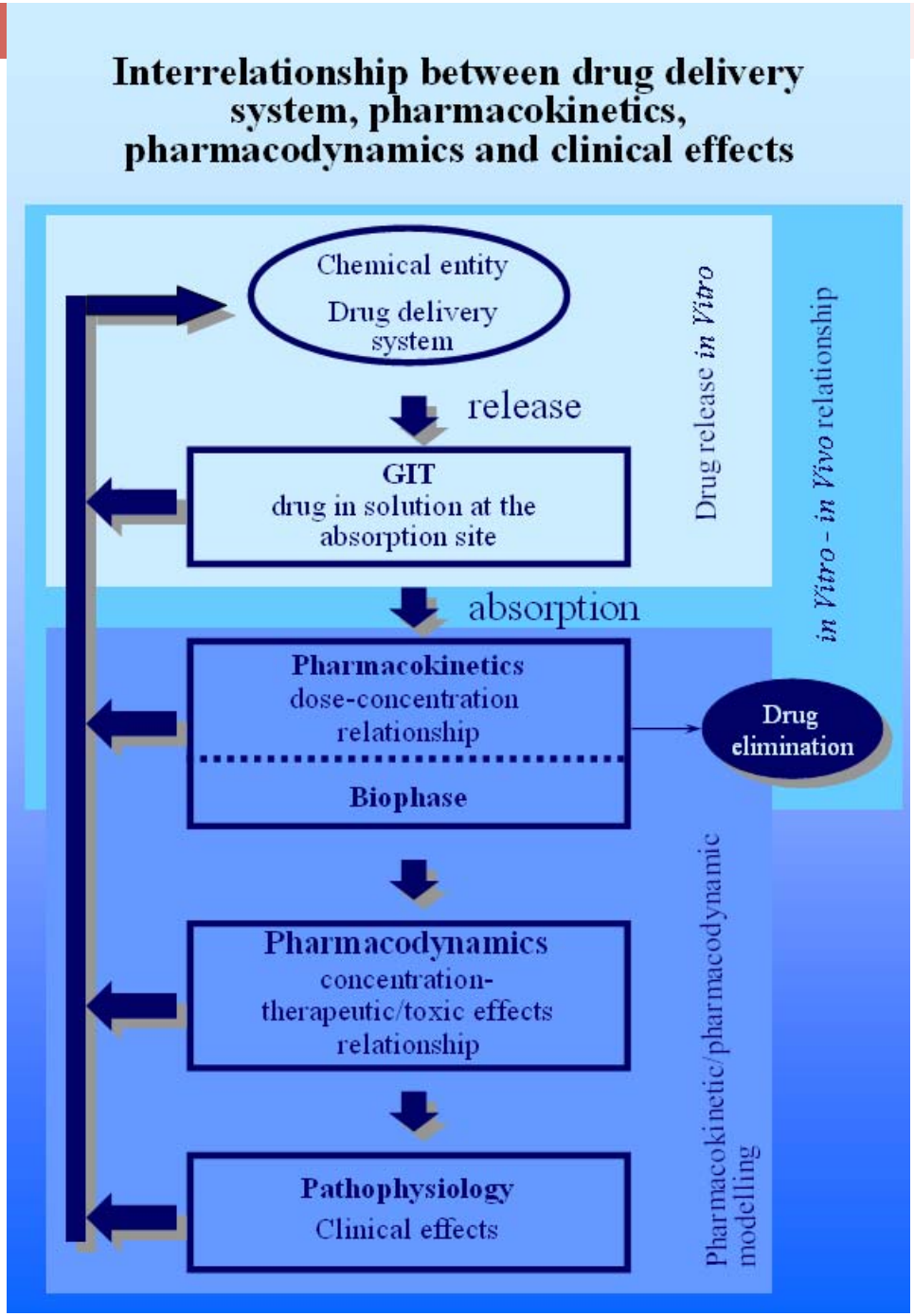
Osnove farmakokinetike

Aleš Mrhar
Univerza v Ljubljani
Fakulteta za farmacijo
Katedra za biofarmacijo in farmakokinetiko

Prirejeno po

A First Course in Pharmacokinetics and Biopharmaceutics by David Bourne, College of Pharmacy, University of Oklahoma

Interrelationship between drug delivery system, pharmacokinetics, pharmacodynamics and clinical effects



Pharmacokinetics/Pharmacodynamics

- **Pharmacokinetics:**

  Transolaction of drug molecules around the body by

  1. **Convectional transfer**
  2. **Diffusional transfer**

- **Biophase (Targets)**

- **Pharmacodynamics:**

  Interactions of drug molecules with the targets

  1. **Receptors**
  2. **Enzymes**
  3. **Ion channels**
  4. **Carriers**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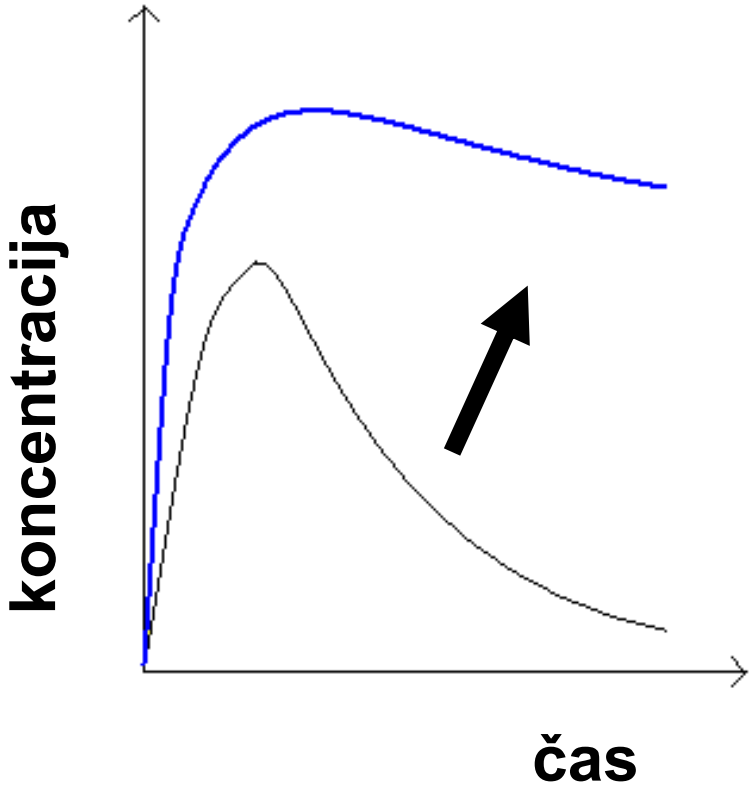
ODMEREK
PG
PLAZEMSKA KONCENTRACIJA
MESTO DELOVANJA
PD
PG
UČINEK


koncentracija
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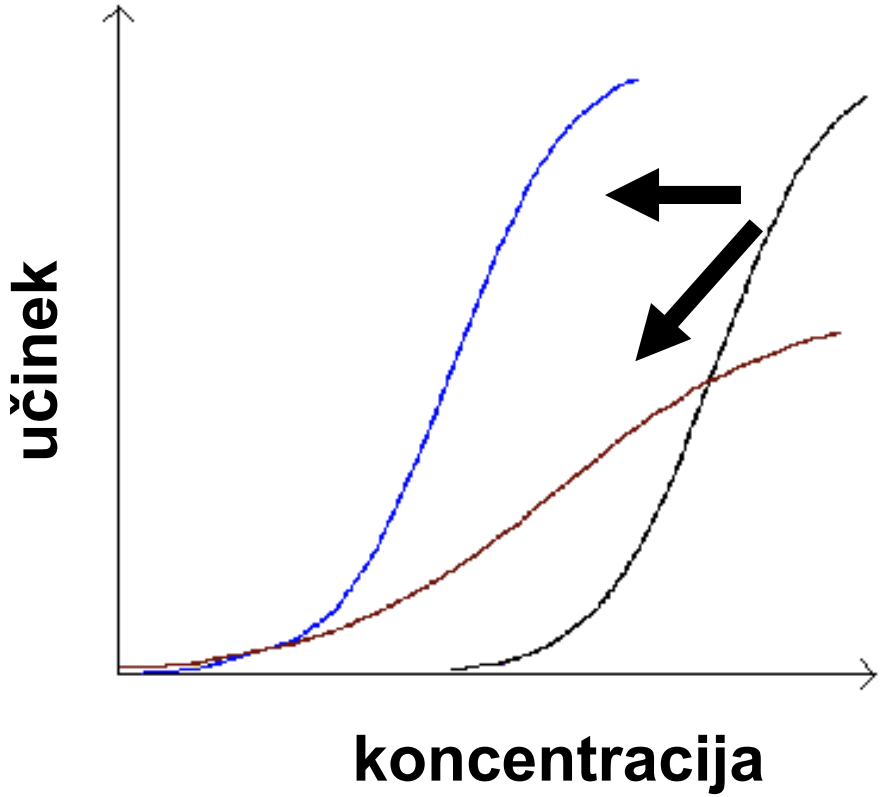
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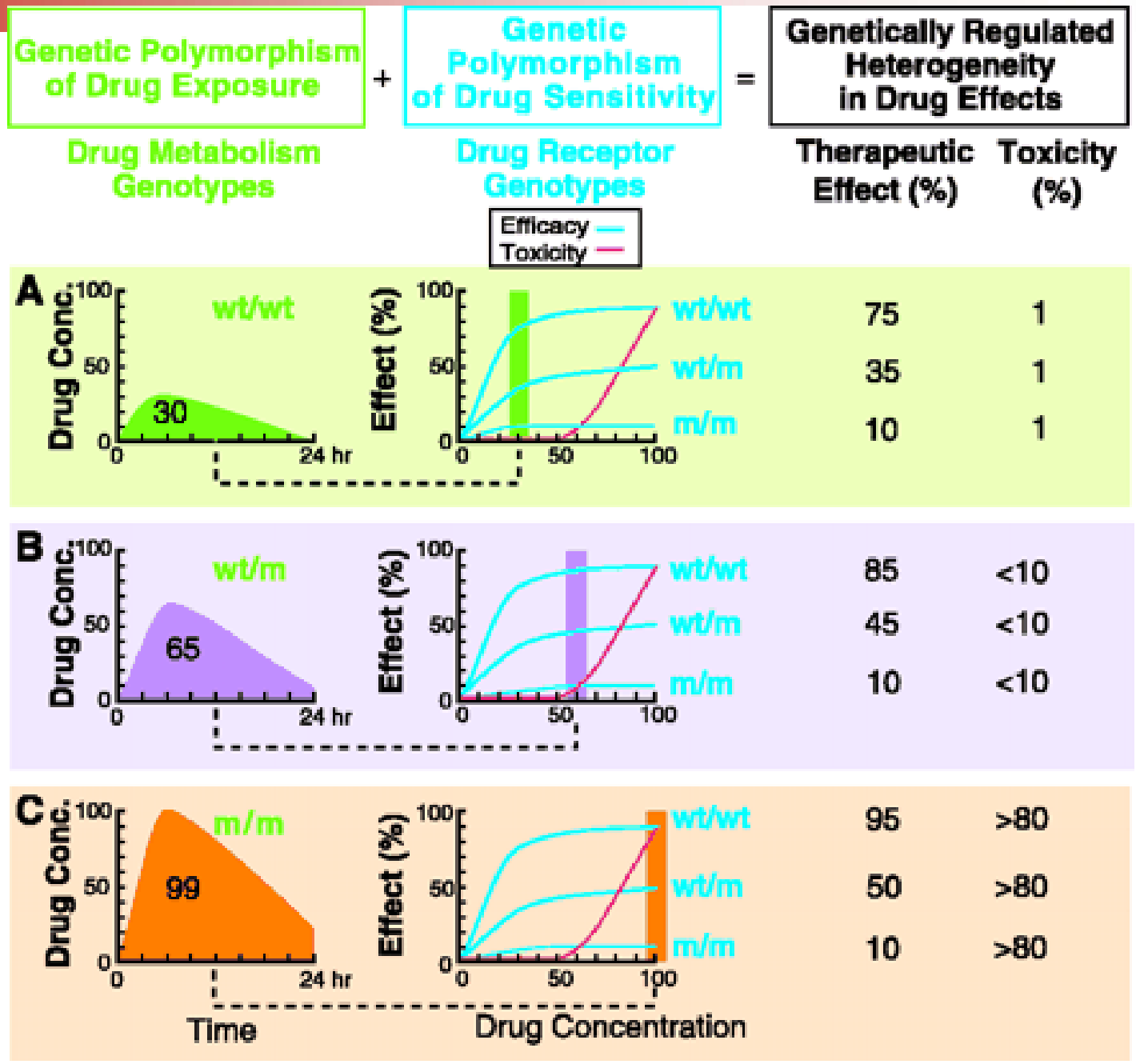
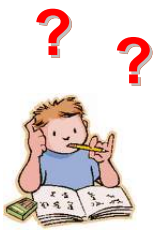


From: Evans WE, Relling MV. *Science* 286:487-491, 1999.

Vpliv interakcij varfarina na odmerek varfarina
Vpliv polimorfizma CYP2C9 na odmerek varfarina

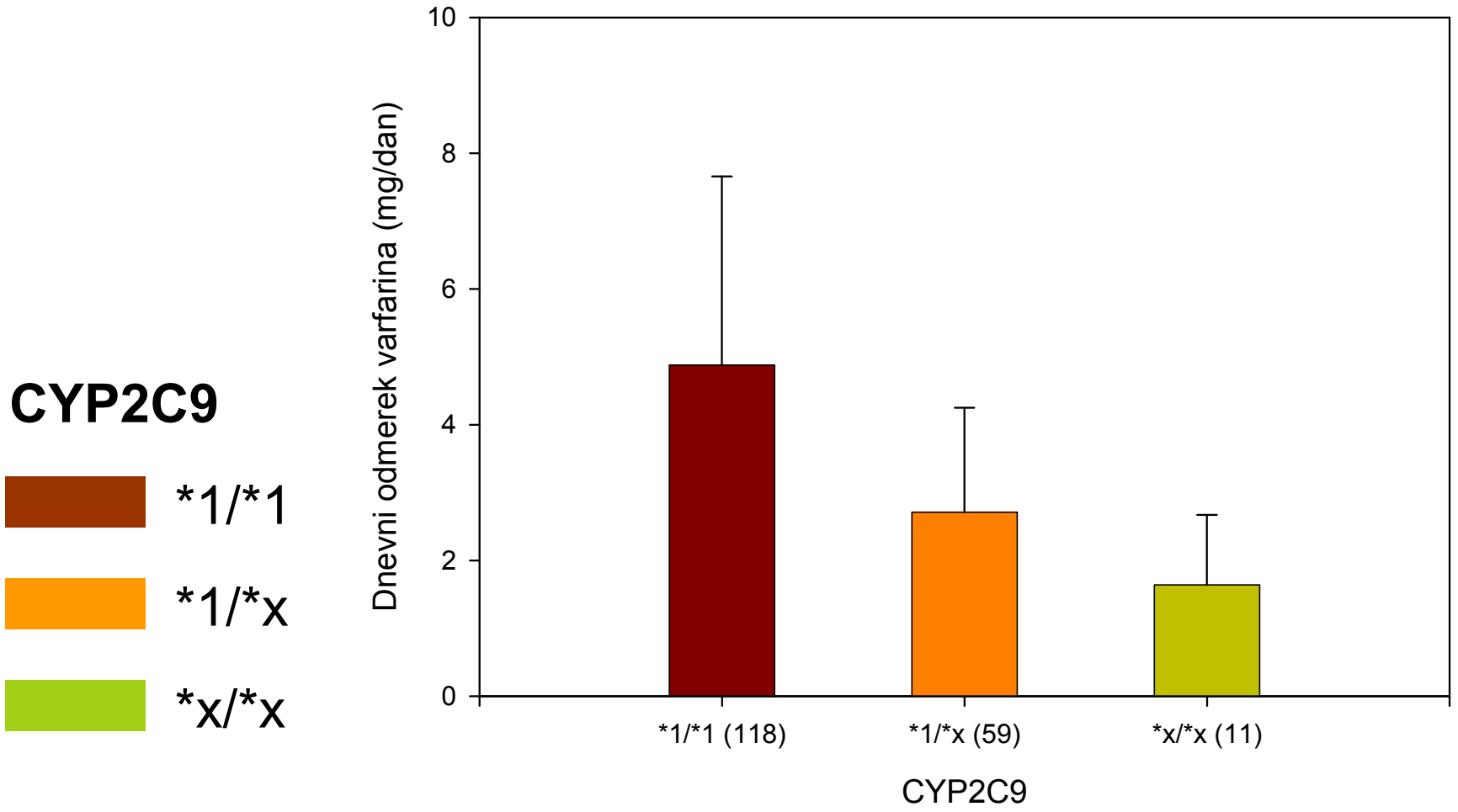
- zelo različen dnevni odmerek (0,5 do 50 mg).
- spremljanje protrombinskega časa (izražen kot INR).
- pogoste kontrole zaradi ozkega terapevtskega okna (krvavitev).

Interakcije VARFARINA z zdravili (vir LEXI-interact; LEXI-COMP on line)



- [C] Acetaminophen
- [D] Allopurinol
- [D] Aminoglutethimide
- [D] Amiodarone
- [D] Androgens
- [A] Antacids
- [C] Anticoagulants
- [D] Antifungal Agents (Imidazole)
- [C] Antiplatelet Agents
- [D] Antithyroid Agents
- [C] Aprepitant
- [C] Azathioprine
- [D] Barbiturates
- [C] Bile Acid Seqestrants
- [C] Bosentan
- [D] Capecitabine
- [D] Carbamazepine
- [C] Cephalosporins
- [D] Cimetidine
- [A] Clopidogrel
- [C] Coenzyme Q-10
- [A] Conivaptan
- [D] Contraceptive (Progestins)
- [C] Cranberry
- [C] CYP2C9 Inducers (Highly Effective)
- [C] CYP2C9 Inhibitors (Moderate)
- [D] CYP2C9 Inhibitors (Strong)
- [C] CYP2C9 Substrates (High risk with Highly Effective Inhibitors)
- [C] Dicloxacillin
- [C] Disulfiram
- [D] Drotrecogin Alfa
- [C] Etoposide
- [D] Fenugreek
- [D] Fibric Acid Derivatives
- [D] Fluconazole
- [C] Fluorouracil
- [C] Gefitinib
- [D] Ginkgo Biloba
- [C] Ginseng (American)
- [C] Glucagon
- [C] Glucosamine
- [D] Glutethimide
- [C] Griseofulvin
- [D] Herbs (Anticoagulant/Antiplatelet Properties)
- [C] HMG-CoA Reductase Inhibitors
- [C] Ifosfamide
- [B] Isoniazid
- [C] Leflunomide
- [C] Macrolide Antibiotics
- [C] Mefloquine
- [C] Mercaptopurine
- [B] Methylphenidate
- [D] Metronidazole
- [C] Mitotane
- [D] Nafcillin
- [C] NSAID (COX-2 Inhibitor)
- [D] NSAID (Nonselective)
- [C] Omega-3-Acid Ethyl Esters
- [D] Oral Contraceptive (Estrogens)
- [C] Orlistat
- [D] Phenytoin
- [B] Potassium-Sparing Diuretics
- [C] Propafenone
- [C] Propoxyphene
- [C] Proton Pump Inhibitors
- [B] Proton Pump Inhibitors
- [C] Quinidine
- [C] Quinolone Antibiotics
- [C] Rifamycin Derivatives
- [C] Ropinirole
- [D] Salicylates
- [C] Selective Serotonin Reuptake Inhibitors
- [D] St Johns Wort
- [B] Sucralfate
- [C] Sulfasalazine
- [D] Sulfinpyrazone
- [D] Sulfonamide Derivatives
- [C] Tetracycline Derivatives
- [D] Thyroid Products
- [C] Tigecycline
- [C] Tolterodine
- [C] Treprostinil
- [C] Tricyclic Antidepressants
- [B] Valproic Acid
- [C] Vitamin A
- [C] Vitamin E
- [C] Voriconazole
- [C] Zafirlukast
- [C] Zileuton
- [D] Phytonadione

Vpliv polimorfizma CYP2C9 na odmerek varfarina



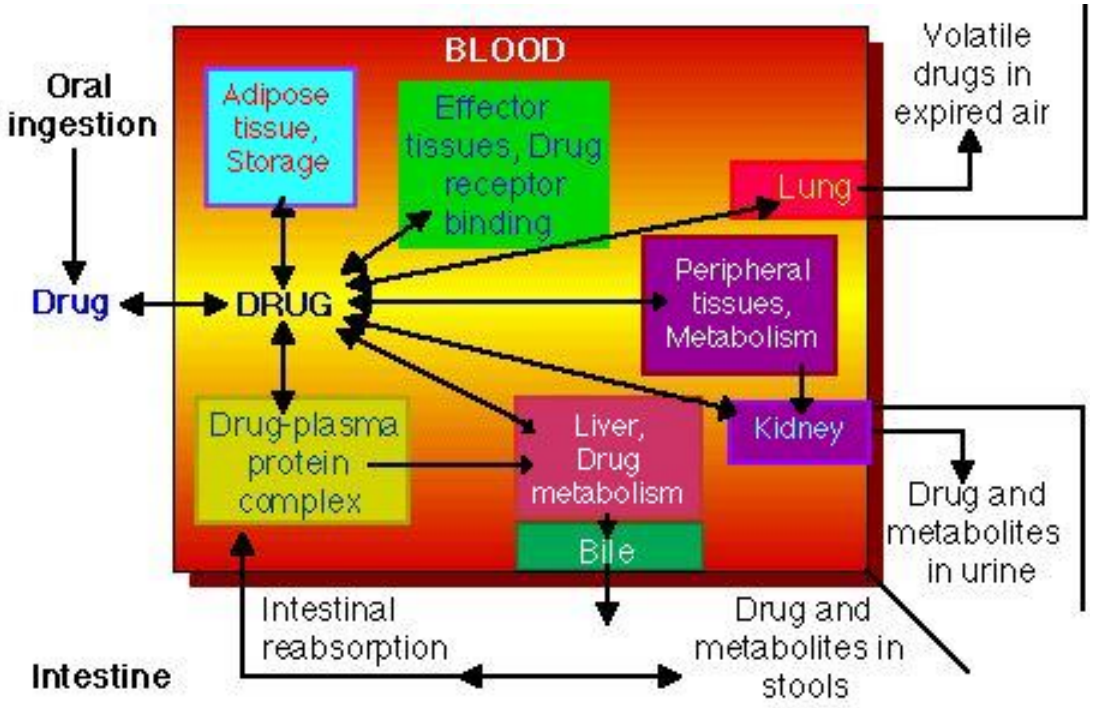
Pharmacokinetics?

A young child given an intramuscular injection might ask "How will that 'ouch' get from there to my sore throat"?

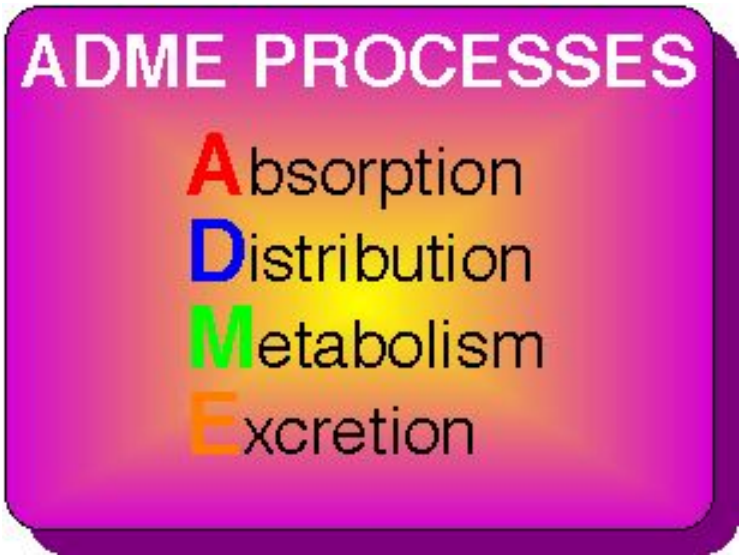
The answer to this question is the basis of pharmacokinetics.

That is, how drugs move around the body, how quickly drugs come to and how long they stay in biophase and how quickly drugs leave the body.

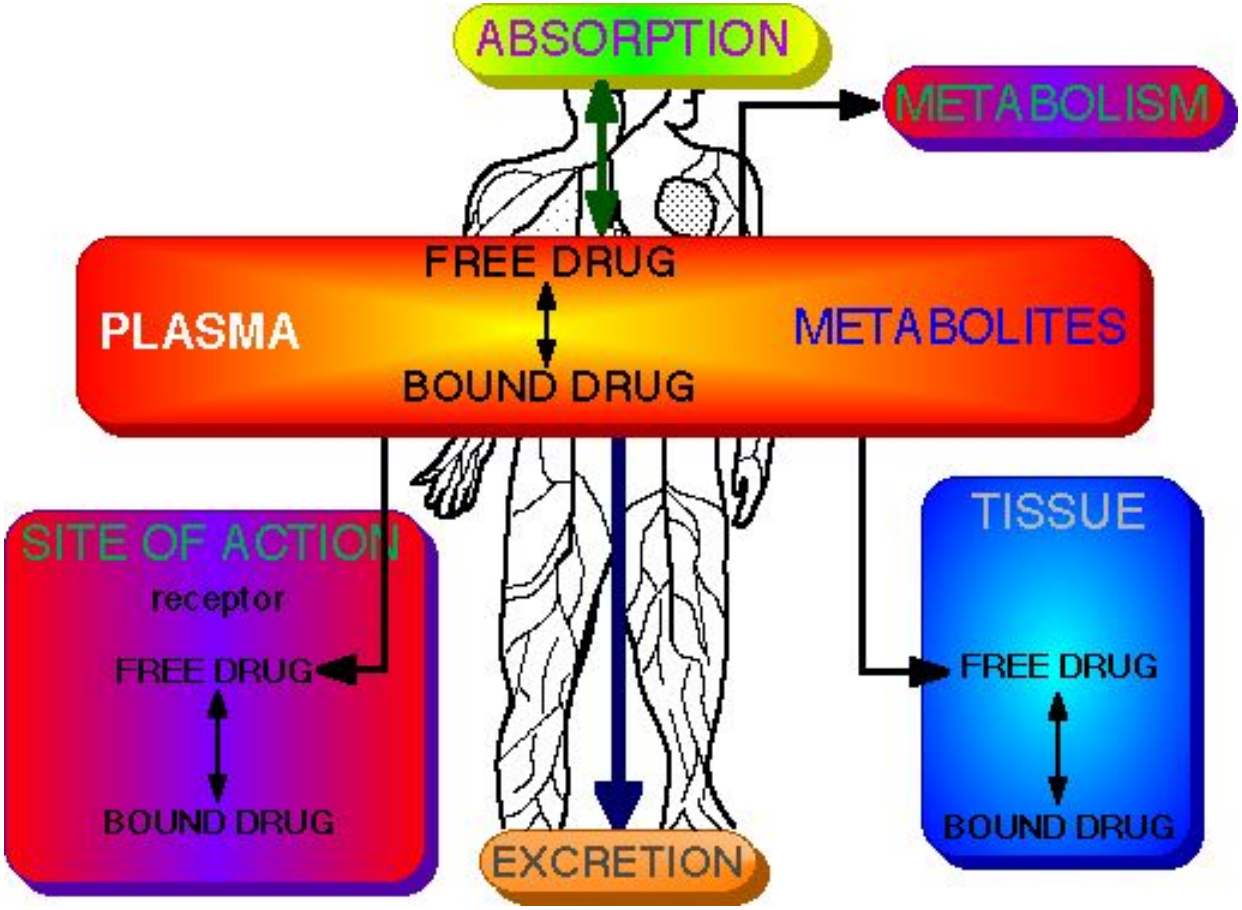
Many of the technologic and biologic parameters which control the dissolution, absorption, distribution, metabolism, and excretion of drugs will be discussed.



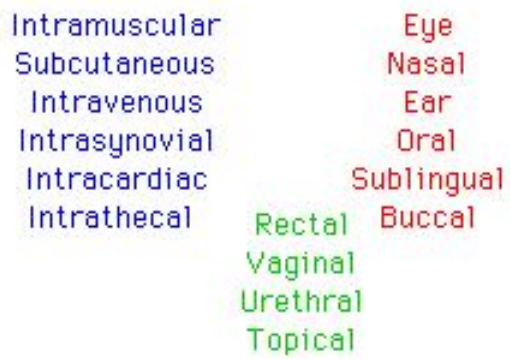
Complex picture of drug interactions in the body. It gives an idea of the complexity of drug disposition. Shown in this picture are many of the steps to getting drug from one site in the body to another. Many of these processes are enzyme induced. However, the overall picture is often much simpler. Many of these processes may be fast or not significant for any given drug.



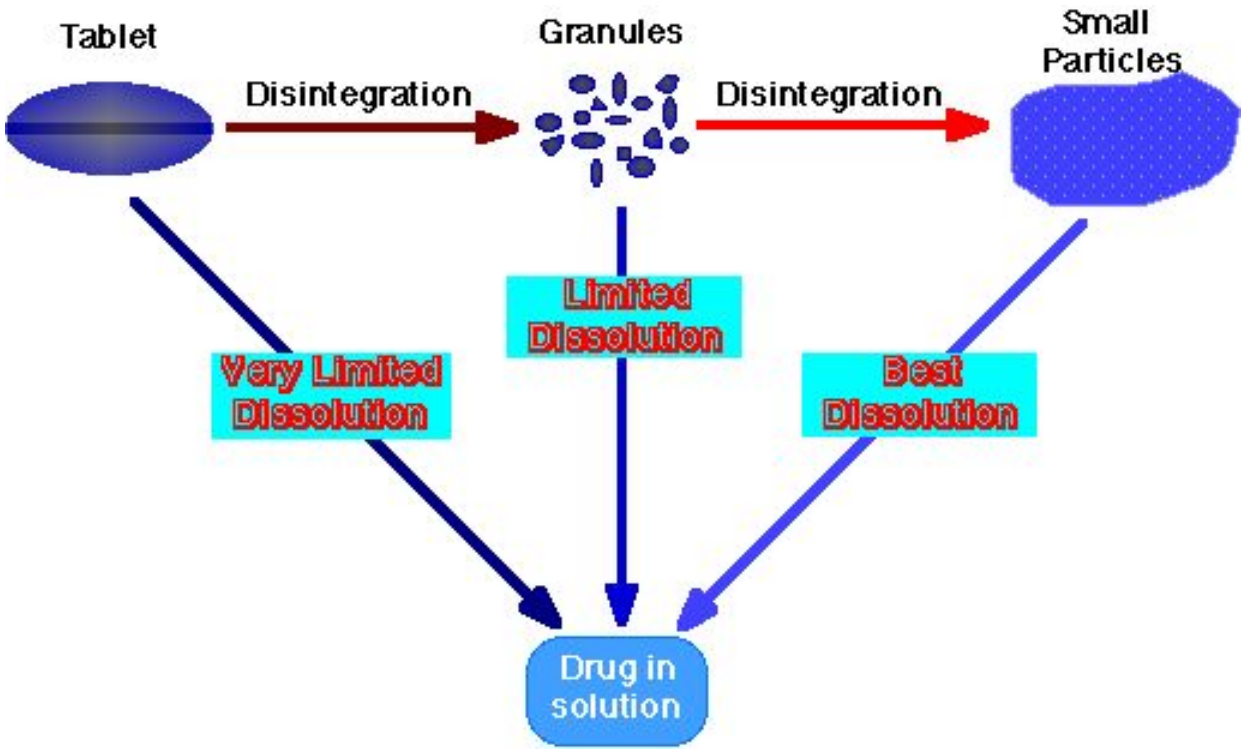
The four pharmacokinetic processes. Each of these processes will be briefly considered in turn. **A**(bsorption) **D**(istribution) **M**(etabolism) **E**(xcretion).



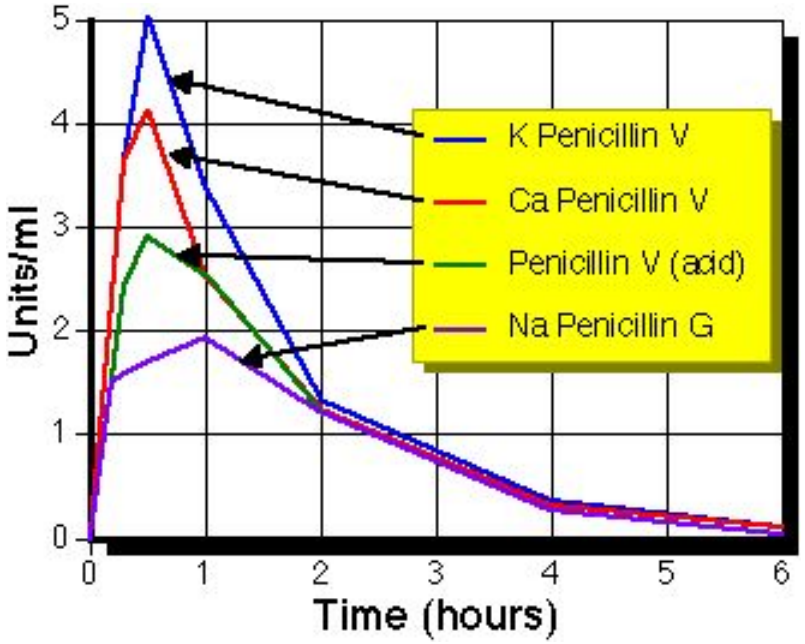
Processes involved in drug transport. Here the major processes are represented in a less physiological fashion. The headings (**A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion**)** are important.



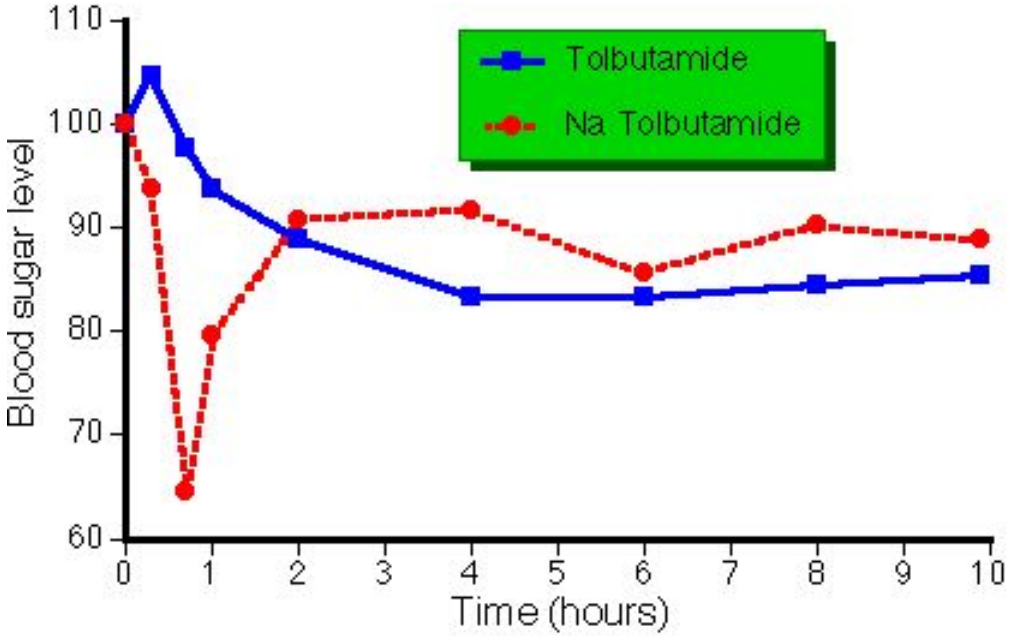
A model with the various routes of administration. For example absorption through the lining of the mouth, buccal absorption, often results in rapid absorption without the drug passing through the liver where it can be broken down. However, only low dose drugs can be accommodated by this route of administration. Orally absorbed drugs are absorbed in the stomach or intestines and enter the portal blood supply and go to the liver before getting into the central blood supply. This can result in extensive metabolism of the drug before it can take any action. For this reason some drugs are very inefficient when given orally.



The processes involved in the dissolution of a tablet before absorption. A drug cannot be absorbed across the intestinal wall as a solid. It must first dissolve in the fluid of the G-I tract. Tablets are carefully formulated, designed, to stay together in the bottle during transport but break up quickly once they are in an aqueous environment. This can be an easy or difficult job depending on the drug and the dose required. There are therefore dissolution tests specified to ensure that tablet formulations work. Also it may be appropriate to conduct experiments with human volunteers to ensure that the tablet does release the drug as it should.

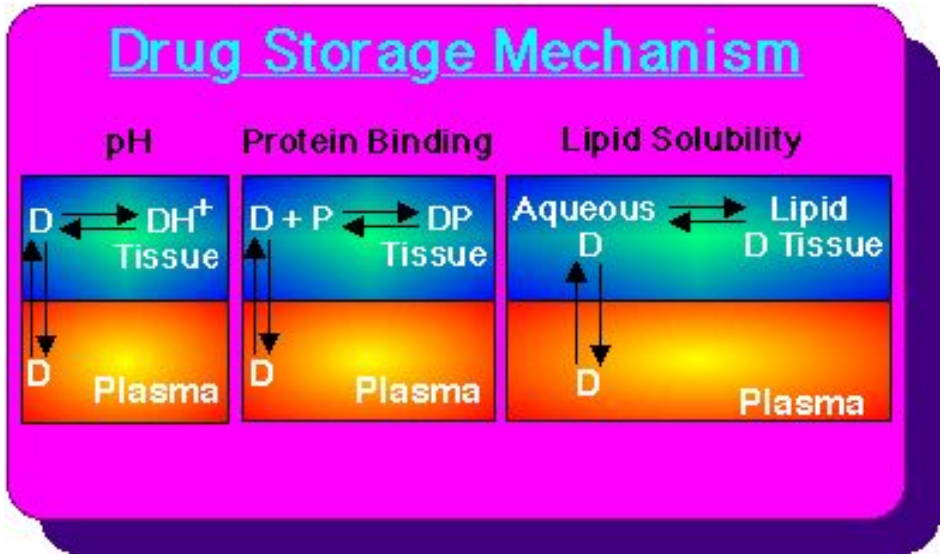


Plasma penicillin concentration versus time curve after oral administration of various salts (redrawn from Juncher, H. and Raaschou, F. 1957 The solubility of oral preparations of penicillin V, *Antibiot. Med. Clin. Therap.*, **4**, 497). The rate at which a drug dissolves is dependent on the solubility of the drug. A common occurrence is that different salts will have quite different solubility characteristics, and again somewhat different to the free acid (or base) form. In the case of penicillin V it appears that only drug which is dissolved quickly can be absorbed.

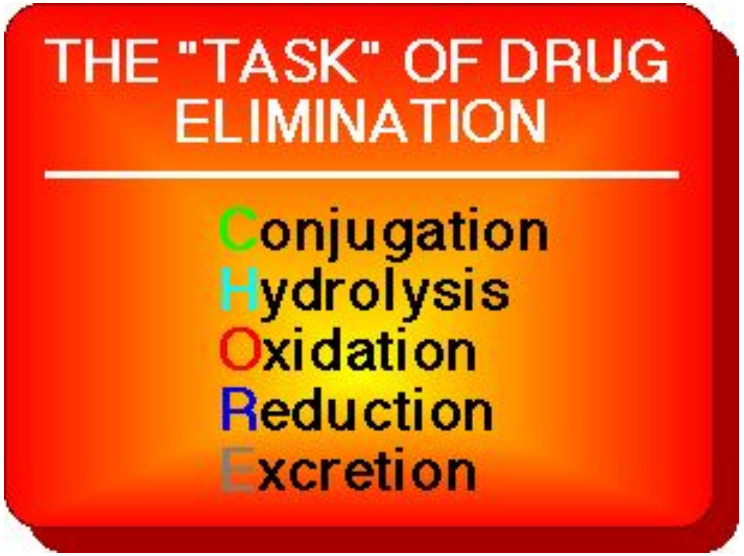


The effect of dissolution rate on the absorption and biological response of tolbutamide (1.0 g) and sodium tolbutamide (1.0 g equivalent) when formulated in compressed tablets.

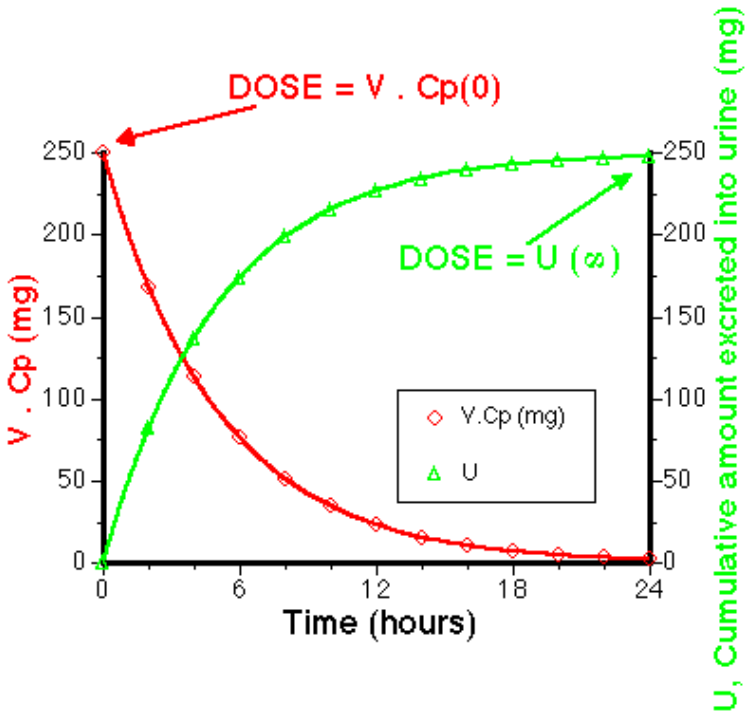
Blood sugar levels after tolbutamide acid and salt (redrawn from Wagner, J.G. 1961 Biopharmaceutics: absorption aspects, *J. Pharm. Sci.*, **50**, 359). Rapid dissolution and absorption is not always the objective. Sometimes a slower release is required. In the case of tolbutamide, used to lower blood sugar concentrations, a more sustained release is better causing a more gradual reduction in blood sugar.



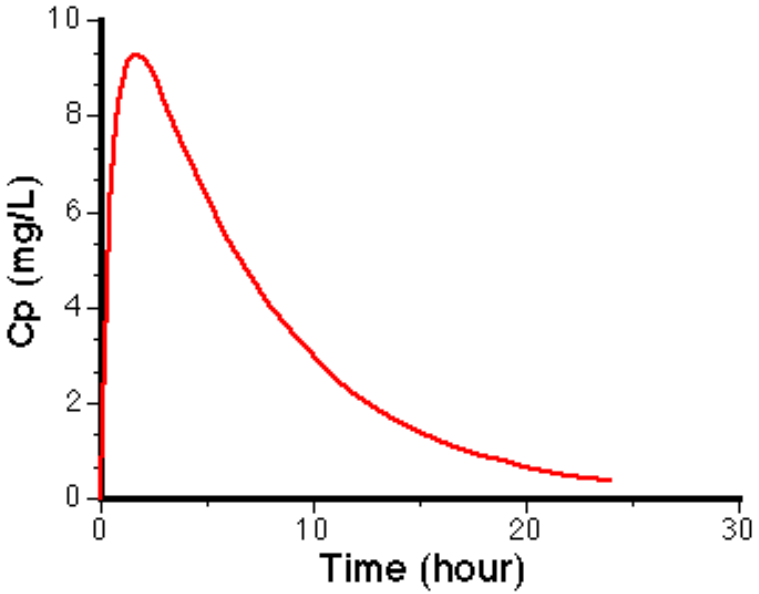
Distribution mechanisms. Methods by which drug is kept in the body for extended action. pH, protein binding and fat storage are three major processes by which drug may be kept within the body. These are mechanisms by which drugs can be distributed throughout the body, protected from elimination, and cause a more prolonged activity.



Methods of drug elimination, metabolism and excretion. Drugs are eliminated by a number of processes. Polar drugs are easily filtered from the blood in the kidneys and removed into urine. However non polar material is generally reabsorbed from the kidney or distributed into fat tissue. The liver however is capable of metabolizing many drugs, generally producing compounds which are more polar and more easily excreted. Enzymes in the liver are able to form conjugates with drugs or hydrolyze and oxidize drugs. Drug kinetics can be markedly altered by changes in metabolism or excretion of drugs. These processes together result in the elimination of a drug.



intravenska aplikacija



peroralna aplikacija

- plazemski koncentracijski profil
- urinski količinski kumulativni profil

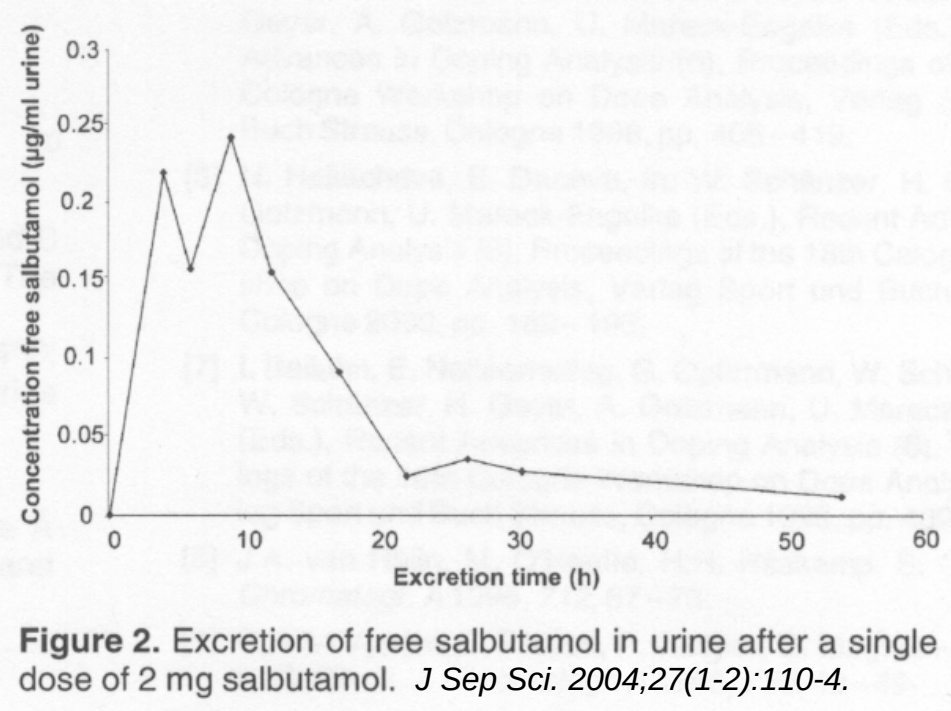
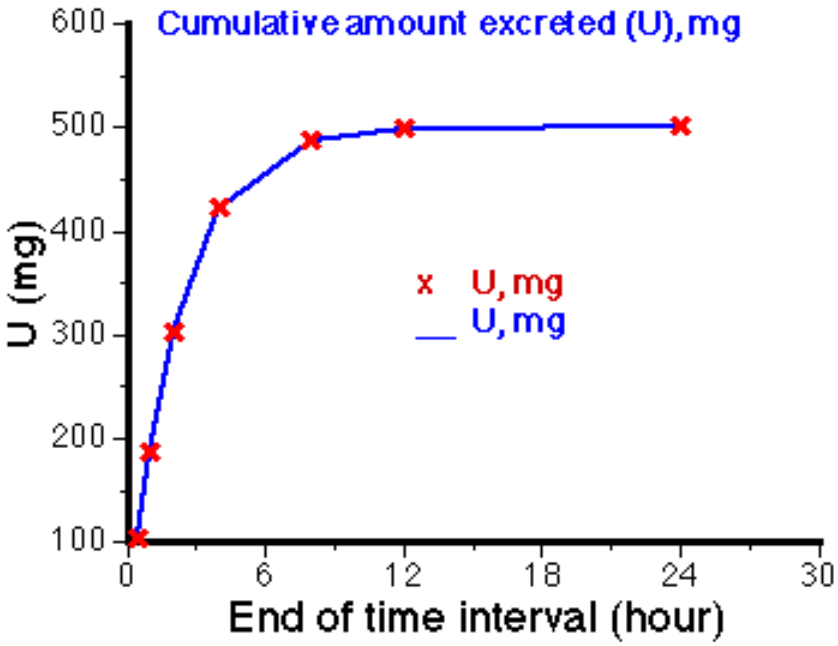
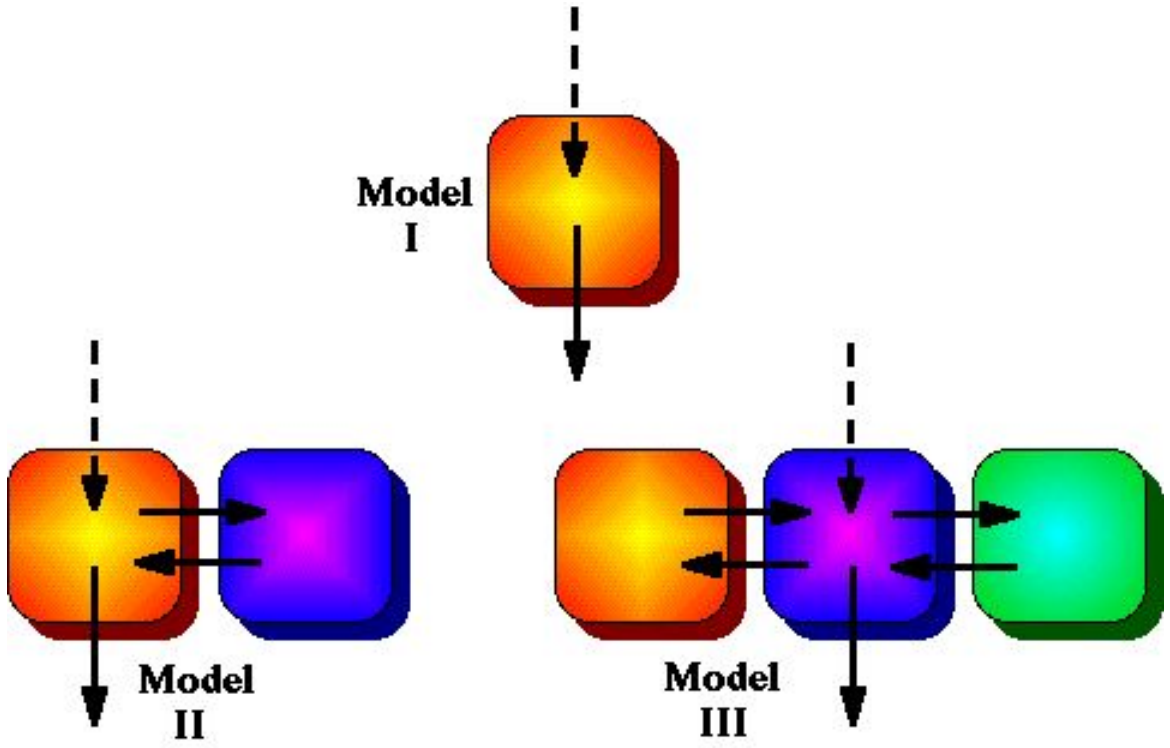


Figure 2. Excretion of free salbutamol in urine after a single dose of 2 mg salbutamol. *J Sep Sci. 2004;27(1-2):110-4.*

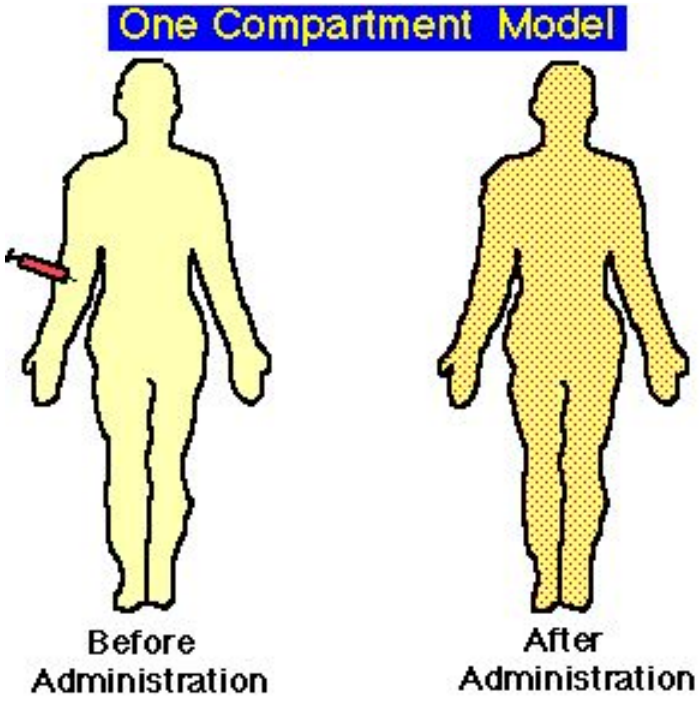
urinski koncentracijski profil



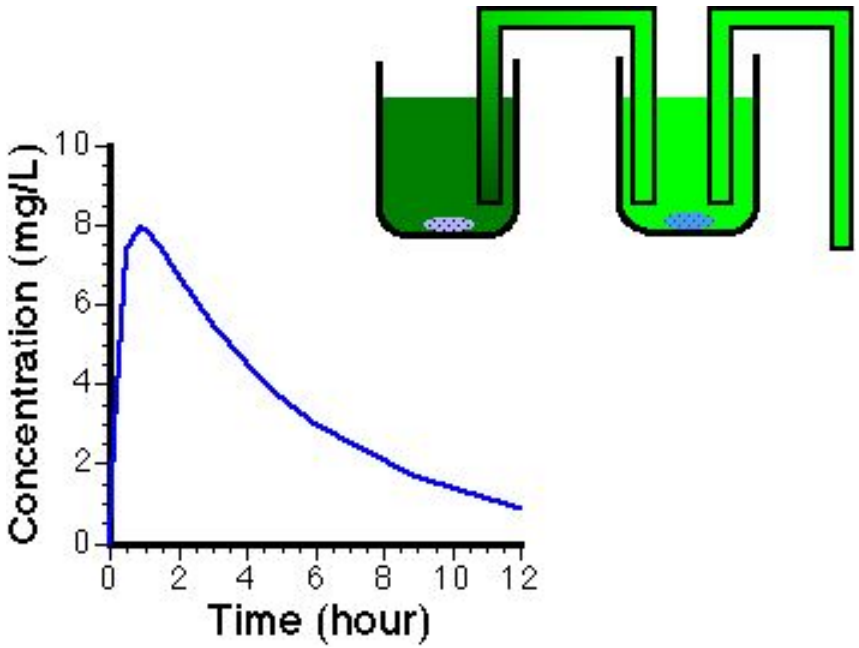
urinski količinski kumulativni profil



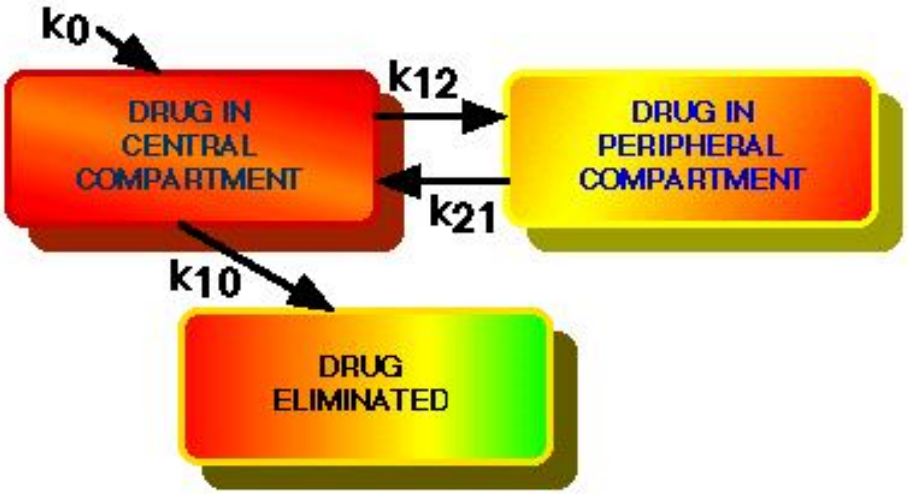
One, two, and three compartment pharmacokinetic models. Fortunately many of the processes involved in drug movement around the body are not saturated at normal therapeutic dose levels. The body may even be represented as a single compartment or container for some drugs. For other drugs a two or three compartment model is found to be necessary.



Body before and after a rapid intravenous injection, considering the body to behave as a single compartment. In order to simplify the mathematics it is often possible to assume that a drug given by rapid intravenous injection, a bolus, is rapidly mixed. This slide represents the uniformly mixed drug very shortly after administration.

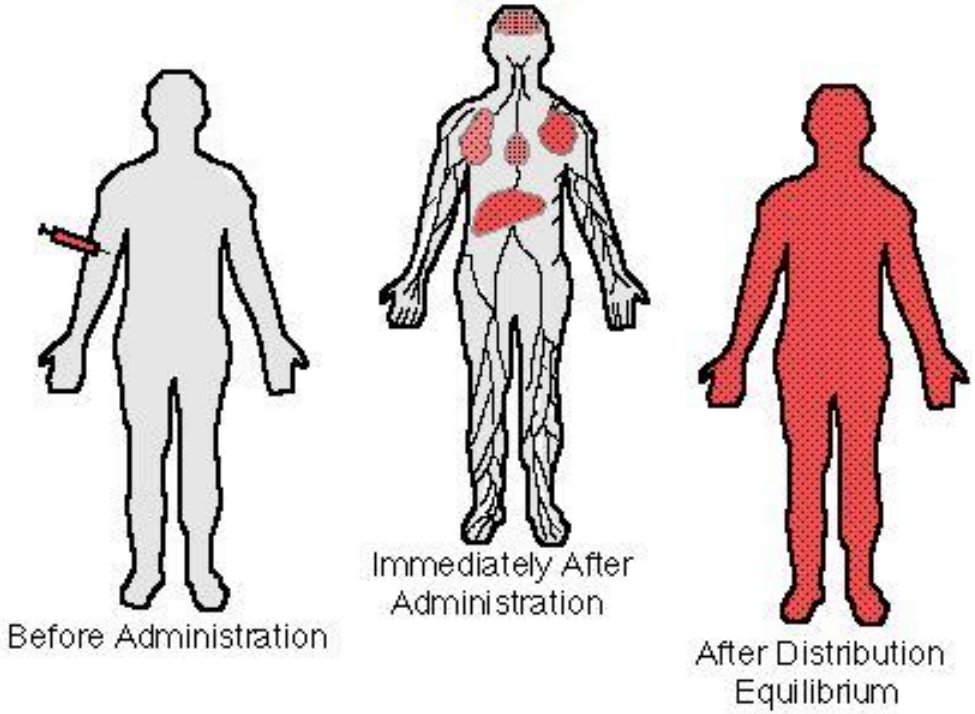


Oral curve and beakers. We can picture oral administration as water flowing from one bucket (representing the GI tract) into a second beaker (representing the body). At first drug flows into the 'body' beaker and the level rises, as drug concentration rises, then after peaking the levels start to fall as elimination overtakes absorption.

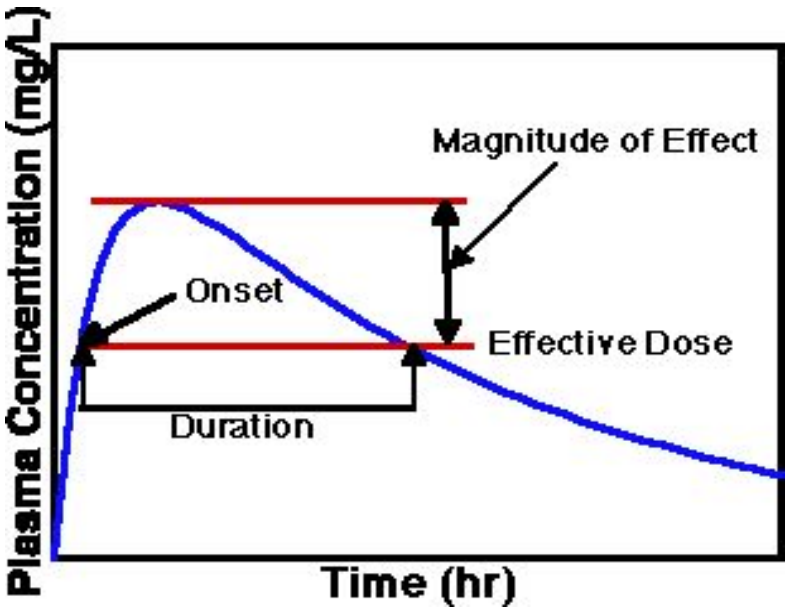


A diagram of a two compartment model showing the parameters to be measured. The processes of distribution and excretion can be represented by the rate constants k12, k21, and k10. The rate constant k0 represents an infusion or absorption process. The drug appears to be dissolved in the body volume. This volume is the 'apparent' volume of distribution.

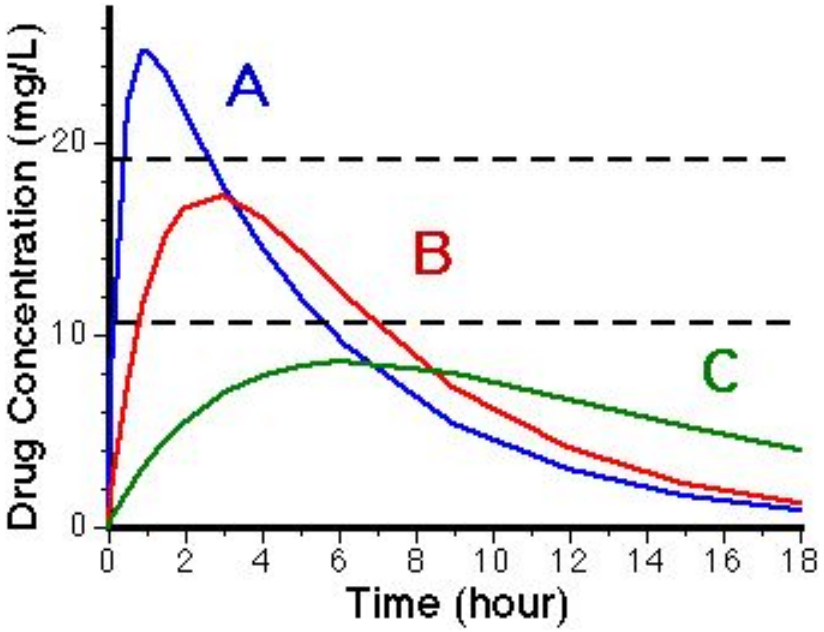
Two Compartment Model



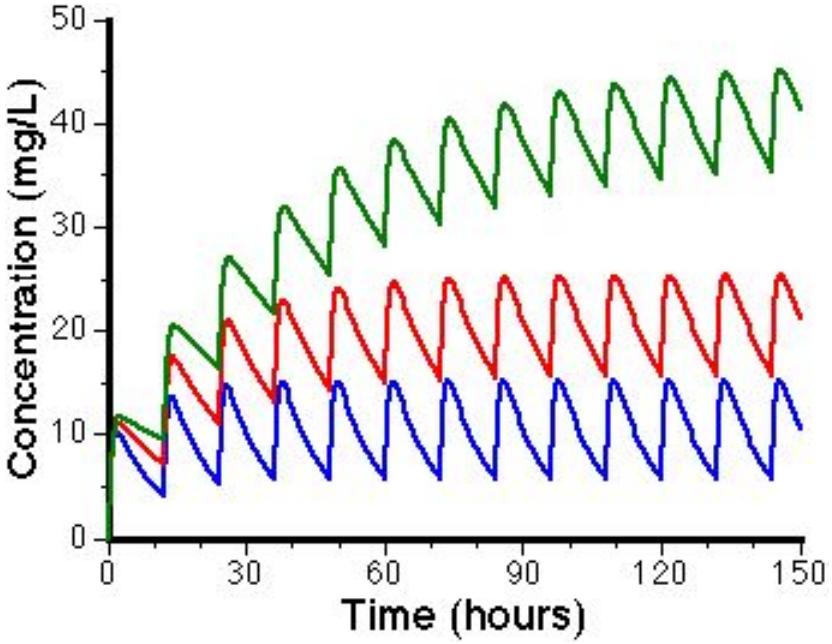
Intravenous bolus injection with a two compartment model. Often a one compartment model is not sufficient to represent the pharmacokinetics of a drug. A two compartment model has wider application. Here we consider the body is a central compartment with rapid mixing and a peripheral compartment with slower distribution. The central compartment is uniformly mixed very shortly after drug administration, whereas it takes some time for the peripheral compartment to reach a pseudo equilibrium.



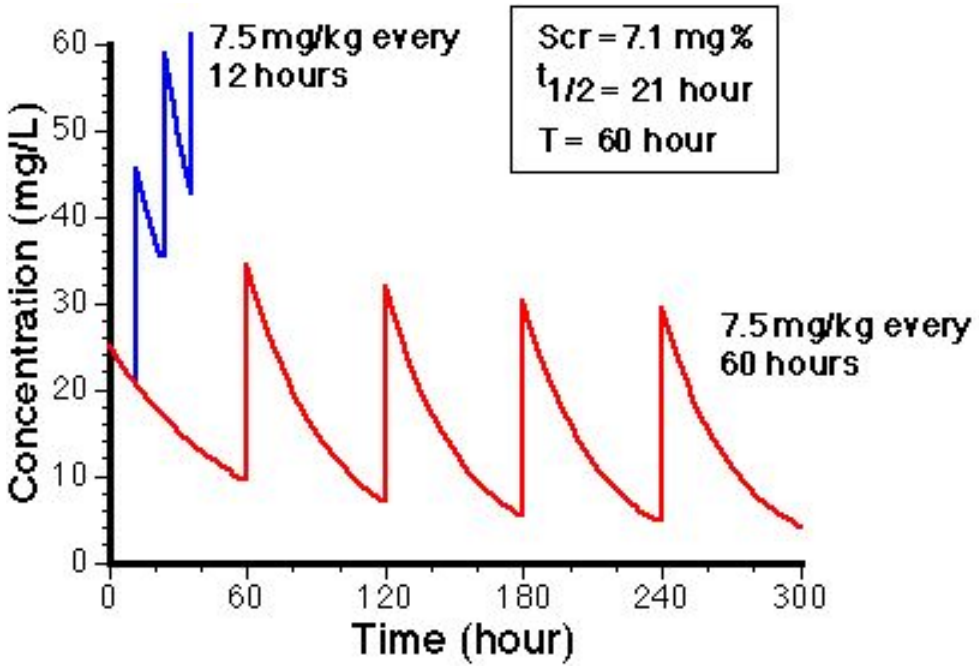
Effect as a function of time. From a graph such as this we can see the relationship between drug concentration and drug effect. If a drug has to reach an effective concentration at a target site this will be reflected as a required blood concentration.



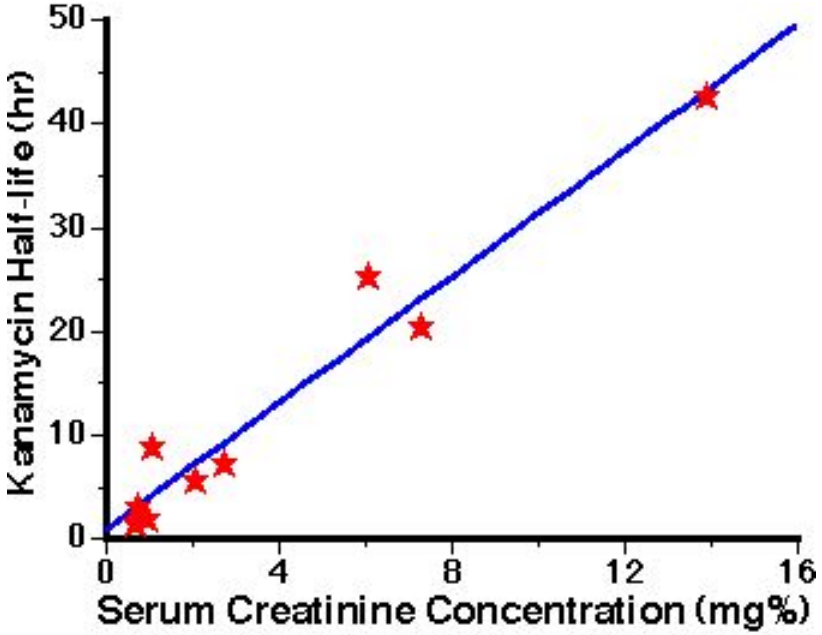
Plasma concentration time curves for three theoretical formulations with different ka values. The plasma concentrations achieved can be controlled by the rate of drug absorption. As shown product I would be toxic. A smaller dose, or a slower formulation should be considered. Formulation II appears to be effective in the dose and formulation used. The dosage form III appears to be too slow and thereby ineffective. If it is a drug requiring a sustained effect this formulation may be more useful at a higher dose or after repeated doses.



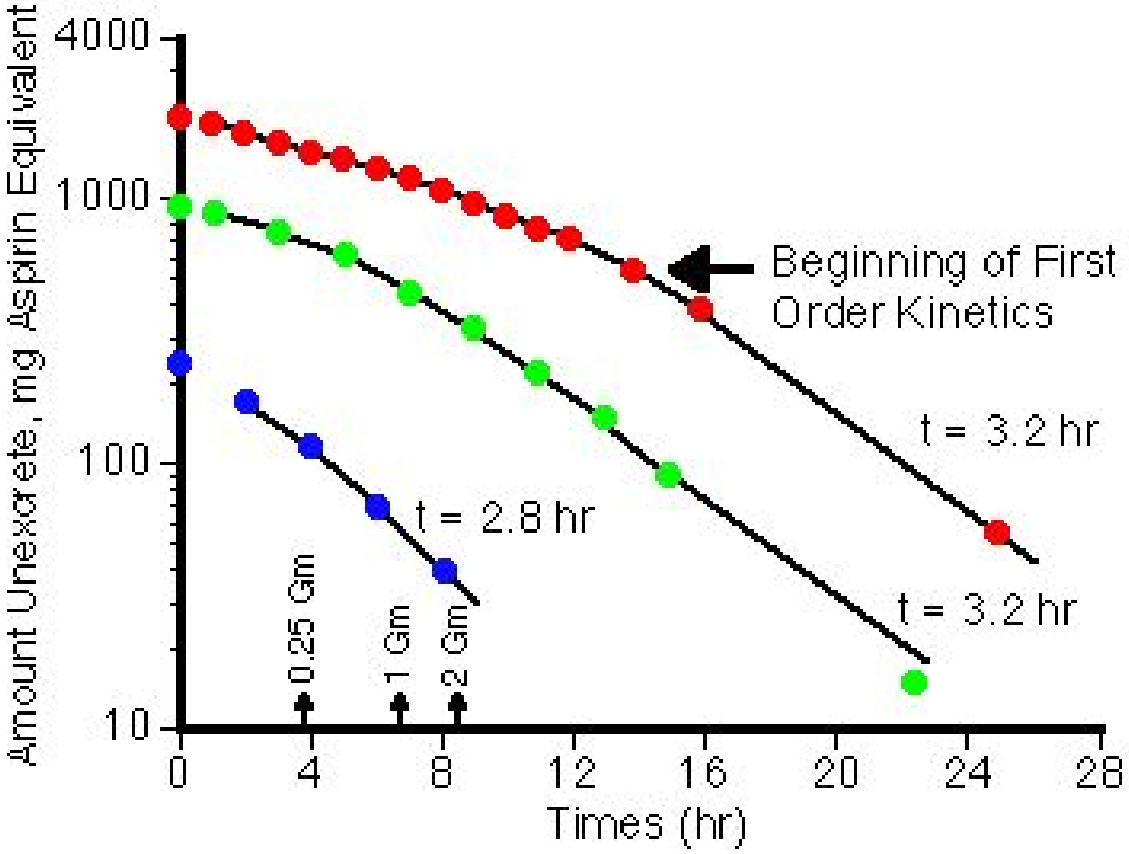
Multiple dose curves with slow, medium, and fast excretion. Alteration of drug elimination is particularly important when drugs are given repeatedly. If it is assumed that the drug is eliminated normally when in fact it is slowly eliminated, drug accumulation may occur with toxic concentrations reached. Alternately faster elimination than expected may cause sub therapeutic concentrations to be reached.



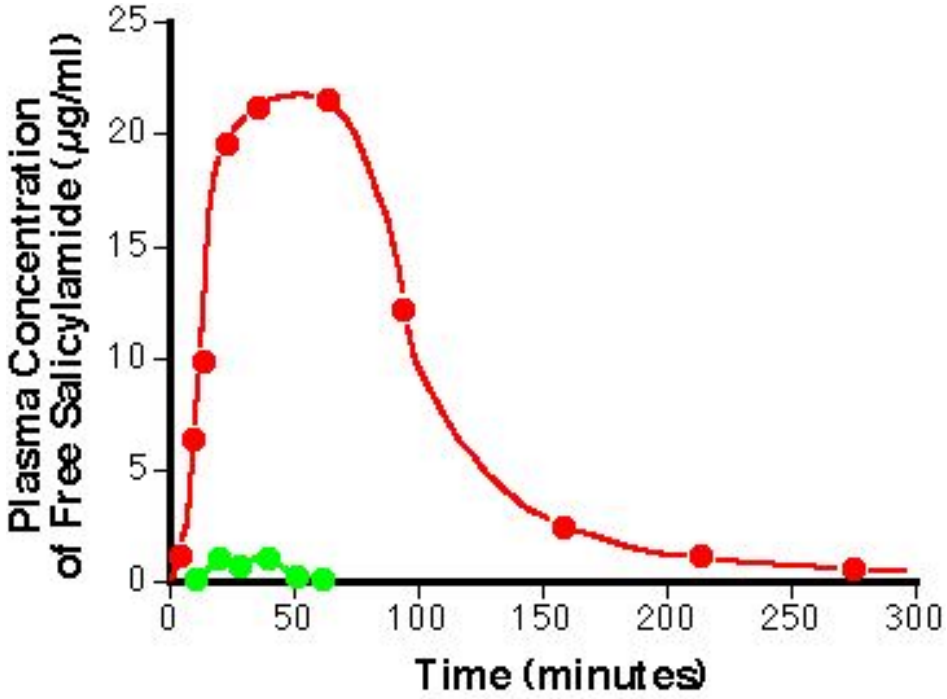
A clinical example with kanamycin, showing theoretical curve after multiple dose and a better curve after dose adjustment. Kanamycin is a useful drug but it can cause some serious side effects. By controlling the blood concentration of this drug it is possible to use it effectively. In the case of patients with impaired renal, or kidney function it is possible to determine the kidney function ahead of time and adjust the kanamycin dosing schedule accordingly.



Relationship between kanamycin half-life and serum creatinine level. As kidney function is reduced the serum creatinine level increases and the also the kanamycin takes longer to be eliminated from the body.

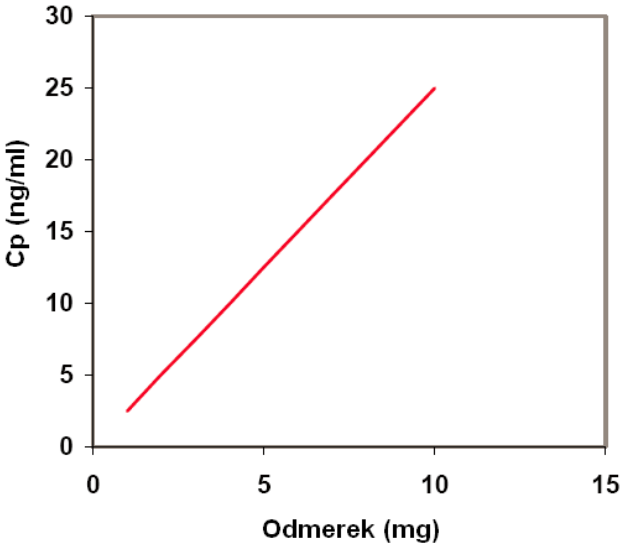


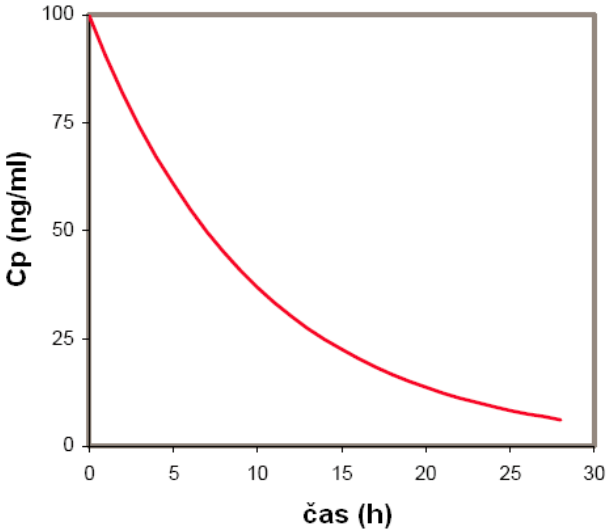
Aspirin plasma concentration as a function of time (redrawn from Levy, G. 1965 *J. Pharm. Sci.*, **54**, 959). At higher doses the metabolism of aspirin is reduced by saturation. The elimination rate constant (as represented by the slope) is reduced.



Extra absorption of salicylamide at higher doses (redrawn from Barr, W.H. *Drug Info. Bull.*, p27, 1969). Normally the amount of drug present in the body is no more than the enzymes can handle easily. Metabolism then proceeds in apparent first order fashion. However for some drugs the enzymes can not keep up. Illustrated here is one example, saturation of first pass metabolism allowing more or a higher fraction of drug to be absorbed.

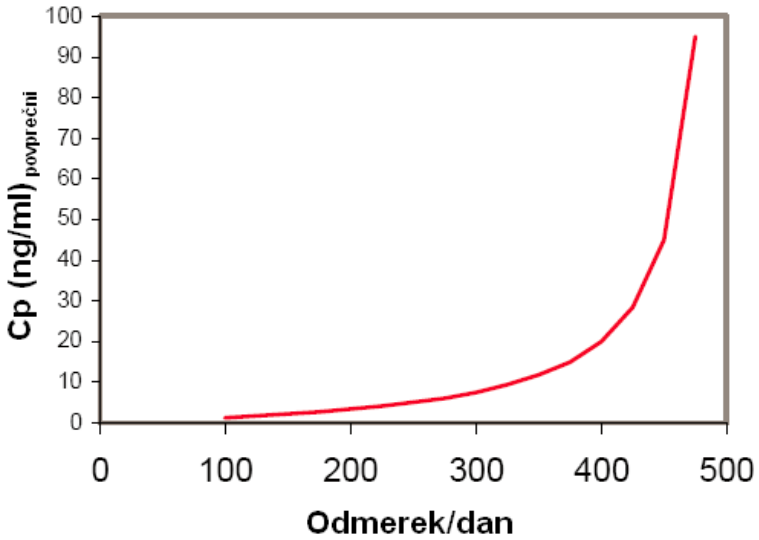
Linearna farmakokinetika

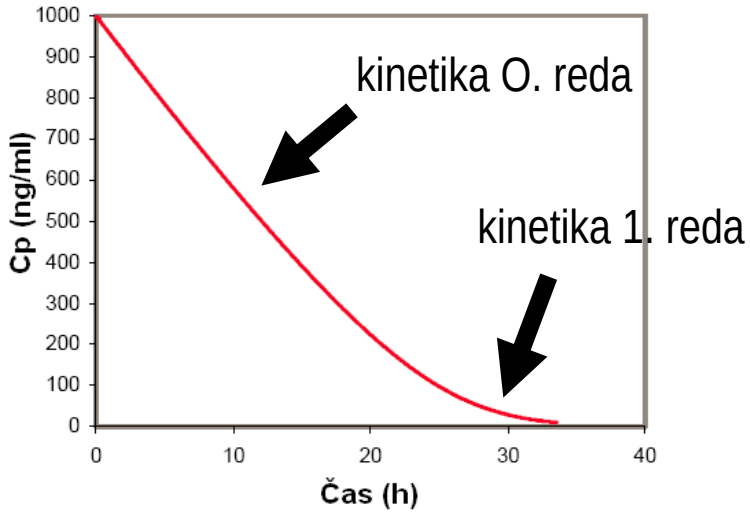




- krvna koncentracija je PROPORCIONALNA odmerku
- hitrost izločanja je PROPORCIONALNA koncentraciji

Nelinearna farmakokinetika





- krvna koncentracija NI PROPORCIONAL NA odmerku
- hitrost izločanja NI PROPORCIONAL NA koncentraciji ⇨ Michaelis-Mentenova encimska kinetika

Odvisnost koncentracije fenitoina od časa

Odvisnost koncentracije fenitoina od časa

(točke predstavljajo povprečne vrednosti vsaj sedmih podatkov)