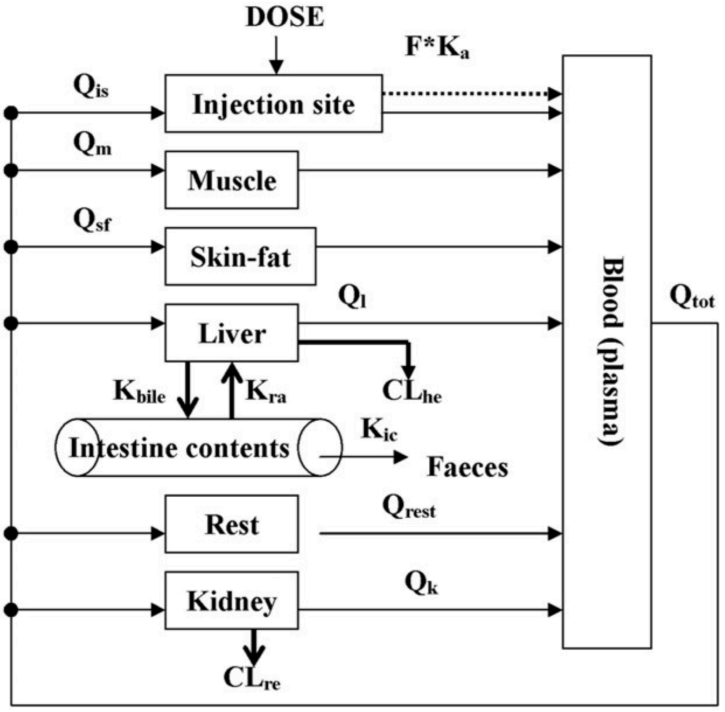
BME 200
Lesson 5
Sep 8, 2020

By the end of the class students should be able to:
- Calculate the plasma concentration of drug after a single dose
- Calculate the plasma concentration of drug after multiple doses

I. Pharmacokinetics
   A. Put the two concepts together from last time and we can model how drugs behave in the body.
      1. **Pharmacokinetics** = tissue compartments + exponential decay
   B. Pharmacokinetics is the modeling of drug kinetics in the body. In other words, how fast drugs are metabolized and leave the system.
   C. A single compartment looks like this:

   D. But, you can get really complicated with the models, like a pharmacist would.
      1. Zooming into this level lets you study how the drug concentration changes in different tissues (compartments) of the body
      2. The math for these types of models gets complicated fast. Each compartment gets its own differential equation and a computer is needed to solve the curves for systems with many compartments.
      3. Example, injection of doxycycline (antibiotic) into pigs.

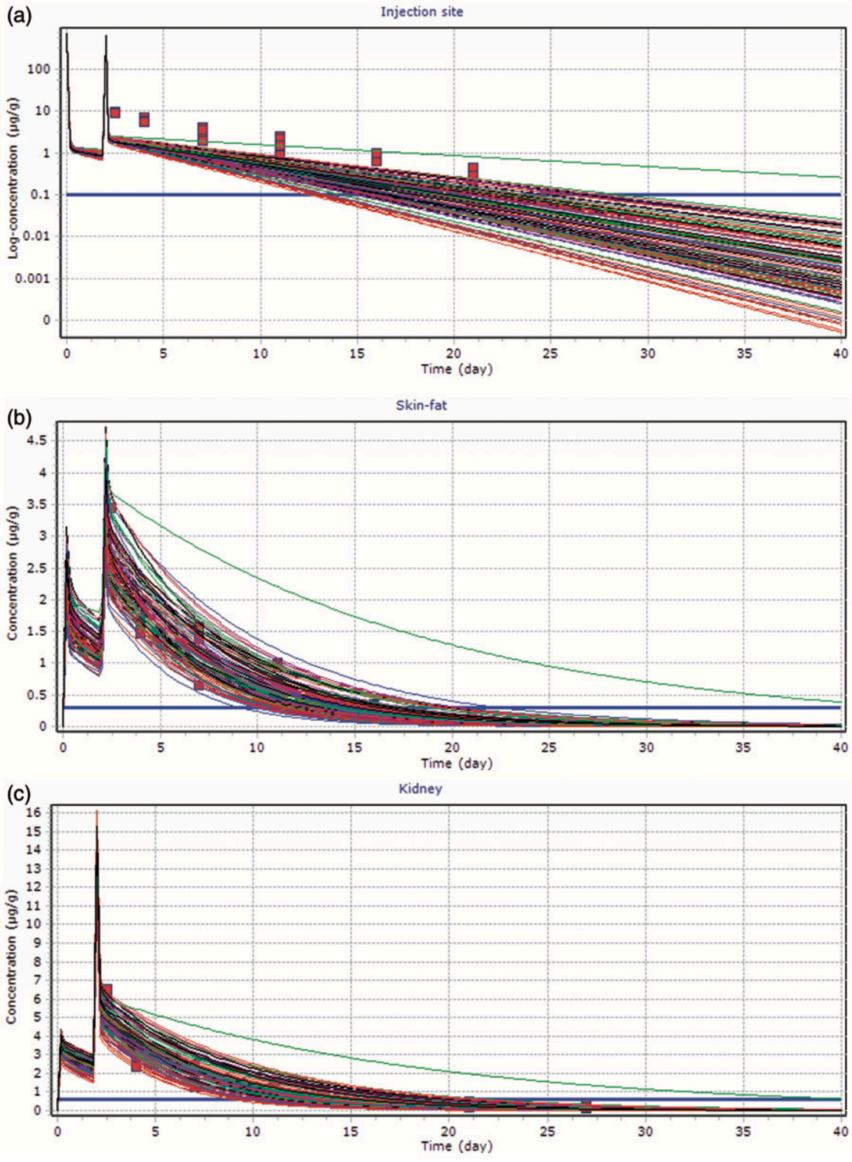


Yang, F., et al. "Use of a Monte Carlo analysis within a physiologically based pharmacokinetic model to predict doxycycline residue withdrawal time in edible tissues in swine." *Food Additives & Contaminants: Part A* 29.1 (2012):

Table 1. Differential equations describing the rate of change of doxycycline concentration in each compartment.

Compartment	Differential equation
Injection site	$V_{is} \times \frac{dC_{is}}{dt} = -F \times K_a \times A_{is} + \left(C_{blood} - \frac{C_{is}}{P_{is}}\right) \times Q_{is}$
Skin+fat	$V_{sf} \times \frac{dC_{sf}}{dt} = \left(C_{blood} - \frac{C_{sf}}{P_{sf}}\right) \times Q_{sf}$
Muscle	$V_m \times \frac{dC_m}{dt} = \left(C_{blood} - \frac{C_m}{P_m}\right) \times Q_m$
Kidney	$V_k \times \frac{dC_k}{dt} = \left(C_{blood} - \frac{C_k}{P_k}\right) \times Q_k - CL_{re} \times \frac{C_k}{P_k}$
Liver	$V_l \times \frac{dC_l}{dt} = \left(C_{blood} - \frac{C_l}{P_l}\right) \times Q_l - CL_{he} \times \frac{C_l}{P_l} - K_{bile} \times A_l + K_{ra} \times A_{ic}$
Intestine contents	$\frac{dA_{ic}}{dt} = K_{bile} \times A_l - K_{ra} \times A_{ic} - K_{ic} \times A_{ic}$
Rest	$V_{rest} \times \frac{dC_{rest}}{dt} = \left(C_{blood} - \frac{C_{rest}}{P_{rest}}\right) \times Q_{rest}$
Blood	$V_{blood} \times \frac{dC_{blood}}{dt} = F \times K_a \times A_{is} + \frac{C_{rest}}{P_{rest}} \times Q_{rest} + \frac{C_{is}}{P_{is}} \times Q_{is} + \frac{C_{sf}}{P_{sf}} \times Q_{sf} + \frac{C_m}{P_m} \times Q_m + \frac{C_k}{P_k} \times Q_k + \frac{C_l}{P_l} \times Q_l - Q_{tot} \times C_{blood}$
Plasma	$\frac{dC_{plasma}}{dt} = \frac{\int \frac{dC_{blood}}{dt}}{V_{plasma}} = \frac{A_{blood}}{V_{blood} \times (1-pcv)}$

Notes: A_X (μg) and C_X (μg/ml or μg/g) are the amount and concentration of doxycycline in each compartment, respectively. Subscript X is the name of a compartment. The t is time (h), whereas Q_{tot} is cardiac output. The pcv is hematocrit.



II. Compartment models
    A. A compartment model in pharmacokinetics makes three very important **assumptions**:
        1. The drug is well-mixed within the compartment.
            a) In other words, the drug is at the same concentration in every location throughout the body at all times.
            b) This is not a realistic assumption, but it is a valid assumption for a simple model.
        2. The drug entering the compartment is instantly mixed.
            a) In other words, the starting mass is instantly distributed throughout the model when you take the pill or get the injection.
        3. The loss of drug from the compartment is proportional to the concentration in the compartment.
            a) In other words, the drug leaves the system like a tracer does, and we can use a formula that looks like the one we used:

$$m(t) = m_o e^{-kt}$$

III. Single-compartment models
    A. Single-compartment models are appropriate for injections because the drug goes straight into the plasma.
        1. Note true for a pill since the pill has to get to your intestines and then get absorbed into the blood stream.
    B. We are modeling the concentration of the drug in *blood plasma* over time, since the level of drug in the plasma is what all the tissue in the body "sees".
    C. The drug concentration in plasma can easily be measured with a blood draw.
    D. There are about 5L of blood in an average adult human and about 60% of that volume is plasma.
    E. Steps for solving single-compartment models with a single injection
        1. Draw system (use either chemE or pharmaco notation):

2. Write equation (NOTE UNITS!; in particular the values for k and t):

k_e = elimination rate constant
D = initial drug mass
V_d = plasma volume
$c(t)$ = plasma concentration of drug over time
t = time

3. Solve for unknown(s):

Student Exercise 1

You're in the hospital hooked up to an IV with saline. It's noon and you have a headache so a physician injects 325 mg aspirin (salicylate) into your IV. Assume that aspirin has a half-life of 4 hours and that your total plasma volume is $V_d = 3$ L. What is your plasma concentration of aspirin at 5 PM (in g/L)?

IV. Multiple injections

A. Often times you take more than one dose. Why?

B. Sketch of plasma concentration of drug when given multiple injections over time.

C. How do we model this?

D. Just add together the exponential formula for each injection. The formulas for multiple injections are:

$$c(t) = \frac{D}{V_d}\left(e^{-k_e t} + e^{-k_e(t-\tau)} + e^{-k_e(t-2\tau)} + \cdots + e^{-k_e(t-(n-1)\tau)}\right)$$

$$c_{max} = \frac{D}{V_d}\left(\frac{1}{1-e^{-k_e\tau}}\right)$$

$$c_{min} = \frac{D}{V_d}\left(\frac{e^{-k_e\tau}}{1-e^{-k_e\tau}}\right)$$

$$\overline{c}_{ss} = \frac{D}{V_d k_e \tau}$$

n = dose #
τ = period between injections

E. Example. You've still got a headache so you get two more injections: one at 5 PM and then another at 10 PM. Assuming the same k value as in problem 1, what is your plasma concentration at 11:30 PM?

V. Two-compartment models
   A. These models are appropriate for pills.
   B. One compartment for intestines and the other for plasma.

C. Two compartments means two differential equations

$$\frac{dC_I}{dt} = -k_a C_I$$

$$\frac{dC_P}{dt} = k_a C_I - k_e C_P$$

D. But we only care about the second differential equation because it is the plasma drug concentration. Calculate the plasma concentration over time with the formula

$$c(t) = \frac{FDk_a}{V\left(k_a - k_e\right)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

$k_a =$ absorption rate constant
$k_e =$ excretion rate constant
$F =$ fraction absorbed, or bioavailability

E. The change in plasma concentration over time will look something like this

F. Find the time at which plasma concentration is maximum with the formula

$$t_{max} = \ln\left(\frac{k_a}{k_e}\right)\frac{1}{k_a - k_e}$$

G. Calculate the plasma concentration from taking multiple pills with the formula

$$c(t) = \frac{FDk_a}{V(k_a - k_e)}\left(\left(e^{-k_e t} - e^{-k_a t}\right) + \left(e^{-k_e(t-\tau)} - e^{-k_a(t-\tau)}\right) + \cdots + \left(e^{-k_e(t-(n-1)\tau} - e^{-k_a(t-(n-1)\tau)}\right)\right)$$

H. Examples of the different pharmacokinetic parameters for ibuprofen

Age Category	Birth to < 2 months	6 months to < 2 years	2 to < 6 years	6 to 16 years
N	1	5	12	25
AUC0-t (µg•hr/mL)	51.18	71.15	79.19	80.67
AUC0-4 (µg•hr/mL)	69.14	70.92	80.25	85.73
Cmax (µg/mL)	49.83	59.24	64.18	61.89
Tmax# (min)	10*	10 (10-30)	12 (10-46)	10 (10-40)
T½ (hr)	1.18	1.78	1.48	1.55
CL (mL/hr)	619.97	1172.5	1967.27	4878.47
Vz (mL)	1053.72	2805.73	3695.76	10314.21
CL/WT (mL/hr/kg)	129.16	133.66	130.064	109.22
Vz/WT (mL/kg)	219.53	311.2	227.23	226.824

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.
AUC0-4: Area under the concentration-time curve from time zero to 4 hours.
Cmax: Maximum observed concentration.
Tmax#: Median (min-max)
*: Observed Tmax value (N=1).
T½ el: Elimination half-life, calculated as ln(2)/Kel
Cl: Total body clearance, calculated as Dose/AUC0-inf.
Vz: Volume of distribution, calculated as Dose/(Kel x AUC0-inf).
WT^: body weight (kg)
Study report CPI-CL-012

https://www.accessdata.fda.gov/drugsatfda_docs/pediatric/22348%20ibuprofen%20clinpharm%20prea.pdf

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ibuprofen (oral) (eye-byoo-**proe**-fen)

Advil, Advil Migraine Liqui-Gels, Children's Advil, Children's Motrin, Excedrin IB, Junior Strength Advil, Medipren, Midol Maximum Strength Cramp Formula, Motrin, Motrin Drops, Motrin IB, Motrin Junior Strength, Motrin Migraine Pain, Nuprin, PediaCare Children's Fever

ibuprofen (injection)

Caldolor, NeoProfen (ibuprofen lysine)

Classification

Therapeutic: antipyretics, antirheumatics, nonopioid analgesics, nonsteroidal anti-inflammatory agents

Pharmacologic: nonopioid analgesics

Pregnancy Category C (up to 30 wk gestation), D (starting at 30 wk gestation)

Indications

PO, IV: Treatment of: Mild to moderate pain, Fever. **PO** Treatment of: Inflammatory disorders including rheumatoid arthritis (including juvenile) and osteoarthritis, Dysmenorrhea. **IV** Moderate to severe pain with opioid analgesics. Closure of a clinically significant PDA in neonates weighing 500–1500 g and ≤32 weeks gestational age (ibuprofen lysine only)

Action

Inhibits prostaglandin synthesis. **Therapeutic Effects:** Decreased pain and inflammation. Reduction of fever.

Pharmacokinetics

Absorption: Oral formulation is well absorbed (80%) from the GI tract; IV administration results in complete bioavailability.

Distribution: Does not enter breast milk in significant amounts.

Protein Binding: 99%.

Metabolism and Excretion: Mostly metabolized by the liver; small amounts (1%) excreted unchanged by the kidneys.

Half-life: Neonates: 26–43 hr; Children: 1–2 hr; Adults: 2–4 hr.

TIME/ACTION PROFILE

ROUTE	ONSET	PEAK	DURATION
PO (antipyretic)	0.5–2.5 hr	2–4 hr	6–8 hr
PO (analgesic)	30 min	1–2 hr	4–6 hr
PO (anti-inflammatory)	≤7 days	1–2 wk	unknown
IV (analgesic)	unknown	unknown	6 hr
IV (antipyretic)	within 2 hr	10–12 hr†	4–6 hr

† With repeated dosing.

Contraindications/Precautions

Contraindicated in: Hypersensitivity (cross-sensitivity may exist with other NSAIDs, including aspirin); Active GI bleeding or ulcer disease; Chewable tablets contain aspartame and should not be used in patients with phenylketonuria; Peri-operative pain from coronary artery bypass graft (CABG) surgery; ***OB:*** Avoid after 30 wk gestation (may cause premature closure of fetal ductus arteriosus); ***Pedi:*** Ibuprofen lysine: Preterm neonates with untreated infection, congenital heart disease where patency of PDA is necessary for pulmonary or systemic blood flow, bleeding, thrombocytopenia, coagulation defects, necrotizing enterocolitis, significant renal dysfunction.

Use Cautiously in: Cardiovascular disease (may ↑ risk of cardiovascular events); Renal or hepatic disease, dehydration, or patients on nephrotoxic drugs (may ↑ risk of renal toxicity); Aspirin triad patients (asthma, nasal polyps, and aspirin intolerance); can cause fatal anaphylactoid reactions; ***Geri:*** ↑ risk of adverse reactions secondary to age-related ↓ in renal and hepatic function, concurrent illnesses, and medications; Chronic alcohol use/abuse; Coagulation disorders; ***OB:*** Use cautiously up to 30 wk gestation; avoid after that; ***Lactation:*** Use cautiously; ***Pedi:*** Safety not established for infants <6 mo (oral) and children <17 yr (IV Caldolor); Ibuprofen lysine: Hyperbilirubinemia in neonates (may displace bilirubin from albumin-binding sites).

Exercise Extreme Caution in: History of GI bleeding or GI ulcer disease.

Adverse Reactions/Side Effects

CNS: headache, dizziness, drowsiness, intraventricular hemorrhage (ibuprofen lysine), psychic disturbances. **EENT:** amblyopia, blurred vision, tinnitus. **CV:** arrhythmias, edema, hypertension. **GI:** GI BLEEDING, HEPATITIS, constipation, dyspepsia, nausea, necrotizing enterocolitis (ibuprofen lysine), vomiting, abdominal discomfort. **GU:** cystitis, hematuria, renal failure. **Derm:** EXFOLIATIVE DERMATITIS,