

More details at <http://www.health.auckland.ac.nz/courses/Humanbio355/>

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Time Course of Physiological and Pharmacological Effect

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Objectives

- Consider the importance of time when thinking about physiology and pharmacology
- Appreciate the close links between physiology and pharmacology in the time course of drug effects
- Recognize how disease progression may be altered by treatment

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Time Scale

- What determines the time course of physiological changes in blood pressure?
- What determines the time course of drug effects on blood pressure?
- What determines disease associated progression of blood pressure?

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Physiology and Blood Pressure

- Rapid (seconds)
 - » Autonomic nervous system
 - » Noradrenaline/Acetyl Choline
 - » Cardiac output
 - Rate and force
 - » Peripheral resistance
 - Arteriolar constriction/dilatation
- Slow (days)
 - » Kidney/Sodium
 - » Renin/Angiotensin/Aldosterone
 - » Blood Volume
- Very Slow (months)
 - » Heart and Blood Vessels
 - » Angiotensin?
 - » Remodelling

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Time Scale

- What determines the time course of physiological changes in blood pressure?
- What determines the time course of drug effects on blood pressure?
- What determines disease associated progression of blood pressure?

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Drugs and Blood Pressure

- Rapid (seconds)
 - » Autonomic nervous system
 - » Noradrenaline/Acetyl Choline
 - » Propranolol
 - » Prazosin
 - » Clonidine
- Slow (days)
 - » Kidney/Sodium
 - » Renin/Angiotensin/Aldosterone
 - » Enalapril
 - » Bendrofluazide
- Very Slow (months)
 - » Heart and Blood Vessels
 - » Simvastatin?
 - » Enalapril?

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Time Scale

- What determines the time course of physiological changes in blood pressure?
- What determines the time course of drug effects on blood pressure?
- What determines disease associated progression of blood pressure?

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Disease and Blood Pressure

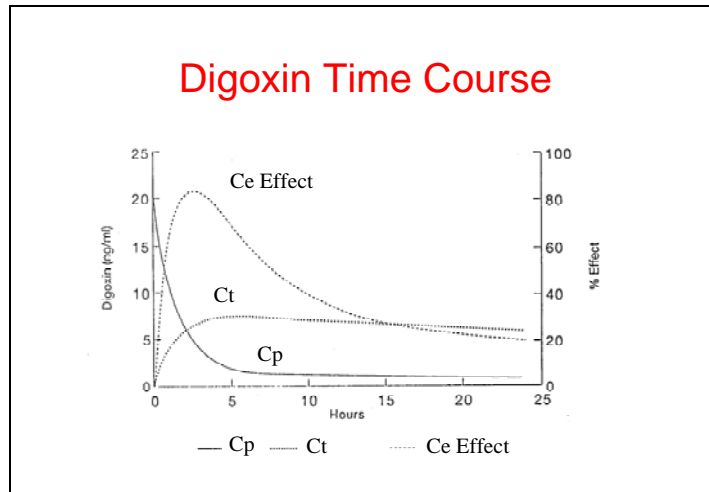
- Rapid (seconds)
 - » Autonomic nervous system
 - » Noradrenaline/Acetyl Choline
 - » Fainting (vaso-vagal syncope)
 - » Phaeochromocytoma
 - » Cardiac arrhythmia
 - » Haemorrhage
- Slow (days)
 - » Kidney/Sodium
 - » Renin/Angiotensin/Aldosterone
 - » Dehydration/Fluid Overload
 - » Renal hypertension
- Very Slow (months)
 - » Heart and Blood Vessels
 - » Myocardial Infarction?
 - » Atherosclerosis?
 - » Idiopathic hypertension?

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Delayed Drug Effects

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

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Digoxin Pharmacokinetics

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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Digoxin Physiokinetics

- Seconds
 - » Inhibition of NaK-ATPase
 - » Increased Na Clearance from cell
 - » Decreased Ca Clearance from cell
- Minutes/Hours
 - » Loss of intracellular Na
 - » Gain if intracellular Ca

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Physiological Intermediate

Drug Action

» inhibition of Vit K recycling

Drug Effect

» decreased synthesis of clotting factors

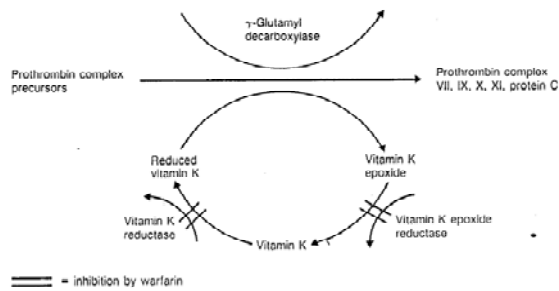
Drug Response

» prolonged coagulation time (INR)

INR=International Normalised Ratio

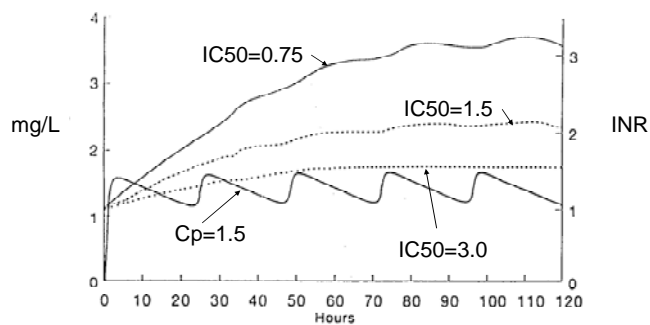
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The Vitamin K Cycle



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Warfarin Time Course



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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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Physiological Intermediate

Angiotensin Converting Enzyme Inhibitors
(enalapril)

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

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Physiological Intermediate

Anti-Depressants (amitriptyline)

- » Delayed effect on depression (2 weeks)
- » Unidentified mediator
- » A protein with a 4 day half-life?
- » Perhaps down regulation of pre-synaptic inhibition which damps acute changes in neurotransmitter action?