General Pharmacology

Dr Asita de Silva

Drug therapy

- Drug given to produce – EFFECT
- Two ways of administration:
  - Local (topical application, inhalation)
  - Systemic (oral, parenteral)

Local administration

Advantages of local drug therapy:

- Small dose delivered to site of pathology
- Rapid onset of action – rapid relief
- Less unwanted/adverse effects

Majority of diseases - site of pathology not directly accessible

Cannot be treated by local administration of drugs - require systemic administration

Systemic administration

- Objective - get drug into systemic circulation
- Usual route - ORAL
- Disadvantages:
  - Larger dose required
  - Slower onset of action
  - Carried to all tissues (not only the site of pathology)
  - Greater risk of adverse effects

Drugs

- Produces an effect - changes in patient
- ‘What the drug does to the patient’

  PHRAMACODYNAMICS
- Drug undergoes changes
- ‘What the patient does to the drug’

  PHARMACOKINETICS
- Successful therapy - dynamic/kinetic knowledge
- Failure of therapy - dynamic/kinetic reasons

Drug therapy

Four main processes in drug therapy:

- Is the drug getting into patient?

  Pharmaceutical process

- Is the drug getting to the site of action?

  Pharmacokinetic process

- Is the drug producing pharmacological effect?

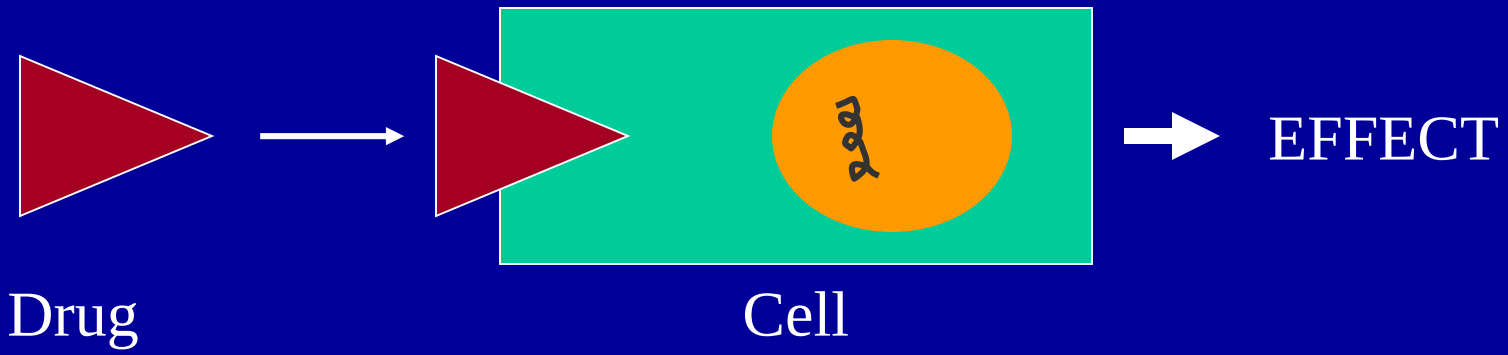
  Pharmacodynamic process

- Is pharmacol. effect giving therapeutic benefit?

  Therapeutic process

PHARMACODYNAMICS

- Drug must exert chemical influence on constituent(s) of cells to produce EFFECT
- Drug must be BOUND to cell constituents



- Drugs bind to targets - protein molecules (exceptions – some antitumour drugs/antibiotics)

Drug binding

Protein targets:

- Receptors - atenolol
- Carrier molecules – furosemide
- Enzymes – captopril
- Ion channels - lignocaine

Specificity of drug action

- Drugs must act selectively on cells/tissues
- For selective action

  - drugs show binding site specificity

  - binding targets show ligand specificity
- No drug acts with complete specificity

  (higher doses – affect other targets)
- Results in unwanted/adverse effects

Mechanism of drug action

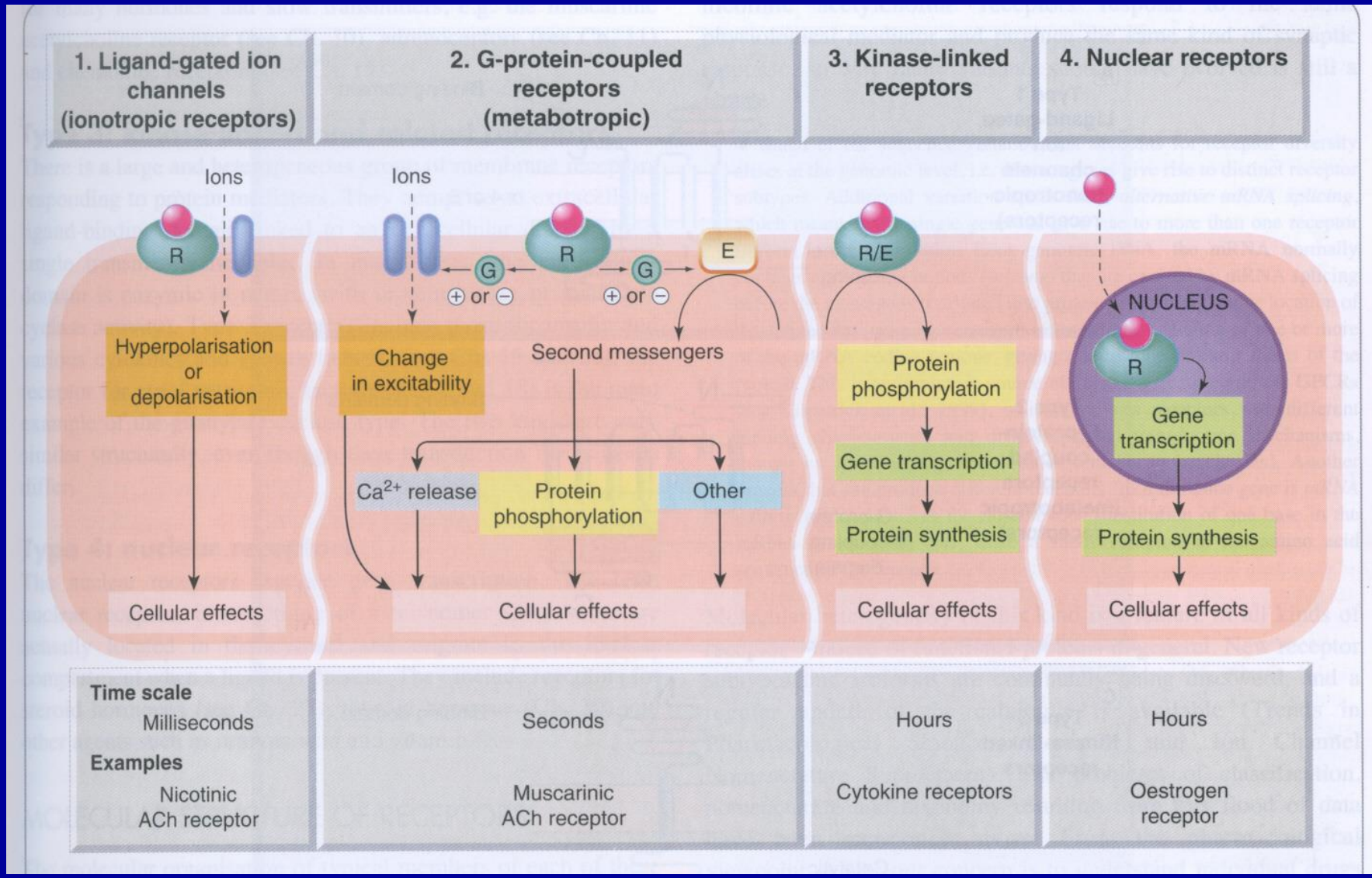
Considered at four levels:

- System
- Tissue
- Cellular
- Molecular

Best classification - molecular mechanism

(e.g. propranolol is a beta-blocker))

Drug-receptor interaction



Receptors

- Protein macromolecules
- Usually situated on the cell membrane
- Specific for a ligand – e.g. insulin receptor
- Three types of ligands:
  - agonists
  - antagonists
  - partial agonists (e.g. oxprenolol)

Changes in receptors

- Up regulation – prolonged exposure to antagonist (worsening of angina after abrupt withdrawal of propranolol)
- Down regulation – prolonged exposure to agonist (worsening of asthma after long-term therapy with salbutamol)

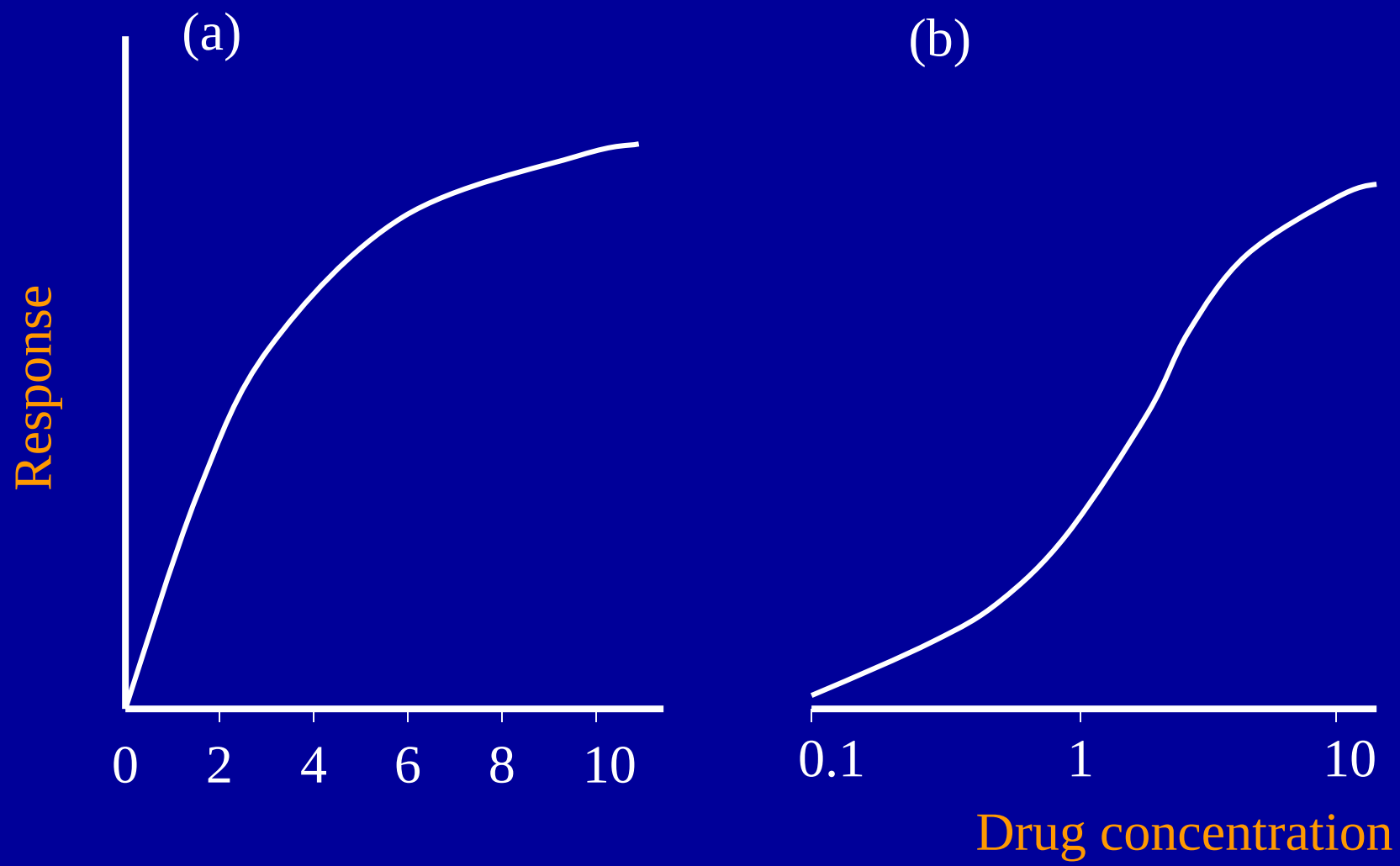
Tachyphylaxis (tolerance)

- Reduced responsiveness of a drug due to previous (long-term) exposure to that drug
- Mechanisms:
  - Receptor down regulation
  - Change in receptors
  - Exhaustion of mediators

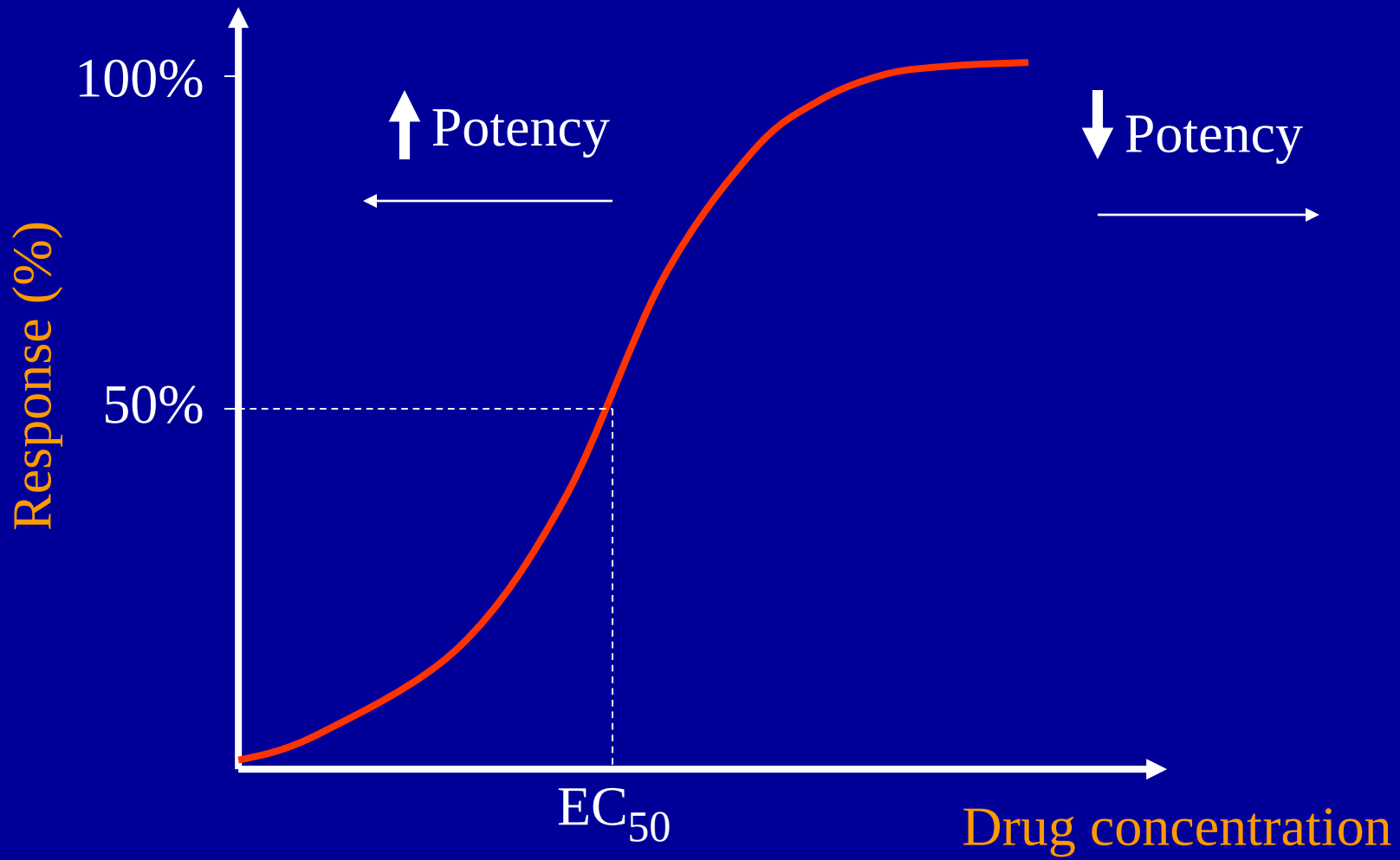
Dose-response in drug therapy

- Effect of a drug is related to concentration of the drug at the site of action
- Higher the concentration – greater the effect
- The relationship between drug concentration and effect: dose-response curve

Dose-response curve

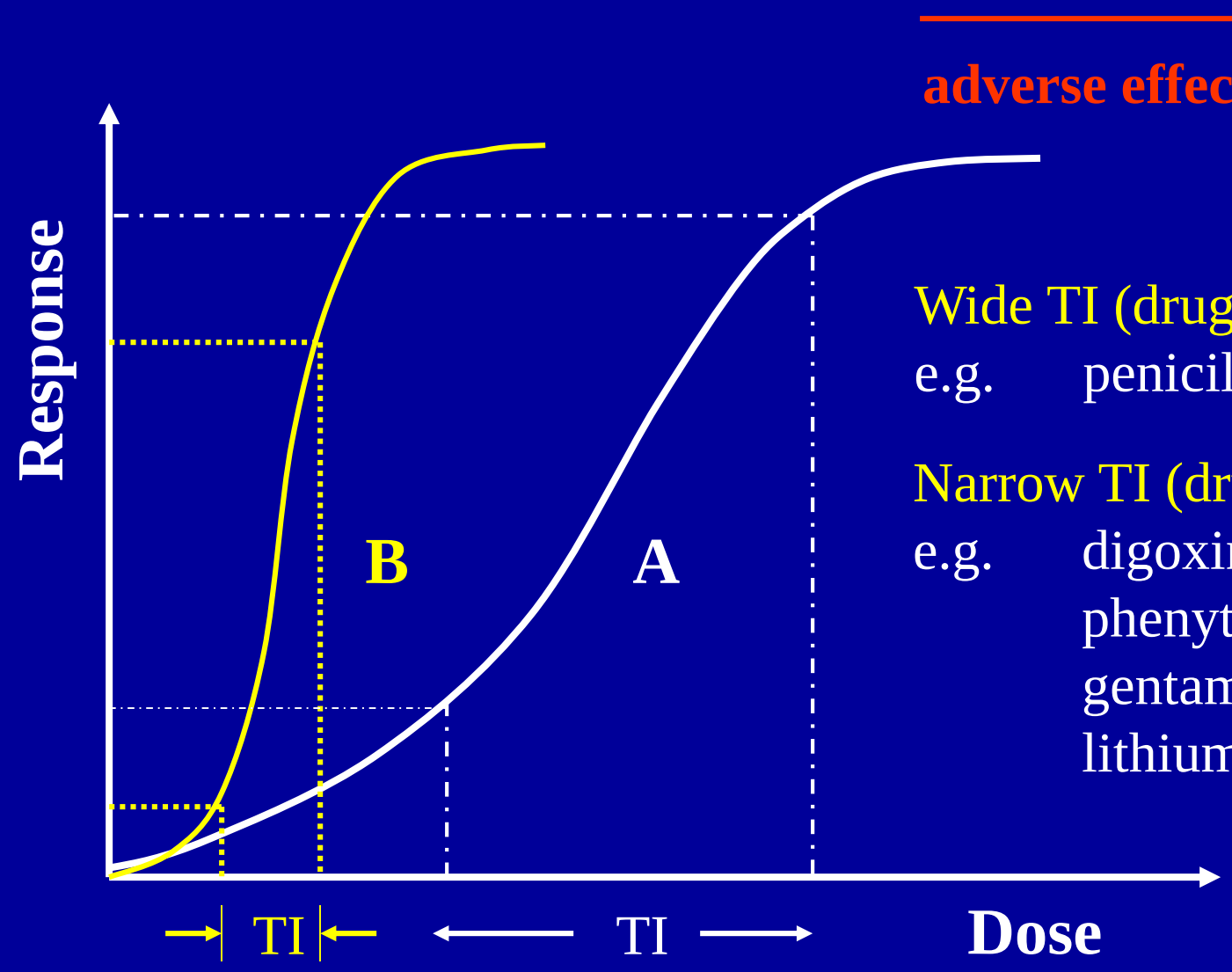


D-R curve: relates concentration of drug to the biological effect



- EC_{50} – concentration of drug producing 50% of maximum effect
- Most drugs are used at doses close to the top of D-R curve

Therapeutic index (TI)



Wide TI (drug A)
e.g. penicillin

Narrow TI (drug B)
e.g. digoxin
phenytoin
gentamicin
lithium

PHARMACOKINETICS

Pharmacokinetic process comprises:

- Absorption
- Distribution
- Metabolism
- Excretion

Absorption & bioavailability

- Movement of drug from GIT (site of administration) into systemic circulation
- Oral drugs – mainly upper small intestine
- To cross cell barriers (GIT, renal tubule) drugs must cross lipid membranes
- Drugs cross lipid membranes mainly by:
  - passive diffusion
  - carrier mediated transfer

Absorption

Factors affecting absorption :

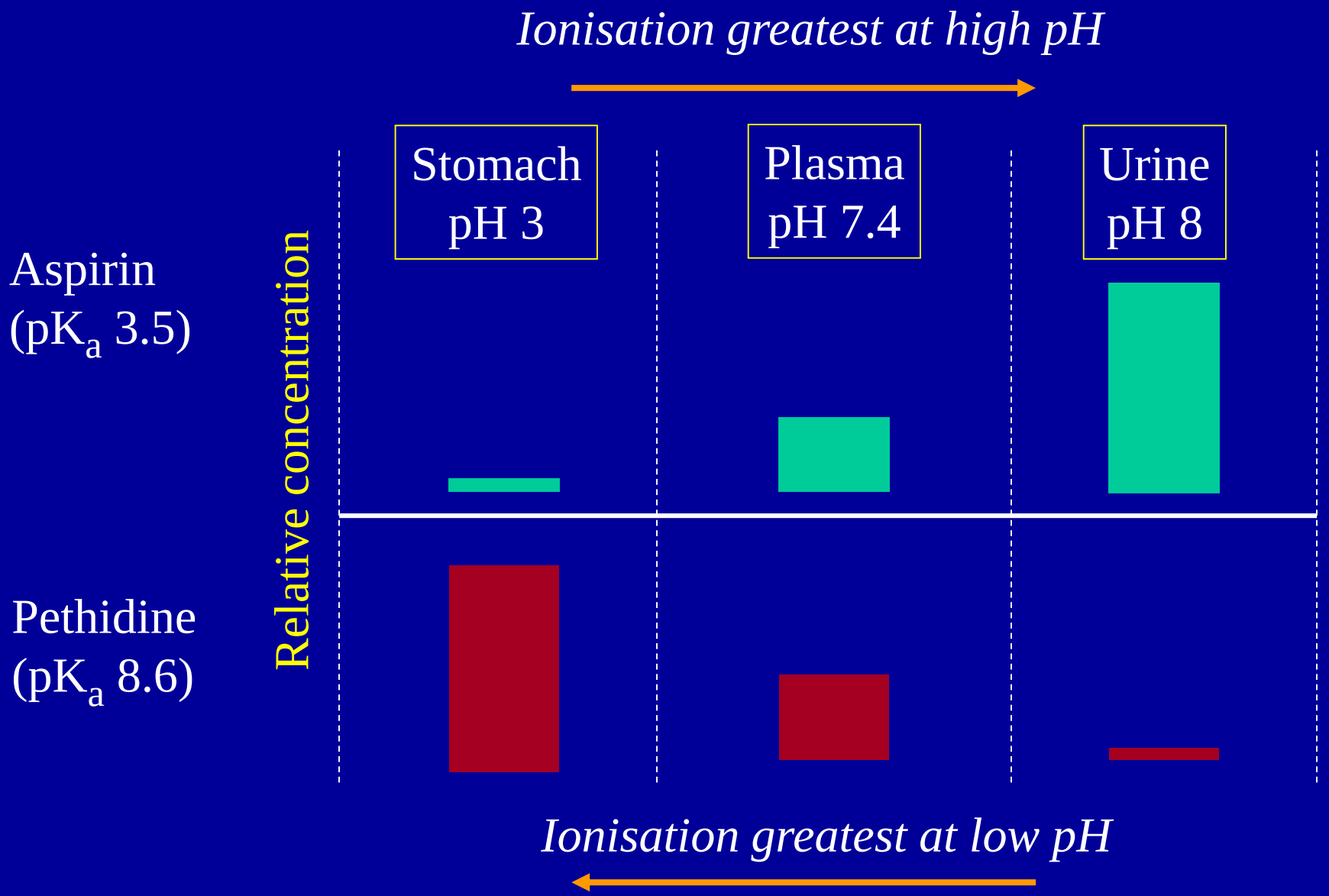
i. Lipid solubility
ii. Molecular weight and state of ionization
iii. Malabsorptive states
iv. Presence of food

pH partitioning

- Unionized drug molecules cross membranes better
- Acidic drugs concentrated in body compartments with alkaline (high) pH: “ion trapping”

  e.g. aspirin concentration: renal tubule > plasma
- pH partitioning not the main factor for absorption from GIT – surface areas of stomach & jejunum
- Absorption of acidic drug (aspirin) promoted by drugs accelerating gastric emptying (metoclopramide)
- Urinary alkalinisation promotes excretion of weak acids (e.g. aspirin)

pH partitioning of drugs – ion trapping



Bioavailability (systemic availability)

Bioavailability defined in terms of:

i. The amount (%) of given drug that reaches systemic circulation, and

ii. The speed at which that happens

Indicates the proportion of drug entering systemic circulation after oral administration

100% bioavailabilty – only with iv administration

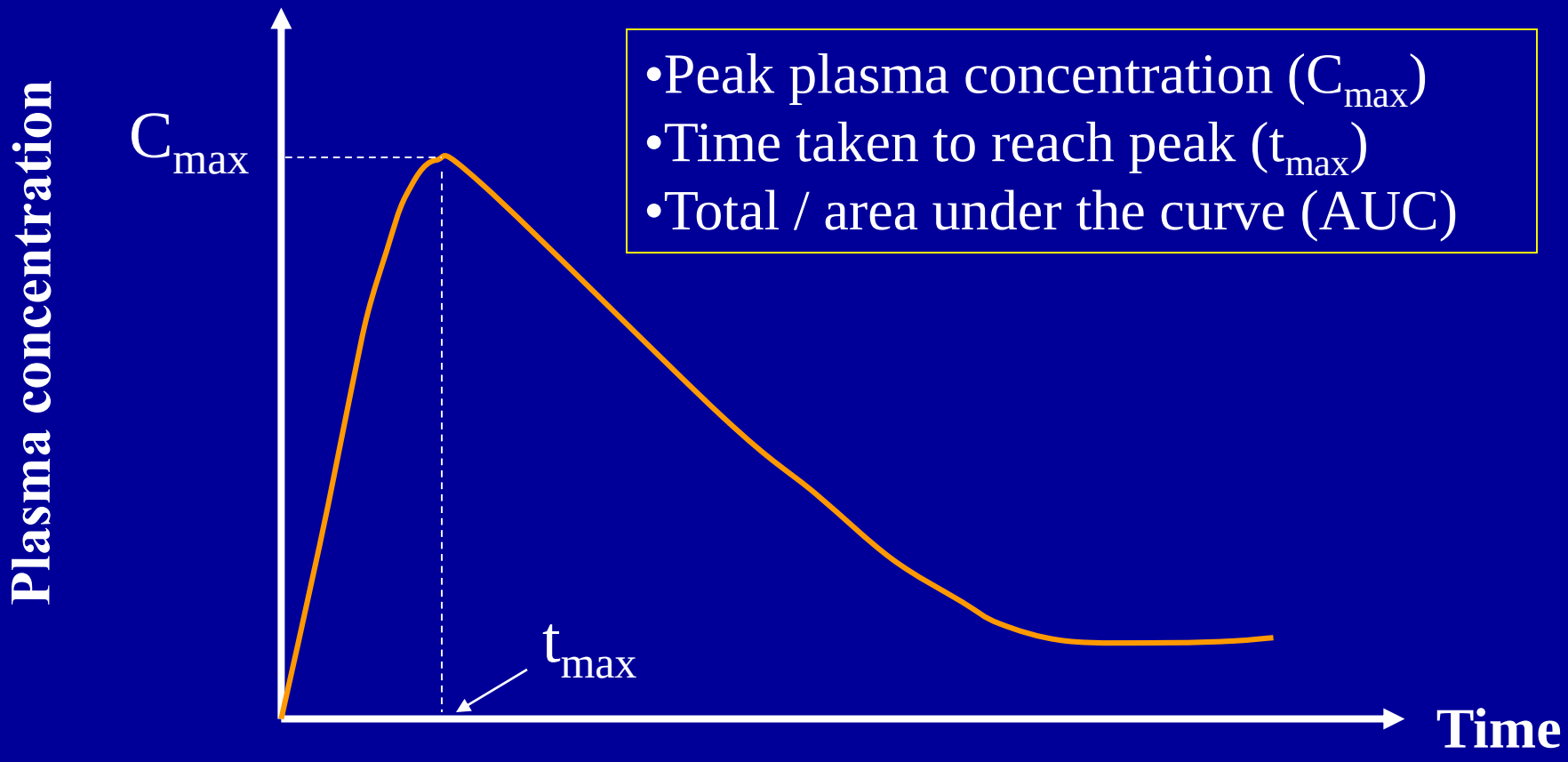
Bioavailability

Factors affecting bioavailability:

- Pharmaceutical factors
- Biological factors
- First pass (pre-systemic) metabolism (e.g. nitrates)

Avoid first pass metabolism - sublingual administration

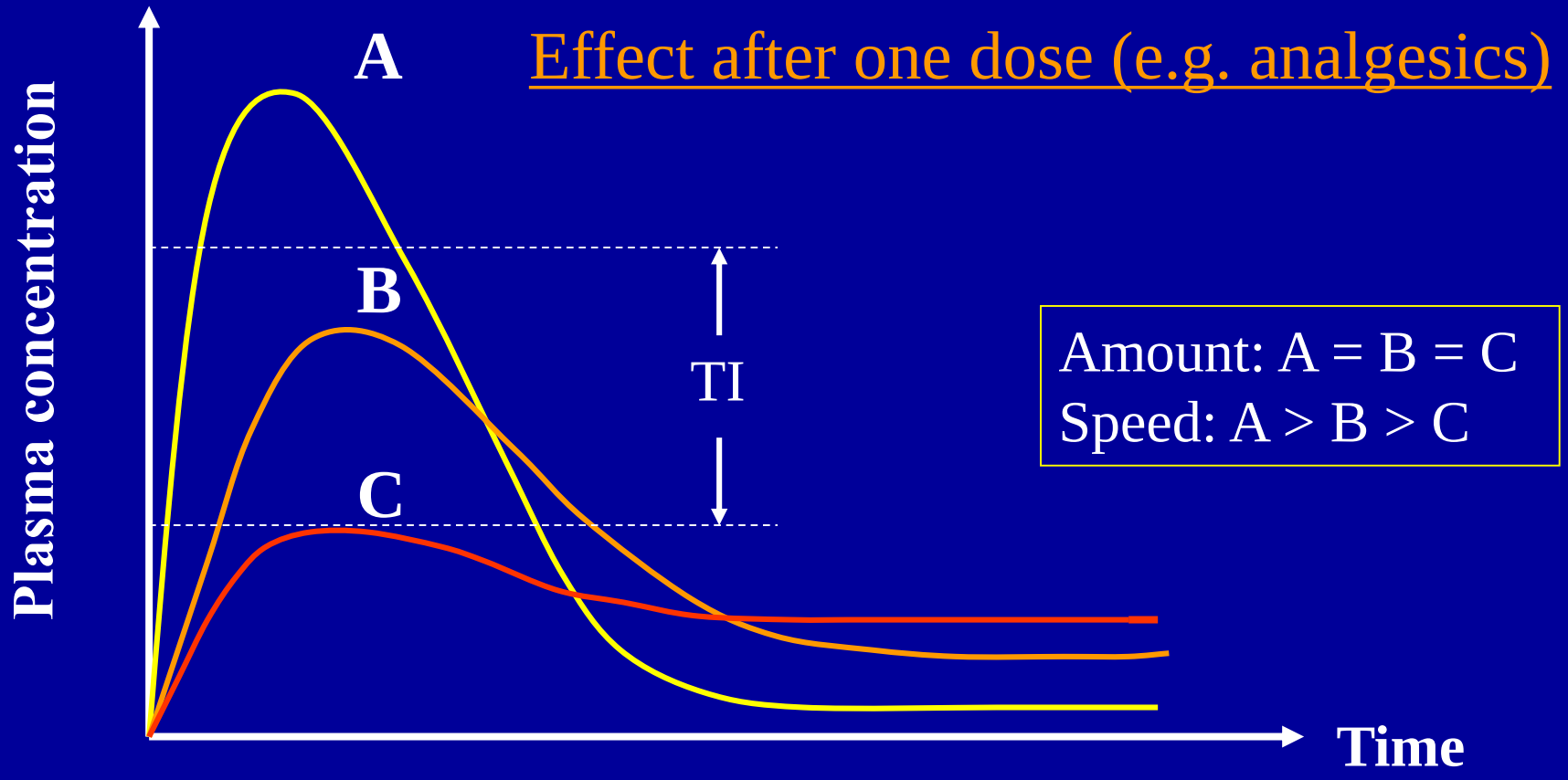
Speed of availability may be influenced by other factors (e.g. motility stimulants in migraine)



- Peak plasma concentration (C_{max})
- Time taken to reach peak (t_{max})
- Total / area under the curve (AUC)

- C_{max} and t_{max}: influenced by speed/rate of availability
- C_{max} and AUC: measures of extent of availability

Effect after one dose (e.g. analgesics)



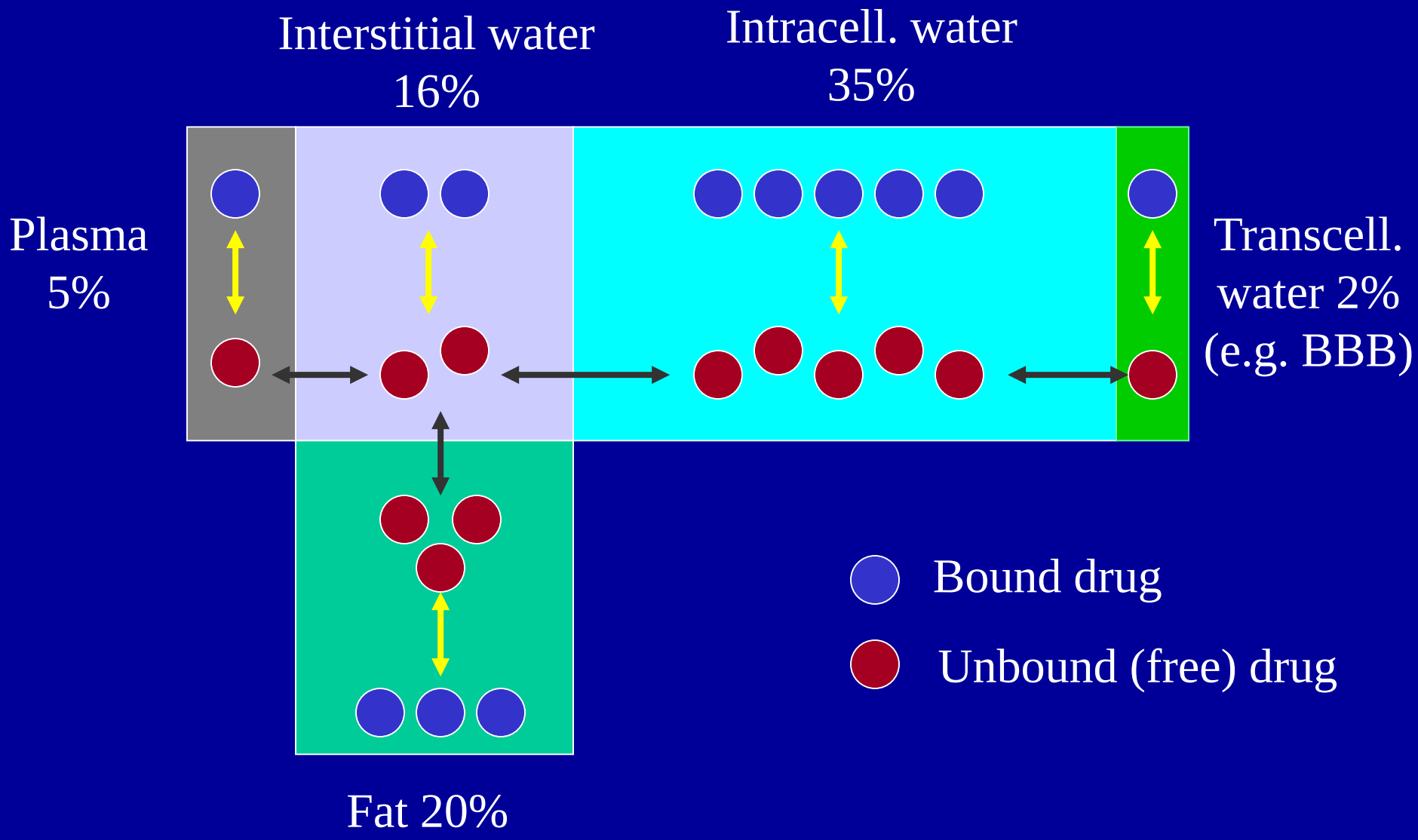
Amount: A = B = C
Speed: A > B > C

B: rapid relief of acute pain (aspirin in headache)

C: long-term/sustained relief (slow release aspirin in RA)

A: very rapid therapeutic effect (GTN in angina)

Distribution



Distribution

Distribution between compartments depend on:

- Permeability across barriers (e.g. blood brain barrier: use of domperidone in nausea)
- Binding within compartments
- pH partition
- Fat:water partition

Volume of distribution (Vd)

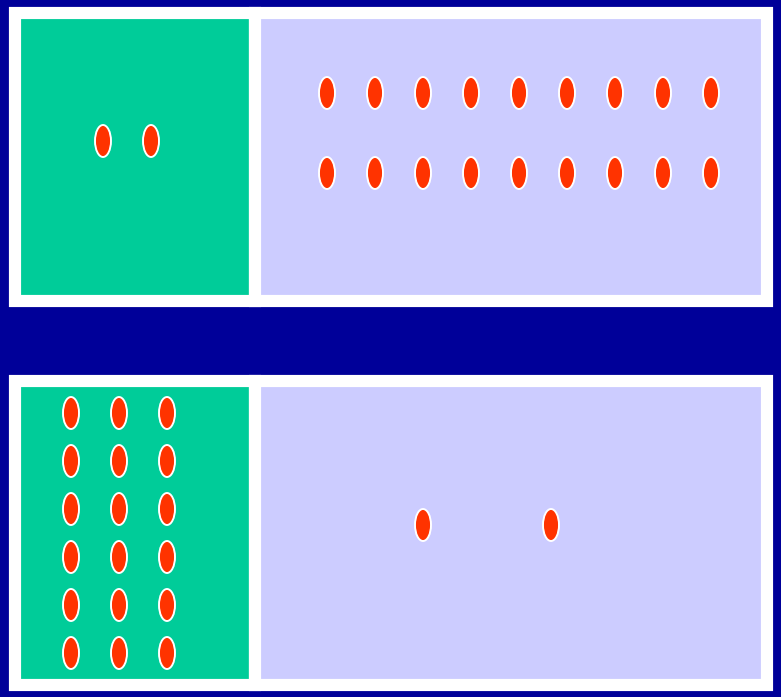
- Volume of fluid needed (in litres) to contain the total amount of drug (Q) in the body at the same concentration as that in the plasma (Cp)

$$Vd = Q / Cp$$

- Measure of how widely a drug distributes in the body
- Fat soluble drugs with low mw – large Vd
  (e.g. cyclosporin 100 L)
- H_2O soluble drugs with high mw – small Vd
  (e.g. heparin 3 L)

Volume of distribution

Vd: relates amount of drug in the body to plasma conc.
Therefore, Vd = amount of drug in body / plasma conc.



Factors affecting distribution

- Specific receptors in tissues – Na/K pump
- Disease - obesity & fat soluble drugs
  - hyperthyroidism & digoxin
- Regional blood flow – heart, liver, kidneys
- Other drugs – TCA drugs inhibit active transport of adrenergic neuron blockers
- Plasma protein binding – phenytoin, warfarin

Factors affecting protein binding

- Renal impairment
- Hypoalbuminaemia (< 25g/L)
- T3 of pregnancy
- Saturability
- Displacement by other drugs (e.g. warfarin & aspirin)

Volume of distribution

Drug with a large Vd (TCA drugs, haloperidol):

- Likely to be highly lipid soluble
- Likely to reach all compartments
- May accumulate in body fat
- Vd may be beyond total body water
- Haemodialysis unhelpful in overdosage

Metabolism

- Occurs mainly in the liver
- Results in two major changes to drug:
  - Reduced lipid solubility (for renal elimination)
  - Reduced biological activity (inactive compounds)
- Metabolism
  - drug to inactive compounds
  - drug to active compound (nitrates, spironolactone, diazepam)
  - inactive drug to active (e.g. enalapril): prodrugs

Metabolism

Occurs in two phases: phase I & II

Phase I

- Alters chemical structure of drug: catabolic reactions such as oxidation or hydroxylation
- Enzymes cytochrome P_{450} system in hepatic ER
- Phase I products – eliminated directly / further metabolism in phase II (conjugation)

Metabolism

Phase II

- Reactions are anabolic (synthetic): conjugation of the parent drug / metabolite of phase I
- After conjugation – excreted in urine (mw<300) or in bile (mw>300)
- Some deconjugated by gut bacteria – parent drug reabsorbed (enterohepatic recirculation)

Determinants of drug metabolism

- Genetic factors

Acetylation: fast and slow acetylators

- susceptible drugs: INAH / procainamide
- acetylation: autosomal recessive gene

Oxidation: Metoprolol, some TCA drugs

- Gender – ethanol
- Smoking – theophylline
- Other drugs – enzyme inducers / inhibitors

Pharmacologically active drug metabolites

- Pro-drugs: enalapril, azathioprine
  (designed to overcome drug delivery problems)
- Alter pharmacological action qualitatively
  (salicylic acid has no antiplatelet activity)
- Metabolite has similar activity to parent drug
  (benzodiazepines and sedation)
- Metabolite responsible for toxicity (paracetamol)
- Active metabolite lacking toxicity of parent drug
  (terfenadine & fexofenadine – cardiotoxicity)

Enzyme induction / inhibition

Inducers: rifampicin, ethanol, carbamazepine

- Induce enzymes when given repeatedly
- Increases metabolism of inducing drug / other drugs (e.g. rifampicin & OCP)
- Increased metabolism – increase drug effect (e.g. paracetamol toxicity)

Inhibitors: cimetidine, ketoconazole

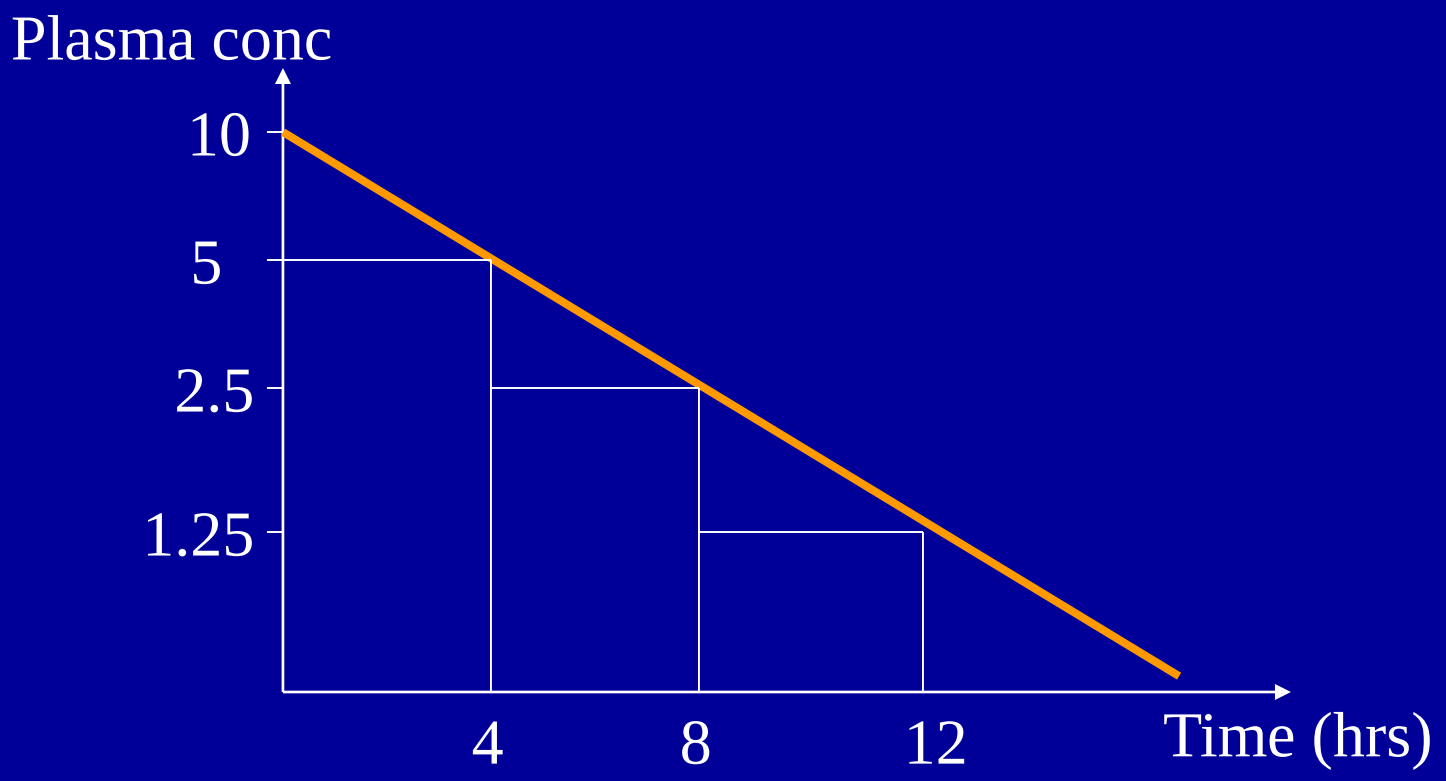
- Increases activity of other drugs - toxicity

Excretion / clearance (CL)

- Kidney is the main route
- glomerular filtration: most drugs
- tubular secretion: usually carrier mediated (e.g. penicillin blocked by probenicid)
- tubular reabsorption
- Other routes: bile, lungs, sweat, tears

Plasma elimination half-life (t½)

Time taken for plasma conc of a drug to reduce by half (50%)



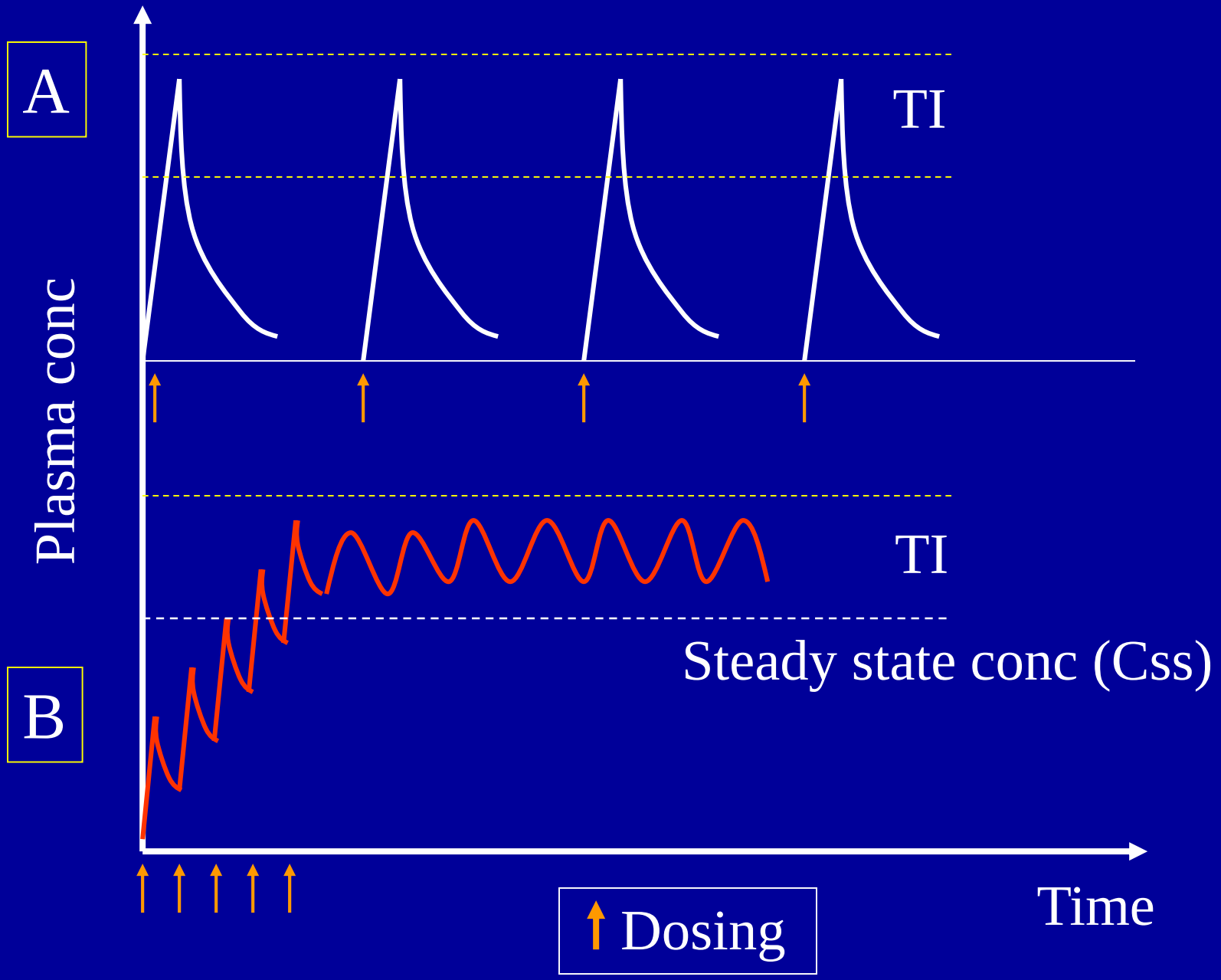
Time taken for plasma conc to fall from any value by half is constant – 4 hrs. Half-life of the drug is 4 hrs

Half-life (t½)

Half-life = Volume of dist (Vd) / Clearance (CL)

- t½ is directly proportional to Vd
- t½ is inversely proportional to CL

(e.g. drugs with large Vd will have long t½)


A
TI
Plasma conc
TI
B
Steady state conc (Css)
Time
Dosing

Steady state concentration

- For sustained therapeutic effect conc of drug must be maintained within the TI
- Plasma level must not fluctuate too much
- A single dose will not usually achieve this
- Rate of absorption = rate of elimination plasma conc will be steady: steady state (Css)
- Time to Css = 3-5 half-lives of the drug

Half-life indicates …

- Duration of action after a single dose
- Rate at which drug conc falls after stopping drug
- Dosing frequency (along with TI)

  - drug with ↑ t½ & ↓TI: regular dosing

  - drug with ↓ t½ & ↓TI: infusion

  - drug with ↑↑t½: accumulate if given repeatedly

  many drugs have pharmacol action > than t½

  e.g. glibenclamide, omeprazole

Half-life indicates …

- Time taken to reach steady state (3-5 t½)
- Need for a loading / bolus dose

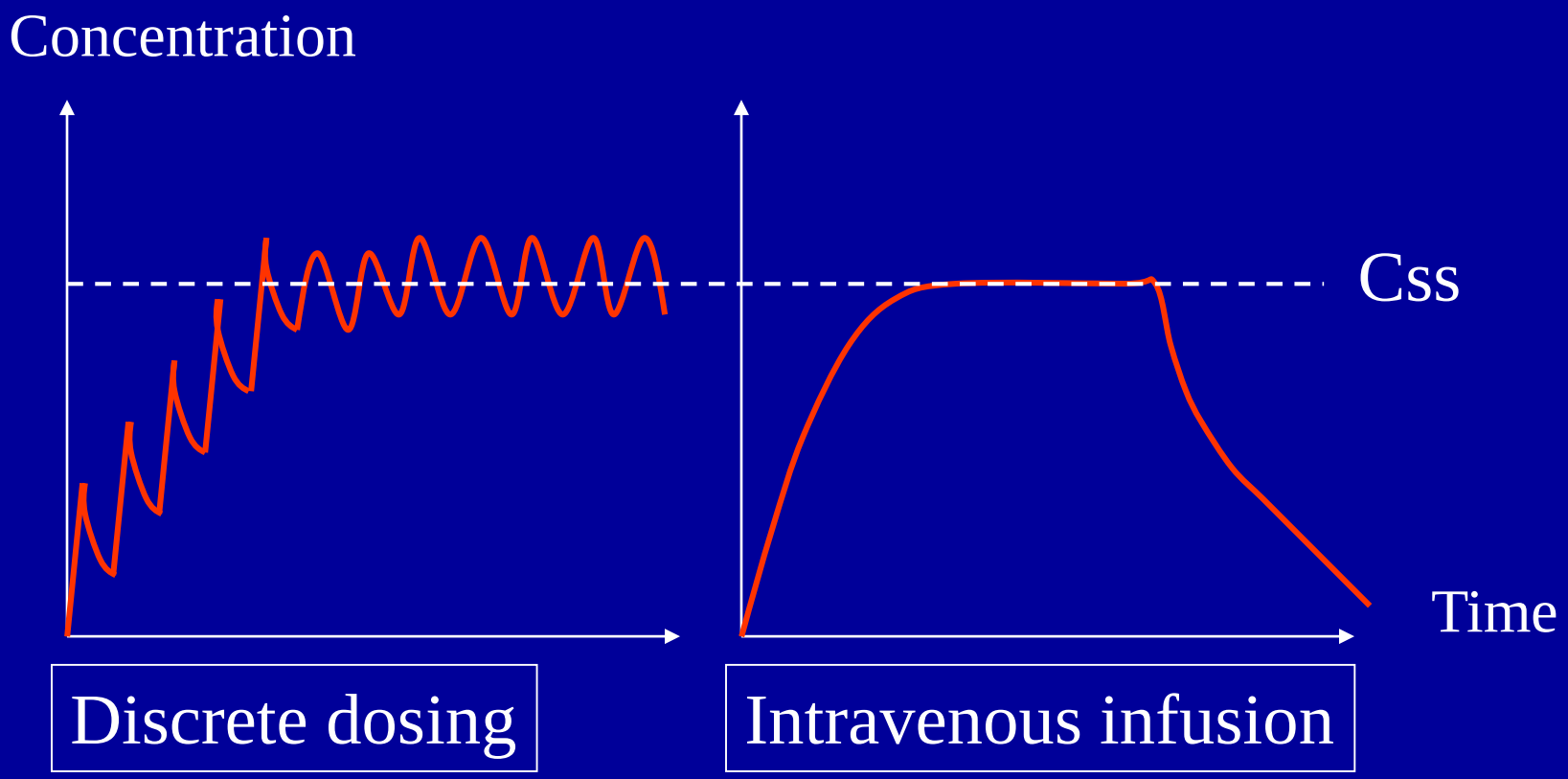
  - digoxin t½ = 36 hrs

  - lignocaine t½ = 1 hr

Size of the loading dose is determined by TI and is a function of Vd of the drug

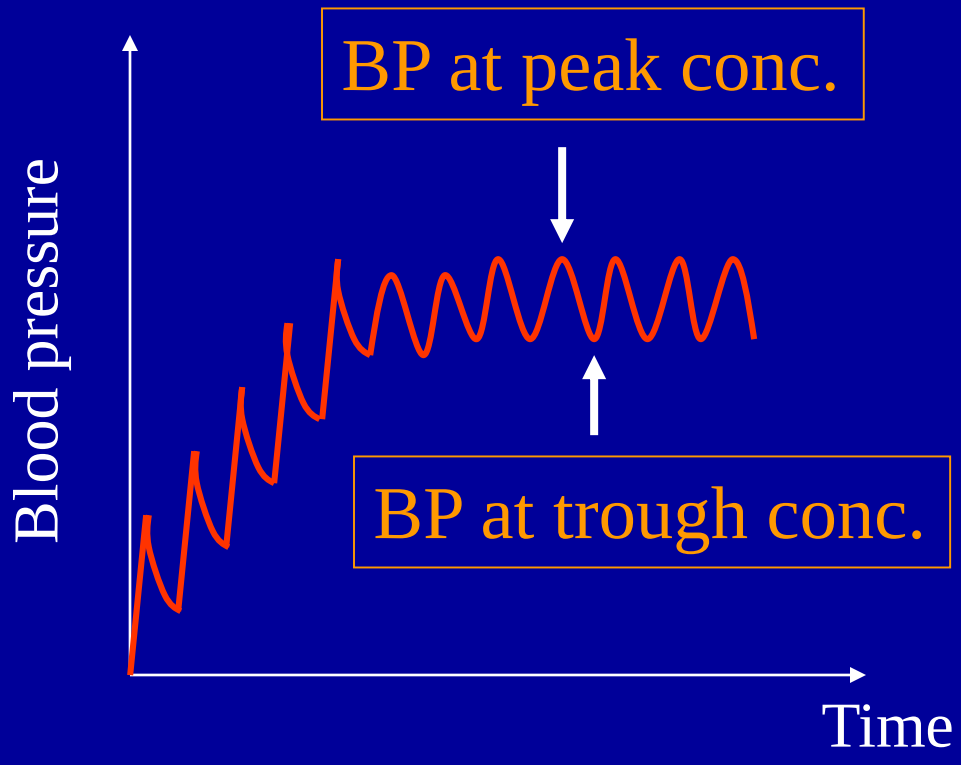
Drug with extremely short t½ - needs to be infused and activity stops when drug is withdrawn (e.g. nitroprusside in emergency therapy of hypertension)

Multiple dosing



- Objective: reach Css with minimal toxicity (within TI)
- Maintain Css for minutes, hours, or days

Peak trough ratio



- BP at peak conc : BP at trough conc – peak : trough
- Antihypertensives should have peak : trough close to ONE

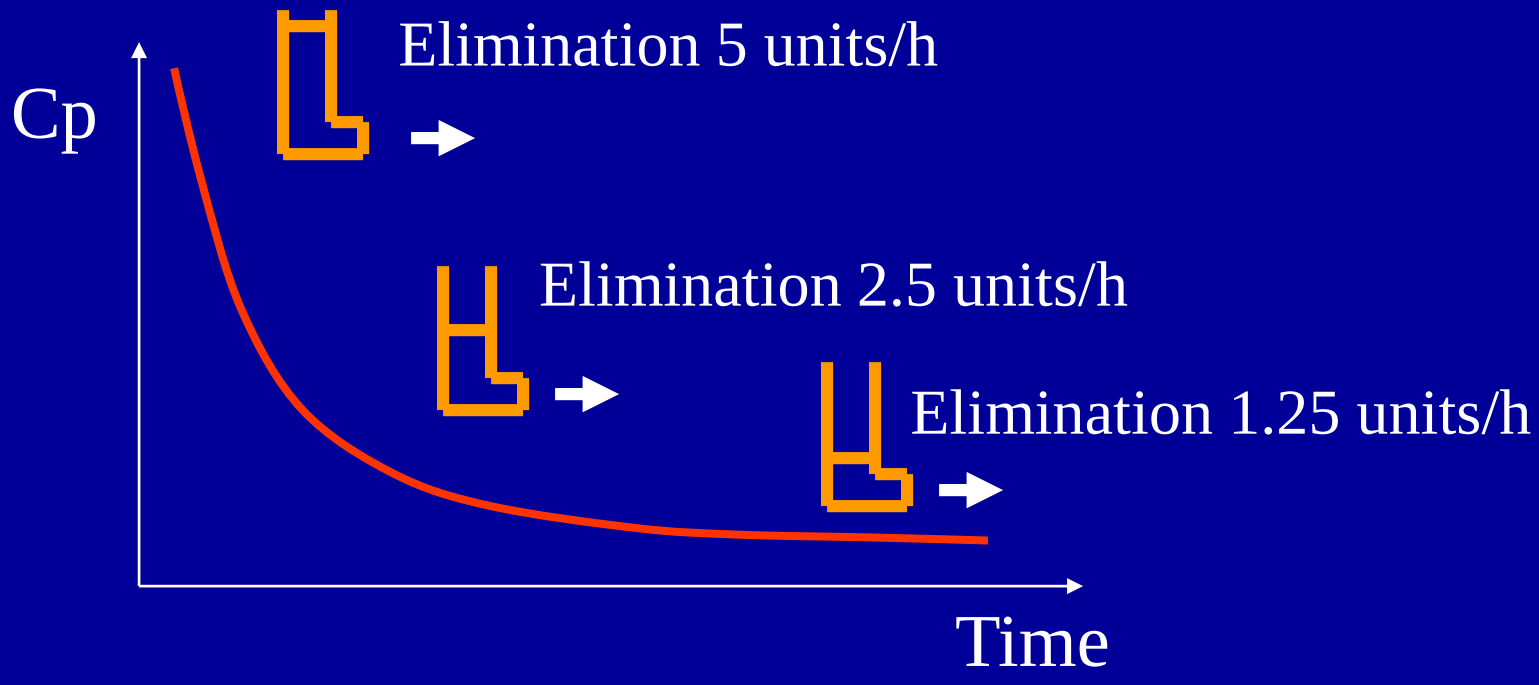
Clearance (CL)

- Volume of plasma cleared of drug per unit time
- Clearance (unlike t½) is independent of Vd
- Therefore, CL is the best measure of the rate at which a drug is eliminated from the drug

$$t_{½} = Vd / CL$$

Clearance (CL)

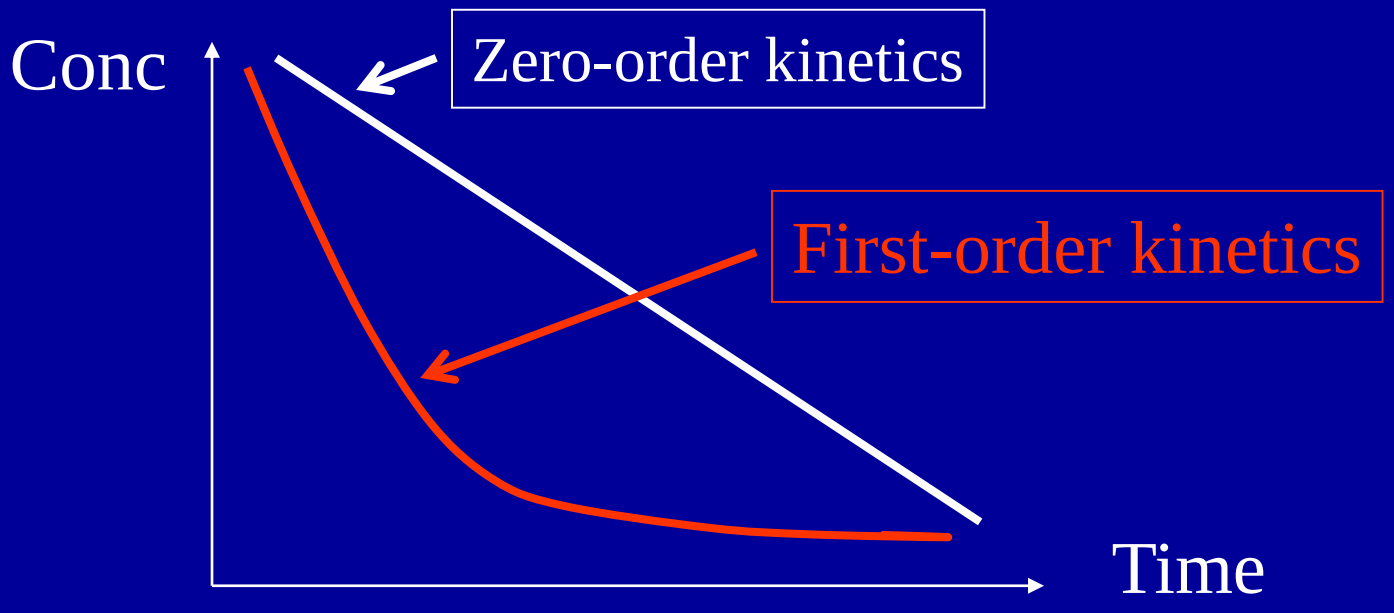
- Relates rate of elimination to plasma concentration (Cp)
- Rate of elimination = CL x Cp
- Rate of elimination is reduced if renal function impaired (e.g. reduce dosage in the elderly)



Kinetic order

Describes the rate at which kinetic processes take place

- First order kinetics - most common
- Zero-order (saturation kinetics)
- Mixed order



Zero-order kinetics

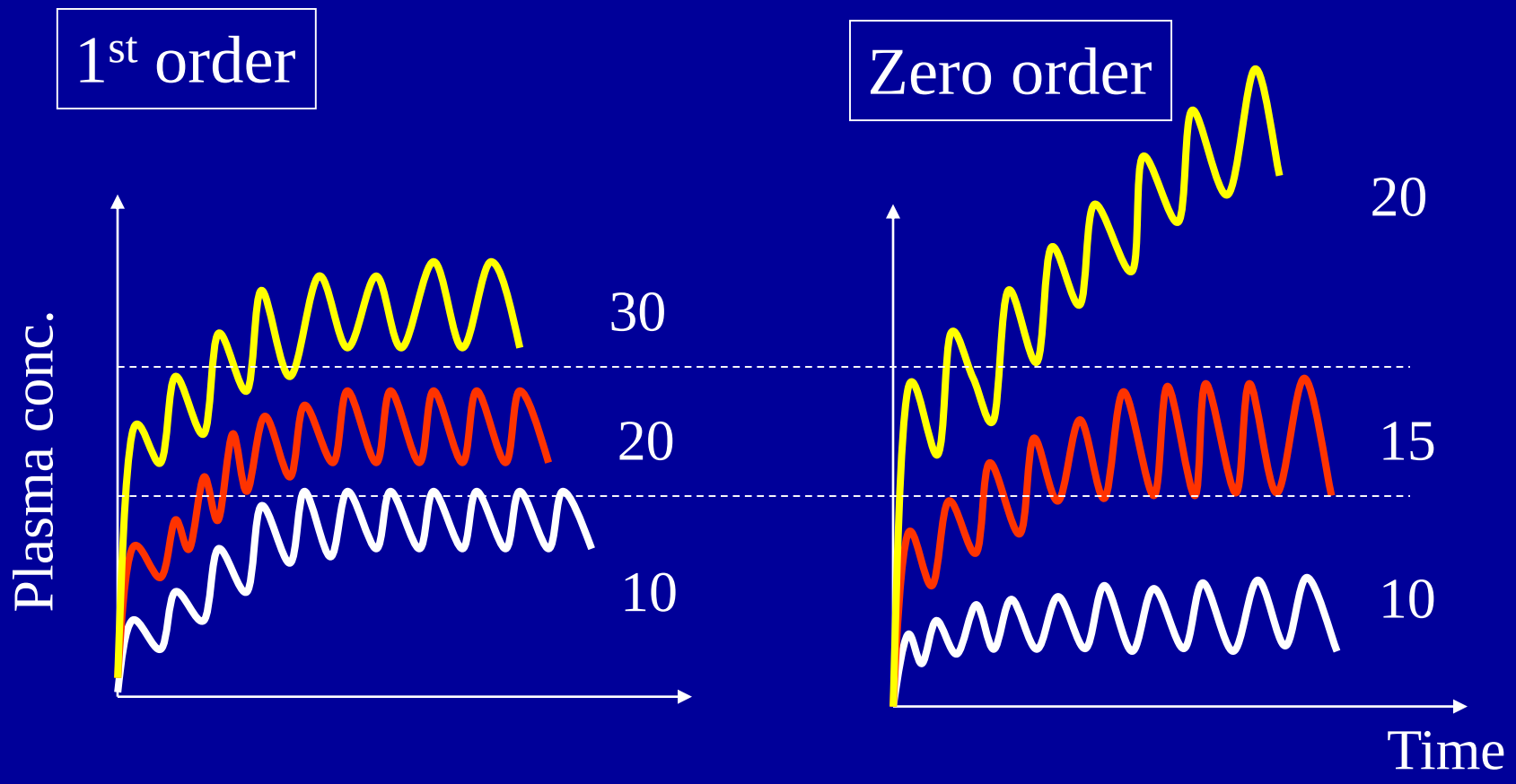
- Kinetic processes proceed at a constant rate
- Rate is independent of the amount of drug

Examples:

- Absorption of depot preparations: drug is released from formulation at a uniform rate

  (e.g. oestrogen pellets, fluphenazine in oil)
- Saturable metabolism: when metabolizing enzymes are saturated rate becomes uniform

  (e.g. alcohol, phenytoin, aspirin)



With zero order / saturation kinetics

- Small increase in dose – large effect on plasma
- No steady state is reached with higher doses

Problem faced related to kinetics

Use of digoxin in a 65 yr old for atrial fibrillation:

- Long t½ (36 hrs) and large Vd
- Used in a medical emergency – bolus dose
- Narrow TI and toxicity serious
- Elimination renal – pt's renal function impaired