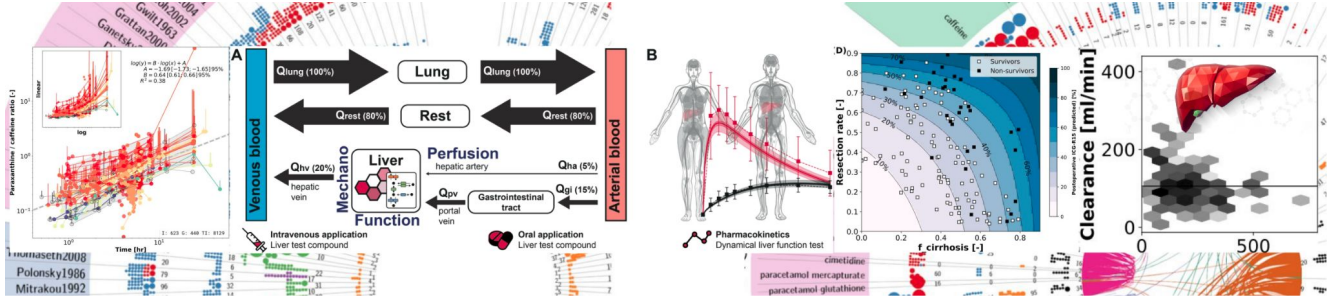

Pharmacokinetics Modeling Course

Introduction Pharmacokinetics

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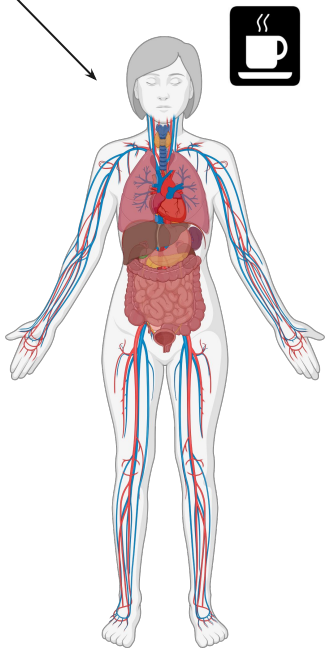
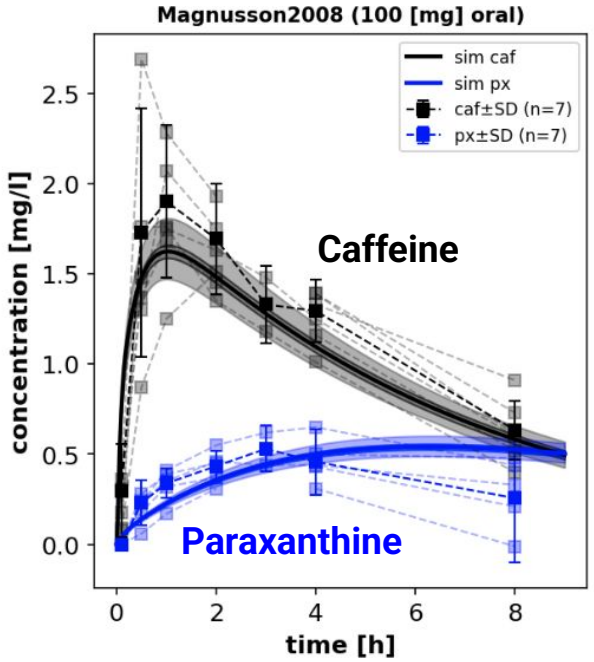
🎯 Teaching Goals

By the end of the lesson, you should be able to:

1. **Define pharmacokinetics (PK)** and differentiate it from pharmacodynamics (PD).
2. **Explain the four ADME processes** (Absorption, Distribution, Metabolism, Excretion).
3. Understand the **importance of PK in therapy optimization** and **personalized medicine**.
4. Identify key **PK parameters** (e.g., AUC, half-life, clearance, volume of distribution).
5. Recognize **factors influencing drug disposition** (e.g., bodyweight, pharmacogenomics, organ function).

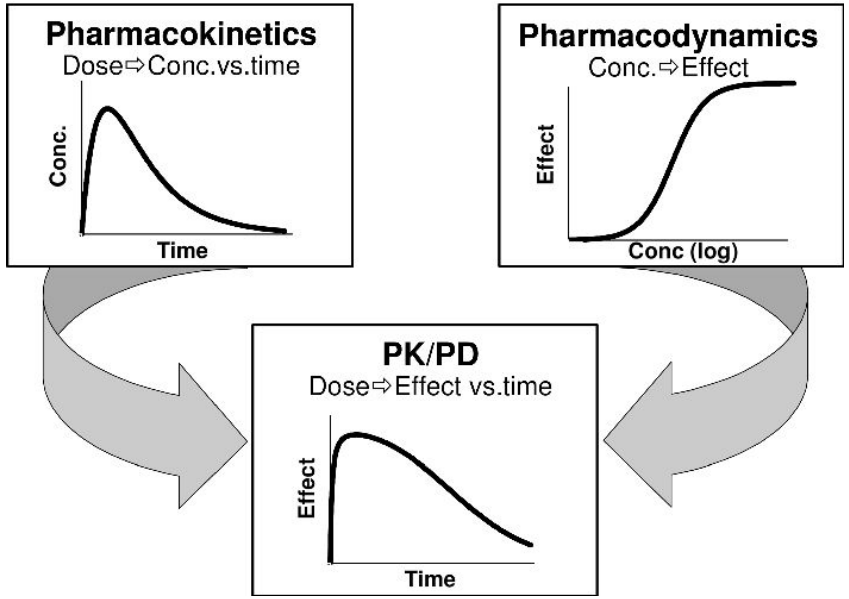
Pharmacokinetics of drugs

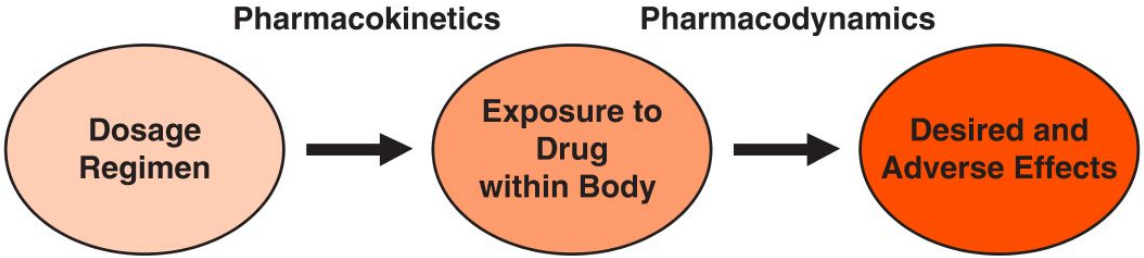




Pharmacokinetics (PK) & pharmacodynamics (PD)

- **Pharmacokinetics** is **what the body does to the drug**
  - study of the time course of drug absorption, distribution, metabolism, and excretion
  - **drug disposition**
- **Pharmacodynamics** is **what the drug does to the body**
  - **desired** (and adverse) **effects**





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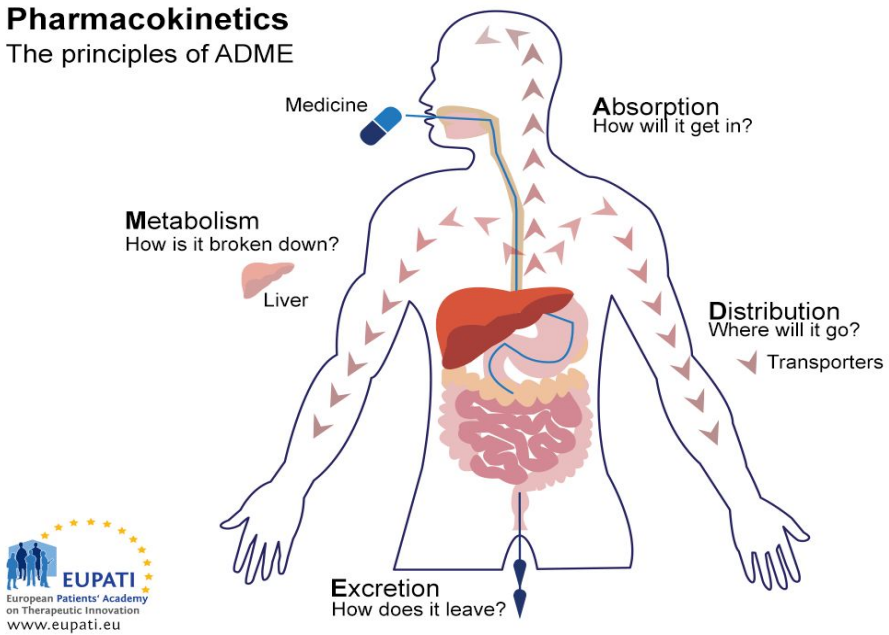
ADME



ADME processes determine pharmacokinetics

- **A**bsorption
- **D**istribution
- **M**etabolization
- **E**limination

ADME - Compartment Model

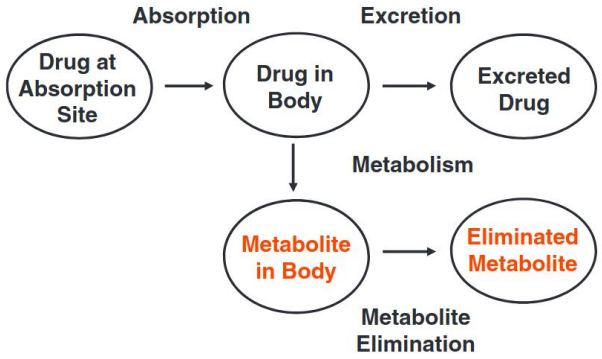


FIGURE 2-5 A drug is simultaneously absorbed into the body and eliminated from it by excretion and metabolism. The processes of absorption, excretion, and metabolism are indicated with arrows, and the compartments with ovals. The compartments represent different locations and different chemical species (color = metabolite). Metabolite elimination may occur by further metabolism (not shown) or excretion.

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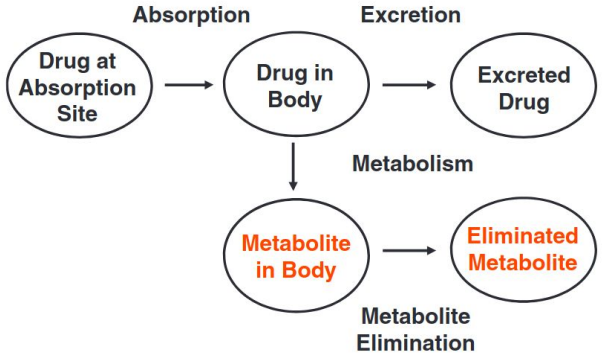
ADME - Compartment Model



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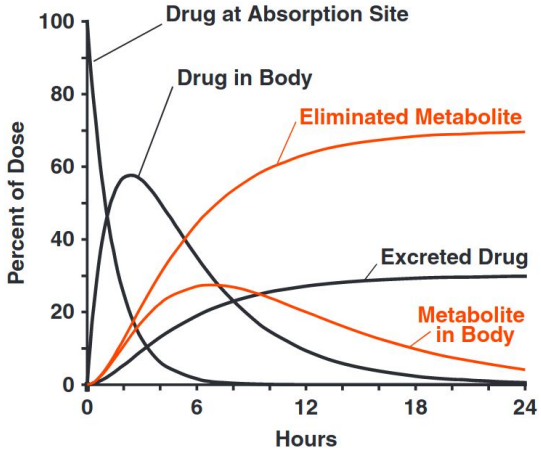

FIGURE 2-6 Time course of drug and metabolite in each of the compartments shown in Fig. 2-5. The amount in each compartment is expressed as a percentage of the dose administered. In this example, the dose is completely absorbed. At all times, the sum of the molar amounts in the five compartments equals the dose.

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Therapeutic Window

- optimal dosing regime
- avoid adverse effects
- avoid ineffective therapy (**efficacy**)

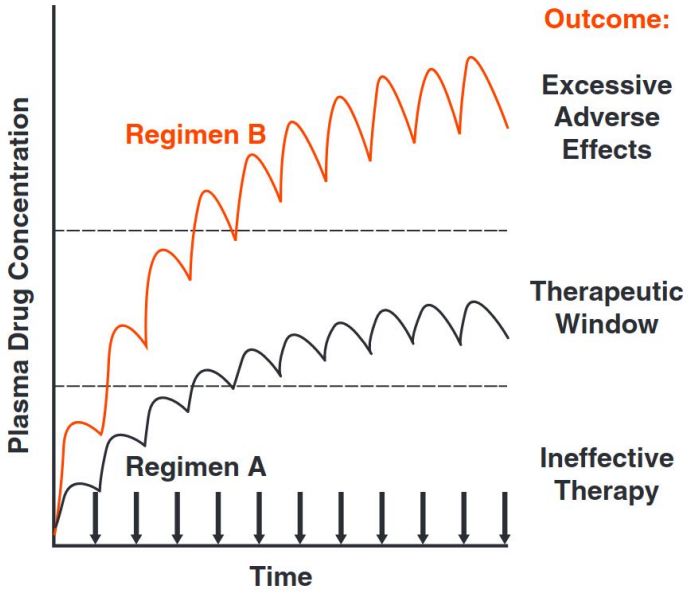

FIGURE 1-4 When a drug is given repetitively in a fixed dose and at a fixed time interval (*arrows*), it accumulates within the body until a plateau is reached. With regimen A, therapeutic success is achieved, although not initially. With regimen B, the therapeutic objective is achieved more quickly, but the drug concentration is ultimately too high, resulting in excessive adverse effects.

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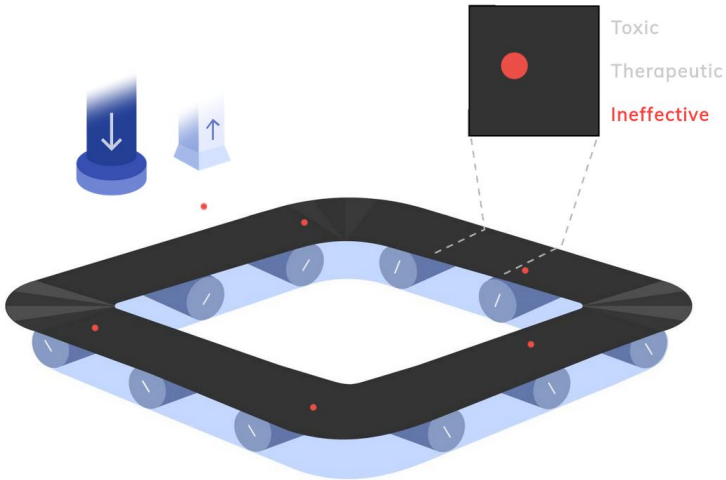
🏃 Therapeutic Window 🏃

https://www.icp.org.nz/drug-clearance



Dose Rate	Low	High
Clearance	Small	Large

Pharmacokinetic Parameters

- **C_{max}** : Maximal concentration
- **T_{max}** : time of maximal concentration
- **AUC** : area under the curve
- **k_{el}**: elimination rate
  fitting linear part of terminal phase (log)
- **$t_{1/2}$** : half-life (= ln2/k_{el})
  time for concentration to fall to half
- **Vd**: volume of distribution
  (= CL/k), dilution space
- **CL**: clearance (=Dose/AUC, =Dose/$C(0)_{extrapolated}$)

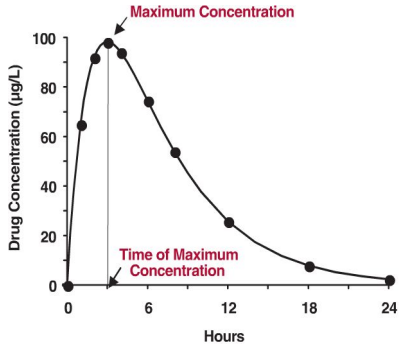


FIGURE 2-1. Drug concentration–time curve following a single oral dose showing the maximum systemic exposure (C_{max}) and the time of its occurrence (t_{max}). The concentration could represent drug in whole blood, plasma, or serum.

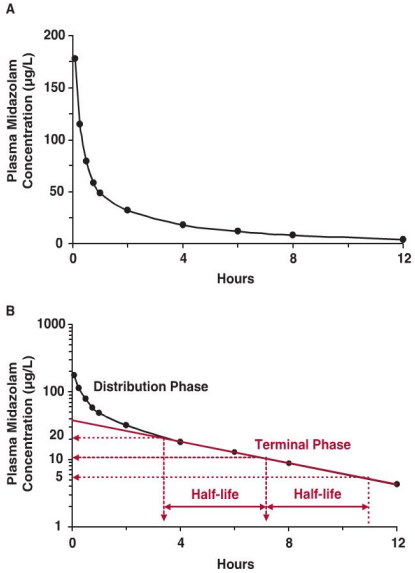


FIGURE 3-4. **A.** Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. **B.** The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Välisalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29: 272–277.)

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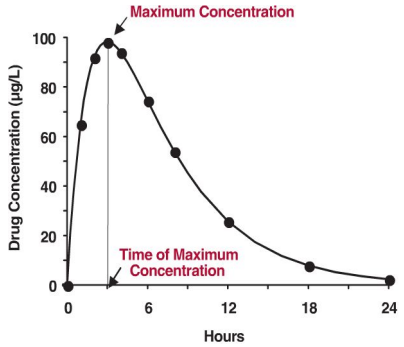
Pharmacokinetic Parameters

- Pharmacokinetic properties
  - determine route of administration
  - dose and frequency of dosing
  - onset of action
  - peak action time
  - duration of action



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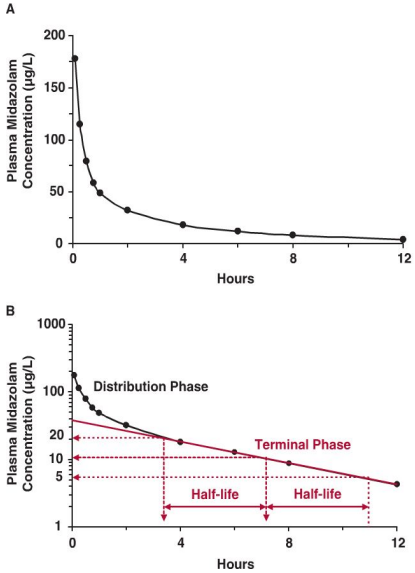

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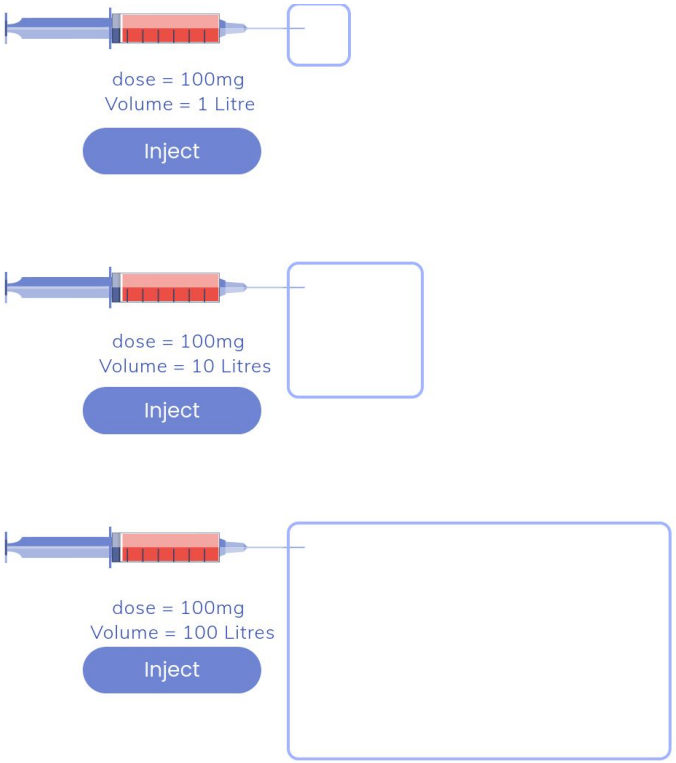
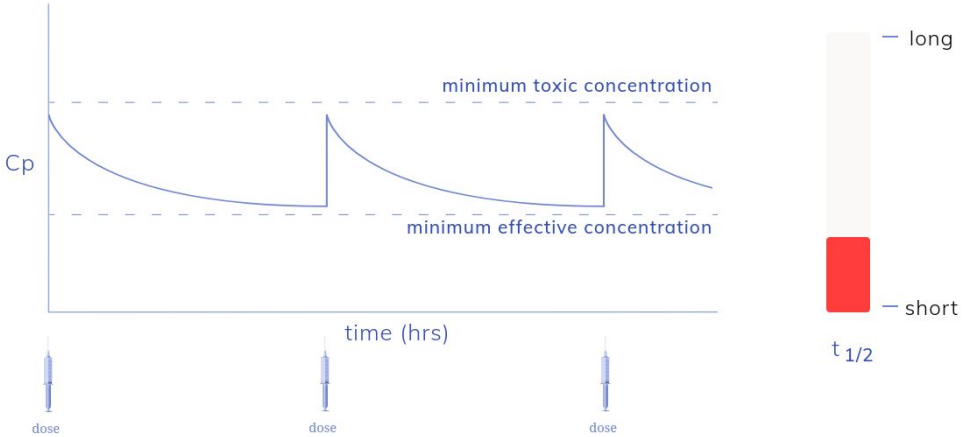
🏃 Volume of Distribution 🏃

https://www.icp.org.nz/volume-of-distribution



🏃 Half-life 🏃

https://www.icp.org.nz/the-half-life



Dose size	Small	Large
Dose interval	Small	Large
Vd	Low	High
Cl	Low	High

Variability between drugs

- large differences in physico-chemical properties between compounds
- large differences in pharmacokinetic parameters

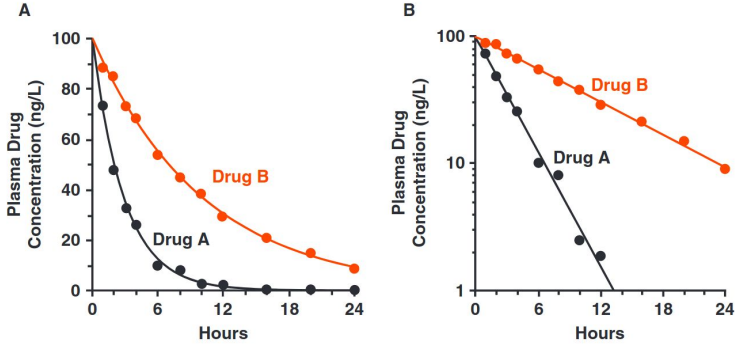


FIGURE 5-1 Drugs A (*black circle*) and B (*colored circle*) show the same initial (peak) exposure, but have different half-lives and total exposure–time profiles (AUC). Regular (cartesian) plot (*left*). Semilogarithmic plot (*right*). Doses of both drugs are the same.

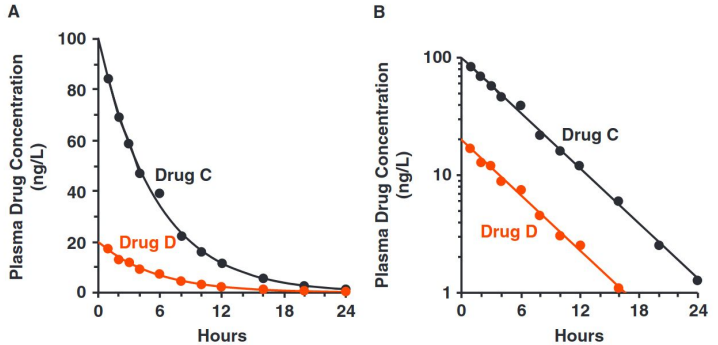


FIGURE 5-2 Drugs C (*black circle*) and D (*colored circle*) have the same half-life but different initial and total exposure–time (AUC) profiles. Regular (cartesian) plot (*left*). Semilogarithmic plot (*right*). Doses of both drugs are the same.

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Variability between drugs

- large variability in pharmacokinetics between drugs

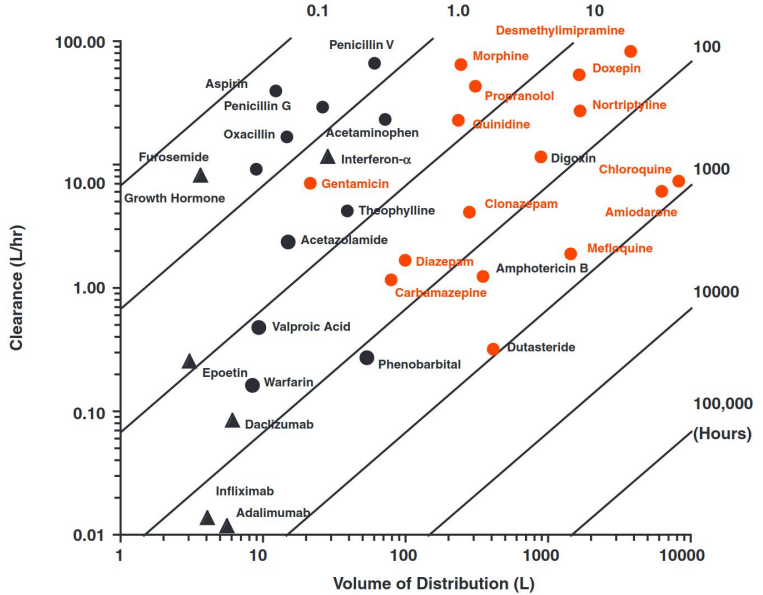

FIGURE 5–8 Clearance (*ordinate*) and volume of distribution (*abscissa*) of selected acidic (*black circle*) and basic (*colored names*), as well as protein (*black triangle*), drugs vary widely. Diagonal lines on the fully logarithmic plot show the combinations of clearance and volume values with the same half-lives (hours). Note that drugs with very low clearance and very large volumes (*lower right-hand quadrant*) are uncommon; their half-lives are often too long for these drugs to be used practically in drug therapy. Note also that large protein drugs have volumes of distribution close to plasma volume (3 L) and that basic compounds tend to have larger volumes of distribution than acids. Digoxin and dutasteride are neutral compounds, while amphotericin B is both a weak acid and a weak base.

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