

## Pharmacology week 1 – General

**Pharmacodynamics** - actions of the drug on the body

**Receptors** - component of cell/ organism that interact with drug and initiates chain of biochemical events leading to effects

**Dose response** - Relationship between drug concentration and effect – in vitro

**Antagonist** - drug which binds to a receptor but does not activate it, preventing agonists from binding

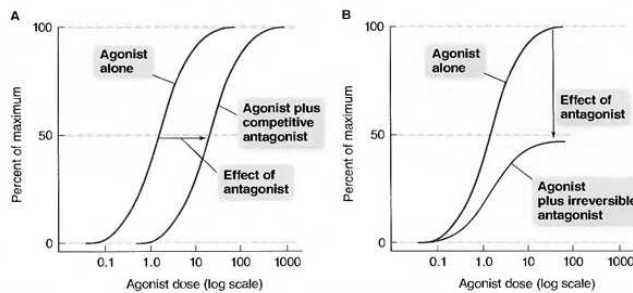
**Pharmacological antagonist** - binds to a receptor without activating it

**Physiological antagonist** - counters effects of another by binding to different receptor causing opposing effects eg insulin decreases glucose with steroids

**Chemical antagonist** - counters effects of another by binding drug and blocking action eg protamine and heparin

**Competitive antagonist** - In presence of fixed agonist conc, increasing concs of competitive antagonists progressively inhibit agonist response and vice versa. Bind reversibly, parallel shift of log dose/effect curve

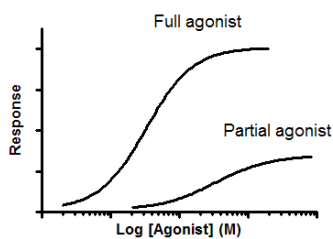
**Irreversible antagonist** - Pharmacologic antagonist that cannot be overcome by increasing dose of agonist



**Figure 2-5.** Agonist dose-response curves in the presence of competitive and irreversible antagonists. Note the use of a logarithmic scale for drug concentration. **A.** A competitive antagonist has an effect illustrated by the shift of the agonist curve to the right. **B.** A noncompetitive antagonist shifts the agonist curve downward.

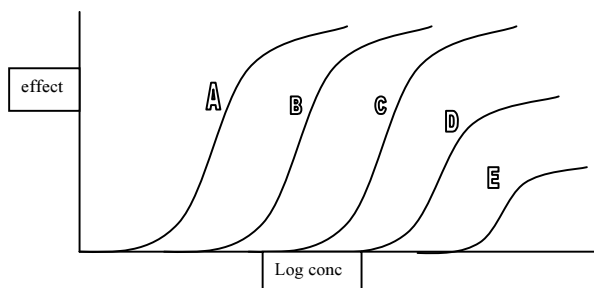
**Agonist** - drug which binds to and activates a receptor which directly or indirectly brings about an effect

**Full agonist or Partial agonist** - produce lower than max response at full occupancy eg pindolol, buprenorphine



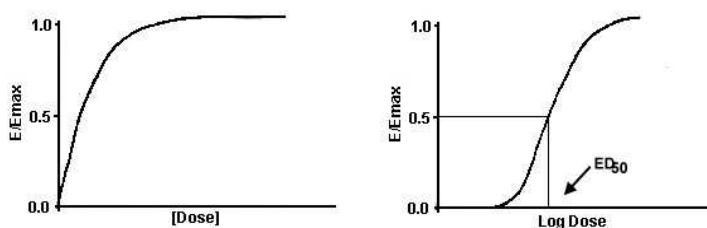
(full agonist plus partial agonist half way in between)

**Spare receptors** - If a given conc of agonist causes maximal effect without binding to all receptors



A—agonist; B—agonist+low dose antagon; C—agonist uses all spare receptors; D,E—high conc antagon diminish submax response

**Dose-response curves**



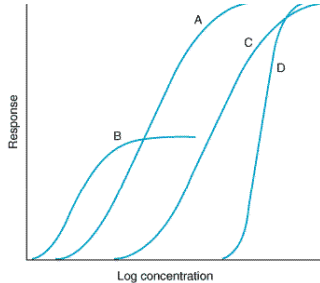
## Dose and Response

**Potency** - conc ( $EC_{50}$ ) or dose ( $ED_{50}$ ) of drug required to produce 50% of maximal effect' (smaller  $EC_{50}$  = greater potency) (left curve) eg fentanyl vs morphine

Dependent on affinity of receptors and efficiency of drug receptor interaction/coupling

**Efficacy** - measure of maximum clinical response of drug regardless of dose' (highest curve)

Determined by interaction with receptors and characteristics of receptors

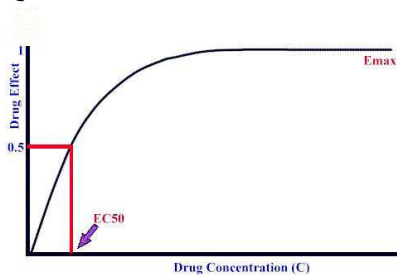


A and B more potent than C and D

Potency of A less than B, a partial agonist, because  $EC_{50}$  of A is greater than  $EC_{50}$  of B

A, C and D equally efficacious

## Quantal dose-effect definitions



**$EC_{50}$**  – median effective dose – the dose at which 50% of subjects exhibit a quantified effect

**$TD_{50}$**  – median toxic dose – dose required to produce a toxic effect in 50% of subjects

**$LD_{50}$**  – median lethal dose – dose required to produce a lethal effect in 50% of subjects

**Therapeutic index** - ratio dose drug required to produce desired effect to dose produce toxic ( $TD_{50}$  to  $ED_{50}$ )

**Duration of action** - Generally depends on termination of drug action at receptor level:

Effect lasts as long as drug is bound but action can persist *after the drug has dissociated* if coupling molecule present.

## Variation in drug response

Alteration in #/fxn of receptors (eg B receptors in thyrotoxicosis)

Changes in components distal to receptor

Alteration in [ ] of drug at receptor - rate of absorption, distribution, clearance

[ ] of endogenous ligand (eg adrenaline in phaeochromocytoma)

**Tachyphylaxis** - Rapid diminution of effect following administration of drug

**Tolerance** - gradual loss clinical effectiveness after repeat dosing – produce original response need larger dose eg GTN

## Dependence

**Physiological dependence** - characteristic withdrawal syndrome when drug stopped or antagonist given

**Psychological dependence** - Compulsive drug seeking behaviour despite adverse effects of the drug being taken.

**Types of receptors:** Receptors – protein molecules normally activated by transmitters/hormones

Regulatory proteins, Enzymes, Transport proteins (eg Na K ATPase), Structural proteins

## Transmembrane signaling:

1 Lipid soluble ligand that cross membrane and acts on an intracellular/nuclear receptor.

Corticosteroids, mineralocorticoids, sex steroids, vitamin D

Bind directly to the nucleus to stimulate transcription of genes.

Characteristic lag of 30 minutes to several hours (time to make new proteins)

Persistent effect over days (after agonist conc has reached zero) - slow turnover of enzymes/proteins

**2 Ligand gated ion channels** - Eg nicotinic ACh receptors - pentamer

Protein subunits forming a central pore

Occurs in milliseconds (cf other receptor types)

**3 Ligand gated transmembrane enzymes** - Surface receptor with cytoplasmic enzyme activity

**4 Ligand binds to receptor bound to a tyrosine kinase** - eg insulin receptors

**5 G protein coupled receptors** - intermediate GTP binding proteins between surface receptor/cytoplasmic 2<sup>nd</sup> messenger

Extracellular ligand binds to cell surface receptor

Receptor triggers activation G protein on cytoplasmic face of membrane

Activated G protein changes activity of effector element (enzyme or ion channel)

Changes conc of intracellular second messenger

**6 Cytokine receptors** - eg GH, EPO, interferon

**Second messengers**

Chemicals whose intracellular [ ] changes in response to receptor activation

*cAMP, IP3, DAG, Calcium, cGMP*

**Pharmacokinetics** - *action of body on the drug*

The study of A, D, M, and E of drugs

**PB** - Determined by:

Affinity drug for protein

Conc binding protein eg albumin

Conc drug relative to conc protein (capacity limited protein binding) eg aspirin

Competition with other drugs or fatty acids

*Unbound drug = active drug*

**Vd** - *total apparent volume necessary to contain amount of drug homogeneously*

relates amount of drug in body to its concentration in blood or plasma, Assumes single compartment model

Affected by disease states

Determinants:

pKa of drug (tissue penetration)

plasma protein binding

partition coefficient

degree of tissue binding

**Vd=Amount of drug in body /concentration.** In L/kg

Drugs with high volumes of distribution are not removed by haemodialysis.

Large Vd (5-10L/kg) (tissue bound drugs) - *Chloroquine, TCAs, Amiodarone, Fluox., Phenothiazines, Propranol, Verapamil*

Small Vd (<1L/kg) (plasma protein bound drugs) - *Theophylline, Salicylate, Phenobarb, Li, Phenytoin, Hep, Warf, Fruse*

**T1/2** - *time required to change amount of drug in body by one half during elim or constant infusion*

$T_{1/2} = 0.7 \times V_d / CL$

can refer to the drug itself or the active metabolites of the drug

Short t1/2 – adenosine; long t1/2 – amiodarone

Importance: duration of action single dose, time required to reach steady state ( 3-5 half lives), dosing frequency to avoid large fluctuations of plasma [ ], accumulation

Half lives	1	2	3	4	5	6
% drug left	100	50	25	12.5	6.25	3.125

**Maintenance Dose** - Drugs usually administered in order to achieve a steady state where dosing equals elimination.

Dosing rate=CL x target concentration (TC)

Maintenance dose=dosing rate x dosing interval

**Infusion kinetics** - Steady state dependent on t1/2  $C_{ss} = DR/Cl_t$

Long t1/2 may require loading dose

**Loading dose** - Aims to quickly raise conc of drug in plasma to target conc

required if half-life prolonged

Drugs administered in order to achieve steady state of drug in body  
 If target concentration is known clearance will determine dosing rate  
 $\text{Loading dose} = V_d \times TC \text{ (desired conc)}$

**Clearance** - measure of volume of plasma cleared of drug per unit time

can pertain to each organ, additive in effect -  $CL_{\text{renal}} + CL_{\text{liver}} + CL_{\text{other}} = CL_{\text{systemic}}$

Clearance equals the **ratio** of the rate of elimination by all routes to the concentration of drug.

$CL = \text{rate elimination} / \text{conc}$

**Creatinine clearance** -  $160 - \text{age} / (250 \times \text{creatinine (mmol/l)})$  - use ideal body weight, correct for females (0.9)

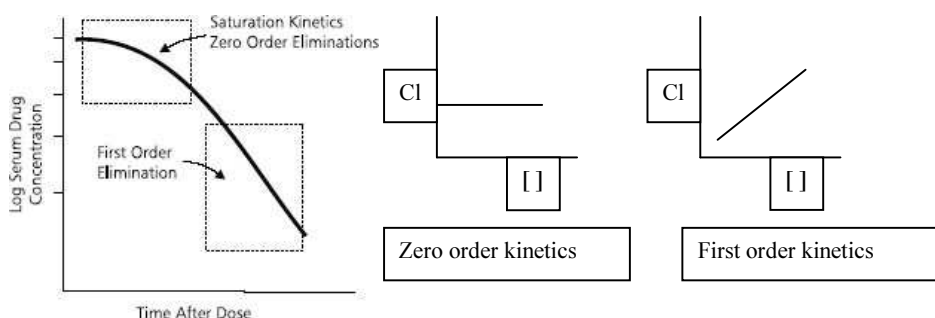
**Capacity limited elimination (zero order kinetics-mixed order kinetics) aka dose-dependent**

Rare of elimination limited by capacity of elimination pathways if a certain conc is reached

Elimination proportional to conc of drug at low concentrations but at high concentrations elimination constant (saturated) - *Phenytoin, Ethanol, Aspirin*

Rate of elimination =  $V_{\text{max}} \times C / (K_m + C)$

$V_{\text{max}}$  = maximum elimination capacity;  $K_m$  = drug concentration at which elimination is 50% of  $V_{\text{max}}$



First order – rate reaction proportional to conc (constant proportion drug metabolized per unit time), measured by AUC:

$Cl = \text{Dose} / \text{AUC}$

Zero order – rate of reaction independent of conc (constant amount metabolized per unit time) - cannot be measured by AUC, cannot achieve steady state

Mixed order kinetics – metabolism initially first order, then zero order when enzymes saturated = phenytoin

**Flow dependent elimination** - Extraction chiefly dependent on blood flow through organ and drug is almost completely extracted by organ on first pass - *Morphine, Lignocaine, Propanolol*

**Bioavailability** - fraction of unchanged drug reaching systemic circulation following administration by any route

Routes of administration include

iv – 100% bio

im – painful, 75-100% bio, sc – painful, 75-100% bio

po, pr – variable 1<sup>st</sup> pass, inhal – rapid onset, nasal

transdermal – slow absorption, prolonged action

Low oral F – verapamil, morphine, adrenaline

High oral F – aspirin, diazepam, lithium

**Factors Influencing Absorption**

DRUG

1. Disintegration rate
2. Dissolution rate  
(particle size, crystal, salt, excipients)
3. Water and lipid solubility
4. Degree of ionisation in GIT
5. Chemical stability in GIT contents

PATIENT

1. Gastric emptying rate
2. Intestinal motility
3. Interaction with other drugs
4. Interactions with food
5. GIT disease
6. Hepatic disease

Oral bioavailability limited by:

**Extent of absorption**

Lipophilic (*acyclovir*) versus hydrophilic (*atenolol*) drugs

Bacterial metabolism within gut (*digoxin*)

Absorption abnormalities in small bowel.

### ***First pass elimination***

Can occur in gut wall, portal blood, or by excretion in bile.  
Most important is metabolism by liver  
Extraction ratio defines the effect of first pass metabolism on bioavailability  
 $ER = CL_{liver} / Q$  (hepatic blood flow – 90l/h)  
Systemic bioavailability can be predicted from extent of absorption and ER  
Systemic bioavailability  $F = f \cdot (1 - ER)$   
Hepatic first pass metabolism avoided by sl, transdermal and pr administration  
Low hepatic ER drugs (good F) eg diazepam, digoxin, phenytoin, warfarin  
High hepatic ER drugs - Larger variation F due to change in hepatic flow and function  
Enzymes have major effect on F  
If high ER can still get therapeutic levels but metabolites also increase  
eg lignocaine, verapamil, isoniazid, morphine, propranolol

**Biotransformation** - metabolism of drugs that allows for renal excretion of lipophilic, un-ionised or partially ionised drugs that would otherwise fail to be effectively excreted and have prolonged action

**Phase 1 reactions** - Convert parent drug to more polar metabolite - Hydrolysis, oxidation, reduction, deamination

#### ***Mechanism***

Mixed function oxidases located on the ER of liver cells and other tissues.  
Require oxygen and NADPH to function.  
Mixed function oxidases include NADPH-cytochrome P450 reductase and cytochrome P450  
7 main isoforms account for most metabolism - CYP3A4 largest component

**Phase 2 reactions** - functional group combines with endogenous substrate to form polar inactive conjugate.  
Glucuronidation, acetylCoA, sulphate, glutathione

### ***Biotransformation can be affected by:***

*Individual differences, Genetic factors (sux- pseudocholinesterase def; EtOH)*

*Diet and environmental factors* - Enzymes induced or inhibited; Charcoal - induce, grapefruit – inhibit CYP3A

*Enzyme induction/inhibition* - induce cypP450 by enhancing rate of synthesis or reducing rate of degradation.

Inducers: smoking, losec, rifamp, St Johns, isoniazid, CBZ, phenobarb, pheny, EtOH

Inhibitors: fluconazole, disulf, grapefruit, paroxetine, erythromycin, cipro, cimetidine

*Disease processes* - disease which affects liver function: hepatitis, cirrhosis, haemachrom, Ca

Cardiac disease can affect drugs that are flow-limited - **Morphine, Verapamil**

*Intestinal biotransformation* - gut metabolism/microbes, gastric acid–penicillin, digestive enzymes–insulin, enzymes in cell MAOIs/catecholamines

### **Distribution of drug to site of action**

*Aqueous diffusion* – determined by fixed law though if drug is charged flux will be influenced by electrical fields.

*Lipid diffusion* – most important limiting factor for drug permeation.

Lipid:aqueous partition coefficient determines how readily the molecule moves between acid aqueous and lipid media.

The ability of weak acids and bases to move between aqueous and lipid mediums depends on pH.

*Special carriers(active transport/facilitated diffusion)* – molecules too large or too insoluble – eg peptides, aa's, glucose

*Endocytosis and exocytosis* – very large molecules – vit B12, iron

**Ficks law of diffusion** - passive flux of molecules down a concentration gradient equals difference in conc across membrane (C1- C2) multiplied by area of membrane and permeability coefficient, divided by thickness of membrane

**Ionisation of weak acids and weak bases** - electrostatic charge of ionized molecule results in polar, relatively water soluble and lipid insoluble complex. Ionisation of drugs reduces ability to permeate membranes

**Weak acid** – ‘a neutral molecule that can readily dissociate into an anion and a proton’.

**Weak base** – ‘a neutral molecule that can combine with a proton to form a cation’.

**Henderson-Hasselbalch equation** – ratio protonated:unprotonated weak acid/base to molecule's pKa and pH of medium.

$\text{Log}(\text{protonated} / \text{unprotonated form}) = \text{pKa} - \text{pH}$

**pKa** – pH at which conc ionized and unionized forms are equal

More of a weak acid will be in a lipid soluble form at an acid pH.

More of a weak base will be in a lipid soluble form at an alkaline pH.

pH – important for excretion of drugs by kidney