

Slide
1

Pharmacodynamics

Delayed Drug Effects

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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.

Slide
2

Objectives

- Distinguish drug action, effect and response
- Describe the difference between pharmacokinetic and physiokinetic models for delayed drug response
- Be able to describe the reasons for delayed response to thiopentone and warfarin
- Understand why drug responses can be markedly delayed and appear to have little relationship to elimination half-life

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Slide
3

Delayed Drug Effects

- Distribution to Effect Site
 - » pharmaco-kinetics
- Physiological Intermediate
 - » physio-kinetics

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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.

Slide
4

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 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.

Slide
5

Distribution to Effect Site

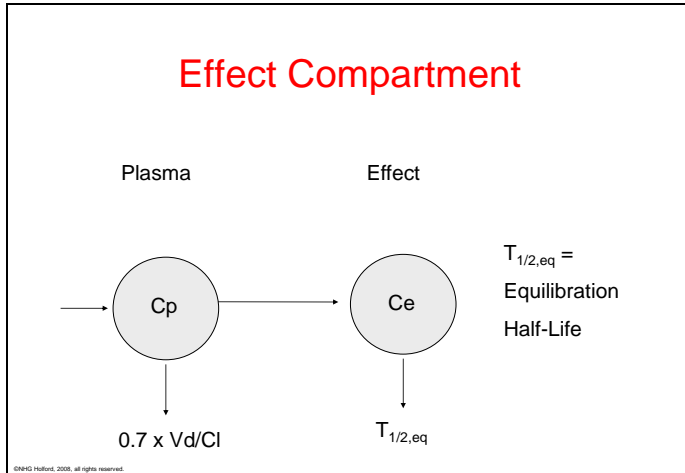
Effect site not in 'central compartment'

- » heart
 - digoxin increases contractility
- » 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.

Slide
6



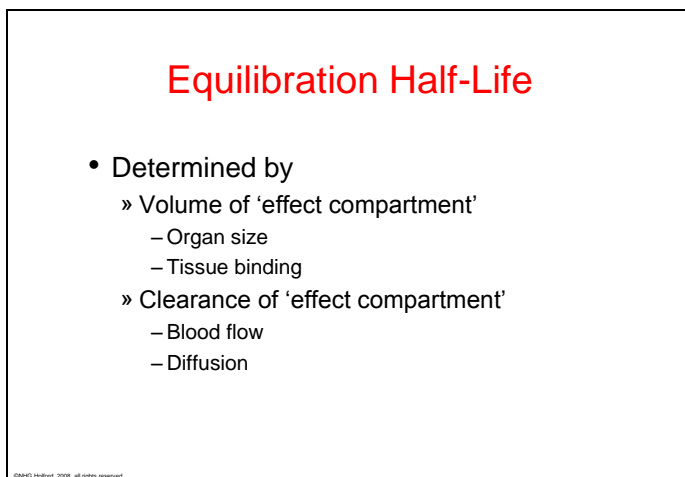
Because it is usually difficult or impossible to measure drug concentration at the site of action the time course of distribution can be described empirically by proposing an effect compartment. The time course of observed drug effect is then used to deduce the time course of drug concentration at the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

Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to D-tubocurarine. *Clin Pharmacol Ther.* 1979;25(3):358-71.

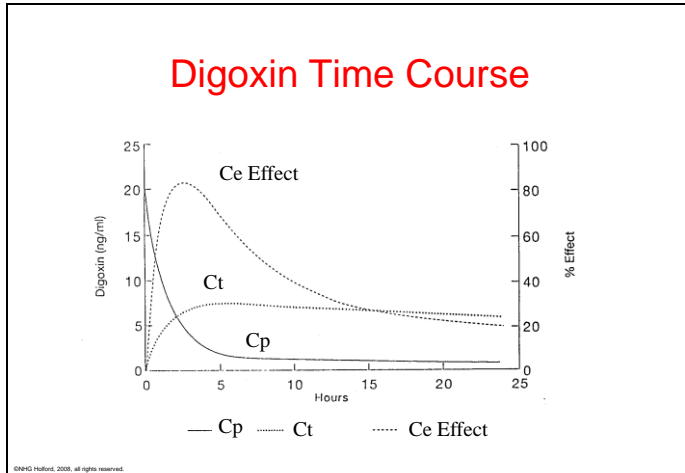
Slide
7



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

Dutta S, Matsumoto Y, Muramatsu A, Matsumoto M, Fukuoka M, Ebling WF. Steady-state propofol brain:plasma and brain:blood partition coefficients and the effect-site equilibration paradox. *Br J Anaesth.* 1998;81(3):422-4.

Slide
8



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 describes 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.

A more physiological explanation for delayed effects of digoxin comes from considering the slow equilibration of binding to NaKATPase.

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.

Slide
9

Digoxin

Volume

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

Clearance

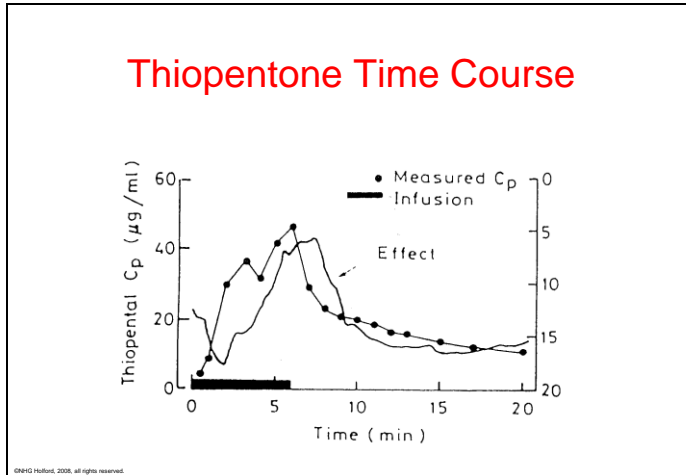
- » rapid perfusion of heart

Equilibration Half-life = 3 h

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Despite rapid perfusion of the heart the equilibration half-life of digoxin is quite slow. This may be because extensive binding of digoxin to $\text{Na}^+\text{K}^+\text{ATPase}$ in the heart makes the apparent volume of distribution large.

Slide
10



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.

Slide
11

Thiopentone

Volume

- » limited binding to GABA_A receptors

Clearance

- » rapid perfusion of brain

Equilibration Half-life = 1 min

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.

Slide
12

Physiological Intermediate

Drug Action

- » inhibition of Vit K recycling

Drug Effect

- » decreased synthesis of clotting factors

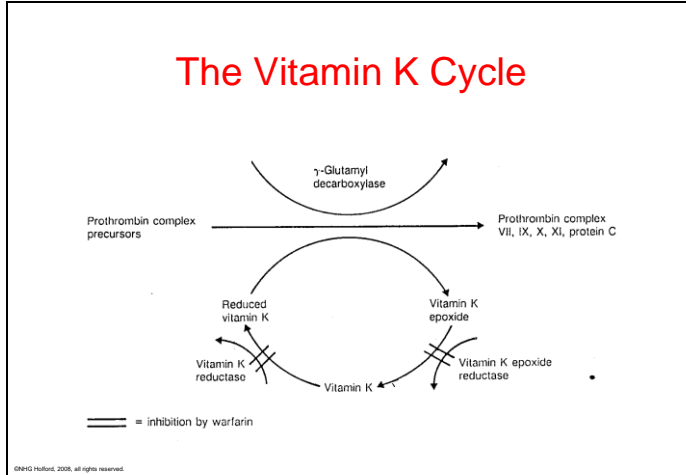
Drug Response

- » prolonged coagulation time (INR)

INR=International Normalised Ratio

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).

Slide 13

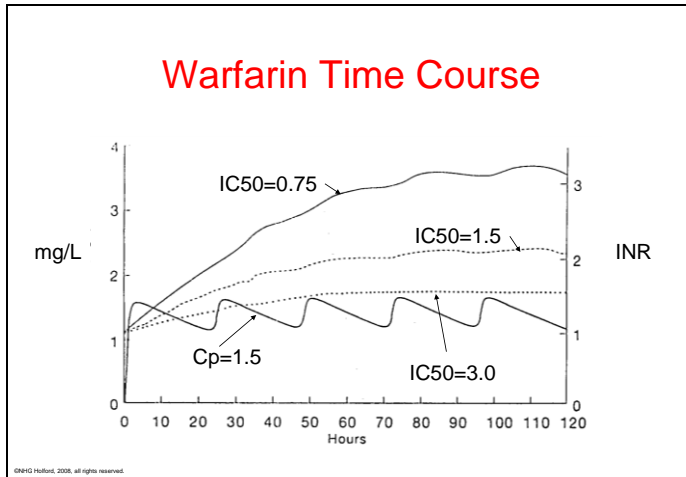


Vitamin K is an essential co-factor for the synthesis of clotting factors. When the prothrombin complex precursors are activated by gamma-glutamyl decarboxylase Vitamin K is inactivated and forms Vitamin K epoxide. The action of warfarin is rapid. Warfarin is absorbed quickly from the gut and reaches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

Sheiner LB. Computer-aided long-term anticoagulation therapy. *Comput Biomed Res.* 1969;2(6):507-18.

Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet.* 1986;11:483-504.

Slide 14



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 IC50 for warfarin inhibition of Vitamin K recycling. The IC50 is like the EC50 but refers to an inhibitory drug action.

3 INR profiles are shown with different IC50 values. The steady state INR is higher when the IC50 is low and the INR is lower when the IC50 is high. However, the time to reach a new steady state INR is not affected by the IC50 because it is only determined by the half-life of the clotting factors.

Slide
15

Warfarin Delayed Response

IC50 for synthesis is 1.5 mg/L

- » Synthesis is reduced 50% at the IC50
- » [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

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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.

Slide
16

Warfarin Dosing

Target Conc is 1.5 mg/L (IC50)

Loading Dose

- » LD= $1.5 \text{ mg/L} \times 10 \text{ L} = 15 \text{ mg}$

Maintenance Dose

- » MD= $1.5 \text{ mg/L} \times 3 \text{ L/d} = 5 \text{ mg/day}$

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The target concentration for warfarin is the same as its IC50. 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.

Slide
17

Warfarin Dose Adjustment

Measure INR daily

Wait at least 2 days before changing dose

Warfarin takes 7 days to reach a new steady state

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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.

Physiological Intermediate

Angiotensin Converting Enzyme Inhibitors (enalapril)

- » Delayed effect on blood pressure (1 week)
- » Half-life of Na⁺ is about 2 days

Anti-Depressants (amitriptyline)

- » Delayed effect on depression (2 weeks)
- » Unidentified mediator
- » A protein with a 4 day half-life?

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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.

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.

Jusko WJ, Ko HC. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. Clin Pharmacol Ther. 1994;56(4):406-19.