

<p>Slide 1</p>	<p style="text-align: center;"><b>Pharmacodynamics</b></p> <p style="text-align: center;"><b>Delayed and Cumulative Effects</b></p> <p style="text-align: center;">Nick Holford Dept Pharmacology &amp; Clinical Pharmacology University of Auckland, New Zealand</p>	<p>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.</p> <p>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.</p>
<p>Slide 2</p>	<p style="text-align: center;"><b>Pharmacodynamics</b></p> <p style="text-align: center;"><b>Delayed Drug Effects</b></p> <p style="text-align: center;"><small>©NHG Holford, 2012. 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 3</p>	<p style="text-align: center;"><b>Objectives</b></p> <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 style="text-align: center;"><small>©NHG Holford, 2012. all rights reserved.</small></p>	

<p>Slide 4</p>	<h2 style="text-align: center; color: red;">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>● Binding to Drug Receptor <ul style="list-style-type: none"> <li>» ligand-kinetics</li> </ul> </li> <li>● Physiological Intermediate <ul style="list-style-type: none"> <li>» physio-kinetics</li> </ul> </li> </ul> <p style="font-size: small; margin-top: 10px;">©HMG Healthcare 2012. all rights reserved.</p>	<p>Delayed drug effects may be due to any of these mechanisms but usually one is dominant. It takes time for drug to distribute to the site of action and then bind to its receptor. After receptor binding it then takes time for the drug action to change physiological intermediate substances before the drug response is observed.</p> <p>While it is possible sometimes to distinguish all of these 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. Receptor binding delays are usually short but there some well understand examples (e.g. digoxin) where the delay can be measured in hours.</p>
<p>Slide 5</p>	<h2 style="text-align: center; color: red;">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 style="font-size: small; margin-top: 10px;">©HMG Healthcare 2012. all rights reserved.</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.</p> <p>The first step is for a drug to have it's action at a receptor. This is at it's site of action and reflects the instantaneous consequences of the drug at it's 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 and binding to the receptor take place before the drug action.</p> <p>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.</p> <p>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

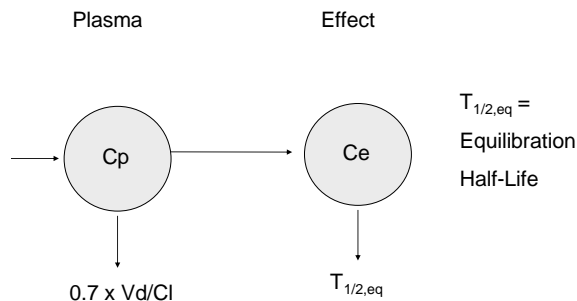
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Distributional delays are readily understood in terms of anatomy. It takes time for a drug molecule to get from the blood to a target tissue because of delays in perfusion of tissues and diffusion across blood vessel walls and through extracellular 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 difficult (and often 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

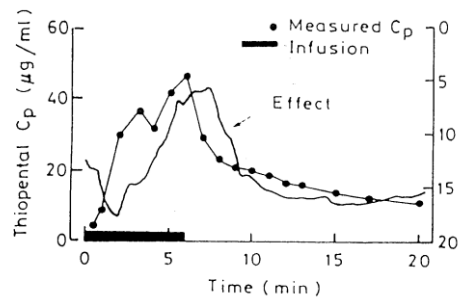
- Determined by
  - » Volume of 'effect compartment'
    - Organ size
    - Tissue binding
  - » Clearance of 'effect compartment'
    - Blood flow
    - Diffusion

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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

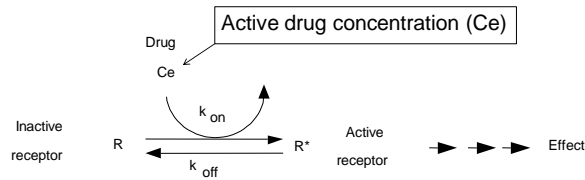
- Volume
  - » limited binding to GABA<sub>A</sub> receptors
- Clearance
  - » rapid perfusion of brain
- Equilibration Half-life = 1 min

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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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## Delayed Effect: At Receptor



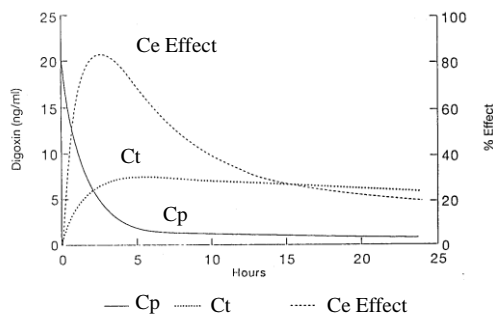
R is the concentration of unbound receptor.  
 $R^*$  is the concentration of receptor bound to drug  
 $k_{on}$  is a second order rate constant determining the rate of binding of drug and R  
 $k_{off}$  is a first order rate constant determining the dissociation rate of drug from  $R^*$

Note  $R^*$  not at equilibrium. Usually because  $k_{off}$  is small and thus rate of deactivation of active receptor complex (due to unbinding from receptor) is "slow"

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## Digoxin Time Course



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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 provides an empirical description of 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.

The delay in digoxin effect is better explained by slow binding to cardiac  $Na^+K^+ATPase$  because the distribution delay to cardiac muscles is rapid (minutes).

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## Digoxin

Volume

- » extensive binding in heart to  $Na^+K^+ATPase$

Clearance

- » rapid perfusion of heart

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

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Despite rapid perfusion of the heart the apparent equilibration half-life of digoxin is quite slow. This is because extensive binding of digoxin to  $Na^+K^+ATPase$  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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## Digoxin Effects in Humans

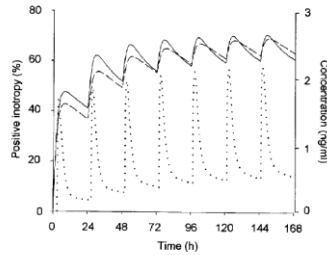


Fig. 6. Inotropic response to multiple dosing of digoxin (0.25 mg/day) simulated with the mechanistic (—) and empirical (---) model, respectively, assuming a three-exponential disposition function (4) and first-order absorption ( $k_a = 0.6 \text{ h}^{-1}$ ).

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Note that there is not a big difference in the prediction of digoxin time course based on an empirical effect compartment compared with a more mechanistic binding model. The mechanism based model was developed using in vitro measurements of digoxin binding to cardiac muscle.

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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## Delay Due to 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

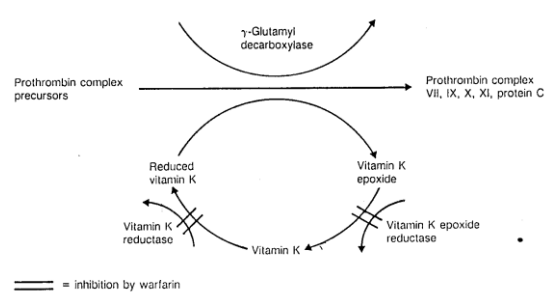
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Warfarin is an anticoagulant used to treat conditions such as deep vein thrombosis or to prevent blood clots and emboli associated with atrial fibrillation. It acts by inhibiting the recycling of Vitamin K in the liver. The effect of reduced Vitamin 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).

The target INR is 2.5 to reduce the risk of further thrombosis and embolism while reducing the risk of bleeding events.

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## The Vitamin K Cycle

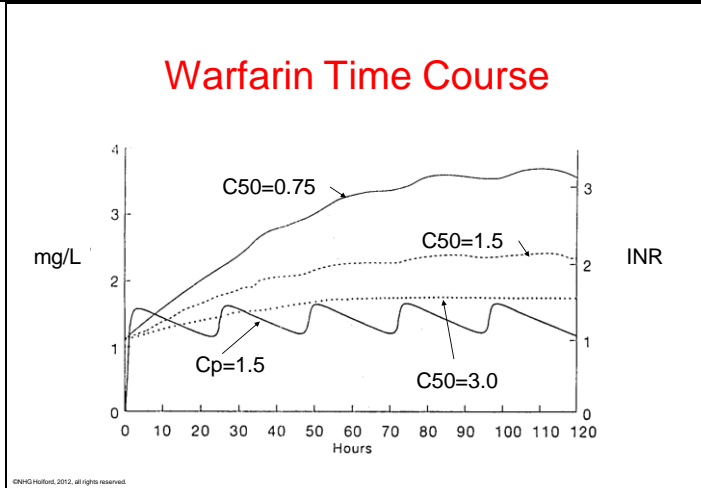


— = inhibition by warfarin

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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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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.

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### Warfarin Delayed Response

C50 for synthesis is 1.5 mg/L

- » Synthesis is reduced 50% at the C50
- » [prothrombin complex] is reduced 50%

Critical parameter is

- » Half-life of prothrombin complex
- » about 14 h

Takes 4 half-lives to reach SS

- » 2 to 3 days

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.

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### Warfarin Dosing

Target Conc is 1.5 mg/L (C50)

Loading Dose

- » LD= 1.5 mg/L x 10 L = 15 mg

Maintenance Dose

- » MD= 1.5 mg/L x 3 L/d = 5 mg/day

The target concentration for warfarin is the same as its 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>Slide 20</p>	<h2 style="text-align: center;">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>©2012 Pearson Education, Inc. 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 21</p>	<h2 style="text-align: center;">Physiological Intermediate Examples</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>©2012 Pearson Education, Inc. 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 might 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 22</p>	<h2 style="text-align: center;">Pharmacodynamics</h2> <h3 style="text-align: center;">Cumulative Drug Responses</h3> <p><small>©2012 Pearson Education, Inc. 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>



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## Objectives

- Understand the concepts of drug exposure
- Appreciate the difference between immediate action, delayed effect and cumulative response to a drug
- Describe the response to frusemide with different dosing schedules
- Appreciate the basis of schedule dependence of drug response e.g. in cancer chemotherapy

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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.

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## Acid Pump Inhibitors

- Gastric/Duodenal ulcers are dependent on acid secretion
- Acid Pump inhibitors block gastric acid secretion
  - » e.g. omeprazole
- Inhibition is due to irreversible binding

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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.

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## Acid Pump Inhibition

- Omeprazole is a prodrug
- Metabolised under acid conditions to a sulphenamide metabolite
- Sulphenamide forms a covalent disulphide bond with cysteine which is part of the acid pump
- Restoration of acid secretion depends on synthesis of new pump molecules

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## Acid Pump Inhibitors

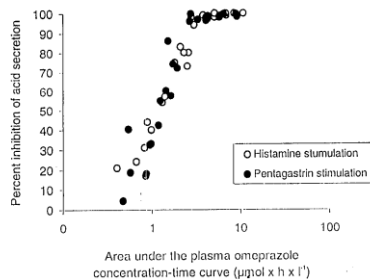
- Action
  - » inhibition of gastric acid pump
- Effect
  - » decreased acid secretion and increased pH
- Response
  - » ulcer healing

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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.

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## Acid Pump Inhibition and AUC



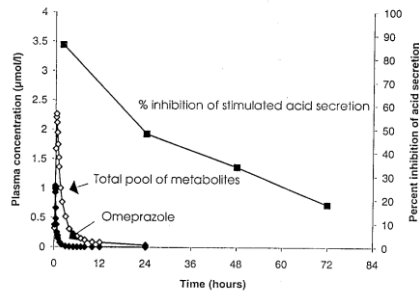
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The strong relationship between area under the curve (AUC) for omeprazole and inhibition of acid secretion is independent of the method used to stimulate acid production.

Complete inhibition of acid secretion occurs when omeprazole AUC is above 3 µmol/L x h.

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## Recovery of Acid Pump



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The exposure to omeprazole is very short (short half-life) after a single dose but the effect on the acid pump lasts a long time (24 h with more than 50% inhibition of acid secretion). This is because recovery depends on formation of new pump molecules.

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## Ulcer Healing Response

- Takes several weeks of acid inhibition to heal an ulcer
- Acid inhibition Effect is constant but the Response continues to develop (e.g. smaller size of ulcer)
- Response is proportional to AUC and independent of time course of omeprazole

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With usual doses of omeprazole the secretion of acid is almost 100% inhibited. The healing of the ulcer is then only determined by natural repair processes that are independent of exposure to omeprazole.

If acid inhibition is less than 100% (e.g. with lower doses of omeprazole) the time course of acid secretion is independent of the time course of omeprazole concentration. Acid secretion reflects the cumulative previous concentration exposure (AUC of omeprazole).

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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 Na<sup>+</sup> reabsorption
- Diuretic Effect
  - » Increased Na<sup>+</sup> and H<sub>2</sub>O excretion
- Diuretic Response
  - » Cumulative fluid loss

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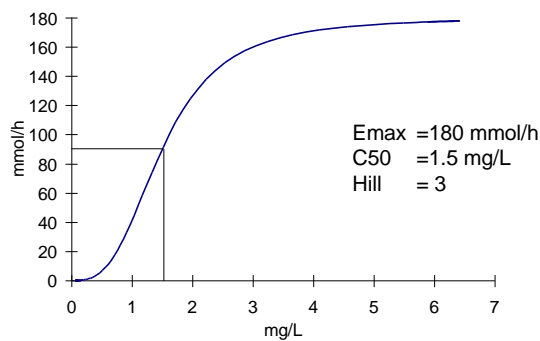
A diuretic such as frusemide acts on sodium transporters in the loop of Henle (proximal tubule). The sodium transporters normally re-absorb sodium from tubular fluid and pump it back into the tubular cells. Sodium acts as an osmotic diuretic so that more water is lost if more sodium is lost in the urine.

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

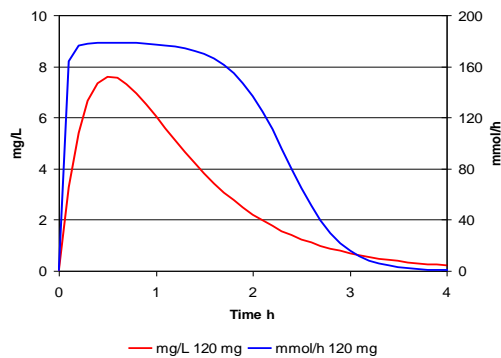


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Frusemide has a rapidly reversible action on the sodium transporter in the proximal tubule. The relationship between plasma concentration of frusemide and the excretion rate of sodium can be described by a sigmoid Emax model. The maximum excretion 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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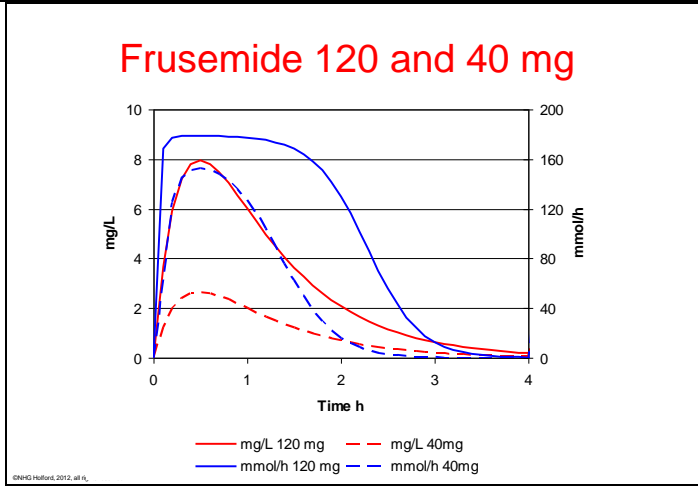
## Frusemide Diuretic Effect



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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.

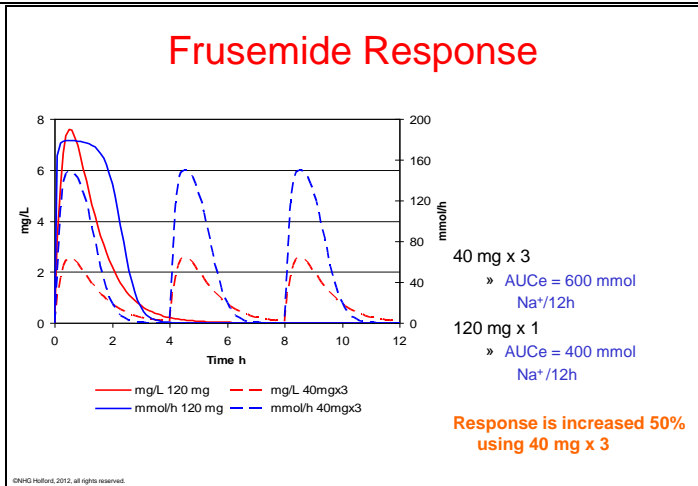
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Compare the concentrations and effects from a large dose (120 mg) and a small dose (40 mg) of frusemide. The concentrations from the smaller dose are always exactly 1/3 of those seen at the same time with the larger dose.

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  $E_{max}$ .

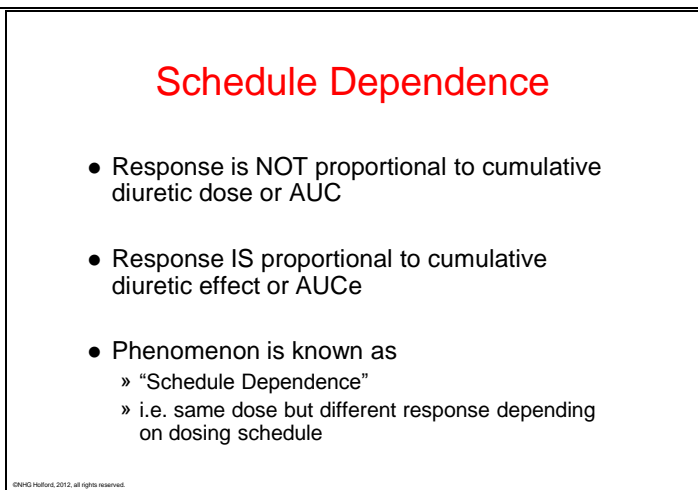
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The cumulative sodium excretion can be calculated from the area under time versus sodium excretion curve ( $AUC_e$ ). The  $AUC_e$  over a 12 hour interval has been calculated following the same total dose given either as a single dose of 120 mg or 3 doses of 40 mg given every 4 hours. The cumulative response is predicted by the  $AUC_e$ . 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.

Holford NHG, Atkinson AJ. Time course of drug response. In: Atkinson A, editor. Principles of Clinical Pharmacology. 2nd ed. San Diego: Academic Press; 2007. p. 301-11.

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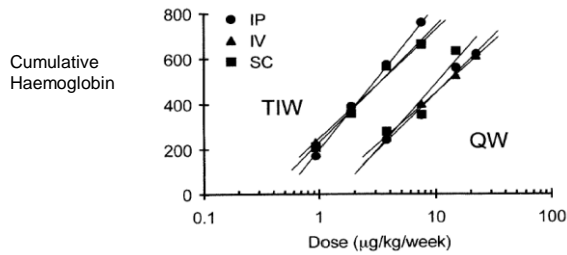


Schedule dependence can be identified by a response that is not proportional to the cumulative dose (or AUC). However, the response is proportional to the cumulative effect ( $AUC_e$ ).

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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).

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## Anti-Cancer Agents

- Alkylating agents
  - » Irreversible binding to cell components
  - » Schedule independent
    - E.g. carboplatin
- Anti-Metabolites
  - » Reversible effects on cell metabolism
  - » Schedule dependent
    - E.g. methotrexate

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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.

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.

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## Anti-Cancer Agents

- Action
  - » Irreversible binding to cell structure
  - » Competition for metabolites
- Effect
  - » Block of cell division/cell death
- Response
  - » Slowing or reversal of tumour growth

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## Anti-Cancer Agents

- Schedule Dependence is common
- Large intermittent doses are often more toxic and less effective than smaller repeated doses
- Note: AUC may be used to guide individual treatment
  - » Evans et al. 1998

Evans W, Relling M, Rodman J, Crom W, Boyett J, Pui C. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. New England Journal of Medicine 1998;338:499-505.

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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.

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