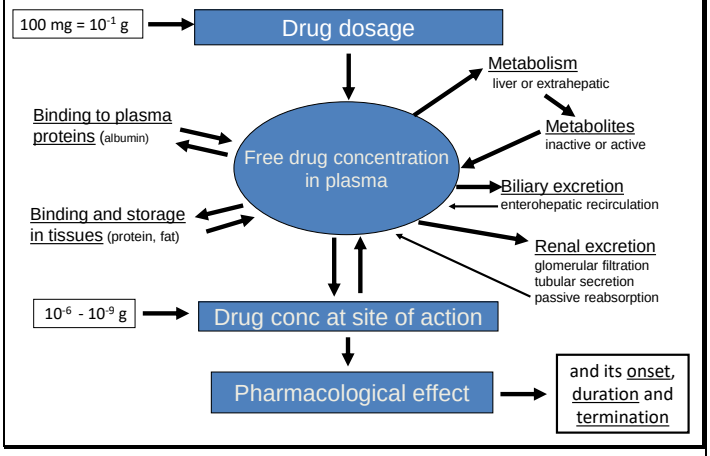
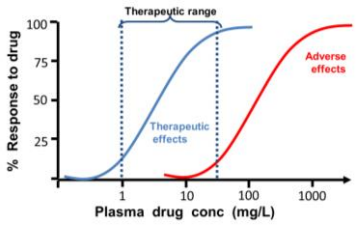
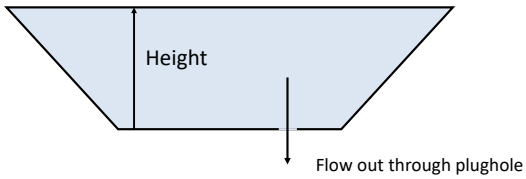
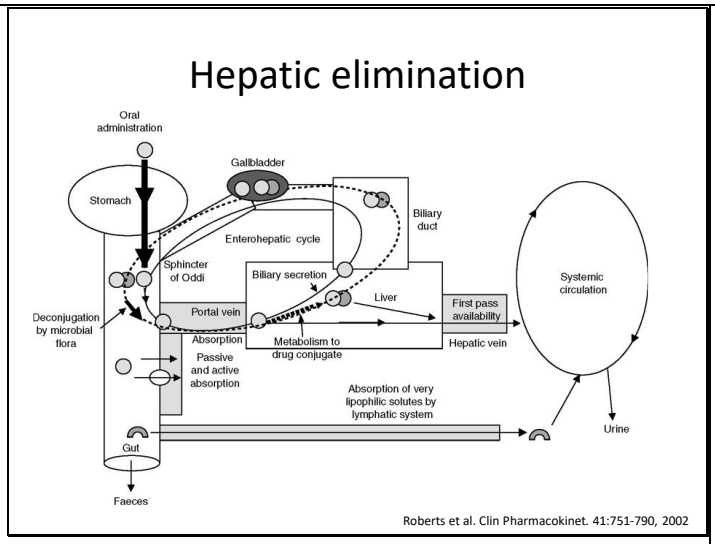
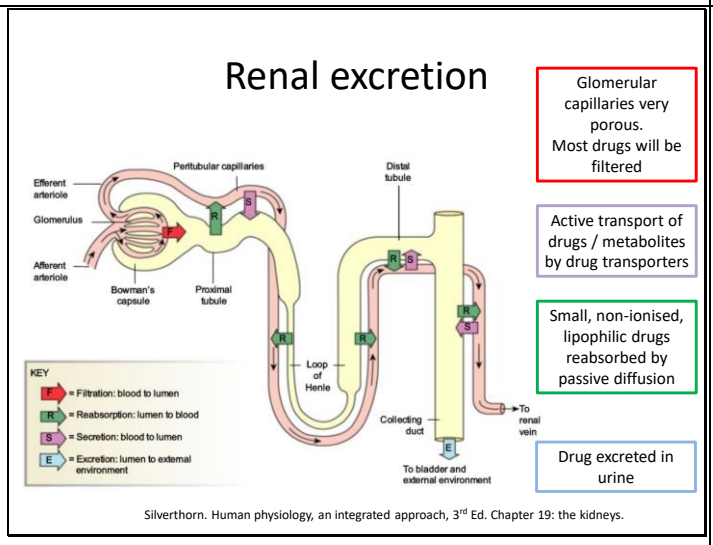
Slide 1	# Clearance MBChB 221B Dr Stephen Jamieson Dept of Pharmacology and Clinical Pharmacology Auckland Cancer Society Research Centre	
Slide 2	## Learning objectives • Understand the importance of pharmacokinetics • Learn the definition of clearance • Understand the physiological determinants of clearance • Be able to define clearance classes • Appreciate the applications of clearance concepts to clinical practice	
Slide 3	## Summary of drug disposition  	Drug disposition refers to all the processes involved in the absorption, distribution, metabolism and excretion of drugs in a living organism. These processes influence the free drug concentration that is achieved in the plasma after a drug has been administered and is the reason why there is a much stronger relationship between free drug concentration in plasma and pharmacological effect then there is between drug dosage and pharmacological effect.

Slide 4	**Pharmacokinetics** • Pharmacokinetics is the study of the concentration-time profile of a drug in the body. – Blood (plasma) – Tissues – Saliva, milk, urine, faeces • Important pharmacokinetic parameters include: – Clearance, Volume of distribution, Half-life	Definition of pharmacokinetics: the study of the concentration-time profile of a drug in the body. It is Important to determine drug concentrations in plasma or tissues, as drug concentrations are more predictive of pharmacological effect than dose is. Drug concentrations are typically determined in plasma rather than tissues due to ease of sampling. The three most important pharmacokinetic parameters are clearance, volume of distribution and half-life which we will cover over the next 3 sessions.
Slide 5	**Why is Pharmacokinetics important** • Knowledge of PK allows more rational dosing – Can identify therapeutic window • Gives drug its best chance of achieving efficacy and minimising side effects  	Drug concentrations in the body can be used to predict effect and allow more rational dosing. Matching drug concentrations to therapeutic and adverse effects allows for the identification of a therapeutic window, which is a range of concentrations where the drug is effective and causes minimal toxicity. Dosing a drug in a way that it maintains concentrations within the therapeutic window for as long as necessary gives the drug its best chance of being effective and having minimal adverse effects.
Slide 6	**Why is Pharmacokinetics important** • Knowledge of PK allows more rational dosing – Can identify therapeutic window • Gives drug its best chance of achieving efficacy and minimising side effects – Identifies optimal routes of administration and schedules of dosing • e.g. oral or IV • e.g. once daily or 3x daily	Knowledge of the drug concentrations that are achieved over time after a dose can also be used to identify an optimal route of administration and optimal dosing schedules. If a drug is poorly absorbed in the gut after oral dosing, an alternative route may be required. If a drug is rapidly eliminated from the body than a more frequent dosing schedule will be preferred.

Slide 7	## Clearance (CL) • Describes the relationship between concentration and elimination of the drug from the body – Clearance (L/h) = Elimination rate (mg/h) / concentration (mg/L) • Plasma clearance = sum of clearances from individual organs – $CL_{plasma} = CL_{renal} + CL_{hepatic} + Cl_{other}$	Clearance describes the relationship between the concentration of the drug in the plasma and the elimination rate of the drug. Note that elimination and clearance are not the same thing. Clearance is a constant for a particular drug in a particular patient, therefore the elimination rate is proportional to drug concentration. Total clearance of the drug from the plasma equals the sum of drug clearance from individual organs.
Slide 8	## Bathtub model of CL  Flow out = plughole size *x* height Elimination rate = Clearance *x* Concentration	Clearance can be compared to the plughole in a bath. In a bath, the flow of water out of a bath is equal to the size of the plughole multiplied by the height of water in the bath. The plughole size is constant, therefore the flow of water out of the bath is proportional to the height of water in the bath. When the bath is full and the water level is high, the flow out will be greatest. As the height of water falls, the flow rate will slow. Drug elimination occurs in the same way. When drug concentration is highest, the rate of elimination will be high. As concentration falls, the rate of elimination will slow, but clearance will stay the same as it is a constant. Clearance provides a measure of how efficient the body is at eliminating the drug. A high clearance value indicates the body is highly efficient at eliminating the drug.
Slide 9	## Drug elimination • Processes by which a drug is removed from the body – Metabolism • Predominantly in liver – Biliary excretion in liver – Excretion by glomerular filtration or tubular secretion in the kidney	There are 3 main processes by which drugs are removed from the body: metabolism, biliary excretion and renal excretion.

Slide 10		Drugs can be eliminated in the liver by hepatic metabolism and biliary excretion. An orally administered drug is absorbed in the gut into the hepatic portal vein and onto the liver. It may pass unchanged through the liver and enter the systemic circulation. It may be metabolised in the liver, a process which will usually inactivate the drug, and then pass through into the systemic circulation. Or the drug or metabolite may be secreted into the bile duct and re-enter the intestinal tract. This process can be repeated multiple times and is known as enterohepatic circulation. Any drug that is not absorbed in the gut is excreted in the faeces. Most lipophilic drugs are eliminated in the liver
Slide 11		Hydrophilic drugs or polar metabolites of lipophilic drugs are typically eliminated in the kidney. Drug in the systemic circulation travels to the kidney and reaches the glomerulus. Large pores exist in the glomerular capillaries, allowing drug to flow out of the capillaries into the Bowman's Capsule. This process is known as glomerular filtration. All drugs will be partially filtered in the glomerulus except for large drugs or drugs that are extensively bound to plasma proteins. Unfiltered drug can be actively transported from the peritubular capillaries to the proximal or distal tubules by transporter proteins by the process of tubular secretion. However, any drug present in the proximal or distal tubules can be reabsorbed by passive diffusion into the peritubular capillaries. This process known as tubular reabsorption requires drugs to diffuse across cell membranes, so drugs must be small, non-ionised and lipophilic. Any drug that remains in the collecting duct that has not been reabsorbed will be excreted from the body in the urine.

Slide 12

Physiological basis for clearance

- Liver and kidney are the 2 organs most responsible for drug clearance
  - Organ clearance can not exceed blood flow to that organ
- Liver blood flow ≈ 90 L/h
  - Cleared by metabolism and biliary excretion
- Kidney blood flow ≈ 70 L/h
  - Cleared in urine
  - Glomerular filtration rate ≈ 6 L/h
  - Tubular secretion (variable rate)
  - Tubular reabsorption

The two organs most responsible for drug clearance are the liver and the kidney, but they can only eliminate drug that is delivered to them and therefore drug clearance in the liver or kidney can not exceed hepatic or renal blood flow. This means that drugs solely cleared by the liver can not have clearance values that exceed approximately 90 L/h, while drugs solely cleared by the kidneys can not have clearance values that exceed approximately 70 L/h. Renally cleared drugs are eliminated by a combination of glomerular filtration and tubular secretion minus tubular reabsorption. Glomerular filtration occurs at a standard rate of approximately 6L/h so any drugs that are filtered but not secreted or reabsorbed will have a renal clearance of approximately 6 L/h.

Slide 13

Clearance of common drugs

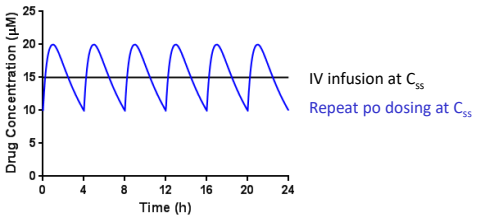
- Hepatic CL drugs
  - High (40-90 L/h)
    - Propranolol, verapamil, morphine
  - Low (<20 L/h)
    - Theophylline (3 L/h), warfarin (3 L/day)
- Renal CL drugs
  - High
    - Benzyl penicillin (≈ 36 L/h, Filtration & secretion)
  - Low
    - Gentamicin (≈ 6 L/h, filtration)
- Drugs cleared by multiple routes
  - Digoxin: liver (2.5 L/h) and kidney (6.5 L/h)

Drugs that are rapidly cleared by the liver are not suitable for oral dosing as would be eliminated during first pass metabolism, while drugs with low hepatic clearance values are good candidates for oral dosing. Gentamicin is an example of a drug that is cleared solely by glomerular filtration, while benzyl penicillin is a substrate for a drug transporter involved in tubular secretion so is cleared by both filtration and secretion. Some drugs (e.g. digoxin) can be cleared by both the liver and the kidney.

Slide 14

Maintenance dose rate (MD)

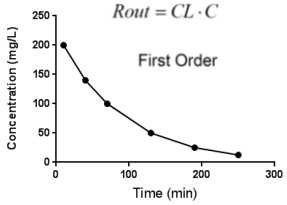
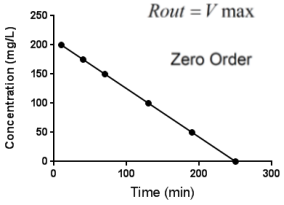
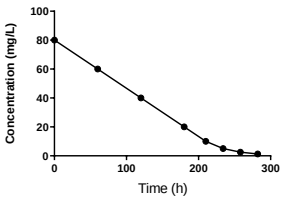
- Dose rate to achieve and maintain a target concentration
  - Steady state concentration (C_{ss})
    - Dose rate in = rate of elimination

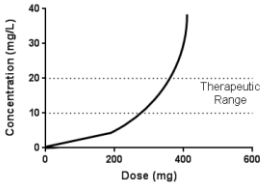


Clearance can be used to calculate a maintenance dose rate – which is the dose rate required to achieve and maintain a target concentration. Usually we will want to achieve our target concentration at a steady state concentration within the therapeutic window of the drug. Steady state occurs when the rate of drug administration into the plasma (rate in) is equal to the rate of elimination. In our bath analogy, this would be the same scenario where water is entering the bath through a tap at the same rate that water is exiting the bath through the plughole. In this example the height of water in the bath would remain steady.

For IV dosing, an IV infusion can be administered to keep drug concentrations at steady state. For oral dosing, steady state concentration will be reached when the peak and trough concentrations achieved after each dose are similar.

Slide 15	## Maintenance dose rate (MD) • Dose rate to achieve and maintain a target concentration – Steady state concentration (C_{ss}) • Dose rate in = rate of elimination **Maintenance dose (mg/h) = CL (L/h) x target concentration (mg/L)** • A rapidly cleared drug will need a large maintenance dose to keep drug concs at target levels	Maintenance dose rate can be predicted if the target (or steady state) concentration and clearance are known. Units of clearance are typically L/h and concentration is mg/L so maintenance dose therefore has units of mg/h
Slide 16	## Maintenance dose calculation • Calculate the dose rate of theophylline for a patient with asthma to maintain a target concentration of 10 mg/L – The clearance of theophylline is 2.8 L/h – Maintenance dose rate (mg/h) = CL (L/h) x target conc (mg/L) = 2.8 x 10 = 28 mg/h	Theophylline is a drug used for the treatment of asthma. It is no longer widely used but has been extensively studied worldwide so is a very useful example drug for explaining pharmacology concepts. Studies at the University of Auckland determined that an appropriate target concentration to maintain theophylline within its therapeutic window is 10 mg/L (Holford et al., Clin Pharmacokinet. 25:495-505, 1993).
Slide 17	## Clearance Classification • Constant – Independent of concentration and organ blood flow – First-order or linear elimination – e.g. glomerular filtration, most metabolism • Concentration-dependent – CL changes with concentration – Mixed order or non-linear elimination – e.g. tubular secretion of benzyl penicillin, metabolism of phenytoin • Flow-dependent – CL approximates organ blood flow – e.g. morphine CL = 60L/h	Clearance can be classified in three ways: constant clearance, concentration-dependent clearance and flow-dependent clearance. Up until now we have focussed on constant clearance, where clearance does not change and is independent of concentration and organ blood flow. Constant clearance is regarded as first-order or linear elimination. For some drugs, elimination mechanisms become saturated in which case clearance is concentration dependent and the drug follows mixed-order or non-linear elimination. For some rapidly cleared drugs, clearance is limited by the delivery of the drug to the eliminating organ and so clearance of the drug will approximate blood flow to the organ. These three clearance processes are not exclusive. A drug can be eliminated by a combination of these processes.

Slide 18	## Concentration-dependent clearance $$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$ Mixed Order $Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$ $Rout = CL \cdot C$ First Order  $Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$ $Rout = V\max$ Zero Order  	Rout = Rate out Enzymatic reactions are typically saturable and can be described in terms of the maximum rate of elimination (Vmax) and the concentration producing 50% of Vmax (Km). Most enzymatic drug metabolism is driven primarily by the drug concentration. If concentration is small in relation to Km then the elimination rate will appear to be first-order (elimination rate is linearly dependent on concentration as clearance is constant). If concentrations are large in relation to Km then the elimination rate will appear to be zero-order (elimination rate is independent of concentration as clearance changes). Concentrations that are neither small nor large in relation to Km will give rise to a mixed -order reaction. Most drugs that are metabolised will follow first-order elimination, while drugs that have saturable elimination at high concentrations will follow mixed-order elimination. True zero-order elimination does not occur in reality, but may be approximated at very high concentrations.
Slide 19	## Mixed order kinetics: phenytoin • At low concentrations, phenytoin metabolism is a first-order process • At higher concentrations, metabolism is saturated  	The anticonvulsant drug phenytoin is an example of a drug that follows mixed-order elimination. At low concentrations, clearance is concentration-independent and elimination is a first-order process. At high concentrations, phenytoin metabolism is saturated and so clearance becomes concentration-dependent and elimination is a zero-order process.

Slide 20	**Mixed order kinetics: phenytoin** • At low concentrations, phenytoin metabolism is a first-order process • At higher concentrations, metabolism is saturated • Small increases in dose, cause large increases in plasma drug levels  	Mixed-order elimination can alter the dose-dependency of drug pharmacokinetics. At low doses drug concentrations will increase linearly with dose, but at high concentrations, once elimination is saturated, concentrations may increase exponentially with dose.
Slide 21	**Elimination kinetics summary** • First order elimination – Elimination rate is dependent on concentration – Clearance is independent on concentration • Zero order elimination – Elimination rate is independent of concentration – Clearance is concentration-dependent • Mixed order elimination – At low concentrations clearance is independent of concentration • Follow first order elimination – At high concentrations, elimination is saturated • Elimination rate becomes independent of clearance • Follows zero order elimination – Overall effect for these drugs is that clearance is dependent on concentration • At low concentrations, clearance remains constant, but at high concentrations once saturation occurs, clearance changes with concentration	First order elimination = constant clearance Zero order elimination = concentration-dependent clearance Mixed order elimination: at low concentrations, clearance is constant; at high concentrations, clearance is concentration-dependent.
Slide 22	**Revision questions** • Describe clearance and a formula used for calculating it • Describe the processes involved in the elimination of benzyl penicillin • Phenytoin shows mixed order elimination. Describe the clinical consequences of this	