

# **PHARMACOKINETICS: A REFRESHER**

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**Learning Objectives**

1. Identify and solve pharmacotherapy problems using basic pharmacokinetic concepts, including bioavailability, volume of distribution, clearance, and the elimination rate constant.
2. Describe clinically relevant issues related to drug transport proteins, cytochrome P450 metabolism, pharmacogenomics, and drug sampling and interpretation.
3. Describe specific pharmacokinetic characteristics and target concentrations of commonly used therapeutic agents, including aminoglycosides, vancomycin, phenytoin, valproic acid, and digoxin, as well as pharmacokinetic alterations in patients with renal and hepatic disease.

**Self-Assessment Questions**

*Answers and explanations to these questions may be found at the end of this chapter.*

1. J.H., a 65-year-old woman (weight 65 kg), was recently initiated on tobramycin and piperacillin/tazobactam for the treatment of hospital-acquired pneumonia. After the first tobramycin dose of 120 mg (infused from noon to 1:00 p.m.), serum tobramycin concentrations are obtained. They are 4.4 mg/L at 3:00 p.m. and 1.2 mg/L at 7:00 p.m. Which is the best assessment regarding the calculation of tobramycin pharmacokinetic parameters in this patient?
  - A. Data are sufficient to determine the half-life but not the volume of distribution (Vd).
  - B. Data are sufficient to determine both the half-life and the Vd.
  - C. Data are insufficient to determine either the half-life or the Vd.
  - D. Data are sufficient to determine the Vd but not the half-life.
2. P.L. is a 60-year-old woman (60 kg) recently initiated on gentamicin and clindamycin. After the first gentamicin dose of 110 mg (infused from 6:00 p.m. to 6:30 p.m.), serum gentamicin concentrations are obtained. They are 3.6 mg/L at 7:30 p.m. and 0.9 mg/L at 11:30 p.m. Which is the best assessment of this patient's gentamicin pharmacokinetic parameters?
  - A. The half-life is about 2 hours.
  - B. The half-life is about 3 hours.
  - C. The maximum concentration (C<sub>max</sub>) is about 3.8 mg/L.
  - D. The Vd is about 11.6 L.
3. R.O. is a 74-year-old woman initiated on gentamicin 100 mg intravenously every 24 hours for pyelonephritis. On admission, her serum creatinine (SCr) is 1.8 mg/dL. She has heart failure and is fluid overloaded because of her diminished renal function, and she is nonadherent to her angiotensin-converting enzyme inhibitor and diuretic. A few days into her hospitalization, her SCr is down to 1.1 mg/dL, and she is reinitiated on furosemide and enalapril. Which most likely happened to the gentamicin half-life in R.O. during her hospitalization?
  - A. Her clearance increased, which increased her Vd and decreased her half-life.
  - B. Her clearance increased, which increased her elimination rate constant and decreased her half-life.
  - C. Her Vd decreased, which increased her clearance and decreased her half-life.
  - D. Her Vd decreased, which increased her elimination rate constant and increased her half-life.
4. A patient receives vancomycin 1000 mg intravenously every 24 hours and has a trough concentration, obtained 30 minutes before the next dose, of 6 mg/L, with an estimated vancomycin 24-hour AUC of 210 mg \* hour/L. Which regimen is best for this patient if the goal AUC/MIC is 400–600 (assuming an MIC of 1 mg/L)?
  - A. Maintain the dosage at 1000 mg intravenously every 24 hours.
  - B. Lower the dosage to 500 mg but keep the interval at every 24 hours.
  - C. Keep the dosage at 1000 mg but shorten the interval to every 12 hours.
  - D. Lower the dosage to 500 mg and shorten the interval to every 12 hours.
5. R.K., a 39-year-old man who is HIV positive, receives a diagnosis of cryptococcal meningitis and begins taking amphotericin B and flucytosine.

- You want to keep flucytosine peak concentrations at 50–100 mg/L. Assuming a steady-state trough concentration of 25 mg/L, dosing every 6 hours, and 100% bioavailability, which is the best dosage to achieve a peak concentration within the desired range (flucytosine volume of distribution of 0.7 L/kg and half-life of 3 hours)?
- 12.5 mg/kg.
  - 37.5 mg/kg.
  - 75 mg/kg.
  - 150 mg/kg.
6. L.R. is a 49-year-old patient with diabetes mellitus and renal failure on hemodialysis. He was recently in a car accident and sustained a head trauma. He currently receives phenytoin 100 mg intravenously three times a day, and his most recent concentration was 5.6 mg/L. You are asked to suggest a new dosage to achieve a concentration within the therapeutic range. Laboratory results include sodium 145 mEq/L, potassium 3.9 mEq/L, chloride 101 mEq/L, carbon dioxide 26 mEq/L, blood urea nitrogen (BUN) 95 mg/dL, SCr 5.4 mg/dL, glucose 230 mg/dL, and albumin (Alb) 2.8 g/dL. Which is the best recommendation?
- Increase the dosage to 200 mg intravenously three times a day.
  - Increase the dosage to 200 mg intravenously two times a day.
  - Decrease the dosage to 100 mg intravenously two times a day.
  - Keep the dosage the same.
7. You are asked how the fluorescence polarization immunoassay (TDx) and enzyme multiplied immunoassay technique (EMIT) assays compare with each other. Which statement is most accurate?
- Although both are immunoassays, one uses antibodies to bind the molecule of interest, whereas the other uses antigens.
  - Although both are immunoassays, one uses an enzyme label, whereas the other uses a radioisotope label.
  - Although both are immunoassays, one uses an enzyme label, whereas the other uses a fluorescent label.
  - They are both names for the same assay technique.
8. An older adult is seen in the morning medicine clinic for a routine follow-up. Medication history includes digoxin 0.25 mg/day by mouth, furosemide 40 mg/day by mouth, and potassium chloride 10 mEq/day by mouth. All doses were last taken at 8:00 a.m. today at home. The patient has vague complaints of stomach upset, which began 2 days ago, but is otherwise in no apparent distress. A serum digoxin concentration obtained today at 10:00 a.m. is 2.5 mcg/L. Which statement best describes what should be done next?
- Admit the patient for administration of digoxin Fab.
  - Tell the patient to skip tomorrow's dose of digoxin and begin 0.125 mg/day by mouth.
  - Administer a dose of activated charcoal.
  - Do nothing today with the digoxin.
9. A research group is analyzing the relationship between various independent patient demographics (e.g., age, height, weight, albumin, creatinine clearance [CrCl]) and phenytoin pharmacokinetics. Which is the best statistical test to use in assessing the relationship?
- One-way analysis of variance.
  - Analysis of covariance.
  - Multiple regression.
  - Spearman rank correlation.
10. N.T. is a 24-year-old woman receiving valproic acid for tonic-clonic seizures. Her most recent trough valproic acid concentration was 22 mg/L. Her most recent albumin concentration was 4.1 g/dL. Given this albumin, which recommendation is best regarding her dosage?
- Continue with the current dosage; the concentration is close enough to the therapeutic range.
  - Assess adherence and increase her dosage; the concentration is below the therapeutic range.
  - Decrease her dosage; the concentration is slightly above the therapeutic range.
  - Assess adherence and then check a free valproic acid concentration and adjust accordingly.

11. N.G. is a 54-year-old woman with a recent head injury. She comes to your pharmacy with complaints about the prescription for acetaminophen with codeine you dispensed to her yesterday. She says that it does not seem any stronger than when she uses acetaminophen alone. On her profile, you notice results from pharmacogenomics testing performed 3 years ago that shows she is a CYP2D6 poor metabolizer. In addition to acetaminophen and codeine, she is receiving aspirin, clopidogrel, omeprazole, lisinopril, citalopram, metoprolol succinate, docusate, and trazodone. Which is the best explanation why N.G. does not seem to benefit from codeine?
- A. Omeprazole inhibited CYP2C19, causing less codeine activation.
  - B. Codeine is not as active in N.G. because of her genetic profile.
  - C. Codeine is metabolized faster in N.G., leading to lower concentrations.
  - D. Metoprolol inhibited CYP2C9, causing less codeine activation.
12. At your hospital you are responsible for making dosing adjustments in patients with poor renal function. While working with you, a student asks why you are using the Cockcroft-Gault method for estimating CrCl instead of the newer Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations. Which is the best response to provide to this student?
- A. MDRD and CKD-Epi are not as good estimates of renal function and may lead to inappropriate changes in drug dosing.
  - B. MDRD and CKD-Epi were developed in an ambulatory care population and cannot be used for hospitalized patients.
  - C. The Cockcroft-Gault estimate of CrCl has units that are different from the glomerular filtration rate estimates calculated using the MDRD and CKD-Epi equations.
  - D. Recommendations for renal dosing adjustments in package inserts are usually based on CrCl estimates using the Cockcroft-Gault equation.
13. An assay used for therapeutic drug monitoring at your institution has a low sensitivity and low precision. Which is the best statement about the impact of this assay on drug monitoring?
- A. The assay may be unable to detect concentrations that are therapeutic, and it will report highly variable values when repeatedly run on the same sample.
  - B. The assay may be unable to detect concentrations that are therapeutic, and it will consistently over- or under-measure the true concentration.
  - C. The assay will be unable to differentiate between like substances, and it will consistently over- or under-measure the true concentration.
  - D. The assay will be unable to differentiate between like substances, and it will report highly variable values when repeatedly run on the same sample.

***BPS Pharmacotherapy Specialty Examination Content Outline***

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain I: Patient-Centered Pharmacotherapy
  - a. Task 1: Knowledge statements: a-c, f, h, j-l

**Patient Cases**

1. H.R. is receiving vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia. H.R. has chronic kidney disease. A 1-g intravenous dose of vancomycin is given at noon on March 21. A concentration obtained at 2:00 p.m. on March 21 is 27.8 mg/L. After no additional doses, a concentration obtained at 2:00 p.m. on March 24 is 14.1 mg/L. If you were to give a 1-g dose at 4:00 p.m. on March 24 and your goal trough concentration to achieve an appropriate AUC/MIC ratio was 10–15 mg/L, which would be the best time to give the next dose?
  - A. 1 day after the dose on the 24th.
  - B. 3 days from the dose on the 24th.
  - C. 6 days from the dose on the 24th.
  - D. Insufficient information to calculate when to redose.
2. After the administration of 100 mg of a drug intravenously and 200 mg of the same drug by mouth, the areas under the curves (AUCs) are 50 and 25 mg\*hr/L, respectively. Which best describes the bioavailability of this drug?
  - A. 25%.
  - B. 37.5%.
  - C. 50%.
  - D. 100%.

**I. BASIC PHARMACOKINETIC RELATIONSHIPS**

Table 1 contains definitions of terms.

**Table 1.** Pharmacokinetic Term Definitions

AUC	Area under the curve
AUC <sub>ev</sub>	Area under the curve after an extravascular dose
AUC <sub>iv</sub>	Area under the curve after an intravenous dose
C <sub>max</sub>	Maximum concentration
C <sub>min</sub>	Minimum concentration
C <sub>0</sub>	Concentration at time zero
C <sub>ss</sub>	Concentration at steady state
C <sub>ss avg</sub>	Average concentration at steady state
C <sub>ss max</sub>	Maximum concentration at steady state
Dose <sub>EV</sub>	Dose given extravascularly
Dose <sub>IV</sub>	Dose given intravenously
F	Bioavailability
k	Elimination rate constant
R <sub>0</sub>	Rate of infusion
τ	Dosing interval
t	Time of the intermittent infusion
t <sub>i</sub>	Time from initiation of the continuous infusion
Vd	Volume of distribution



A. Absorption  $F = \frac{\text{dose}_{iv} * AUC_{ev}}{\text{dose}_{ev} * AUC_{iv}}$

B. Distribution

Rapid intravenous (or oral) bolus:  $V_d = \frac{F * \text{dose}}{C_0}$

Continuous intravenous infusion at steady state:  $V_d = \frac{R_0}{k * C_{ss}}$

Continuous intravenous infusion before steady state:  $V_d = \frac{R_0}{C * k} (1 - e^{-kt_i})$  and  $C = \frac{R_0}{V_d * k} (1 - e^{-kt_i})$

Multiple intravenous bolus at steady state:  $V_d = \frac{\text{dose}}{C_{ss \max} * (1 - e^{-k\tau})}$

Multiple intermittent intravenous infusion at steady state:  $V_d = \frac{R_0}{k} * \frac{1 - e^{-kt}}{C_{\max} - (C_{\min} * e^{-k\tau})}$

$C_{ss \max} = \frac{R_0 * (1 - e^{-kt})}{V_d * k * (1 - e^{-k\tau})}$   $C_{ss \min} = C_{ss \max} * e^{-k(\tau - t)}$

C. Clearance

$\text{Clearance} = \frac{\text{dose}}{AUC}$   $k = \frac{Cl}{V_d}$   $k = \frac{(\ln C_1 - \ln C_2)}{(t_2 - t_1)}$   $t_{1/2} = \frac{0.693}{k}$

Continuous intravenous infusion at steady state:  $\text{Clearance} = \frac{R_0}{C_{ss}}$

Continuous intravenous infusion before steady state:  $\text{Clearance} = \frac{R_0}{C} * (1 - e^{-kt_i})$

Multiple intravenous (or oral) bolus at steady state:  $\text{Clearance} = \frac{F * \text{dose}}{C_{ss, \text{avg}} * \tau}$

$\tau = \frac{(\ln C_{\max} - \ln C_{\min})}{k}$

## II. ABSORPTION

A. First-Pass Effect

1. Blood that perfuses almost all the gastrointestinal (GI) tissues passes through the liver by means of the hepatic portal vein.
  - a. Fifty percent of the rectal blood supply bypasses the liver (middle and inferior hemorrhoidal veins).
  - b. Drugs absorbed in the buccal cavity bypass the liver.

## 2. Examples of drugs with significant first-pass effect

Amitriptyline	Isosorbide dinitrate	Nicardipine	Propranolol
Desipramine	Labetalol	Nifedipine	Verapamil
Diltiazem	Lidocaine	Nitroglycerin	
Doxepin	Metoprolol	Pentazocine	
Imipramine	Morphine	Propoxyphene	

## B. Enterohepatic Recirculation (Table 2)

1. Drugs are excreted through the bile into the duodenum, metabolized by the normal flora in the GI tract, and reabsorbed into the portal circulation.
2. Occurs with drugs that have biliary (hepatic) elimination and good oral absorption
3. Drug is concentrated in the gallbladder and expelled on sight, smell, or ingestion of food.

**Table 2.** Examples of Compounds Excreted in Bile and Subject to Enterohepatic Cycling

Compound	Entity in Bile
Chloramphenicol	Glucuronide conjugate
Digoxin	Parent
Estrogens	Parent
Imipramine	Parent and desmethyl metabolite
Indomethacin	Parent and glucuronide
Nafcillin	Parent
Rifampin	Parent
Sulindac	Glucuronides of parent and metabolites
Testosterone	Conjugates
Tiagabine	Glucuronide conjugate
Valproic acid	Glucuronide conjugates
Vitamin A	Conjugates

**Patient Case**

## 3. Which statement best describes P-glycoprotein?

- A. It is a plasma protein that binds basic drugs.
- B. It transfers drugs through the GI mucosa, increasing absorption.
- C. It diminishes the effect of cytochrome P450 3A4 (CYP3A4) in the GI mucosa.
- D. It is an efflux pump that decreases GI mucosal absorption.

C. P-Glycoprotein (*ABCB1*)

1. P-glycoprotein is an efflux pump (located in the esophagus, stomach, and small and large intestines) that pumps drugs back into the GI lumen; it is a more important factor in drug interactions during drug absorption than intestinal CYP3A4.
2. Both CYP3A4 and P-glycoprotein are located in small intestinal enterocytes and work together to decrease the absorption of xenobiotics.
3. Most CYP3A4 substrates are also P-glycoprotein substrates.
4. Many CYP3A4 inhibitors/inducers also inhibit/induce P-glycoprotein, leading to an increase or decrease in bioavailability.

**Table 3.** P-glycoprotein Drug Interactions

Substrate	Enhanced P-gp effects (decreased serum concentrations)	Diminished P-gp effects (increased serum concentrations)
Apixaban Colchicine Cyclosporine Dabigatran Digoxin Edoxaban Ranolazine Rivaroxaban Tacrolimus	Carbamazepine Phenytoin Rifampin St. John's wort	Amiodarone Clarithromycin Dronedarone Erythromycin Hepatitis C direct-acting antivirals Itraconazole Ivacaftor Ketoconazole Propafenone Quinidine Ranolazine Verapamil

### III. DISTRIBUTION

- A. Definition: Apparent Vd: Proportionality constant that relates the amount of drug in the body to an observed concentration of drug
- B. Protein Binding (Table 4)

**Table 4.** Common Proteins Involved in Drug Protein Binding

Protein	Types of Drugs Bound	Molecular Weight	Normal Concentrations	
			g/L	mcmol
Albumin	Acidic	65,000	35–50	500–700
$\alpha$ -1-Acid glycoprotein	Basic	44,000	0.4–1.0	9–23
Lipoprotein	Lipophilic and basic	200,000–3,400,000	Variable	Variable

- C. P-Glycoprotein
1. Functions as an efflux pump on the luminal surface of the blood-brain barrier, limiting entry to the central nervous system
  2. It may be especially important with opioids: Induction of P-glycoprotein by chronic use of opioids may decrease the opioid effect (tolerance).
  3. P-glycoprotein is also found in tumor cells, resulting in the efflux of chemotherapeutic agents from the cell and, ultimately, multidrug resistance.

## IV. CLEARANCE

A. Metabolic enzymes (Table 5) and transport proteins (Table 6) involved in drug clearance

**Table 5.** Enzymes Involved in Drug Metabolism

<b>Oxygenases</b> CYPs Monoamine oxygenases Alcohol dehydrogenases Aldehyde dehydrogenases Xanthine dehydrogenases	<b>Hydrolytic enzymes</b> Esterases Amidases Epoxide hydrolases Dipeptidases
<b>Conjugating enzymes</b> Uridine diphosphate–glucuronyl transferases Glutathione <i>S</i> -transferase Acetyltransferases Methyltransferases	

CYP = cytochrome P450.

**Table 6.** Drug Transport Proteins

Transport Protein Superfamily	Transport Protein (Gene [Protein])	Location and Function	Drugs Affected by Transport Protein	Inhibitors of Transport Protein
SLC	<i>SLC01A2</i> [OATP1A2]	Hepatocyte: Bile acid uptake	Digoxin Levofloxacin Methotrexate Statins	Naringin
	<i>SLC01B1</i> [OATP1B1]	Hepatocyte: Hepatic uptake of drugs	Hepatitis C direct-acting antivirals Rifampin Statins Valsartan	Clarithromycin Cyclosporine Gemfibrozil Hepatitis C direct-acting antivirals Teriflunomide
	<i>SLC01B3</i> [OATP1B3]	Hepatocyte: Hepatic uptake of drugs	Digoxin Fexofenadine Rifampin Statins	Cyclosporine Erythromycin Teriflunomide
	<i>SLC22A1, SLC22A2, SLC22A6, SLC22A8</i> [OAT and OCT]	Hepatocyte: Hepatic uptake of drugs Renal tubule (interstitial side): Secretion of drugs	Dofetilide <sup>b</sup> Methotrexate <sup>a</sup> Organic anions and cations <sup>b</sup> Salicylate <sup>a</sup> Tetracycline <sup>a</sup> Zidovudine <sup>a</sup>	Cimetidine Teriflunomide
	<i>SLC02B1</i> [OATP2B1]	Hepatocyte: Hepatic uptake of drugs	Fexofenadine Glyburide Statins	Cyclosporine Gemfibrozil
	<i>SLC15A1, SLC15A2</i> [PEPT1, PEPT2]	Renal tubule Intestinal enterocytes	Captopril Cephalexin Enalapril Valacyclovir	
	<i>SLC47A1, SLC47A2</i> [MATE1, MATE2-K]	Renal tubule	Metformin	Cimetidine

**Table 6.** Drug Transport Proteins (*Cont'd*)

Transport Protein Superfamily	Transport Protein (Gene [Protein])	Location and Function	Drugs Affected by Transport Protein	Inhibitors of Transport Protein
ABC	<i>ABCB11</i> [BSEP]	Hepatocyte: Bile acid excretion into bile	Pravastatin	
	<i>ABCC2</i> , 3, 4, and 5 [MRP2, 3, 4, and 5]	Hepatocyte: Excreting water-soluble drugs and metabolites into blood Renal tubule (luminal side): Secretion of drugs	Glucuronide, sulfate, and glutathione metabolites <sup>a</sup> Methotrexate <sup>a</sup> Pravastatin <sup>a</sup> Rifampin <sup>a</sup>	Probenecid Ritonavir
	<i>ABCB1</i> [MDR1] (P-glycoprotein)	Hepatocyte: See text in handout Renal tubule (luminal side): See text in handout	See text	Amiodarone Quinidine Verapamil
	<i>ABCB4</i> [MDR3]	Hepatocyte	Digoxin Paclitaxel Vinblastine	Itraconazole Ritonavir
	<i>ABCG2</i> [BCRP]	Hepatocyte: Biliary excretion	Cladribine Daunorubicin Doxorubicin Imatinib Methotrexate Mitoxantrone Ozanimod Statins Topotecan	Omeprazole Ritonavir Teriflunomide

<sup>a</sup>Drugs affected by transport proteins in hepatocytes.<sup>b</sup>Drugs affected by transport proteins in the renal tubule.**Patient Case**

4. A renal transplant patient receiving cyclosporine is given a diagnosis of community-acquired pneumonia. The patient is admitted to the hospital and initiated on ceftriaxone and a macrolide. A physician asks you to choose a macrolide that will not interact with the patient's cyclosporine. Which macrolide is the best choice to meet the physician's criteria?
- Erythromycin.
  - Clarithromycin.
  - Azithromycin.
  - Any macrolide (all macrolides inhibit CYP3A4).

**B. Cytochrome P450****1. Introduction**

- A group of heme-containing enzymes responsible for phase 1 metabolic reactions
- Characteristic absorbance of light at 450 nm (hence CYP450)
- Located primarily in the membranes of the smooth endoplasmic reticulum in the liver, small intestine, brain, lung, and kidney
- Encoded by a supergene family and subfamily; separate genes code for different isoenzymes
- Drugs generally have a high affinity for one particular CYP, but most drugs also have secondary pathways (see Table 7).

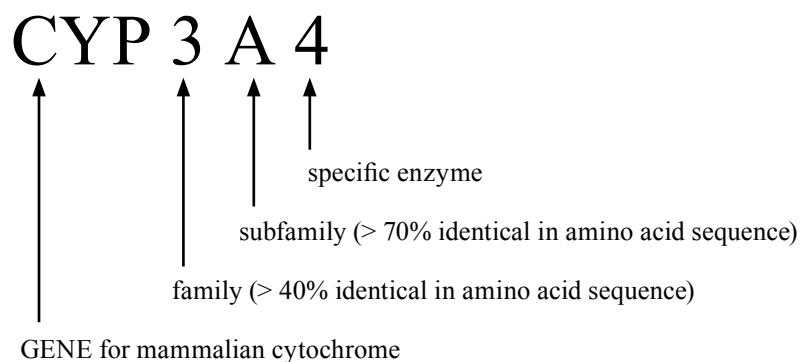
**Table 7. CYP Drug Interactions**

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4
Induction	Carbamazepine Modafinil Nafcillin Omeprazole Rifampin	Enzalutamide Phenobarbital Phenytoin Rifampin Rifapentine	Carbamazepine Efavirenz Enzalutamide Phenobarbital Prednisone Rifampin St. John's wort	Not an inducible enzyme	Carbamazepine Efavirenz Enzalutamide Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin
Inhibition	Amiodarone Cimetidine Ciprofloxacin Diltiazem Efavirenz Erythromycin Fluvoxamine Mexiletine Norfloxacin	Amiodarone Efavirenz Fenofibrate Fluconazole Fluvoxamine Isoniazid Lovastatin Metronidazole Paroxetine Sertraline Sulfamethoxazole Trimethoprim Voriconazole	Cimetidine Esomeprazole Fluoxetine Fluvoxamine Isoniazid Ketoconazole Lansoprazole Modafinil Omeprazole Oxcarbazepine Pantoprazole Topiramate Voriconazole	Amiodarone Bupropion Celecoxib Chlorpheniramine Cimetidine Cinacalcet Citalopram Diphenhydramine Duloxetine Escitalopram Fluoxetine Haloperidol Methadone Metoclopramide Midodrine Paroxetine Propafenone Quinidine Ritonavir Sertraline Terbinafine Thioridazine	Amiodarone Aprepitant Atazanavir Boceprevir Cimetidine Clarithromycin Darunavir Delavirdine Diltiazem Erythromycin Fluconazole (large doses)

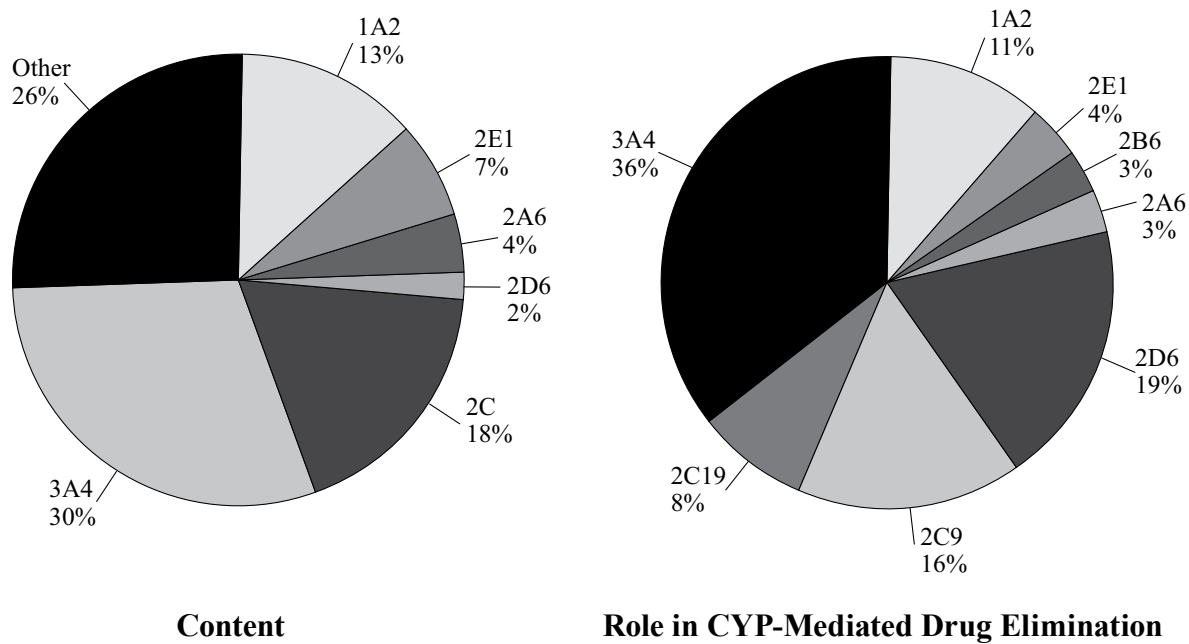
**Table 7.** CYP Drug Interactions (*Cont'd*)

Gene Designation	CYP1A2	CYP2C9/10	CYP2C19	CYP2D6	CYP3A4	
Substrates	Acetaminophen Amitriptyline Caffeine Clomipramine Clozapine Cyclobenzaprine Estradiol Fluvoxamine Haloperidol Imipramine Mirtazapine Olanzapine Riluzole Ropinirole R-warfarin Theophylline Zolmitriptan	Amitriptyline Celecoxib Diclofenac Fluoxetine Glimepiride Glipizide Glyburide Ibuprofen Indomethacin Irbesartan Losartan Phenytoin Rosuvastatin S-warfarin Siponimod Tamoxifen	Amitriptyline Cilostazol Citalopram Clomipramine Clopidogrel Diazepam Imipramine Lansoprazole Naproxen Omeprazole Pantoprazole Phenobarbital Phenytoin Propranolol	Amitriptyline Aripiprazole Atomoxetine Carvedilol Clomipramine Clozapine Codeine Dextromethorphan Donepezil Duloxetine Flecainide Fluoxetine Fluvoxamine Haloperidol Hydrocodone Imipramine Metoprolol Mirtazapine Nebivolol Nortriptyline Oxycodone Paroxetine Propafenone Propranolol Risperidone Tamoxifen Thioridazine Timolol Tramadol Trazodone Venlafaxine	Alprazolam Amiodarone Amlodipine Aprepitant Aripiprazole Atorvastatin Boceprevir Buspirone Carbamazepine Cilostazol Citalopram Clarithromycin Cyclosporine Dapsone Darunavir Delavirdine Diazepam Diltiazem Donepezil Efavirenz Eplerenone Erlotinib Erythromycin Ethinyl estradiol Felodipine Fentanyl Finasteride Fosamprenavir Gefitinib Imatinib Irinotecan Itraconazole Ketoconazole Lapatinib Lidocaine	Lovastatin Methadone Midazolam Mirtazapine Nateglinide Nevirapine Nifedipine Quetiapine Quinidine Repaglinide Rifabutin Ritonavir Sertraline Sibutramine Sildenafil Simvastatin Siponimod Sirolimus Sorafenib Sunitinib Tacrolimus Telaprevir TCAs (amitriptyline, clomipramine, imipramine) Tiagabine Trazodone Triazolam Vardenafil Verapamil Voriconazole Zaleplon Ziprasidone Zolpidem Zonisamide

f. Nomenclature

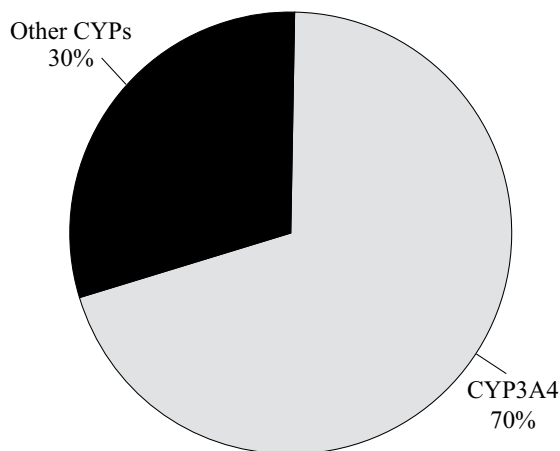
**Figure 1.** Nomenclature.

## 2. Distribution of CYP isoenzymes in human liver



**Figure 2.** Distribution of CYP isoenzymes in human liver.

## 3. Distribution of CYP isoenzymes in human GI tract



**Figure 3.** Distribution of CYP isoenzymes in human gastrointestinal tract.

## 4. Characteristics of CYP metabolism

- Inhibition is substrate-independent.
- Some substrates are metabolized by more than one CYP (e.g., tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]).
- Enantiomers may be metabolized by different CYP isoenzymes (e.g., R- vs. S-warfarin).
- Differences in inhibition may exist in the same class of agents (e.g., fluoroquinolones, azole antifungals, macrolides, calcium channel blockers, histamine-2 blockers).
- Substrates can also be inhibitors (e.g., erythromycin, verapamil, diltiazem).



- f. Most inducers and some inhibitors can affect more than one isozyme (e.g., cimetidine, ritonavir, fluoxetine, erythromycin).
- g. Inhibitors may affect different isozymes at different dosages (e.g., fluconazole inhibits CYP2C9 at dosages of 100 mg/day or greater and inhibits CYP3A4 at dosages of 400 mg/day or greater).
- 5. Drug interactions
  - a. Induction – Adaptive increase in enzyme activity in response to another agent – Slow, regulatory process
    - i. Induction is dose-dependent.
    - ii. Onset – Usually begins after several days, with a maximal effect within 2 weeks (somewhat dependent on the potency and half-life of the inducer)
    - iii. Offset – Usually longer to eliminate enzymes than to generate enzymes; enzyme activity returns to normal within 2–3 weeks (somewhat dependent on the half-life of the inducer)
  - b. Inhibition – Direct action on an enzyme that renders the enzyme inactive
    - i. Inhibition is dose-dependent.
    - ii. Onset – Quicker than induction (inhibition begins as soon as the inhibiting agent is in the system), but dependent on the half-life of the inhibiting agent and the substrate (i.e., time to steady state for both agents)
    - iii. Offset – Effect is gone as soon as the inhibiting agent is eliminated.

C. P-Glycoprotein

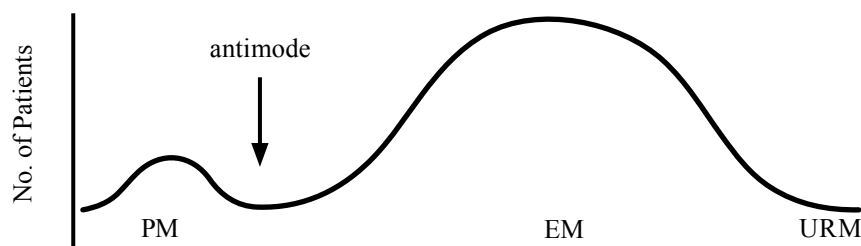
- 1. P-glycoprotein is an efflux pump that pumps drugs into the bile; the clinical effect of P-glycoprotein drug interactions in the bile is unknown.
- 2. P-glycoprotein pumps drugs from renal tubules into the urine; it also potentially limits the degree of reabsorption.
- 3. Examples of drug interactions: quinidine/digoxin, cyclosporine/digoxin, and propafenone/digoxin

**Patient Case**

5. W.T., a 62-year-old man who presents to the emergency department with chest pain, is given a diagnosis of a non-ST-segment elevation myocardial infarction. He goes to the catheterization laboratory, where two drug-eluting stents are placed. After stent placement, he is initiated on aspirin 81 mg daily and clopidogrel 75 mg daily. A CYP2C19 pharmacogenetic test shows that he is a poor metabolizer (*CYP2C19*\*3/\*3 genotype). The patient also receives losartan 25 mg daily, carvedilol 25 mg twice daily, amitriptyline 100 mg daily, acetaminophen 500 mg as needed, and simvastatin 20 mg daily. Given his pharmacogenetic profile, which is most likely to occur in this patient?
- A. He will form a metabolite of clopidogrel that will block the action of aspirin, increasing the risk of a thrombotic event.
  - B. He will not activate clopidogrel well, increasing the risk of a thrombotic event.
  - C. He will not metabolize clopidogrel well, increasing the risk of a bleeding event.
  - D. He will overproduce an active metabolite of clopidogrel, increasing the risk of a bleeding event.

D. Pharmacogenomics and Pharmacogenetics

- 1. Population in general is divided into poor, intermediate, extensive, and ultrarapid metabolizers; therefore, metabolism is considered polymorphic.
- 2. Definition of polymorphism: Coexistence of more than one genetic variant (alleles), which are stable components in the population (more than 1% of population)
- 3. Clear antimode (separation between the two populations) results



Metabolic ratio of metabolite to unchanged drug → (increasing metabolic capacity)

**Figure 4.** Distribution of patients in a drug that follows polymorphic metabolism.

EM = extensive metabolizer; PM = poor metabolizer; URM = ultrarapid metabolizer.

4. Phenotype: Expression of the trait; interaction of gene with environment
  - a. Manifestation of the trait clinically
  - b. Not necessarily constant
5. Genotype: Genetic makeup
6. Pharmacogenomics in clinical practice (Table 8)

**Table 8.** Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug metabolism	<i>CYP2C9</i>	<i>CYP2C9*2</i> (70%–90% activity) <i>CYP2C9*3</i> (10%–30% activity)	NSAIDs Phenytoin Siponimod Warfarin
Drug metabolism	<i>CYP2C19</i>	<i>CYP2C19*2</i> (poor) <i>CYP2C19*3</i> (poor) <i>CYP2C19*17</i> (ultrarapid) <i>CYP2C19*4</i> (null variant)	Clopidogrel Diazepam Omeprazole SSRIs Tricyclic antidepressants Voriconazole
Drug metabolism	<i>CYP2D6</i>	<i>CYP2D6*10</i> (poor) <i>CYP2D6*17</i> (poor) <i>CYP2D6*3, *4, and *5</i> (null)	Antiarrhythmics Antipsychotics Beta blockers Codeine, hydrocodone, oxycodone Dextromethorphan SSRIs Tamoxifen Tramadol Tricyclic antidepressants
Drug metabolism	UDP-glucuronosyltransferases	<i>UGT1A1*6</i> <i>UGT1A1*28</i> <i>UGT2B7*2</i> <i>UGT2B7*28</i>	Atazanavir Irinotecan Mycophenolate NSAIDs
Drug metabolism	N-acetyltransferase	<i>NAT2*4</i> <i>NAT2*5</i> <i>NAT2*6</i> <i>NAT2*7</i>	Hydralazine Isoniazid Sulfasalazine

**Table 8.** Pharmacogenetics in Drug Metabolism, Drug Transport, Drug Target, and Adverse Drug Reactions (*Cont'd*)

Type	Enzyme/Target	Most Common Variant Alleles	Drug Examples
Drug transport	<i>SLCO1B1</i>	<i>SLCO1B1</i> *1A, *1B <i>SLCO1B1</i> *5, *15, *17	Simvastatin
Drug target	<i>VKOR</i>	<i>VKORC1</i> *2 ( <i>increases</i> ) <i>VKORC1</i> *3 ( <i>decreases</i> )	Warfarin
Adverse drug reactions	<i>HLA-B</i>	<i>HLA-B</i> *57:01	Abacavir
		<i>HLA-B</i> *58:01	Allopurinol
		<i>HLA-B</i> *15:02	Carbamazepine, phenytoin

NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

6. Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Designed to facilitate translation of pharmacogenetics information from research to clinical practice
- Developing guidelines for use of pharmacogenetic test results in drug dosing
- Focused on specific drug-gene pairs (Table 9)

**Table 9.** CPIC Clinical Recommendations for Drug-Gene Pairs

Drug	Gene	Recommendation
Abacavir	<i>HLA-B</i>	Avoid using because of increased incidence of hypersensitivity reactions in patients with the <i>HLA-B</i> *57:01 allele
Allopurinol	<i>HLA-B</i>	Severe cutaneous adverse reactions associated with carriers of the <i>HLA-B</i> *58:01 allele Avoid using allopurinol in these patients
Atazanavir	<i>UGT1A1</i>	For patients who carry 2 decreased function <i>UGT1A1</i> alleles, increased risk of jaundice and subsequent nonadherence Consider alternative agents
Atomoxetine	<i>CYP2D6</i>	Slower dose titration in intermediate and poor metabolizers. In addition, obtain plasma concentrations 2–4 hr after dosing instead of 1–2 hr
Capecitabine/5-fluorouracil/tegafur	<i>DPYD</i>	Increased risk of serious or fatal toxicity in patients with reduced or absent dihydropyrimidine dehydrogenase activity
Carbamazepine/oxcarbazepine	<i>HLA-B</i>	Avoid using because of increased incidence of severe cutaneous adverse reactions in patients with the <i>HLA-B</i> *15:02 allele
Clopidogrel	<i>CYP2C19</i>	Normal dosing for ultrarapid metabolizer; alternative antiplatelet therapy in intermediate or poor metabolizers
Codeine	<i>CYP2D6</i>	Avoid using codeine because of potential toxicity or lack of efficacy in ultrarapid and poor metabolizers Specific dosing recommendations for extensive and intermediate metabolizers
Efavirenz	<i>CYP2B6</i>	In intermediate and poor metabolizers, consider initiating lower doses of efavirenz (200–400 mg/day)
Irinotecan	<i>UGT1A1</i>	Reduce the starting dose of irinotecan for <i>UGT1A1</i> *28 homozygous patients receiving more than 250 mg/m <sup>2</sup>
Ivacaftor	<i>CFTR</i>	Recommended only for patients with cystic fibrosis who are either homozygous or heterozygous for the <i>G551D-CFTR</i> variant

**Table 9.** CPIC Clinical Recommendations for Drug-Gene Pairs (*Cont'd*)

Drug	Gene	Recommendation
NSAIDs (celecoxib, ibuprofen, meloxicam)	<i>CYP2C9</i>	In intermediate metabolizers, start with lowest recommended starting dose (celecoxib/ibuprofen) or 50% of lowest recommended starting dose (meloxicam) and titrate to clinical effect. In poor metabolizers, start with 25%–50% of the lowest recommended starting dose and titrate to clinical effect or 25%–50% of the maximum recommended dose (celecoxib/ibuprofen). Do not use meloxicam in poor metabolizers
Ondansetron	<i>CYP2D6</i>	Select an alternative drug that is not predominantly metabolized by <i>CYP2D6</i> (i.e., granisetron) in <i>CYP2D6</i> ultra-rapid metabolizers
Phenytoin	<i>HLA-B</i>	Reduce initial dosage by 25% in <i>CYP2C9</i> intermediate metabolizers and by 50% in poor metabolizers Severe cutaneous adverse reactions associated with carriers of the <i>HLA-B*58:01</i> allele Use an alternative anticonvulsant
Rasburicase	<i>G6PD</i>	Contraindicated in those with <i>G6PD</i> deficiency
Simvastatin	<i>SLCO1B1</i>	Dosing recommendations based on genotype at rs4149056 in <i>SLCO1B1</i> , including starting at lower dosages or using alternative statins
Siponimod	<i>CYP2C9</i>	Maximum 1 mg dose in poor/intermediate metabolizers (*1/*3, *2/*3) and 2 mg in normal/intermediate metabolizers (*1/*1, *1/*2, *2/*2)
SSRIs Citalopram: 2C19 Escitalopram: 2C19 Sertraline: 2C19 Fluvoxamine: 2D6 Paroxetine: 2D6	<i>CYP2D6</i> , <i>CYP2C19</i>	Alternative drug not predominantly metabolized by <i>CYP2C19</i> for <i>CYP2C19</i> ultrarapid metabolizers, and for <i>CYP2C19</i> poor metabolizers, consider a 50% reduction of recommended starting dosage For <i>CYP2D6</i> poor metabolizers, consider a 25%–50% reduction of recommended starting dosage
Tacrolimus	<i>CYP3A5</i>	Increase starting dosage by 1.5 to 2 times in <i>CYP3A5</i> intermediate or extensive metabolizers (not to exceed 0.3 mg/kg/day)
Tamoxifen	<i>CYP2D6</i>	Use alternative hormonal therapy for <i>CYP2D6</i> poor metabolizers (also consider alternative for <i>CYP2D6</i> intermediate metabolizers)
Thiopurines (azathioprine, 6-mercaptopurine, thioguanine)	<i>TMPT</i> <i>NUDT15</i>	Dosing recommendations for each drug based on <i>TMPT</i> and <i>NUDT15</i> genotypes (normal/high, intermediate, and low activity)
Tricyclic antidepressants	<i>CYP2D6</i> , <i>CYP2C19</i>	Dosing recommendations for depression based on metabolizer status (ultrarapid, extensive, intermediate, poor) Limited recommendations when using for peripheral neuropathy
Voriconazole	<i>CYP2C19</i>	Select an alternative agent that is not dependent on <i>CYP2C19</i> metabolism, such as isavuconazole, liposomal amphotericin B, or posaconazole, in ultra-rapid and rapid <i>CYP2C19</i> metabolizers Select an alternative agent that is not dependent on <i>CYP2C19</i> metabolism in poor <i>CYP2C19</i> metabolizers, or initiate at a lower-than-normal dose and perform careful therapeutic drug monitoring
Warfarin	<i>VKORC1</i> / <i>CYP2C9</i>	Use available table or algorithms to initiate warfarin dosing based on <i>VKORC1</i> and <i>CYP2C9</i> genotypes

## V. NONLINEAR PHARMACOKINETICS

### Patient Case

6. C.M. is a 55-year-old man who is initiated on phenytoin after a craniotomy. His current steady-state phenytoin concentration is 6 mg/L at a dosage of 200 mg/day by mouth. If his affinity constant ( $K_m$ ) is calculated to be 5 mg/L, which is most likely to occur if the dosage is doubled (to 400 mg/day by mouth)?
- His concentration will double because phenytoin clearance is linear above the  $K_m$ .
  - His concentration will more than double because phenytoin clearance is nonlinear above the  $K_m$ .
  - His concentration will stay the same because phenytoin is an autoinducer, and clearance increases with time.
  - His concentration will increase by only 50% because phenytoin absorption decreases significantly with dosages greater than 300 mg.

### A. Michaelis-Menten Pharmacokinetics

$$\text{velocity} = \frac{V_{\max} * S}{K_m + S}$$

$V_{\max}$  = capacity constant (amount/time)

$K_m$  = affinity constant (amount/volume)

$S$  = substrate concentration (amount/volume)

### B. Nonlinear Elimination

- Saturation or partial saturation of the elimination pathway

$$\text{rate of elimination (dose)} = \frac{V_{\max} * C}{K_m + C}$$

$V_{\max}$  = maximum rate of elimination (amount/time)

$K_m$  = concentration where elimination is  $\frac{1}{2} V_{\max}$  (affinity constant)

$C$  = drug concentration

- Note: Nonlinearity occurs when concentration is at or above  $K_m$ .

Example: Phenytoin

- $V_{\max}$  normal = 7 mg/kg/day
- $K_m$  normal = 5.6 mg/L
- 50% variability between individuals

## VI. NONCOMPARTMENTAL PHARMACOKINETICS

### A. Why Noncompartmental Pharmacokinetics?

- Identification of the “correct” model is often impossible.
- A compartmental view of the body is unrealistic.
- Linear regression is unnecessary; it is easier to automate analysis.
- Requires fewer and less stringent assumptions
- More general methods and equations
- There is no need to match all data sets to the same compartmental model.

**B. Definitions**

1. Zero moment concentration versus time curve

- Area under the curve (AUC)

$$AUC = \sum \frac{(C_{n+1} + C_n)}{2} * (t_{n+1} - t_n) \dots + \frac{C_{last}}{k}$$

2. First moment concentration \* time versus time curve

- Area under the first moment curve (AUMC)

$$AUMC = \sum \frac{(C_{n+1} * t_{n+1} + C_n * t_n)}{2} * (t_{n+1} - t_n) \dots + \frac{C_{last} * t_{last}}{k} + \frac{C_{last}}{k^2}$$

3. Mean residence time (MRT)

$$MRT = \frac{AUMC}{AUC}$$

4. Mean absorption time (MAT)

$$MAT = MRT_{ev} - MRT_{iv}$$

**C. Pharmacokinetic Parameter Estimation**

1. Clearance

$$\text{Clearance} = \frac{\text{dose}}{AUC}$$

2. Vd at steady state

$$V_{ss} = \frac{\text{dose} * AUMC}{AUC^2}$$

3. Elimination rate constant

$$k = \frac{1}{MRT}$$

4. Absorption rate constant

$$k_a = \frac{1}{MAT}$$

5. Bioavailability

$$F = \frac{D_{iv} * AUC_{ev}}{D_{ev} * AUC_{iv}}$$

**VII. DATA COLLECTION AND ANALYSIS****A. Timing of Collection**

1. Ensure completion of absorption and distribution phases (especially digoxin [8–12 hours] and aminoglycosides [30 minutes after infusion]).
2. Ensure completion of redistribution after dialysis (especially aminoglycosides [3–4 hours after hemodialysis]).

**B. Specimen Requirements**

1. Whole blood: Use anticoagulated tube. Examples: cyclosporine, amiodarone
2. Plasma: Use anticoagulated tube and centrifuge; clotting proteins and some blood cells are maintained.
3. Serum: Use red top tube, allow to clot, and centrifuge. Examples: most analyzed drugs including aminoglycosides, vancomycin, phenytoin, and digoxin

**Patient Case**

7. A drug assay is touted as having high specificity but low sensitivity. Which statement best describes what this means?
- The assay cannot distinguish the drug from like products but cannot detect extremely low concentrations.
  - The assay cannot distinguish the drug from like products and cannot detect extremely low concentrations.
  - The assay can distinguish the drug from like products and can detect extremely low concentrations.
  - The assay can distinguish the drug from like products but cannot detect extremely low concentrations.

**C. Assay Terminology**

- Precision (reproducibility): Closeness of agreement between the results of repeated analyses performed on the same sample
  - Standard deviation (SD): Average difference of the individual values from the mean
  - Coefficient of variation (CV): SD as a percentage of the mean (relative rather than absolute variation)

$$CV = \frac{SD}{\text{Mean}}$$

- Accuracy: Closeness with which a measurement reflects the true value of an object
  - Correlation coefficient: Strength of the relationship between two variables
- Predictive performance (measure of accuracy): Precision, expressed as the root mean squared error (RMSE)

$$MSE = \frac{1}{N} \sum_{i=1}^N pe_i^2 \quad RMSE = \sqrt{mse}$$

Bias: a.k.a. mean prediction error (ME)

$$ME = \frac{1}{N} \sum_{i=1}^N pe_i$$

- Prediction error ( $pe$ ) is the prediction minus the true value.
- Sensitivity: Ability of an assay to quantitate low drug concentrations accurately; usually the lowest concentration an assay can differentiate from zero
  - Specificity (cross-reactivity): Ability of an assay to differentiate the drug in question from like substances

**D. Assay Methods**

- Immunoassays
  - Radioimmunoassay
    - Advantages: Extremely sensitive (picogram range)
    - Disadvantages: Radioimmunoassay kits have limited shelf life because of the short half-life of labels, radioactive waste, and cross-reactivity.
      - Clinical use for assaying digoxin and cyclosporine
  - Enzyme immunoassay, e.g., enzyme multiplied immunoassay technique
    - Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
    - Disadvantages: Measuring enzyme activity more complex than radioisotopes, enzyme activity may be affected by plasma constituents, less sensitive than radioimmunoassays

- c. Fluorescence immunoassay: TDx (e.g., fluorescence polarization immunoassay): Most common therapeutic drug monitoring assay
    - i. Advantages: Simple, automated, highly sensitive, inexpensive and stable reagents, inexpensive and widely available equipment, no radiation hazards
    - ii. Disadvantages: Background interference attributable to endogenous serum fluorescence
  - 2. Assays used primarily in pharmacokinetic research studies
    - a. High-pressure liquid chromatography
    - b. Gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry
    - c. Flame photometry
    - d. Bioassay
- E. Population Pharmacokinetics in Therapeutic Drug Monitoring
- 1. Population pharmacokinetics useful when
    - a. Drug concentrations are obtained during complicated dosing regimens.
    - b. Drug concentrations are obtained before steady state.
    - c. Only a few drug concentrations are feasibly obtained (limited sampling strategy).
  - 2. Bayesian pharmacokinetics
    - a. Prior population information is combined with patient-specific data to predict the most probable individual parameters.
    - b. When patient-specific data are limited, there is greater influence from population parameters; when patient-specific data are extensive, there is less influence.
    - c. With a small amount of individual data, Bayesian forecasting generally yields more precise results.

**Patient Cases**

8. K.M., an 80-year-old white woman (52 kg, 64 inches), is admitted to the hospital for pyelonephritis with sepsis. She has a history of myocardial infarction  $\times 2$ , congestive heart failure, hypertension, osteoporosis, rheumatoid arthritis, and cerebrovascular accident. On admission, her BUN is 25 mg/dL, SCr is 0.92 mg/dL, and Alb is 2.9 g/dL. K.M. is initiated on the following drugs: trimethoprim/sulfamethoxazole (240 mg of the trimethoprim component) intravenously every 12 hours, lisinopril 10 mg daily by mouth, digoxin 0.125 mg daily by mouth, furosemide 40 mg daily by mouth, cimetidine 400 mg twice daily by mouth, acetaminophen 650 mg every 6 hours by mouth, calcium carbonate 500 mg three times daily by mouth, and carvedilol 6.25 mg twice daily by mouth. Which is the best assessment of K.M.'s renal function?
- A. Her SCr is in the normal range, and no dosage adjustments are necessary.
  - B. Because of her age, K.M. will have some degree of renal dysfunction, and dosages may need to be adjusted.
  - C. Because of the pyelonephritis, K.M. will have renal dysfunction, and dosages may need to be adjusted.
  - D. Her SCr is in the normal range but her BUN is elevated, so dosages may need to be adjusted.
9. Which of K.M.'s drug combinations is most likely to alter her SCr concentrations?
- A. Lisinopril and digoxin.
  - B. Trimethoprim/sulfamethoxazole and cimetidine.
  - C. Furosemide and calcium carbonate.
  - D. Acetaminophen and carvedilol.



**VIII. PHARMACOKINETICS IN RENAL DISEASE****A. Estimation of Kidney Function Through Glomerular Filtration Rate (GFR) and Creatinine Clearance (CrCl)****1. Creatinine production and elimination**

- a. Creatinine is produced in the liver.
- b. Creatinine is the product of creatine metabolism in skeletal muscle, formed at a constant rate for any one person.
- c. Creatinine is filtered at the glomerulus, where it undergoes limited secretion.
- d. CrCl is useful in approximating GFR because:
  - i. At normal concentrations of creatinine, secretion is low.
  - ii. The creatinine assay picks up a noncreatinine chromogen in the blood but not in the urine.

**2. CrCl calculation to estimate GFR**

- CrCl is calculated from a 24-hour urine collection and the following equation:

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{\text{volume of urine/1440 minutes} \times \text{urine creatinine concentration}}{\text{serum creatinine concentration}}$$

- Normal CrCl

Healthy young men = 125 mL/minute/1.73 m<sup>2</sup>

Healthy young women = 115 mL/minute/1.73 m<sup>2</sup>

- After age 30, 1% of GFR is lost per year.

**3. CrCl estimation to estimate GFR****a. Factors affecting SCr concentrations**

- i. Sex
- ii. Age
- iii. Weight and muscle mass
- iv. Renal function. Caveats: CrCl estimations worsen as renal function worsens (usually an overestimation).

**b. Jelliffe**

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = \frac{98 - 0.8 (\text{age} - 20)}{\text{SCr}}$$

Women: Use 90% of the above equation.

- Limitations

SCr concentration must be stable.

Adults 20–80 years of age (equation only applies to this age group)

Controversy: Rounding up SCr in patients with low concentrations (less than 0.7–1 mg/dL)

**c. Cockcroft-Gault**

$$\text{CrCl(mL/min)} = \frac{(140 - \text{Age}) * (\text{weight})}{72 * \text{Scr}}$$

Women: Use 85% of the above equation.

- For “weight”: Use actual body weight (ABW) in patients with body mass index (BMI) less than 18.5 kg/m<sup>2</sup>, ideal body weight (IBW) in patients with BMI 18.5–25 kg/m<sup>2</sup>, and IBW plus 40% of (ABW – IBW) in patients with BMI greater than 25 kg/m<sup>2</sup>.

IBW (men) = 50 kg + 2.3 kg for each inch over 5 feet

IBW (women) = 45.5 kg + 2.3 kg for each inch over 5 feet

- Generally recommended when making drug dosage adjustments in patients with renal dysfunction, because package insert recommendations generally use this formula to estimate creatinine clearance, and the use of the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equations to make dosing adjustments has not been validated.
- Limitations
  - SCr concentration must be stable.
  - Developed for adults only
  - Not corrected for creatinine standardization (results in lower estimations)
  - Not developed in patients with obesity (see weight recommendations above)

d. Salazar-Corcoran

$$\text{CrCl male (mL/min/1.73 m}^2\text{)} = \frac{(137 - \text{age}) * [(0.285 * \text{weight}) + (12.1 * \text{height}^2)]}{51 * \text{SCr}}$$

$$\text{CrCl female (mL/min/1.73 m}^2\text{)} = \frac{(146 - \text{age}) * [(0.287 * \text{weight}) + (9.74 * \text{height}^2)]}{60 * \text{SCr}}$$

- For “weight”: Use actual body weight in kg
- For “height”: Use meters
- Used for patients with obesity. No better than using Cockcroft-Gault with appropriate weight adjustments (see above)

e. MDRD study equation

Full equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-0.999} * (\text{age in years})^{-0.176} * 1.180 \text{ (if patient is African American)} * 0.762 \text{ (if patient is a woman)} * (\text{BUN})^{-0.170} * (\text{Alb})^{0.318}$$

Simplified four-variable equation

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = 161.5 * (\text{Scr})^{-1.154} * (\text{age in years})^{-0.203} * 1.212 \text{ (if patient is African American)} * 0.742 \text{ (if patient is a woman)}$$

- These equations directly estimate GFR (*not* CrCl) and were developed using standardized creatinine concentrations to stage kidney function.
  - These equations are recommended by the American Kidney Foundation and the European Renal Association to estimate renal function.
  - Not as accurate when GFR is greater than 60 mL/minute/1.73 m<sup>2</sup>
  - If used for drug dosing, convert value from milliliters per minute per 1.73 m<sup>2</sup> to milliliters per minute.
  - If used for drug dosing and significantly different from Cockcroft-Gault, use clinical judgment and optimize risk versus benefit.
- f. CKD-Epi equation (Table 10)
- These equations directly estimate GFR (*not* CrCl).
  - These equations are more accurate than MDRD at higher GFRs (i.e., greater than 60 mL/minute/1.73 m<sup>2</sup>). CKD-Epi is recommended by KDIGO as the preferred equation for chronic kidney disease staging.

**Table 10.** Chronic Kidney Disease Epidemiology Collaboration Equation

Race and Sex	Serum Creatinine (mg/dL)	Equation
<b>African American</b>		
Female	< 0.7	$166 * (\text{Scr}/0.7)^{-0.329} * (0.993)^{\text{Age}}$
	> 0.7	$166 * (\text{Scr}/0.7)^{-1.209} * (0.993)^{\text{Age}}$
Male	< 0.9	$163 * (\text{Scr}/0.9)^{-0.411} * (0.993)^{\text{Age}}$
	> 0.9	$163 * (\text{Scr}/0.9)^{-0.411} * (0.993)^{\text{Age}}$
<b>White or other</b>		
Female	<0.7	$\text{GFR} = 144 * (\text{Scr}/0.7)^{-0.329} * (0.993)^{\text{Age}}$
	> 0.7	$\text{GFR} = 144 * (\text{Scr}/0.7)^{-1.209} * (0.993)^{\text{Age}}$
Male	< 0.9	$\text{GFR} = 141 * (\text{Scr}/0.9)^{-0.411} * (0.993)^{\text{Age}}$
	> 0.9	$\text{GFR} = 141 * (\text{Scr}/0.9)^{-1.209} * (0.993)^{\text{Age}}$

GFR = glomerular filtration rate; SCr = serum creatinine.

- g. Pediatric formulas (Table 11). Do not round up low SCr values in pediatric patients.

Schwartz:

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = \frac{K * \text{ht (cm)}}{\text{SCr}}$$

**Table 11.** Schwartz Equation Constants

Age	K
Low birth weight ≤ 1 year	0.33
Full term ≤ 1 year	0.45
1–13 years	0.55
13- to 18-year-old adolescent female	0.55
13- to 18-year-old adolescent male	0.7

Note:  $K = 0.413$  for 1–13 years old and 13- to 18-year-old adolescent females when using standardized creatinine concentrations (other  $K$  values have not been updated); this is known as the bedside Chronic Kidney Disease in Children (CKiD) equation.

Counahan-Barratt:

$$\text{GFR (mL/minute/1.73 m}^2\text{)} = \frac{0.43 * \text{ht (cm)}}{\text{SCr}}$$

4. Factors influencing CrCl estimates
  - a. Patient characteristics
    - i. Age (↓ production of creatinine with age)
    - ii. Female sex (↓ production of creatinine)
    - iii. Race (↑ production of creatinine in African Americans)
  - b. Disease states and clinical conditions
    - i. Spinal cord injuries (↓ muscle mass; ↓ creatinine)
    - ii. Amputations (↓ muscle mass; ↓ creatinine)
    - iii. Cushing syndrome (↓ muscle mass; ↓ creatinine)
    - iv. Muscular dystrophy (↓ muscle mass; ↓ creatinine)
    - v. Guillain-Barré syndrome (↓ muscle mass; ↓ creatinine)
    - vi. Rheumatoid arthritis (↓ muscle mass; ↓ creatinine)
    - vii. Liver disease (↓ creatine; ↓ creatinine)
    - viii. Glomerulopathic disease (greater amount of creatinine secretion in relation to filtration)
    - ix. Hydration status (dehydration vs. fluid overload)

- c. Diet
    - i. High-meat protein diets ( $\uparrow$  creatinine ingestion)
    - ii. Vegetarians ( $\downarrow$  creatinine ingestion)
    - iii. Protein calorie malnutrition ( $\downarrow$  creatinine ingestion)
  - d. Drugs and endogenous substances
    - i. Laboratory interaction: Kinetic alkaline picrate method
      - (a) Noncreatinine chromogens: In blood but not in urine
      - (b) Cephalosporins (especially cefoxitin): Chromogenic, causing false elevations that are much greater in urine than in blood
      - (c) Acetoacetate (elevated in fasting patients, patients with diabetic ketoacidosis): Chromogenic, causing false elevations
    - ii. Pharmacokinetic interaction: Drugs compete with creatinine for renal secretion (causing false elevations), cobicistat, trimethoprim, cimetidine, fibric acid derivatives (other than gemfibrozil), and dronedarone.
- B. Drug Dosing in Renal Disease
1. Loading dose
    - a. In general, no alteration is necessary, but it should be given to hasten the achievement of therapeutic drug concentrations.
    - b. Alterations in loading dose must occur if the Vd is altered secondary to renal dysfunction. Example: Decrease digoxin loading doses in renal disease because of a decreased Vd.
  2. Maintenance dosage: Alterations should be made in either the dosage or the dosing interval.
    - a. Changing the dosing interval
      - i. Use when the goal is to achieve similar steady-state concentrations.
      - ii. Less costly
      - iii. Ideal for limited-dosage forms (i.e., oral medications)
    - b. Changing the dosage
      - i. Use when the goal is to maintain a steady therapeutic concentration.
      - ii. More costly
    - c. Changing the dosage and the dosing interval
      - i. Often necessary for substantial dosage adjustment with limited-dosage forms
      - ii. Often necessary for narrow therapeutic index drugs with target concentrations
        - (a) If a drug is given more than once daily, then adjust the interval.
        - (b) If a drug is given once daily or less often, then adjust the dosage.

**Patient Case**

10. S.J. is a 55-year-old man with hepatic dysfunction and an anaerobic infection caused by *Prevotella* spp. He has a small amount of ascites but is not encephalopathic. He is initiated on metronidazole, and the package insert states that dosages should be decreased by 50% in patients with a Child-Pugh score greater than 9. If he has the following hepatic laboratory values, which best estimates his Child-Pugh score?

Aspartate transaminase = 85 U/L, alanine transaminase = 56 U/L, alkaline phosphatase = 190 U/L, total bilirubin = 1.8 mg/dL, Alb = 2.9 g/dL, lactic dehydrogenase = 270 U/L, prothrombin time/international normalized ratio = 14.6/1.7,  $\gamma$ -glutamyl transferase = 60 U/L

- A. 3.
- B. 5.
- C. 8.
- D. 11.

## IX. PHARMACOKINETICS IN HEPATIC DISEASE

### A. Dosage Adjustment in Hepatic Disease

1. Clinical response is the most important factor in adjusting dosages in hepatic disease.
2. Low–hepatic extraction ratio drugs
  - a. Adjustment of maintenance dosage is necessary only when hepatic disease alters the intrinsic clearance ( $Cl_{int}$ ).
  - b. Alterations in protein binding alone do not require alteration of maintenance dosage, even though total drug concentrations decline.
  - c. Loading doses may require reduction.
  - d. Examples: carbamazepine, diazepam, phenytoin, warfarin
3. High–hepatic extraction ratio drugs
  - a. Intravenous administration
    - i. Usually necessary to decrease maintenance dose rate as hepatic blood flow changes
    - ii. Consider effect of hepatic disease on protein binding as it alters free concentrations.
  - b. Oral administration: Similar to low–hepatic extraction ratio drugs; necessary to decrease maintenance dose rate when hepatic disease alters  $Cl_{int}$
  - c. Examples: haloperidol, morphine, metoprolol, propranolol, verapamil

### B. Rules for Dosing in Hepatic Disease

1. Hepatic elimination of high–extraction ratio drugs is more consistently affected by liver disease than hepatic elimination of low–extraction ratio drugs.
2. The clearance of drugs that are exclusively conjugated is not substantially altered in liver disease.
3. Adjustments for some drugs based on Child-Pugh scores (Table 12).

**Table 12.** Child-Pugh Classification for Liver Disease

	Points		
	1	2	3
Encephalopathy	0	1 or 2	3 or 4
Ascites	0	+	++
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds over control) or INR (values in brackets)	0–4 [< 1.7]	4–6 [1.7–2.3]	> 6 [> 2.3]

Pugh score: 5 = normal; 6 or 7 = mild (A); 8 or 9 = moderate (B); >9 = severe (C).

## X. PHARMACODYNAMICS

### Patient Case

11. Which is the most likely reason that a drug will follow clockwise hysteresis?
  - A. Formation of an active metabolite.
  - B. Delay in equilibrium between the blood and the site of action.
  - C. Tolerance.
  - D. Increased sensitivity with time.

A. Definition: Relationship Between Drug Concentrations and the Pharmacologic Response

B. Hill equation

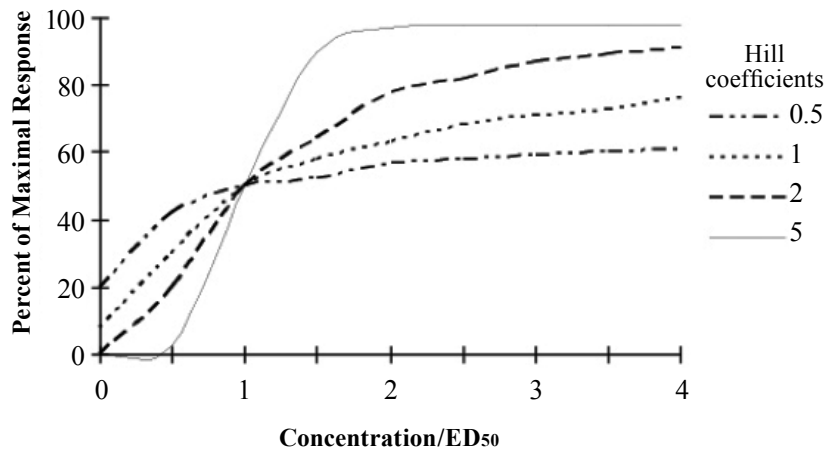
$$E = \frac{E_{\max} * C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

E = pharmacologic response

$E_{\max}$  = maximum drug effect

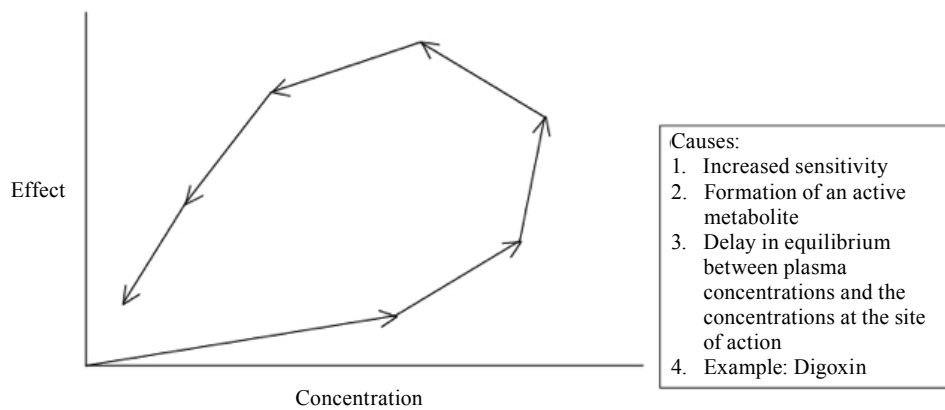
$EC_{50}$  = concentration producing half of the maximum drug effect

$\gamma$  = Hill coefficient that accommodates the shape of the curve

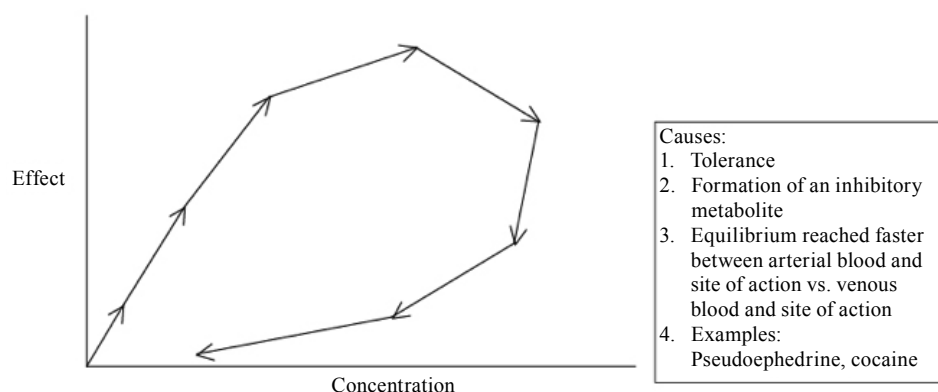


**Figure 5.** Concentration response plot.

C. Hysteresis Loops. Definition: Concentrations late after a dose produce an effect different from that produced by the same concentration soon after the dose.



**Figure 6.** Counterclockwise hysteresis.



**Figure 7.** Clockwise hysteresis.

### Patient Cases

12. P.L., a 45-year-old man with end-stage renal disease on dialysis is receiving phenytoin 400 mg/day for a history of tonic-clonic seizures. His phenytoin concentration today is 13.6 mg/L, and his Alb concentration is 4.2 g/dL. Given his current concentrations, which change would best be recommended?
  - A. Make no changes to his drug regimen.
  - B. Keep the total daily dosage the same, but change the regimen to 200 mg two times/day.
  - C. Increase the dosage for better seizure control.
  - D. Decrease the dosage to prevent toxicity.
  
13. N.R. is a 63-year-old man with renal insufficiency who comes to the emergency department in atrial fibrillation with a ventricular rate of 120 beats/minute. Because of his history of ventricular dysfunction, it is decided to initiate him on digoxin for rate control. Which is the best dosing for this patient?
  - A. The loading dose should remain the same, but the maintenance dose should be decreased.
  - B. The loading dose should be decreased, and the maintenance dose should remain the same.
  - C. Neither the loading dose nor the maintenance dose should be adjusted.
  - D. Both the loading dose and the maintenance dose should be decreased.
  
14. P.P. is a 34-year-old man with a history of cerebral palsy and chronic urinary tract infections. He is admitted to the hospital with a *Pseudomonas* urinary tract infection that is resistant to all antibiotics except for aminoglycosides. He is initiated on once-daily tobramycin at 400 mg/day intravenously. Which statement best describes this high-dose, extended-interval aminoglycoside regimen?
  - A. It takes advantage of the concentration-dependent killing of aminoglycoside.
  - B. It is more efficacious than standard aminoglycoside dosing.
  - C. It does not require the monitoring of aminoglycoside concentrations.
  - D. It will not cause nephrotoxicity.

## XI. THERAPEUTIC DRUG MONITORING (Table 13)

Table 13. Therapeutic Drug Monitoring of Specific Drugs

Drug	Therapeutic Range	Sampling Issues	Comments
Aminoglycosides	Cp = 4–10 mg/L maximum Amikacin = 20–30 mg/L Cp < 2 mg/L minimum Amikacin < 10 mg/L Higher maximum concentrations for high-dose extended-interval dosing	Duration of infusion, timing of first sample after infusion (generally should be ½–1 hour)	High-dose extended-interval (“once-daily”) aminoglycoside dosing is generally recommended to decrease toxicity and improve efficacy  These regimens are just as effective as traditional dosing, and meta-analyses have demonstrated less nephrotoxicity or no difference
Vancomycin	Bayesian-derived AUC/MIC ratio of 400–600	AUC derived by (1) collecting two concentrations (a near steady-state, post-distributional Cmax at 1–2 hr post-infusion, and a trough) during the same dosing interval and using first-order PK equations to estimate the AUC or (2) collecting one or two concentrations (at least one trough) and using Bayesian software programs to estimate the AUC	Trough-only monitoring of vancomycin is no longer recommended, and clinical PK services should move to AUC/MIC monitoring. If an MIC is not available, assume 1 mg/L. Loading doses are recommended for ICU patients, those receiving renal replacement therapy, and those receiving continuous infusions
Phenytoin	10–20 mg/L Free: 1–2 mg/L	In general, obtain trough concentrations	Percentage free increases with renal failure and hypoalbuminemia  Equations to correct:  <u>Changes in albumin:</u> $Cp = \frac{Cp'}{(0.9 * \frac{Alb}{4.4}) + 0.1}$  <u>Renal failure:</u> $Cp = \frac{Cp'}{0.5}$  <u>Renal failure with change in albumin:</u> $Cp = \frac{Cp'}{(0.48 * 0.9 * \frac{Alb}{4.4}) + 0.1}$  Induces liver enzymes; susceptible to metabolic drug interactions
Carbamazepine	4–12 mg/L		Autoinduction; active metabolite 10,11 epoxide
Phenobarbital	15–40 mg/L		Enzyme inducer
Valproic acid	50–100 mg/L		Saturable protein binding; percentage free increases with renal failure and hypoalbuminemia
Digoxin	0.8–2 mcg/L	Prolonged distribution period necessitates sampling > 6–12 hours after dose	Volume of distribution decreases in renal disease; susceptible to drug interactions
Cyclosporine	100–250 mcg/L	Whole blood samples	Many drug interactions
Lithium	0.3–1.3 mmol/L	Prolonged distribution necessitates sampling 12 hours after dose	
Theophylline	10–20 mg/L		Treat as continuous infusion with sustained-release dosage forms

Cp = concentration of drug in plasma; Vd.



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## ANSWERS AND EXPLANATIONS TO PATIENT CASES

**1. Answer: C**

In 6 days (2 half-lives), the concentration will decrease from 41.9 mg/L to about 10.5 mg/L; now is the time to redose (Answer C is correct). A 1-g dose given on March 24 will increase the concentration in the blood from 14.1 mg/L to 41.9 mg/L ( $14.1 + 27.8$  mg/L). Given that the half-life is about 3 days, it will take longer than 1 day to reach a concentration of about 10 mg/L (Answer A is incorrect). In 3 days (1 half-life), the concentration will decrease from 41.9 mg/L to about 21 mg/L—still too early to redose (Answer B is incorrect). Redosing can be determined because plenty of information exists about how to calculate when to redose (Answer D is incorrect).

**2. Answer: A**

$F = (100 \text{ mg} * 25 \text{ mg*hr/L}) / (200 \text{ mg} * 50 \text{ mg*hr/L}) = 25\%$  (Answer A is correct). (Answers B, C, and D are all incorrect).

**3. Answer: D**

P-glycoprotein is an efflux pump that pumps drugs back into the GI lumen (Answer D is correct). P-glycoprotein is not a plasma protein (Answer A is incorrect), and it does not transfer drugs through the GI mucosa (Answer B is incorrect); rather, it pumps drugs back into the GI lumen. In addition, P-glycoprotein acts in concert with CYP3A4 to diminish oral absorption (Answer C is incorrect).

**4. Answer: C**

Azithromycin does not inhibit CYP3A4 (Answer C is correct). Erythromycin and clarithromycin are potent inhibitors of CYP3A4 and would be expected to increase cyclosporine concentrations (Answers A and B are incorrect). Cytochrome P450 inhibition is not a drug class effect (Answer D is incorrect).

**5. Answer: B**

Clopidogrel is a prodrug. Therefore, to be effective, it must be metabolized into the active form. Because this metabolism is primarily performed by CYP2C19 and this patient is a CYP2C19 poor metabolizer, he will not produce as much active drug, increasing the risk of a thrombotic event (Answer B is correct). The clopidogrel metabolite formed does not block the action of

aspirin (Answer A is incorrect). Because the clopidogrel metabolite is the active form of the medication, slowing metabolism will not increase bleeding, but instead will have the opposite effect (Answer C is incorrect). Because he is a slow metabolizer of CYP2C19, he will not overproduce the active metabolite (Answer D is incorrect).

**6. Answer: B**

By definition, clearance becomes nonlinear once the concentration exceeds the  $K_m$  (Answer A is incorrect); therefore, the concentrations will more than double (Answer B is correct). Phenytoin is not a significant autoinducer (Answer C is incorrect). Although phenytoin absorption decreases as the dosage is increased, it is not clinically significant until a single dose exceeds 400 mg (Answer D is incorrect).

**7. Answer: D**

The correct answer is that the assay will be able to distinguish the drug from like products but will not be able to detect extremely low concentrations (Answer D is correct). High specificity means the assay can distinguish the drug from like products (Answers A and B are incorrect), and low sensitivity means the assay cannot detect extremely low concentrations (Answer C is incorrect).

**8. Answer: B**

Although her SCr is in the normal range, her renal function is decreased because of her age (Answer A is incorrect). After age 30, patients lose around 1 mL/minute/year of CrCl. Therefore, her CrCl needs to be calculated to assess drug dosing (Answer B is correct). Patients with pyelonephritis do not have a decrease in their renal function (Answer C is incorrect). Her elevated BUN is probably a sign of prerenal azotemia caused by dehydration associated with her infection. The BUN measurement is generally not used to assess renal function for drug dosing purposes (Answer D is incorrect).

**9. Answer: B**

Both trimethoprim/sulfamethoxazole and cimetidine compete with creatinine for secretion in the kidneys, increasing SCr concentrations (Answer B is correct). Although angiotensin-converting enzyme inhibitors may transiently increase SCr concentrations, digoxin does not affect renal function (Answer A is incorrect). Although furosemide may secondarily affect SCr concentrations, calcium carbonate does not affect renal function (Answer C is incorrect). Acetaminophen and carvedilol generally do not affect SCr concentrations (Answer D is incorrect).

**10. Answer: C**

This patient has 1 point for not being encephalopathic, 2 points for mild ascites, 1 point for the bilirubin concentration, 2 points for the albumin concentration, and 2 points for the INR, for a total of 8 points (Answer C is correct). Normal patients have a Child-Pugh score of 5, which means no hepatic dysfunction (Answers A, B, and D are incorrect).

**11. Answer: C**

Tolerance leads to a decrease in effect with time; this is clockwise hysteresis (Answer C is correct). The formation of an active metabolite, a delay in equilibrium between the blood and the site of action, and the increased sensitivity with time would lead to an increase in effect with time; this is counterclockwise hysteresis (Answers A, B, and D are all incorrect).

**12. Answer: D**

The dosage should be decreased to prevent toxicity (Answer D is correct). In renal failure, acidic byproducts build up in the blood and compete with phenytoin for protein binding. Total concentrations must be corrected, and this correction leads to a doubling of the concentration. Therefore, the current concentration is too high, and the dosage should be decreased (Answers A and C are incorrect). Single doses of 400 mg are fine (doses higher than 400 mg should be divided) (Answer B is incorrect).

**13. Answer: D**

Both the loading dose and the maintenance dose should be decreased (Answer D is correct). In general, loading doses need not be altered in renal dysfunction because they primarily depend on the Vd. However, the digoxin Vd is decreased in renal dysfunction (Answers A and C are incorrect). Because digoxin is eliminated renally, the maintenance dose should be decreased (Answers B and C are incorrect).

**14. Answer: A**

Aminoglycosides have concentration-dependent killing, and a high-dose, extended-interval aminoglycoside regimen takes advantage of this characteristic (Answer A is correct). However, it has not proved more efficacious than traditional dosing (Answer B is incorrect). Aminoglycoside concentrations still need to be monitored with high-dose, extended-interval therapy (Answer C is incorrect). In addition, high-dose, extended-interval aminoglycoside dosing can still cause nephrotoxicity (although the incidence is generally diminished) (Answer D is incorrect).

## ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

**1. Answer: B**

With two concentrations, data are sufficient to calculate an elimination rate constant and, therefore, a half-life (Answers C and D are incorrect; Answer B is correct). In addition, the  $V_d$  can be calculated by back extrapolation to the  $C_{max}$  and use of appropriate equations (because this was the first dose, and therefore it is known that the tobramycin concentration was 0 mg/L before the dose was given) (Answer A is incorrect and Answer B is correct).

**2. Answer: A**

The elimination rate constant equals  $(\ln 3.6 \text{ mg/L} - \ln 0.9 \text{ mg/L})/4 \text{ hours} = 0.35/\text{hour}$ . The half-life is  $0.693/0.35 = 2 \text{ hours}$ . The concentration at the end of the infusion equals  $3.6 \text{ mg/L} \cdot e^{-(0.35 \cdot 1)} = 5.1 \text{ mg/L}$ . The patient's  $V_d = \text{dose}/\text{change in concentration}$ , or  $110 \text{ mg}/5.1 \text{ mg/L} = 21.5 \text{ L}$  (Answer A is correct; Answers B, C, and D are all incorrect).

**3. Answer: B**

Her clearance increased because of the improvement in renal function, which increased her elimination rate constant and decreased her half-life (Answer B is correct). The  $V_d$  would not be altered by changes in clearance (they are independent) (Answer A is incorrect). With the diuresis and angiotensin-converting enzyme inhibitor, her  $V_d$  probably decreased, but clearance would not be altered by changes in  $V_d$  (they are independent) (Answer C is incorrect). In addition, if her  $V_d$  decreased, her half-life would decrease, not increase (Answer D is incorrect).

**4. Answer: C**

Because the trough and AUC/MIC are too low, the interval will have to be shortened to increase the concentration (Answers A and B are incorrect). Maintaining the total daily dose will not increase the AUC/MIC to the appropriate range (Answer D is incorrect). Vancomycin largely has linear PK. In the absence of changes to clearance and volume, doubling the dose in a 24-hour period will double the exposure (AUC). Therefore, increasing from 1000 mg daily to 1000 mg every 12 hours will increase the AUC/MIC from 210 to 420 (Answer C is correct).

**5. Answer: B**

To achieve flucytosine peak concentrations of 50–100 mg/L (assuming a trough concentration of 25 mg/L, dosing every 6 hours, and 100% bioavailability; flucytosine volume of distribution of 0.7 L/kg; half-life of 3 hours), the concentration must be changed by 25–75 mg/L. Using the equation  $\Delta C_p = \text{dose}/V$ , a dosage of 12.5 mg/kg would increase the concentration by only 17.8 mg/L. A dosage of 75 mg/kg would increase the concentration by 107 mg/L, whereas a dosage of 150 mg/kg would increase the concentration by 214 mg/L. The correct dosage is 37.5 mg/kg because it would increase the concentration by 53.6 mg/L. (Answer B is correct; Answers A, C, and D are all incorrect).

**6. Answer: D**

Because of the patient's renal failure and low Alb, the total concentration must be corrected. The patient's corrected phenytoin concentration is 14.9 mg/L ( $C_p = 5.6 / \{ [0.48 \times 0.9 \times (2.8/4.4)] + 0.1 \} = 14.9 \text{ mg/L}$ ). Therefore, no changes should be made to the dosage (Answer D is correct; Answers A, B, and C are all incorrect).

**7. Answer: C**

Both of these are immunoassays but they are different (Answer D is incorrect). Because they are both immunoassays, they both use antibodies to bind the molecule of interest (Answer A is incorrect). A brand name for the Abbott fluorescence polarization immunoassay is TDx, which uses a fluorescent label. The term *EMIT* stands for *enzyme multiplied immunoassay technique*, which is an immunoassay that uses an enzyme label (Answer C is correct). Neither of them use radioisotopes (Answer B is incorrect).

**8. Answer: D**

The digoxin concentration was obtained too close to the 8:00 a.m. dose. The digoxin had not yet had a chance to complete its distribution phase. Once distribution is complete (generally 6–12 hours after the dose), the concentration will be lower and probably within the therapeutic range (Answer D is correct). Therefore, there is no need for the digoxin antibody (Answer A is incorrect), activated charcoal (Answer C is incorrect), or lowering of the dosage (Answer B is incorrect).

**9. Answer: C**

The correct statistical test is multiple regression. Multiple regression is used to describe the relationship between a dependent variable and two or more independent variables when both the dependent and independent variables are numeric (Answer C is correct). Analysis of variance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal (Answer A is incorrect). Likewise, analysis of covariance is used to describe the relationship between a dependent variable and two or more independent variables when the dependent variable is numeric and the independent variables are nominal with confounding factors (Answer B is incorrect). Spearman rank correlation is a nonparametric test used to describe the relationship between one dependent and one independent variable when the data are ordinal or numeric and not normally distributed (Answer D is incorrect).

**10. Answer: B**

Assessing adherence and increasing her dosage is the best recommendation, because the concentration is below the therapeutic range (Answer B is correct). The valproic acid therapeutic range is 50–100 mg/L, and she is well below this concentration. Although some patients are controlled at lower concentrations, this concentration is probably too low (Answer A is incorrect). She definitely does not need a decrease in dosage (Answer C is incorrect). Although total valproic acid concentrations are affected by changes in Alb, her Alb is normal, and obtaining a free concentration is unnecessary (Answer D is incorrect).

**11. Answer: B**

Codeine's activity is due primarily to its metabolism to morphine by CYP2D6 after administration. Because this patient is a CYP2D6 poor metabolizer, less of the codeine will be metabolized to its active metabolite (Answer B is correct and Answer C is incorrect). Omeprazole does inhibit CYP2C19, but this enzyme does not metabolize codeine (Answer A is incorrect). Metoprolol is a substrate of CYP2D6 but is not an inhibitor or inducer of CYP2C9 Answer D is incorrect).

**12. Answer: D**

The MDRD and CKD-Epi are actually better estimates of renal function because they directly estimate GFR instead of CrCl (Answer A is incorrect). Although the Cockcroft-Gault equation was developed in hospitalized patients and the MDRD and CKD-Epi equations were developed in ambulatory patients, this does not affect the setting where they can be used (Answer B is incorrect). Moreover, although the equations do have different units (mL/minute vs. mL/minute/1.73 m<sup>2</sup>), this can easily be corrected by converting the result of the MDRD or CKD-Epi equation to milliliters per minute (Answer C is incorrect). The best reason for not using MDRD or CKD-Epi for drug dosing is that renal dosing adjustment recommendations published in package inserts are almost always based on CrCl estimates using the Cockcroft-Gault equation (Answer D is correct).

**13. Answer: A**

Assays with low sensitivity will not be able to detect low drug concentrations, which may still be therapeutic (Answer A is correct). Assays that cannot differentiate between like substances have low specificity (Answers C and D are incorrect). Assays that report highly variable values when repeatedly run on the same sample have low precision (Answer A is correct). Assays that consistently over- or under-measure the true concentration have low accuracy (Answers B and C are incorrect).

