  - (2) Preservative – Benzethonium chloride (in only the 50 and 100 mg/mL solutions)
  - (3) Water

Mechanism of action of ketamine:
- (1) Main mechanism – Inhibits activation of excitatory NMDA receptors by glutamate in a non-competitive manner:
  - NMDA receptor is an excitatory pentameric ligand-gated receptor with a central cation channel. Receptor binding by glutamate and glycine (co-agonist) activates the receptor by displacing a Mg^{2+} "plug", thereby permitting influx of cations (Ca^{2+}, Na^{+}) and depolarising the neuron
  - Ketamine (esp S+ isomer) non-competitively binds to the receptor's phencyclidine site, thereby inhibiting its activation by glutamate
- (2) Minor mechanism – Ketamine also acts at other receptors:
  - Potentiates inhibitory effects of GABA at GABA-A receptors
  - Antagonises mAChR

- Acts on opioid receptors (μ, δ, κ)
- Inhibits monoamine receptors in pain pathways
- Acts via VG Na^+ channel (similar to local anaesthetics)
- Acts at L-type Ca^{2+} channels

Pharmacokinetics of ketamine:

- Overview:
  - When given as an IV bolus, ketamine has a very rapid onset due to its:
    - (i) Very high lipid solubility (Ie. crosses the BBB)
    - (ii) Small proportion of protein-binding
  - When given as an IV bolus, ketamine is associated with a rapid offset:
    - This is caused by rapid distribution of ketamine (Ie. short "distribution half-life" or t ½ α) from the central compartment to peripheral tissues (esp VRG, muscle and fat) due to its low amount of protein-binding, which causes the effect-site and plasma concentrations to fall rapidly
    - Clearance (hepatic metabolism and renal excretion) plays a negligible role
  - When given as an IV infusion, the emergence time is prolonged:
    - Peripheral compartments are saturated with ketamine, such that with cessation of the infusion, it redistributes back into plasma and maintains the plasma and effect-site concentrations
    - Clearance of ketamine (hepatic metabolism and renal excretion) plays a more important role now in reducing plasma concentrations and causing offset

Absorption	- PO: Oral bioavailability 20% (large first-pass hepatic metabolism) - IM: Large doses need to be given due large first-pass hepatic metabolism - Given as an IV bolus or infusion
Distribution	- $V_{DISTRIBUTION}$ ~ 2.5-3.5 L/kg - pKa ~ 7.5 - 25% protein-bound - Moderate effect-site equilibrium time - Short "Distribution half life" (t ½ α) ~ 11 minutes
Metabolism and Excretion	- Clearance rate (16-18 mL/kg/min): - Metabolism – High HER (1.0). Hepatic CYP450 demethylates ketamine to norketamine (30% active and has prolonged analgesic effects), which is then hydroxylated and conjugated to glucuronide to form an inactive water-soluble metabolite - Excretion – < 4% renal excretion unchanged (96% excreted as inactive metabolites) - Slightly longer "Elimination half-life" (t ½ β) ~ 2-3 hrs

Clinical uses of ketamine:

- Ketamine is deemed a "complete" anaesthetic as it causes:
  - (i) Unconsciousness
  - (ii) Amnesia
  - (iii) Analgesia
- Its indications for clinical use include:
  - (1) Induction and maintenance of anaesthesia
    - Produces "dissociative anaesthesia":
      - Characterised by apparent wakeful state with eyes open, slow nystagmus gaze, purposeful movements (independent of surgical stimulus) BUT non-communicative

- Onset of within 30-60 secs (2-4 mins IM), with awakening in 5-10 mins (10-20 mins IM). Full level of consciousness is achieved within 60-90 minutes
- Caused by dissociation of the thalamus (relays sensory input from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with sensory awareness)

▪ Dose:
- IV 1-2 mg/kg (or IM 5-10 mg/kg), followed infusion of 10-30 μg/kg/min
- For brief procedures, IV 10-20 mg bolus (titrated to effect)

▪ Useful for certain cases:
- (i) Its indirect CVS effects are beneficial in patients with compromised CVS function (Eg. shock, elderly, hypovolaemia), and can reduce inotropic support requirements also
- (ii) Asthmatic patients due to its bronchodilatory effects (Nb. can be used to manage status asthmaticus!)
- (iii) Patients undergoing a brief procedure (Eg. dressing change (esp for burns), wound debridement, skin grafting) – Can be used as a sole agent as it provides analgesia, permits spontaneous ventilation without AW compromise
- (iv) Children and mental patients (IM ketamine is useful)

▪ Issues:
- (i) Emergence delirium due to psychotomimetic effects
- (ii) Excess AW secretion and salivation (requires premedication with an antisialogogue – preferably glycopyrryolate to minimise CNS effects)
- (iii) Should be avoided in patients with IHD, CCF, arterial aneurysms, uncontrolled HTN, pulmonary HTN due to its indirect CVS effects
- (iv) Raises ICP (an issue with neurosurgical patients)
- (v) Cannot be used for ophthalmic procedures (due to nystagmus and raised IOP)
- (vi) Increased lactate levels (despite adequate BP) – Due to increased SVR and decreased tissue perfusion
- (vii) Aspiration risk remains despite intact UAW reflexes due to increased salivation
- (viii) Tolerance to its effects occur with repeated dosing/infusions (esp analgesia)

o (2) Analgesia

▪ Mechanism:
- Dissociates the thalamus from the limbic cortex, thus preventing relaying of pain sensation from the RAS to the limbic cortex for processing
- Inhibits spinal cord sensitisation to pain (Eg. allodynia, hyperalgesia) caused by activation of NMDA receptors in the dorsal horn
- Blocks polysynaptic reflexes in the spinal cord

▪ Ideal for:
- (i) Post-operative pain and chronic pain (esp somatic pain; but not visceral pain)
- (ii) Preventing and reversing opioid tolerance when given concurrently with them
- (iii) Treating tourniquet pain and HTN under GA

- Administration:
    - IV bolus/infusion at subanaesthetic doses – IV bolus of 0.2-0.5 mg/kg +/- IV infusion at 2-10 μg/kg/min
    - Oral ketamine provide better analgesia than IM ketamine due to hepatic metabolism to norketamine
    - Neuraxial ketamine has limited value (intrathecal ketamine provides brief and variable analgesia, and requires Adr to slow absorption; epidural ketamine has little effects alone and requires opioids/LAs for synergistic effect)
    - Can also be given rectally and nasally
- (3) Preoperative sedative (esp for children)
    - Oral (6 mg/kg) or IM with sedative effect within 15-30 minutes, but may require premedication with an antisialogogue or opioid/benzodiazepine to reduce excess secretions and emergence delirium

Pharmcodynamic effects of ketamine:

CNS effects	
General effects	- Dissociative anaesthesia - Analgesia (at subanaesthetic doses) - Amnesia
CBF	Increased due to cerebral vasodilation
ICP (and IOP and CPP)	- Increased ICP due to rise in CBF (Nb. this can be reduced by mechanical ventilation, or pharmacologically with thiopentone) - Raised IOP
$CMRO_2$	Increased
EEG and seizure activity	- Dose-related decrease in cortical EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage), then burst suppression - Excitatory EEG activity is seen ONLY at the thalamic and limbic systems - Used as an anticonvulsant
CVS effects	
HR CO BP SVR Haemodynamic sequelae of AW instrumentation Arrhythmogenicity Coronary BF and CMRO2	- Ketamine has indirect effects on the CVS via – (i) direct central (CNS) stimulation of SNS outflow, and (ii) inhibition of NAd reuptake (centrally and peripherally) - This leads to: - Increased HR (as BRR is maintained) - Increased CO - Increased BP - Increased $CMRO_2$ (and also increased coronary blood flow) - Nb. SVR is unchanged despite increased SNS activity - Nb. There are no arrhythmogenic effects (even with the use of Adr) - These indirect effects are beneficial in patients with compromised CVS function (Eg. shock, elderly, hypovolaemia), and can reduce inotropic support requirements also. BUT they should be avoided in patients with IHD, CCF, arterial aneurysms, uncontrolled HTN, pulmonary HTN - Ketamine is a –ve inotrope as it has direct myocardial depressive effects (esp R- isomer) – This produces a fall in CO and BP when SNS outflow is exhausted (Eg. end-stage shock) or inhibited (Eg. SAB, use of volatile agents, opioids, benzodiazepines) - Ketamine (only the R- isomer) inhibits ischaemic preconditioning as it inhibits the K_{ATP} channel
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Minimal effect on MV, BUT decreased RR and apnoea can occur with rapid IV bolus or concurrent opioids/benzodiazepines

	- Resting $PaCO_2$ unchanged
Ventilatory response to $PaCO_2$ and PaO_2	Maintained. No increase in apnoeic threshold
Effect on AW	- Potent bronchodilator (good for bronchospasm) - UAW reflex maintained - Increased UAW gland secretions
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact

GI, GU, metabolic and other effects

- No hepatic/renal effects
- Increased salivation
- Increased PONV
- Increased uterine tone
- Does not trigger MH
- Does not trigger acute porphyric crisis
- Does not cause histamine release or allergic reactions
- Inhibits platelet aggregation

Issues with injection

- None

Relevant adverse or undesired effects

- Emergence delirium:
    - Psychotomimetic effects (Eg. vivid and unpleasant dreams, illusions, hallucinations, and delirium) can occur in the post-operative period
    - It has an incidence of 5-30%
    - It generally occurs with – (i) Increasing age > 15 y.o. (less common in children and elderly), (ii) Female gender, (iii) Doses > 2 mg/kg IV, (iv) Known psychiatric/personality issues, (v) Use of the R- isomer, and (vi) Concurrent use with atropine and droperidol
    - Prevented by – (i) Premedication with benzodiazepine (and also opioids), (ii) Concurrent use of thiopentone or inhaled agents, (iii) Frequent IV dosing of ketamine, (iv) Prospective discussion of side-effects with patient, and (v) Being left undisturbed in recovery
- Addictive and subject to abuse
- Tolerance with infusion/repeated doses (esp to analgesia) due to induction of hepatic enzymes
- Causes hypertonia and can precipitate myoclonic seizure-like activity

Drug interactions

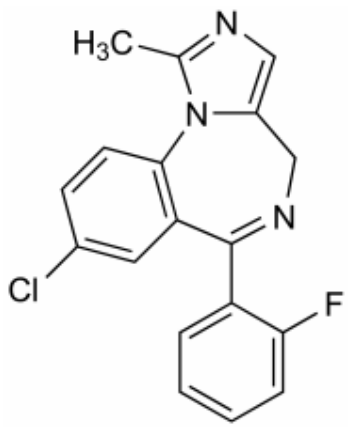
- Muscle relaxants – Ketamine potentiates the effects of non-depolarising agents, and can prolong "sux apnoea" (as it inhibits plasma cholinesterase)
- Theophylline – Both drugs together reduce the seizure threshold, and can stimulate seizures
- Volatile agents (esp halothane) – Both agents depress myocardial function
- Thiopentone – Both drugs are incompatible together
- Diazepam – Attenuates the CVS effects of ketamine and prolongs its t ½

(V) **<u>Midazolam</u>**

<u>Chemical structure of midazolam</u>:

- Basic structure of benzodiazepines:
    - Basic two ring structure – Benzene ring fused to a seven-membered diazepine ring (5 C-atom; 2 N-atom)
    - For pharmacological activity, benzodiazepines will generally have:

        - (i) Another benzene ring is added to the diazepine ring at position-5 – This forms 5-aryl-1,4-benzodiazepine
        - (ii) Halogen fused onto the original benzene ring
        - (iii) Carbonyl group on position-2
- Midazolam possesses an "Imidazole" ring structure that displays pH-dependent ring opening and closing:
    - At pH < 4 – Ring opens to form an ionised molecule (water-soluble). Thus, the parental solution is buffered at pH 3.5!
    - At pH > 4 – Ring closes to form an unionised molecule (lipid-soluble). This occurs at physiological pH



Formulation of midazolam:

- Midazolam is prepared as a clear and colourless aqueous solution at pH 3.5 – This favours the ionised open imidazole-ring structure (Ie. this makes it water-soluble so that it does not require a solubilising agent)
- Concentrations of 1, 2 and 5 mg/mL

Mechanism of action of midazolam:

- Benzodiazepines potentiates the inhibitory effects of GABA on GABA-A receptor in the CNS (esp the brain):
    - GABA-A receptor is a pentameric ligand-gated receptor (2α, 2β, γ) that is associated with a central Cl^- channel pore. It is found widespread in the CNS and is mainly postsynaptic in location
    - Benzodiazepines act at the α-subunit of the receptor (similar to GABA, BUT at a separate binding site on the α-subunit):
        - Acts via α1-subunit (most abundant in the brain; 60%) to cause sedation, and α2-subunit to cause anxiolysis
        - They do NOT activate the receptor directly – Instead they enhance the affinity of the receptor for GABA (Ie. prolonged GABA-A receptor activation when the receptor is bound by GABA), leading to prolonged central Cl^- channel opening, increased Cl^- influx, and hyperpolarisation/inhibition of the postsynaptic neuron
- The receptor complex has separate binding sites for other agents (Eg. barbiturates, propofol, etomidate, EtOH):
    - Synergistic effects on GABA-A receptor-mediated CNS inhibition (Ie. risk of OD/life-threatening CNS depression) occur when other GABA-mediated agents are given concurrently
    - Cross-tolerance occurs between different agents acting on the receptor (Ie. benzodiazepines can be used for EtOH detoxification)

Pharmacokinetics of midazolam:

- Overview:
  - IV midazolam has rapid onset (30-60 seconds) because it can rapidly cross the BBB due to its (i) high lipid solubility, (ii) largely unionised at physiological pH (despite large degree of protein-binding), and (iii) Small V_D
  - However, its requires sufficient time for peak clinical effect (3-5 minutes) due to its slow effect-site equilibrium time
  - IV midazolam has a short duration of action (30 minutes) because:
    - (i) It rapidly redistributes to peripheral tissues (t ½ α ~ 6-15 minutes)
    - (ii) It has rapid clearance by hepatic/intestinal metabolism and renal excretion

Absorption	- PO: Rapid absorption from GI tract with 50% bioavailability (heavy first-pass metabolism) - IM: 80-100% bioavailability - Given as IV bolus or infusion
Distribution	- High lipid solubility - $V_{DISTRIBUTION}$ ~ 1-1.5 L/kg - pKa ~ 6.15 (Nb. 90% unionised at physiological pH) - 98% protein-bound - Long effect-site equilibrium time (1-5.5 minutes) - Short "Distribution half life" (t ½ α) ~ 6-15 minutes

Metabolism and Excretion	- Clearance rate (6-8 mL/kg/min):
	  - Metabolism – Oxidative metabolism by hepatic and small intestinal CYP450 3A4, which produces:
	  o Main metabolite – 1-hydroxymidazolam (50% activity), which is rapidly conjugated to glucuronide-1-hydroxymidazolam (high activity at high concentrations, which occurs with chronic use, prolonged infusions or with renal disease)
	  o Minor metabolite – 4-hydroxymidazolam, which is glucuronidated also
	  o Nb. Metabolism is slowed by liver disease, age, and inhibitors of CYP450 3A4 – Fentanyl, alfentanyl, cimetidine, erythromycin, CCBs, antifungals
	  - Excretion – Both inactive and active metabolites are renally excreted
	- Slightly longer "Elimination half-life" (t ½ β) ~ 1-4 hrs
	- Small CSHT (cf. diazepam, lorazepam) – Can be used for infusion
	- Note – Due to EXTENSIVE hepatic metabolism, elimination half-life, V_D and renal clearance is NOT affected by renal failure

Clinical uses of midazolam:

- (1) Induction of anaesthesia:
  - IV 0.1-0.2 mg/kg provides rapid onset (30-60 seconds) but delayed peak clinical of anaesthesia (3-5 minutes) that lasts for 30 minutes
  - Co-administering other CNS depressants that act synergistically (Eg. fentanyl) help to (i) Hasten the onset of LOC, and (ii) Reduce the dose of midazolam required
  - Causes minimal CVS depression (unless given with other CNS depressants)
- (2) Maintenance of anaesthesia:
  - Given to supplement opioid, propofol and inhaled anaesthetic agents in maintaining GA

    - Benefits – (i) Allows lower doses of midazolam and co-administered agents (Eg. MAC-sparing, reduces opioid requirements), (ii) Minimises PONV, and (iii) Minimises emergence excitement
    - Issues – (i) Prolonged awakening following GA, (ii) Slightly longer CSHT (cf. propofol)
- (3) IV sedation for brief procedures or during regional anaesthesia:
    - IV 1 to 2.5 mg with similar onset/offset profile as induction of GA
    - Benefits – (i) Rapid onset, (ii) Greater amnesic effects (cf. sedation), (iii) Less post-operative sedation, (iv) Minimal CVS depression
    - Issues – (i) Ventilatory depression (esp if other CNS depressants given, elderly or COPD), and (ii) Slightly longer CSHT (cf. propofol)
- (4) IV sedation in ICU
    - IV 0.5-4 mg bolus, then infusion of 1-7 mg/hr
    - Issues of "delayed emergence" after cessation of a prolonged infusion:
        - This is because midazolam has a slightly prolonged CSHT due to:
            - (i) Clearance being dependent more on hepatic clearance/metabolism rather than distribution (as peripheral tissues are saturated)
            - (ii) Presence of pharmacologically active metabolites
        - This is exacerbated if – (i) Larger doses are given, (ii) Longer infusion, (iii) Older patient (less clearance), and (iv) More obese patient (more V_D)
        - This can be prevented by giving concurrent opioids (Eg. morphine), which reduces the doses of midazolam used
- (5) Preoperative medication (esp for children)
    - PO 0.25 mg/kg to 0.5 mg/kg syrup (up to max 1 mg/kg) given 20-30 minutes prior to surgery permits sedation and anxiolysis without respiratory depression, delayed emergence and significant amnesia
- (6) Anticonvulsant (to treat grand-mal seizures and status epilepticus)

Pharmacodynamic effects of midazolam:

CNS effects	
General effects	- (i) Anxiolysis - (ii) Sedation/hypnosis - (iv) Spinal cord-mediated skeletal muscle relaxation (but not adequate for surgery; does not change dose of NMBD) - (v) Anterograde amnesia – Note that amnesic effects more potent than sedative (Ie. awake but remain amnesic of events thereafter) - Absence of analgesic effects
CBF	Dose-dependent decrease due to cerebral vasoconstriction from decreased metabolism
ICP (and IOP and CPP)	- No rise in ICP for patients with IC pathology - Increase in ICP if severe head trauma with ICP < 18 mmHg or if given rapidly - Does not prevent rise in ICP caused by AW instrumentation
$CMRO_2$	Dose-dependent decrease
EEG and seizure activity	- Dose-related decrease in EEG activity – Gradual progression from awake α pattern (high frequency, low voltage) to δ- and θ-waves (synchronised slow frequency, high voltage) BUT unable to produce silent (isoelectric) EEG (even at very high doses) - Potent anticonvulsant used to treat grand-mal seizures and status epilepticus
CVS effects	
HR	Dose-dependent increase in HR (up to 20%; especially if hypovolaemic) due

	to activation of BRR with the fall in BP
CO	Unchanged
BP	Dose-dependent fall in MAP (up to 5%; especially if hypovolaemic) due to decreases in SVR
SVR	Dose-dependent decrease by 15-30% due to peripheral vasodilation
Haemodynamic sequelae of AW instrumentation	- Hypertensive response to AW instrumentation CANNOT be blunted by the fall in BP caused by midazolam – Thus, opioids must be given concurrently - Hypotensive effects of midazolam can be prevented by the hypertensive response to AW instrumentation
Arrhythmogenicity	Nil. Does not prolong QTc
Coronary BF and CMRO2	Decreased O_2 metabolism and increased O_2 delivery (due to coronary vasodilation)
Respiratory effects	
Minute ventilation and resting $PaCO_2$	- Dose-dependent decrease in MV (TV decreases but RR increases) - Significant ventilatory depression and apnoea can occurs, especially with – (i) COPD, (ii) rapid bolus of large dose (> 0.15 mg/kg IV for induction), (iii) Concurrent opioids - Increased resting $PaCO_2$
Ventilatory response to $PaCO_2$ and PaO_2	Impaired
Effect on AW	- No bronchodilatory effects - Depresses UAW reflexes (risk of aspiration and AW obstruction)
Pulmonary vasculature	Hypoxic pulmonary vasoconstriction intact
GI, GU, metabolic and other effects	
- Decreased HBF - Decreased GFR, RBF and U/O - Decreased PONV - Decreased platelet activity	
Issues with injection	
- None	
Relevant adverse or undesired effects	
- Lower potential for abuse as less tolerance (cf. other benzodiazepines), BUT dependence and withdrawal symptoms still occur - Delayed awakening	
Drug interactions	
- Synergistic effects with other CNS depressants (Eg. volatile agents, other IV induction agents, opioids, EtOH) - Prolonged duration of action by inhibitors of hepatic CYP450 (Eg. cimetidine, erythromycin, Etc.) - Antagonised by flumazenil	

(e) ***To describe total intravenous anaesthesia with reference to the underlying pharmacological principles.***

Overview of TIVA and TCI:

- "Total Intravenous Anaesthesia" (TIVA) is the method of inducing and maintaining GA by attaining and maintaining a central compartment concentration (and thus, effect-site concentration) of an anaesthetic agent (Eg. propofol) purely via continuous IV infusion of the anaesthetic agent
- Forms of TIVA using propofol:
    - (1) "Target controlled infusion" (TCI)
        - TCI is a computer controlled infusion device that uses a mathematical algorithm based upon a multicompartmental pharmacokinetic model to provide a constant specific plasma concentration of the IV anaesthetic agent (Eg. propofol)
        - Two algorithms are used for propofol TCI:
            - (a) Marsh algorithm – Estimates the plasma concentration of propofol based upon patient weight and an estimated "Effect-site equilibrium half-life" ($t\ ½_{KEO}$) of 2.6 minutes for propofol. Better used for longer surgical procedures
            - (b) Schneider algorithm – Estimates effect-site concentration (Ie. at the brain) of propofol based upon patient age and weight, and an estimated "Effect-site equilibrium half-life" ($t\ ½_{KEO}$) of 1.5 minutes for propofol
        - Depending on the algorithm used, the "effect-site concentration" or "plasma concentration" is entered:
            - Induction of GA – Target concentration ~ 4-8 μg/mL. This dose will vary depending on premedication (Ie. give lower dose), and patient factors (Ie. start induction by minute increases in concentration by 1 μg/mL when haemodynamically unstable or elderly)
            - Maintenance of GA – Target concentration ~ 3-6 μg/mL (Note that most patients wake up at concentrations of 1-2 μg/mL)
            - Sedation – Target concentration ~ 0.5-2 μg/mL
    - (2) Simple infusion pump
        - Bristol algorithm aims to achieve a target plasma concentration of 3 μg/mL within 2 minutes and then maintain it:
            - Induction of GA – Rate of 12 mg/kg/hr for 10 minutes (if no premedication with PO temazepam and IV fentanyl 3 mcg/kg given), then 10 mg/kg/hr for 10 minutes, then 8 mg/kg/hr for 10 minutes, then 6 mg/kg/hr for 10 minutes
            - Maintenance of GA – Rate of 6-12 mg/kg/hr
            - Sedation – Rate of 1-4 mg/kg/hr
- With TIVA, there is no "point of delivery" measurement of target concentration of the IV agent (cf. ET concentration monitoring with inhalational agents) – With TCI, however, a "calculated" plasma concentration value based on the algorithm used is displayed (Ie. it may differ from the actual plasma levels due to interindividual pharmacokinetic variations)
- As a result, with TIVA the target concentration and infusion rates should be titrated to desired clinical outcome (Eg. adequate depth of anaesthesia for surgery) – This can be done clinically (Eg. signs of awareness) or using monitoring (Eg. BIS/Entropy)

Pharmacokinetic principles of TIVA:

Phase 1:

- Bolus (or loading dose) of propofol is given at a high infusion rate (~ 1200 mL/hr) to quickly raise the concentration of propofol within the central compartment (and thus the effect-site) and establish anaesthesia

  Loading dose = Target conc. x Volume of central compartment

- Note that a large loading dose (or infusion rate) of propofol is needed due to its (i) high lipid solubility, (ii) high $V_{DISTRIBUTION}$, and (iii) high protein-binding

Phase 2:
- Re-distribution of propofol to peripheral compartments and metabolism of propofol causes the central compartment concentration (and effect site concentration) to decrease
- Thus, following the loading dose, the infusion rate continues at a diminishing rate but at a high enough rate to match redistribution of propofol (and to a much lesser degree, metabolism/elimination of propofol)

Phase 3:
- As the infusion continues, the peripheral compartments become saturated and distribution becomes a less important factor. Metabolism and elimination of propofol becomes the main factor causing the fall in central compartment concentration (and effect site concentration) of propofol
- Thus, a lower rate of infusion is required to match the metabolism/elimination rate of propofol

Effect of changes in target concentration with TCI:
- Increase in target concentration – Causes infusion rate to rise rapidly (Ie. small bolus given) to reach the desired central compartment concentration. The rate then decreases to maintain the new target concentration as per above means
- Decrease in target concentration – Causes infusion rate to cease until the desired central compartment concentration is reached. Then the infusion restarts at a lower rate to maintain the new target concentration

Cessation of the infusion:
- "Context sensitive half-time" (CSHT):
  - Refers to the time taken for plasma concentration of a drug to fall to half its value at the time of stopping an infusion (whereby context refers to the duration of the infusion)
  - This is influenced by the (i) distribution of drug between central and peripheral compartments, and (ii) clearance of a drug in a multi-compartmental model
- Once the infusion is ceased, propofol will re-distribute from peripheral compartments to the central compartment and then be metabolised/eliminated:
  - With short infusions, steady state is not reached and the peripheral compartments are not saturated – Fall in plasma concentration of propofol will be dependent on redistribution of propofol from peripheral to central compartments. Thus, CSHT of propofol will approach the distribution half-life ($t_{½\,\alpha}$ ~ 1-4 minutes)
  - With longer infusions, steady state is reached and the peripheral compartments are saturated – Fall in plasma concentration of propofol is dependent on the BOTH clearance (metabolism and excretion) and redistribution from the central compartment. Thus, CSHT will approach the elimination half life ($t_{½\,\beta}$ ~ 0.5-1.5 hrs)
  - Of note, the CSHT of propofol is only slightly increased with prolonged infusions (5 minutes at 10 minutes; 9 minutes at 3 hours; < 40 minutes at 8 hours) – This is because the rate of redistribution of propofol to the central compartment ($t_{½\,\alpha}$) is only moderately faster than the rate at which it is eliminated from the central compartment by clearance (metabolism and excretion) and redistribution ($t_{½\,\beta}$)

- Most TCI pumps will calculate the "Decrement time" for propofol:
    - This is time required for the plasma level of propofol to reach 1.2 μg/mL (Ie. point of awakening) from the time the infusion is ceased
    - It is calculated based upon (i) CSHT in setting of infusion duration, and (ii) the plasma concentration of propofol at the time

Advantages of TIVA:

- (1) Maintains plasma (and effect site) concentration of propofol without overshoot or undershoot (Ie. level of anaesthesia achieved more consistent)
- (2) Reduces overall use of propofol (Ie. cheaper cost cf. anaesthetist-controlled propofol delivery)
- (3) No "twilight period" between offset of IV induction agent and onset of volatile agent (Ie. usually occurs at time of intubation)

Disadvantages of TIVA:

- (1) There is no "point of delivery" measurement of target concentration of the IV agent (cf. ET concentration monitoring with inhalational agents) – Thus, infusion rates with TIVA should be titrated against clinical outcome (Eg. BIS/entropy monitoring or clinical signs of awareness)
- (2) With TCI, the "calculated" plasma concentration value displayed is based on an the algorithm derived from population statistics of fit and healthy patients – In effect, due to interindividual pharmacokinetic variations the "calculated" plasma value may differ from the actual plasma levels, and an expected clinical effect may occur at different target concentrations with different patients
- (3) No autoregulation of GA unlike with inhaled anaesthetic agents (Ie. spontaneously ventilating patients autoregulate uptake of inhaled agents through –ve feedback of the agent's effect on minute ventilation)
- (4) Inadvertent discontinuation of infusion and risk of awareness/awakening – This is minimised by using a dedicated IVC/lumen of a CVC, use of a non-refluxing valve, maintaining visualisation of the line at all times, and co-inducing with midazolam