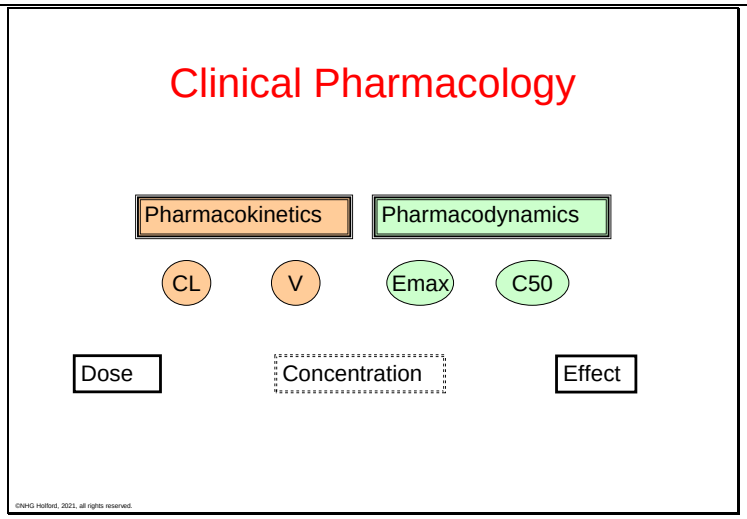
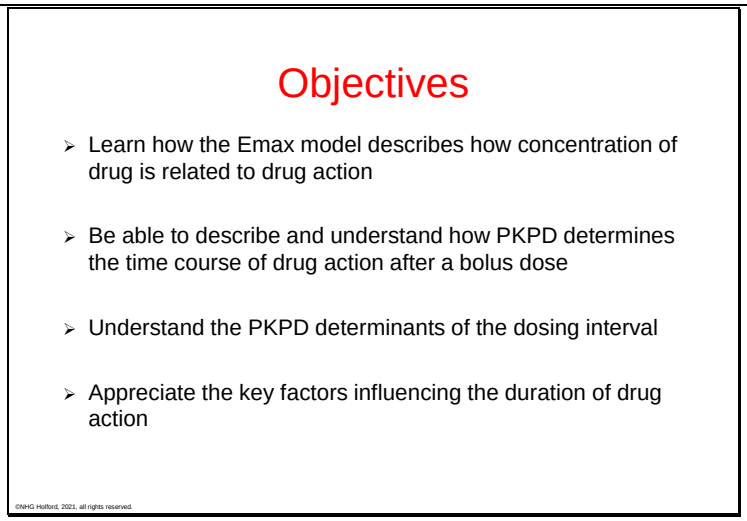
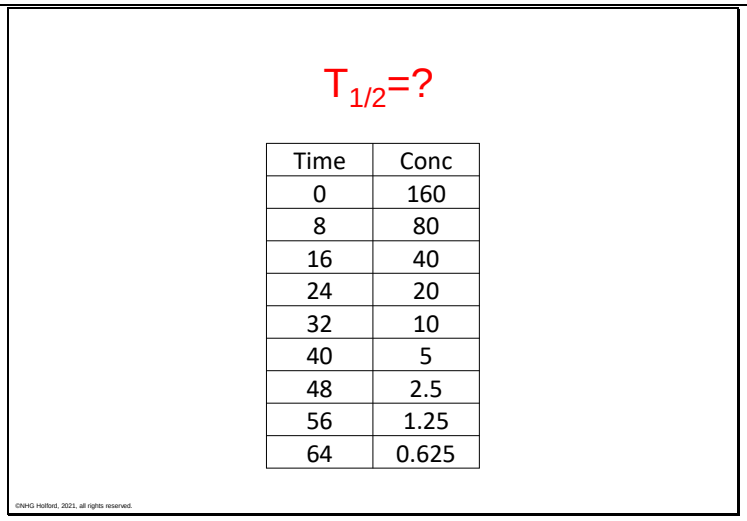
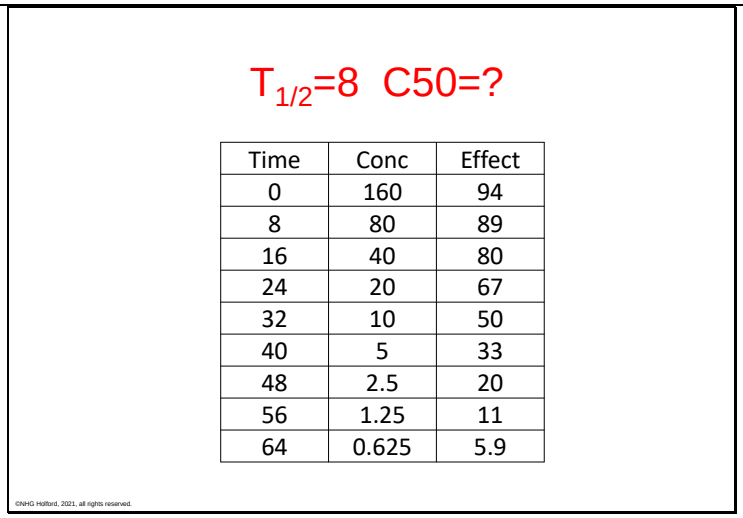
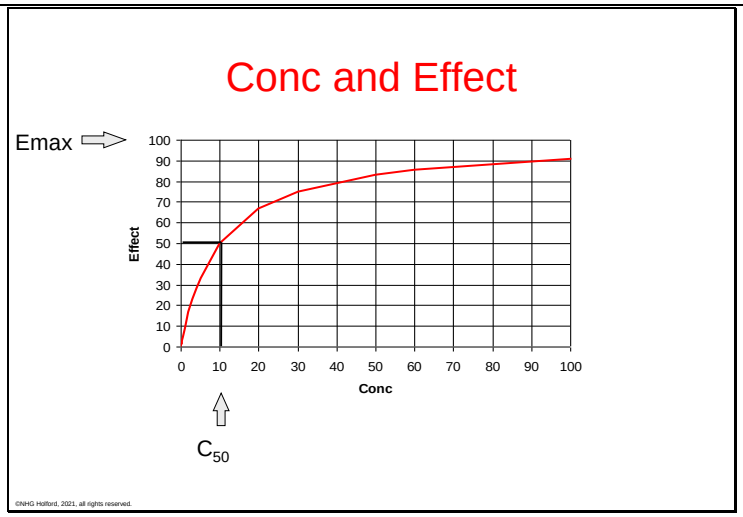
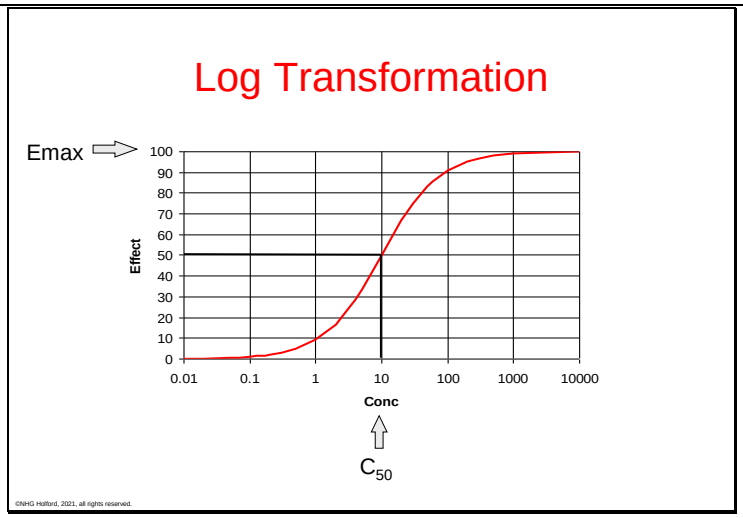
Slide 1	# Pharmacodynamic Principles and the Time Course of Immediate Drug Effects Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	The time course of drug action combines the principles of pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the time course of concentration while pharmacodynamics describes how effects change with concentration. There are 3 ways to think of the time course of effects: • Drug effects are immediately related to observed drug concentration (e.g. in plasma) • Drug effects are delayed in relation to observed drug concentration • Drug effects are determined by the cumulative action of the drug This presentation outlines the basic principles of the concentration-effect relationship (pharmacodynamics) and illustrates the application of pharmacokinetics and pharmacodynamics to predict the time course of immediate drug effects.
Slide 2		

Slide 3		Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50). The C50 is also known as EC50 but C50 is preferred to make it clearer this is a concentration and not an effect scaled parameter.
Slide 4		PKPD = Pharmacokinetics and pharmacodynamics
Slide 5		What is the half-life?

Slide 6		The half-life was 8 time units. Can you guess the C50 of the drug? You will have to make an assumption about the maximum possible effect of the drug (Emax)
Slide 7		Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the C50 will be the same as the Kd. The Kd is the equilibrium binding constant. It is the concentration of unbound drug at which 50% of binding sites are occupied. Notice that Emax can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the C50 only reaches 90% of Emax.
Slide 8		This figure shows the identical values for concentration and effect as that shown on the previous figure. The only change is in the X-axis of the graph to a logarithmic scale. The log transformation changes the shape of the curve so that it now looks “S-shaped” (sigmoid) but this is not a sign of a sigmoid Emax model (see later). The transformed X-axis allows a wider range of concentrations to be plotted and it can be seen that at very high concentrations the effect approaches Emax. The portion of the curve between 20 and 80% of Emax is approximately a straight line. This almost linear relationship was helpful before the days of computers because the slope could be described by simple calculations. Older textbooks commonly refer to ‘log-dose response curves’. It is important to appreciate that there

		is no underlying biological or physical reason to think that drug effects are related more closely to the log of concentration than untransformed concentrations. A problem arises from thinking that effects are related to the log of concentration when the concentration is known to be zero: E=a+b*log(C) At zero concentration is obvious that the effect must be zero but the log of zero is mathematically undefined and so the effect is also undefined. The log concentration model also does not recognize that effects will approach a maximum which is always the case for biological systems. The log transformation is useful for visualising a wide range of concentrations but the log concentration model has no basis in pharmacological theory.
Slide 9	Emax Model $E = \frac{E\,\max \bullet Conc}{C_{50} + Conc}$ ➢ E is the drug effect ➢ Conc is the conc at the receptor ➢ Emax is the maximum drug effect ➢ C_{50} is the conc at 50% of Emax ©NHG Holford, 2021, all rights reserved.	The Emax model is the most fundamental description of the concentration effect relationship. It has strong theoretical support from the physicochemical principles governing binding of drug to a receptor (the law of mass action). All biological responses must reach a maximum and this is an important prediction of the Emax model. When concentrations are low in relation to the C50 then the concentration effect relationship can be approximated by a straight line (the linear pharmacodynamic model): E=Slope*Conc

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Emax Model Predictions

$$E = \frac{E\,\max \bullet Conc}{C_{50} + Conc}$$

- Emax=100
- C_{50}=1

$$E = \frac{100\ x\ 4}{1+4} = 80$$

Conc	Effect	
0	0	
0.25	20	C_{20}
1	50	
2	67	
3	75	
4	80	C_{80}
5	83	
6	86	
7	88	
8	89	
9	90	
10	91	
99	99	

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The C50 is the concentration producing 50% of Emax
There are two other useful concentrations to remember:
C20 – the concentration at 20% of Emax. It is ¼ of C50
C80 – the concentration at 80% of Emax. It is 4 times the C50
This means the Emax model predicts a 16 times change in concentration is needed to change the effect from 20 to 80% of Emax.
Many drugs seem to have a steeper relationship of concentration and effect so that a smaller change is required. These steeper relationships can be described by the sigmoid Emax model.

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Sigmoid Emax Model

$$E = \frac{E\,\max \bullet Conc^{Hill}}{C_{50}^{Hill} + Conc^{Hill}}$$

- E is the drug effect
- Conc is the conc at the receptor
- Emax is the maximum drug effect
- C_{50} is the conc at 50% of Emax
- Hill determines 'steepness'

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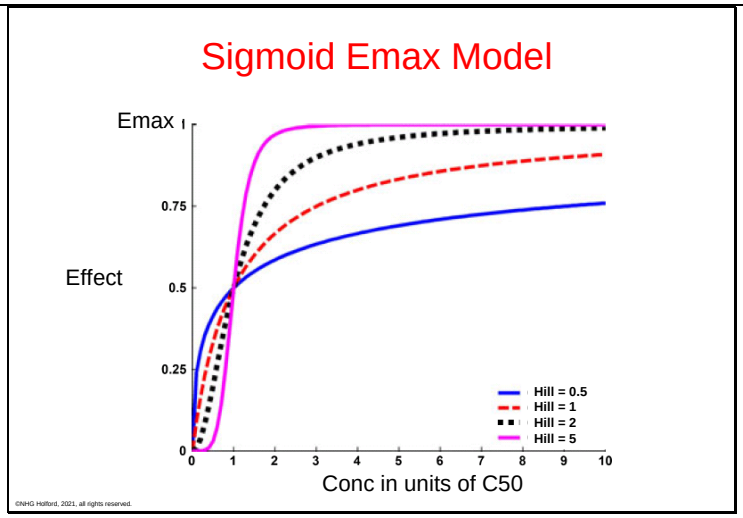
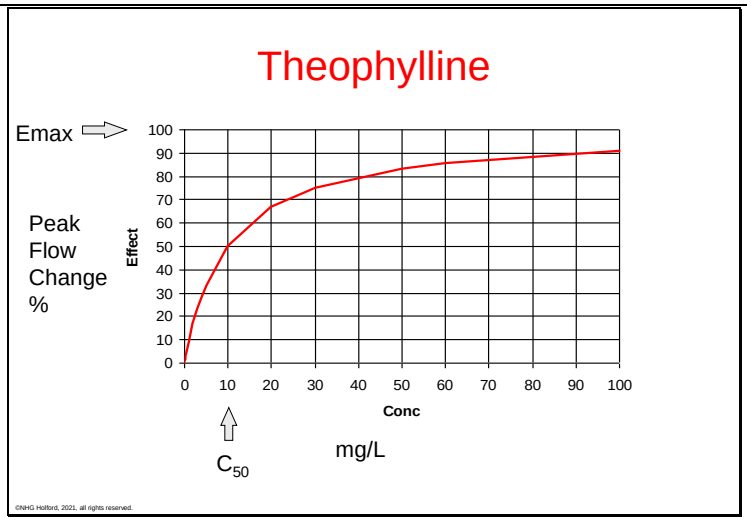
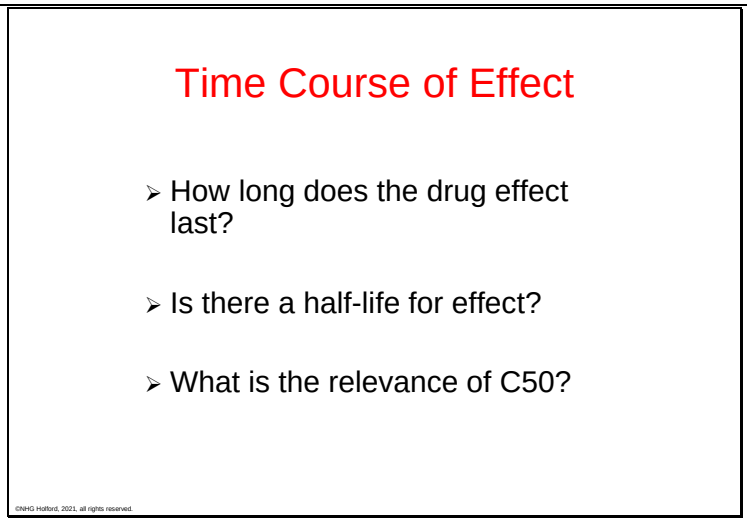
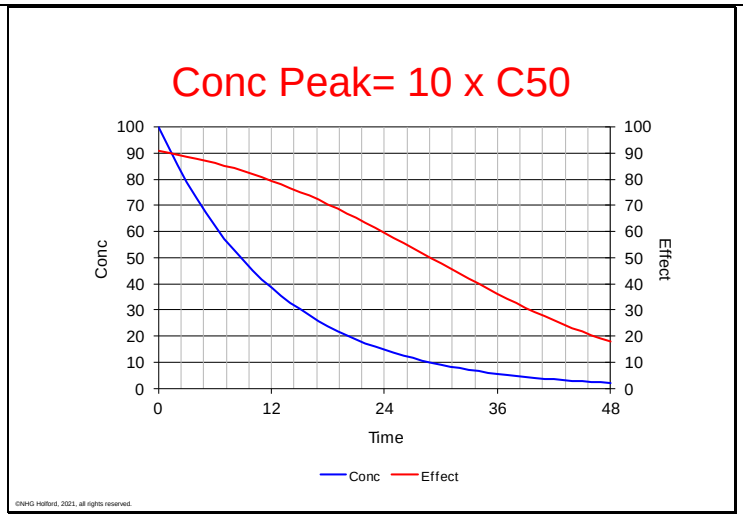
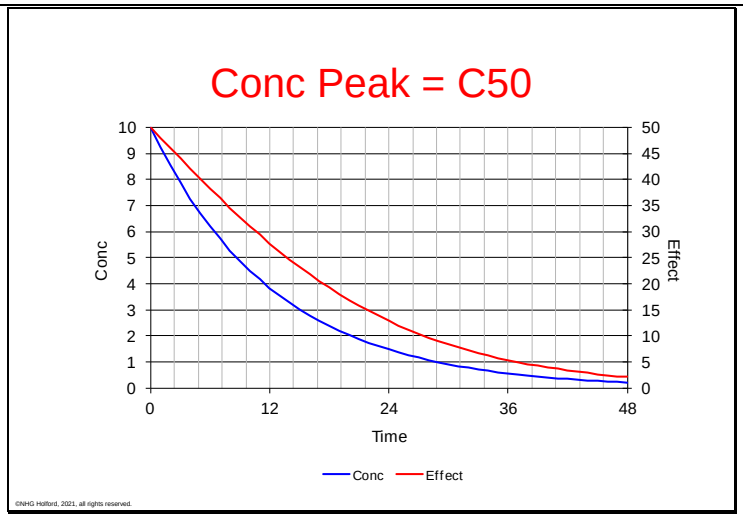
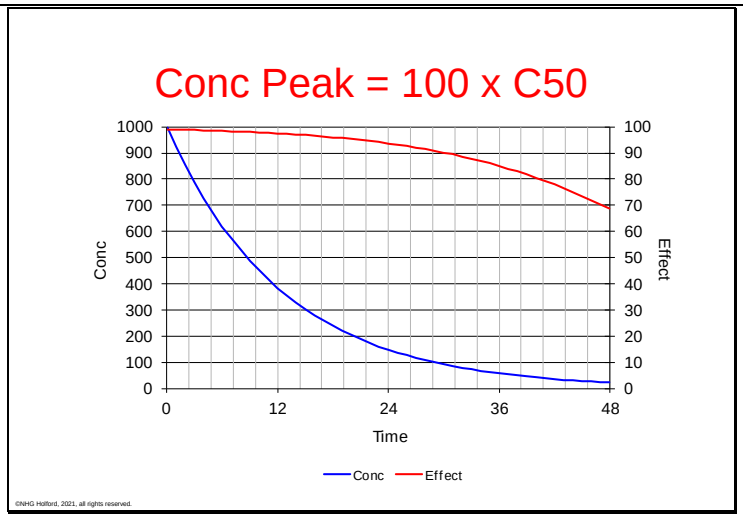
In 1910, the physiologist Hill was investigating the shape of the oxygen – haemoglobin saturation relationship. He noted it was steeper than the simple binding predictions of the Emax model. By trial and error he found that adding an exponential parameter to the concentration and C50 terms in the model the shape of the relationship could be made steeper. This extra parameter is known as the Hill exponent. Subsequently the molecular biologist Perutz won a Nobel prize for describing the structure of haemoglobin which incorporates 4 binding sites for oxygen. The binding of each oxygen atom affects the other binding sites and causes the steep oxygen-haemoglobin binding curve.

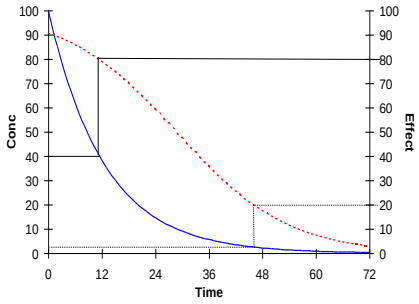
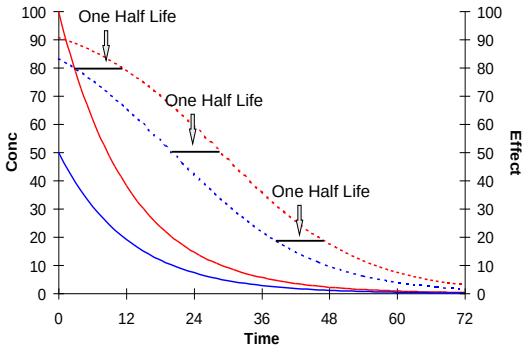
Hill AV. The possible effects of the aggregation of the molecules of hemoglobin on its dissociation curves. J Physiol (Lond). 1910;40:iv-vii.

Perutz MF. Nobel Lecture: X-ray Analysis of Haemoglobin. Nobelprize.org. Nobel Media AB 2014 http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/perutz-lecture.html. 2017.

Goutelle S, Maurin M, Rougier F, Barbaut X, Bourguignon L, Ducher M, et al. The Hill equation: a review of its capabilities in pharmacological modelling. Fundam Clin Pharmacol. 2008;22(6):633-48.

Slide 12		The sigmoid Emax model is shown with 4 different values for the Hill coefficient. When Hill=1 the curve is the same as the Emax model. When Hill is greater than 1 the curve is steeper and when it is less than 1 it is shallower than the Emax model. When Hill=2 it only takes as 4 fold change in concentration to go from C20 to C80. When Hill is very large (>10) the concentration effect relationship is almost like an on-off switch. The effect turns 'on' at a threshold concentration close to the C50. I doubt if there are any convincing examples of this kind of 'threshold' concentration response. Figure modified from: Goutelle S, Maurin M, Rougier F, Barbaut X, Bourguignon L, Ducher M, et al. The Hill equation: a review of its capabilities in pharmacological modelling. Fundam Clin Pharmacol. 2008;22(6):633-48.
Slide 13		Theophylline is used to treat severe asthma. It is a bronchodilator. Airway constriction slows the peak flow rate of air from the lungs. Theophylline can increase the peak flow rate and as an C50 of about 10 mg/L. In the example shown here the maximum effect of theophylline (Emax) is to increase peak flow by 100% above the baseline peak flow.
Slide 14		The following slides illustrate the time course of drug effect and offer answers to the questions on this slide.

Slide 15		This is the first of three figures showing how the time course of immediate drug effect depends upon the initial concentration as well as the pharmacokinetics of the drug. This figure shows the time course of concentration (blue line) after a bolus dose at time zero. The half-life is about 9 hours (similar to theophylline). The initial concentration is 10 times the C50 for theophylline and this produces an initial effect of 90% of Emax (red line). After one half-life the concentration is halved but the effect has changed by less than 10%. As concentration falls the effect disappears more quickly.
Slide 16		If a smaller dose is given so that the initial concentration is the same as the C50 then the initial effect will only be 50% of Emax. At these lower concentrations the time course of effect is almost parallel to the time course of concentration.
Slide 17		When a very big dose is given so that the initial concentration is 100 times the C50 then the initial effect is close to 100% of Emax. The effect changes very little despite big changes in drug concentration. After more than 5 half-lives when nearly all the initial dose will have been eliminated from the body the effect is still 70% of Emax. This figure is important because it shows how drugs which have short half-lives can have big effects even if the dosing interval is many half-lives. This is quite common for receptor antagonists e.g. beta-blockers and angiotensin-converting enzyme inhibitors.

Slide 18	**Time Course of Effect Three Regions** ➢ Flat » Conc > C_{80} ➢ Linear » C_{80} > Conc > C_{20} ➢ Exponential » Conc < C_{20}  ©NHG Holford, 2021, all rights reserved.	In summary the time course of effect can be described by three regions by considering if concentrations are above the C80 or below the C20. When concentrations are very high (greater than C80) the curve is almost flat. There is little change in effect despite big changes in concentration. When concentrations are very low (less than C20) the curve is almost exponential. The time course of concentration and effect are almost parallel to one another. This is the only time it makes sense to describe the effect as having a 'half-life'. In between the C20 and C80 the time course of loss of drug effect is almost a straight line.
Slide 19	**Duration of Response**  ©NHG Holford, 2021, all rights reserved.	This looks like a complicated figure but it illustrates a very simple principle -- "If the dose of a drug is doubled then the duration of response will increase by one half-life." The duration of response means the time that the drug effect is above a pre-defined critical value e.g. the time above 50% of Emax. With a low dose (blue lines) the duration of effect is about 20 hours. At 20 h the concentration is equal to 10 mg/L (the C50). Doubling the dose (red lines) prolongs the duration of effect to nearly 30 h (one half-life). At 30 h the concentration is equal once again to 10 mg/L – with the same level of effect (50) that was used to mark the end of the response for the lower dose. The increase in duration of response from doubling the dose is independent of the size of effect that is chosen to mark the end of the response. https://en.wikipedia.org/wiki/Semaglutide Semaglutide is a glucagon like peptide that stimulates insulin secretion and lowers plasma glucose. The Wikipedia article says it has a duration of action of 63.2 h and a half-life of one week. Assume the observed effect is based on plasma glucose. What would the duration of action be if the dose was doubled?

Slide 20	# Applications ➢ Prediction of the target concentration from the target effect $$Conc = \frac{C50 \cdot Effect}{E\max - Effect}$$ ©NHG Holford, 2021, all rights reserved.	The most important application is to translate the desired clinical effect (the target effect) into a target concentration. Re-arrangement of the Emax equation leads to a prediction of the target concentration to reach the target effect.
Slide 21	# Applications ➢ Selection of an appropriate dosing interval depends on more than the **half-life** – the target concentration and it's relation to the **C50** must be considered too. e.g. half life of hours but effective daily dosing » Beta blockers » Ace Inhibitors » Prednisone/prednisolone ©NHG Holford, 2021, all rights reserved.	Selection of a dosing interval so sustain a desired level of effect has to take into account the time course of effect. In the simplest case this depends on both the half-life and the C50. Many drugs have short half-lives (hours) yet are effective with once a day dosing. This can be explained by concentrations being above the C50 for most of the day.
Slide 22	# Applications ➢ Doubling the dose usually does **not** lead to doubling of effect ➢ Doubling the dose **will** increase the duration of effect by 1 half-life ©NHG Holford, 2021, all rights reserved.	Concentration effect curves are non-linear (Emax model) effects do not increase in direct proportion to the dose.

Slide 23	**Assessment Short Answer Question Examples** 1. Describe the Emax model of drug action. 2. Draw a graph of the time course of drug concentration and effect with an initial concentration 10 times larger than the concentration producing half of the maximum effect. 3. What are the pharmacodynamic determinants of the dosing interval? 4. Explain how much longer drug action lasts if the dose is doubled. ©NHG Holford, 2021, all rights reserved.	
Slide 24