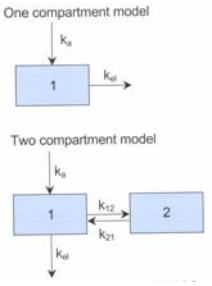
Toxicokinetics

- Classic Toxicokinetics

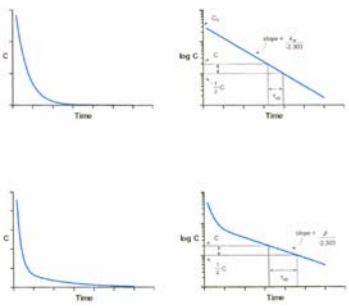


Classical Toxicokinetics

- One Compartment Model
  - Log Plasma Conc vs. Time
  - 1st order process
    - Elimination = biotransformation, exhalation, excretion
  - Mono-exponential Expression

$$C = C_0 e^{-k_{el} t}$$

Classic Toxicokinetics



Classical Toxicokinetics

- Characteristics of 1st Order Kinetics
  - Rate of elimination proportional to plasma concentration
  - Semi log plot- straight line
  - $T_{1/2}$ Biological Half-life independent of dose

$$\frac{C}{C_0} = e^{k_{el}t} \qquad 0.5 = e^{k_{el}t_{1/2}} \qquad \ln(0.5) = k_{el}t_{1/2} \qquad t_{1/2} = \frac{\ln(0.5)}{k_{el}} = \frac{-0.693}{k_{el}}$$

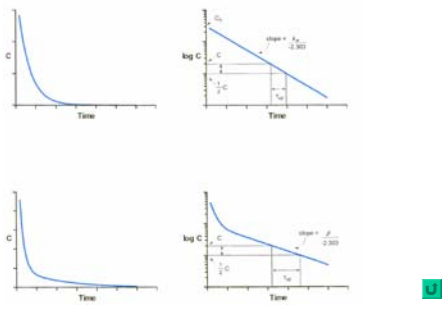
  - Fractional decrease constant with time- k_{el}

Classical Toxicokinetics

- Two Compartment Model
  - Multi-exponential

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

Classic Toxicokinetics



Apparent Volume of Dist. V_d

- V_d is not a real volume. It is the apparent space into which an amount of chemical is distributed in the body to result in a given plasma concentration
- $V_d = D_{iv}/(\beta \times AUC_0^{\infty}) = Dose_{iv}/C_0$

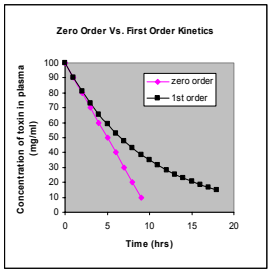
Clearance

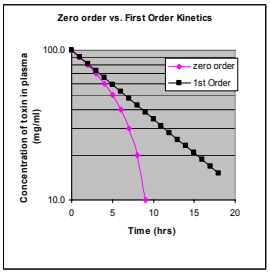
- **Rate of elimination from the body via excretion and biotransformation processes.**
  - (mg/min)/(mg/ml) = ml/min
- **Characterizes efficiency of elimination**
- **Total Body Clearance (TBC)**
  - **$Cl = Cl_r + Cl_h + Cl_i = Dose_{iv}/ AUC_0^{\infty}$ individual organs**
  - **$Cl = V_d \times k_{el}$ one compartment**
  - **$Cl = V_d \times \beta$ two compartments**

Saturation of Elimination

- When elimination kinetics deviates from first order kinetics
- Criteria of non linear kinetics
  - Elimination is not exponential decline
  - AUC is not proportional to the Dose
  - V_d , Cl, k_{el} (β), or $T_{1/2}$ change with increase in dose
  - Composition of excretory products change with dose
  - Competitive inhibition occurs
  - Non proportional changes in response vs. dose

Zero Order VS First Order Kinetics





Saturation of Elimination

- Zero order kinetics
  - Plasma concentration vs. time
  - Elimination constant & independent of amount present
  - $T_{1/2}$ or k_{el} does not exist
- First order kinetics
  - Elimination rate proportional to concentration
  - Semi log plot a straight line
  - K_{el}, V_d, Cl, & $T_{1/2}$ independent of dose
  - Concentration decreases by constant fraction over time

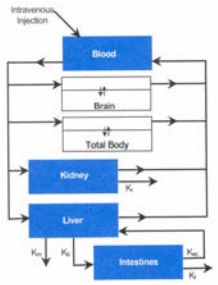
Bioavailability

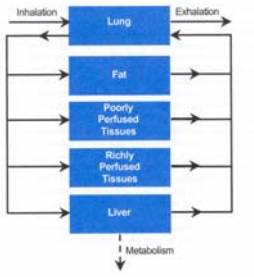
- $$F = \frac{Cl_{iv}}{Cl_{oral}} = \frac{(Dose_{iv})(AUC_{oral\,0\to\infty})}{(Dose_{oral})(AUC_{iv\,0\to\infty})}$$
- Factors Altering availability of oral dose
  - limited absorption
  - intestinal 1st pass effect
  - hepatic 1st pass effect
  - formulation

Physiological Toxicokinetics

- Classic Vs physiologic
- Advantages of physiological models?
  - Time course of distribution
  - Effects of changing physiology
  - Predict across species – allometric scaling
  - Accomodates complex dosing and saturation
- Disadvantages of physiological models?
  - Requires more information
  - Math!!
  - Parameters ill defined- species, strains, diseases

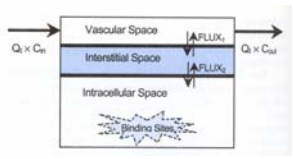
Basic Model Structure





Physiological Compartments

- A compartment is a single region of the body with uniform xenobiotic concentration
- Compartment parts:
- mg/t=Q_t x C_{in}



Physiological Compartments

- Parameters
  - Anatomic
  - Physiologic
  - Thermodynamic – relates the total concentration of xenobiotic in tissue, C, to the concentration of free xenobiotic in that tissue, C_f
  - Affinity of xenobiotic
    - $C = C_f \times P$ P = partition coefficient
  - Transport
    - Flux = [PA] x (C_1-C_2)
      - [PA] permeability coefficient

Physiological Compartments

- Perfusion Limited Compartments

- Diffusion Limited Compartments