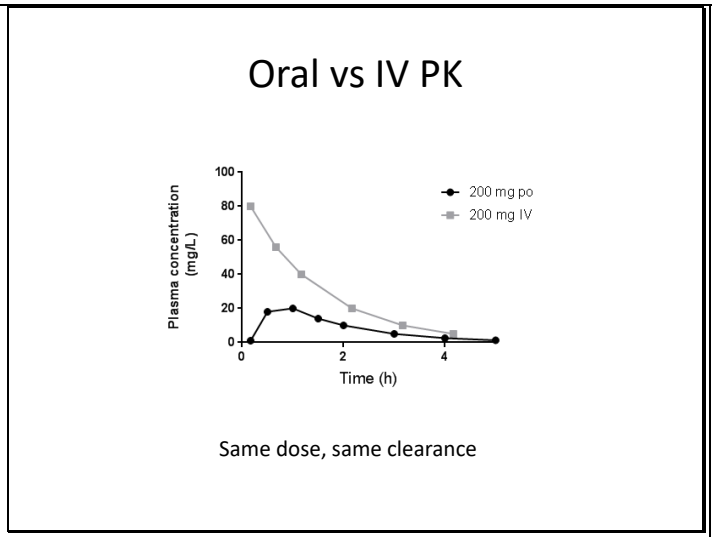
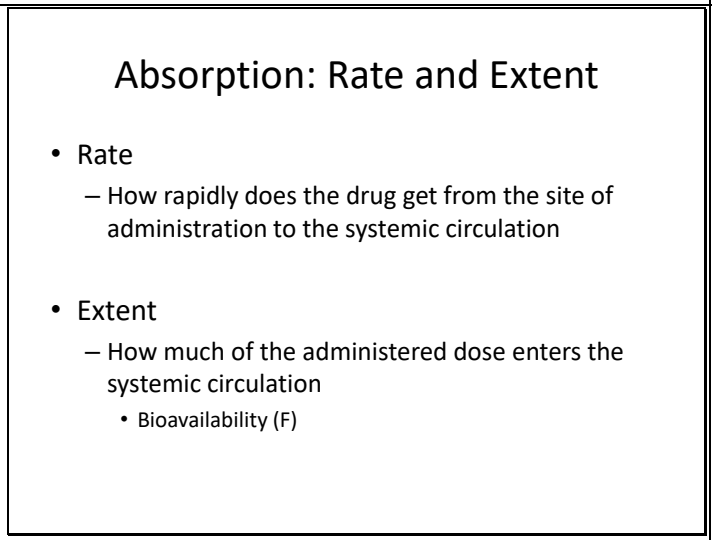
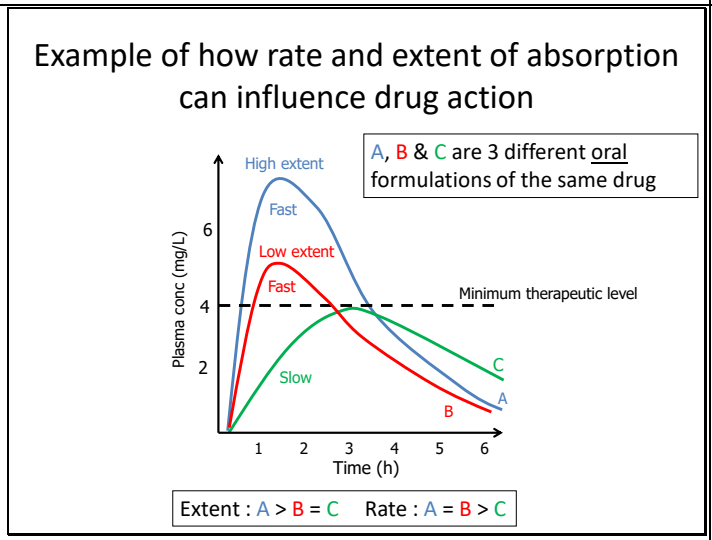
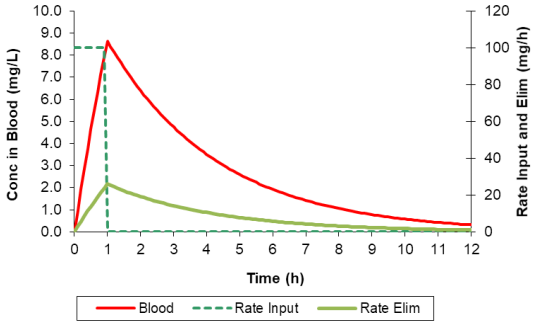
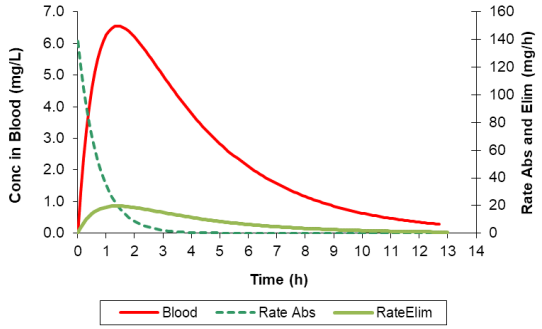
Slide 1	# Absorption and Half-life MBChB 221B Dr Stephen Jamieson Dept of Pharmacology and Clinical Pharmacology Auckland Cancer Society Research Centre	
Slide 2	## Learning objectives • Understand the physiological determinants of extent and rate of absorption • Be able to describe bolus, first-order and zero-order input processes • Learn the definition of half-life • Be able to describe the time course of drug accumulation during constant rate input and elimination after input stops • Appreciate the applications of absorption and half-life concepts to clinical practice	
Slide 3	## Drug absorption • Transfer of drug from administration site to the systemic circulation – Requires passage through biological membranes • Drugs administered orally must be absorbed before they can cause their pharmacological effect – Has several barriers to overcome, so absorption is usually delayed and incomplete • A drug that is injected intravenously (IV) is immediately and completely (100%) absorbed	Drug absorption is the process of drug transfer from the site of administration to the systemic circulation. Oral drugs need to be absorbed across the gut wall and avoid first pass metabolism in the liver before they reach the systemic circulation. IV administered drugs are injected directly into the systemic circulation.

Slide 4		Here is an example pharmacokinetic profile of a drug administered by IV injection or oral dosing. Orally administered drugs take time to be absorbed and are typically not fully absorbed so maximum concentrations take longer to be achieved and are lower than peak concentrations after IV administration at the same dose.
Slide 5		Drug absorption can be described by two quite distinct factors: • The rate of absorption determines how quickly the drug enters the systemic circulation. • The extent of absorption reflects the total amount of drug entering the systemic circulation. It can be described by the pharmacokinetic parameter bioavailability (F)
Slide 6		Here we have a PK profile for three oral formulations for the same drug. Formulation A has a fast rate of absorption – its maximum concentration is reached quickly. It also has a high extent of absorption. Formulation B has the same fast rate of absorption, but has a low extent of absorption. Its maximum concentration is achieved at the same time as formulation A, but less drug is absorbed. Formulation C has a slow rate of absorption – it takes a long time to achieve maximum concentration, but the amount of drug that reaches the plasma is equivalent to formulation B. How might these different rates and extent of absorption influence drug action? We need to be above the minimum therapeutic level for the drug to be active. Even though formulations B and C achieve the same extent of absorption, because the rate of absorption of B is faster than C, the concentrations of B achieve the minimum therapeutic level and would likely have some effect, while formulation C does not achieve the

		minimum therapeutic level so will be inactive.
Slide 7	**Extent of Absorption (F)** • Fraction absorbed (f) – Into portal vein from gut – Physicochemistry • Small, non-ionised, lipophilic • Soluble in gut fluids • e.g. theophylline (f = 100%) • e.g. gentamicin (f < 5%) – Metabolism/efflux • Enzymes present in gut wall – Simvastatin metabolised by CYP3A4 (f ≈ 50%) • Drug transporters – Digoxin effluxed by P-glycoprotein (f = 65%)	The extent of oral absorption can be considered in 2 parts. The first part is the fraction of drug absorbed across the gut wall (f). Drugs need to be small, non-ionised and lipophilic to passively diffuse across the gut wall. Some drugs may be transported across the gut wall, while others that do diffuse across the gut wall can be transported out of the cell back into the gut lumen by efflux transporters, such as P-glycoprotein. The gut wall also contains some drug metabolising enzymes, e.g. CYP3A4, which can metabolise drugs and limit their absorption across the gut wall.
Slide 8	**Extent of Absorption (F)** • First pass metabolism in liver – Drug absorbed in gut passes through liver before reaching systemic circulation • Hepatic extraction ratio (ER) – Fraction of drug entering the liver that is extracted – Dependent on organ clearance and blood flow • e.g. morphine ER = 60% • e.g. ethanol ER = 10-70%	Once the drug has been absorbed across the gut wall it will then travel to the liver, where it must avoid metabolism before it can reach the systemic circulation. The hepatic extraction ratio (ER) is the fraction of drug entering the liver that is extracted. The hepatic extraction is determined both by the blood flow and by the ability of the liver to eliminate the drug (the intrinsic clearance of the liver).
Slide 9	**Extent (F)** $F = f \cdot (1 - ER)$ e.g. morphine $F = 1 \cdot (1 - 0.6) = 0.4$	The overall extent of absorption is called bioavailability. This is the fraction of the administered dose that reaches the systemic circulation. It can be calculated as the fraction absorbed across the gut (f) multiplied by (1 – ER).

Slide 10	**Input Processes** • Bolus – e.g. intravenous injection • Zero-Order – e.g. constant rate IV infusion • First-Order – e.g. intramuscular injection	The rate of drug absorption can be described by three input processes – bolus input, zero-order input or first-order input. Bolus input is instantaneous. The drug is injected directly into the systemic circulation. Zero-order input means absorption occurs at a constant rate. First-order input is where the rate of absorption is dependent on drug concentration. Most oral drugs follow a first-order rate of absorption.
Slide 11	**Rate** • Zero-Order – IV infusion – Stomach emptying • physiological control – Slow Release Formulation • pharmaceutical control $C(t) = \frac{Rate}{CL} \bullet \left(1 - e^{-\frac{CL}{V} \bullet t}\right)$	Like zero-order elimination, zero-order input occurs at a constant rate. Zero-order input occurs most commonly with IV infusion, oral drugs where gastric emptying rate controls the rate of absorption and some slow-release formulations. The equation here predicts the time course of drug concentrations in the blood from a zero-order input (see excel spreadsheet for an example).
Slide 12	**Zero-order input**  	This graph shows the time course of drug concentration and associated rates of input and elimination for a constant rate input over 1 h. Note that the peak concentration occurs at the end of the constant rate input (see excel spreadsheet for more details on how this was calculated).

Slide 13	**Rate** • First Order – Intestinal absorption • Diffusion limited • Dependent on concentration • Explained by Ka (= 0.7/ absorption $T_{1/2}$) • 90% complete after 4 x absorption $T_{1/2}$ $C(t) = \frac{Dose \bullet Ka}{V \bullet \left(Ka - \frac{CL}{V}\right)} \bullet \left(e^{-\frac{CL}{V} \bullet t} - e^{-Ka \bullet t}\right)$	Absorption rate across the gut wall can be described by a first order process. In first order input, the rate of input is dependent on concentration, just like how in first order elimination, the rate of elimination is dependent on concentration. Ka is the proportionality constant that relates the amount of drug at the site of absorption to the rate of absorption. This is a first order rate constant and is exactly related to the corresponding half-life for the absorption process. The absorption half life equals the natural log of 2 (which is approximately 0.7) divided by Ka. The equation here predicts the time course of drug concentration in the blood from a first-order input process (see excel spreadsheet for an example).
Slide 14	**First-Order Input**  	This graph shows the time course of drug concentration and associated rates of elimination and input for a first-order input. Note that the peak concentration occurs when the absorption rate is equal to the elimination rate at around 1.5 hours.
Slide 15	**Applications** • IV/oral dose conversion – Divide IV dose by F to get equivalent oral dose • Time to peak concentration/effect – e.g. paracetamol formulations • Substitution of generic medicines – Rate (C_{max}, T_{max}) – Extent (Area under the curve, AUC)	Extent of absorption is used to convert IV dose to an equivalent oral dose. An intravenous dose should be divided by F to get the equivalent oral dose The rate of drug absorption determines the time of peak concentration and thus of the peak effect. Note that for drugs with an immediate effect the peak effect is the effect at the time (Tmax) of the peak concentration (Cmax). The peak effect is not the same as the maximum possible effect of a drug (Emax). Rate and extent of absorption can be used to determine if generic medicines are likely to behave in the same way as the original drug. Specifically, are the Cmax, Tmax and AUC similar between the generic and original drug.

Slide 16

Elimination Half-Life ($T_{1/2}$)

- Time required for drug concentration to fall by half
- Depends on V and CL

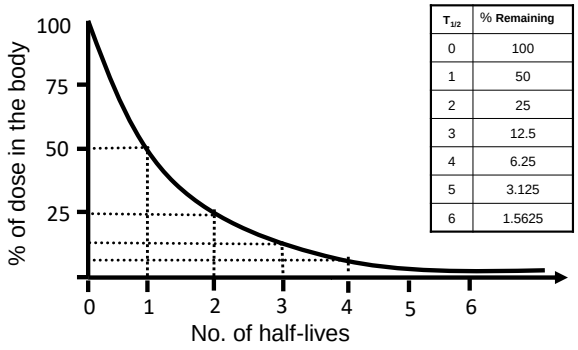
$$T_{1/2} = 0.7 \times V / CL$$

- Usually a constant irrespective of drug concentration
- The amount of drug in the body at any time is related to the number of half-lives from drug administration
- If the half-life is known, then it is possible to estimate:
  - How much drug is left in the body
  - How long it will take to reach steady state

Half-lives are commonly used in pharmacokinetics to describe drug absorption and elimination. The elimination half-life is determined by clearance (CL) and the volume of distribution (V). A proportionality constant, ln(2), is needed to calculate the half-life. A useful approximation to ln(2) is 0.7. Since they describe a first-order process, half-lives are independent of concentration., and therefore can be used to predict how much drug remains at any time after the rate of input has ended.

Slide 17

Relationship between $T_{1/2}$ and elimination



$T_{1/2}$	% Remaining
0	100
1	50
2	25
3	12.5
4	6.25
5	3.125
6	1.5625

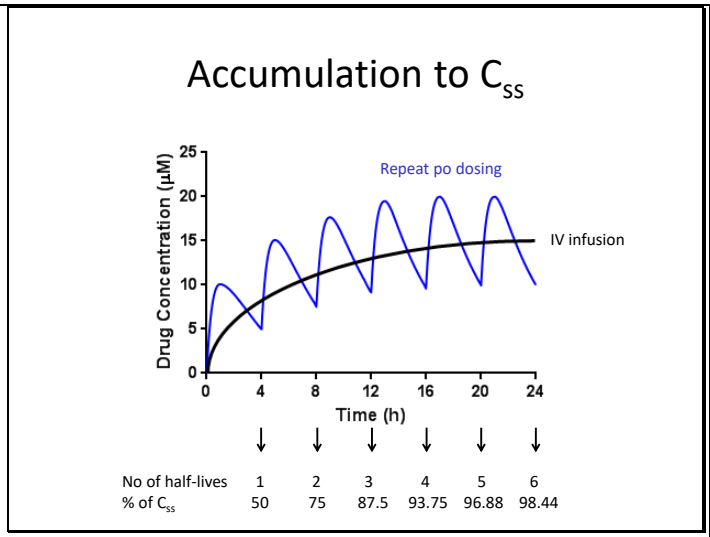
After one half-life a drug will be 50% eliminated. After two half-lives 75% will be eliminated. After four to five half-lives elimination can be considered essentially complete. Note: this is only true if drug input has ended.

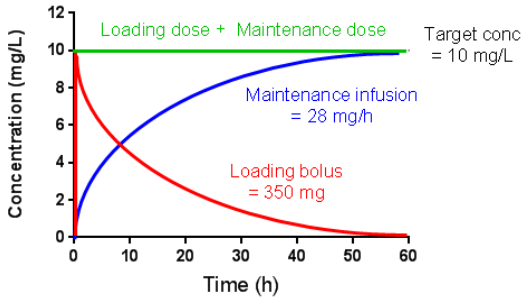
Slide 18

Accumulation

- With repeated dosing or infusion, drug will accumulate in the body until input rate = elimination rate
- Steady state occurs when drug accumulation is complete and concentrations have plateaued
- The time required to reach steady state is related to half-life
  - Accumulation is >90% complete after 4 half-lives
  - Generally agreed that steady state is reached after 4-5 half-lives
  - If wait >5 half-lives before re-administration, drug will not accumulate

The elimination half-life also determines how quickly a drug accumulates. If dosing is continued a drug will accumulate until the rate of input equals the rate of elimination at which point steady state will occur. The drug will accumulate to 50% of steady state by one elimination half-life, 75% by two elimination half-lives and will reach steady state after four to five half-lives.

Slide 19		This figure illustrates the time course of two drugs given by constant rate infusion or by repeat oral dosing every 4 h. Note that for the oral drug, the concentrations take 1 h to reach Cmax and then have an elimination half-life of 3 h, while the IV drug has an elimination half-life of 4 h. Both drugs accumulate to steady state after 16-20 h. The oral drug has peak and trough concentrations but will take the same number of half-lives to accumulate to steady state, although the time taken for the oral drug to be absorbed also has to be factored in.
Slide 20	**Accumulation Factor** The accumulation factor (AF) is the ratio of the concentration at steady state to the concentration after the first dose *at the same time after the dose.* $AF = \frac{Conc(t) \text{ at Steady State}}{Conc(t) \text{ after First Dose}}$ $AF = \frac{1}{1 - e^{-CL/V \cdot \text{Dosint}}}$ Dosint = Dosing Interval	All drugs accumulate. The extent of accumulation depends on the dosing interval and the half-life. A formula for predicting accumulation is shown here. The accumulation factor (AF) is the ratio of the concentration at steady state to the concentration after the first dose *at the same time after the dose.* If the dosing interval is equal to the half-life then the accumulation factor is exactly 2. For oral drugs, the time taken for the drug to be absorbed needs to be excluded, so the dosing interval can be adjusted to the time between peak and trough concentrations.
Slide 21	**Applications** • Accumulation/Elimination – Time to Steady State – Time to Eliminate Drug *~ 4-5 x Elimination Half-Life* • Absorption – Time to Reach Peak Concentration *T_{max} is ~ 3 x Absorption Half-life*	Half-life can be used to predict that after 4-5 elimination half-lives the drug will have accumulated to steady state with continued dosing or been eliminated if input has stopped. The absorption half-life can be used to predict the time (Tmax) of peak concentration for many drugs. Because the peak occurs when drug absorption is equal to drug elimination it happens before drug absorption is complete. Tmax can be approximated to occur after three absorption half-lives.

Slide 22	**Theophylline** 	Knowledge of CL, V and T1/2 can help us achieve and maintain target concentrations in the therapeutic window. V can be used to identify a loading dose, CL to identify a maintenance dose and T1/2 to inform us how long it will take for the loading dose to be eliminated and for the maintenance dose to reach steady state. If we administer a loading dose followed by a maintenance dose we can achieve the target concentration for a prolonged time.
Slide 23	**Revision questions** • Describe the impact if morphine was administered orally at the IV dose • Explain the rate of absorption and elimination of ethanol • The elimination half-life of theophylline is 9h. How is this information used to optimise dosing	