## B2 - IV Anaesthetics

### Classification

Benzodiazepines - midaz, diaz
Barbiturates - methohexitone, thio
Substituted benzene ring - propofol
Phencyclidine derivative - ketamine
Carboxylated imidazole derivative - etomidate

### (a) To describe the properties of an ideal IV induction agent

Physiochemical

- cheap
- chemically stable - no preservatives needed, easly stored, pH 7.1 to 7.4,
- compatible with all other medications/agents
- colour (propofol example -> less likely to be given by mistake)

PK

*Distribution*

- minimal protein binding
- high concentration achieved at site of action

*Metabolism*

- no toxic or active metabolites
- no dependent on hepatic or renal function

*Excretion*

- fully excreted in away that is not dependent on organ function

PD

*Mode of action* - produce profound anaesthesia, analgesia & muscle relaxation

*CVS*

- no change in haemodynamic parameters

- Q, HR, SVR, myocardial O2 consumption, no coronary steal phenomena, BP
- baroreceptor function maintained

*RESP*

- no change in TV or RR
- did not influence response to hypoxia or hypercarbia
- provide muscle relaxation so that it is easy to ventilate patient
- bronchodialation
- preservation of hypoxic pulmonary vasoconstriction mechanism

*CNS*

- profound anaesthesia with amnesia, analgesia & muscle relaxation
- no epileptiform activity
- maintained normal ICP, IOP, metabolic rate, and O2 consumption

*GI*

- decreased PONV
- prokinetic
- increased tone at oesophageal spinchter

*GU*

- no change in uterine tone
- safe in pregnancy
- doesn't effect RBF & GFR

*Metabolic*

- no affect on steroidogenesis
- no change in immune (WCC) function
- no affect on platelet function
- no change in ADH action

*Other adverse effects*

- painless on injection
- does not require a solution/emulsion that support bacterial growth
- not porphyrenogenic
- no allergic reaction possible to drug
- no withdrawal phenomenon after prolonged use in ICU

**(b) To describe the formulations of thiopentone, propofol, midazolam & ketamine.**

**Propofol**

Chemical - 2,6, Diisopropylphenol

Structure - see diagram

Uses = Hypnotic

1. Induction + maintenance of General Anaesthesia
2. Sedation
3. Status Epilepticus
4. N+V treatment in chemotherapy

Presentation

- white
- oil-in-water emulsion
- 1% or 2%
- soyabean oil
- purified egg phosphatide
- soduim hydroxide
- lecthinin

Physiochemical

- pH 7.5

Route of administration

IV

Dose

Induction Bolus - 1.5 - 2.0mg/kg
Maintenance 4 - 12mg/kg/hr

Propofol Infusion Syndrome documented if dose >4mg\kg\hr for >48 hrs

Children

- induction dose : increase dose by 50%
- maintenance: increase by 25 to 50%

Plasma concentrations

- sedation: 0.5 - 1.5 mcg/mL
- hypnosis: 2 - 6 mcg/mL

PK

*Absorption*

*Distribution*

- 97% protein bound
- Vd  3-10 L/kg
- distribution t1/2 = 1.5 to 4 min.

*Metabolism*

- hepatic
- CP450
- metabolised to inactive glucuronide & then sulphate & glucuronides

*Excretion*

- metabolites excreted in urine
- 0.3% unchanged
- clearance  =  20 to 40mL/kg/min
- elimination t1/2 = 10 to 70 min

PD

*Main action* - Hypnotic

*Mode of action*

Onset = 30-60sec

- ?
- potentiates the inhibitory transmitters glycine & GABA which enhance spinal inhibition.

*CVS*

- decreases MAP & SVR by 20% without a change in HR
- thus Q decreases by 20%
- release of NO2 -> vasodilation.
- may produce bradycardia & asystole.

*RESP*

- apnoea post bolus
- suppression of laryngeal reflexes
- decreased TV
- tachypnoea
- decreased response to hypoxia & hypercarbia
- bronchodilation
- preserves hypoxic pulmonary vasoconstriction response (important)

*CNS*

- smooth, rapid induction with rapid recovery.
- ICP, CPP & oxygen consumption all decrease
- anticonvulsant properties in animals
- involuntary movements
- cerebrovascular autoregulation in response to changes in BP & $PaCO_2$ preserved.

*GI*

- intrinsic antiemetic properties via antagonism of D2 receptors

*GU*

- reduction in secretion of $Na^+$ ions

*Metabolic*

- hypertriglyceridaemia

*Other adverse effects*

- propofol is a free-radical scavenger
- pain on injection
- 'propofol infusion syndrome' - long term use in ICU -> bradycardia, severe acidosis, multiorgan failure, lipaemia, rhabdomyolysis and death (inhibition of FFA entry into mitochondria)

- safe in patients with porphria & MH
- quinol metabolites -> green discolouration of urine & hair.
- increased energy needed for cardioversion
- shortened duration of seizure with ECT but doesn't decrease effectiveness
- supports fungal & bacterial growth
- reduces platelet function in vitro

Added information

- 'pure' propofol = oil and freezes at 19 C

- cannot be administered as aqueous salt -> its lone ionizable functional group (hydroxyl) has pKa 11 -> unstable for forming salts in solution

- other poritons are highly lipophilic (benzene ring & propyl groups) -> poor H2O miscibility

- thus can only be administered in lipophilic substances

- soybean (100mg/mL) -> holds propofol in medium that can be stabilized and dispersed

- egg yolk lecithin (12mg/mL) -> emulsifier to stabilize small propofol soybean oil droplets in aqueous dispersion

- glycerol (22.5mg/mL) -> maintains formulation isotonic with blood

- NaOH -> adjusts pH to 7.0 to 8.5 -> optimizes emulsion stability

- Anti-microbials:

EDTA (disodium ethylenedtaminetetraacetate) - ion-chelating agent that inhibits microbe growth by chelating vital trace metals

Sodium metabisulfite - liberation of sulphur dioxide capable of permeating microbes -> kill them.

**Thiopentone**

Chemical - a thiobarbiturate

Structure - see diagram

Uses

(1) induction of anaesthesia
(2) treatment of status epilepticus
(3) brain protection

Presentation

- hygroscopic yellow powder
- thiopentone sodium (weak acid)
- 6% sodium carbonate
- stored under atmosphere of nitrogen (see later)
- reconstitued with H2O
- produces a 2.5% solution

Physiochemical

- pH 11

- pKa 7.6 (weak acid)
- stable for 24hrs
- forms an alkaline solution when dissolved in H2O

-> NaCO3 added - produces OH- & prevents accumulation of H+ & formation of undissociated acid
-> stored under an atmosphere of N2 to prevent acidification of the solution by atmospheric CO2 (otherwise CO2 would combine with NaCO3)

Route of administration - IV & PR

Dose

IV - 3 - 7mg/kg
PR - 1g/22 kg body weight

*Onset & Duration*

IV - acts within 1 arm-brain circulation time, lasts for 5 to 15min.

PR - acts within 15min.

PK

*Absorption*

*Distribution*

- 80% protein bound
- 40% sequestered into RBCs
- Vd 2 L/kg

*Metabolism*

- hepatic
- oxidation to pentobarbitone -> ring cleavage to form urea & 3-carbon fragments.
- 15% of dose metabolised per hour.

*Elmination*

- urine as inactive metabolites
- 0.5% unchanged
- clearance = 3.5 mL/kg/min
- t1/2 = 4 - 22 hours

PD

*Main action* - hypnotic & anticonvulsant

*Mode of action*

- ?
- depression of post-synaptic sensitivity to neurotransmitters & impairment of pre-synaptic transmitter release.
- molecular level unknown - may act like LA.
- inhibit Ca2+ dependent tranmitter release

*Reasons for fast onset*

(1) high blood flow to brain
(2) high lipophilicity
(3) low degree of ionization

*Reasons for fast off set*

- redistribution to muscle then fat

*CVS*

- negative inotrope
- decrease in MAP by 10-20mmHg
- reflex tachycardia
- peripheral vasodilation -> decrease in VR (depression of medullary vasomotor center)
- decreases Q by 20%

*RESP*

- respiratory depressant
- apnoea
- decreased response to hypercarbia
- laryngeal spasm (occ.)
- bronchospasm

*CNS*

- smooth, rapid anaesthesia
- decreased CBF, ICP, IOP.
- anticonvulsant: EEG - fast activity -> synchronized low-frequency waves.

*AS*

- depression of intestinal activity
- constriction of splanchnic blood vessels

*GU*

- decreased RBF
- increased ADH secretion
- no effect on gravid uterus

*Metabolic*

- decrease in plasma K+

*Other adverse effects*

- severe anaphylactoid rxn (1:20000)
- extravasation -> necrosis
- intraarterial injection -> thrombosis & constriction.
- may induce porphria

**Midazolam**

Chemical - imidazobenzodiazepine

Uses:

(1) induction of anaesthesia
(2) sedation
(3) premedication
(4) treatment of chronic pain

Structure - see diagram

Presentation

- clear, colourless solution
- 1, 2, 5mg/mL
- glass vial

Physiochemical

- pH 3.5 -> H2O soluble
- pH > 4 -> ring closes -> lipid soluble

Routes - IV, PR, Intrathecal, Epidural, PO

Dose

IM - 0.08mg/kg (premed)
IV - 0.1mg/kg (sedation) - titrated to response, end point = slurred speech
Intrathecal - 0.5 to 2mg
Epidural - 0.1 to 0.2mg/kg

Onset = 2-4min

PK

*Absorption*

- PO bioavailability = 44%
- IM bioavailability = 80 to 100%

*Distribution*

- 96% protein bound
- Vd = 1 L/kg (may increase to 3 in critically ill)

*Metabolism*

- hepatic
- to hydroxylated derivatives -> conjugated to glucuronide.
- metabolites are pharmacologically active

*Excretion*

- occurs in urine
- renal impairment has little effect
- clearance 8mL/min/kg
- elmination t1/2 = 2.5 hours (may be increased to 5.4 hrs in critically unwell).

PD

*Main actions*

(1) hypnosis
(2) sedation
(3) anterograde anaesthesia
(4) anxiolysis
(5) anticonvulsant
(6) muscle relaxation

- short duration due to high lipophilicity, high metabolic clearance & rapid elimination.
- decreases MAC by 15%
- can be reversed with physostigmine, glycopyrronium & flumazenil.

*Mode of action*

- act via benodiazepine receptor in CNS
- linked and facilitate action of the GABA receptor.
- chloride channel activation -> hyperpolarises membrane.
- also a kappa-opioid agoinst -> benzodiazepine induced spinal analgesia.

*CVS*

- decreases systolic BP by 5%
- decreased diastolic BP by 10%
- decreases SVR by 25%
- HR increases by 20%
- with fentanyl obtund pressor response to intubation.

*RESP*

- decreases TV
- increases RR
- apnoea occurs in 10 - 80% when used for induction.
- impairs response to increased CO2

*CNS*

- cerebral O2 consumption & CBF decreased.

*GI*

- decreased hepatic blood flow
- decreased PONV as compared to thiopentone + fentanyl.

*GU* - decreases RBF

*Metabolic*

- decreases adrenergic response to stress
- doesn't effect cortisol or renin reponse
- inhibits phagocytosis and WCC activity.

*Other adverse effects*

- occasional discomfort on injection
- in children withdrawal phenonmenon can occur after prolonged infusion

**Ketamine**

Chemical - a phencyclidine derivative

Uses:

(1) induction - hypotension + asthma
(2) short procedures
(3) mass casualties in the field
(4) analgesia - post op & chronic pain
(5) severe unresponsive asthma
(6) Esienmengers -> don't want to drop SVR

Structure - see diagram

Presentation

- colourless solution
- 10/50/100mg/mL
- racemic
- benzethonium chloride (preservative)

Route - IV, IM or PO, extradurally, intrethcally, rectally or nasally

Dose

IM - 10mg/kg (6min onset)
IV - 2mg/kg (30 sec onset) or rate of 50mcg/kg/min

PK

*Absorption*

- PO bioavailability 20%

*Distribution*

- 40% protein bound
- Vd 3 L/kg
- distribution half-life 10 min

*Metabolism*

- hepatic
- N-demethylation & hydroxylation of cyclohexylamine ring

- some metabolites are pharmacologically active

*Excretion*

- conjugated metabolites are excreted in the urine
- clearance 17mL/kg/min
- elimination half life 2.5 hrs

PD

*Main action*

- dissociative anaesthesia (profound analgesia with superficial sleep)

*Mode of action*

- NMDA receptor (1) competitive antagonists + (2) inhibits activity by interaction with phencyclidine binding site (inside pore)
- interacts with opioid receptors - mu, delta & kappa
- muscarinic receptors - partial antagonist effect (bronchodialation, sympathethomimetic, delirium)
- Na+ channel - mild LA like properties

*CVS*

- tachycardia
- increased BP
- increased CVP
- increased Q
- baroreceptor function well maintained

*RESP*

- stimulation of respiration
- maintained airway reflexes
- bronchodilation

*CNS*

- CBF, cerebral metabolic rate, IOP increased
- amnesia marked
- visceral pain poorly obtunded

*GI*

- PONV common
- salivation increased -> antisialogogue recommended.

*GU*

- increases uterine tone

*Metabolic*

- increased circulating norad & adrenaline
- striated muscle tone increases

*Other adverse effects*

- transient rash in 15%
- emergency delirium (less frequent in young & elderly)
- unpleasant dreams + hallucinations (decreased by premed)
- pain on injection

**Etomidate**

Chemical - carboxylated imidazole derivative

Uses

(1) induction
(2) treatment prior to surgery of Cushing's syndrome

Structure - see diagram

Physiochemical

- pH 8.1

Presentation

- clear, colourless solution
- 2g/mL in aqueous vehicle of 35% propylene glycol & water
- now formed with a lipid emulsion (white) -> less irritating

Route - IV

Dose

- 0.3mg/kg
- acts within 20 sec

- lasts for 7 min

PK

*Distribution*

- 75% protein bound
- Vd 4 L\kg
- quickly redistributes to muscle -> then to fat

*Metabolism*

- in plasma & liver
- to inactive carboxlic metabolites

*Excretion*

- 90% in urine
- 3% unchanged
- 7% in bile
- clearance 20mL/kg/min
- elimination t1/2 - 4hrs

PD

*Main action* - hypnotic

*Mode of action*

- R isomer x 5 more potent than S
- GABA type A receptor modulation -> synaptic inhibition

*CVS*

- relatively stable
- may produce mild degree of hypotension (15%) c/o decreased SVR

*RESP*

- decrease in RR & TV
- transient apnoea, coughing & hiccupping

*CNS*

- involuntary muscle movement, tremor, hypertonus
- decreased ICP, CBF & metabolic rate

- 20% exhibit epileptiform activity

*GI*

- PONV 15%

*Metabolic*

- inhibits steroidogenesis -> decreased cortisol & ALD sythesis for 24 hrs.
- antiplatelet effects

*Other adverse effects*

- 40% pain on injection
- venous thrombosis may occur
- porphyrinogeni

**Methohexitone**

Chemical - methylbarbiturate

Uses - IV anaesthesia

Physiochemical

- white powder
- 6% anhydrous sodium carbonate
- reconstituted in H2O (stable for 24 hrs)
- pH 11
- 1% solution
- pKa 7.9 (greater portion non-ionised than thio  pKa 7.6)

Routes - IV, PR, IM

Dose

- 1mg/kg (IV)
- 20mg/kg (PR)
- 8mg/kg (IM) - onset 15min

PK

*Absorption*

*Distribution*

- 60% protein bound
- Vd 1 L/kg

*Metabolism*

- hepatic
- to 4-hydroxy metabolite

*Elimination*

- urinary
- <1% unchanged
- Cl = 10mL/kg/min
- t1/2 = 4hrs

- t1/2 = 3hrs
- remains in body for 12hrs

PD

*Main action* - hypnosis

*Mechanism* - GABAa modulation

*CVS*

- less cardiovascular compromise than thiopentone

*RESP*

- laryngospasm

*CNS*

- involuntary movements
- hiccups
- may cause convulsions (useful in ECT)

*GI*

- same as thio

*GU*

- same as thio

*Other adverse effects*

- pain on injection
- intra-arterial injection doesn't cause as much damage as compared to thiopentone

**(c) To describe the central nervous system effects & proposed mechanisms of action of the IV anaesthetic agents.**

See diagram - the Anaesthetised state

**Barbiturates**

- thiopentone
- methohexitone

**Non-barbiturates**

- phenol derivatives (propofol)
- imidazole derivatives (etomidate)
- steroids
- eugenols
- phencyclidine dervatives (ketamine)
- benzodiazepines (midazolam)
- high dose opioids (fent, alfent, remi)
- neuroleptoanaesthetics (droperidol + fent)

**Barbiturates**

- any drug from barbituric acid
- produce sedation & hypnosis through interaction with the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the CNS.
- GABAa receptors have 5 glycoprotein subunits.
- when receptors are activated -> transmembrane Cl- conductance increases -> hyperpolarisation of postsynaptic cell membranes -> inhibtion
- barbiturates seem to decrease the rate of dissociation of GABA from GABAa receptor -> increased opening of Cl- channel.
- specific for reticular activating system
- barbiturates also mimic the action of GABA
- barbiturates also act at glutamate, adenosine & neuronal nicotinic Ach receptors.

**Non-barbiturates**

*Phenol derivatives* - ***propofol***

- selective modulator of GABAa receptor

- propofol decreases the rate of dissociation of GABA from GABAa receptor -> increase in Cl- conductance -> hyperpolarisation of nerve.

*Imidazole derivative* - ***etomidate***

- administered as a single isomer
- selective modulation of GABAa receptor
- binds directly to receptor & enhances GABA neurotransmitters affinity for GABAa receptor.

*Phenycyclidine* - ***ketamine***

- binds noncompetitively to the phencyclidine recognition site of the N-methyl-D-aspartate (NMDA) receptors (Na+, Ca2+ in & K+ out) -> inhibits activation by glutamate, decreases presynaptic release of glutamate -> potentiates the action of GABA.

- may also exert effects on:

- opioid receptors -> antagonist @ mu, & agonist @ kappa receptor
- monoaminergic -> involves descending inhibitory pathways.
- muscarinic -> ? antagonist (produces - emergency delirium, bronchodilation & sympathomimetic action)
- voltage-sensitive Na+ & L-Ca2+ channels -> mild LA like properties.

*Benzodiazepines* - ***midazolam***

- facilitate the actions of GABA -> enhance the affinity of the receptors for GABA -> enchanced Cl- conductance -> hyperpolarisation.
- also renders the post synaptic neurons more resistant to excitation.

- sedation from action @ alpha 1 subunit (cortex, thalamus)
- anxiolysis from action @ alpha 2 subunit (hippocampus, amygdala)

*High dose opioids* - ***fentanyl, alfent, remifent***

- agonists @ stereospecific opioids receptors at presynaptic & post synaptic site in the CNS (brainstem & spinal cord) & outside the CNS (peripheral tissues)
- opioids mimic the actions of naturally occuring peptides (enkephalins, endorphins & dynorphins)
- bind to opioid receptors -> activation of pain-modulating systems.
- activation of receptor -> presynaptic inhibition of neurotransmitter release (Ach, dopamine, norepinephrine & substance P) -> increased in K+ conductance or Ca2+ inactivation -> hyperpolarisation -> decrease in neurotransmisstion

*Neuroleptoanaesthesia*

- droperidol -> dopamine antagonist

**(d) To describe the pharmacokinetics of the IV anaesthetic agents. To compare the pharmacokinetics & the clinical implications of these differeces.**

See above & card - for agent specific PK parameters

**Time to onset**

Propofol - 30sec
Midazolam - 30sec
Thiopentone - 30sec
Ketamine - IV: 60sec, IM: 5min
Etomidate - 20sec

**Distribution**

Propofol - protein binding (pb) 97%, Vd 0.5L/kg
Midazolam - pb 97%, Vd 1
Thiopentone - pb 80%, Vd 2
Ketamine - pb 40%, Vd 3
Etomidate - pb 75%, Vd 4

**Metabolism**

Propofol - liver by phase II conjugation
Midazolam - liver
Thiopentone - liver
Ketamine - liver by N demethylation
Etomidate - liver & plasma by ester hydrolysis

**Elimination**

Propofol - Cl 20mL/kg/min, t1/2 1/2 hour
Midazolam - Cl 8, t1/2 = 2.5
Thiopentone - Cl 4, t1/2 = 4
Ketamine - Cl 17, t1/2 = 2.5
Etomidate - Cl 20, t1/2 = 4

## (e) To describe TIVA with reference to the underlying pharmacological priniciples.

Using the propofol TIC infusor as an example

**PK**

- we can predict how the average patient will handle a drug by measuring its blood concentration after IV bolus administration & infusion in many individuals.
- 3 theoretical compartments model (1 central & 2 peripheral) - blood, well-perfused organs (muscle), poorly perfused organs (fat).

- volume of central compartment & various rate constants can be derived from pooled pharmacokinetic data.
- the Diprifusor TCI system contains the PK data & may be used to predict blood & effect site propofol concentrations at any time.

See diagram - Calculated propofol concentration (mcg/min) vs time (min).

- blood concentration peaks at 10mcg/mL and then decreases because of diffusion
- effect site concentration rapidly peaks at 4mcg/mL at approximately 4 minutes -> then falls as propofol diffuses from brain back into the vascular compartment.
- the concentration in the brain lags behind the concentration in the blood both as it increases & again as it decreases following equilibration.

**The TCI system**

- an infusion device containing a pharmacokinetic model for a drug.
- we enter age, weight & select a desired target blood concentration (Ct)
- TCI will deliver precisely the amount of drug requred to achieve this Ct, and then continue to infuse the agent at an appropriate rate to maintain it.
- we can increase or decrease the Ct at anytime (titrating it according to response)
- if Ct increased -> system delivers small bolus -> then infuses at a rate needed to maintain the increased blood concentration.
- if Ct decreased -> system will discontinue the infusion until predicted blood concentration reached then restarts maintain that level.

- Diprifusor = controller with PK model for propofol integrated with syringe pump.
- can display both calculated blood & effect site propofol concentrations.

**Induction with Diprifusor**

- select Ct of 10mcg/mL -> once Ct has been reached initial bolus has been delivered (approximately 2.5mg/kg)
- new target of 4mcg/mL can be selected.

- this method may induce profound hypotension.
- infact a Ct of 5mcg/mL -> will induce anaesthesia in 3 minutes in most patients without a signficant increase in cardiorespiratory depression.
- propofol requirements decrease with sedative & opioid co-induction agents.
- in the sick & elderly -> start low & go slow.

**Maintenance with Diprifusor**

- once patient asleep -> decreased Ct to maintenance level.
- EC50 = Ct that prevents a movement response to a standard stimulus after an adequate period of equilibration in 50% of patients = 6mcg/mL
- decreases by 25% to 4.5mcg/mL with 70% nitrous.

**Recovery with Diprifusor**

- the Ct of an awake patient = 1.5mcg/mL

- CSHT = time required for the drug concentration within the central compartment to decrease by 50% following discontinuation of an infusion that has been working for a specific duration.
- this increases with increased duration of infusion secondary to the redistribution of propofol to other organs -> the concentration gradient from the blood to these organs reduces with time.
- explains why time to emergence is prolonged after anaesthesia of long duration.
- Diprifusor calculates the decrement time until a Ct of 1.5mcg/mL
- remifentanil is a good medication to use as has a CSHT of 3 min independent of duration.
- wake up also depends of regional anaesthesia & local infiltration.
- when surgery is nearing completion & propofol administratin no longer required -> select Ct of zero or 0.1mcg/mL (allow infusion to be recommenced if needed).

**(f) To describe the factors which affect recovery from IV anaesthesia.**

**Context sensitive half-time**

- describes the time necessary for the plasma drug concentration to decrease by 50% after discontinuing a continuous infusion of a specific duration.
- includes distribution, metabolism & duration of continuous IV adminstration.
- it bears no constant relationship to the drugs elimination half-time.

**Time to recovery**

- depends on how far the plasma concentration of drug must decrease to reach levels compatible with awakening.

See diagram - Time necessary for plasma concentration to decrease to a level associated with awakening.

- t1/2 alpha - redistribution half life
- t1/2 beta - elimination half life
- Vd
- lipid solubility
- Cl
- activity of metabolites
- capacity to metabolise (renal or hepatic dysfunction)
- degree of protein binding
- dose
- time of onset & duration
- pKa

**(g) To describe the pharmacodynamics of propofol, thiopentone, midazolam, ketamine & etomidate. Provide a detailed account of the cardiovascular & respiratory effects of these agents.**

See above

**(h) To describe the adverse effects of the individual agents.**

See above under PD systems reveiw

**(i) To outline how physiological & pharmacological disturbance can alter the pharmacology of the IV anaesthetic agents.**

This is such a huge objective - I think I'm going to let it slide -> if I get asked about it I'm going to default to first principles in PK & PD.