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## Pharmacodynamic Principles and the Time Course of Drug Effects

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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.

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 drug effects.

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## Time Course Of Drug Effects

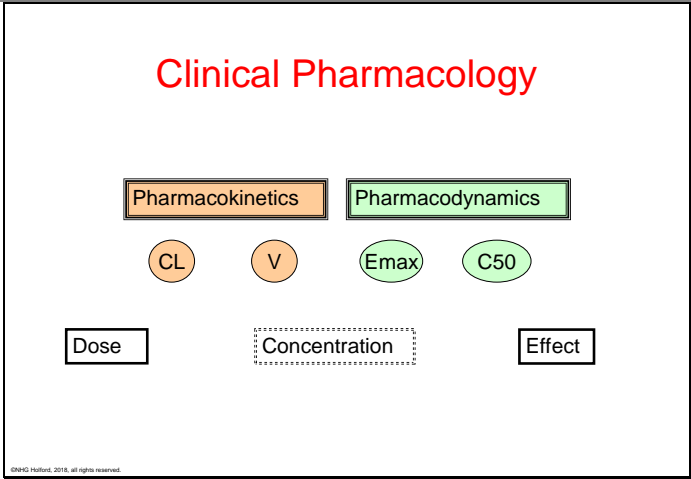
1. Immediate
2. Delayed
3. Cumulative

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There are 3 ways to think of the time course of effects:

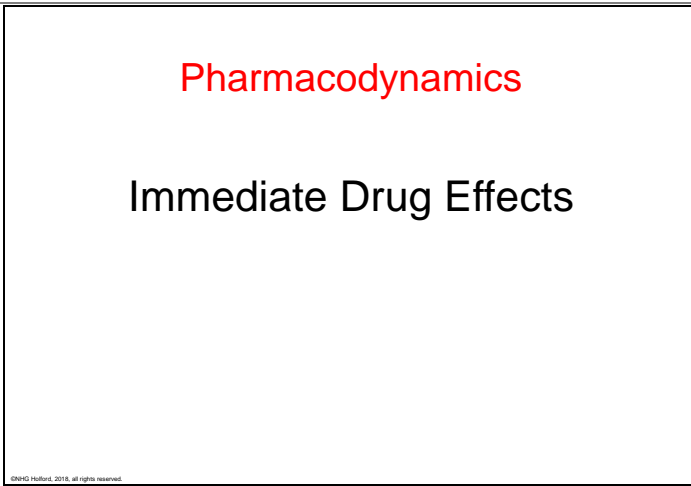
- Drug effects are immediately related to observed drug concentration (e.g. in plasma)
- Drug effects are delayed in relation to observed drug concentration
- Drug effects are determined by the cumulative action of the drug

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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).

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In reality all drug effects are delayed in relation to plasma drug concentrations. Some drug actions e.g. anti-thrombin III binding and inhibition of Factor Xa by heparin have negligible delay because the drug site of action is in the plasma itself.

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- The diagram shows 'Objectives' in red at the top, followed by a bulleted list of learning goals. A small copyright notice '©2012 Hallford, 2016, all rights reserved.' is at the bottom left.
- Learn the Emax model of drug action
  - Understand why log concentration models are misleading
  - Be able to describe the time course of drug action after a bolus dose
  - Appreciate the determinants of the duration of drug action

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## What is $T_{1/2}$ ?

Time	Conc	Effect
0	32	
4	16	
8	8	
12	4	
16	2	
20	1	
24	0.5	
28	0.25	
32	0.125	

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Can you guess the half-life of this drug?

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## $T_{1/2}=4$ $C_{50}=?$

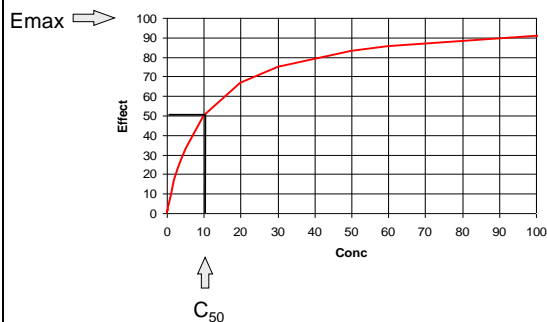
Time	Conc	Effect
0	32	94
4	16	89
8	8	80
12	4	67
16	2	50
20	1	33
24	0.5	20
28	0.25	11
32	0.125	5.9

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The half-life was 4 time units.  
Can you guess the  $C_{50}$  of the drug?  
You will have to make an assumption about the maximum possible effect of the drug ( $E_{max}$ )

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## Conc and Effect

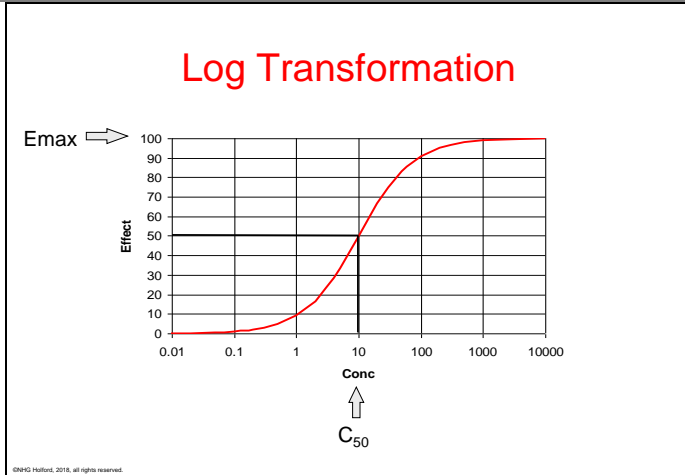


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Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the  $C_{50}$  will be the same as the  $K_d$ .

Notice that  $E_{max}$  can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the  $C_{50}$  only reaches 90% of  $E_{max}$ .

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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:

$$E = a + b \cdot \log(C)$$

At zero concentration it 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.

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### Emax Model

$$E = \frac{E_{\max} \cdot Conc}{C_{50} + Conc}$$

- E is the drug effect
- Conc is the conc at the receptor
- Emax is the maximum drug effect
- C<sub>50</sub> is the conc at 50% of Emax

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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 C<sub>50</sub> then the concentration effect relationship can be approximated by a straight line (the linear pharmacodynamic model):

$$E = \text{Slope} \cdot \text{Conc}$$

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## Emax Model Predictions

$$E = \frac{E_{max} \cdot Conc}{C_{50} + Conc}$$

- Emax=100
- C<sub>50</sub>=1

Conc	Effect
0	0
0.25	20
1	50
2	67
3	75
4	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

$$E = \frac{E_{max} \cdot Conc^{Hill}}{C_{50}^{Hill} + Conc^{Hill}}$$

- E is the drug effect
- Conc is the conc at the receptor
- Emax is the maximum drug effect
- C<sub>50</sub> is the conc at 50% of Emax
- Hill determines 'steepness'

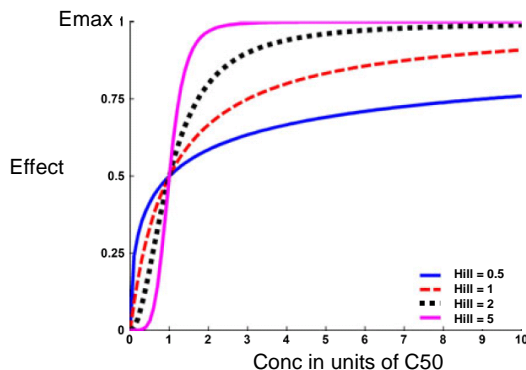
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In 1910, the physiologist Hill was investigating the shape of the oxygen – haemoglobin saturation relationship. He noted it was steeper than the simple binding predictions of the Emax model. By trial and error he found that adding an exponential parameter 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 coefficient.

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.

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## Sigmoid Emax Model



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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.

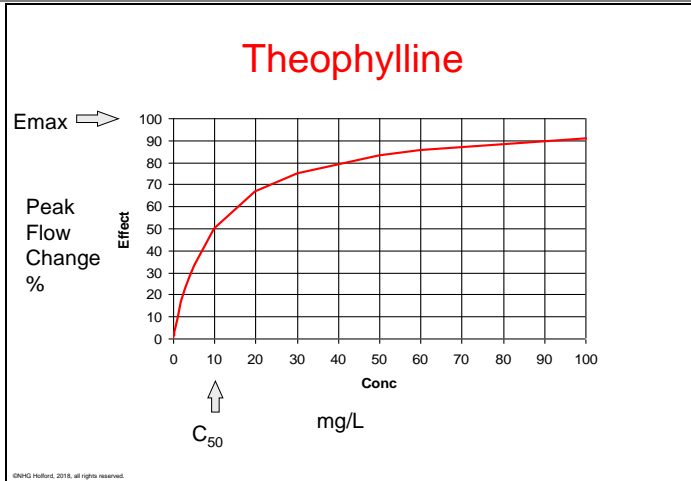
When Hill is greater than 1 the curve is steeper and when it is less than 1 it is shallower than the Emax model.

When Hill=2 it only takes a 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.

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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 C<sub>50</sub> 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.

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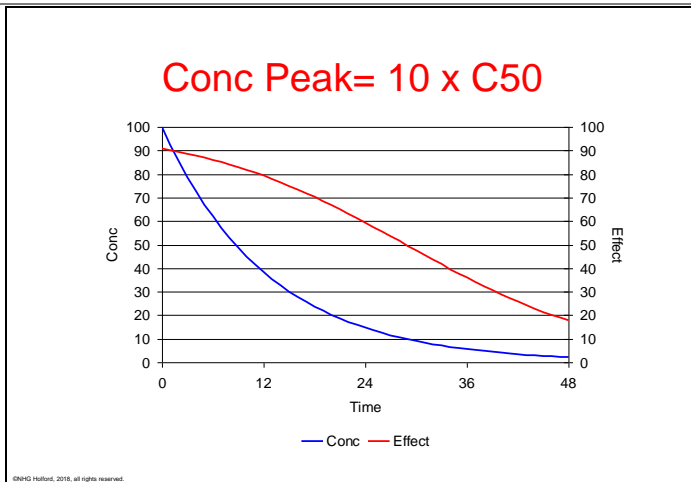
### Time Course of Effect

- How long does the drug effect last?
- Is there a half-life for effect?
- What is the relevance of C<sub>50</sub>?

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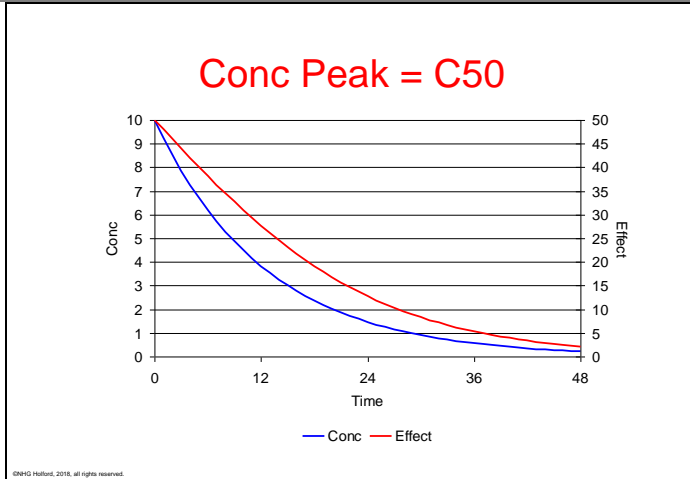
The following slides illustrate the time course of drug effect and offer answers to the questions on this slide.

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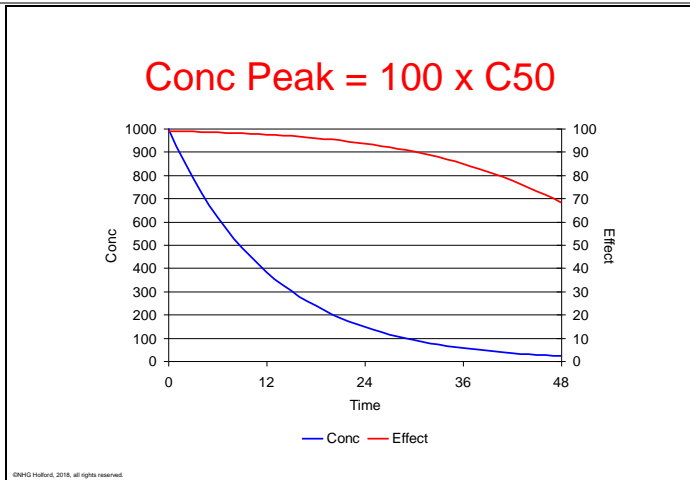
This is the first of three figures showing how the time course of immediate drug effect depends upon the initial concentration as well as the pharmacokinetics of the drug. This figure shows the time course of concentration (blue line) after a bolus dose at time zero. The half-life is about 9 hours (similar to theophylline). The initial concentration is 10 times the C<sub>50</sub> 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.

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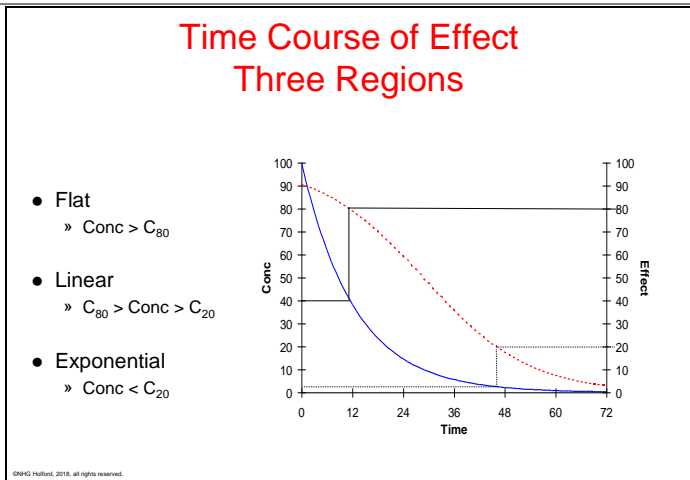
If a smaller dose is given so that the initial concentration is the same as the C50 then the initial effect will only be 50% of Emax. At these lower concentrations the time course of effect is almost parallel to the time course of concentration.

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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.

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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.

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## Disappearance of Response

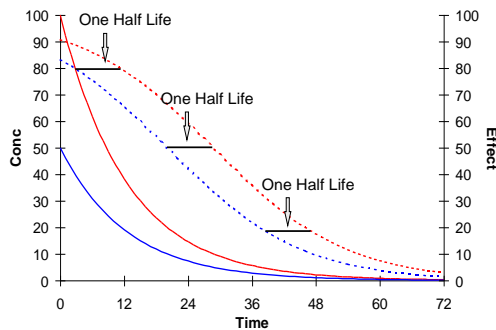
- Flat
  - » Almost independent
- Linear
  - » Proportional to Time
  - » eg 10 mm/Hg per hour
- Exponential
  - » Proportional to Concentration
  - » eg 50% fall per hour (half-life)

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The three regions of the time course of effect curve can be described as flat, linear and exponential.

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## Duration of Response



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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 – the same level of effect 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.

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## Applications

- Prediction of the target concentration from the target effect

$$Conc = \frac{C50 \cdot Effect}{E_{max} - Effect}$$

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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.

<p>Slide 24</p>	<h2 style="text-align: center;">Applications</h2> <ul style="list-style-type: none"> <li>● Selection of an appropriate dosing interval depends on more than the <b>half-life</b> – the target concentration and it's relation to the <b>C50</b> must be considered too.</li> </ul> <p>e.g. half life of hours but effective daily dosing</p> <ul style="list-style-type: none"> <li>» Beta blockers</li> <li>» Ace Inhibitors</li> <li>» Prednisone/prednisolone</li> </ul> <p><small>©BMJ 2016. All rights reserved.</small></p>	<p>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 is usually because concentrations are above the EC50 for most of the day.</p>
<p>Slide 25</p>	<h2 style="text-align: center;">Applications</h2> <ul style="list-style-type: none"> <li>● Doubling the dose usually does <b>not</b> lead to doubling of effect</li> <li>● Doubling the dose <b>will</b> increase the duration of effect by 1 half-life</li> </ul> <p><small>©BMJ 2016. All rights reserved.</small></p>	<p>Concentration effect curves are non-linear (Emax model) effects do not increase in direct proportion to the dose.</p>
<p>Slide 26</p>	<h2 style="text-align: center;">Pharmacodynamics</h2> <h3 style="text-align: center;">Delayed Drug Effects</h3> <p><small>©BMJ 2016. All rights reserved.</small></p>	<p>In reality all drug effects are delayed in relation to plasma drug concentrations. There are several mechanisms which can explain delayed effects:</p> <ul style="list-style-type: none"> <li>• Distribution to the receptor site</li> <li>• Binding to and unbinding from receptors</li> <li>• Turnover of a physiological mediator of the effect</li> </ul>

<p>Slide 27</p>	<h2 style="text-align: center;">Objectives</h2> <ul style="list-style-type: none"> <li>● Distinguish drug action, effect and response</li> <li>● Describe the difference between pharmacokinetic and physiokinetic models for delayed drug response</li> <li>● Be able to describe the reasons for delayed response to thiopentone and warfarin</li> <li>● Understand why drug responses can be markedly delayed and appear to have little relationship to elimination half-life</li> </ul> <p><small>©2010 Holford, 2010, all rights reserved.</small></p>	
<p>Slide 28</p>	<h2 style="text-align: center;">Delayed Drug Effects</h2> <ul style="list-style-type: none"> <li>● Distribution to Effect Site <ul style="list-style-type: none"> <li>» pharmaco-kinetics</li> </ul> </li> <li>● Physiological Intermediate <ul style="list-style-type: none"> <li>» physio-kinetics</li> </ul> </li> </ul> <p><small>©2010 Holford, 2010, all rights reserved.</small></p>	<p>Delayed drug effects are usually due to both of these mechanisms. It takes time for drug to distribute to the site of action and then it takes time for the drug action to change physiological intermediate substances before the drug response is observed. While it is possible sometimes to distinguish both mechanisms it is most common to identify only one delay process. If the delays are short (minutes) then the mechanism is probably a distribution process whereas if the delay is long (hours or longer) then the mechanism is more likely to be physiological.</p>
<p>Slide 29</p>	<h2 style="text-align: center;">Terminology</h2> <ul style="list-style-type: none"> <li>● Drug Action <ul style="list-style-type: none"> <li>» on a receptor</li> </ul> </li> <li>● Drug Effect <ul style="list-style-type: none"> <li>» receptor mediated change in a physiological intermediate</li> </ul> </li> <li>● Drug Response <ul style="list-style-type: none"> <li>» observed consequence of physiological intermediate</li> </ul> </li> </ul> <p><small>©2010 Holford, 2010, all rights reserved.</small></p>	<p>It can be helpful when dealing with delayed drug effects to use a special set of words to describe what a drug is doing. The first step is for a drug to have its action at a receptor. This is at its site of action and reflects the instantaneous consequences of the drug at its binding site. Binding may be to a receptor e.g. a beta agonist binding to an adrenoceptor in the lung. Other sites of action include an enzyme, a transporter, an ion channel, etc. Drug delays due to distribution take place before the drug action. Physiological changes e.g. production of cyclic AMP, then lead to a drug effect e.g. bronchial smooth muscle relaxation. The effect of a drug is the observable consequence of the drug action and is usually delayed as a consequence of the turnover of one or more physiological mediators. Finally a drug response is observed e.g. increased airway peak flow in an asthmatic. There may be additional delays due to other physiological interactions and feedback mechanisms.</p>

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## Distribution to Effect Site

Effect site not in 'central compartment'

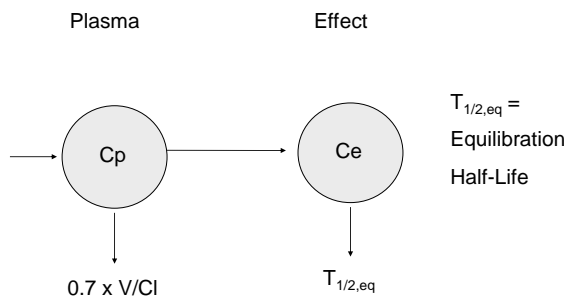
- » brain
  - thiopentone      anaesthetic

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Distributional delays are readily understood in terms of anatomy. It takes time for a drug molecule to get from the blood to a target tissue because of delays in perfusion of tissues and diffusion across blood vessel walls and through extracellular spaces. The rapidly mixing central blood volume is the driving force compartment for the delivery of drug to the tissues.

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## Effect Compartment



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Because it is usually difficult or impossible to measure drug concentration at the site of action the time course of distribution can be described empirically by proposing an effect compartment. The time course of observed drug effect is then used to deduce the time course of drug concentration at the site of action.

The simplest model for an effect compartment is very similar to a one compartment model for pharmacokinetics. The time needed to reach steady state in a pharmacokinetic system receiving a constant rate input is determined by the elimination half-life from the plasma compartment. If drug concentrations in the plasma are constant then the rate of input to the effect compartment will also be constant and the time to steady state in the effect compartment will be simply determined by the equilibration half-life.

More complex pharmacokinetic systems are readily described by the effect compartment model in the same way that plasma concentrations from complex inputs can be predicted with a pharmacokinetic model.

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## Equilibration Half-Life

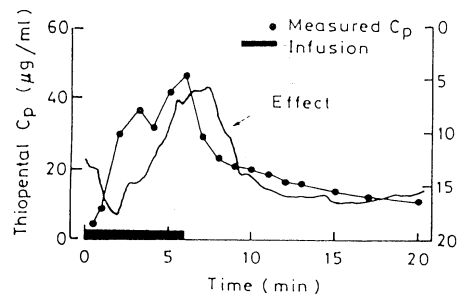
- Determined by
  - » Volume of 'effect compartment'
    - Organ size
    - Tissue binding
  - » Clearance of 'effect compartment'
    - Blood flow
    - Diffusion

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The effect compartment half-life is also known as the equilibration half-life. The elimination half-life of a pharmacokinetic system is determined by the volume of distribution and clearance. The same factors affect the equilibration half-life

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## Thiopentone Time Course



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Thiopentone is used for the rapid induction of anaesthesia. This figure shows the time course of measured thiopentone concentrations (black symbols) compared with the effect of thiopentone on the EEG. Thiopentone slows the frequency of EEG electrical activity (right hand axis scale). The EEG scale is inverted so that slowing of the EEG causes the EEG curve to move up and down in parallel with plasma concentration. Note however the delay in the EEG curve in relation to plasma concentration.

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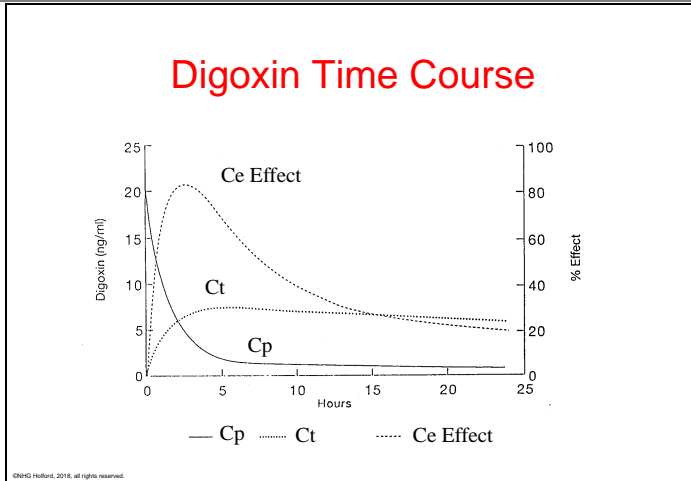
## Thiopentone

- Volume
- » limited binding to GABA<sub>A</sub> receptors
- Clearance
- » rapid perfusion of brain
- Equilibration Half-life = 1 min

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Thiopentone reaches the brain quickly and is washed out rapidly because of the high blood flow to the brain. It is the rapid washout of thiopentone that leads to a short equilibration half-life of about a minute.

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The time course of digoxin concentration in plasma ( $C_p$ ) can be used to predict the average concentration in all the other tissues of the body ( $C_t$ ). Note that  $C_t$  is not specific for any particular organ or tissue so it is not likely to reflect the distribution and equilibration at the site of action. This figure shows the time course of concentration in an effect compartment that explains the delayed increase in cardiac contractility produced by digoxin. The effect compartment reaches a peak before the average tissue concentration in part because of the more rapid perfusion of the heart compared with other tissues such as fat.

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### Digoxin

Volume

- » extensive binding in heart to  $\text{Na}^+\text{K}^+\text{ATPase}$

Clearance

- » rapid perfusion of heart

Slow unbinding from  $\text{Na}^+\text{K}^+\text{ATPase}$  is the most likely cause of the delayed onset of digoxin effects

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Despite rapid perfusion of the heart the equilibration half-life of digoxin is quite slow. This is because extensive binding of digoxin to  $\text{Na}^+\text{K}^+\text{ATPase}$  in the heart takes a long time to reach binding equilibrium. This is because the dissociation half-life is long. The slow dissociation is part of the explanation of why digoxin is such a potent drug (works at nanomolar concentrations).

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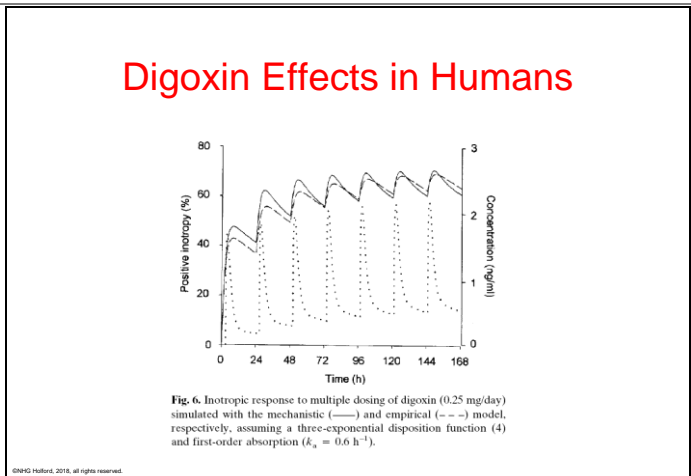


Fig. 6. Inotropic response to multiple dosing of digoxin (0.25 mg/day) simulated with the mechanistic (—) and empirical (---) model, respectively, assuming a three-exponential disposition function (4) and first-order absorption ( $k_a = 0.6 \text{ h}^{-1}$ ).

Weiss M, Kang W. Inotropic effect of digoxin in humans: mechanistic pharmacokinetic/pharmacodynamic model based on slow receptor binding. *Pharm Res.* 2004 Feb;21(2):231-6.

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## Physiological Intermediate

### Drug Action

» inhibition of Vit K recycling

### Drug Effect

» decreased synthesis of clotting factors

### Drug Response

» prolonged coagulation time (INR)

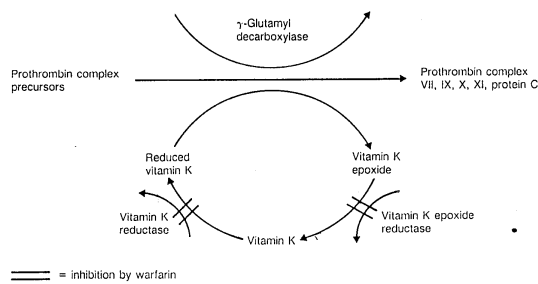
INR=International Normalised Ratio

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Warfarin is an anticoagulant used to treat conditions such as deep vein thrombosis or to prevent blood clots and emboli associated with atrial fibrillation. It acts by inhibiting the recycling of Vitamin K in the liver. The effect of reduced Vitamin K is a decrease in the synthesis rate of clotting factors. The observable response is an increase in the time taken for blood to clot e.g. as measured by the international normalized ratio (INR).

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## The Vitamin K Cycle

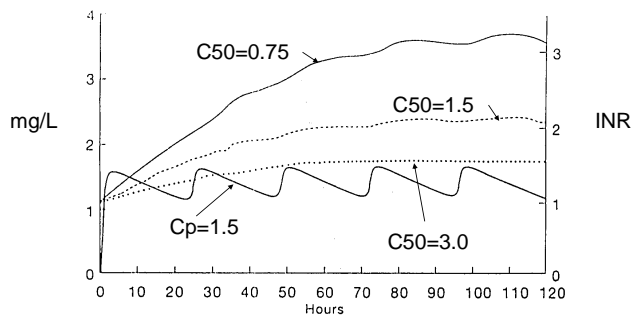


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Vitamin K is an essential co-factor for the synthesis of clotting factors. When the prothrombin complex precursors are activated by gamma-glutamyl decarboxylase Vitamin K is inactivated and forms Vitamin K epoxide. The action of warfarin is rapid. Warfarin is absorbed quickly from the gut and reaches the liver where it enters the cells and inhibits Vitamin K reductase and Vitamin K epoxide reductase. This stops the re-cycling of Vitamin K epoxide back to the active Vitamin K form and prothrombin complex synthesis is reduced.

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## Warfarin Time Course



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The time course of change in prothrombin complex is determined by the half-life of the proteins e.g. Factor VII, which are involved in blood coagulation. The slow elimination of the prothrombin complex clotting factors eventually leads to a new steady state with an associated change in INR. This figure illustrates the INR response to a loading dose and maintenance dose of warfarin. The average concentration of warfarin is 1.5 mg/L which is close to the C50 for warfarin inhibition of Vitamin K recycling. 3 INR profiles are shown with different C50 values. The steady state INR is higher when the C50 is low and the INR is lower when the C50 is high. However, the time to reach a new steady state INR is not affected by the C50 because it is only determined by the half-life of the clotting factors.

<p>Slide 41</p>	<h2 style="text-align: center; color: red;">Warfarin Delayed Response</h2> <p>C50 for synthesis is 1.5 mg/L</p> <ul style="list-style-type: none"> <li>» Synthesis is reduced 50% at the C50</li> <li>» [prothrombin complex] is reduced 50%</li> </ul> <p>Critical parameter is</p> <ul style="list-style-type: none"> <li>» Half-life of prothrombin complex</li> <li>» about 14 h</li> </ul> <p>Takes 4 half-lives to reach SS</p> <ul style="list-style-type: none"> <li>» 2 to 3 days</li> </ul> <p><small>©2010 Hallford, 2016, all rights reserved.</small></p>	<p>The prothrombin complex of clotting factors has an average elimination half-life of about 14 hours. This means it typically takes 2 to 3 days to reach a new steady state INR value.</p>
<p>Slide 42</p>	<h2 style="text-align: center; color: red;">Warfarin Dosing</h2> <p>Target Conc is 1.5 mg/L (C50)</p> <p>Loading Dose</p> <ul style="list-style-type: none"> <li>» LD= 1.5 mg/L x 10 L = 15 mg</li> </ul> <p>Maintenance Dose</p> <ul style="list-style-type: none"> <li>» MD= 1.5 mg/L x 3 L/d = 5 mg/day</li> </ul> <p><small>©2010 Hallford, 2016, all rights reserved.</small></p>	<p>The target concentration for warfarin is the same as it's C50. This leads to a 50% reduction in synthesis and a doubling of the INR. The loading dose and maintenance dose can be calculated using typical values for warfarin volume of distribution and clearance.</p>
<p>Slide 43</p>	<h2 style="text-align: center; color: red;">Warfarin Dose Adjustment</h2> <p>Measure INR daily</p> <p>Wait at least 2 days before changing dose</p> <p>Warfarin takes 7 days to reach a new steady state</p> <p><small>©2010 Hallford, 2016, all rights reserved.</small></p>	<p>Because of the long half-life of warfarin it is always helpful to use a loading dose to reach the target concentration more quickly. However, it also takes 2 days after reaching the new warfarin steady state before the INR steady state is reached. This means that dose adjustments of warfarin must be based on INR measurements made at least 2 days previously.</p>

<p>Slide 44</p>	<h2 style="text-align: center; color: red;">Physiological Intermediate</h2> <p>Angiotensin Converting Enzyme Inhibitors (enalapril)</p> <ul style="list-style-type: none"> <li>» Delayed effect on blood pressure (1 week)</li> <li>» Half-life of Na<sup>+</sup> is about 2 days</li> </ul> <p>Anti-Depressants (amitriptyline)</p> <ul style="list-style-type: none"> <li>» Delayed effect on depression (2 weeks)</li> <li>» Unidentified mediator</li> <li>» A protein with a 4 day half-life?</li> </ul> <p><small>©2010 Hallford, 2010, all rights reserved.</small></p>	<p>Other examples of drug with delayed responses due to physiological intermediates are shown. The physiological mediators of the blood pressure fall due to angiotensin converting enzyme inhibition are angiotensin (rapid effect) and sodium (slow effect). It can take at least a week to see the full blood pressure lowering effect because of the long half-life of sodium.</p> <p>Anti-depressants are commonly said to take 2 weeks to reach full effect. This can be explained by the turnover of a mediator with an half-life of several days. This is much slower than the change in synaptic amine concentrations produced by the action of these drugs on amine transporters.</p>
<p>Slide 45</p>	<h2 style="text-align: center; color: red;">Pharmacodynamics</h2> <h3 style="text-align: center;">Cumulative Drug Responses</h3> <p><small>©2010 Hallford, 2010, all rights reserved.</small></p>	<p>Many clinical outcome benefits and adverse effects are a consequence of cumulative drug action. The time course of drug action can be used to predict cumulative responses and explain phenomena such as schedule dependence.</p>
<p>Slide 46</p>	<h2 style="text-align: center; color: red;">Objectives</h2> <ul style="list-style-type: none"> <li>● Understand the concepts of drug exposure</li> <li>● Appreciate the difference between immediate action, delayed effect and cumulative response to a drug</li> <li>● Describe the response to frusemide with different dosing schedules</li> <li>● Appreciate the basis of schedule dependence of drug response e.g. in cancer chemotherapy</li> </ul> <p><small>©2010 Hallford, 2010, all rights reserved.</small></p>	

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## Terminology

- Drug Action
  - » on a receptor
- Drug Effect
  - » receptor mediated change in a physiological intermediate
- Drug Response
  - » observed consequence of physiological intermediate

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It can be helpful when dealing with cumulative drug response to use a special set of words to describe what a drug is doing.

The first step is for a drug to have its action at a receptor. This is at its site of action and reflects the instantaneous consequences of the drug at its binding site. Binding may be to a receptor e.g. binding of frusemide to a sodium transporter in the kidney. Other sites of action include an enzyme, a receptor, an ion channel, etc. Drug delays due to distribution take place before the drug action. Physiological changes e.g. decrease in sodium reabsorption, then lead to a drug effect e.g. increased rate of excretion of sodium and water in the urine. The effect of a drug is the observable consequence of the drug action and is usually delayed as a consequence of the turnover of one or more physiological mediators. There is usually a delay of a few minutes before increased urinary excretion can be observed because it takes time for the fluid contents of the nephron to reach the urinary bladder.

The clinical response e.g. reduction of oedema in heart failure, is a consequence of cumulative sodium and water loss.

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## Drug Exposure

- Response is related to drug exposure
- Exposure Indicators

### Dose

- Single Dose
- Daily Dose Rate
- Cumulative Dose

### Concentration

- Area under Time vs Conc Curve (AUC)
- Average Steady State Conc (C<sub>ss</sub>)
- Area under Time vs Effect Curve (AUC<sub>e</sub>)

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The term drug exposure is commonly used to describe the overall (or cumulative) dose, concentration or effect leading to a clinical response. Dose based measures of exposure cannot account for pharmacokinetic influences on the time course of effect.

The area under the curve (AUC) is the integral of drug concentration with respect to time and thus, like dose, it does not contain information to predict the time course of effect.

The average steady state concentration (C<sub>ss</sub>) is closely related to AUC. It is the AUC over a dosing interval divided by the dosing interval. It also does not contain information to predict the time course of effect.

By observing an intermediate effect it is possible to integrate the effect with respect to time. This is the cumulative effect and can be used to predict cumulative responses. It is affected by changes in the time course of concentration.

<p>Slide 49</p>	<h2 style="text-align: center;">Acid Pump Inhibitors</h2> <ul style="list-style-type: none"> <li>● Gastric/Duodenal ulcers are dependent on acid secretion</li> <li>● Acid Pump inhibitors block gastric acid secretion <ul style="list-style-type: none"> <li>» e.g. omeprazole</li> </ul> </li> <li>● Inhibition is due to irreversible binding</li> </ul> <p style="font-size: small; margin-top: 10px;">©2012 Holford, 2016, all rights reserved.</p>	<p>One of the most common drug responses reflecting cumulative drug action is the healing of peptic ulcers. A peptic ulcer in the stomach or duodenum is caused by the action of gastric acid on the mucosa. Drugs which block gastric acid secretion reduce the exposure of the mucosa to acid and allows healing of the ulcer. Omeprazole is an irreversible inhibitor of the gastric proton pump that is directly involved in production of acid by the stomach.</p>
<p>Slide 50</p>	<h2 style="text-align: center;">Acid Pump Inhibition</h2> <ul style="list-style-type: none"> <li>● Omeprazole is a prodrug</li> <li>● Metabolised under acid conditions to a sulphenamide metabolite</li> <li>● Sulphenamide forms a covalent disulphide bond with cysteine which is part of the acid pump</li> <li>● Restoration of acid secretion depends on synthesis of new pump molecules</li> </ul> <p style="font-size: small; margin-top: 10px;">©2012 Holford, 2016, all rights reserved.</p>	
<p>Slide 51</p>	<h2 style="text-align: center;">Acid Pump Inhibitors</h2> <ul style="list-style-type: none"> <li>● Action <ul style="list-style-type: none"> <li>» inhibition of gastric acid pump</li> </ul> </li> <li>● Effect <ul style="list-style-type: none"> <li>» decreased acid secretion and increased pH</li> </ul> </li> <li>● Response <ul style="list-style-type: none"> <li>» ulcer healing</li> </ul> </li> </ul> <p style="font-size: small; margin-top: 10px;">©2012 Holford, 2016, all rights reserved.</p>	<p>The action of omeprazole is to inhibit the gastric acid (proton) pump. This happens rapidly with negligible delay in relation to plasma concentration. Because omeprazole binds irreversibly to the pump the extent of inhibition is determined by the cumulative exposure to concentration (AUC). The recovery of pump function is slow because it requires the synthesis of a new pump molecule in the absence of omeprazole. The time course of effect of omeprazole can be observed by sampling gastric acid fluid and measuring acid secretion rates of pH of the stomach contents. The clinical response to omeprazole occurs when the ulcer is healed. This takes time and is controlled by the turnover of mechanisms involved in regenerating the tissues that have been damaged by the ulcer.</p>



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## Diuretics and Heart Failure

- Digoxin, ACE inhibitors, beta blockers
  - » Used to improve survival
- Diuretics provide relief of symptoms
  - » Mainly produced by excess fluid
    - breathlessness, ankle swelling, (dropsy)
  - » Benefit is related to net reduction in fluid

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The major symptoms of congestive heart failure are associated with excess fluid in the body. Removal of the excess fluid can help relieve symptoms of breathlessness and ankle swelling.

Diuretics are commonly used to make the kidneys retain less fluid and thus encourage a loss of fluid.

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## Diuretic Action/Effect/Response

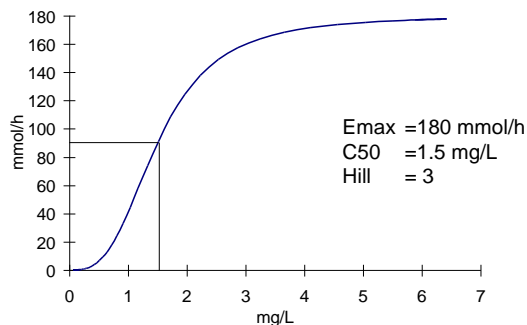
- Diuretic Action
  - » Inhibition of  $\text{Na}^+$  reabsorption
- Diuretic Effect
  - » Increased  $\text{Na}^+$  and  $\text{H}_2\text{O}$  excretion
- Diuretic Response
  - » Cumulative fluid loss

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A diuretic such as frusemide acts on sodium transporters in the loop of Henle (proximal tubule). The sodium transporters normally reabsorb sodium from tubular fluid and pump it back into the tubular cells. Sodium acts as an osmotic diuretic so that more water is lost if more sodium is lost in the urine. The time course of the diuretic effect can be measured by collecting urine and measuring sodium and water excretion rates. The clinical response in heart failure is determined by the cumulative fluid loss.

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## Frusemide Diuretic Effect

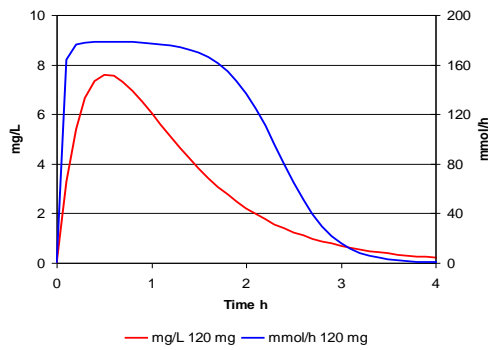


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Frusemide has a rapidly reversible action on the sodium transporter in the proximal tubule. The relationship between plasma concentration of frusemide and the excretion rate of sodium can be described by a sigmoid Emax model. The maximum excretion rate of sodium is 180 mmol/h. Compare this maximum rate with the 140 mmol of sodium per liter of plasma.

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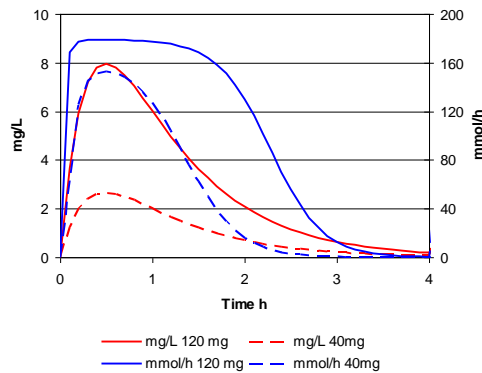
## Frusemide Diuretic Effect



The time course of frusemide effect is illustrated with a large oral dose (120 mg). The effect starts quickly and reaches a plateau for nearly 2 hours then drops away quite rapidly. The loss of effect is quicker than the plasma concentration of frusemide disappears. This is a consequence of the steep concentration effect relationship with a Hill coefficient of 3.

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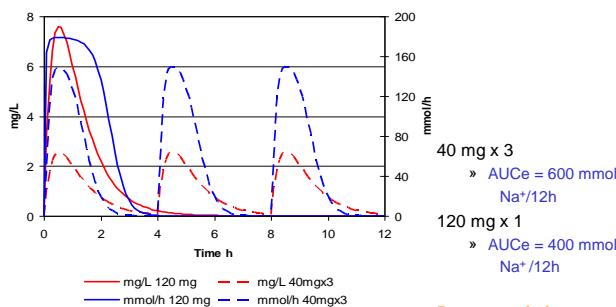
## Frusemide 120 and 40 mg



Compare the concentrations and effects from a large dose (120 mg) and a small dose (40 mg) of frusemide. The concentrations from the smaller dose are always exactly 1/3 of those seen at the same time with the larger dose. In contrast the maximum effect of the smaller dose is nearly as big as the maximum effect of the larger dose. This is because the peak concentration (around 2.5 mg/L) can achieve nearly 80% of Emax.

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## Frusemide Response



40 mg x 3  
 »  $AUC_e = 600 \text{ mmol Na}^+ / 12h$   
 120 mg x 1  
 »  $AUC_e = 400 \text{ mmol Na}^+ / 12h$

**Response is increased 50% using 40 mg x 3**

The cumulative sodium excretion can be calculated from the area under time versus sodium excretion curve (AUCe). The AUCe over a 12 hour interval has been calculated following the same total dose given either as a single dose of 120 mg or 3 doses of 40 mg given every 4 hours. The cumulative response is predicted by the AUCe. Giving smaller doses more frequently can increase the overall response by 50%. Note that exposure measured by cumulative dose or by cumulative AUC (frusemide concentrations) is the same for both methods of dosing.

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## Schedule Dependence

- Response is NOT proportional to cumulative diuretic dose or AUC
- Response IS proportional to cumulative diuretic effect or AUC<sub>e</sub>
- Phenomenon is known as
  - » “Schedule Dependence”
  - » i.e. same dose but different response depending on dosing schedule

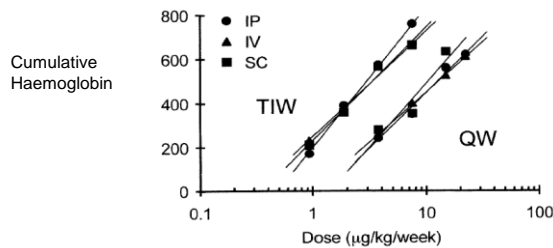
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Schedule dependence can be identified by a response that is not proportional to the cumulative dose (or AUC). However, the response is proportional to the cumulative effect (AUC<sub>e</sub>).

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## Darbepoetin Schedules

What does potency mean?



Egrie JC, Dwyer E, Browne JK, Hitz A, Lykos MA. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Experimental Hematology* 2003;31(4):290-9

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Darbepoetin is an erythropoietin like substance that increases red cells in the blood. The cumulative formation of haemoglobin was measured by calculating the area under the curve of the time course of haematocrit changes in mice. The haematocrit is proportional to the amount of red cells and haemoglobin in the blood. The AUC of the haematocrit can be considered a marker of the cumulative response to darbepoetin. The dose response relationship for darbepoetin is shown for 3 routes of administration (intravenous, intraperitoneal and sub-cutaneous). The dose-response curve is essentially independent of the route. However, the curve is shifted to the right when the same total dose is given by dividing it up and giving the dose three times a week (TIW) when compared to a single dose given once a week (QW). The ‘potency’ of darbepoetin is strongly influenced by the dosing schedule – a clear example of schedule dependence. The term ‘potency’ when applied to darbepoetin doses is of limited value because it will depend on the dosing schedule (and the pharmacokinetics of darbepoetin).

<p>Slide 63</p>	<h2 style="text-align: center; color: red;">Anti-Cancer Agents</h2> <ul style="list-style-type: none"> <li>● Alkylating agents <ul style="list-style-type: none"> <li>» Irreversible binding to cell components</li> <li>» Schedule independent <ul style="list-style-type: none"> <li>– E.g. carboplatin</li> </ul> </li> </ul> </li> <li>● Anti-Metabolites <ul style="list-style-type: none"> <li>» Reversible effects on cell metabolism</li> <li>» Schedule dependent <ul style="list-style-type: none"> <li>– E.g. methotrexate</li> </ul> </li> </ul> </li> </ul> <p style="font-size: small; margin-top: 10px;">©2012 Holford, 2018, all rights reserved.</p>	<p>Some anti-cancer agents bind irreversibly to cell components to cause cancer cell death (e.g. carboplatin). It would be expected that the cumulative response would be predictable from the cumulative dose (or AUC) of the drug.</p> <p>Other anti-cancer agents have reversible actions on cell metabolism (e.g. methotrexate). The cumulative response from a intermittent large doses would be predicted to be less than smaller more frequent doses i.e. schedule dependence.</p>
<p>Slide 64</p>	<h2 style="text-align: center; color: red;">Anti-Cancer Agents</h2> <ul style="list-style-type: none"> <li>● Action <ul style="list-style-type: none"> <li>» Irreversible binding to cell structure</li> <li>» Competition for metabolites</li> </ul> </li> <li>● Effect <ul style="list-style-type: none"> <li>» Block of cell division/cell death</li> </ul> </li> <li>● Response <ul style="list-style-type: none"> <li>» Slowing or reversal of tumour growth</li> </ul> </li> </ul> <p style="font-size: small; margin-top: 10px;">©2012 Holford, 2018, all rights reserved.</p>	
<p>Slide 65</p>	<h2 style="text-align: center; color: red;">Anti-Cancer Agents</h2> <ul style="list-style-type: none"> <li>● Schedule Dependence is common</li> <li>● Large intermittent doses are often more toxic and less effective than smaller repeated doses</li> <li>● Note: AUC may be used to guide individual treatment <ul style="list-style-type: none"> <li>» Evans et al. 1998</li> </ul> </li> </ul> <p style="font-size: x-small; margin-top: 10px;">Evans W, Relling M, Rodman J, Crom W, Boyett J, Pui C. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. <i>New England Journal of Medicine</i> 1998;338:499-505.</p> <p style="font-size: x-small; margin-top: 5px;">©2012 Holford, 2018, all rights reserved.</p>	<p>An important study by Evans et al. (1998) reported a major benefit on 5 year survival when methotrexate doses were individualised using methotrexate plasma concentrations to achieve a target AUC.</p>

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The way to go!