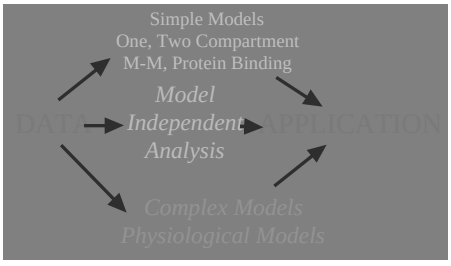
Physiologically Based Pharmacokinetic Models

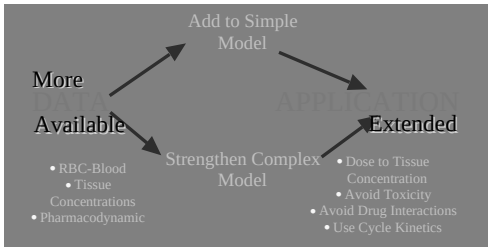
Objectives

- To Understand the Development and Use of Physiologically Based Pharmacokinetic (PBPK) Models

Modelling Approaches



Modelling Approaches



Classical Pharmacokinetics

- Plasma, serum, blood data
- One, Two, Three Compartment Models
- Receptor Highly Perfused
- High Therapeutic Index Drugs
- Dose Adjustment to Achieve Desired Cp

Flow Limited - Physiological Models (PBPK)

- Plasma, Serum, Blood AND Tissue Data
- Compartments Based on Organs
- Model Parameters Derived from Physiology
- Diverse Receptors
- Lower Therapeutic Index Drugs
- Dose Adjustment to Achieve Desired Tissue Concentration

Drugs Modelled with PBPK Models

- Anticancer
  - Actinomycin D 1977
  - Adriamycin 1978
  - ARA-C 1978
  - Cyclocytidine 1977
  - Cis Platinum 1978
  - Mercaptopurine 1977
  - Methotrexate 1971, 1978

Drugs Modelled with PBPK Models

- Other Drugs
  - Cephalosporins 1978
  - Digixon 1977
  - Salicylate 1978
  - Thiopental 1968, 1975
  - Pentobarbital 1968
  - PCB 1977

  Ref. Chen and Gross, Cancer Chemotherap.
  - Pharmacol., 2, 85-94 (1979)

Flow Limited - PBPK Models

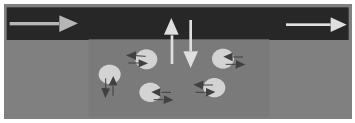
- Body Organs
- Organ Blood Flow Rates
- Drug Partitioning

- *A Priori* Prediction
- Scale-up From Animal Experiments
- Dosage Regimens for Tissue Delivery

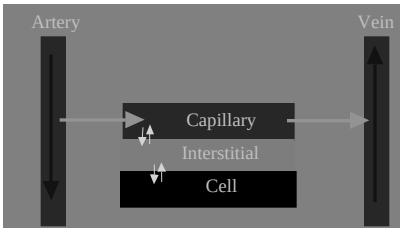
First, Assumptions

- Drug Distribution is Flow-Limited
  - Diffusion is Fast
  - $Ct \propto Cp_{out}$ I.e. ($Ct = R \bullet Cp_{out}$)
- Binding Linear (Plasma and Tissue)
- Concentration in Each Compartment is Homogeneous

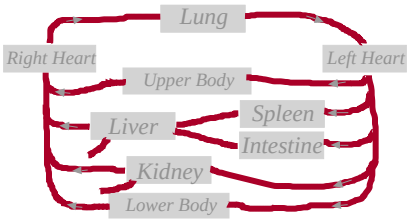
Transport Processes



Transport Processes



The Model



The Equations

Change in Amount in Compartment
= + Dose Administered to Compartment
- Drug Cleared by Excretion or Metabolism
+ drug Flow In
- Drug Flow Out

Equations

Plasma - Blood

$$V_P \cdot \frac{dC_P}{dt} = (\text{Injection}) + Q_L \cdot \frac{C_L}{R_L} + Q_K \cdot \frac{C_K}{R_K} + \ldots - (Q_L + Q_K + \ldots) \cdot C_P$$

Muscle

$$V_M \cdot \frac{dC_M}{dt} = Q_M \cdot \left(C_P - \frac{C_M}{R_M} \right)$$

Bischoff, K.B. 1975 Some fundamental considerations of the application of pharmacokinetics to cancer chemotherapy, Cancer Chemotherapy Reports, **Part 1, 59(4), 777-793**

More Equations

Kidney

$$V_K \cdot \frac{dC_K}{dt} = Q_K \cdot \left(C_P - \frac{C_K}{R_K} \right) - k_K \cdot \frac{C_K}{R_K}$$

Liver

$$V_L \cdot \frac{dC_L}{dt} = (Q_L - Q_G) \cdot \left(C_P - \frac{C_L}{R_L} \right) + Q_G \cdot \left(C_G - \frac{C_L}{R_L} \right) - \frac{k_L \cdot C_L / R_L}{Km_L + C_L / R_L}$$

Steps to Simulation

- Develop All the Differential Equations
- Obtain Parameter Values
  - Q Organ Blood flow
  - V Organ Volumes
  - R Partition Coefficient
  - k Clearance Terms
- Numerically Integrate (usually ‘stiff’)

Q Organ Blood Flows

- Book 1964 Guyton (man)
- Ref 1959 Altman (mouse)
- Ref 1962 Mandel (rat)
- Ref 1959 Ditmer (dog)

V Organ Volumes

- Book 1964 Guyton (man)
- Ref 1949 Adolph (mouse)
- Ref 1924 Donaldson (rat)
- Ref 1972 Altman (dog)

R Partition Coefficient

- Thiopental - Peanut Oil/Water (Ref Mark 1958 Price 1960)
- Thiopental - Lipid Solubility
- Methotrexate - Constant Infusion, Post-distribution I.V. bolus
- Ara-C - Assumed R = 1

Tissue Concentration Measurement

- Remove Tissue
- Blotting
- Rinsing - Perfused
- Blood Marker

k Clearance Term

k_K = Slope of U vs $\int_0^t Cp \cdot dt$

$$k_K = \frac{U^\infty}{\int_0^\infty Cp \cdot dt} = \frac{U^\infty}{AUC}$$

$$k_L = \frac{V_M}{K_M + C_L}$$

Vm and Km from in vitro

Further Complications

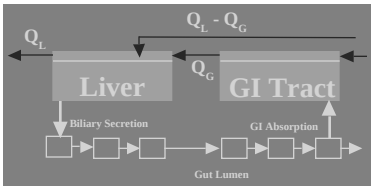
Non-Linear Tissue Binding - Thiopental

$$x_B = \frac{B_1 \cdot K_1 \cdot C_B}{1 + K_1 \cdot C_B} + \frac{B_2 \cdot K_2 \cdot C_B}{1 + K_2 \cdot C_B}$$

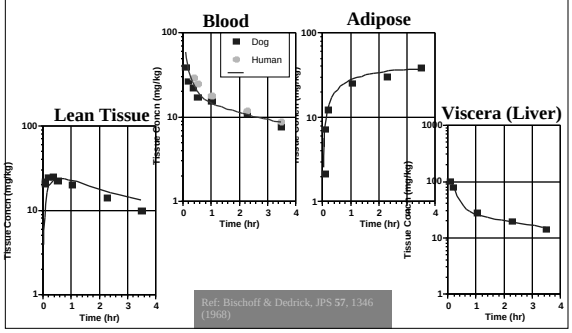
x_B Bound Concentration
B_1 Binding Site
C_B Free Concentration
K_1 Binding Constant

Further Complications

- Entero-hepatic Recycling - Methotrexate

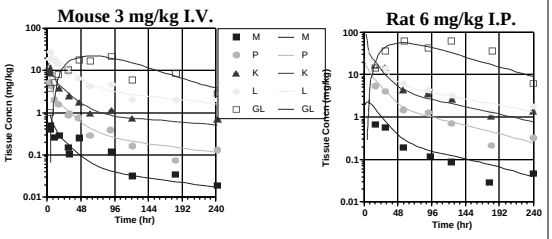


Thiopental Example



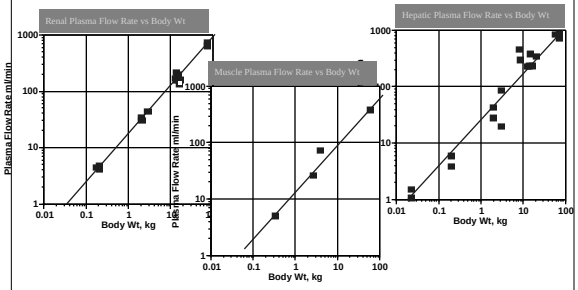
Ref: Bischoff & Dedrick, JPS 57, 1346 (1968)

Methotrexate Example



Ref: Bischoff et al. JPS, 60, 1128-33 (1971)

Scale-Up Example



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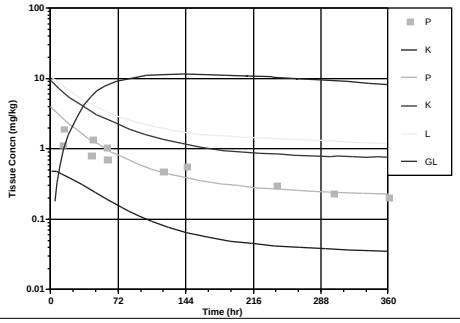

Future (?)

- Physiological Model and Cycle Kinetics
- Disease State - Liver, Renal, Cardiac
  - Changes in kk and kl, R (tumor)
- Interspecies Scale-Up
  - As with Methotrexate
- Avoid Toxicity
  - cis Platinum (Renal)

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