Basisbegrippen farmacologie

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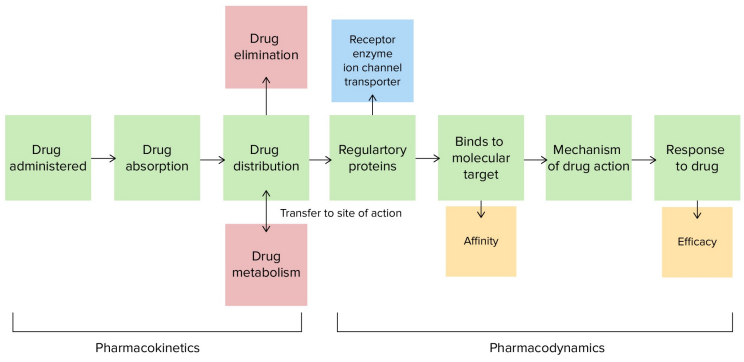
Lesinhoud



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1. Farmacokinetiek

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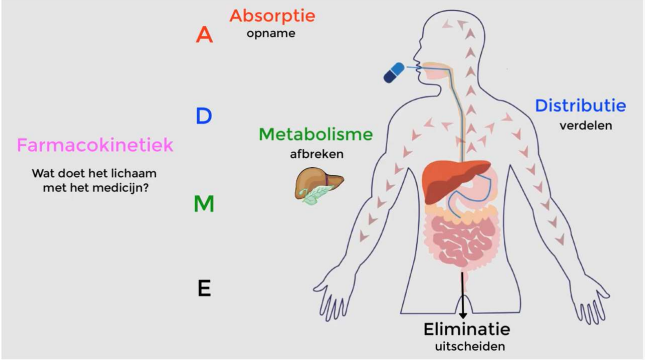
Farmacokinetiek



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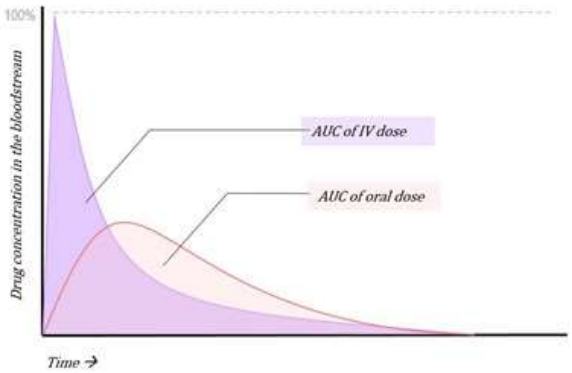
Farmacokinetiek



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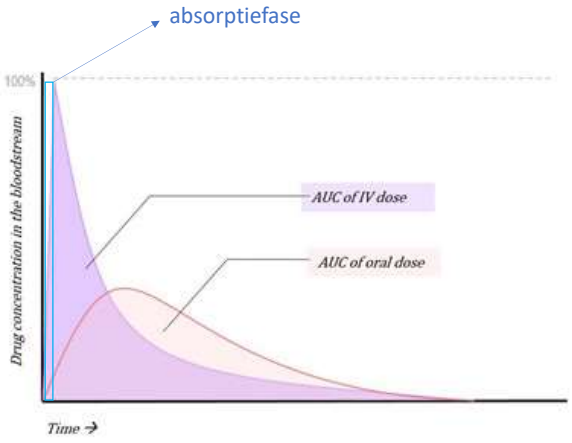
Farmacokinetiek



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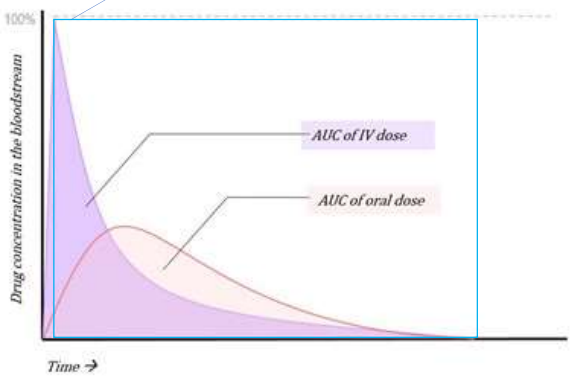
Farmacokinetiek

eliminatiefase: metabolisme, (redistributie) en excretie



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Farmacokinetiek

1. Absorptie

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Farmacokinetiek

1. Absorptie: intraveneuze toegangsweg (IV)
   → biologische beschikbaarheid = 100%

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Farmacokinetiek

1. Absorptie
2. Distributie

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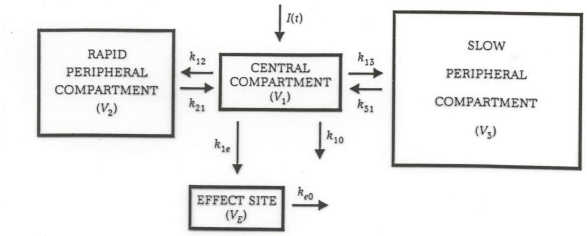
Farmacokinetiek

2. Distributie: verdeling over de weefsels



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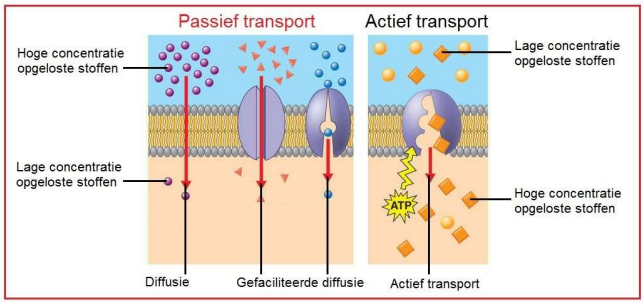
Farmacokinetiek

2. Distributie



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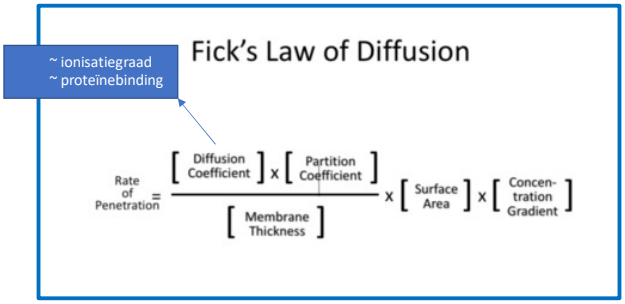
Farmacokinetiek

2. Distributie



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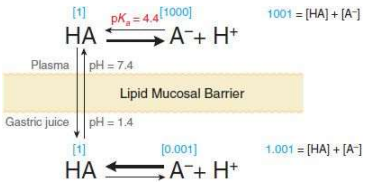
Farmacokinetiek

2. Distributie

Ionisatie:
* meeste farmaca zijn zwakke zuren/basen
* Henderson-Hasselbach: pH = pKa + log ([base]/[zuur])
→indien pH = pKa: [base] = [zuur]
→ion trapping (pH partition theory):



$$\mathrm{Log}\ \frac{\mathrm{base}(A^-)}{\mathrm{acid}(HA)} = \mathrm{pH} - \mathrm{pK_a}$$

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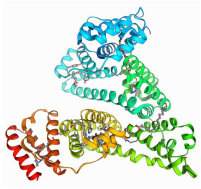
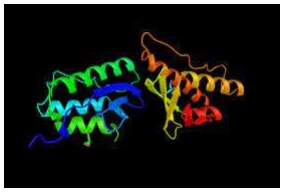
Farmacokinetiek

2. Distributie

Proteïnebinding:



albumine



α1-glycoproteïne

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Farmacokinetiek

2. Distributie

Distributievolume (V_d) = dosis / concentratie (L of L/kg LG)

V_d klein	V_d intermediair	V_d groot
sterke eiwitbinding/ionisatie/ weinig vetoplosbaar	lage proteïne-binding en slechte vetoplosbaarheid	weinig gebonden/lage ionisatie/sterk lipofiel; spec. bindingsplaatsen
enkel in plasma: V_d 60 mL/kg	in extracellulair water: V_d = 200 ml/kg	in total body water (ook intracellulair): V_d 600 mL/kg
warfarine, heparine, ICG	mannitol	EtOH

TABLE 3–2 Physical volumes (in L/kg body weight) of some body compartments into which drugs may be distributed.

Compartment and Volume	Examples of Drugs
Water	
Total body water (0.6 L/kg[1])	Small water-soluble molecules: eg, ethanol
Extracellular water (0.2 L/kg)	Larger water-soluble molecules: eg, gentamicin
Blood (0.08 L/kg); plasma (0.04 L/kg)	Strongly plasma protein-bound molecules and very large molecules: eg, heparin
Fat (0.2-0.35 L/kg)	Highly lipid-soluble molecules: eg, DDT
Bone (0.07 L/kg)	Certain ions: eg, lead, fluoride

[1]An average figure. Total body water in a young lean man might be 0.7 L/kg; in an obese woman, 0.5 L/kg.

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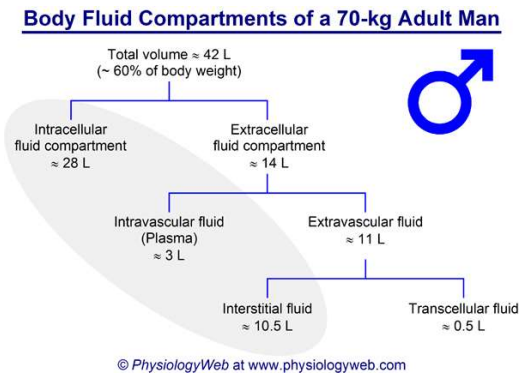
Farmacokinetiek

2. Distributie

Distributievolume (V_d)



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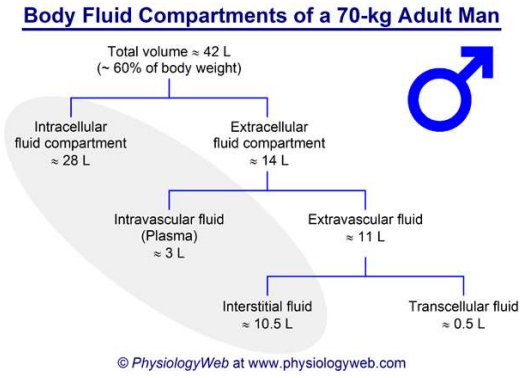
Farmacokinetiek

2. Distributie

Distributievolume (V_d)



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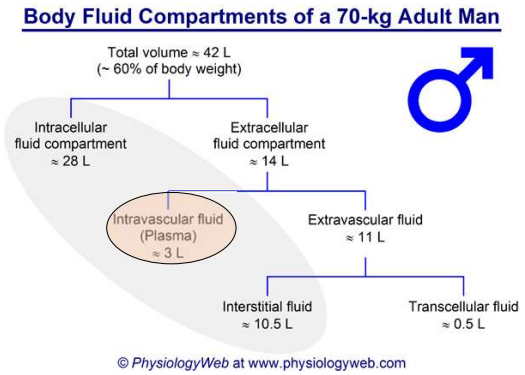
Farmacokinetiek

2. Distributie

Distributievolume (V_d)

$V_d \leq 3L$



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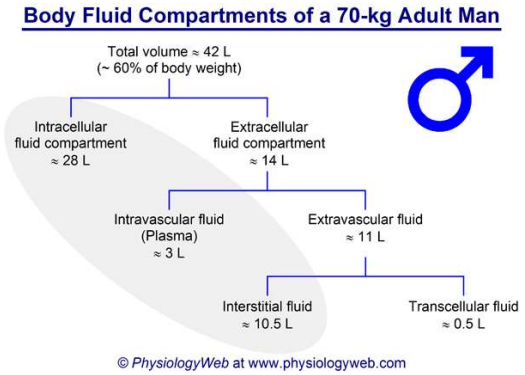
Farmacokinetiek

2. Distributie

Distributievolume (V_d)

$V_d \geq 42L$



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Farmacokinetiek

2. Distributie

Distributievolume (V_d)

$V_d \geq 42L$

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Farmacokinetiek

2. Distributie

Snelheid van distributie ~ bloedflow:

	% van lichaamsmassa	% van hartdebiet
Vaatrijk (hart, longen, lever, nieren, hersenen)	10	75
Spieren	50	19
Vetweefsel	20	5
Vaatarm (huid, been, …)	20	< 1

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Farmacokinetiek

1. Absorptie
2. Distributie
3. Metabolisme (biotransformatie)

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Farmacokinetiek

3. Metabolisme: doel = geneesmiddel wateroplosbaar te maken

fase	0	I	II	III
orgaan	**lever e.a.**	**lever e.a.**	**lever e.a.**	**bacteriën**
reacties		oxidatie; reductie; hydrolyse; dealkylering; deaminering	conjugatie: glucuronidering sulfatering glutathionconjug. glycineconjug. acetylering e.a.	deconjugatie: deglucuronidering desulfatering etc.
product	moedermolekuul	fase I metaboliet	conjugatie-metaboliet	moedermolekuul
enzym		cytochroom P450: CYP2C9; CYP2C8	glucuronyl-transferase etc.	ß-glucuronidase sulfatase etc.
reactiviteit	(meestal) actief	inactivatie (soms) activatie	(meestal) inactivatie	reactivatie
wateroplos baarheid	lipofiel	hydrofiel	meer hydrofiel	lipofiel
polariteit	apolair	polair	meer polair	apolair

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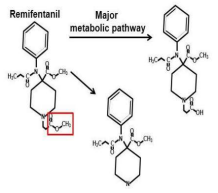
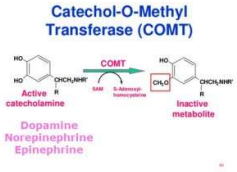
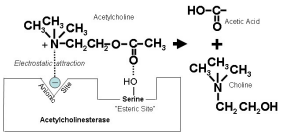
Farmacokinetiek

3. Metabolisme







CYP1	CYP1A	*CYP1A1, CYP1A2*	Drug and steroid (especially estrogen) metabolism, benzo(a)pyrene toxification
	CYP1B	*CYP1B1*	
	CYP1D	*CYP1D1P*	
CYP2	CYP2A	*CYP2A6, CYP2A7, CYP2A13, CYP2AB1P, CYP2AC1P*	Drug and steroid metabolism
	CYP2B	*CYP2B6, CYP2B7P*	
	CYP2C	*CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2C23P, CYP2C58P, CYP2C59P, CYP2C60P,*	
	CYP2D	*CYP2D6, CYP2D7, CYP2D8P*	
	CYP2E	*CYP2E1*	
	CYP2F	*CYP2F1, CYP2F2P*	
CYP3	CYP3A	*CYP3A4, CYP3A5, CYP3A7, CYP3AA1, CYP3A51P, CYP3A52P, CYP3A54P, CYP3A137P*	Drug and steroid (including testosterone) metabolism
CYP4	CYP4A	*CYP4A11, CYP4A22, CYP4A26P, CYP4A27P, CYP4A44P, CYP4B1*	Arachidonic acid or fatty acid metabolism
	CYP4F	*CYP4F2, CYP4F3, CYP4F8, CYP4F9P, CYP4F10P, CYP4F22, CYP4F23P, CYP4F24P, CYP4F11, CYP4F12, CYP4F35P*	
CYP5	CYP5A	*CYP5A1*	Thromboxane A2 synthase
CYP7	CYP7A	*CYP7A1*	Bile acid biosynthesis 7-alpha hydroxylase of steroid nucleus
	CYP7B	*CYP7B1*	
CYP8	CYP8A	*CYP8A1*	Varied (bile acid biosynthesis; prostacyclin synthase)
	CYP8B	*CYP8B1*	

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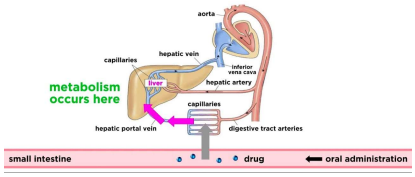
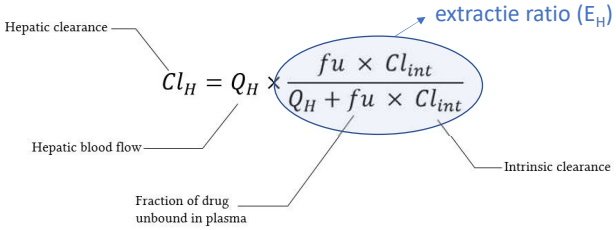
Farmacokinetiek



3. Metabolisme

Hepatische klaring:



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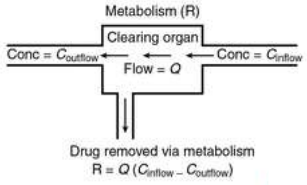
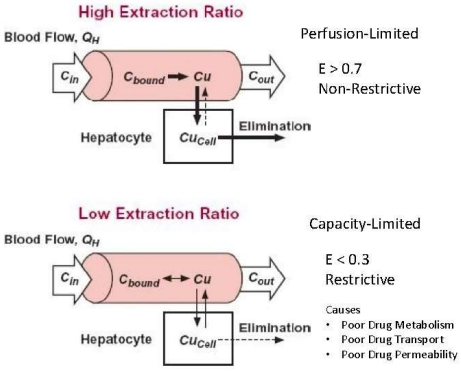
Farmacokinetiek

3. Metabolisme

Hepatische klaring:



$$ER = \frac{(C_{inflow} - C_{outflow})}{C_{inflow}} = \frac{Cl_{intrinsic}}{(Cl_{intrinsic} + Q_{hepatic})}$$



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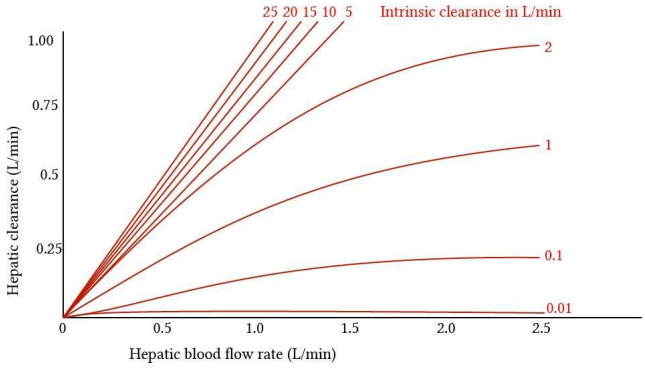
Farmacokinetiek

3. Metabolisme

Hepatische klaring:



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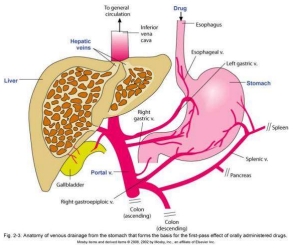
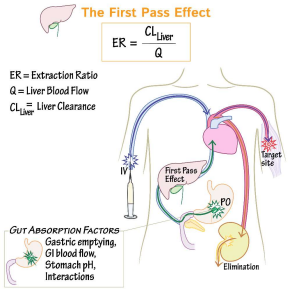
Farmacokinetiek

3. Metabolisme

Hepatische klaring:





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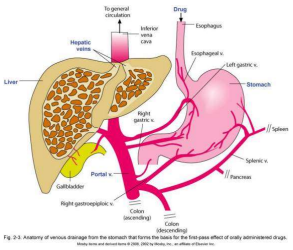
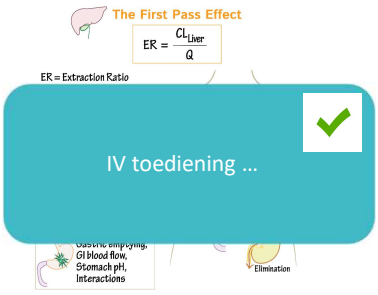
Farmacokinetiek

3. Metabolisme

Hepatische klaring:





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Farmacokinetiek

1. Absorptie
2. Distributie
3. Metabolisme
4. Excretie

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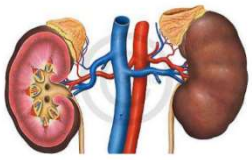
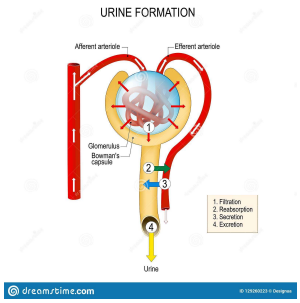
Farmacokinetiek

4. Excretie

Renale klaring:





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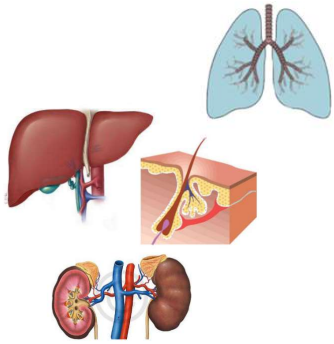
Farmacokinetiek

4. Excretie



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Farmacokinetiek

1. Absorptie
2. Distributie
3. Metabolisme
4. Excretie

} eliminatie

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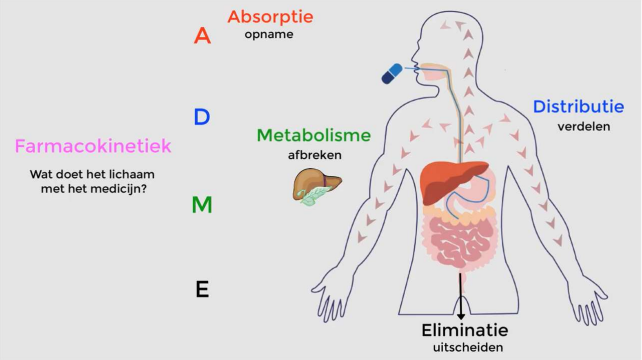
Farmacokinetiek



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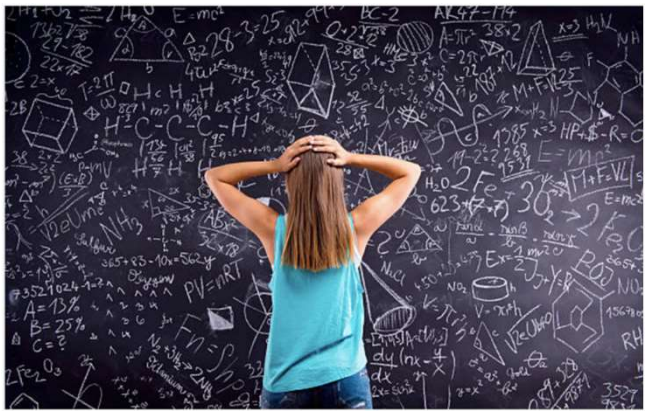
Farmacokinetiek: wiskunde



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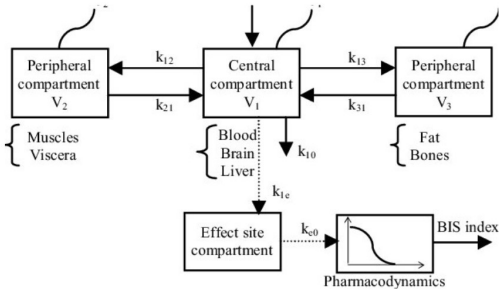
Farmacokinetiek: wiskunde



Figure

Caption

Figure 1. Pharmacokinetics-pharmacodynamic compartmental model with the effect site [5].

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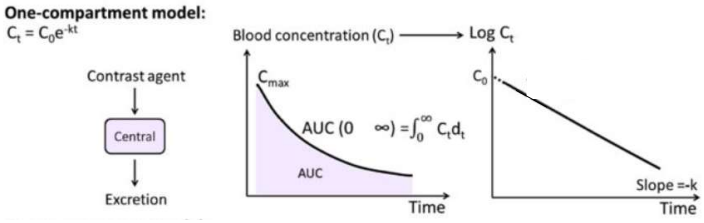
Farmacokinetiek: wiskunde



$dC/dt = - k.C^n$

dC/dt = snelheid waarmee concentratie (C) verandert

k = snelheidsconstante

n = 0 (0^{de} orde kinetiek) of n = 1 (1^{ste} orde kinetiek)

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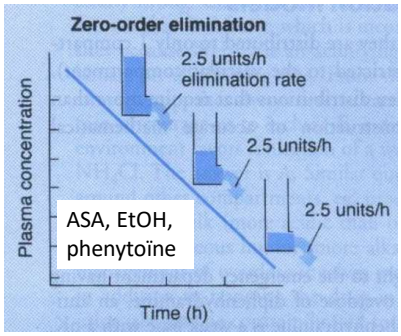
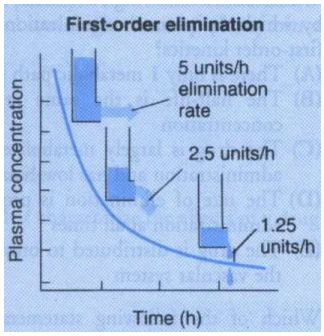
Farmacokinetiek: wiskunde





- **Michaelis-Menten elimination**

$$\text{Rate of elimination} = \frac{V_{max} X\ C}{K_m + C}$$

Km = Michaëlis-Menten cst: de concentratie substraat waarbij de reactie verloopt aan ½ max snelheid

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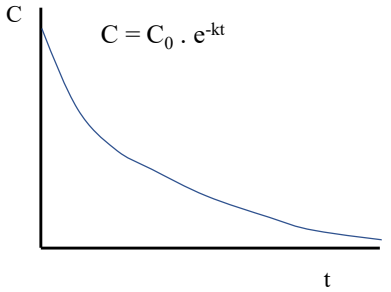
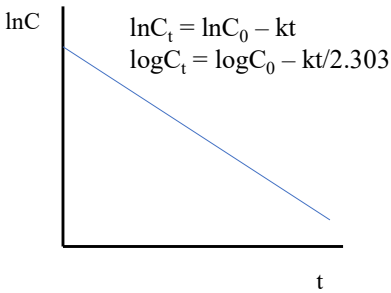
Farmacokinetiek: wiskunde

1ste orde kinetiek:





k = eerste orde eliminatieconstante die aangeeft met welke proportie concentratie daalt

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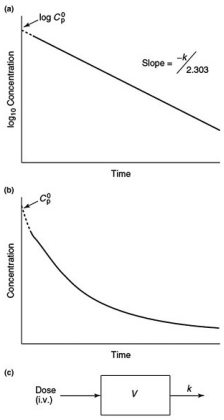
Farmacokinetiek: wiskunde



- Eliminatie snelheidsconstante, k_{eo}: fractie van GM dat wordt geëlimineerd uit het lichaam over een bepaalde tijdsperiode
- Beïnvloed door (distributie), metabolisme en excretie
- Meestal 1ste orde snelheidsconstante

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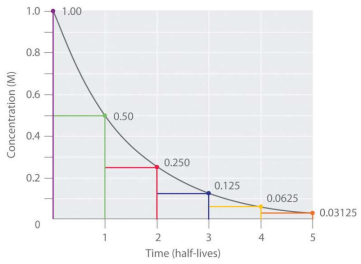
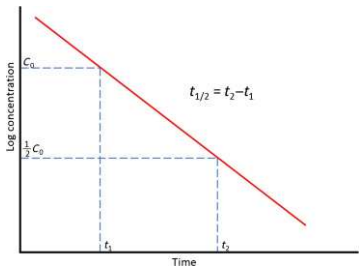
Farmacokinetiek: wiskunde

1ste orde kinetiek: halfwaardetijd:





$$t_{½,elim} = \frac{\ln(2)}{k} \approx \frac{0.693}{k}$$

$$k = \frac{\ln(2)}{t_{½,elim}} \approx \frac{0.693}{t_{½,elim}}$$

$T_{½} = 0.693 \times V_d / Cl$

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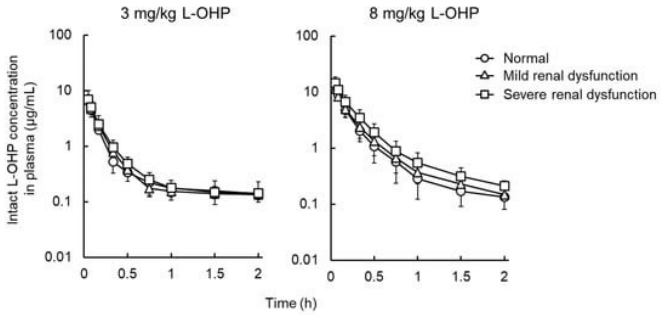
Farmacokinetiek: wiskunde

1ste orde kinetiek: renale klaring:



$$CL = \frac{F \cdot Dose}{AUC} = K_{10} \cdot Vd$$

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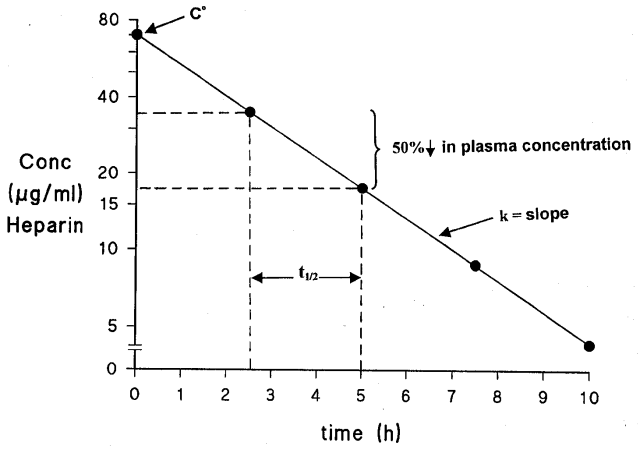
Farmacokinetiek: wiskunde

heparine



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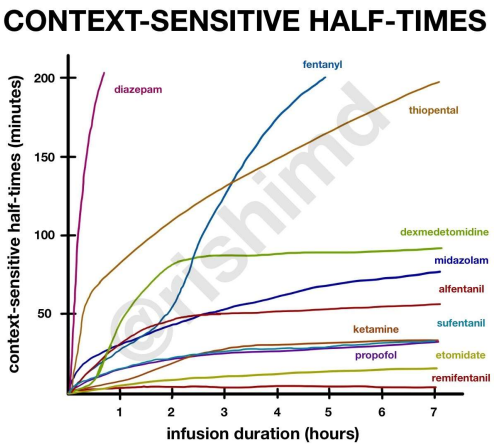
Farmacokinetiek: wiskunde



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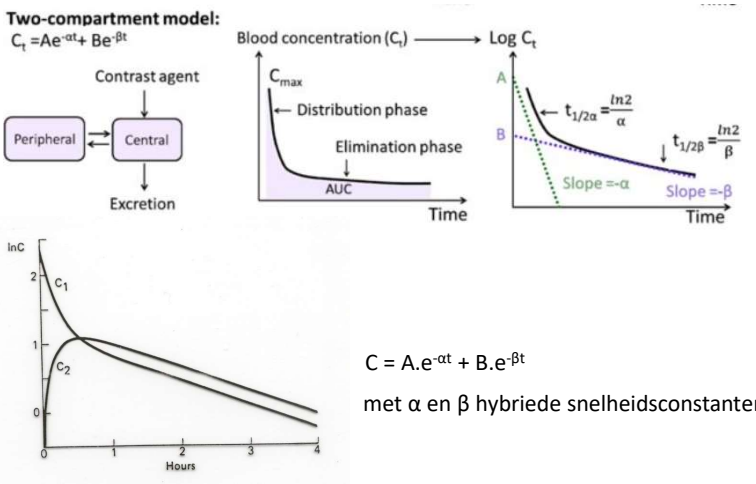
Farmacokinetiek: wiskunde



$C = A.e^{-\alpha t} + B.e^{-\beta t}$

met α en β hybriede snelheidsconstanten

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Farmacokinetiek: wiskunde

Drie compartimenteel model

$C = A.e^{-\alpha t} + B.e^{-\beta t} + C.e^{-Ct}$

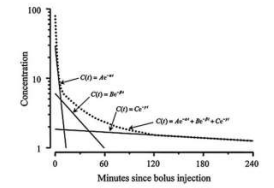
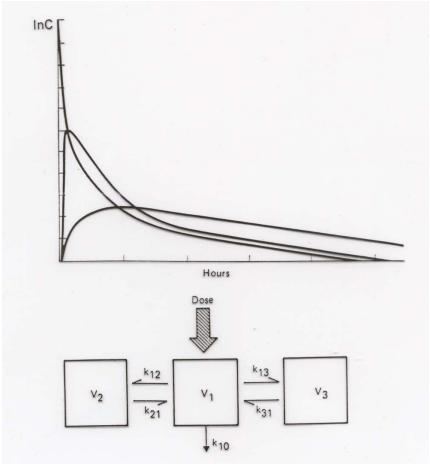


Fig 1 Plasma concentration vs time curve demonstrating tri-exponential decline after a bolus injection. In conventional pharmacokinetic terminology, these are phases A-C. The plasma concentration at time t(Ct) may be derived from $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where t is time since i.v. bolus. C, concentration after a bolus dose. A-C represent the phase coefficients which sum to the plasma concentration after an i.v. bolus. α, β, and γ represent phase rate constants. e, natural logarithm.



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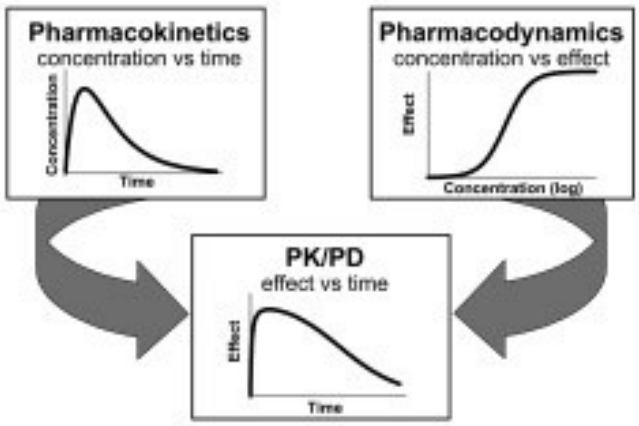
PK/PD



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PK/PD

- Studie populatie: jonge, gezonde, niet-obese ptn
- Meestal Δ < 25% tussen geschatte en gemeten concentratie
- Totaal lichaamsgewicht? Gecorrigeerd lichaamsgewicht?

=> vb. EEG monitor

PK model	Relevant groups
Marsh (adult)	Adults, elderly
Marsh (children)	Children
Schnider	Adults, obese, elderly
Kataria	Children
Kataria (no covariates)	Children
Cortinez	Adults, obese, elderly
Coppens	Children
Wietasch	Adults, elderly
Paedfusor	Children
Short	Children
Knibbe	Children, adults, elderly
Rigby-Jones	Young children, children
Rigby-Jones (multicenter)	Young children, children
Schuttler	Children, adults, elderly
ShangGuan	Children
VanKralingen (obese)	Obese
VanKralingen (obese and lean)	Obese, adults
Dyck	Adults, elderly
Tackley	Adults, elderly
White	Adults, elderly
Wang	Children, adults, elderly

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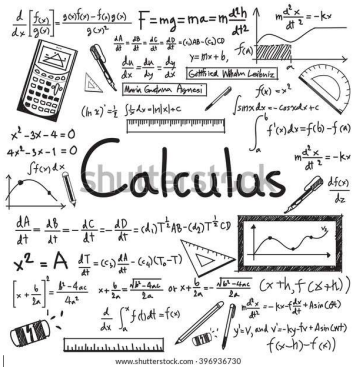
PK/PD



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PK/PD

V_d → loading dose

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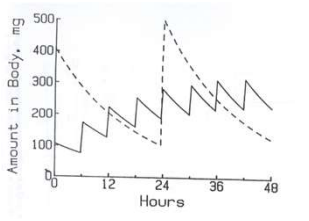
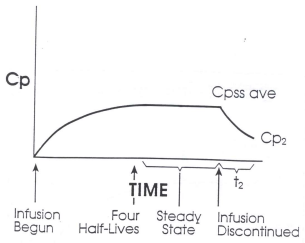
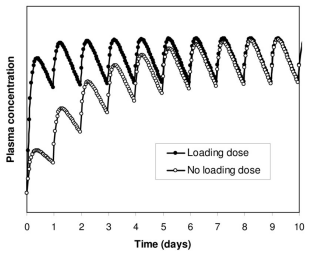
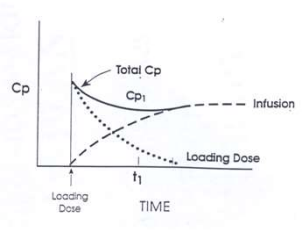
PK/PD









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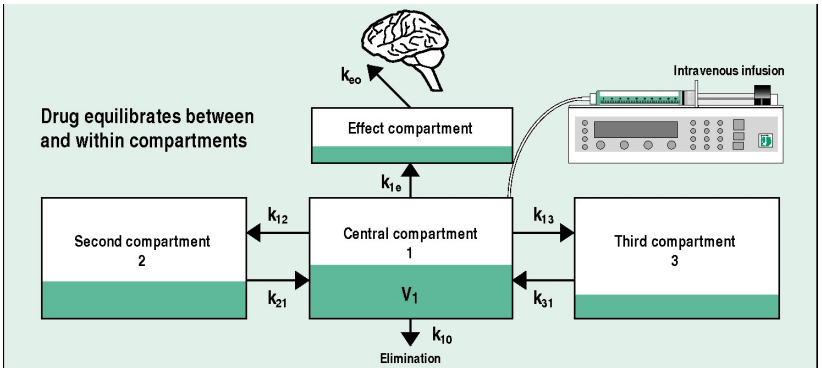
PK/PD

Effect site



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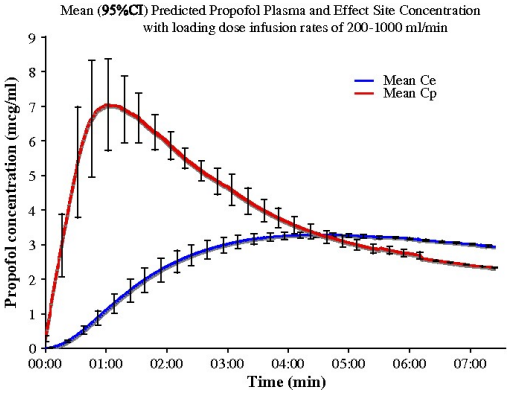
PK/PD

Hysteresis



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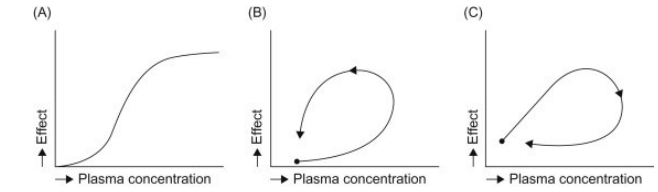
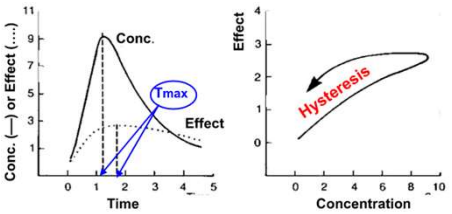
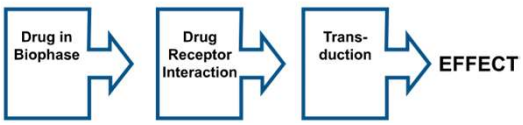
PK/PD

Hysteresis:







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2. Farmacodynamiek

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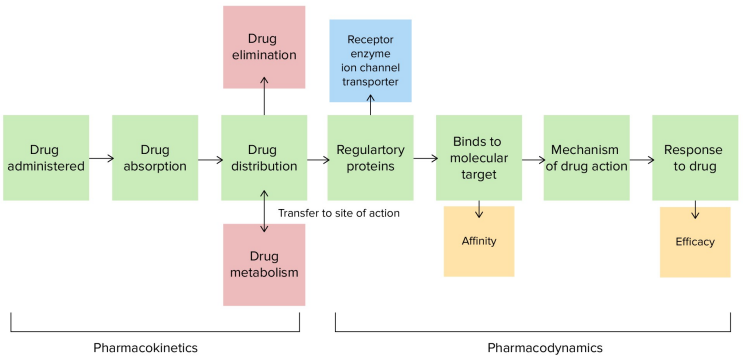
Farmacodynamiek



= wat doet het farmacon met het lichaam?

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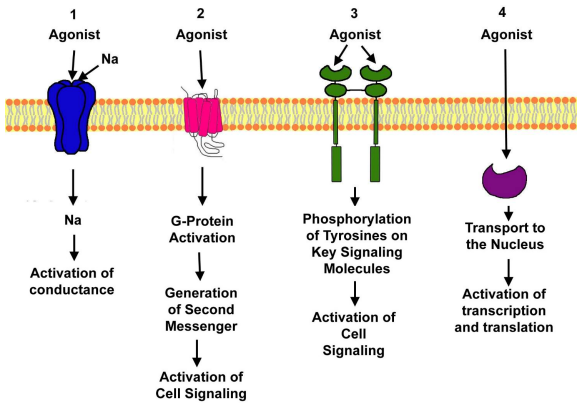
Farmacodynamiek



1) Ion Channels
   a) Ligand Gated
   b) Voltage gated
   c) Second Messenger Regulated
2) G-Protein Coupled Receptors
3) Receptor Tyrosine Kinase
4) Intracellular Hormone Receptors

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Farmacodynamiek

Membraanverankerde receptoren:

- Catecholamine receptor: a, b1, b2, dopamine…
- Serotonine receptor
- Histamine receptor: H1, H2
- Acetylcholine receptor: muscarine en nicotine
- GABA receptor
- N-methyl-D-Aspartaat (NMDA) receptor
- Opiaatreceptor: µ1, µ2, k, s, d…

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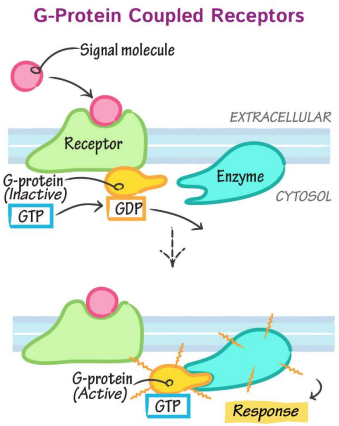
Farmacodynamiek



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Farmacodynamiek

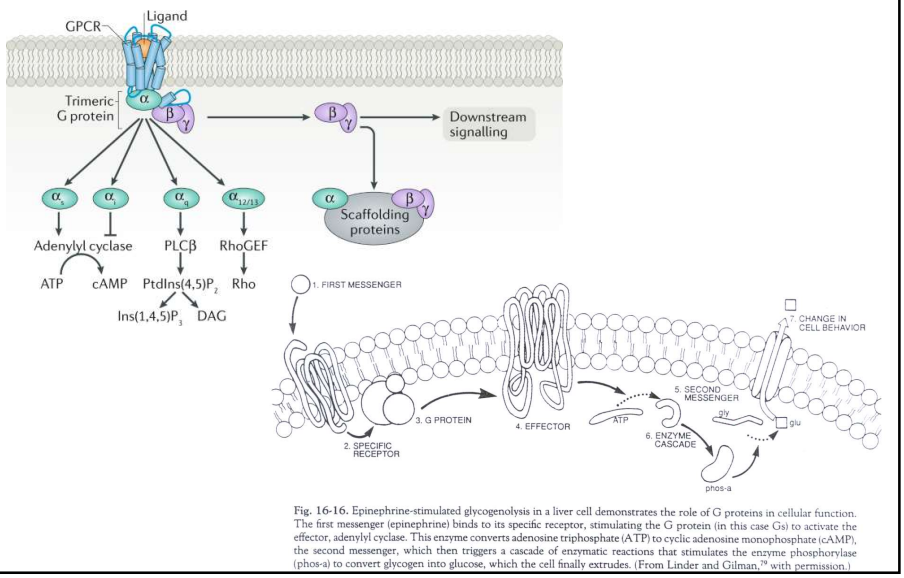

Fig. 16-16. Epinephrine-stimulated glycogenolysis in a liver cell demonstrates the role of G proteins in cellular function. The first messenger (epinephrine) binds to its specific receptor, stimulating the G protein (in this case Gs) to activate the effector, adenylyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), the second messenger, which then triggers a cascade of enzymatic reactions that stimulates the enzyme phosphorylase (phos-a) to convert glycogen into glucose, which the cell finally extrudes. (From Linder and Gilman,[79] with permission.)

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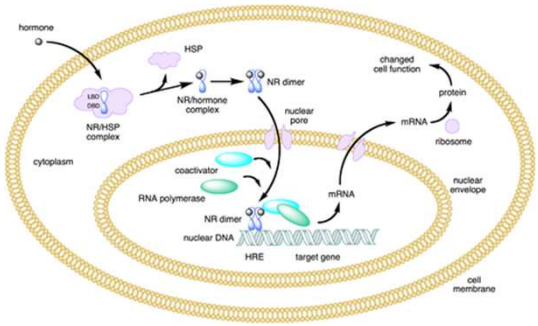
Farmacodynamiek

Cytoplasmatische/nucleaire receptoren:



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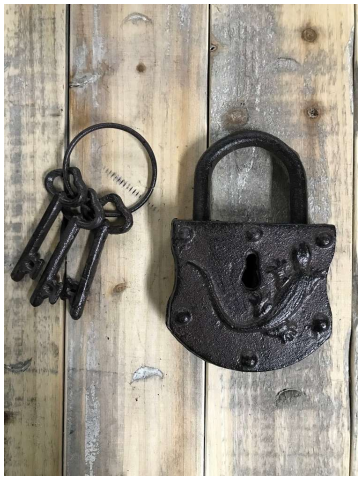
Farmacodynamiek

Agonist-receptor: sleutel-slot principe



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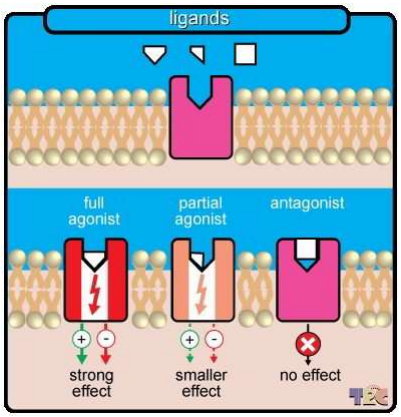
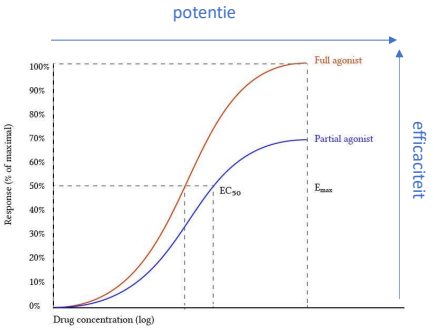
Farmacodynamiek

Intrinsieke activiteit van geneesmiddel:





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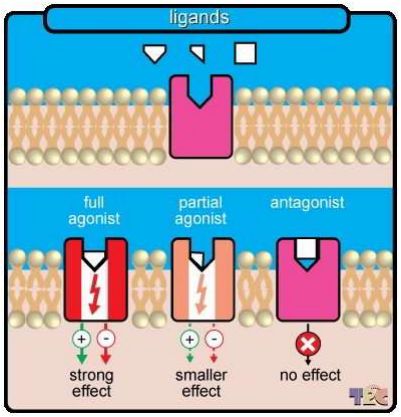
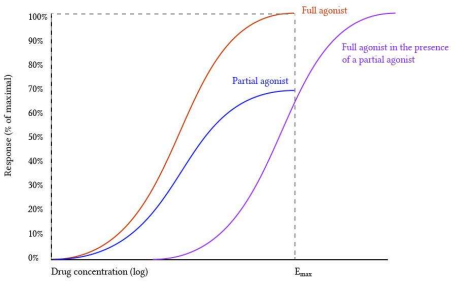
Farmacodynamiek

Intrinsieke activiteit van geneesmiddel:





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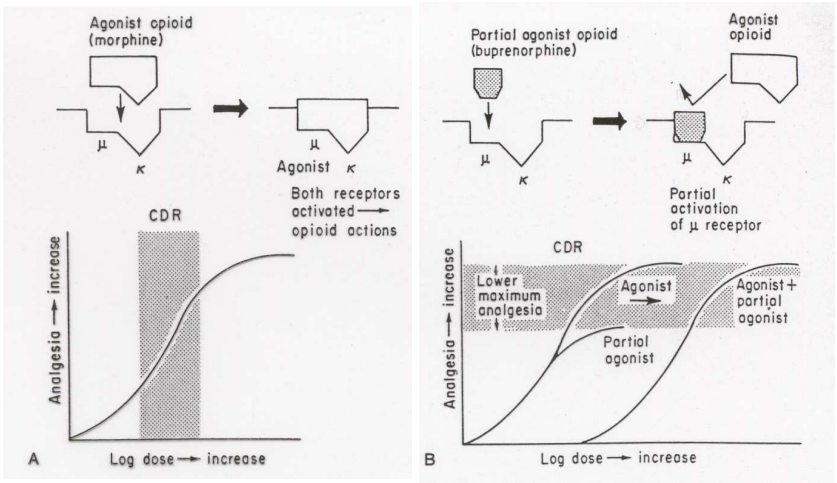
Farmacodynamiek



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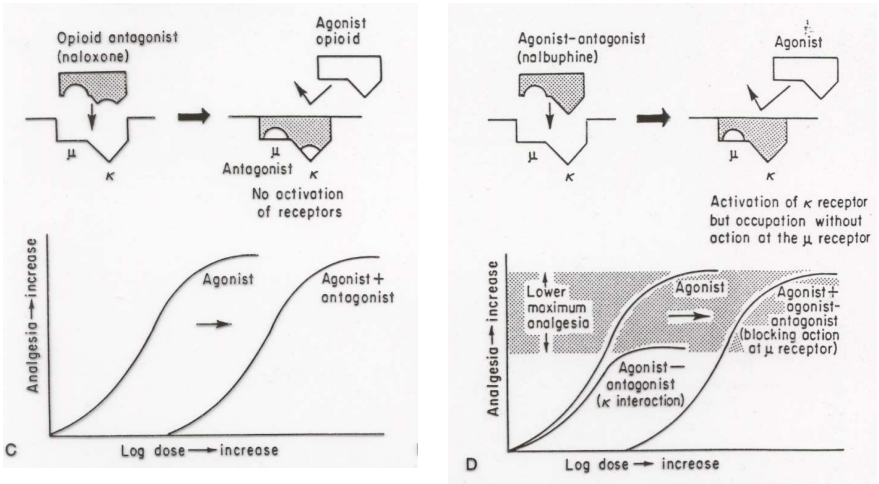
Farmacodynamiek



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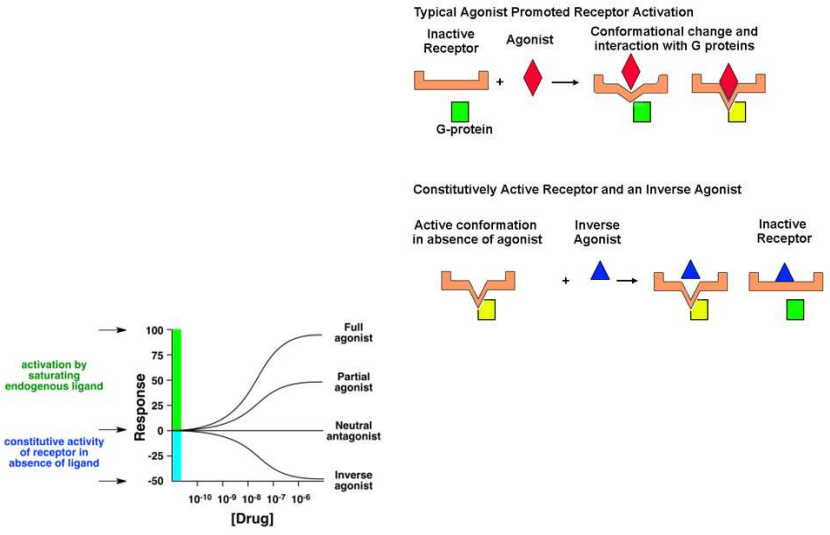
Farmacodynamiek



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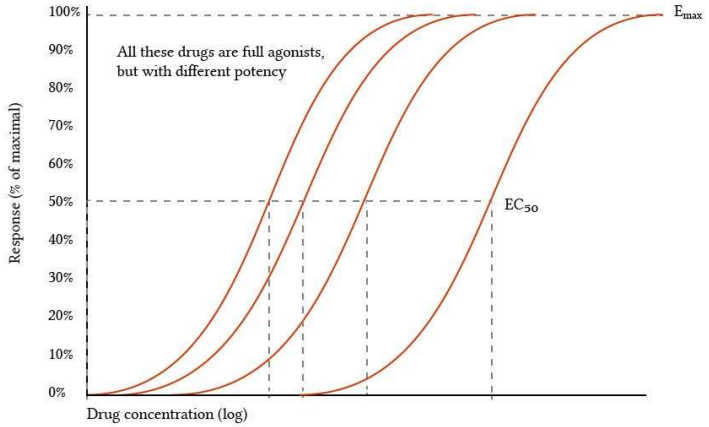
Farmacodynamiek

Intrinsieke activiteit van geneesmiddel:



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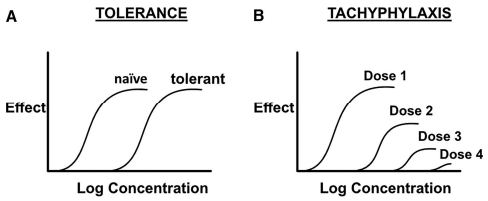
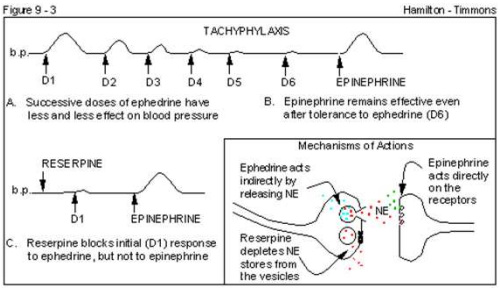
Farmacodynamiek





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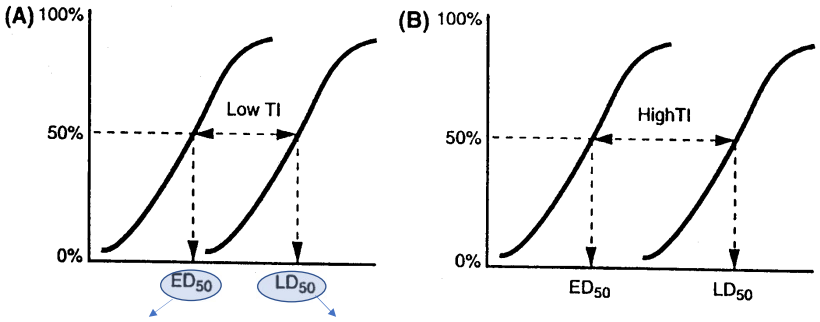
Farmacodynamiek

LD50/ED50: therapeutische index



dosis met 50% vh max effect

letale dosis voor 50% vd proefdieren

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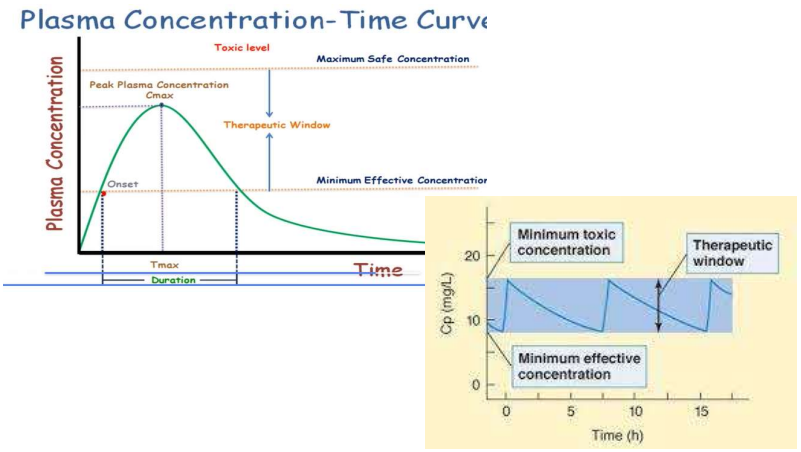
Farmacodynamiek

therapeutisch concentratievenster:



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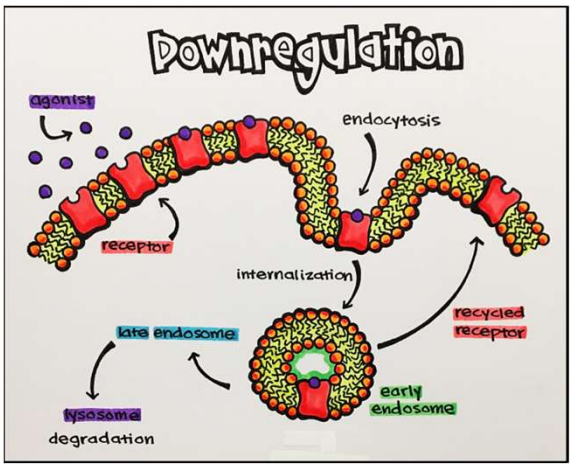
Farmacodynamiek



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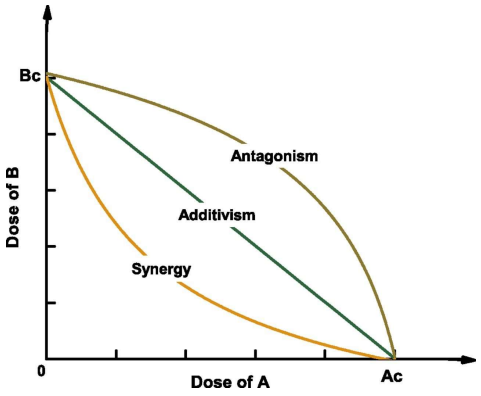
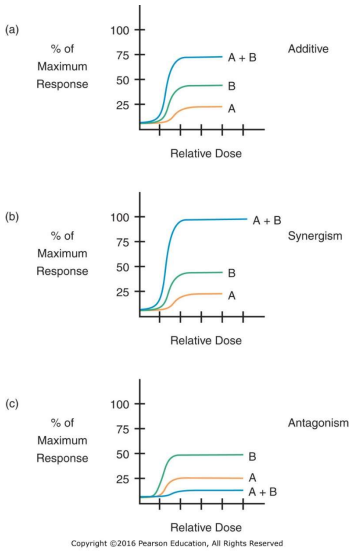
Farmacodynamiek





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+32 16 34 72 58

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Referenties

Referenties

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Slide 41: farmacokinetiek: wiskunde

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(helling . 2.303)

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Slide 53: PK/PD

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