

<p>Slide 1</p>	<h2 style="text-align: center; color: red;">Pharmacodynamic Principles and the Time Course of Delayed Drug Effects</h2> <p style="text-align: center;">Nick Holford Dept Pharmacology & 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 delayed and cumulative drug effects.</p>
<p>Slide 2</p>	<h2 style="text-align: center; color: red;">Time Course Of Drug Effects</h2> <ol style="list-style-type: none"> 1. Immediate 2. Delayed 3. Cumulative <p style="font-size: small; text-align: left;">©NHG Holford, 2017, all rights reserved.</p>	<p>There are 3 ways to think of the time course of effects:</p> <ul style="list-style-type: none"> • 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
<p>Slide 3</p>	<h2 style="text-align: center; color: red;">Clinical Pharmacology</h2> <div style="text-align: center;"> <div style="display: flex; justify-content: space-around; margin-bottom: 10px;"> <div style="border: 1px solid black; padding: 2px 10px;">Pharmacokinetics</div> <div style="border: 1px solid black; padding: 2px 10px;">Pharmacodynamics</div> </div> <div style="display: flex; justify-content: space-around; margin-bottom: 10px;"> <div style="border: 1px solid black; border-radius: 50%; padding: 5px;">CL</div> <div style="border: 1px solid black; border-radius: 50%; padding: 5px;">V</div> <div style="border: 1px solid black; border-radius: 50%; padding: 5px;">Emax</div> <div style="border: 1px solid black; border-radius: 50%; padding: 5px;">C50</div> </div> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; padding: 5px;">Dose</div> <div style="border: 1px dashed black; padding: 5px;">Concentration</div> <div style="border: 1px solid black; padding: 5px;">Effect</div> </div> </div> <p style="font-size: x-small; text-align: left;">©NHG Holford, 2017, all rights reserved.</p>	<p>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.</p> <p>The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V).</p> <p>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).</p>

<p>Slide 4</p>	<p style="text-align: center;">Pharmacodynamics</p> <p style="text-align: center;">Delayed Drug Effects</p> <p><small>©NHG Hobbes, 2017, 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"> • Distribution to the receptor site • Binding to and unbinding from receptors • Turnover of a physiological mediator of the effect
<p>Slide 5</p>	<p style="text-align: center;">Objectives</p> <ul style="list-style-type: none"> • Describe the difference between pharmacokinetic and physiokinetic models for delayed drug response • Be able to describe the reasons for delayed response to thiopentone, digoxin and warfarin • Understand why drug responses can be markedly delayed • Appreciate when cumulative responses are important for clinical outcome • Learn the concept of schedule dependence <p><small>©NHG Hobbes, 2017, all rights reserved.</small></p>	
<p>Slide 6</p>	<p style="text-align: center;">Delayed Drug Effects</p> <ul style="list-style-type: none"> • Distribution to Effect Site <ul style="list-style-type: none"> » pharmaco-kinetics • Binding to Receptor <ul style="list-style-type: none"> » receptor-kinetics • Physiological Intermediate <ul style="list-style-type: none"> » physio-kinetics <p><small>©NHG Hobbes, 2017, 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. After reaching the receptor the process of binding to the receptor may be slow and contribute to delay in response. It then takes time for the drug action to change physiological intermediate substances before the drug response is observed. While it is possible sometimes to distinguish all three 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>

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Distribution to Effect Site

Effect site not in blood ('central compartment')

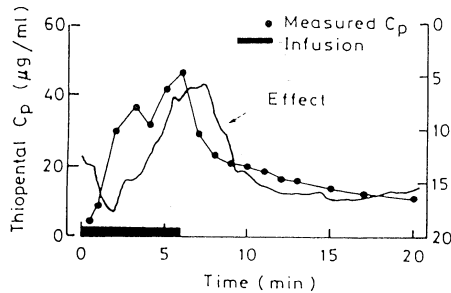
- » brain
 - thiopentone anaesthetic

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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 for the delivery of drug to the tissues.

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Thiopentone Time Course



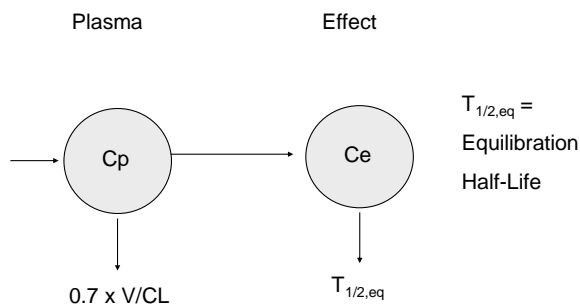
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Thiopentone is used for the rapid induction of anaesthesia. This figure shows the time course of measured thiopentone concentrations (black symbols) compared with the effect of thiopentone on the EEG. Thiopentone slows the frequency of EEG electrical 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.

Stanski DR, Maitre PO. Population pharmacokinetics and pharmacodynamics of thiopental: the effect of age revisited. *Anesthesiology*. 1990; 72(3):412-22.

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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

- Volume
- » limited binding to GABA_A 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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Binding to Receptor

Drug reaches effect compartment then binds to receptor

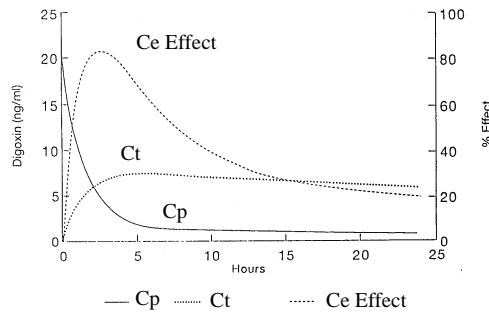
- » heart
 - digoxin slows AV conduction and increases cardiac contractility

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After distribution to the site of action a drug binds to its receptor. This process is usually quite rapid and does not contribute in a noticeable way to the delayed drug effect. However, some drugs dissociate slowly from their receptor and this can be the main factor determining the delay in drug effect. Very potent drugs typically dissociate slowly and examples include digoxin (effects on heart) and ergotamine (effects on uterus and blood vessels).

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Digoxin Time Course



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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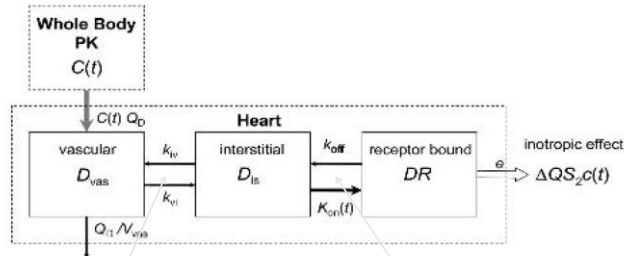
Digoxin

- 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

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 as a consequence of its long dissociation half-life. The slow dissociation is part of the explanation of why digoxin is such a potent drug (works at nanomolar concentrations). Equilibrium receptor binding is determined by the ratio of the association half-life to the dissociation half-life. A long dissociation half-life means the concentration producing 50% of binding at equilibrium will be small and thus the potency of the drug will be high.

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Two Part Mechanistic Model



Distribution

Receptor Binding

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

A mechanistic model incorporated both a distribution delay from the blood to the heart interstitial tissues (based on a PBPK model) and subsequent slow binding to the receptor (NaK-ATPase) for digoxin. The receptor occupancy was used to predict the inotropic effect.

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

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Physiological Intermediate

Drug Action

- » inhibition of Vit K recycling

Rapid Effect

- » decreased synthesis of clotting factors

Delayed Response

- » prolonged coagulation time (INR)

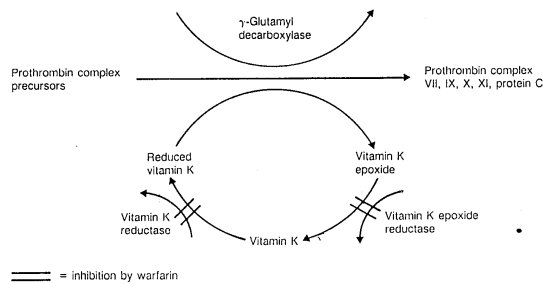
INR=International Normalised Ratio

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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

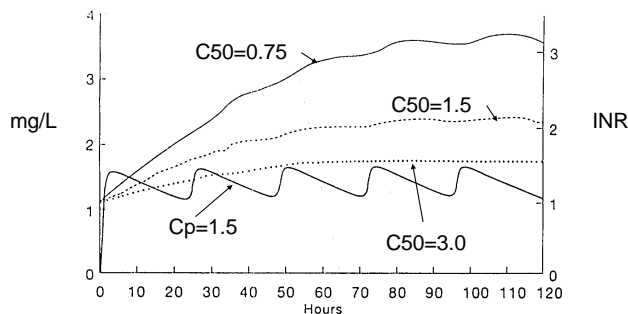


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Vitamin K is an essential co-factor for the synthesis of clotting factors. When the prothrombin complex precursors are activated by gamma-glutamyl decarboxylase Vitamin K is inactivated and forms Vitamin K epoxide. The action of warfarin is rapid. 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



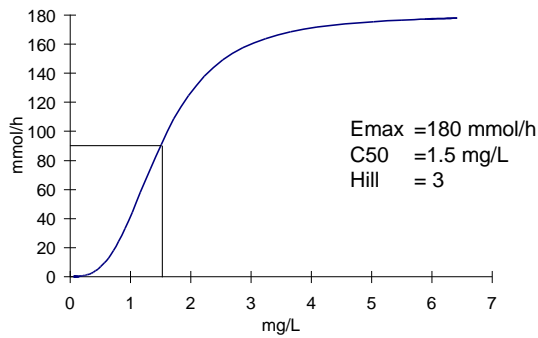
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The time course of change in prothrombin complex is determined by the half-life of the proteins e.g. Factor VII, which are involved in blood coagulation. The slow elimination of the prothrombin complex clotting factors eventually leads to a new steady 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 19</p>	<h2 style="text-align: center;">Warfarin Delayed Response</h2> <p>C50 for synthesis is 1.5 mg/L</p> <ul style="list-style-type: none"> » Synthesis is reduced 50% at the C50 » [prothrombin complex] is reduced 50% <p>Critical parameter is</p> <ul style="list-style-type: none"> » Half-life of prothrombin complex » about 14 h <p>Takes 4 half-lives to reach SS</p> <ul style="list-style-type: none"> » 2 to 3 days <p><small>©2012 Hubbel, 2017, 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>Many drugs have delayed effects due to physiological turnover e.g. the effect of ACE inhibitors (e.g. enalapril) have a slow effect on blood pressure related to loss of sodium and decrease in plasma volume. Sodium turnover takes about a week to reach a new steady state.</p>
<p>Slide 20</p>	<h2 style="text-align: center;">Pharmacodynamics</h2> <h3 style="text-align: center;">Cumulative Drug Responses</h3> <p><small>©2012 Hubbel, 2017, 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 21</p>	<h2 style="text-align: center;">Diuretics and Heart Failure</h2> <ul style="list-style-type: none"> ● Digoxin, ACE inhibitors, beta blockers <ul style="list-style-type: none"> » Used to improve survival ● Diuretics provide relief of symptoms <ul style="list-style-type: none"> » Mainly produced by excess fluid <ul style="list-style-type: none"> – breathlessness, ankle swelling, (dropsy) » Benefit is related to net reduction in fluid <p><small>©2012 Hubbel, 2017, all rights reserved.</small></p>	<p>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.</p> <p>Diuretics are commonly used to make the kidneys retain less fluid and thus encourage a loss of fluid.</p>

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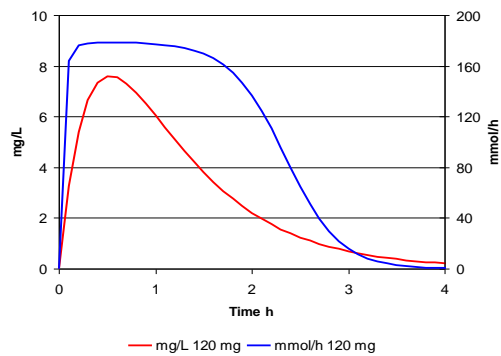
Frusemide Diuretic Effect



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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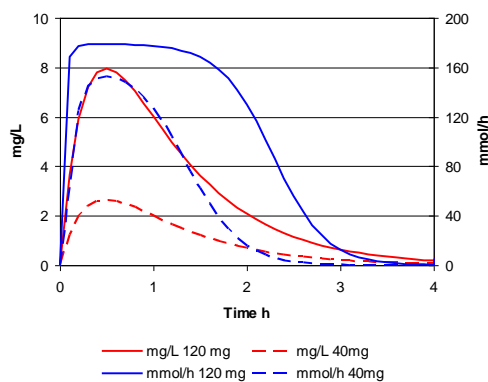
Frusemide Diuretic Effect



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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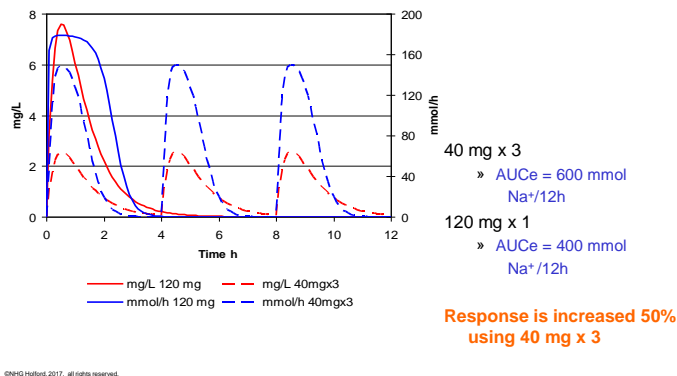
Frusemide 120 and 40 mg



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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Schedule Dependence



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.

The total loss of sodium and water (reflected in AUCe) and the effect on oedema in congestive heart failure depends on the dosing schedule not just the total dose. This is the phenomenon of schedule dependence. It is commonly seen with drugs whose outcome depends on the cumulative response to a drug effect which approaches its maximum after each dose.

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Irreversible Anti-Cancer Agents

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

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Drugs which bind irreversibly do not show schedule dependence. Many anti-cancer agents are in this category e.g. cisplatin, cyclophosphamide, busulfan.

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Dose Individualization

- Busulfan is used to ablate the bone marrow before bone marrow transplant
- Response is due to cumulative exposure (AUC)
- Plasma concentrations used to guide individual treatment

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Area under the concentration time curve (AUC) of the anti-cancer drug reflects the individual exposure. Measuring concentrations of busulfan after the first dose is very commonly used to adjust subsequent doses.

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The way to go!