A2 - Pharmacokinetics

(a) To explain the concept of pharmacokinetic modeling of single & multiple compartment models & define:

- half life
- clearance
- zero & first order kinetics
- volume of distribution
- bio-availability
- area under the plasma concentration time curve
- extraction ratio

See diagram - Link Model

PK = what the body does to drug

- describes the relationship between dose & unbound [drug] @ site of action (receptor) and the time course of [drug] in body

- includes: absorption, distribution, metabolism & excretion.

Clearance

- parameter that describes the efficiency of elmination of a drug from the body

- efficiency of irreversible elimination of a drug from the systemic circulation

- unchanged -> urine, gut, expired air, sweat...
- changed -> metabolic converstion into a chemical compound in liver or some other organ.

-> uptake of drug by tissues is NOT clearance if the unchanged drug eventually comes back out of the tissue!

- definition = volume of blood cleared of drug/unit time (mL/min or L/hr)

- NOT concentration

- can refer to clearance by kidney, liver, a metabolic pathway...
- total clearance is the sum of all of them
- concerns irreversible drug elimination NOT redistribution.

Total body clearance = sum of the clearance rates by renal, hepatic & other routes of elimination (see later)

Other routes:

- Hoffman elimination (atracurium, cisatracurium)
- Hydrolysis by plasma esterases (atracurium, esmolol, remifentanyl)

- Hydrolysis by cholinesterases (sux, mivacurium, procaine)

Extration ratio

= 1 - ratio of [drug] in blood leaving the organ to that entering the organ.

= 1 - ([drug] out / [drug] in)

- minimum clearance by an organ = 0.0
- maximum clearance by an organ = blood flow to the organ

Clearance & elimination rate

- clearance also is the constant relating [drug] in plasma to rate of elimination.

Elimination rate (mg/hr)
= Cl (L/hr) x [drug] (mg/L)

Why is clearance important?

- determines maintenance dose rate required to reach target [plasma] and thus steady state.

- steady state is achieved when administration rate = elimination rate

- maintenance dose rate (mg/hr) = Cl (L/hr) x steady state [drug]

See diagram - concentration of drug vs time

How is clearance measured?

(1) Classical method - renal clearance

Cl = UV / P

Cl = clearance (mL/min)
U = urinary concentration of drug (mg/mL)
V = flow rate of urine produced (mL/min)
P = plasma concentration (mg/mL)

(2) Total clearance

= dose rate / steady state [plasma]

Cl = DR / Css

(3) Area under the curve

See diagram - [plasma] vs time

Cl = dose / AUC

Cl - mL/min

Dose - mg

AUC - mg.min/mL

Plasma or Blood drug concentration?

- we talk about [plasma] as this is what is measured in the lab -> however, organs are perfused by blood not plasma.

- remember:

Blood:Plasma concentration ratio =
[drug] in whole blood / [drug] in plasma

Y = Cb / C

Therefore, Cb = C x Y

Ratio usually = 1

It cannot be <0.5 (haematocrit)

- important in lipophilic meds that concentrate in RBC's (cyclosporin, chloroquine)

Clearance by Liver

- fraction of drug irreversibly removed during one pass.

Eh = 1 - [out] / [in]

Eh = hepatic extraction ratio

0 = no drug extracted

1 = all drug extracted

Clearance by liver determined by:

(1) hepatic blood flow (rate of delivery) - 90mL/hour

(2) extraction ratio (removal of drug)

Clh = Qh x Eh

Clh = hepatic clearance

Qh = hepatic blood flow
Eh = hepatic extraction ratio

What determines hepatic extraction ratio?

Eh = fu x Clint / Qh + fu Clint

Eh = extraction ratio

fu = unbound fraction - only this portion is available for diffusion + metabolism in hepatocytes

Clint = intrinsic clearance - ability of the liver to remove drug in the absence of restriction of supply.
- cannot be higher than blood flow

Qh = blood flow

Clint = intrinsic clearance

= Vmax / Km

Vmax = maximal velocity of the rxn @ saturating substrate concentration.
Km = michalis constant - expresses how tightly the enzyme binds the drug substrate (lowery Km - tighter bound)

Clh = Qh x (fu.Clint / Qh + fu.Clint)

Simplifing:

- at low enzyme activity - intrinsic clearance << hepatic blood flow...

Clh = unbound fraction x intrinsic clearance

- hepatic clearance not dependent on hepatic blood flow.

- at high enzyme activity - intrinsic clearance >> hepatic blood flow...

Clh = hepatic blood flow

- even bound drugs are stripped of by liver metabolism.

Clearance by Kidneys

- many drugs have a low metabolic clearance relative to their renal clearance -> renal clearance becomes the dominant factor in their handling in body.

How are drugs cleared by the kidney?

- net result of 3 different processes

1. Filtration
2. Secretion
3. Reabsorption

Glomerular filtration

- blood passes through the glomerulus @ 1200mL/min
- 10% filtered into renal tubule (GFR = 120mL/min)
- drug in plasma water (unbound) goes with it.
- drug bound to plasma proteins is not filitered.

CLgf = fu x GFR

CLgf = renal clearance by filtration
fu = fraction unbound
GFR = GFR

- if nothing more happens to the drug (neither secreted or reabsorbed) = net renal clearance.

Active tubular secretion

- PT contains atleast 2 active transport mechanisms to move drug from blood -> renal tubule.
= secretion clearance (CLs)
- these mechanisms are so active that even bound drug can be stripped off their plasma proteins -> secreted.
- most of drug have low intrinsic clearance by secretion and only unbound drug is secreted -> fu x CLs
- 2 major active transport systems - one for weak acids & one for weak bases.
- produce two important consequences:

(1) competitive drug interactions - weak acids compete with other weak acids (same with bases).

(2) saturable kinetics - active processes are saturable -> renal clearance can become non-linear at high doses.

Passive tubular reabsorption

- most of 120mL/min filtered is reabsorbed so that only 2mL/min finally appears in the urine.
- as H2O is reabsorbed -> increase in unbound drug concentration in tubule -> diffusion down concentration gradient.

(1) Urine flow rate:

- for drugs which are reabsorbed, renal clearance varies with urine flow rate.
- if flow rate high then less H2O reabsorbed -> less concentration gradeint -> less passvie reabsorption -> greater the clearance.

(2) Permeability

- ionisation
- lipid solubility of the non-ionised drug.
- pH
- pKa of drug

Renal clearance

- assembling 3 components

CLr = fu (GFR + CLs) (1-FR)

CLr = renal clearance
fu = fraction of unbound drug
GFR = GFR
CLs = secretion clearance
FR = fraction escaping from reabsorption from renal tubule

How do I tell if a drug is secreted or reabsorbed?

- all drugs are filtered -> thus fu x GFR = baseline renal clearance
- if actual clearance > than fu x GFR -> secreted
- if acutal clearance < than fu x GFR -> reabsorbed

Predictrion of disease & drug interaction

- no matter what the elimination mechanism, the renal clearance of drug is reduced in proportion with the reduction in creatinine clearance (GFR) -> the intact tubule hypothesis

- adjustment only needed when drug is more than 50% of cleared by renal elimination & renal function half of normal or less.

- reduce dose rate proportionally with reduction in creatinine clearance.

CrCl
=
(140-age) (weight in kg)
/
814 x serum Cr (mmol/L)

- multiply by 0.85 for females

Volume of Distribution

- relationship between the drug concentration in the accessible body fluid (blood) and the drug in tissues of the body at the site of the action.

- not real volume

- relates [drug] in plasma to total amount of drug in body.

= total amount of drug in body / [plasma] of drug

= A / C

- determined by strength of binding of drug to tissue components as compared to plasma proteins

> tissue binding -> large Vd
> plasma binding -> small Vd

- main determinants = fraction of unbound drug in plasma : fraction unbound in tissues

fu : fut

Vd = plasma volume + (fu/fut) x tissue volume

Vd = V + fu/fut x Vt

How is it measured?

See diagram - Measurement of Vd

- plot log [drug] post dose
- extrapolate back to find [drug] @ time zero

Vd =
amount of drug / plasma [drug]

Vd (L)
Amount of drug (mg)
Plasma drug concentration (mg/L)

What is Vd used for?

- determines size of loading dose
- so we don't have to give a repitive number of maintenance doses to achieve steady state.
- the loading dose fills up the Vd

Loading dose = Vd x [target plasma]

Loading dose (mg)

Vd (L)

Target plasma concentration (mg/L)

Is the rate of distribution from blood to tissues important?

- once drug gets into blood the concentration is initally high.
- the drug distributes from the blood into various tissues at rate dependent on:

(1) perfusion of tissue (brain = fast, fat = slow)

(2) lipid solubility

Vd varies with:

- pKa
- degree of binding to plasma proteins
- partition coefficient of drug in fat
- degree of binding to other tissues
- age
- gender
- disease
- body composition

Half Life

- elimination rate constant
- exponential process
- determined by Vd and Clearance

= time taken for amount of drug in body to decrease by half (50%)

See diagram - Time course of drug elimination

- examples of first order elimination
- straight line on log scale

- alpha t1/2 = distribution half life - plasma into vessel rich group of tissues
- beta t1/2 = elimination half life

- rate of distribution is the most important indicator of drug action (not necessarily long t1/2)

Elimination rate constant

- fall in [plasma] post a single dose is an exponential (logrhythmic) function of the time after dose.

$$Ct = Co \times e^{-kt}$$

Ct = concentration @ various times (t) after dose
Co = initial concentration @ time zero
kt = elimination rate constant (per hour)

How does the elimination rate constant relate to t1/2?

- t1/2 = the reciprocal function of the elimination rate constant
- solve equation when Ct = 0.5 x Co (plasma concentration fallen by half)

$$k = 0.693 / t1/2$$

0.693 = natural logarithm of 2

What determines half-life?

- Clearance & Vd

$$t1/2 = 0.693 \times Vd / Cl$$

- from this equation k =

$$k = Cl / Vd$$

- t1/2 increased by (1) increased Vd, & (2) decreased clearance
- vice versa
- the greater the Vd is, the greater drug concentrated in the tissues to the blood.

Why is half life important?

(1) Determines duration of action after a single dose

- doubling the dose -> increases the duration of action by 1 half-life

(2) Determines the time required to reach steady state in chronic dosing.

- to reach steady state it takes between 3-5 half-lifes.

(3) It determines the dosing frequency required to avoid to large fluctuations in plasma concentration during dosing interval.

- if drug is given evey half-life -> rapidly absorbed to reach maximum peak concentration -> then over one half-life will fall to half-peak concentration

Elimination half time = time necessary for the plasma concentration of a drug to decrease to 50% during elimination phase (slightly difference than t1/2)

Context sensitive half time = time necessary for the plasma drug concentration to decrease by 50% after discontinuing a continuous infusion of a specific duration (context refers to infusion duration)

Effect site equilibration = half time equilibration between drug concentration in the plasma and drug effect.
- reflects the fact that the plasma is not the usual site of action but merely a route to the effect site (biophase)
- short effect-site equilibration time -> remifentanyl, alfentanyl, thiopentone, proprofol
- longer effect-stie equilibration time -> fentanyl, sufentanil, midazolam

Bioavailability

Absorption = fraction of dose absorbed from gut luMen -> portal circulation (fg)

First pass clearance - extent to which drug removed by liver during its first passage in portal vein -> liver -> systemic circulation (fh) = 1-hepatic extraction ratio

Bioavailability - fraction of dose which reaches the systemic circulation (F)

$$F = fg.fh$$

Measuring bioavailability

- measured against IV reference doses (100% bioavailability)
- compare IV vs oral by graphing [drug] plasma vs time & calculating AUC

$$AUCiv = Dose(iv) / clearance$$

and

$$AUCoral = F.Dose(oral) / clearance$$

so

$$AUCoral / AUCiv$$
$$=$$
$$F. Dose(oral) / clearance$$

if oral & IV doses are the same

$$F = AUCoral / AUCiv$$

What determines first-pass clearance?

- assume all absorbed -> portal veins
- bioavailability proportional to fraction escaping first pass hepatic extraction.

F = (1-Eh)

- low ER drugs -> all dose into circulation
- high ER drugs -> enzyme inducition/inhibition has small effects on systemic clearance but, large effect on proportion escaping extraction (1-ER) -> bioavailability.

Why is first pass clearance important?

(1) Variability in drug response

- small changes in hepatic extraction ration -> large changes in bioavailability

(2) Relationship between oral & IV doses.

- extraction ratio determines how many more times a dose needs to be as compared to IV -> to achieve same plasma concentration.

(3) Alternative routes of administration

- ie. GTN adminstered SL or transdermally c/o hepatic extraction 99% (very high)

(4) Drug interactions

- enzyme induction or inhibition -> marked changes in bioavailability.

(5) Liver disease

- with liver disease there is less hepatocytes to metabolize drug -> intrahepatic shunt -> decreases extraction ratio, increased bioavailabilty -> increase in effective dose + increased risk of adverse effects.

Absorption = rate at which a drug leaves its site of administration

Bioavailability = extent to which a drug reaches its site of action.

First Order Kinetics

- assumption that distribution of drug takes place within a single body compartment.
- most drugs exhibit this
- rate of elimination proportional to [drug]
- rate of [drug] decay exponential

Zero Order Kinetics

- ie, ethanol, phenytoin & salicylate

- elimination is saturable -> linear rate that is independent of [plasma]
- relationship between dose & steady state plasma concentration is steep & unpredictable.
- intrinsic activity of enzymes determines the constant amount of drug metabolised per unit time & the kinetcs become non-linear described by Michaelis-Menten equation

$$V = \frac{V_{max} \times C_p}{K_m + C_p}$$

V = velocity of rxn
Vmax = maximum rate of drug metabolism per unit time.
Cp = substrate concentration in plasma
Km = substrate concentration at half Vmax (measure of affinity of drug from enzyme)
Cp = substrate concentration in plasma

See Graphs

Single Compartment Model

- see all of above
- only roughly corresponds with real life as there are other compartments - fat, muscle, brain...

Multiple Compartment Model

- drug can only leave peripheral compartment via central compartment = plasma (see link diagram)
- second compartment adds a second exponential component into the predicted time course of plasma concentration -> fast & slow phase

- fast = transfer of drug from plasma to peripheral compartment (alpha phase) -> redistribution

- slow = beta phase

(b) To describe absorption and factors that will influence it with reference to clinically utilised sites of administration.

Absorption = rate at which a drug leaves its site of administration

Routes:

- PO
- SL
- PR
- Epithelial surfaces - skin, cornea, vagina, nasal
- Inhalation
- Injection - sc, im , iv, intrathecal

-> most drugs act by passage from site of administration -> plasma under the governance of Ficks Law of Diffusion

Flux = -DA (change in C/dx)

A = area across which diffusion is occurring
Change in c = concentration gradient
dx = thickness of barrier

D = diffusion co-efficient
- mobility of drug molecule in medium of the diffusion path relative to molecular mass, ionisation, temperature & viscosity of solvent.
- D = the square root of MW

PO

- gut has large surface area
- absorption favoured by pH changes -> non-ionisation.
- gastic - acidic thus increased absorption with basic drugs.
- intestine - basic thus increased absorption with acidic drugs.
- some drugs have specific carrier proteins (Fe & levodopa)
- gastic motility -> increased by metoclopramide, decreased by large meal, anticholinergics, barbiturates & opioids
- splancnic blood flow -> decreased effective surface area in hypovolaemia
- compliance with nausa & vomiting can be an issue.

IM

- rate of systemic absorption limited by the (1) surface area of the absorbing capillary membranes and by the (2) solubility of the drug in interstitial fluid.
- large aqueous channels in vascular endothelium account for unimpeded diffusion of drug molecules regardless of lipid solubility.

PR

Proximal rectum - absorbed into superior haemorrhoidal veins -> porta vein -> liver -> first pass metabolism -> systemic circulation.

Distal rectum - by pass portal venous system

- this may explain the unpredictable responses

Intranasal

- ie vasopressin = rapidly absored via this route
- absorption via muscoa overlying nasal lymphoid tissue.

SL

- bypasses first pass metabolism
- venous drainage -> SVC

Transdermal

- absorption initally along sweat ducts & hair follicles that function as diffusion shunts.
- rate limiting step = diffusion across stratum corneam of epidermis.
- ie. fentanyl, clonidine, nitroglycerin, hyoscine.

Eye

- absorption via cornea -> conjunctival sac epithelim
- can get local effects without systemic effects (most of the time)

Nebulizer

- lungs = large surface area & blood flow -> rapid adjustment in [plasma].

Intrathecal

- injection into subarachnoid space via LP

(c) To describe factors influencing the distribution of drugs & their alteration in physiological & pathological disturbance.

Protein Binding

- most drugs are reversibly bound to plasma proteins according to the law of mass action

free drug + protein
<->
drug-protein complex

K1 & K2 = rate constants of the association & dissociation reactions.

- bond between drug & protein = weak (ionic, hydrogen or van der Waals)
- can dissociate when plasma concentration declines from clearance.

Extent of binding dependent on:

(1) number of binding sites available
(2) affinity of drug for those sites
(3) concentration of drug
(4) lipid solubility (increase -> increased binding)

- it is the unbound, free drug that is better able to diffuse & become metabolically active.

- acidic drugs (salicylates, barbiturates) bind to albumin
- basic drugs (fentanyl, diazepam) bind to globulins, lipoproteins & glycoproteins.

- renal failure can decrease protein binding -> increase in free drug

- protein binding inversely related to Vd (larger protein binding -> smaller Vd)

- protein binding affects clearance as it is free drug that is easily hepatically metabolised & renally filtered.

Lipid solubility

- non-polar substances dissolve freely in non-polar solvents such as lipids -> penetrate cell membranes by diffusion.

Non-polar = molecules in which electrons are uniformly distributed so that there is no separation of positive & negative.

Permeability co-efficient = number of molecules crossing membrane per unit area.

Partition co-efficient = solubility in the membrane

Lipid solubility can determine:

(1) rate of absorption from GI tract
(2) penetration of BBB
(3) duration of action

pH & pKa

- most drugs are weak acids or bases -> present in solution in both ionised & nonionised forms.

- non-ionised is lipid soluble -> easily diffuses

pKa = the negative logarithm of the [H+] at tehic the ionised or unionized portions of a drug are present in equal portions.

- drugs that are weak bases = neutral, unionised, lipid soluble in tissue/fluid with a basic pH.

- drugs that are weak acids = neutral, unionised, lipid soluble in tissue/fluid with acidic pH.

-> when either placed into an environment with opposite pH -> ionise -> dissociate into anion or cation -> become lipid insoluble

Strong acids & bases = highly ionized @ pH 7.4

Weak bases & acids with pKa values between 6.5 & 8.5 -> partially ionized at pH 7.4 -> show marked changes in ionisation & lipid diffusibility with small changes in pH.

- if drug moves 1 pH unit from pKa -> ionisation will change 75%
- if drug moves 2 pH units from pKa -> ionisation will change 90%

- 3 major compartments:

(1) plasma - pH 7.4
(2) urine - pH 8
(3) gastic juice - pH 3

Ion trapping = acidic drug concentrating in a compartment with high pH because there they become ionised and unable to cross lipid membranes to other compartments. Vice versa for bases.

Examples:

- neuromuscular blockers, glycopyrollate & neostigmine (quaternary ammonium compounds) -> 100% ionized -> cross membranes slowly & doesn't cross BBB.

- volatiles -> unionised -> cross membranes easily

(d) To describe the mechanism of drug clearance & how physiological & pathological disturbance may effect these.

See (a) - Clearance by Liver & Clearance by Liver.

Clearance by Liver

- fraction of drug irreversibly removed during one pass.

$$Eh = 1 - [out] / [in]$$

Eh = hepatic extraction ratio

0 = no drug extracted
1 = all drug extracted

Clearance by liver determined by:

(1) hepatic blood flow (rate of delivery) - 90mL/hour
(2) extraction ratio (removal of drugp

$$Clh = Qh \times Eh$$

Clh = hepatic clearance
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What determines hepatic extraction ratio?

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Simplifing:

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- even bound drugs are stripped of by liver metabolism.

Cytochrome P450 isoenzymes

- superfamily of haemoproteins that are the terminal oxidases of the mixed function oxidase systeim found in the membrane of the cytoplasmic reticulum.
- last letters & numbers tells us designated family & individual enzyme & gene.
- consists of a haem group & prostetic moiety

- catalyse phase I rxns - epoxidation, N-dealkylation, O-dealkylation, S-oxidation & hydroxylation of aliphatic & aromatic residues.
- catalyse phase II rxns - conjugation with glucuronic acid.

- all show saturable Michaelis-Menten kinetics
- need co-factor for their activity

Clearance by Kidneys

- many drugs have a low metabolic clearance relative to their renal clearance -> renal clearance becomes the dominant factor in their handling in body.

How are drugs cleared by the kidney?

- net result of 3 different processes

1. Filtration
2. Secretion
3. Reabsorption

Glomerular filtration

- blood passes through the glomerulus @ 1200mL/min
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= secretion clearance (CLs)
- these mechanisms are so active that even bound drug can be stripped off their plasma proteins -> secreted.
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- 2 major active transport systems - one for weak acids & one for weak bases.
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- pH
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Renal clearance

- assembling 3 components

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Predictrion of disease & drug interaction

- no matter what the elimination mechanism, the renal clearance of drug is reduced in proportion with the reduction in creatinine clearance (GFR) -> the intact tubule hypothesis

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- reduce dose rate proportionally with reduction in creatinine clearance.

CrCl

=

(140-age) (weight in kg)

/

814 x serum Cr (mmol/L)

- multiply by 0.85 for females

- after the age of 40, GFR decreases by 1mL/min each year.

(e) To describe the mechanisms of non-hepatic & non-hepatic metabolism of drugs. To descrbe Phase I & Phase II rxns, hepatic extraction ratio & its significance, first pass effect, enzyme induction & inhibition.

- most drugs are lipid soluble so that they are able to pass through biological membranes
- thus are relatively hydrophobic -> cannot be excreted in bile or urine
- they need to under biotransformation or metabolism
- into hydrophilic and polar componds

Major sites of metabolism:

- liver (most important)
- plasma - hydrolysis by cholineesterases
- kidney
- bowel mucosa
- lungs

Factors affecting drug metabolism:

- genetic polymorphisms
- environmental (pollutants/chemicals)
- liver disease
- hepatic blood flow
- age -> decreased liver mass, enzymatic activity & blood flow.
- enzyme induction or inhibition
- other drugs -> competitive interaction with binding sites on enzymes (methanol with ET-OH)

Hepatic metabolism of drugs

See above - Clearance by the Liver

Cytochrome P450 isoenzymes

- superfamily of haemoproteins that are the terminal oxidases of the mixed function oxidase systeim found in the membrane of the cytoplasmic reticulum.
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- all show saturable Michaelis-Menten kinetics
- need co-factor for their activity

Non-microsomal enzymes

- catalyze rxns especially hydrolysis and all conjugation reactions (except conjugation with glucuronic acid)
- often an ester bond
- found in liver but also plasma, GI tract
- does not under go induction
- hydrolyses ester bonds in:

- atracrurium
- remifentanyl
- esmolol
- etomidate
- sux
- mivacurium
- ester LA

Non-hepatic metabolism of drugs

See - Clearance by Kidneys

See above - Non-microsomal enzymes

Phase I rxns

- simple chemical reactions - oxidation, reduction, hydroxylation, acetylation
- takes place via enzymes (microsomal) on ER
- can lead to pharmacologically active metabolites

Phase II rxns

- conjugation reactions -> glucuronide, sulfate, glycine, aa, acetate.
- requires energy
- usually takes place in cytosol or on ER
- generally produces inactive compounds
- excreted in urine, faeces or bile
- enterohepatic circulation = conjugated drug excreted in bile -> cleaved by intestinal flora -> re-released parent compound -> reabsorbed.

Hepatic extraction ratio

Eh = fu x Clint / Qh + fu Clint

Eh = extraction ratio

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Drugs with low hepatic extraction ratio:

- diazepam
- digoxin
- phenytoin
- warfarin

Drugs with high hepatic extraction ration:

- lignocaine
- labetalol
- morphine
- fentanyl
- pethidine
- verapamil

First pass effect

- the phenomenon of hepatic drug metabolism when absorbed from the GI tract before the drug reaches the systemic circulation.
- drugs with high first pass extraction = morphine, verapamil, lignocaine, GTN, norad, adrenaline & dopamine.
- drugs poorly extracted from the liver = diazepam, phenytoin, warfarin.
- results in a substaintial decrease in bioavailability

Enzyme induction

- some chemicals can 'induce' P450 by enhancing the rate of its synthesis or reducing its rate of degradation.
- results in an acceleration of substrate metabolism & usually a decrease in pharmacological action.
- if enzyme transforms drug in active metabolites -> may prolong action.

Enzyme inducers:

- phenobarbital (CYP2B1)
- glucocorticoids, macrolides, anticonvulsants, steroids (CYPs3A)
- ethanol & isoniazid (CYP2E1)

Enzyme inhibition

Ezyme inhibitors:

- chloramphenicol (CYP2B1)
- spirinolactone
- etomidate

(f) To explain and apply concepts related to IV & infusion kinetics.

- effect-site

- effect-site equilibrium time & their clinical applications

- context sensitive half time & its clinical applications.

Loading Dose

- used to achieve a target concentration determined by the Vd

Loading Dose = target concentration x Vd

- if loading dose achieves plasma drug concentration the same as the steady state concentration for maintenance infusion -> steady state achieved & maintained.
- if loading dose over or under shoots -> it will take 3-5 half lives to reach Css.
- where dosing interval = half life, a loading dose of **twice** the maintenance dose immediately achieves steady state.
- using of loading dose may be limited by initial high plasma concentration -> adverse effects before redistribution occurs (ie. lignocaine)

IV infusion & intermittent IV bolus dosing

- given as a continuous infusion a drug accumulates to a steady state concentration (Css).
- this is determined by the dose rate & clearance
- the maintenance dose rate to achieve a target concentration can be calculated if the clearance is known

target concentration (Css)

=

maintenance dose rate / Cl

- the time to reach steady state is determined by half-life
- 3-5 half lives
- steady state reached when rate of administration = rate of elimination

See diagram - intermittent bolusing, loading dose + intermittent dosing & continuous infusion.

- the drug concentration flucuates over the dosing interval.
- maximum concentration = Cmax
- minimum concentration (before next dose) = Cmin

IV Bolus Dosing

- the extent of the fluctuation with IV dosing depends on the ratio of half life : dosing interval -> the lower the ratio the greater the fluctuation & vice versa.
- the degree of fluctuation is expressed via Cmax / Cmin

- at steady state during intermittent IV bolus dosing

(1) plasma concentration fluctuates two fold over the dosing interval.

(2) amount of drug in body shortly after each dose = 2 x maintenance dose
(3) Css = the same as steady state plasma concentration for a continuous infusion at the same dose rate.

Effects of varying the dose interval

- a dosing interval of about a half life is appropriate with half lives between 8 - 24hours -> allows dosing of once, twice or tds.

- if drug has a large theraputic index (ie. gentamycin), dosing interval can be longer.
- if drug has a narrow therputic index -> plasma concentration needs to be maintained with in a specific theraputic range.
- the importance of the relationship between dosing interval in hours & elimination half-life -> extend of drug accumulation

$$-kT = 0.693T / t1/2$$

k = elimination rate constant (units/hour)
T = dosing interval (hours)

Offset of action - determined by elimination half-life & context sensitive half time.

Context sensitive half time = time necessary for the plasma drug concentration to decrease by 50% after discontinuing a continuous infusion of a specific duration (context refers to infusion duration)

- loss of drug from central compartment.
- considers the combined effects of distribution & metabolism + duration of continuous IV administration on drug PK.
- depends on lipid solubility & clearance -> increases with duration of continuous IV administration.
- bears no relation to constant relationship to drugs elimination half-time.

Problems with CSHT:

- only reflects changes in plasma concentration not those at effector site
- in peri-operative period effects of anaesthesia & surgerby will alter drug dispostion & clearance.
- represents population CSHT not individual patient.

Computer Assisted Control Infusions

- requires drug to be considered in terms of concentration required to abolish purposeful movement at skin incision in 50% of population (analagous to MAC) rather than mg/kg/min.

Effect site equilibration = half time equilibration between drug concentration in the plasma and drug effect.
- reflects the fact that the plasma is not the usual site of action but merely a route to the effect site (biophase)
- short effect-site equilibration time -> remifentanyl, alfentanyl, thiopentone, proprofol
- longer effect-stie equilibration time -> fentanyl, sufentanil, midazolam

(g) To calculate loading & maintenance dosage regimens

Loading Dose

= Vd x desired plasma concentration (steady state)

- used for rapid onset
- minimum dose that will fill up the central compartment
- amount of drug needed to provide the desired concentration once distribution has been completed.
- disadvantage -> high initial plasma concentration may produce adverse side effects

Maintenance Dose

= Cpss x Clearance

Clearance = (0.693 x Vd) / t1/2

Continuous infusions

- advantages over boluses:

(1) pharmacologic effects more stable
(2) lower total doses given - less PONV, earlier recovery

- suitable for drugs with:

(1) low theraputic index
(2) consistent relationship between plasma concentration & effect
(3) minimal acture tolerance
(4) minimal accumulation of metabolites

-> computer controlled infusion pumps -> consist of PK algorithms programmed and connected to a volumetric pump.

Oral dosing rate = Css x clearance / F

[target] = mg/mL
clearance = mL/min
F = bioavailability

The Diprifusor

- uses algorithm developed by University of Glasgo to adust the infusion rate continuously to maintan a predetermined plasma concentration

- 6-8micrograms/mL - fit, young
- 1.5-2 - sick

- enter patient age & weight

- calculates instantenous effect site concentration (although not targeted)
- algorithm preprogrammed with the PK parameters of propofol
- at start it delivers a bolus
- then a constantly decreasing infusion to maintain the plasma target concentration (5micrograms/mL) = exponential infusion rate -> constantly decreasing rate of infusion that adjusts for decreasing tissue uptake over time
- as tissues reach an equilibrium with the plasma concentration, the exponential infusion rate approaches zero.
- if target raised -> bolus
- if lowered -> infusion drops to 0 as plasma levels fall

Desirable features for IV infusion devices:

(1) low acquisition & operating costs

(2) accuracy over a wide range of flow rates to allow use with multiple drug formulations in adult & paediatric patietns

(3) small size

(4) battery back-up for transporting patients

(5) programmability

- drug identification
- weight
- drug concentrations (in mass units ie. mg/hr)
- preset bolus dose with reversion to continuous infusion
- computer interface for data input & control

(6) display

- all programmed parameters
- current infusion rate & cumulative dose
- visible in low ambient light

(7) safety features

- audio & visual alarms for empty syringe, occulsion, impending battery depletion & other malfunctions.
- sensing & control circuits to detect discreptancies between programmed & actual flow rates.
- microprocessor-based drug identification, patient weight & set dose to alert user of potential overdoses.

(h) To describe the pharmacokinetics of drugs administrated in the epidural & subarachnoid space.

Spinal

Absorption

- directly injected into subarachnoid space.

Distribution

- no protein binding (even small doses of opioid reach high concentrations when introduced into the CSF.)
- spread depends on -

(1) volume
(2) rate of injection
(3) turbulence
(4) size of injected space
(5) tissue & fluid resistance
(6) patient position

- high lipid solubility ensure local cord uptake
- cephalad bulk CSF means LA will move cephalad.

- Morphine (hyrdrophobic) -> risk of respiratory depression when morphine reach the 4th ventricle Mu receptors.
- Fentanyl (lipophilic) -> little caudal spread + rapid uptake by blood vessels, spinal cord & nerve roots.

Epidural

Absorption

- 10 to 20min until blockade by:

(1) diffusion to spinal nerve roots in paravertebral spaces.
(2) where dural cuffs end
(3) diffusion across dura
(4) via blood vessels to cord

Distribution

- larger doses needed as compared to spinal
- dependent spread promoted by lateral position

Causes of a patchy block:

- H shaped ligament
- too much air pushed into space (pocket sequestration)
- insertion not midline
- epidural may be too low (L4-S1)
- over 7cm of catheter in space (side drift)
- catheter in posterior plexus of veins

(i) To explain clinical drug monitoring with regard to peak & trough concentrations, minimum theraputic concentration & toxicity.

What is theraputic drug monitoring?

- individualisation of dosage by maintaining plasma or blood drug concentrations within a target range (theraputic window).
- two main sources of variability =

(1) PK variability
(2) PD variability

See Link Model Diagram

Major sources of PK variability:

- compliance
- age (neonates, children, elderly)
- physiology (gender, pregnancy)
- disease (hepatic, renal, cvs, respiratory)
- drug interactions
- environmental influences on drug metabolism
- genetic polymorphisms of drug metabolism

- by adjusting doses to maintain plasma drug concentrations with a target range, variability in the PK phase can be greatly reduced.

- it must be remembered that we are applying principles to the population with a normal distribution -> some may not experience theraputic effects in range
-> some patients may experience adverse effects in theraputic range.

Which drugs are worth monitoring?

- those with marked PK variability
- adverse effects related to drug concentration
- narrow theraputic index
- defined theraputic concentration range
- desired theraputic effect that is difficult to monitor

Used in two major situations

(1) drugs used to prophylactically to maintain the absence of a condition (seizures, depression)
(2) to avoid serious toxicity (aminoglycosides)

Trough concentrations

- least variable point in dosing interval
- for drugs with short t1/2 use trough dose
- for drugs with long t1/2 it doesn't really matter