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Pharmacokinetic Introduction

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Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- have an basic understanding of the scope and impact of biopharmaceutics and pharmacokinetics
- have a general knowledge of the factors affecting the rate and extent of drug absorption, distribution, metabolism and excretion

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An Introduction to Pharmacokinetics

[A](#) Family Circle cartoon show a young child given an im injection who 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 and how quickly this movement occurs. During this course many of the processes which control the absorption, distribution, metabolism, and excretion of drugs will be discussed.

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Complex Interactions

[C](#)omplex picture of drug interactions in the body. This slide gives an idea of the complexity of drug disposition. Shown in this slide 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 often is much simpler. Many of these processes may be fast or not significant for any given drug.

References

- Creasey, W.A. 1979 **Drug Disposition in Humans, The Basis of Clinical Pharmacology**, Oxford University Press, New York p89

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Drug Transport

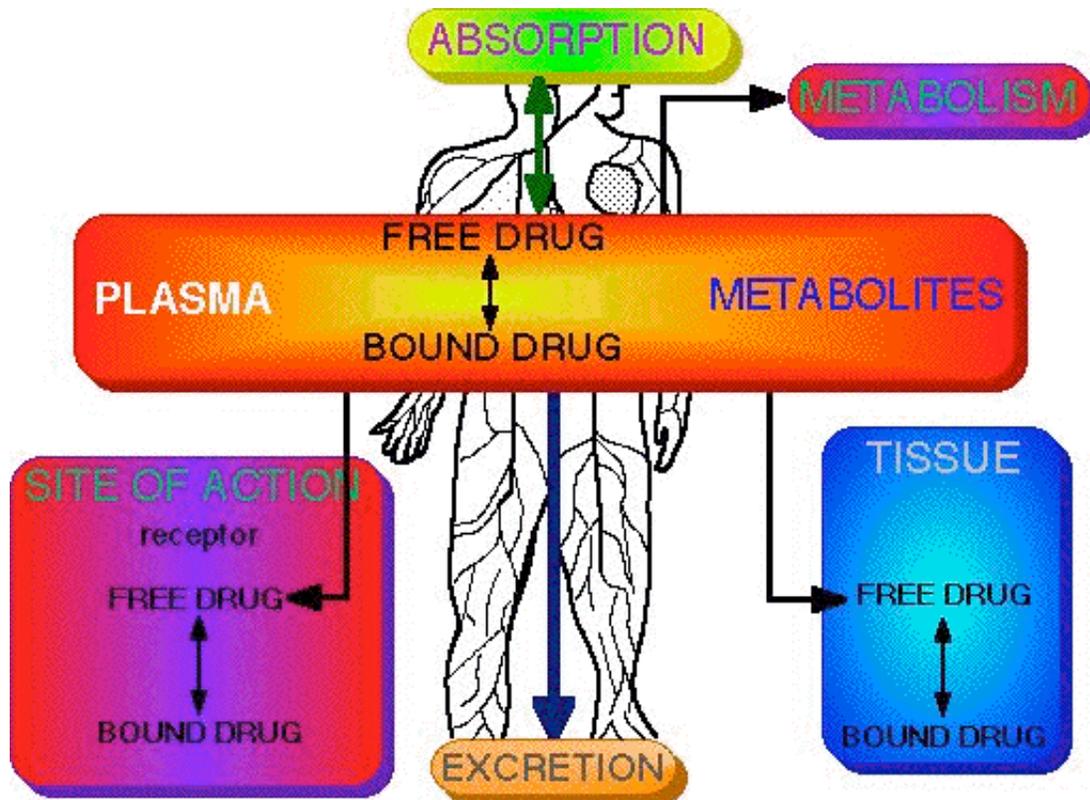


Fig 3.4.1 Slide of processes involved in drug transport. Here the major processes are represented in a less physiological fashion. It is with this approach that we will look at much of the course material this semester. The headings **Absorption, Distribution, Metabolism, and Excretion** are important.

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One, Two and Three Compartment Models

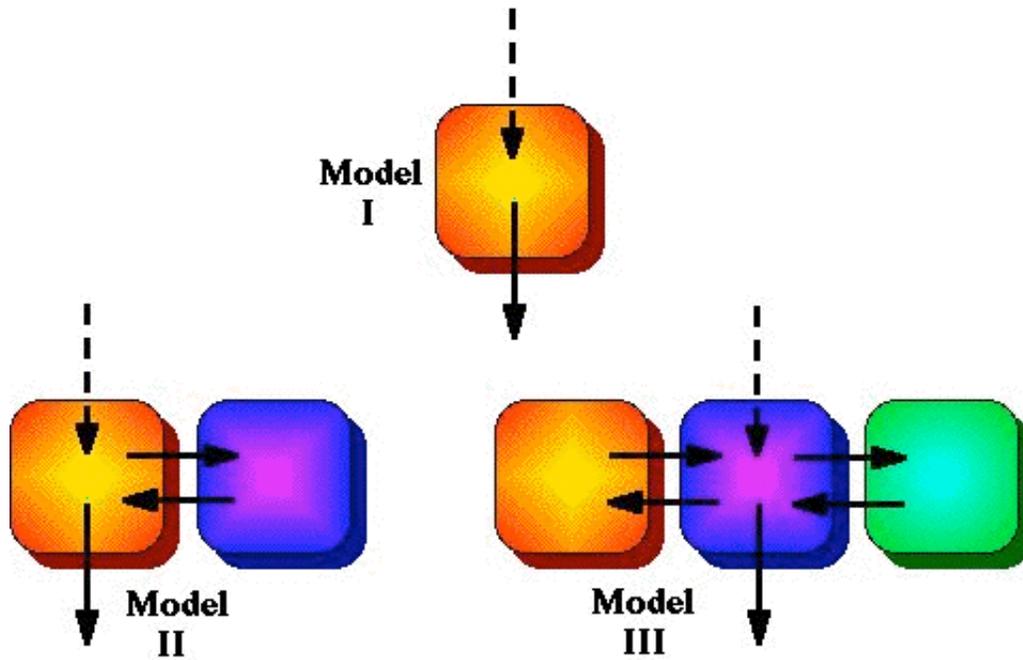


Fig 3.5.1 Slide of one, two, and three compartment pharmacokinetic models. Fortunately many of the processes involved in drug movement around the body are not saturated at normal therapeutic dose levels. The pharmacokinetic - mathematical models that can be used to describe plasma concentration as a function of time can then be much simplified. 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.

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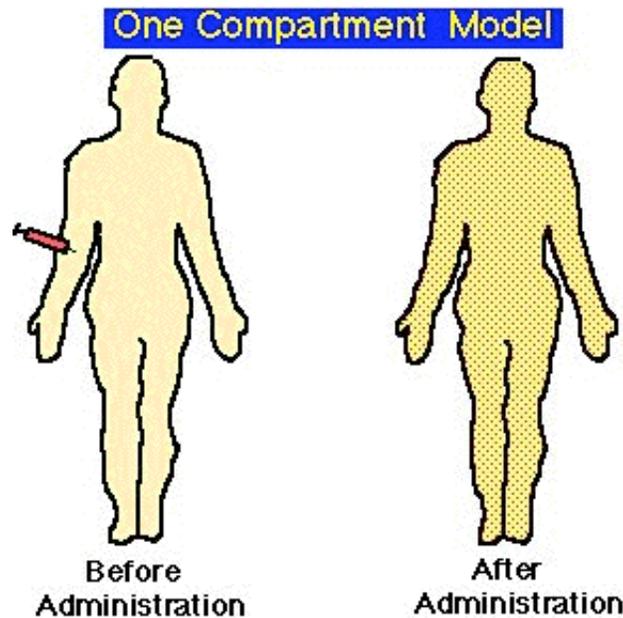
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IV Bolus Dose - One Compartment



redrawn from Niazi, 1979

Fig 3.6.1 Slide of body before and after a rapid IV bolus 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.

References

- Niazi, S. 1979 **Textbook of Biopharmaceutics and Clinical Pharmacokinetics**, Appleton-Century-Crofts, New York, p142

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Absorption and Elimination

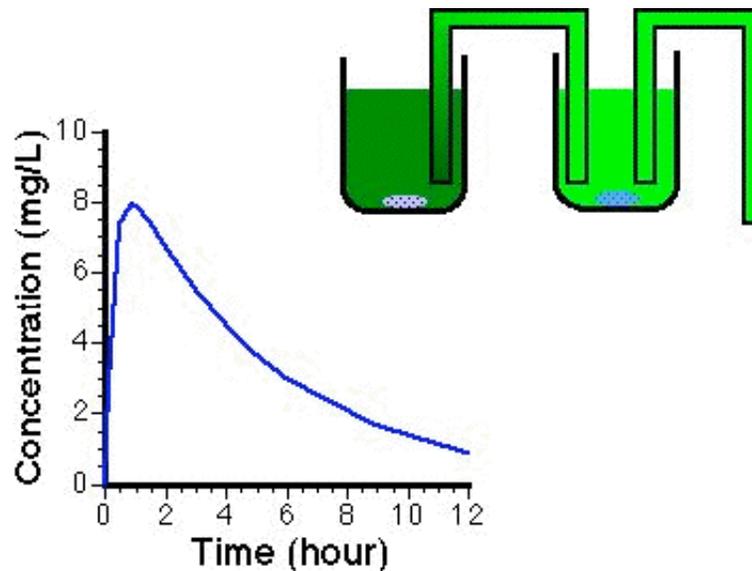


Fig 3.7.1 Slide of oral curve and beakers. We can picture oral administration as water flowing from one bucket (representing the GI tract) into a second beaker (representing the body). At first drug flows into the 'body' beaker and the level rises, as drug concentration rises, then after peaking the levels start to fall as elimination overtakes absorption. This can be represented as an experiment in lab where the body is represented as a beaker. In the lab experiment a dye concentration represents drug concentration in the body.

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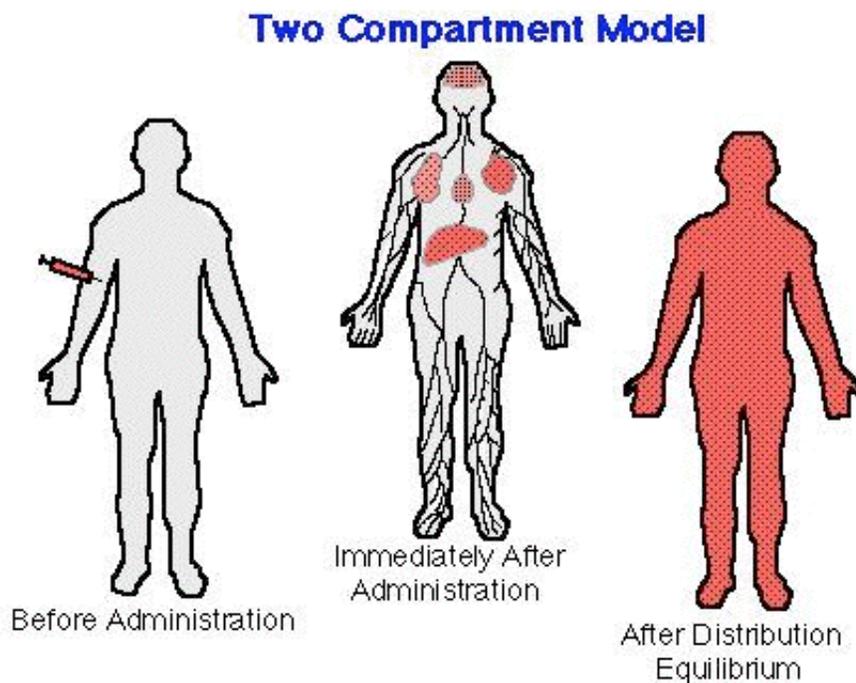
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IV Bolus Two Compartment Model



redrawn from Niazi, 1979

Fig 3.8.1 Slide of an 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 often 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.

References

- Niazi, S. 1979 **Textbook of Biopharmaceutics and Clinical Pharmacokinetics**, Appleton-Century-Crofts, New York, p175

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Two Compartment Model

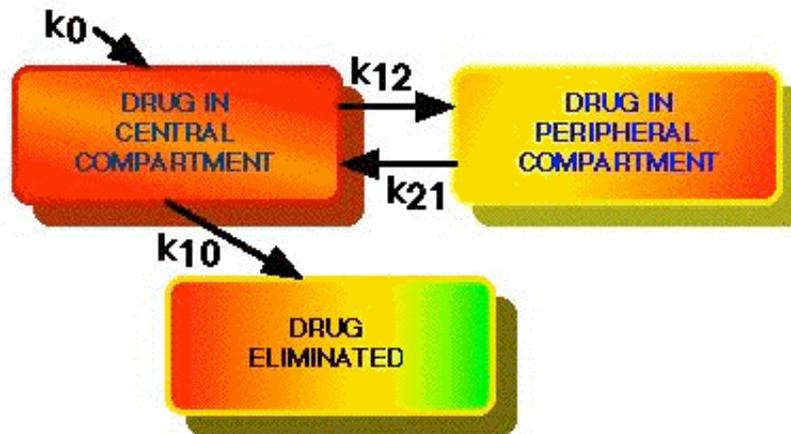


Fig 3.9.1 A diagram of a two compartment model showing the parameters to be measured. The processes of distribution and excretion can be represented by the rate constants k_{12} , k_{21} , and k_{10} . The rate constant k_0 representing an infusion or absorption process. The drug appears to be dissolved in the body volume. This volume is the 'apparent' volume of distribution.

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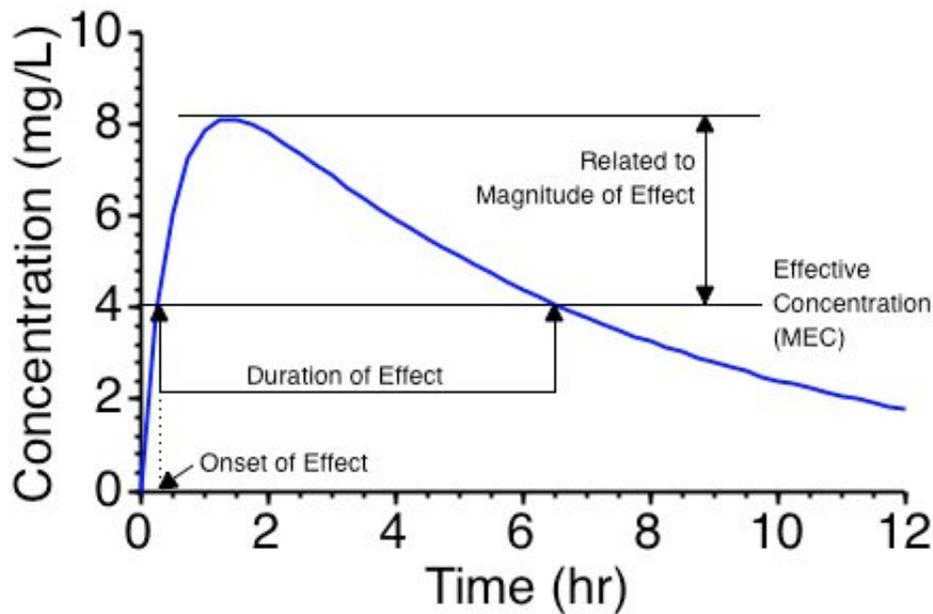
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Drug Effect *versus* Time



redrawn from Barr, 1968

Fig 3.10.1 Slide showing 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 receptor site this will be reflected as a required blood concentration.

References

- Barr, W.H. 1968 Principles of biopharmaceutics, **Amer. J. Pharm. Ed.**, **32**, 958

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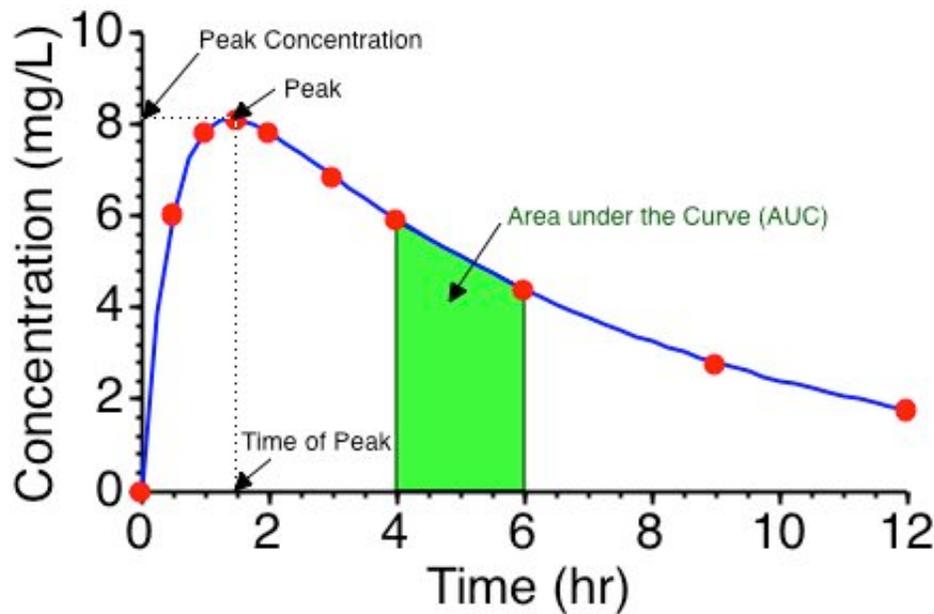
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Drug Product Performance Parameters



redrawn from Dittert and DiSanto, 1974

Fig 3.11.1 Slide of biopharmaceutic parameters over a blood time curve. This slide shows some of the biopharmaceutic parameters which can be used to measure drug product performance. Later in the semester we will use the trapezoidal method of calculating AUC.

References

- Dittert, L.W. and DiSanto, A.R. 1973 The bioavailability of drug products, *J. Amer. Pharm. Assoc.*, **NS13**, 421-432

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A(bsorption) D(istribution) M(etabolism) E(xcretion)

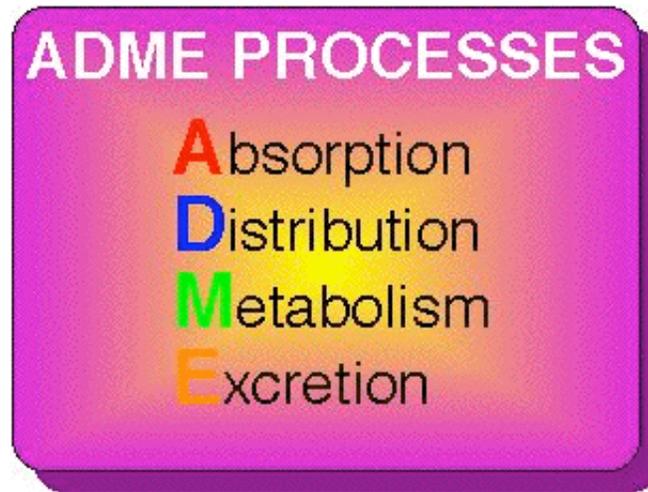


Fig 3.12.1 Slide listing the four pharmacokinetic processes. We will briefly consider each of these processes in turn. A(bsorption) D(istribution) M(etabolism) E(xcretion).

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Routes of Drug Administration

Intramuscular	Eye
Subcutaneous	Nasal
Intravenous	Ear
Intrasynovial	Oral
Intracardiac	Sublingual
Intrathecal	Buccal
	Rectal
	Vaginal
	Urethral
	Topical

information from Benet, 1974

Fig 3.13.1 Slide showing a model with the various routes of administration. Later we will discuss different routes of administration and see how these effect the kinetics of drug disposition. 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 ROA. 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.

References

- Benet, L.Z. 1974 Input factors as determinants of drug activity: route, dose, dosage regimens and the drug delivery system, in **Principles and Techniques of Human Research and Therapeutics**, Vol 3, McMahon, F.G. ed., Futura, New York, pp 9-23 through Oie, S and Benet, L.Z. Chapter 5 **The Effect of Route of Administration and Distribution on Drug Action** in **Modern Pharmaceutics**, 4th ed., ed. Banker, G.S. and Rhodes, C.T. Marcel Dekker, New York, NY, Fig 2, p 121

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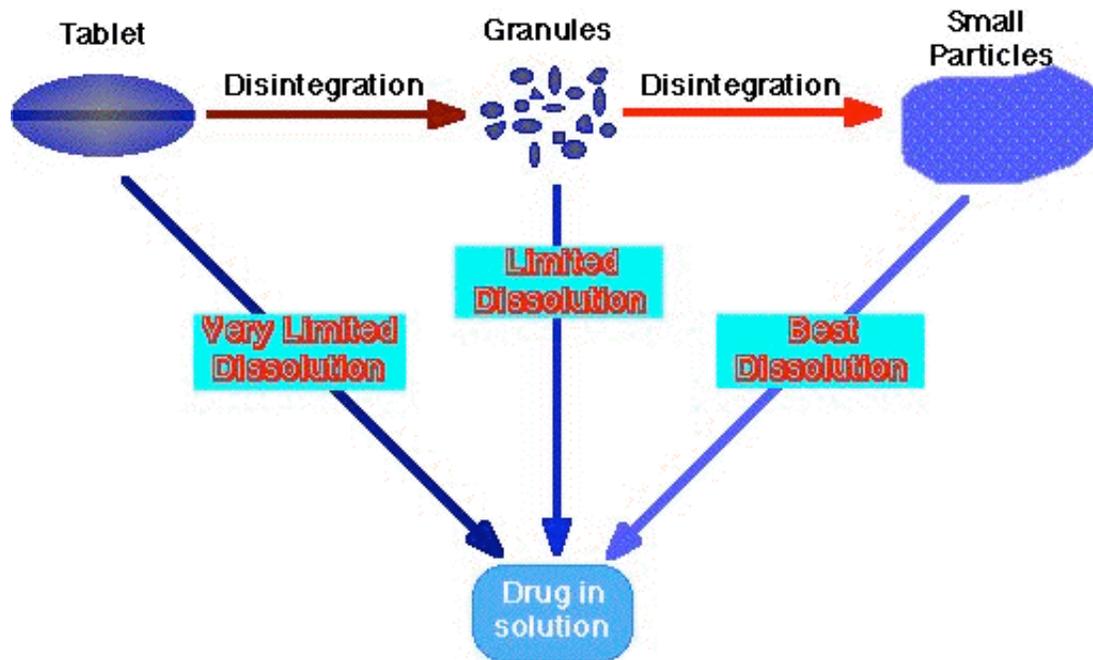
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Tablet Dissolution



redrawn from Cadwallader, 1983

Fig 3.14.1 Slide showing 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.

References

- Cadwallader, D.E. 1983 **Biopharmaceutics and Drug Interactions**, 3rd ed., Raven Press, New York, p72

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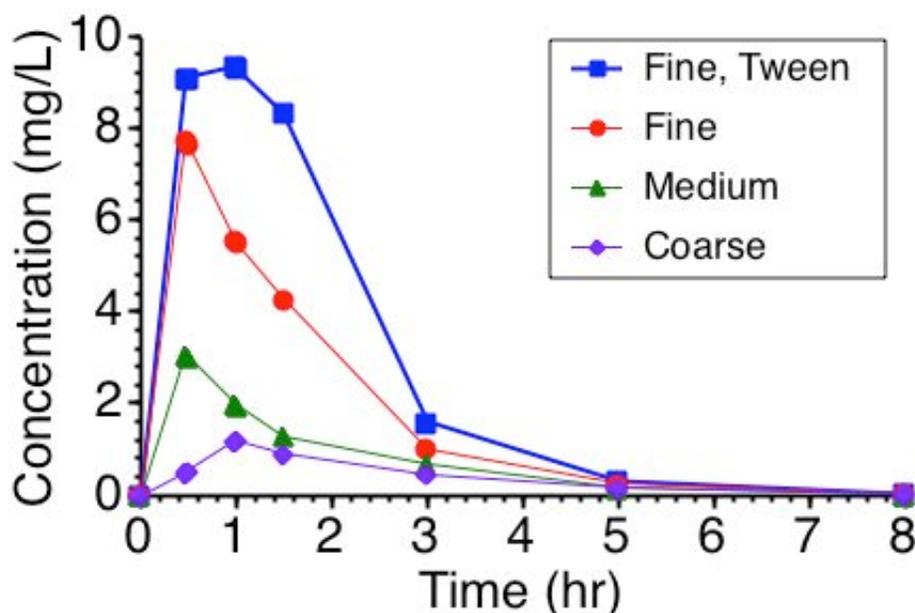
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Absorption *versus* Particle Size



redrawn from Prescott et al., 1970

Fig 3.15.1 Slide showing plasma phenacetin *versus* time curve after oral administration of 1.5 g in various suspension dosage forms. The effect of particle size on drug absorption is shown in this slide. Generally speaking the smaller the particle size the quicker the absorption. By increasing the particle surface area it is possible to increase the dissolution rate. However very small particle can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption. The intestinal fluids usually contain some materials which can act as wetting agents, however drug dissolution testing *in vitro* may neglect this effect.

References

- Prescott, L.F., Steel, R.F. and Ferrier, W.R. 1970 The effects of particle size on the absorption of phenacetin in man, *Pharmacol. Therap.*, **11**, 496-504

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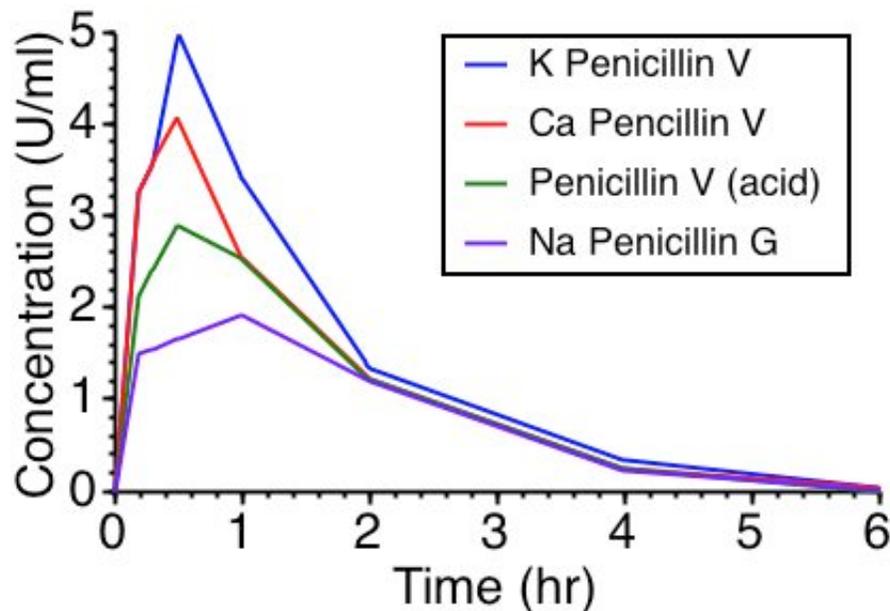
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Absorption of Different Salt Forms



redrawn from Juncher and Raaschou, 1957

Fig 3.16.1 Slide showing plasma penicillin concentration *versus* time curve after oral administration of various salts. 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.

References

- Juncher, H. and Raaschou, F. 1957 The solubility of oral preparations of penicillin V, *Antibiot. Med. Clin. Therap.*, **4**, 497

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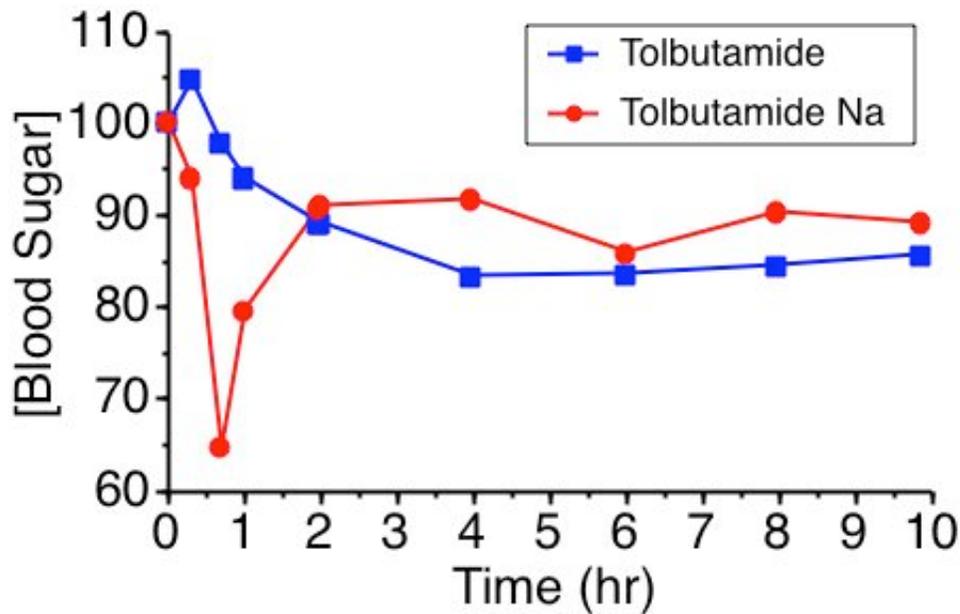
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Drug Effect and Absorption



redrawn from Wagner, 1961

Fig 3.17.1 Slide showing blood sugar levels after tolbutamide acid and salt. 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.

References

- Wagner, J.G. 1961 Biopharmaceutics: absorption aspects, *J. Pharm. Sci.*, **50**, 359

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Effect of Absorption Rate Constant

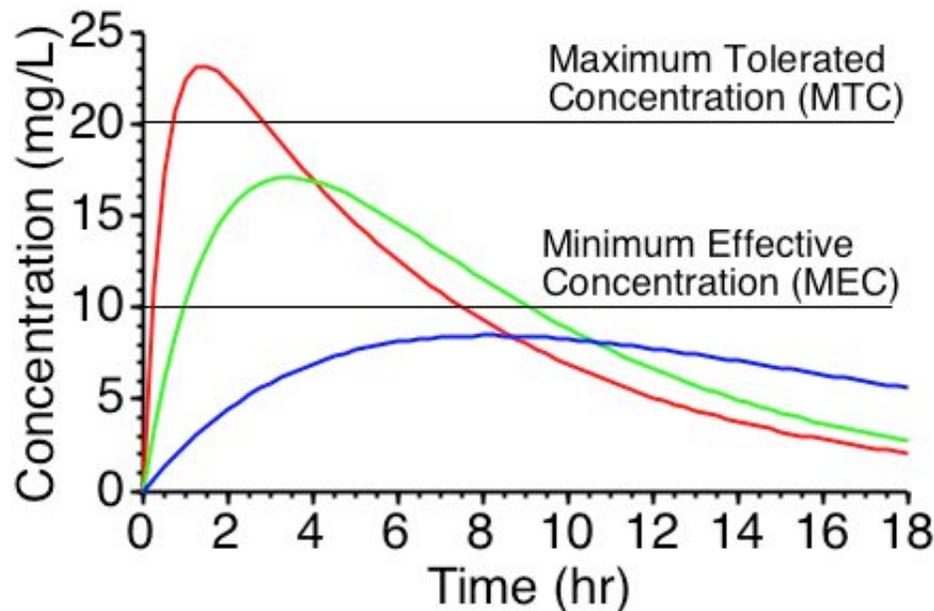


Fig 3.18.1 Slide showing plasma concentration time curves for three theoretical formulations with different k_a values. The plasma concentrations achieved can be controlled by the rate of drug absorption. As shown product I would be toxic. A smaller dose, or a slower formulation should be considered. 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.

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Distribution

In a Family circle cartoon a young patient might asks "How does the medicine know where to go". Drug is distributed throughout the body directed by the physicochemical properties of the drug and the physiology of the body. Once the drug is absorbed what happens to it? The processes of excretion, metabolism, and distribution then take over to move the drug through and out of the body. Drug is distributed throughout the body depending on the physicochemical properties of the drug and the physiological properties of the body membranes and fluids.

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ADME

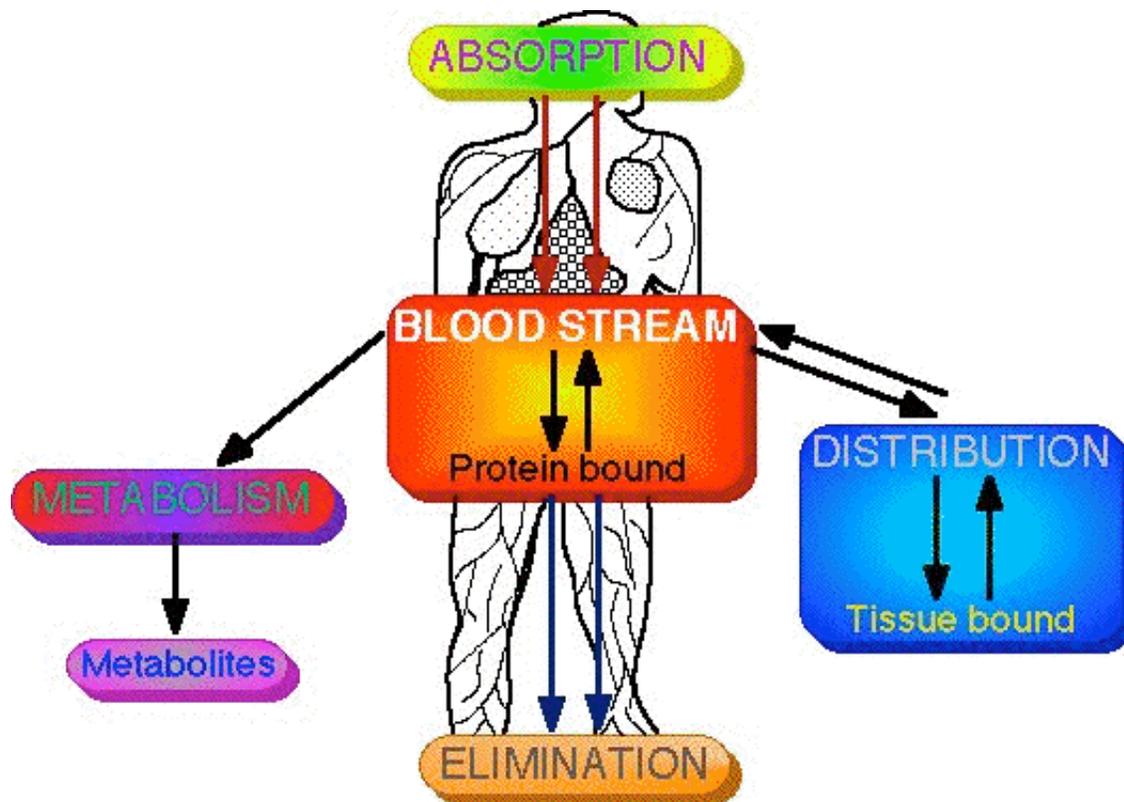


Fig 3.20.1 Slide showing the four processes schematically. Let's consider elimination.

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Drug Elimination

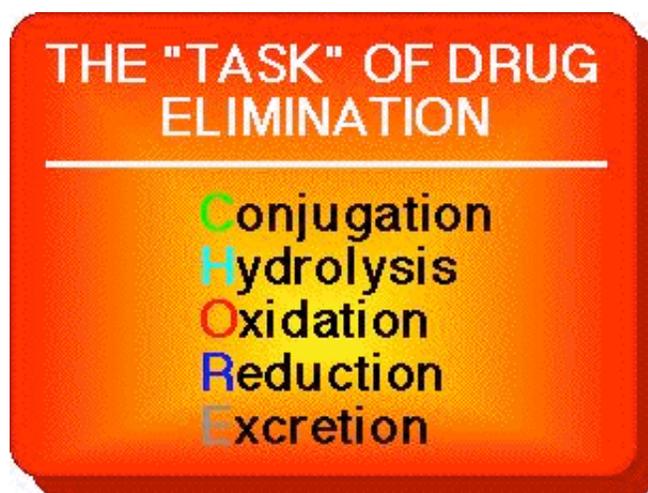


Fig 3.21.1 Slide listing methods of drug elimination, metabolism and excretion. The next topic is excretion. Drugs are eliminated by a number of processes. Polar drugs are easily filtered from the blood in the kidneys and removed into urine. However non polar material is generally reabsorbed from the kidney or distributes 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.

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Elimination and Multiple Dose

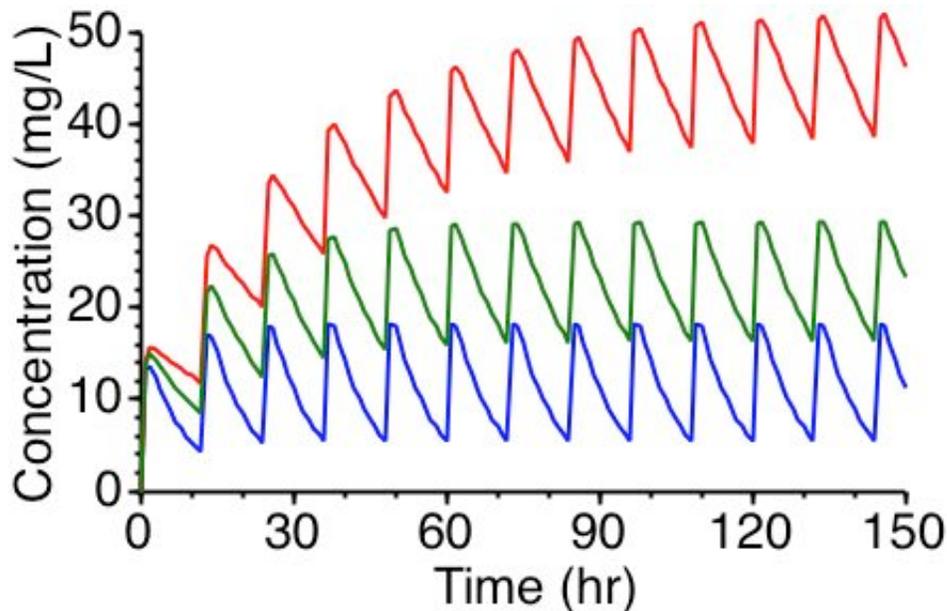


Fig 3.22.1 Slide showing multiple dose curves with slow, medium, and fast excretion. Alteration of drug elimination is particularly important when drugs are given repeatedly. If it is assumed that the drug is eliminated normally when in fact it is slowly eliminated, drug accumulation may occur with toxic concentrations reached. Alternately faster elimination than expected may cause sub therapeutic concentrations to be reached.

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Dosing Kanamycin

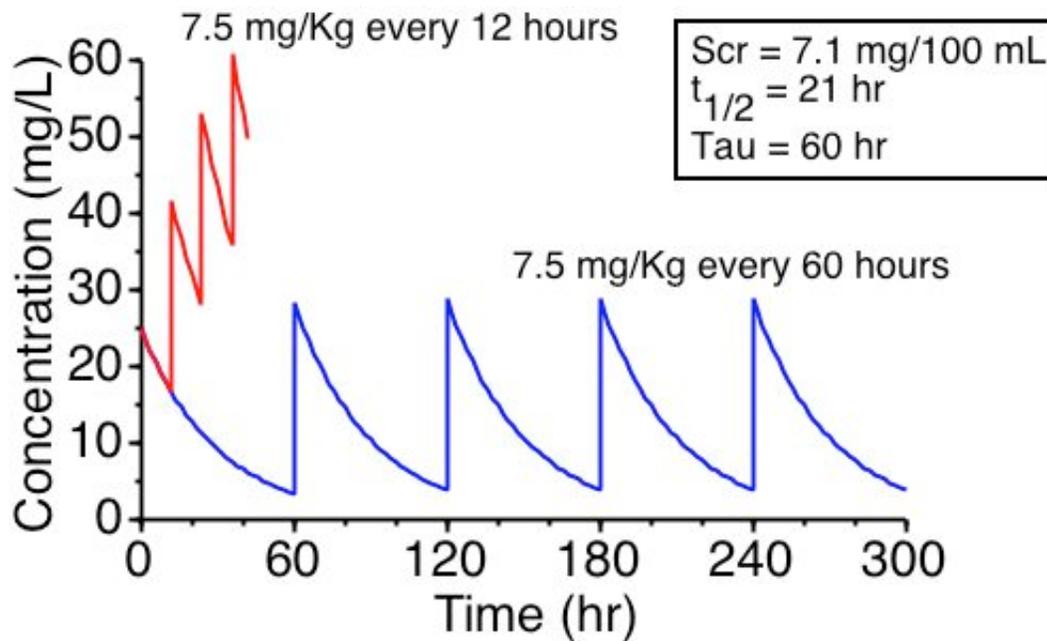


Fig 3.23.1 Slide showing a clinical example with kanamycin, showing theoretical curve after multiple dose and a better curve after dose adjustment. Kanamycin is a useful drug but it can cause some serious side effects. By controlling the blood concentration of this drug it is possible to use it effectively. 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.

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Renal Disease and Drug Elimination

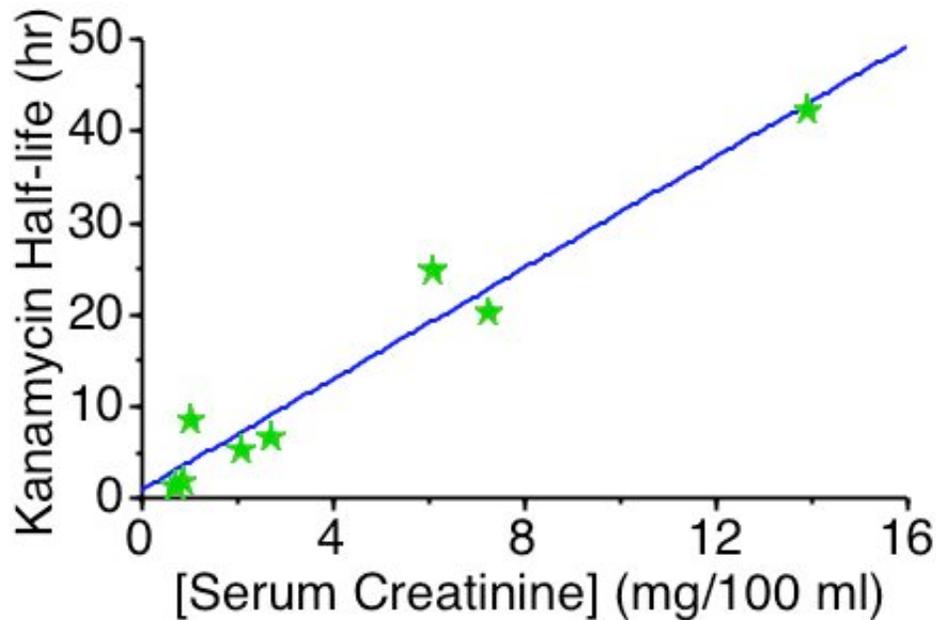


Fig 3.24.1 Slide showing relationship between kanamycin half-life and serum creatinine level. As kidney function is reduced the serum creatinine level increases and the also the kanamycin takes longer to be eliminated from the body.

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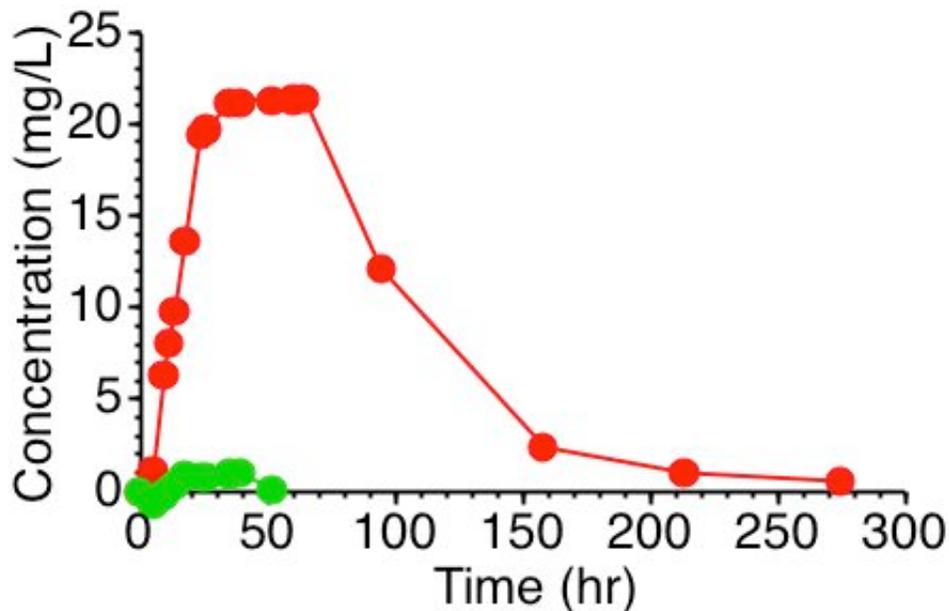
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Absorption and First-Pass Effect



redrawn from Barr, 1969

Figure 3.25.1 Slide showing extra absorption of salicylamide at higher doses. The green dots represent results after a 1 g dose and the red dots represent results after a 2 g dose. The original figure presented results after 0.3 and 0.5 g doses with resulting concentrations below those determined after the 1 g dose. 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.

References

- Barr, W.H. 1969 Factors involved in the assessment of systemic or biologic availability of drug products, *Drug Inform. Bull.*, 3, 27-45

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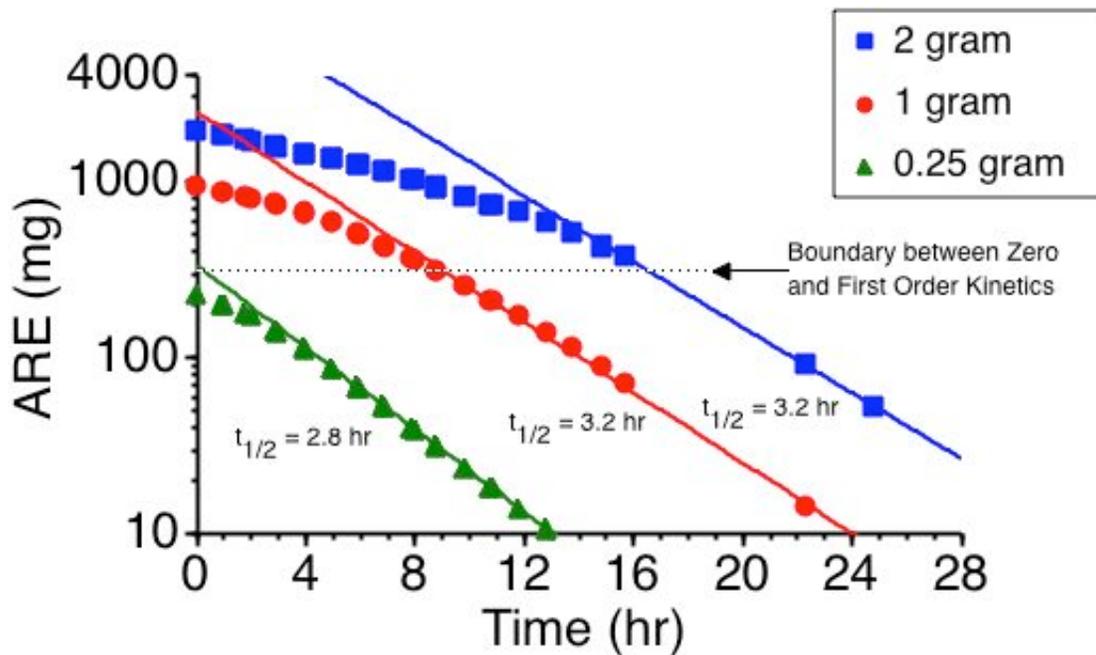
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Aspirin Elimination



redrawn from Levy, 1965

Figure 3.26.1 Slide of aspirin plasma concentration as a function of time after 0.25, 1 or 2g. At higher doses the metabolism of aspirin is reduced by saturation. The elimination rate constant (as represented by the slope) is reduced.

References

- Levy, G. 1965 *J. Pharm. Sci.*, 54, p959

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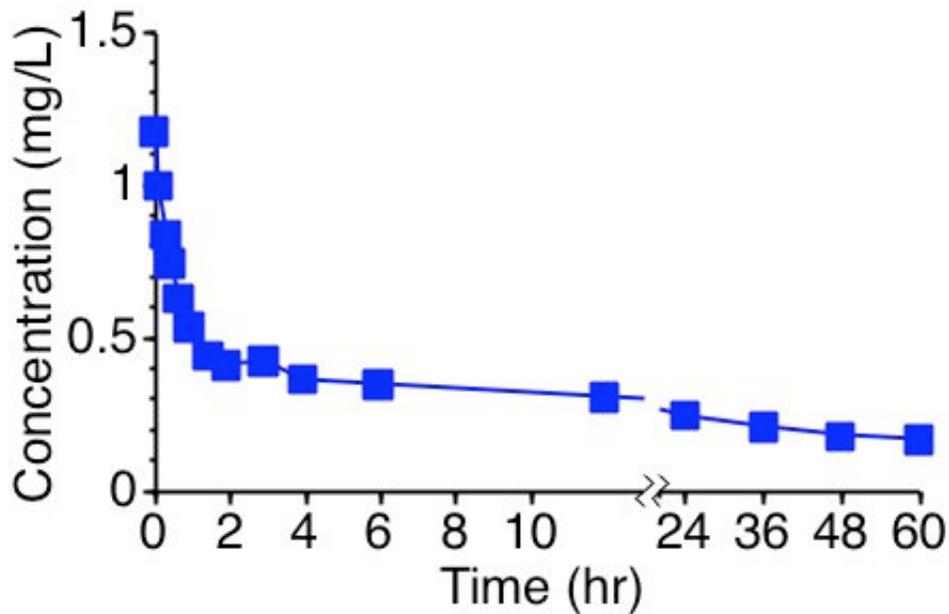
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Multiphasic Drug Elimination?



redrawn from Smith et al., 1973

Figure 3.27.1 Slide of pentobarbital plasma concentration *versus* time illustrating the multiphasic distribution pattern. From a plasma concentration time curve it may appear that this drug is rapidly eliminated from the body. Actually little of the drug is eliminated with much of it being distributed in various tissues of the body. Here distribution is a major factor affecting the overall kinetics of this drug. By looking further we can see the real picture.

References

- Smith, R.B., Dittert, L.W., Griffen Jr., W.O., and Doluisio, J.T. 1973 Pharmacokinetics of Pentobarbital after Intravenous and Oral Administration, *J. Pharmacokin. Biopharm.*, **1**, p5

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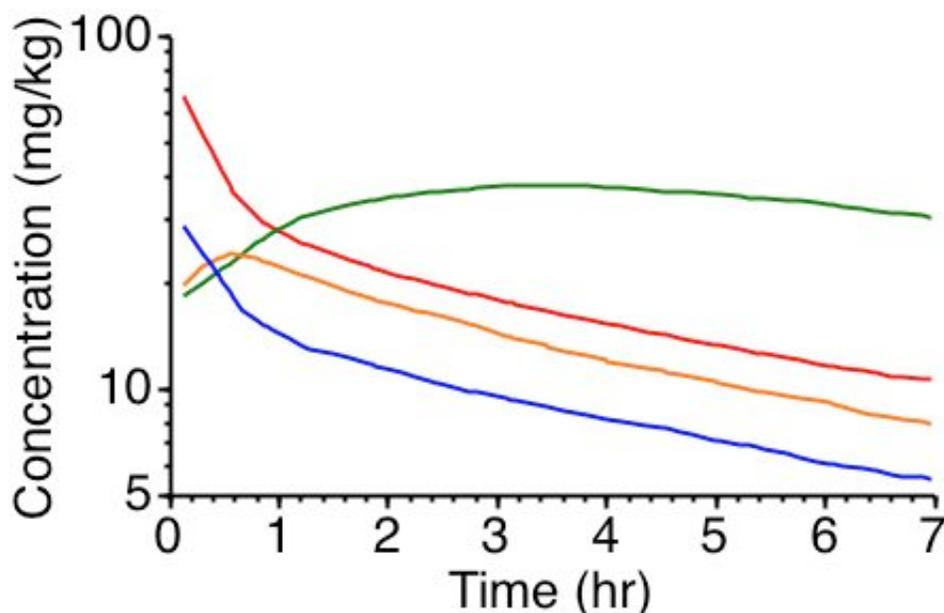
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Tissue Concentration *versus* Time



redrawn from Bischoff and Dedrick, 1968

Figure 3.28.1 Slide showing pentobarbital concentrations in various tissues. This illustrates the slow distribution of some drugs into and out of various tissues. Brain and other rapidly perfused tissues rapidly lose drug while other tissues are building up drug concentrations. Eventually significant amounts of drug will be collected in fat tissue from which it may only slowly be removed. The green line represents concentrations in adipose tissue (poorly perfused), the red line represents concentrations in viscera (highly perfused lean tissue), the orange line represents concentrations in lean tissue (poorly perfused) and the blue line represents concentrations in blood.

References

- Bischoff, K.B. and Dedrick, R.L. 1968 Thiopental Pharmacokinetics, *J. Pharm. Sci.*, **57**, 1347-1357

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Distribution

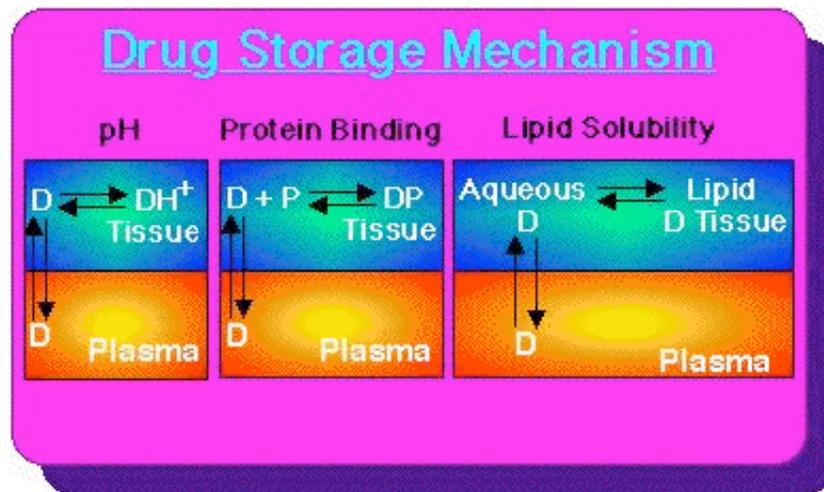


Fig 3.29.1 Slide showing other distribution mechanisms. Methods by which drug is kept in the body for extended action. pH, protein binding and fat storage are three major processes by which drug may be kept within the body. These are mechanisms by which drugs can be distributed throughout the body, protected from elimination, and cause a more prolonged activity.

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Individualized Dosage Regimen

"One for man. Two for a horse". There are many processes controlling drug disposition. Therefore dose adjustment is often necessary to produce the desired response from the patient. During this course we will look at the equations needed to calculate appropriate doses and the factors which can influence the plasma concentration of various drugs.

In the next session we will start to look at the mathematics associated with a one compartment pharmacokinetic model...

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