Ho Medical ANAESTHESIA

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Intravenous Anaesthetic Drugs & Antagonists

Pharm-08A3 Describe the ideal pharmacokinetic and pharmacodynamic properties of agents used for sedation. Outline the pharmacology of midazolam and propofol with reference to these ideal properties.

Ideal Sedative Agent	**Propofol**	**Midazolam**
Pharmacokinetic		
Rapid onset: Largely unionised (pKa) Lipophilic	Yes Acid pKa 11, 90% unionised at pH 7.4 highly	10 Minutes, not as rapid Base pKa 6.2, 89% unionized at pH 7.4 Moderate
Small Vd	Large 8L/kg	1.5L/kg
Low degree protein binding	98% protein bound	98% protein bound
Rapid offset (less hangover) Inactivated by metabolism not redistribution High clearance Nil active metabolites Organ independent extraction	Yes, $T_{1/2}$ = 1-2 min Metabolised liver + extrahepatic clearance CL = 30mL/kg/min None Renal excretion unchanged <1%	No, slow washout, $T_{1/2}$ = 2- 4 hours Metabolised liver (oxidation) CL = 6-8mL/kg/min Active metabolites Renal
Pharmacodynamic		
Predictable dose-effect: Sedation, anxiolysis Amnesia Analgesia Minimal general anaesthesia (hypnosis, unconsciousness)	 Sedation, nil anxiolysis Amnesic Nil analgesia Dose-dependent ↓LOC → high doses used general anaesthesia	 Sedation, anxiolysis Profound amnesia Nil analgesia Ceiling effect, does not produce general anaesthesia
Known mechanism of action	Potentiates GABAA → ↑duration Cl channel	Facilitates GABA binding to GABAA → ↑ frequency Cl channel
Antagonist	None	Flumazenil
Minimal Side effects: Cerebral CV Resp N+V Local Arterial Hypersensitivity Pregnancy	 Anti-epileptic Significant ↓ CO 25%, ↓SV/SVR, ↓ baroreceptor reflex Significant ↓ MV, ↑RR, ↓TV, ↓ response CO_2, ↓ reflexes Anti-emetic 30-80% pain None Egg hypersensitivity	Tolerance / dependence Anti-epileptic, ischaemic preconditioning Mild ↓MAP, ↑ HR, nil change CO Dose dependent mild ↓ MV, ↑TV, ↓RR Anti-emetic Nil Nil Rare
No contraindications	Shock	
Conclusion – midazolam is a safer agent for sedation as it has less propensity to cause anaesthesia, hypnosis and less cardiorespiratory depression. In procedural sedation, where some level of ↓ consciousness is required, midazolam is often combined with low dose propofol.		

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Pharm-97B9/94 List the properties of an ideal intravenous anaesthetic. To what extent does methohexitone/propofol conform to this ideal?

Ideal Anaesthetic Agent	**Methohexitone**	**Propofol**
Physiochemical	0.5g anhydrous white powder in 30mg NaCO3, 1% solution, water. pH 11.	1% solution, 10% soybean oil, 2,25% glycerol, 1.2% purified egg phosphate
Cheap		No
Water soluble	Yes	No
Long shelf life	Stored powder, 6 week life	Needs storage 2-25 degrees
Sterile	At pH 11 (NaCO3) bacteriostatic	After 6 hours open, can grow fungus
Compatible with other drugs	Yes Does interact with sulphonamides, contrast media through protein binding.	Incompatible with atracurium
Pharmacokinetic		
Rapid onset: Largely unionised (high pKa) Lipophilic	Yes, 30 sec pKa 7.9, 75% unionised at pH 7.4 Yes	Yes, 30 sec pKa 11, 90% ionised at pH 7.4 Yes
Small Vd	2L/kg	4L/kg
Low degree protein binding	60%	98% protein bound
Rapid offset: Inactivated by metabolism not redistribution High clearance Nil active metabolites Organ independent extraction	Yes Metabolised liver CYP 450, HER 0.5, saturable CL = 11mL/kg/min No active metabolised Kidney excretion $T_{1/2}$ = 6min, 4 hours	Yes: Metabolised liver CL = 30mL/kg/min > HBF No active metabolites Kidney excretion $T_{1/2}$ = 1-2min, 4-24 hours
Pharmacodynamic		
Predictable dose-effect	Dose dependent LOC 30 sec 1-2mg/kg	Dose dependent LOC 30 sec 1.5-2.5mg/kg
Known mechanism of action	Potentiates GABA binding at $GABA_A$ (↑ duration)	Potentiates GABA binding at $GABA_A$ (↑ duration)
Antagonist	No	No
Minimal Side effects: Cerebral CV depression Resp depression N+V Venous pain Arterial complications Hypersensitivity Pregnancy	Excitatory phenomenon – muscle twitch, cough, seizures 33% ?epileptogenic Mild depressant, ↓SV, ↑HR Mild depressant, ↓RR, ↑ TV Yes Pain 80%, minimal IA complications compared to thio Yes, but low severity	 Preserves cerebral autoregulation, anticonvulsant Significant depression, ↓SV, ↓MAP, inhibits baroreceptor reflex, ↓ CO 25% Significant depressant, ↑ RR, ↓ TV, inhibits response to CO_2, depresses reflexes Antiemetic Pain 30-80% None Egg allergy
No contraindications	Contraindicated porphyria	None
Conclusion – propofol is the more popular drug used for IV anaesthesia, due to its faster offset, anti-emetic		

properties and predictable therapeutic anaesthetic effects.

Pharm-10A4 Describe the time course between an intravenous injection of a general anaesthetic agent to loss of consciousness. Explain the delay using pharmacokinetic principles.

1. The loss of consciousness produced by an anaesthetic agent is dose dependent (clinically), and pharmacokinetically, requires that an adequate concentration of drug reach its site of action (the CNS). The time course depends on factors influencing the time to reach therapeutic concentrations in the CNS which consists of the following processes:
    a. Rate of flow of drug from vascular compartment to BBB
    b. Rate of diffusion across BBB → CNS
    c. Rate of redistribution outside the vascular compartment
    d. Rate of metabolism

2. Rate of flow from the vascular compartment to BBB

$$\textbf{Time} = \frac{\textbf{distance}}{\textbf{flow (Q)}} \textbf{ and,}$$

$$\textbf{Q} = \frac{\Delta \textbf{P x } \pi \textbf{r}^4}{\textbf{8}\eta \textbf{L}}$$

    a. Distance from CNS – injecting the drug in a vein closer to the brain will induce quicker effect (central line quicker than IVC in hand)
    b. Radius of vessel – larger vessel flow is quicker than smaller vessel
    c. Cardiac output – lower cardiac output states will ↑ time taken to reach BBB

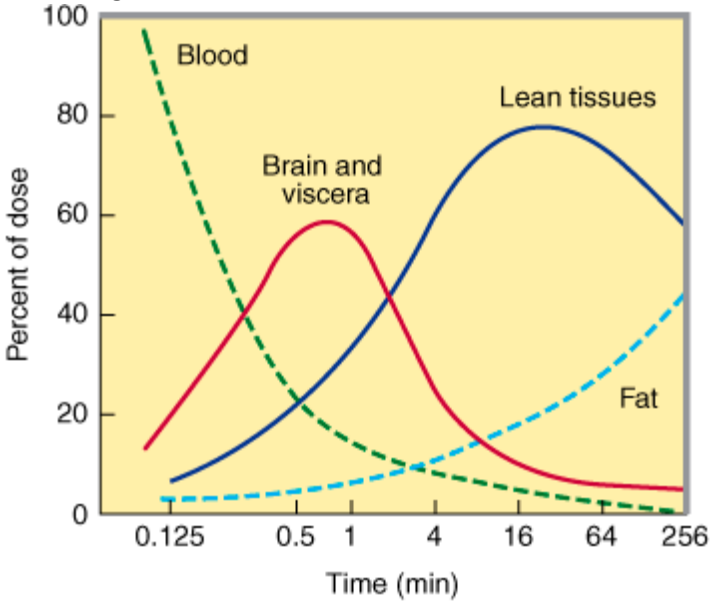
3. Rate of diffusion across BBB → CNS. The BBB is a tight junction formed by astrocyte membrane (lipid bilayer)

$$\textbf{Diffusion} = \frac{\textbf{Sol x A x } \Delta \textbf{P}}{\sqrt{\textbf{MW}}\textbf{xT}}$$

    a. Concentration gradient – bolus doses which are pushed in faster will reach the BBB at higher concentrations and create a stronger gradient for more rapid diffusion
    b. Solubility – lipid soluble drugs will cross more easily (hence given in circulation in unionized form)
    c. MW – smaller drugs will cross more quickly

4. Rate of redistribution – IV anaesthetics redistribute as soon as they are injected. They redistribute into skeletal muscle and fat (3 compartment model) which slows their ability to reach the BBB.
    a. Volume distribution – low VD drugs have less tendency to redistribute and hence act more quickly. It depends on:
        i. Protein binding – highly protein bound drugs are held in the circulation
        ii. Lipid solubility – paradoxically, low lipid solubility confers low VD (can't cross lipid bilayers) and hence speeds distribution to CNS.

5. Rate of metabolism – IV anaesthetics in the circulation are also metabolised in the liver. Rate of metabolism will slow the amount of active drug that reaches the CNS.



Eg. Thiopentone (diagram)

Pharm-05A3 What factors may explain the inter-individual variability in drug response seen with intravenous anaesthetic induction agents?

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1. The response to IV anaesthetic induction agents is clinically important when observed in terms of amount of dose (potency), speed of induction, and recovery. There is considerable pharmacokinetic and Pharmacodynamic variability.

2. Pharmacokinetic: the concentration of the drug administered which reaches the site of action (CNS) is the main pharmacokinetic factor.
    a. Distribution – drugs which distribute rapidly and completely from the blood into the CNS compartment show greater activity.
        i. Protein binding - transports drugs in their inactive state. ↑ protein (pregnancy) → ↓ active drug available for action. ↓ protein (nephritic syndrome, hypoalbuminaemia) → ↑ active drug available → ↑ response
        ii. Intravascular volume - ↓ volume (shock, dehydration) → ↑ concentration of drug → ↑ response.
        iii. Barrier permeability – inflammation of meninges → ↑ permeability → ↑ response to CNS drugs
        iv. Cardiac output – low cardiac output states will slow the delivery of the drug from the vascular compartment to the CNS (↑ arm-brain circulation time).
    b. Redistribution – of drugs into the muscle and fat compartments slows this.
        i. ↑ fat (obesity, older age) → ↑ distribution of drugs into fat → ↓ onset time / slower washout.
        ii. ↓ CO → more time to redistribute → slower offset
    c. Metabolism – drugs held in the vascular compartment are distributed to organs of metabolism (mainly liver), which usually inactivates them and ↓ response:
        i. Liver failure, ↓ hepatic BF → ↓ metabolism → ↑ response
        ii. CYP 450 enzyme induction (phenytoin) → ↓ response, inhibition (antibiotics) → ↑ response
    d. Excretion – some drugs may have active metabolites which need to be excreted by the kidney (thiopentone, methohexitone).
        i. Renal failure → ↓ excretion → ↑ effect

3. Pharmacodynamic:
    a. Receptor sensitivity:
        i. Tolerance – previous repeated exposure to CNS depressants will down-regulate GABA receptors → ↑ dose required for effect
    b. Drug interactions:
        i. CNS depressants generally have synergistic effect of anaesthesia → ↓ dose induction agents required when combining with opioids
        ii. Protein displacement of induction drugs by other drugs will tend to ↑ effect
    c. Organ system sensitivity to adverse effects:
        i. Cardiovascular depression more common in individuals with high cardiac risk (elderly, MI)
    d. Idiosyncratic reactions:
        i. Hypersensitivity reactions – e.g. egg allergy to propofol

4. In general:

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a. Age – extremes of age require lower dosing
b. Body habitus – larger individuals need larger doses

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Pharm-08B2/93 Describe the pharmacokinetic principles of total intravenous anaesthesia using propofol.

1. TIVA – total intravenous anaesthesia is the method of inducing and maintaining general anaesthesia via a continuous infusion of IV anaesthetic (usually propofol) without the use of an inhaled volatile anaesthetic agent.
   The aim of TIVA is to reach and maintain a central compartment concentration of propofol at a level adequate for anaesthesia. Cp_{50} = 4cmg/mL. TIVA is achieved by careful administration of doses at different stages of induction and maintenance.

2. Induction – LD = 1.5-2.5mg/kg
   a. Because propofol has a large VD (8L/kg) a loading dose must be given to fill the central compartment so that propofol reaches its desired concentration.
      LD = plasma conc x VD

3. Distribution – shortly after induction, propofol concentration drops due to:
   a. distribution into the peripheral compartments (muscle, and fat)
   b. metabolism in the liver (and probably other organs)
      Thus an infusion rate of propofol must be given to account for this (4-12mL/kg/hour).

4. Saturation of compartments – as infusion continues, the peripheral compartments become saturated, and distribution becomes less important. Instead, elimination becomes the main mechanism for reducing plasma concentrations. The infusion rate is slowed to approach the rate of elimination (steady state) = 30mL/kg/min.

5. Offset of action – once the infusion is stopped, the plasma concentration of propofol depends on the rate of elimination from the central compartment. This is measured by the context-sensitive half-life.
   a. Short infusions – propofol has not completed distribution and the $T_{1/2}$ will depend on the time taken for redistribution. $T_{1/2}$ α
   b. Long infusions – propofol has completed distribution and saturated into compartments and the $T_{1/2}$ will depend on the time taken for clearance (metabolism and excretion). $T_{1/2}\beta$.

6. TIVA is theatres in now controlled by computer controlled infusion devices. They use mathematical algorithms based on multicompartment model kinetics to provide controlled infusion rates to match a desired plasma concentration. They are corrected for values such as age, weight.

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Pharm-10B6/03B4 Describe the principles of how a computer-controlled infusion device targets and maintains a constant effect site concentration of propofol.

1. Computer controlled devices use mathematical algorithms based on multi-compartment pharmacokinetics for propofol, to provide a constant specific plasma concentration, for its use in total intravenous anaesthesia. This is because IV anaesthetics (unlike inhalational) do not have a direct point of effect monitoring (e.g. end tidal measurement). There are 2 main algorithms used:
    a. Marsh – based on weight alone
    b. Schneider – based on age and weight

    The operator inputs the patient age and weight, and then chooses a particular target concentration. For propofol, this is usually 3-4mcg/mL (1-8mcg/mL depending on clinical situation). In clinical practise, the device is called a Diprofuser and consists of a computer chip device, controlling a syringe driver.

2. The computer rate is useful as it calculates the different rates required for the induction, and stages of maintenance of propofol:

    a. Induction – as propofol has a large VD, a loading (bolus) dose is given, calculated by:
        LD = VD x desired plasma conc
    b. Initial maintenance – as the infusion commences, propofol is rapidly redistributed to the skeletal muscle and the fat compartments. The computer maintains a high infusion rate to account for this loss of drug into other compartments.
    c. Ongoing maintenance – as the infusion continues, the muscle and fat compartments become saturated with propofol. Redistribution slows, and elimination of propofol via metabolism and excretion becomes most important factor ↓ plasma concentration. The computer adjusts infusion rate when this occurs.
    Maintenance dose = elimination rate = plasma concentration x Clearance

3. Adjusting target plasma concentrations – the clinical situation may require ↑ doses (↑ surgical stimulus) or ↓ doses (patient response). The anaesthetist can input the new target concentration and:
    a. ↑ dose – bolus dose given and infusion continues at a calculated higher rate
    b. ↓ dose – infusion ceases for a calculated time, and recommences at a lower rate.

4. Advantages:
    a. Maintains plasma concentrations within 30-60sec, without overshoot of loading doses → more consistent level of anaesthesia
    b. Shown to ↓ overall propofol required

5. Disadvantages:
    a. Based on small population study sample of healthy individuals
    b. Does not take into account individual variability, co-morbidities. Anaesthetist must adjust rates for co-morbidities, adjuvant drugs and degree of surgical stimulation.

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Pharm04-B7 Outline the factors which influence the elimination half life of propofol.

1. Half-life: the time taken for 50% of drug to be completely removed from the plasma during the elimination phase ($T_{1/2\beta}$).

$$T_{1/2\beta} = \frac{0.693 \times VD}{CL}$$

   Usually = 4 hours for propofol.

   The factors which influence it can be divided into volume of distribution and clearance factors. Draw diagram of body compartments

2. Volume of distribution: the theoretical volume of fluid required to hold propofol at its plasma concentration after the drug has reached steady state. It measures the extent to which it distributes to other body compartments (CNS, fat, skeletal muscle). High VD tends to ↑ $T_{1/2\beta}$.

   VD = 4-5L/kg (some say 2-10L/kg), which is large.

   a. Protein binding – tends to hold the drug in the circulation and reduce VD. Although propofol is 98% protein bound, which tends to ↓VD.
      i. ↓ protein states (elderly, pregnancy, liver failure, nephrotic syndrome) → ↑ VD
   b. Plasma volume - ↓ volumes (shock, hypovolaemia) → ↓VD
   c. Lipid solubility – propofol is a small, mostly unionised drug at blood pH (acid, pKa 11) and its hence very able to cross lipid bilayers to enter other compartments.
      i. ↑ fat (obesity, older age) → ↑ VD

3. Clearance: the rate of removal of propofol from the plasma compartment. The clearance of propofol occurs mostly through hepatic metabolism. Its hepatic extraction ratio is > 1.0 (high), and hence its clearance is flow limited (dependent on hepatic blood flow, rather than enzyme saturation). Since its CL > HBF, it is thought to be metabolised in other organs (possibly lungs). Usual value 30mL/kg/min.
   a. ↓ hepatic blood flow (↓ clearance → ↑ $T_{1/2\beta}$)
      i. Age
      ii. Liver disease / cirrhosis
      iii. Drugs (propanolol, octreotide)
      iv. Disease states – shock
      v. Hypothermia
   b. ↑ hepatic blood flow
      i. Pregnancy
   c. Renal disease – 0.3% excreted unchanged in kidney, thus renal failure is a very small factor and will slightly ↑ $T_{1/2\beta}$.

4. Summary:
   a. ↑ $T_{1/2\beta}$: Older age, Liver disease, Hypothermia, Drugs (propanolol, octreotide)
   b. ↓ $T_{1/2\beta}$: Young age
   c. Individual variability is high

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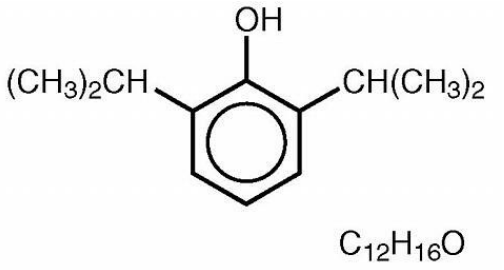
Pharm-09B2/01A13/98A10 What are the potential side effects of propofol and its formulations?

1. Propofol is an isopropyl derivative intravenous induction and maintenance anaesthetic. It is used for:
    a. Induction of anaesthesia
    b. Maintenance of anaesthesia as a sole agent or in combination with GA
    c. Procedural sedation



    These therapeutic uses must be considered when assessed its non ideal features.
    It is stored in suspension: 1 or 2%, 10% soybean oil, 2.25% glycerol isotonic, 1.2% egg phosphatide. It is an acid with pKa 11, stored at pH 6.5-8.5.

2. Pharmaceutical:
    a. Expensive
    b. Necessary storage in glass
    c. Not water soluble
    d. No preservatives, supports bacterial/fungal growth → limited shelf-life once opened (6 hours)
    e. Not compatible with atracurium

3. Pharmacokinetic:
    a. Distribution:
        i. High protein binding – easily displaced by drugs, low protein states
        ii. High VD – significant redistribution in other compartments other than site of action which complicates PK calculations
        iii. Crosses placental barrier (highly lipid soluble, small molecule)
    b. Clearance:
        i. Dependent on liver function and blood flow (depression in liver disease)

4. Pharmacodynamic:
    a. Effects:
        i. Dose response has individual variability and not always predictable → narrow therapeutic window between sedation → anaesthesia
        ii. No analgesic effect and must be used in combination with analgesic
    b. Mechanism of action not clear
    c. No antidote
    d. CNS:
        i. ↓CBF (v/c) → ↓ ICP (less than ↓↓ MAP) → ↓ CPP → ischaemia risk
        ii. ↓ EEG activity, can cause myoclonic jerks
        iii. excitatory movements with induction, vivid dreams
        iv. subclinical doses → euphoria → abuse potential
    e. CVS:
        i. ↓ contractility, ↓SVR (vasodilation due to NO) → ↓ MAP
        ii. Suppresses baroreceptor reflex → ↓CO
        iii. 1:400000 can cause significant bradycardia, asystolic response
    f. Resp:
        i. ↓TV → ↓MV
        ii. ↓ hypercapnoeic, hypoxic response

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   iii. Suppress reflexes → aspiration
g. Metabolic:
   i. Lipid containing solution → lipidaemia in prolonged infusion
   ii. Produces green coloured hair and sputum
   iii. ?propofol infusion syndrome
h. Local: 20-80% report significant pain on injection
i. Allergy: uncommon allergy to soybean and egg phosphatide.

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Pharm-06A4 Describe the pharmacodynamic properties of propofol and how this influences its clinical usage.

1. Propofol (2,6 isopropylphenol) is an IV anaesthetic used for the induction and maintenance of general anaesthesia, or for sedation. Its mechanism of action is unclear, although it is thought potentiate the action of GABA at the $GABA_A$ receptor → ↑Cl conductance → cell hyperpolarisation.

Pharmacodynamic property	**Clinical Usage**
CNS	
Dose-dependent sedation/anxiolysis → anaesthesia	Used for sedation for minor procedures Used for induction and maintenance of general anaesthesia
Rapid onset LOC	Useful for RSI, ED procedures
Rapid emergence	Useful for day procedures
Cerebral v/c → ↓CBF → ↓ICP ↓CPP (MAP ↓ more)	Used in situations of raised ICP (SOL, ICH, neurosurgery) Caution in ↓ cerebral perfusion (ischaemic stroke)
Suppresses EEG	Can be used in status epilepticus Causes myoclonic jerk
CVS	
Potentiates NO → vasodilation → ↓SVR → ↓MAP Depresses contractility, baroreceptor reflex → ↓ HR → ↓ CO Decreases myocardial O_2 consumption	Monitoring requires – ECG, blood pressure, pulse rate. IV fluids and IV resuscitation required. Dangerous, relative CI in shock Can be beneficial in heart failure
Respiratory	
↓TV, may ↑RR → overall ↓MV ↓ response to ↓pO_2, ↑pCO_2	Monitoring required – sats Need airway resuscitation ready
↓ airway reflexes	Useful in airway procedure (laryngeal mask, RSI) ↑ risk aspiration
GI – antiemetic	Useful in patients at risk for PONV
Metabolic – Formulation contains high caloric count	Soybean, glycerol, egg phosphatide
Local – causes pain on injection in 20-80%	Administer in larger veins +/- lignocaine
Hypersensitivity to egg, soybean	Avoid in people with this
Does not rigger MH	Useful in high risk patients with sux
Eye - ↓IOP	Useful in ophthalmic surgery
Toxicity - propofol infusion syndrome: rhabdomyolysis, metabolic acidosis, renal failure	↑ risk in long infusions at high dose

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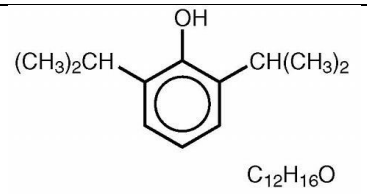
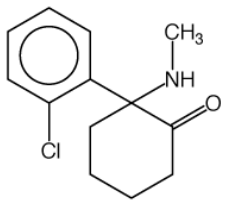
Pharm-07A4 Discuss the suitability of ketamine as a total intravenous anaesthetic agent in comparison with propofol.

Properties (Ideal)	**Propofol**	**Ketamine**
Physiochemical		
Cheap	Expensive, required glass storage.	Yes, used commonly in 3rd world medicine for TIVA
Long shelf-life	Limited due to lipid emulsion	Yes
Low risk bacterial contamination	Risk of contamination > 6 weeks	Low risk
Water soluble	No	Yes, can be used IM
Structure		
Pharmacokinetics	Predictable Computerised infusion devices available	Less predictable No computer infusion devices available
Rapid Onset	Yes – 30sec	Yes
Minimal distribution into peripheral compartment	Little accumulation Short CSHL	More accumulation with longer infusions → longer washout
Complete metabolism independent of organ function	Complete liver metabolism + extra hepatic metabolism CL = 30mL/kg/min	
Inactive metabolites	Yes	
Short half-lives		Longer duration action so can be used more easily with repeated bolus.
Pharmacodynamics		
Predictable general anaesthesia	Yes, dose dependent	
CNS: other favourable effects Analgesia Sedation Anxiolysis	Sedation. No analgesia / anxiolysis.	Very good dissociative analgesia. No anxiolysis
CNS: does not ↑CBF / ICP	↓ICP (favourable)	↑ ICP
CVS: minimal depression	Significant cardiac depression - ↓SVR, MAP, no change HR. Can cause 1:4000 bradycardia → asystole	Myocardial depressant but initiates SNS reflex responses → ↑HR, ↑ CO, ↑ MAP Can be arrhythmogenic
Resp: minimal depression	Resp depression - ↑RR, ↓TV Loss airway reflexes	Stimulates resp Maintains reflexes
No PONV	Anti-emetic	High rate PONV
Other adverse effects	Crosses placental barrier	High rate emergence phenomenon
Local Effects	Painful injection 20-80%	
Hypersensitivity	Egg allergy	Low
Summary	Used more commonly as TIVA in controlled environments because of favourable emergency and pharmacokinetic profiles.	Commonly used in 3rd world environments in less-skilled hands. Favourable in situations of cardio/resp failure. Less requirement for supplementary drugs

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Pharm-00B14/98B9 Write short notes contrasting the cardiovascular effects of propofol and ketamine seen clinically.

Effect	**Propofol**	**Ketamine**
Clinical Use	Procedural sedation IV induction/maintenance anaesthesia	Procedural sedation Analgesia
Mechanism of action	Potentiates $GABA_A$ receptor	Antagonises NMDA receptor
Cardiac effects – the general clinical result of propofol is that it is a cardiac depressant. It effects are dose related. Its use necessitates monitoring, IV fluids and preparation of resuscitation. Its dose-response effects are generally more predictable and cerebrovascular effects mean that it is used more often in neurosurgical situations. Ketamine is known for maintaining cardiovascular function and is useful in situations where this system is compromised (shock, hypovolaemia). It effects are not as predictable and so, in relatively risk-free individuals, propofol is preferred for controlled sedation/anaesthesia.		
SVR	↓ (NO production)	Nil effect
Stroke volume	↓ (negative inotrope)	Complex – At low doses ↑ SV due to SNS activation At high doses ↓ SV due to intrinsic cardiac depression In situ, ketamine alone produces ↓SV
MAP	↓10-20% (dose dependent, due to ↓SV/SVR)	SBP raised 20-40mmHg, diastolic less, ↑Pulse pressure. Rises over 3-5min, then falls back to normal. Blunted by benzos / inhaled anaesthetics.
Sympathetic nervous system effect	↓ (inhibits SNS, blunts baroreceptor reflex response)	Direct SNS stimulation → sensitised SNS response
HR	Normal or ↓	↑ 30% (SNS response, not baroreceptor)
CO	↓ 10-20% (due to ↓SV/HR)	↑ (↑SR/↑HR)
Myocardial O_2 consumption	↓ (↓SV, afterload)	↑ (↑SV, HR)
Arrhythmia	1:4000 bradycardia → asystole	Slight ↑ tendency (↑SNS)
PVR	↓ (NO production)	Small ↑
Cerebrovascular effects -		
Cerebral BF	↓CBF → ↓ICP	↑CBF → ↑ICP
Cerebral PP	↓↓MAP>CBF → ↓CPP	↑CPP
Renal BF	↓ (↓MAP)	↓ (SNS $beta_1$ constriction)

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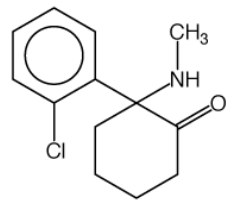
Pharm-08B4 Briefly outline the pharmacology of ketamine with references to its use as an analgesic agent in the post-operative period.

1. Ketamine is a dissociated anaesthetic agent which is used in the induction of general anaesthesia, as a sole anaesthetic agent, or post-operative analgesia and for pain relief in chronic pain.

Property	**Ketamine**
Physiochemical	
Group	Phencyclidine derivative
Structure	
Isomers	Racemic mixture R and S enantiomers S-ketamine: greater analgesia
Formulation	Water soluble solution 10/50/100mg/mL Long shelf-life Suitable storage Cheap
Use	Induction anaesthesia TIVA Analgesia (opioid sparing) Procedural sedation
Pharmacodynamic	
Mechanism	Non-competitive antagonist at NMDA receptor Ca^{2+} channel Opioid, muscurinic receptor modulation
Dose	IV 1-2mg/kg bolus, 4-12mg/hour infusion IM 10mg/kg
Onset	IV 30 sec IM 5-10min
Duration	Relatively rapid offset after prolonged infusion due to high HER metabolism Rapid offset after bolus due to redistribution
CNS	Dissociative anaesthesia – breaks thalamolimbic connection Emergence – dysphoria, nightmares, hallucinations (treated with benzodiazepines) EEG: dominant θ activity, loss α rhythm ↑ CBF → ↑CPP → ↑ICP ↑IOP
CVS	Inotropy: intrinsic negative inotropy in-vitro and high doses Direct stimulation SNS: over-rides → ↑HR, SV, contractility → ↑CO SVR ↑ mild ↑$CMRO_2$, ↑ arrhythmia (mild)
Resp	↑RR → ↑MV Bronchodilation ↑ respiratory secretions Preserved reflexes Nil effect on pCO_2/O_2 response
Other	↓ Renal BF ↑ uterine tone
Toxicity	Emergence (↑ extremes of age) ↑ PONV compared to propofol, thiopentone

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	No local injection complications Abuse potential Allergic rash 15%
Interactions	
Pharmacokinetics	
Absorption	F = 20% Well absorbed IM
Distribution	VD 3L/kg High lipid solubility 25% protein bound $T_{1/2\alpha}$ = 11 min
Metabolism	Hepatic: N-methylation, hydroxylation → norketamine (30% potency)
Excretion	Renal $T_{1/2\beta}$ = 2.5 hours

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Pharm-03A2/99A13 Outline the neuropharmacology of thiopentone, covering only its site of action, EEG changes, effects on cerebral blood flow and intracranial pressure.

1. Thiopentone: is a barbiturate (5-ethyl 5,1methyl butyl , 2 thiobarbituate) used in the IV induction of anaesthetic.

2. Site of action: main site of therapeutic action is in the CNS.
    a. $GABA_A$ receptor:
        i. Ligand gated Cl ion channel
        ii. 5 unit receptor – 2α,2β, γ with central pore
        iii. Thiopentone binds to β subunit and facilitates the binding of GABA to its receptor site on the α-subunit. It ↓ dissociation and ↑ duration of GABA-mediated channel activation
        iv. At higher doses, thiopentone directly activates channels in the absence of GABA
        v. Overall effect → ↑ duration of channel opening → ↑ chloride ion conductance → cell hyperpolarisation → CNS inhibition
        vi. The β subunit also contains binding sites for benzodiazepines and picrotoxin

3. EEG changes
    a. Dose-dependent suppression of EEG activity
    b. Awake (α 8-10Hz → θ 4-6Hz → δ 1-2Hz) → burst suppression → isoelectric (silent) EEG

4. Cerebral blood flow:
    a. Thiopentone ↓ neuronal O_2 consumption → ↓ cerebral metabolism of O_2 → ↓ metabolic demand → ↓ cerebral blood flow → ↓ cerebral blood volume

5. Intracranial pressure:
    a. ↓ cerebral blood volume → ↓ ICP due to the Munro Kellie doctrine (the cranial vault is of fixed volume, so ↓ cerebral blood volume → ↓ ICP)
    b. Cerebral perfusion pressure maintained as long as ↓ MAP < ↓CBF

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Pharm-02A11/99A14/95A9 Briefly outline the effects of thiopentone and ketamine not mediated via the central nervous system. Include a brief account of the mechanisms by which these side effects are exerted.

Effect	Ketamine	Thiopentone	Propofol
Cardiovascular – Ketamine's cardiovascular effects are complex and partly mediated by its stimulation of the SNS (a CNS effect). In-vitro, it actually depresses contractility, but its overall effect is to ↑ myocardial O_2 consumption. The ↓ SVR properties of STP and propofol are primarily related to their ability to stimulate NO production and produce vessel dilatation.			
Contractility / SV	↓ in-vivo	↓ (direct depressant)	↓ (direct depressant)
SVR	No change	↓	↓
HR	↑ (via SNS)	↓ (direct)	Nil change or ↓ (suppresses SNS)
CO	↑ (via SNS)	↓	↓
MAP	↑ (via SNS)	↓	↓
CMO_2	↑ (via SNS)	↓	↓
Arrhythmias	↑(via SNS)	↓	↓
Respiratory			
MV	↑	↓	↓
Response to ↓pO_2	Preserved reflexes	Impaired	Impaired
Airway reflexes	Preserved	Preserved	Impaired
Bronchial tone	Dilatation	Constriction	Dilatation
Secretions	Increased	Nil change	Nil
Neurological			
CMO_2	↑	↓	↓
CBF	↑	↓	↓
ICP	↑	↓	↓
Local			
Pain injection	Yes, esp IM	No	Yes 20-80% pain
Intra-arterial	Nil effect	Pain / thrombosis / necrosis	Nil effect
Metabolic	Nil effect	Nil effect	Metabolic load (egg phosphatate, soya bean)
Gastrointestinal			
N+V	Yes	Yes	Anti-emetic
Motility	Decreased	Decreased	Unchanged
Renal	↓RBF (SNS), unchanged GFR (autoregulation)	↓ RBF, GFR, UO ↑ ADH release	↓ RBF, GFR, UO
Endocrine	↑ circulating catechol	↓ K+ transient	
Immune	Rare	1:20000 anaphylaxis	Egg allergy
Uterine tone	Increased	No change	No change
Other		Acute porphyria – induction D-aminovaulinic synthetase	

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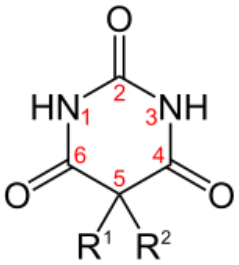
1992/91 Write short notes on Methohexitone

1. Methohexitone is an oxybarbituate intravenous anaesthetic used for the induction and maintenance of anaesthesia.

Property	**Methohexitone**
Pharmaceutical	
Group	Oxybarbituate
Structure	
Preparation	1% white powder 30mg Na_2CO_3 Dissolved in water 1%
pKa	Base 7.9, 75% unionised at pH 7.4
Shelf-life	6 weeks
Pharmacokinetic	
Absorption	Can also be given IM and PR to good effect
Distribution	Highly lipid soluble VD = 2L/kg Protein binding 60% Offset by redistribution
Metabolism	Liver – high HER, but saturable Inactive metabolites
Excretion	Renal excretion < 1% unchanged CL = 11mg/kg/min $T_{1/2\alpha}$ = 5 min, $T_{1/2\beta}$ = 4 hours
Pharmacodynamic	
Mechanism	Binds to barbiturate receptor site on β-subunit of the $GABA_A$ receptor. Slows dissociation of GABA from its site of action → ↑ duration of Cl opening → hyperpolarisation → ↓ CNS excitability. At high doses, causes direct ↑ Cl channel in the absence of GABA.
Clinical Use	Induction and maintenance of anaesthesia Sedation
Dose	1-2mg/kg IV
CNS	EEG – can cause epileptiform waves and cause seizures in susceptible individuals (different from thio) ↓CMO_2, ↓ CBF, ↓ ICP 30% have excitatory responses – cough, hiccups, twitch, hypertonia
CVS – produce NO, ↓ SNS output	↓SV ↓CO 20% ↓SVR ↓ MAP Preserves BR reflex → ↑ HR ↓ O_2 consumption
Resp	↓RR, ↑ TV → overall ↓ MV ↓ response to hypercapnoea, hypoxia Can cause cough, bronchospasm
GI	N+V

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Local	Pain 80% injection Intra-arterial – thrombus < thiopentone Extravasation – mild necrosis < thiopentone
Uterine	Nil effect
Allergy	Mild
Specific toxicity	Triggers porphyria is susceptible individuals (↑D-ALA synthetise)

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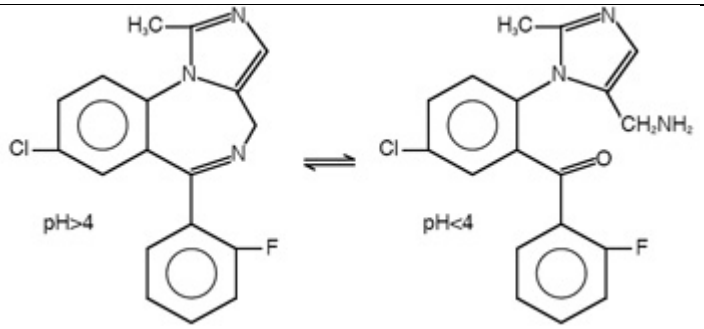
Pharm-07A7/90 Describe the pharmacology of midazolam including its mechanism of action.

Property	Midazolam
Pharmaceutical - imidazobenzodiazepine used commonly in anaesthesia for sedation, hypnosis, anxiolysis and anti-emesis.	
Structure	 Open ring pH < 4 Closed ring pH > 4
Group	Imidazobenzodiazepine
Presentation	1/2/5mg/mL (0.1/0.2/0.5% solution)
pH	3.5
pKa	6.5, with 89% unionised at pH 7.4
Clinical dose:	IV/IM: 0.02-0.2mg/kg Infusion: 0.02-0.2 mg/kg/hour Effect 10min, lasts 20-60min IT: 0.3-2mg Epidural: 0.1-0.2mg
Pharmacokinetic	
Absorption	F = 40%, extensive first pass metabolism
Distribution: VD Protein binding Onset / offset	 1-1.5 L/kg 95% protein bound Offset redistribution, then metabolism
Metabolism: Liver Metabolites	 Hydroxylation by CYP 3A4 → active metabolites Glucoronidation → inactive metabolites
Excretion: Kidney Clearance $T_{1/2}$	 Excreted kidney 7mL/kg/min (10x diazepam) 1-4 hours
Pharmacodynamics	
Mechanism action	Binds to α-unit of GABA receptor (ligand gated Cl channel) → facilitates binding of GABA → ↑ frequency of opening of Cl channel → cell hyperpolarisation → CNS inhibition
Clinical use:	Induction, sedation, anxiolysis, behavioural disturbance, seizures.
CNS: EEG CMO_2 CBF/ICP	Sedation, anxiolysis, anterograde amnesia, hypnosis. Ceiling effect of CNS depression, so can't produce general anaesthesia on its own. Dose dependent α → θ → γ → burst suppression. No isoelectric. ↓ ↓
CVS: SV SVR CO MAP HR	 No change ↓ Maintained ↓ 5% ↑

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CMO_2 Autoregulation	No change Obtunded response to intubation
Resp: MV Airway reflexes Response CO_2/O_2	 ↑ RR, ↓ TV, overall no change MV Reduces at high doses Mildly ↓ response, additive with other resp depressants
GI	Antiemetic
Antagonist	Flumazenil
Drug interactions	Metabolised by CYP3A4, same as alfentanyl → prolonged action MAC sparring with inhalational Blunts response to instrumentation with fentanyl

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Pharm-02A16 Briefly outline the pharmacology of flumazenil.

Flumazenil is an important benzodiazepine antagonist. It is used in anaesthesia in the reversal of benzodiazepine overdose.
Both drugs act at the $GABA_A$ receptor site. This receptor is a ligand-gated Cl channel which has 5 subunits - 2α, 2β and γ. The benzodiazepines binds to a specific α receptor, which facilitates GABA binding to the β receptor and ↑ Cl- channel opening frequency → cell hyperpolarisation.

Property	**Flumazenil**
Pharmaceutical	
Group	Imidazodiazepine
Presentation	Crystalline powder in solution 0.5mg/5mL (0.01% solution)
pKa	1.7
Doses	IV - 0.2 mg bolus, up to 1mg Infusion – 0.1mcg/kg/min
Pharmacokinetic	
Absorption	Well absorbed but high 1st pass, F = 25%
Distribution	VD = 1L/kg Protein binding 50%
Metabolism	Rapid hepatic metabolism by glucoronidation Inactive metabolites
Elimination	Renal excretion CL = 20mL.kg/min $T_{1/2\beta}$ = 1 hour
Pharmacodynamic	
Mechanism action	Competitive antagonist at the benzodiazepine receptor on the $GABA_A$ α-subunit.
Clinical uses	Benzodiazepine overdose – respiratory depression, unconsciousness, sedation, amnesia.
Side effects	Short duration of action as $T_{1/2}$ is generally less than benzodiazepines which it is reversing. Requires repeated administration. Can precipitate benzodiazepine withdrawal.