PC3301
Pharmacokinetics of Digoxin

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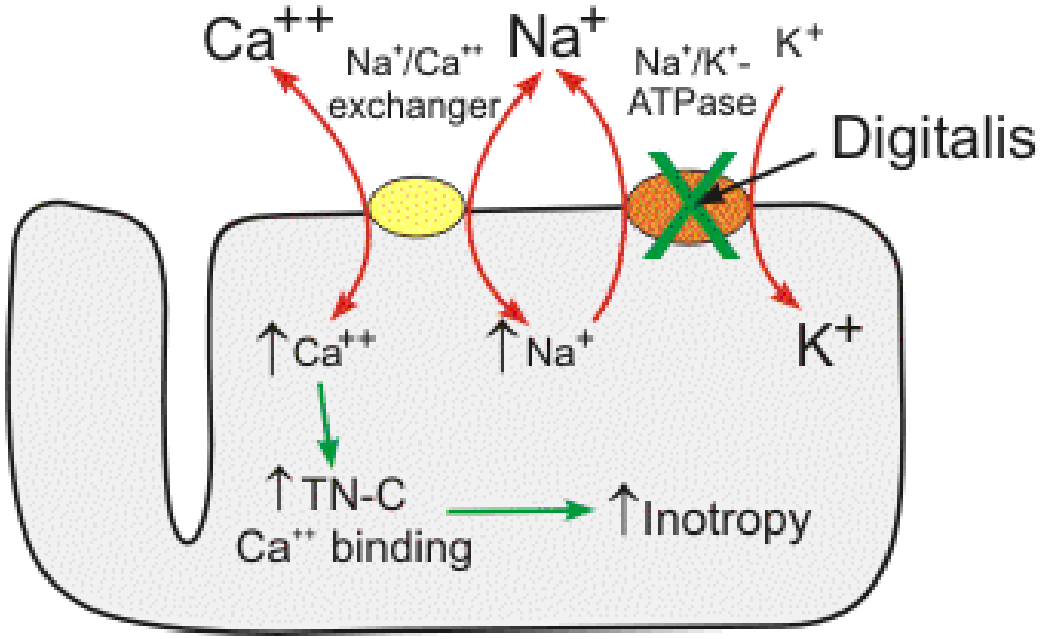
Learning objectives

- Digoxin mechanism of action
- Indications
- Dosages and formulations available
- Adverse effects
- Pharmacokinetic parameters and related chemical structures
- The need for therapeutic drug monitoring
- Drug interactions
- Digoxin use in special populations
- Case study

What is digoxin?

- Cardiac glycoside → effects the intracellular and extracellular fluids in cardiac cells
- Slows down ventricular rate
- Increases contractility
- Increases cardiac output

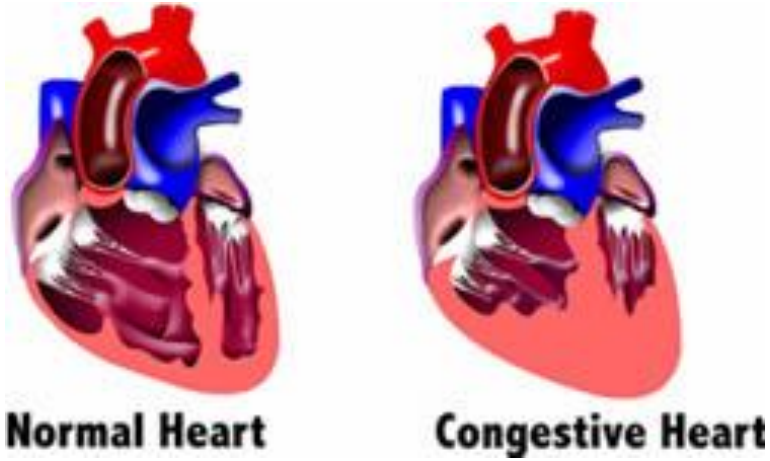
Mechanism of action

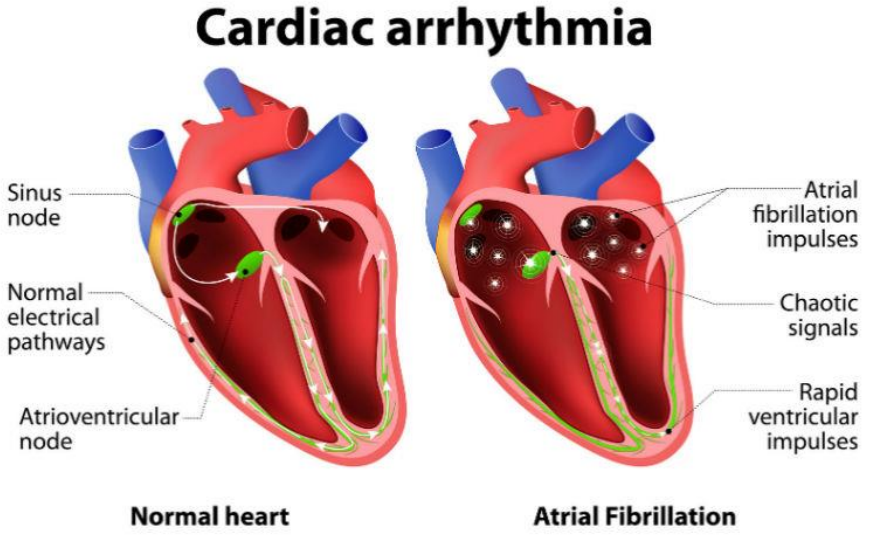


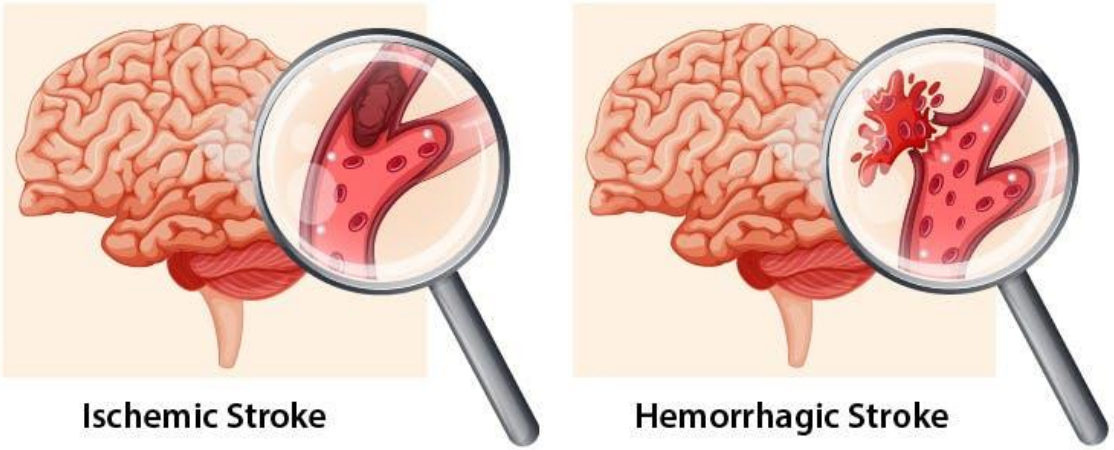
- Reversibly inhibits Na/K-ATPase channels
- Effects of inhibition:
  - *Rise of intracellular Na levels*
  - *Slows Na-Ca exchange mechanism on cell membrane*
  - *Increase intracellular Ca^{2+} accumulation*
  - *Increases Ca^{2+} uptake into sarcoplasmic reticulum*
  - *More Ca^{2+} released from sarcoplasmic reticulum during subsequent action potentials*
  - *Increases cardiomyocyte contractility → positive inotropic effect*

Clinical indications

- Management of arrhythmias
- Removal of risk factors for myocardial infarction
- Controls ventricular heart rate of atrial fibrillation patients
- Prevent risk of CHF and stroke
- Decreases risk of blood clots

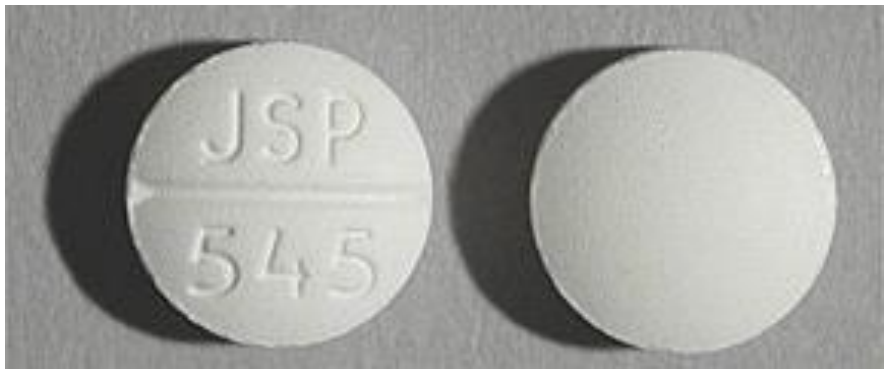






Dosages and formulations

- Three forms:
  - *Tablets → 62.5mcg, 200; 250mcg, 100*
  - *Oral liquid → 50mcg/mL, 60mL*
  - *Injection → 25mcg/mL, 2mL, 5; 250mcg/mL, 2mL, 5*
- Loading dose:
  - *250-500mcg every 4-6 hours*
- Maintenance dose:
  - *125-250mcg once daily, max 500mcg*
  - *Tablets → 62.5mcg, 200; 250mcg, 100*
  - *Oral liquid → 50mcg/mL, 60mL*
  - *Injection → 25mcg/mL, 2mL, 5; 250mcg/mL, 2mL, 5*



Adverse effects

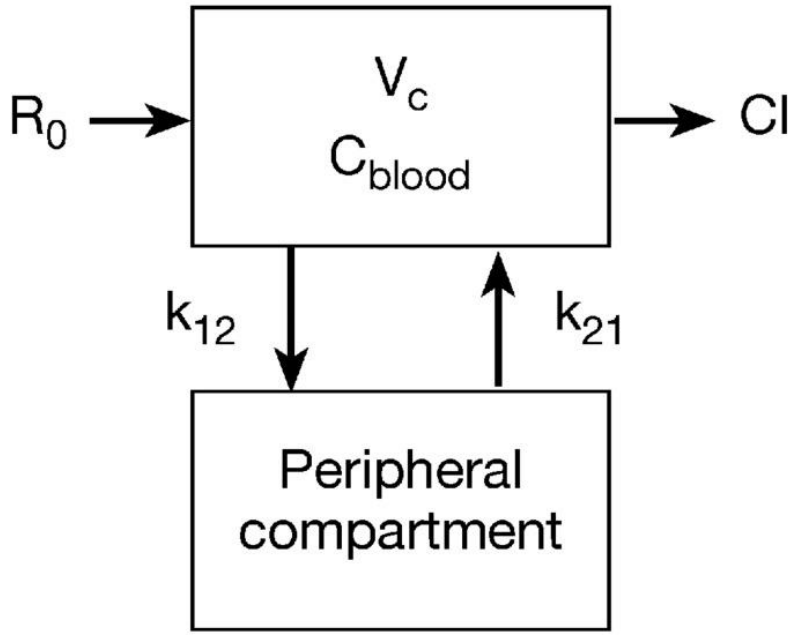
Common (>1%)	Infrequent (0.1-1%)	Rare (<0.1%)
Dizziness	Depression	Thrombocytopenia
Headache	Shortened QRS complex	Seizures
Rash	Atrial or ventricular extrasystoles	Confusion
Bradycardia	Paroxysmal atrial tachycardia with AV block	Psychosis
Nausea	Ventricular tachycardia or fibrillation	Gynaecomastia (long-term use)
Vomiting	Heart block	
Anorexia		
Diarrhoea		
Visual disturbances		
Drowsiness		
Arrhythmia		

Pharmacokinetics - absorption

- Oral bioavailability: 50-90%
- Metabolised by gut flora!
- Absorbed well in GIT
- 70-80% absorbed in initial part of small intestine
- Absorption slowed by food
- High fibres foods reduce absorption → avoid them for two hours following dose

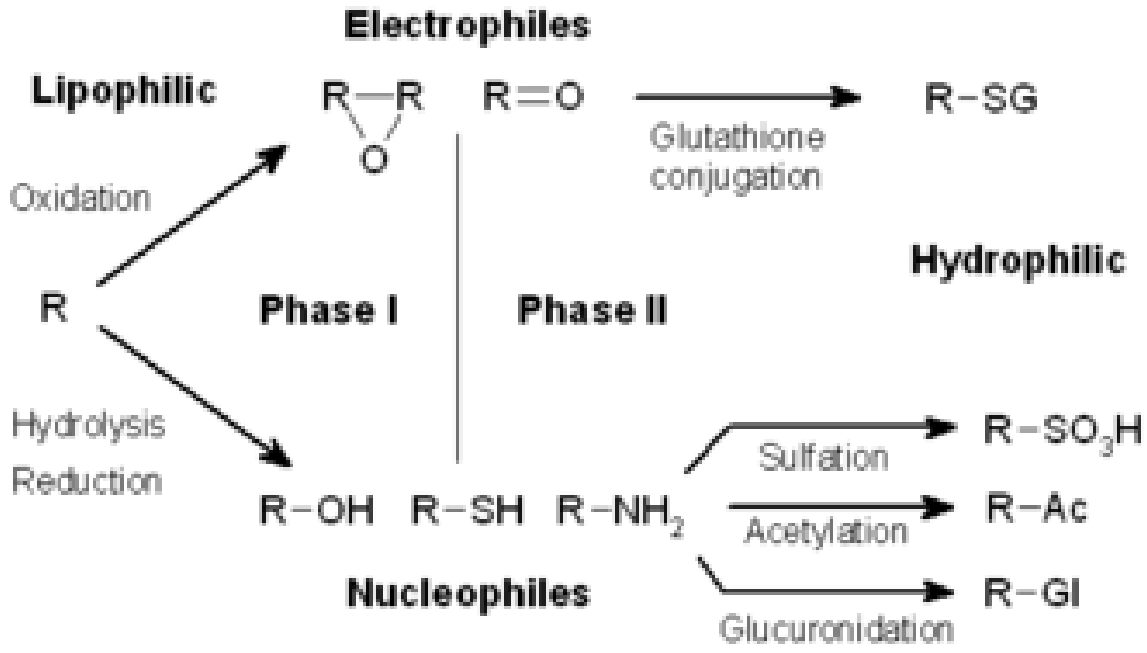
Pharmacokinetics - distribution

- Peak serum concentration 1-3 hours after dose
- Tissue distribution phase around 6-8 hours
- Two –compartmental model
- Concentrated in tissues
- Readily crosses BBB and placenta
- Large Vd: 450-500L, or 7.5L/kg
- IBW better for calculating doses rather than total body weight
- Plasma protein binding: 25%, mainly to albumin

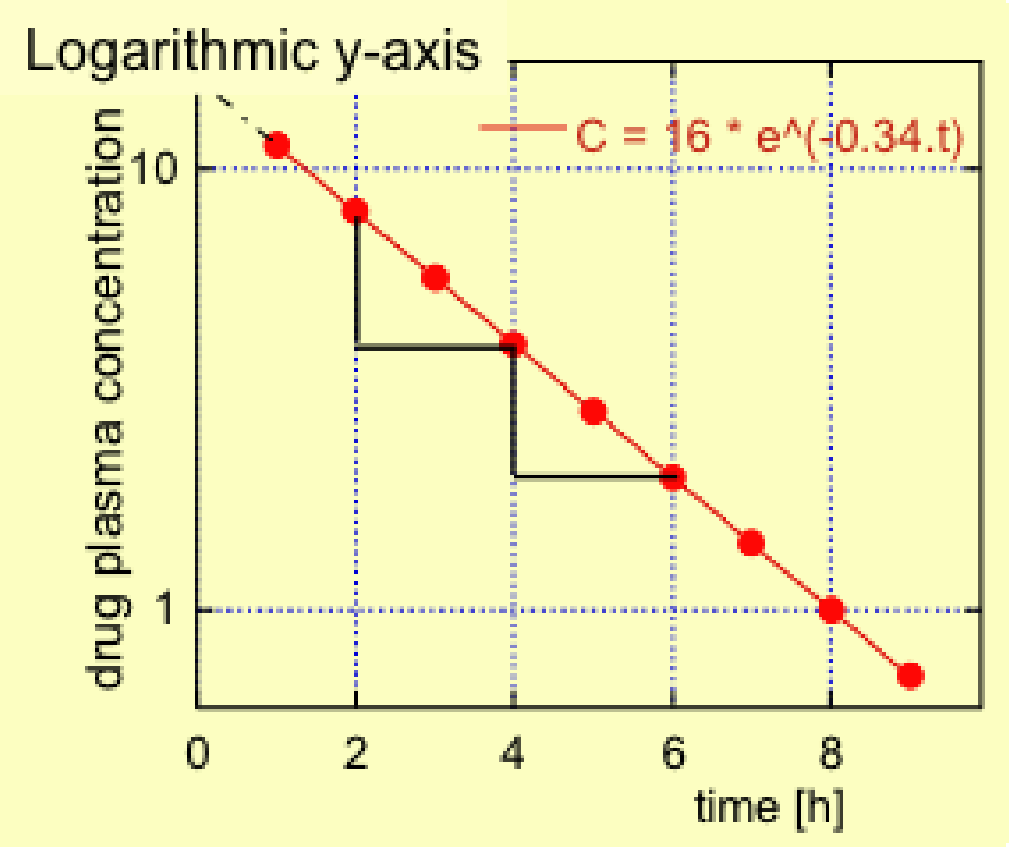


Pharmacokinetics - metabolism

- Occurs to only 1% of dose
- Metabolites formed via hydrolysis, oxidation, and conjugation
- CYP enzymes not inhibited or induced



Pharmacokinetics – elimination

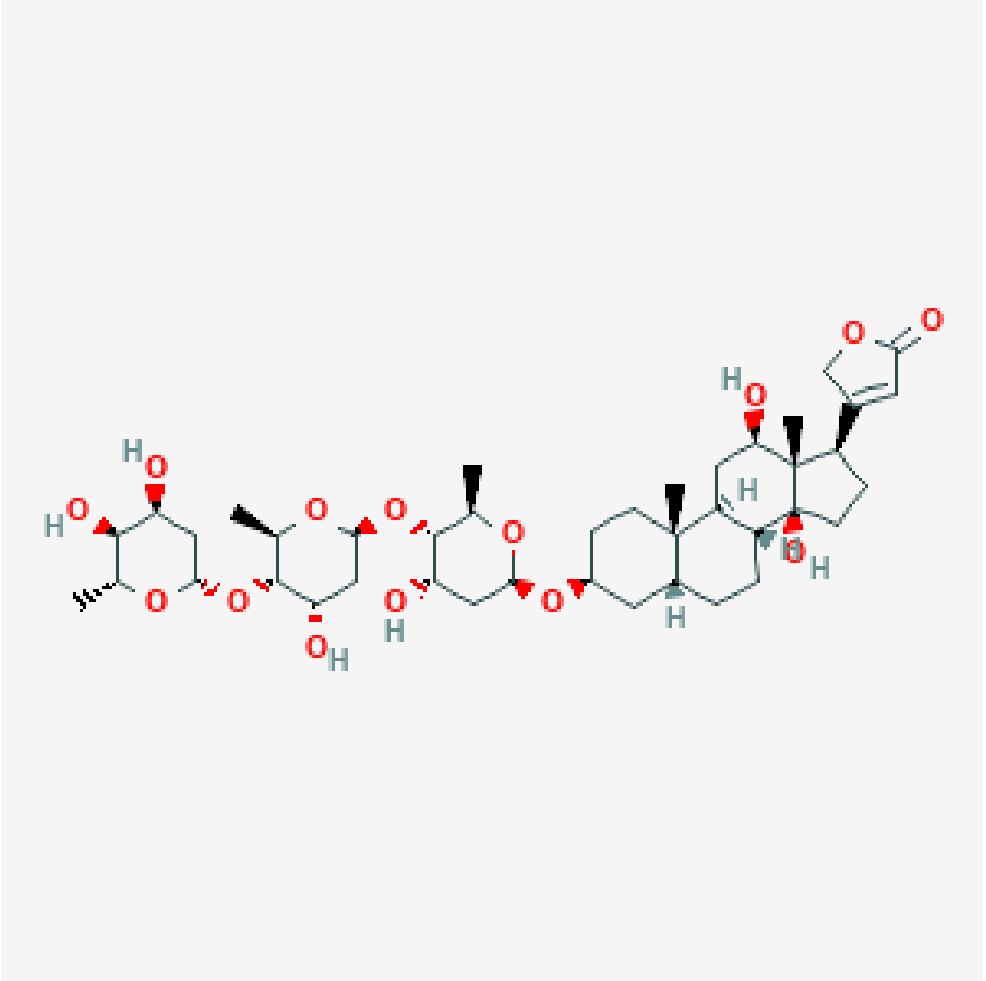


- Follows first-order kinetics
- Main route is the kidney: 50-70% of dose excreted unchanged
- 25-28% excreted by other means , eg – biliary excretion
- Renal excretion proportional to GFR
- Does not depend on urine flow
- Clearance correlates to creatinine clearance
- Long half-life: 1.5-2 days
- Loading dose required, otherwise steady state takes 5-7 days

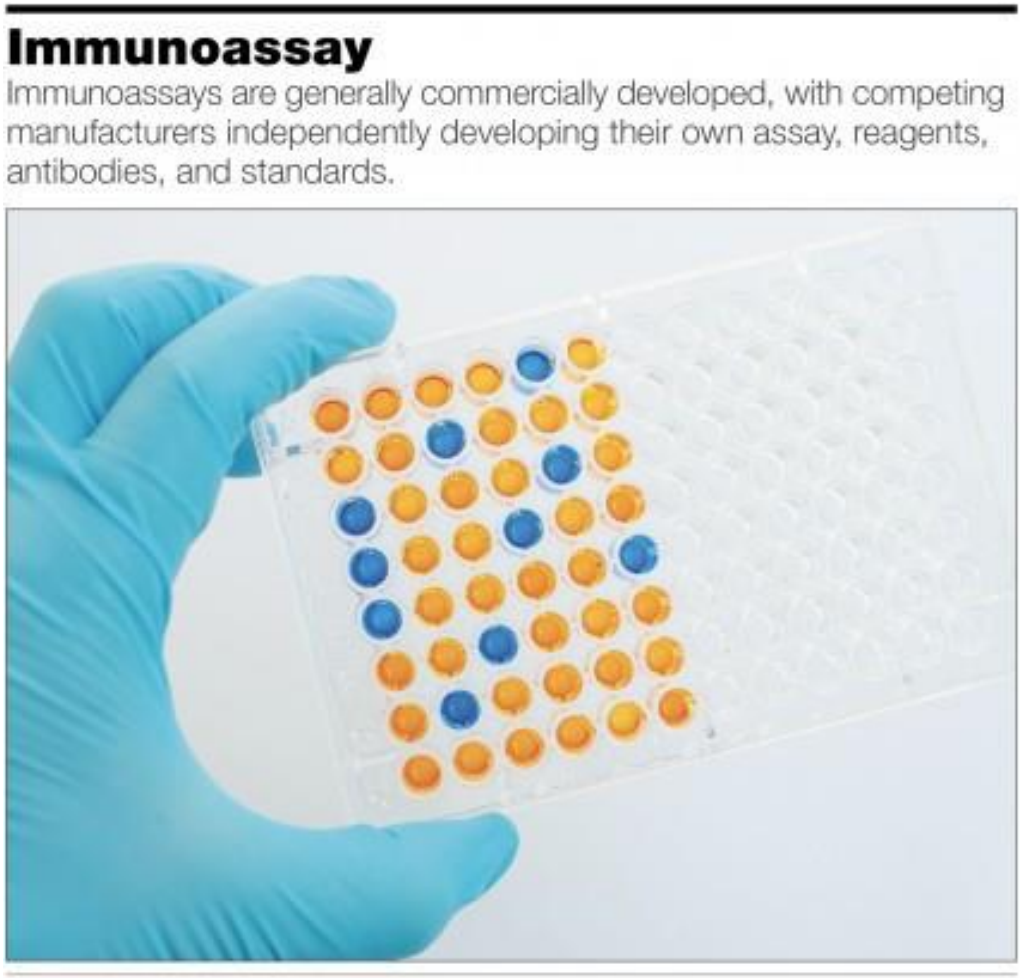
Chemical structures

- Certain functional groups improve chemical functions
- Structure determines absorption through different routes
- Contains hydrogen bonds and pi stacking
- High lipophilicity
- Lipinski's rule of 5 can be applied for oral formulation
  - *5 or less hydrogen bond donors → 6*
  - *10 or less hydrogen bond acceptors → 13*
  - *Molecular weight 500g/mol or less → 780.938g/mol*
  - *logP of 5 or less → 2.37*

  Digoxin doesn't meet majority of the rules, yet is still bioavailable
- 7 rotatable bonds



Therapeutic drug monitoring



- Digoxin has narrow therapeutic range: 0.5-2mcg/L
- Plasma concentrations measured to individualise dosing regime
- Measured using immunoassays
- Measurements taken 5-7 days after treatment initiation or dose change
- Sample taken minimum 6 hours after dose → at trough level

When is TDM required?

- Following initial dose or dose adjustment
- Concern about non-compliance
- Suspected toxicity
- Potential for drug interactions
- No observed therapeutic effect despite high doses
- Change in physiology → renal impairment, pregnancy

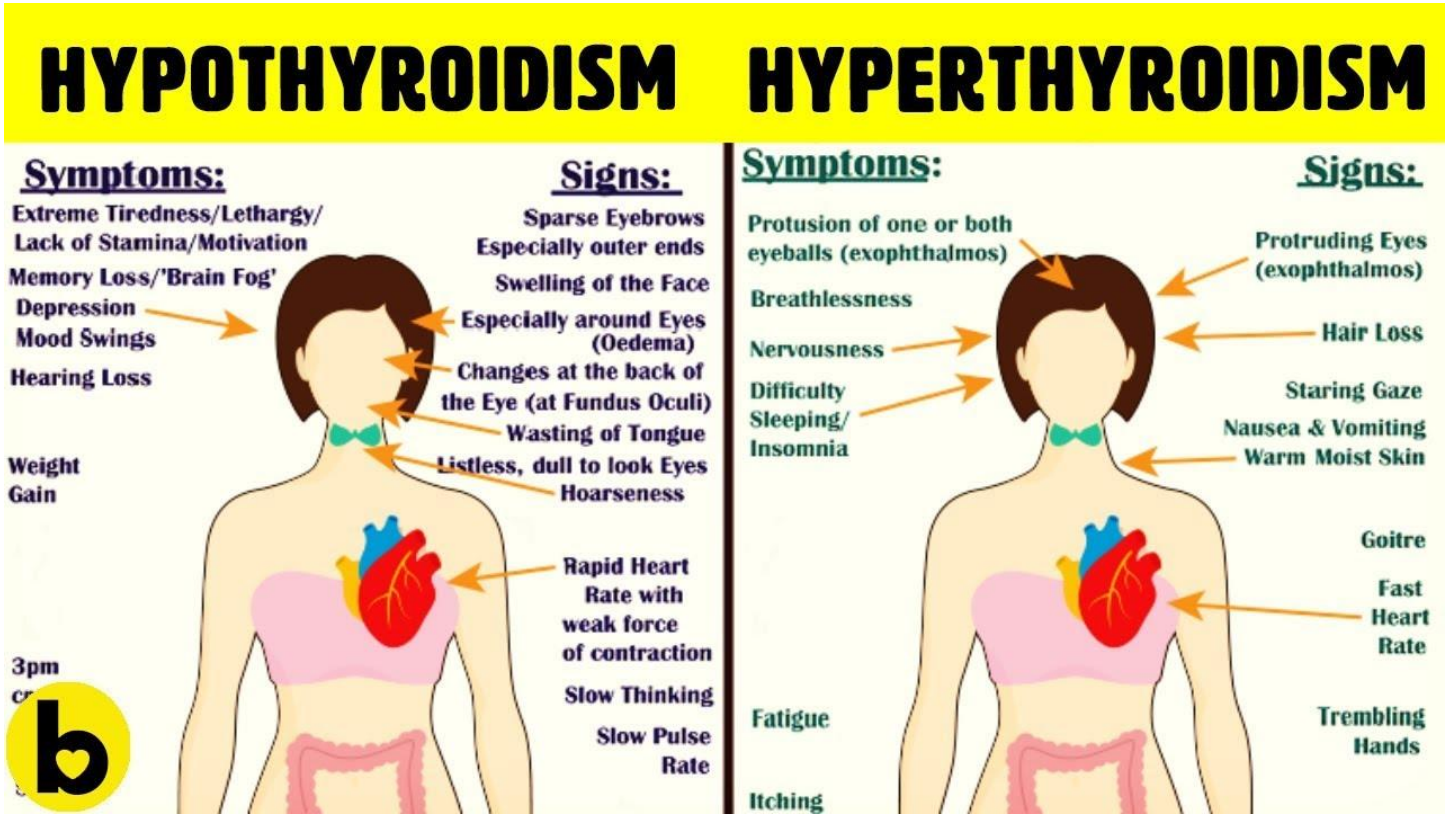
Drug interactions

Severe interactions	Moderate interactions
Macrolide antibiotics	Aminoglycosides
Flecainide	Cholestyramine
Trimethoprim	Tetracyclines
Amiodarone	Acarbose
Ketoconazole	Spironolactone
Quinidine	Metoclopramide
Amphotericin B	Indomethacin
B-blockers	Quinine
Verapamil	Calcium channel blockers
Hydroxychloroquine	St. John’s wort
Cyclosporine	Lapatinib

Drug interactions

- Amiodarone:
  - Increase risk of proarrhythmia
  - Increases digoxin absorption
  - Decreases elimination, Vd, and CL
- Ketoconazole:
  - Increases absorption and serum digoxin concentration
- Calcium channel blockers:
  - Decreases Vd and renal CL
- Metoclopramide:
  - Decreases absorption from GIT

Hypo- and hyperthyroidism



- Hypothyroidism:
  - *Increases concentration*
- Hyperthyroidism:
  - *Decreases concentration*
  - *Increases sympathetic tone*

Monitor concentration and alter dose as required

Use in special populations – renal dysfunction

- Half-life increases → 3.5-5 days
- Increased period of time to reach steady state → 1-3 weeks
- Loading dose → half of the recommended adult dose
- Maintenance dose:
  - *CrCL 30-60mL/min → 62.5-250mcg/day*
  - *CrCL 10-30mL/min → 62.5-125mcg/day*
  - *CrCL <10mL/min → 62.5mcg/day or on alternate days*

Use in special populations – paediatric patients

- Variable tolerance in newborns
- Dose needs to be reduced and based on level of maturity
- Loading dose → half given initially, the one quarter 6-12 hours later, than the final quarter another 6-12 hours later
- Maintenance dose:
  - *<2 years → 30-40mcg/kg*
  - *>2 years → 24-30mcg/kg*
  - *Given in single doses or two doses*
  - *Max → 250mcg/day*

Use in special populations – geriatric patients

- Elderly patients generally have:
  - *Reduced renal function, therefore reduced GFR*
  - *Extended digoxin half-life*
  - *Reduced muscle mass, therefore reduced Vd*
  - *Reduced lean body mass*
  - *Diuretic induced potassium loss*
  - *Polypharmacy*
  - *Co-morbidity*
- Loading dose → 125-250mcg
- Maintenance dose → 62.5-125mcg/day

Use in special populations – electrolyte disorders

- Hypokalaemia:
  - *Increases effects of digoxin*
  - *Decrease in extracellular K^+ for digoxin to compete with*
  - *More digoxin binds*
  - *Can produce toxicity*
- Hypomagnesaemia:
- Hyperkalaemia:
  - *Reduces effects of digoxin*
  - *Increase in extracellular K^+ for digoxin to compete with*
  - *Digoxin has fewer interactions with binding site*

Electrolytes need to be maintained within normal ranges whilst on digoxin

Case study

- A 48 year old 79kg male (171cm in height) was presented to the hospital with atrial fibrillation. After his serum creatinine concentration was determined (83.6μmol/L), digoxin therapy was initiated to control his ventricular rate.
  - *Calculate the loading dose (IV bolus) required (as digoxin has a very long half-life) to control his ventricular rate if the desired plasma digoxin concentration is 1.4ng/mL.*
  - *Calculate the digoxin maintenance dose (IV bolus) for this patient (in mg/day).*
  - *Calculate an oral digoxin maintenance dose (in mg/day) for the patient if he had NYHA Class III moderate heart failure (F = 0.7, ideal plasma concentration = 0.8mg/mL).*

References

- Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2021.
- Therapeutic Guidelines Ltd (eTG) (2021) Cardiovascular Drugs: Digoxin
- Amiodarone - DrugBank [Internet]. Drugbank.ca. 2018 [cited 16 May 2018]. Available from: https://www.drugbank.ca/drugs/DB00390
- Casebook in Clinical Pharmacokinetics and Drug Dosing; Chapter 6 – Digoxin