Pharmacology & Therapeutics

(previously Clinical Pharmacology)

Lecture 1.1

Unit Introduction

&

Pharmacokinetics

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THE UNIVERSITY OF BUCKINGHAM

Can you name one of the 10 most prescribed drugs in the UK?

Drug class + example?

Top UK prescription drugs

Overall rank	Drug, class or BNF grouping	Most commonly prescribed example(s)	Hosp. rank	PCA rank	Hosp. (%)	PCA (%)
1	Proton pump inhibitors	omeprazole, lansoprazole	3	2	3.0%	5.5%
2	Statins	simvastatin, atorvastatin, pravastatin	9	1	2.3%	6.5%
3	Paracetamol		1	11	6.2%	2.3%
4	Beta-blockers	bisoprolol, atenolol, propranolol	17	5	1.8%	3.6%
5	Calcium and vitamin D		11	12	2.1%	2.1%
6	Calcium-channel blockers	amlodipine, felodipine, diltiazem, nifedipine, lercanidipine	21	4	1.8%	3.7%
7	H_1 receptor antagonists	cyclizine, cetirizine, loratadine, fexofenadine, chlorphenamine	6	19	2.7%	1.6%
8	Aspirin		18	8	1.8%	2.8%
9	Opioids: weak/moderate	tramadol, codeine, dihydrocodeine	5	21	2.8%	1.4%
10	Opioids: strong	morphine	2	27	5.2%	1.2%

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Br J Clin Pharmacol. 2018 Nov; 84(11): 2562–2571.
The ‘top 100’ drugs and classes in England: an updated ‘starter formulary’ for trainee prescribers

Plan

- Lecture 1.1
- Break
- Group work & quiz
- Lecture 1.2 (4pm)

Resources

- **Text books** such as Golan: Prionciples of Pharmacology; Rang & Dale, 10th Edition
- **Formularies** such as BNF, Milton Keynes Formulary
- **Web based sources:**
- **Interactive Clinical Pharmacology** website at http://www.icp.org.nz/
- **Script** at https://www.safeprescriber.org/medicine-surgery/ SCRIPT is an eLearning programme to improve safety and competency among healthcare professionals around prescribing, therapeutics and medicines management. Supported by the NHS, UBMS has an institutional subscription.
- **Pharma Factz** at https://pharmafactz.com/ Information about pharmacology and drugs in a variety of formats. It also includes calculations

Clinical Pharmacology

- Develop an understanding of pharmacological options of therapy.
- Provide a broad grounding in general principles applicable to all groups of pharmacotherapeutic agents.
- Scientific knowledge here alongside safe prescribing in Clinical Problem Solving 2.

Clinical Pharmacology

- Key themes will include:
  - Pharmacokinetics and Pharmacodynamics
  - Pharmacological Mechanisms of Action
  - Clinical Indications for Therapeutics
  - Important and Common Adverse Drug Reactions (ADRs)
  - Important Drug-Drug Interactions (DDIs)
  - Drug Monitoring during Therapy

Aim of this lecture

- **Revise** pharmacokinetic principles
- **Highlight** aspects of pharmacokinetics and translate this into clinical scenarios
- Leave you better equipped to prescribe safely

Use the Interactive Clinical Pharmacology website and the workbook alongside the material in this lecture
http://www.icp.org.nz/

What factors determine how much drug you should give a patient?

- Potency at target (Kd)
- Efficacy
- Therapeutic index
- ADME!!!!

-Volume of distribution

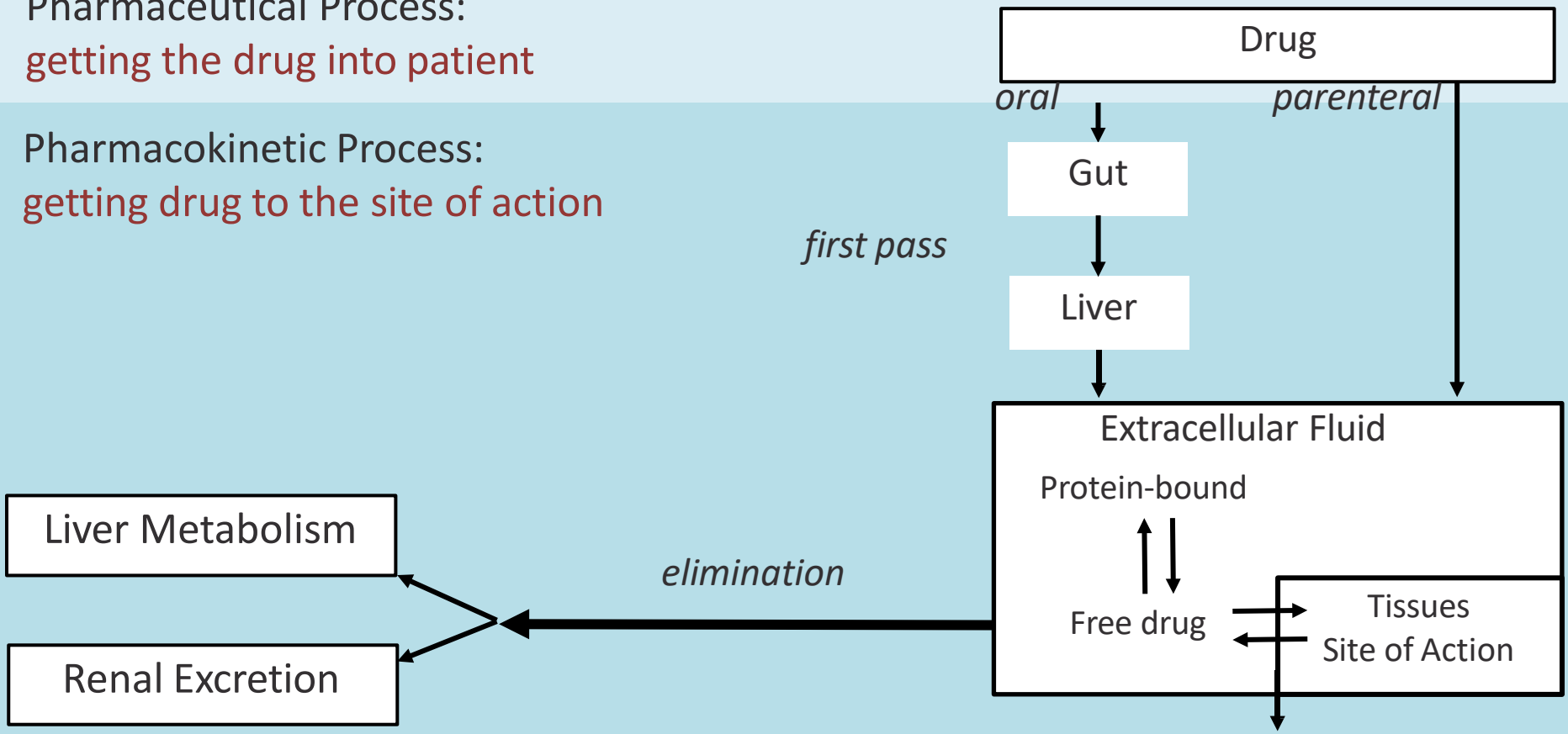
-protein binding

- Height and weight. ...
- Sex. ...
- Age. ...
- Existing medical conditions. ...
- Drug interactions. ...
- Medication intolerance / toxicity / side effects

The Four Main Processes Involved in Drug Therapy

Pharmaceutical Process:
getting the drug into patient

Pharmacokinetic Process:
getting drug to the site of action



Pharmacodynamic Process:
producing required pharmacological effect

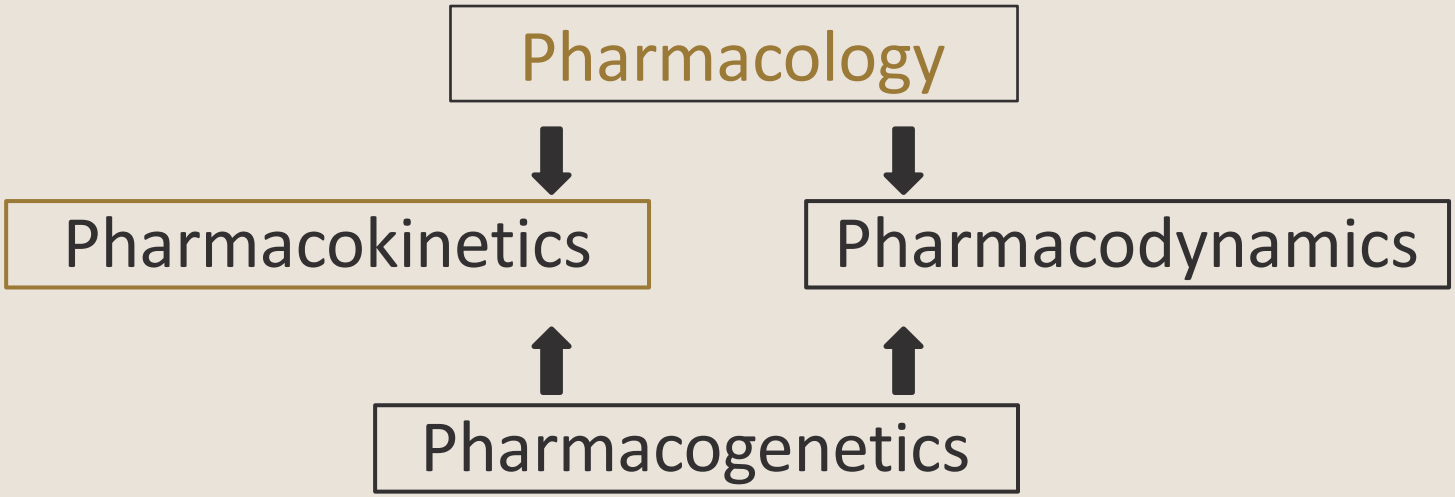
Pharmacological Effect

Therapeutic Process:
Pharm effect translated to a therapeutic effect

Therapeutic Effect

Pharmacology

Pharmacology – Science of drug action on biological systems.



Pharmacokinetics is what the body does to the drug, pharmacodynamics is what the drug does to the body, pharmacogenetics is effect of genetic variability on PK and PD

Importance of Pharmacokinetics

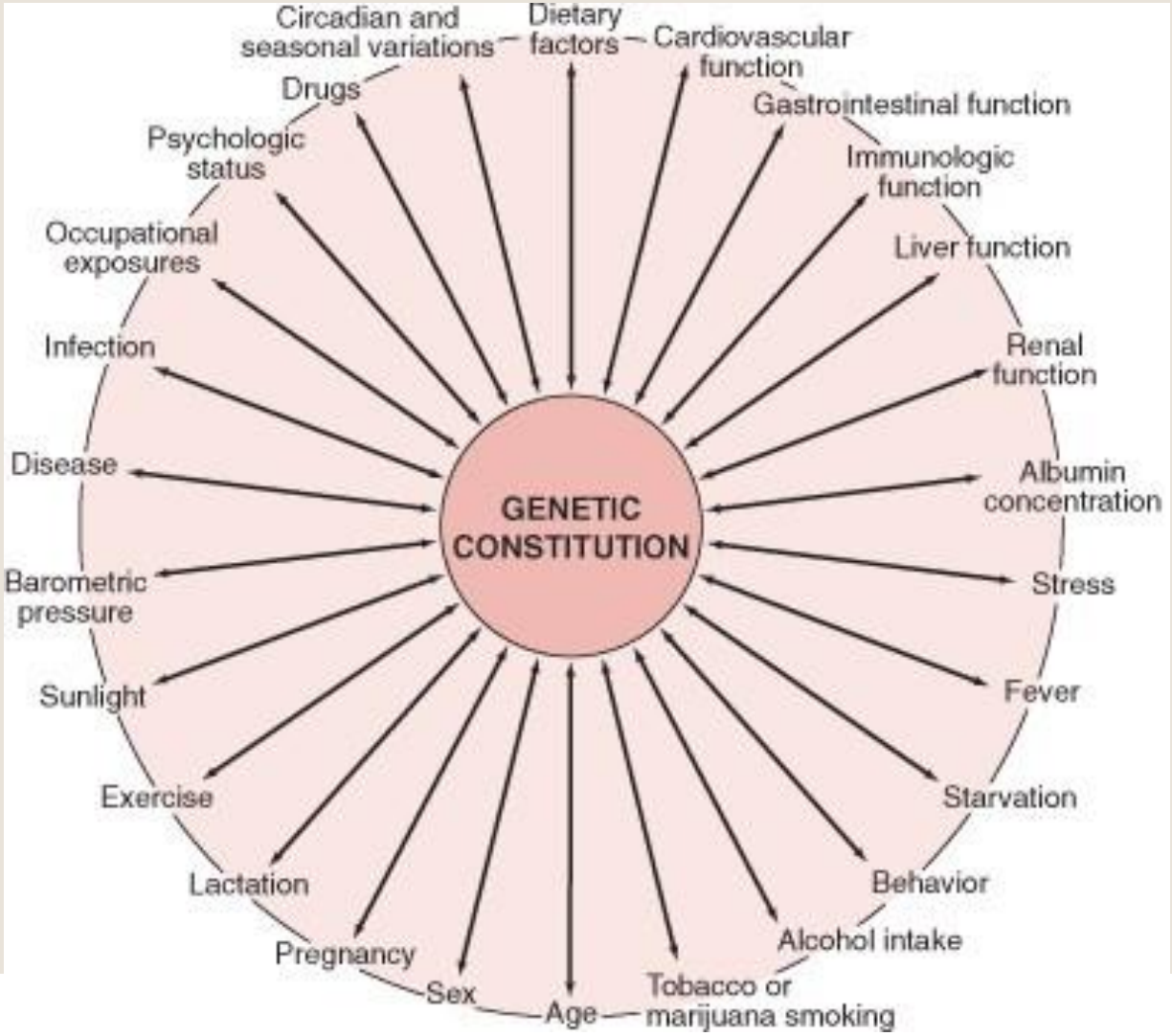
- Essential part of drug regulation: MHRA / FDA
- Elucidates the mechanisms of drug interactions
- Key factors:
  - Bioavailability
  - Half-life
  - Drug elimination
  - Intra-subject variability
  - Drug-Drug interactions

MHRA =Medicines and Healthcare products Regulatory Agency

Translating into Clinical Practice:

- Understanding about bioavailability leads to the correct formulation
- Estimating half-lives allows dosing regimens to be devised
- Understanding intra-subject variability allows appropriate dosing regimens for special patient groups
- Determine why a patient may fail to respond to a treatment
- Or why a drug has caused toxicity

Multiple factors affect drug pharmacokinetics in an individual



Pharmacokinetics

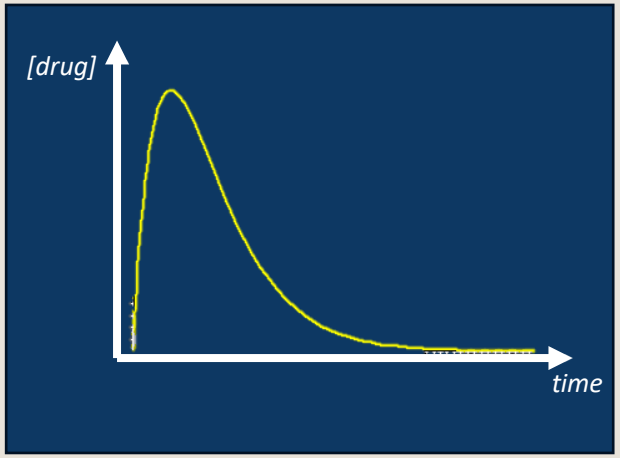
'the study of the movement of drugs and their metabolites through the body'.

Pharmacokinetics :

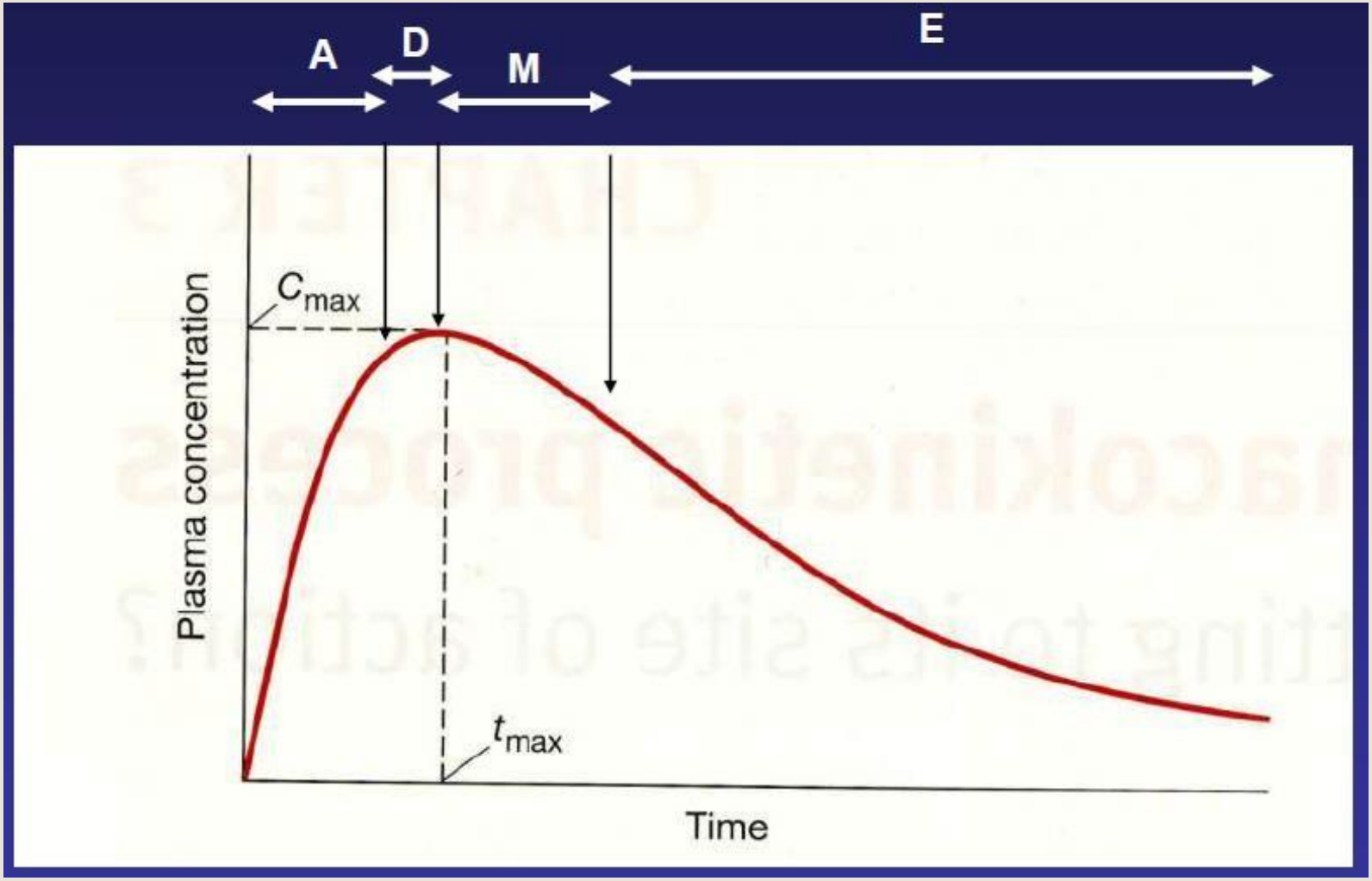
Determined by general processes

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**limination

(ADME)



ADME of a single dose

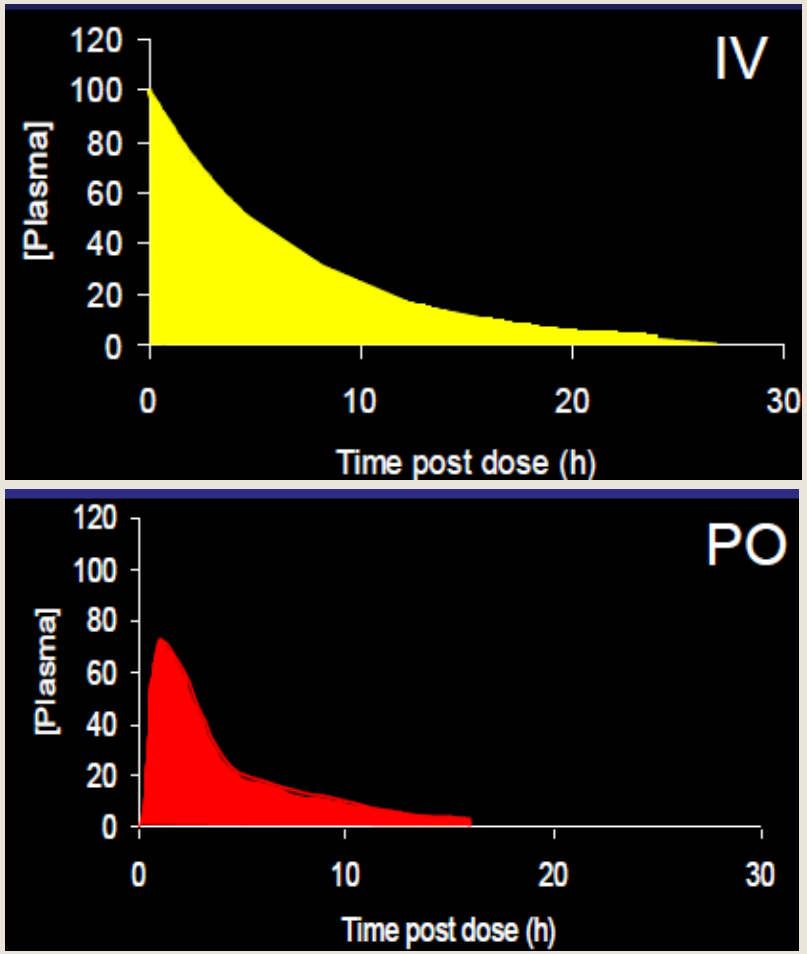


ADME
Absorption

Bioavailability (F)

- Bioavailability is the fraction of administered drug that reaches the systemic circulation. Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form. For an intravenous bolus, bioavailability is 100%
- For other routes, compare amount reaching the body compartment by that route with intravenous bioavailability

Oral bioavailability (F)



Area under the Curve IV
AUC=Total drug Exposure

Oral Bioavailability
F=AUC oral / AUC iv

Factors affecting bioavailability

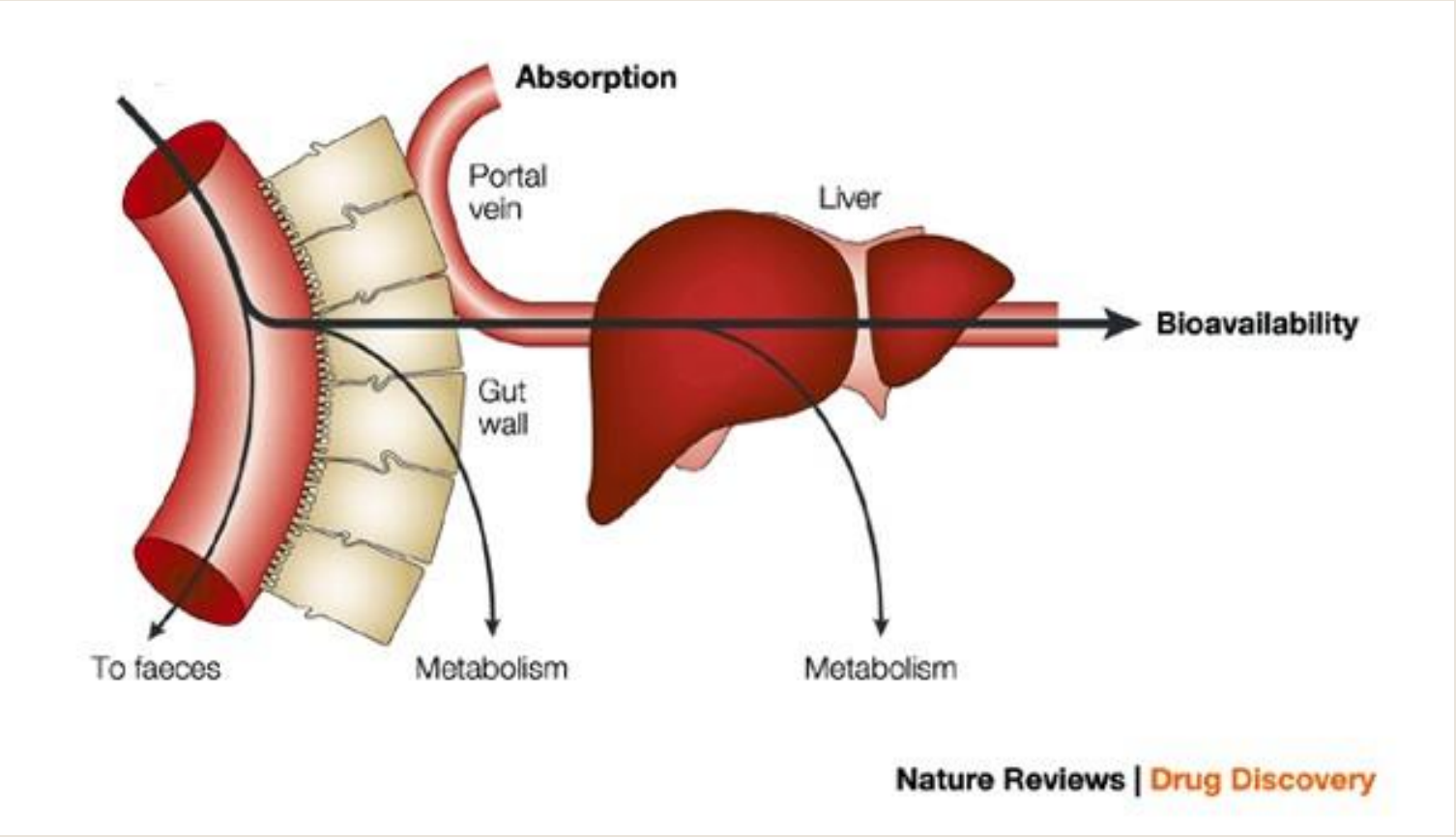
- Absorption
  - Disease
  - Age
  - Food
  - Lipid-soluble>water-soluble
  - Vomiting / malabsorption etc

- First pass metabolism (extraction ratio)

First Pass Metabolism

- Metabolism occurring before the drug enters the systemic circulation the ‘first-pass’ effect
- Can occur in:
  - The Gut Lumen
    - Gastric acid, proteolytic enzymes
    - e.g. Benzylpenicillin (that’s why its given IV/IM)
  - The Gut Wall
    - efflux transporters such as P-glycoprotein pumps drugs out of the intestinal enterocytes back into the lumen e.g. cyclosporin
  - **The Liver**
    - e.g. Propranolol is extensively metabolised

Drug Metabolism During First & subsequent passes through the GI Tract and Liver



ADME
Distribution

Drug Distribution

- The distribution of a drug refers to its ability to 'dissolve' in the body

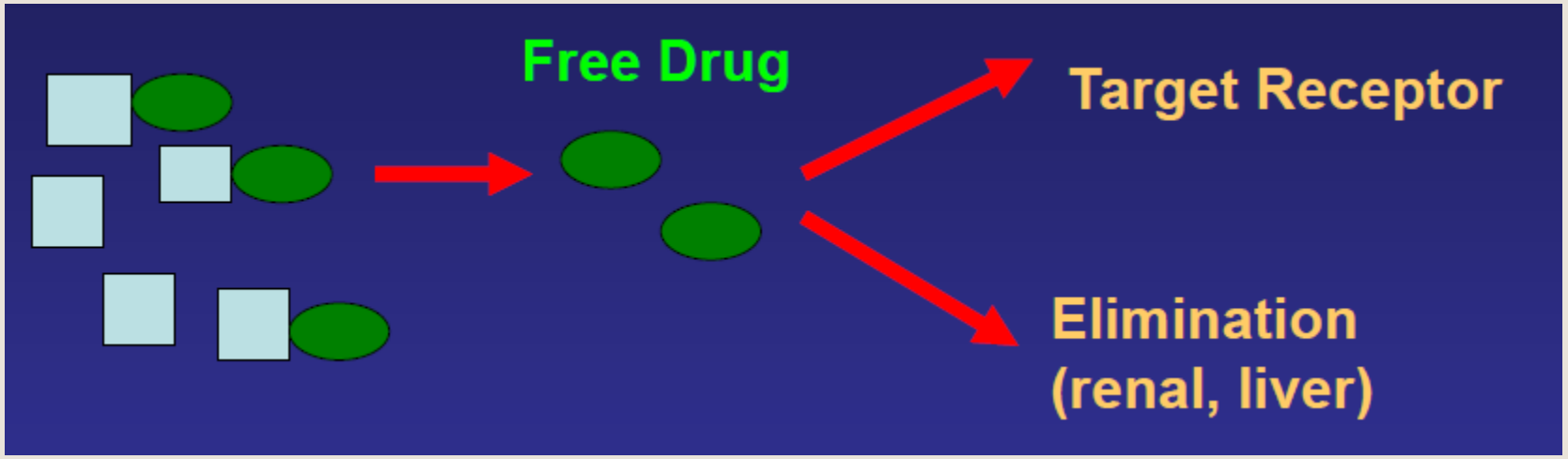
- There are two key factors:
  - Protein binding
  - Volume of Distribution (Vd) (Theoretical Constant)

Drug Distribution – Protein Binding

- Once in the systemic circulation, many drugs are bound to circulating proteins
  - Albumin (acidic drugs)
  - Globulins (hormones)
  - Lipoproteins (basic drugs)
  - Acid glycoproteins (basic drugs)
- Drugs must be unbound (free) to have a pharmacological effect
- Only the fraction of the drug that is not protein-bound can bind to cellular receptors, pass across tissue membranes, gain access to cellular enzymes etc

Drug Binding to Proteins

- Free drug determines its action at receptor



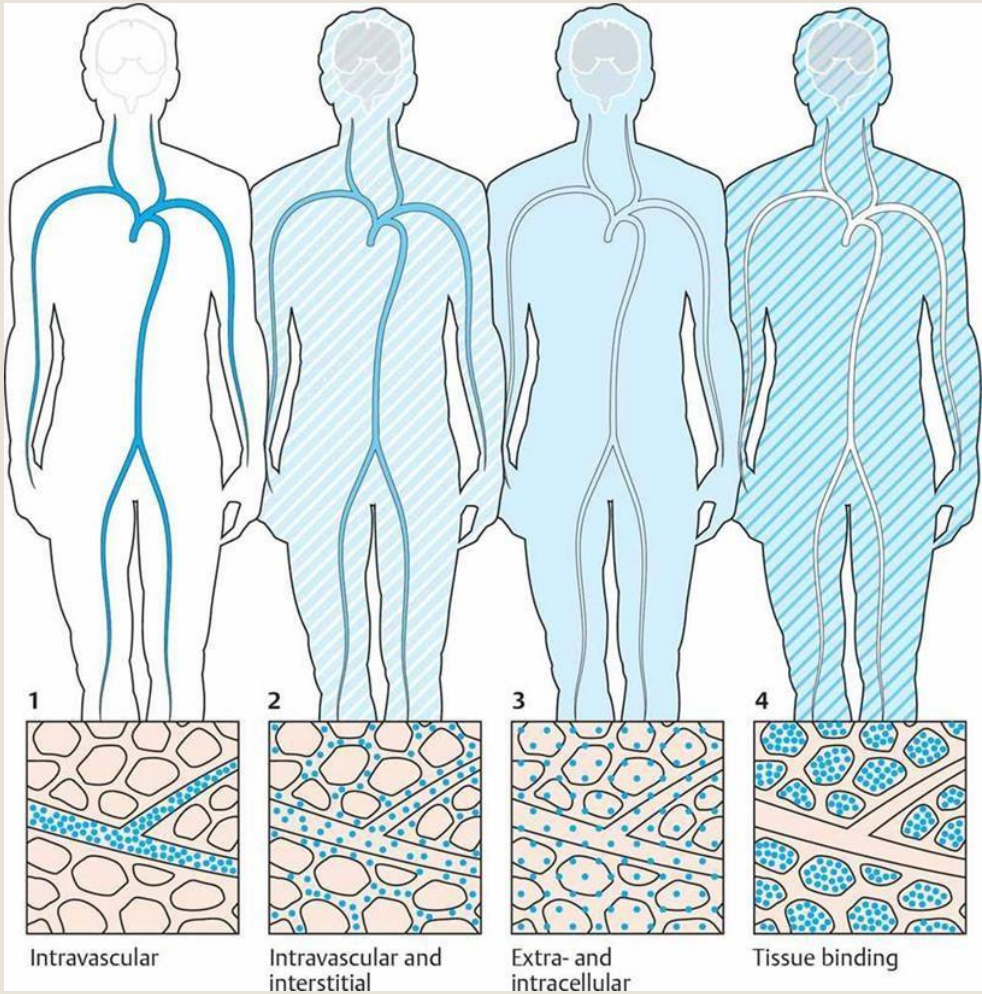
- Displacement of drugs from binding sites causes Protein Binding Drug Interactions

Drug Distribution – Protein Binding

- Changes in protein binding can occur, causing changes in drug distribution. These are only important if 3 criteria are met:
  1. High protein binding
  2. Low volume of distribution (Vd)
  3. Has a narrow therapeutic ratio
- Factors affecting protein binding include:
  - Hypoalbuminaemia
  - Pregnancy
  - Renal failure
  - Displacement by other drugs

Drug Distribution – Tissue Distribution

- Drug not bound to plasma proteins is available for distribution to tissues
- Some are distributed only to the body fluids, while others are bound extensively in body tissues.
- One measure of distribution is the apparent Volume of distribution (Vd)



Drug Distribution – Volume of Distribution (Vd)

- Volume of Distribution - how widely drug is distributed in body tissues. Vd is a proportionality constant that relates the total amount of drug in the body to the plasma concentration of the drug at a given time.
- $Vd \sim Dose / [Drug]_{t0}$ (Plasma concentration of the drug at time 0)
- Hypothetical measure, but useful in understanding dosing regimens e.g. 100mg gentamicin dose, peak plasma concentration 5mg/l, then the Vd will be 20 litres.
- $t_{1/2}$ is proportional to Vd (and clearance)

Apparent Volumes of Distribution of Some Commonly Used Drugs

<12 L (<0.17 L/kg)	12–40 L (0.17–0.57 L/kg)	40–100 L (0.57–1.43 L/kg)	100–200 L (1.43–2.86 L/kg)	>200 L (>2.86 L/kg)
Diclofenac	Acetazolamide	Aciclovir	Atropine	Amiloride
Epoetin	Alcohol	Bendroflumethiazide	Bromocriptine	Amiodarone
Furosemide	Aminoglycosides	Caffeine	Ciprofloxacin	Amlodipine
Ibuprofen	Bezafibrate	Captopril	Cocaine	Bumetanide
Phenylbutazone	Carbimazole	Carbamazepine	Diazepam	Chloroquine
Sulfonylureas	Chlorpropamide	Chloramphenicol	Metoclopramide	Chlorpromazine
Warfarin	Dextrose	Cimetidine	Ondansetron	Ciclosporin
	Digitoxin	Clozapine	Procainamide	Clomethiazole
	Insulin	Diamorphine	Propranolol	Digoxin
	Ketoconazole	Didanosine	Sumatriptan	Diltiazem
	Losartan	Iloprost	Zidovudine	Haloperidol
	Penicillin G	Isoniazid		Tricyclic antidepressants
	Phenytoin	Lidocaine		
	Prednisolone	Lithium		
	Quinidine	Metronidazole		
	Theophylline	Paracetamol		
	Valproate	Ranitidine		
		Vigabatrin		

- What does it mean for a drug to have a high volume of distribution?

- What does it mean for a drug to have a high volume of distribution?

- A drug with a high Vd has a propensity to leave the plasma and enter the extravascular compartments of the body, meaning that **a higher dose of a drug is required to achieve a given plasma concentration**. (High Vd -> More distribution to other tissue). Drugs tend to be lipophyllic / pass through membranes

Low Vd

- **A drug with a low Vd has a propensity to remain in the plasma meaning a lower dose of a drug is required to achieve a given plasma concentration**. (Low Vd -> Less distribution to other tissue)

What factors influence Vd?

What factors influence Vd?

- **concentration of drug transporters in blood (binding proteins), pH, perfusion, body water composition, body fat composition, pregnancy, conditions affecting the kidney and the liver**

- **Clinical Significance of Vd**

- To calculate **the loading dose of a drug**.
- ***Loading doses*** *are a single or multiple set of doses given to a patient to attain desired drug levels more rapidly than the 3–5 half-lives*

- The loading dose is best calculated using the Vd at steady state.

- *Steady-state represents a period of "dynamic equilibrium" of a drug throughout the body in which the drug has completed distribution between the central & peripheral compartments.*
- *At steady state, the net flux of drug between the central & peripheral compartments is 0.*

- The loading dose can be calculated using the following equation:

Loading dose (mg) = [Cp (mg/L) x Vd (L)] / F

Cp =desired plasma concentration of drug

Vd =the volume of distribution

F =the bioavailability of drug (IV administration = 1)

- After administration of a loading dose, additional maintenance doses can be administered to maintain the desired plasma concentration of the drug. Unlike, the loading dose, which is dependent on the drug's Vd, the maintenance dose is dependent on clearance (Cl). Maintenance dosing can be calculated with the following equation:
- **Maintenance dose rate (mg/hr) = [Cp (mg/L) x Cl (L/hr)] / F**

- *Cl*= the clearance rate of drug

Key differences between loading doses & maintenance doses

- The loading dose is contingent on the volume of distribution while maintenance doses are dependent on plasma clearance.

- The loading dose is only required for a few drugs in certain situations while maintenance doses are required for most drugs to maintain the steady-state plasma concentration.

- Loading doses are usually indicated in clinical scenarios where a drug **needs to reach steady-state rapidly** e.g, antiepileptic administration during an active seizure or aspirin loading during a suspected myocardial infarction

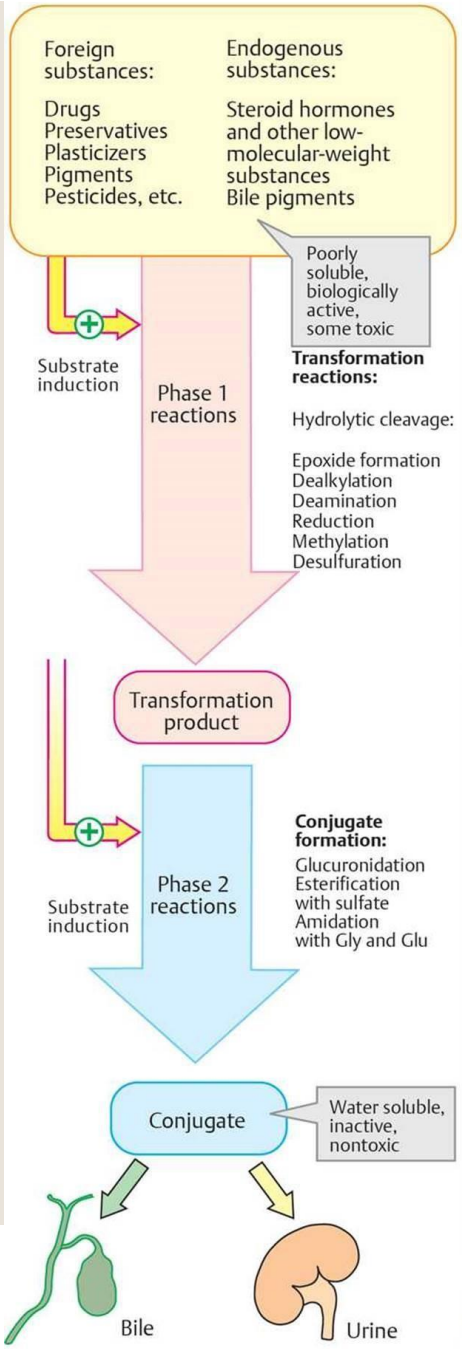
- Because maintenance doses are dependent on drug clearance which is a variable dictated by each individual patient, maintenance doses are often variable as certain patients may take less or more time to clear a drug from the plasma.

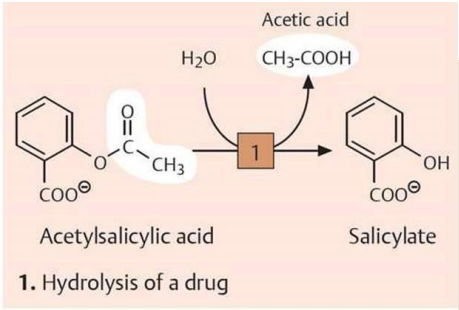
Eg, renal failure patients will take longer to eliminate a drug in the urine. Therefore the maintenance dose is corrected based on the patient's renal function. In these cases, the loading dose will remain the same, and the maintenance dose will undergo correction.

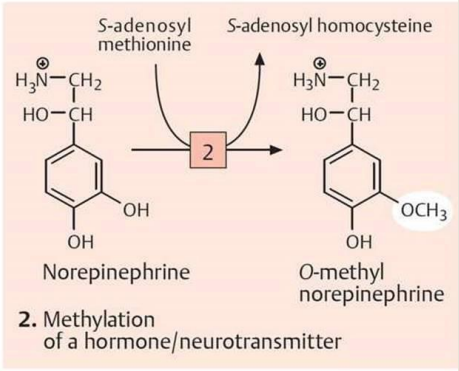
ADME
Metabolism

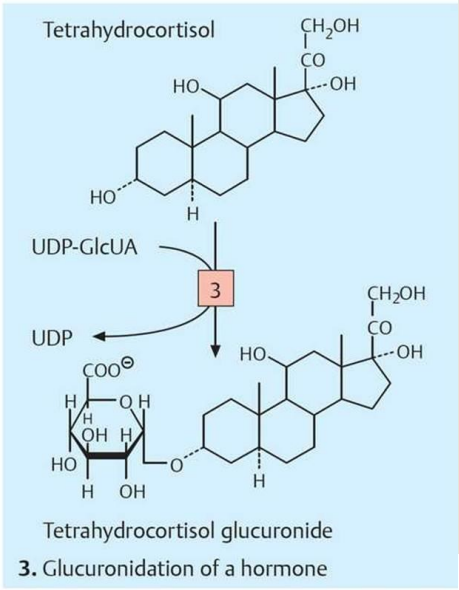
Drug Metabolism

- Phase 1- modification of drug to more reactive or polar metabolite
- Phase 2- conjugation
- The end products of conjugation are water-soluble enabling rapid elimination from the body
- They are usually pharmacologically inactive









1 Arylesterase
2 Catechol-O-methyl-transferase
3 Glucuronosyltransferase

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Active metabolites

- Prodrugs: pharmacologically inactive compound metabolised to an active one, e.g.:
  - Inactive enalapril to active enalaprilat
  - L-Dopa (crosses blood-brain barrier) is metabolised to dopamine
- Metabolism of a pharmacologically active compound to other active compounds eg. codeine to morphine

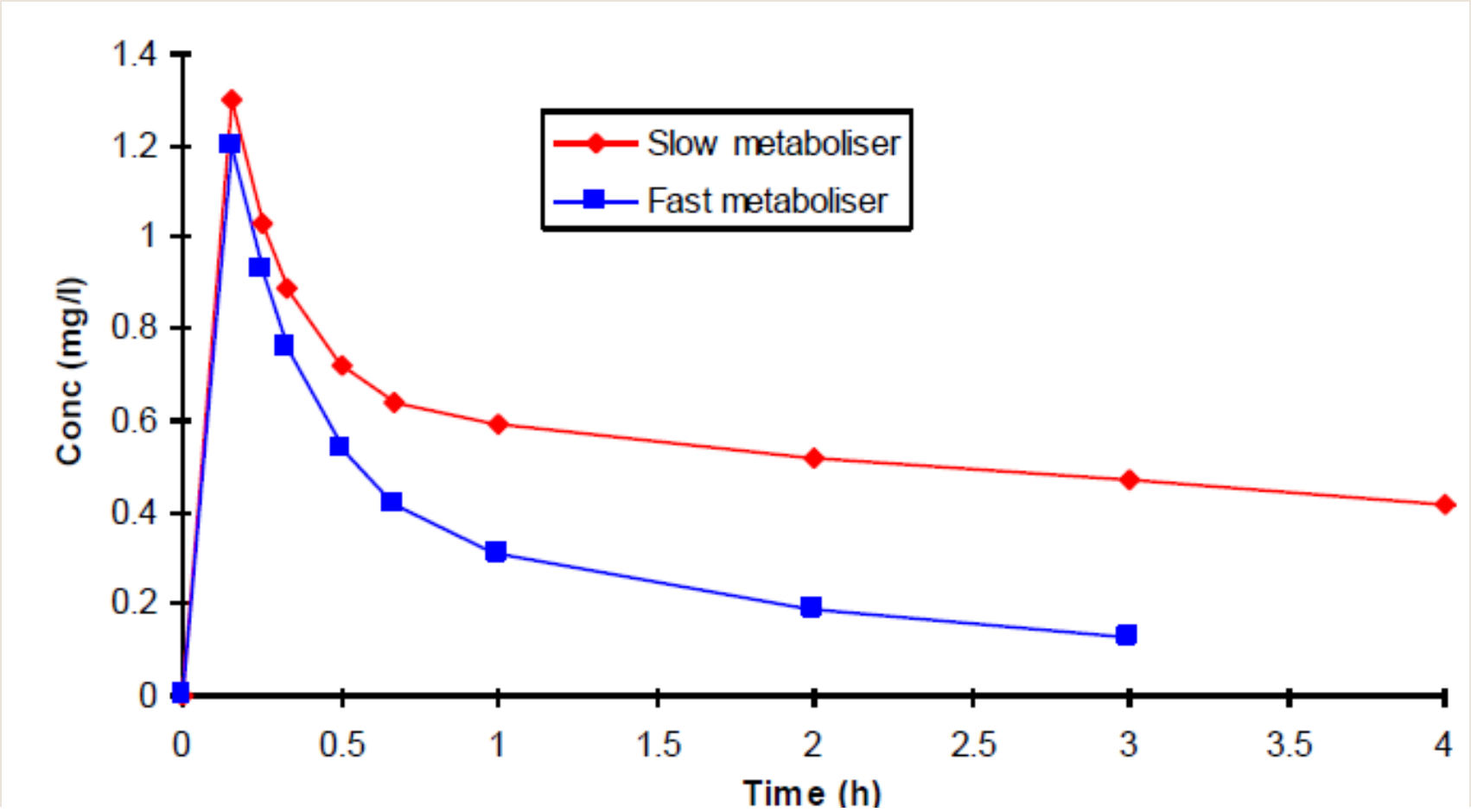
Drug Metabolism – Phase 1

- Oxidation and Reduction are in part dependent on the cytochrome P450 (CYP450) family of enzymes
- Activity of CYP450 enzymes can be influenced by enzyme- inducing and enzyme-inhibiting drugs:
  - these alter the rate of metabolism of other drugs
- Other influences: age, liver disease, hepatic blood flow, cigarette and alcohol consumption

Cytochrome P450 (CYP450) isoenzymes

- Present mainly in the liver (some gut and lung)
- Big ones: CYP2D6, 2C9, 2C19, 3A4
- Super family of isoforms responsible for approximately 90% human drug metabolism through oxidative reactions
- Metabolise toxins such as carcinogens and pesticides
- Genetic differences in metabolism

Effect of ‘metaboliser’ status in a single dosing study



Key Messages re: Metabolism

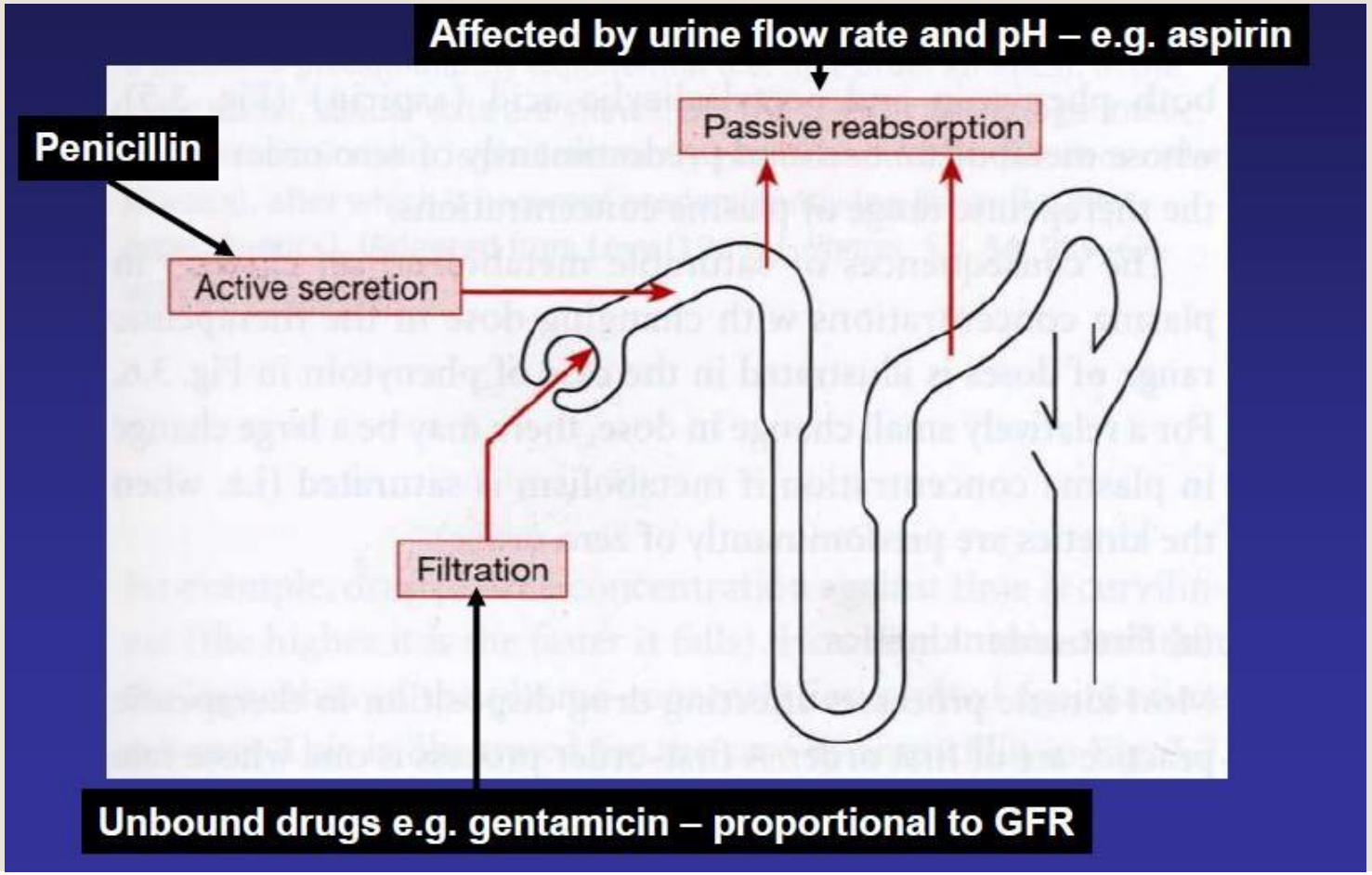
- Important for drug prescribing (common esp. novel drug development)
- Consider OTC and food as drug-drug interactions (grapefruit juice- see next lecture)
- Other Factors:
  - Race/Ethnicity (Development of pharmacogenetics)
  - Age (reduced in aged patients & children)
  - Clinical or physiological condition

ADME
Elimination

Elimination

- The main route of drug elimination is the kidney.
- Other routes include the lungs, breast milk, sweat, tears, genital secretions, bile, saliva
- 3 processes determine the renal excretion of drugs
  - Glomerular Filtration
  - Passive tubular reabsorption
  - Active tubular secretion

Drug Elimination via the Kidney – the Nephron

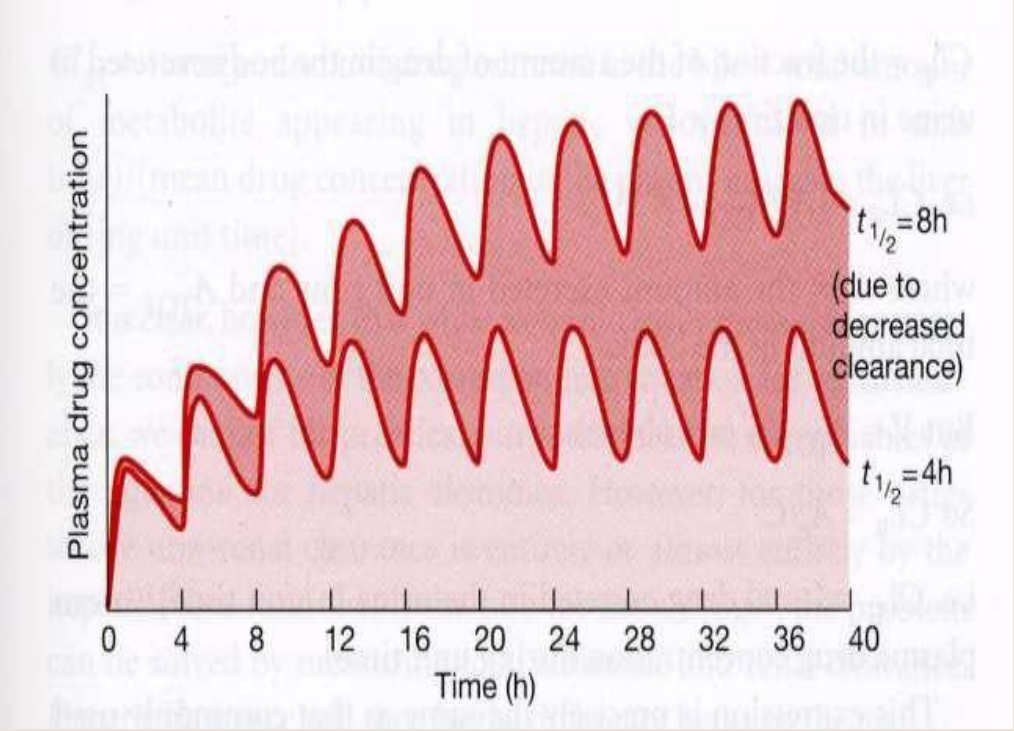


Clearance (Cl) and half life ($t_{1/2}$)

- Clearance
  - The volume of plasma that is completely cleared of the drug per unit time (in L/h or mL/min)
  - Represents the ability of the body to excrete a drug
  - Calculated by the rate of drug elimination divided by plasma concentration of the drug
- Half life
  - the time required for plasma concentration to decrease by half

Clearance (Cl) and half life ($t_{1/2}$)

- Cl = ability of body to excrete drug
- Mostly = GFR
- If the GFR ↓ then Cl ↓
- $t_{1/2}$ is inversely proportional to clearance
- A reduction in clearance (or GFR) increases $t_{1/2}$



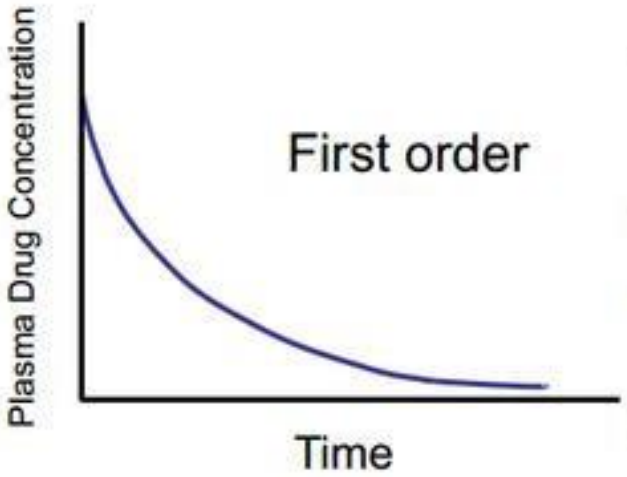
Drug Elimination

- 1st Order kinetics - Linear

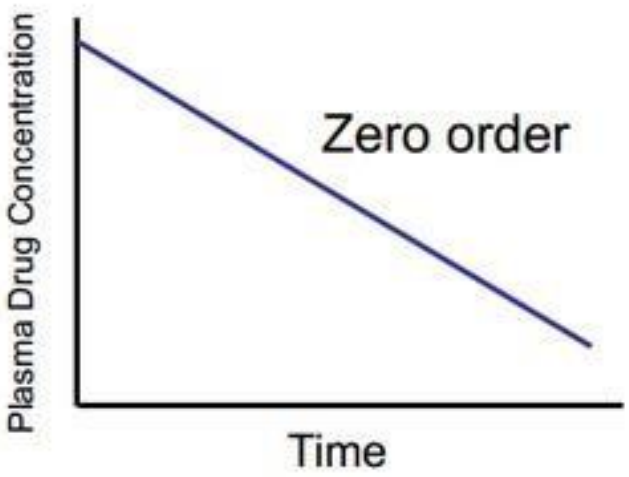
Rate of elimination is proportional to drug level. Constant fraction of drug eliminated in unit time. Half life can be defined. Most drugs follow this.

- Zero Order kinetics – Non-linear

Rate of elimination is a constant. You cannot predict half life.

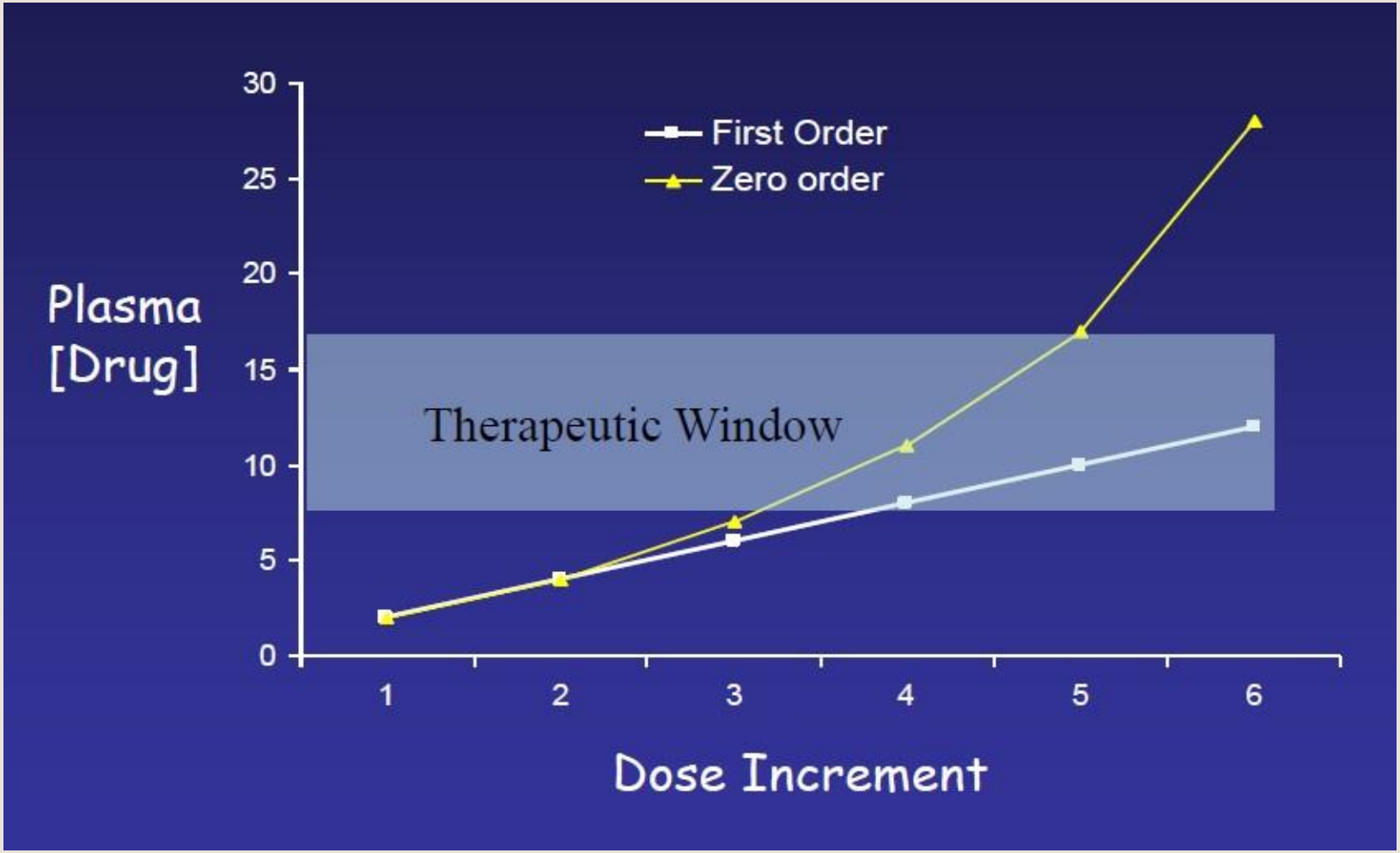


- Constant fraction of drug eliminated per unit time
- Rate of drug elimination proportional to drug plasma concentration



- Constant amount of drug eliminated per unit time
- Rate of drug elimination independent of drug plasma concentration

Dosing easier with 1st order kinetics



Half life

- This is the period of time required for the concentration or amount of drug in the body to be reduced by one-half.
- The time taken for the plasma concentration to halve is the half life of that drug.
- Ibuprofen: short half life (2 hr)
- Warfarin (Mean plasma half life: 40hr)
- Drugs with shorter half life need to be given in regular doses to build up and maintain a high enough concentration in the blood to be therapeutically effective.
- Most drugs are considered to have a negligible effect after four-to-five half-lives
- $t_{1/2} = 0.693.Vd / Cl$

Clinical significance of half life

- The clinical significance of half-life tends to arise in situations involving drug toxicity.

- Overdosed or received an incorrect amount of a particular drug. Hepatic disease also affects the half-life of a given drug due to impaired metabolism

- Half-life is also clinically relevant when physicians must determine the most efficient yet safest dosing schedule to achieve an optimal therapeutic effect, or when a steady-state concentration of a drug is desirable.

Drug Monitoring

- Several PK reasons:
  - Zero order kinetics
  - Long half-life
  - Narrow therapeutic window
  - At greater risk of drug-drug interactions

- Others include:
  - Know toxic effects (e.g. bone marrow suppression)
  - Monitoring therapeutic effect (e.g. BP, glucose etc))