Concepts in Clinical Pharmacokinetics

SIXTH EDITION

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Preface

For students just entering the world of pharmacy or seasoned practitioners, the study of pharmacokinetics and the mathematical equations required for drug dosing can be quite intimidating. Combined with the terminology of the science, this may make a course in pharmacokinetics a considerable challenge. In this sixth edition of *Concepts in Clinical Pharmacokinetics*, we continue to focus on the fundamental pharmacokinetic concepts. These concepts, along with the mathematical equations, are broken down to their simplest forms, and a step-by-step approach is adopted to explain the "how to" of the discipline. We believe that such an approach allows the student to gain greater comprehension of the subject matter, which allows adaptation of concepts to specific clinical drug dosing situations.

Pharmacokinetic concepts are further illustrated by application to clinical dosing cases, including aminoglycosides, vancomycin, theophylline, digoxin, and phenytoin. These cases are designed to show the easily understandable, step-by-step approach for performing appropriate clinical dosing consults. All cases provide the complete mathematical solutions for each calculation, allowing readers to "check their math." Equations are explained in detail, and all similar equations used throughout the text are cross-referenced to the basic concept. In addition there is a valuable appendix containing basic and drug-specific pharmacokinetic equations.

This edition expands on several concepts including proper estimation of renal function, extended-interval aminoglycoside dosing, pharmacogenomic effects on drug metabolism, a phenytoin "cheat sheet" to help you through the calculations maze, and new vancomycin cases based on higher desired vancomycin levels and trough-only dose estimations. As with past editions the reader will find numerous clinical correlates throughout the text to further highlight specific clinical or mathematical explanations.

The goal for this edition, as with the previous five editions, remains the same—to provide the student or practitioner with the concepts and clinical applications needed for a better understanding of this complicated, yet vital, subject.

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A Note from the Authors on Using This Edition

This book teaches the basic biopharmaceutic concepts, mathematical models, and clinical applications needed to determine such values as dose, interval, steady-state concentration, etc. Specific conceptual and mathematical formulas are combined to solve more complex dosing situations. Eleven chapters contain a practice quiz to chart your progress, and there are three practice sets of questions with answers. The last four chapters are completely devoted to clinical cases that fully explain, step-by-step, how to dose several drugs that generally require serum drug concentrations. We strongly encourage you to attempt to solve these cases without looking at the step-by-step answers, and then when finished, check to see if you got them right.

—WS, WW, JD

A complete online course based on this book with four enrollment options is available through the University of Georgia Center for Continuing Education. To learn more go to:

http://www.georgiacenter.uga.edu/courses/healthcare-pharmacy

Abbreviations

α : distribution rate constant for two-compartment model

AUC : area under plasma drug concentration versus time curve

AUMC : area under the (drug concentration × time) versus time (moment) curve

β : terminal elimination rate constant

C : concentration

- $\overline{C}$ average steady-state concentration
- C_0, C_1, C_2 initial (just after infusion), first, second concentrations
- C_{in} concentration in blood on entering organ
- C_{last} last measured concentration
- C_{max} maximum concentration
- C_{max1}, C_{max2} first, second maximum concentrations
- $C_{max\,(steady\ state)}$ steady-state maximum concentration
- $C_{min\,(steady\ state)}$ steady-state minimum concentration
- C_{min} minimum concentration
- C_{out} concentration in blood on leaving organ
- C_{peak} peak concentration
- C_{ss} steady-state concentration
- C_t concentration at time *t*
- C_{trough} trough concentration

Cl : clearance

- Cl_b biliary clearance
- Cl_h hepatic (liver) clearance
- Cl_i intrinsic clearance
- Cl_m clearance by metabolism (mainly liver)
- $Cl_{other\ organs}$ clearance by other organs
- $Cl_{P \to mX}$ formation clearance for a given metabolite *X*
- $Cl_{P \to m\,1}$ fractional clearance of parent drug (*P*) to form metabolite 1 (m_1)
- Cl_r renal clearance
- Cl_t total body clearance

conc : concentration

Δ : change in

E : extraction ratio

continued on next page

- **e** : base of natural logarithm
- ***F*** : fraction of drug absorbed that reaches systemic circulation (bioavailability)
  - F_{m1} fraction of m_1 formed from a single dose of the parent drug
  - F_p fraction of unbound drug in plasma
  - F_t fraction of unbound drug in tissue
- **GFR** : glomerular filtration rate
- **GI** : gastrointestinal
- ***K*** : elimination rate constant
  - K_0 rate of drug infusion
  - K_{12} rate constant for transfer of drug from compartment 1 to compartment 2
  - K_{21} rate constant for transfer of drug from compartment 2 to compartment 1
  - K_a absorption rate constant
  - K_m Michaelis–Menten constant (drug concentration at which elimination rate = ½ Vmax)
- **λ** : terminal elimination rate constant
- m_1, m_2, m_3 : metabolites 1, 2, and 3
- $m_{1,u}, m_{2,u}, m_{3,u}$: amount of m_1, m_2, or m_3 excreted in the urine
- **MRT**: mean residence time
- ***n*** : number of doses
- ***Q*** : bloodflow
  - Q_h hepatic bloodflow
- ***S*** : salt form of drug
- **SST** : serum separator tube
- **τ** : dosing interval
- ***t*** : time (after dose)
  - t' time after end of infusion ($t' = \tau - t$ for trough concentration)
  - t'' time (duration) of loading infusion
  - t_0 time zero
  - $T½$ half-life
  - $t_{90\%}$ time required to reach 90% of steady-state concentration
- ***V*** : volume; volume of distribution
  - V_{area} volume of distribution by area
  - V_c volume of central compartment
  - V_{extrap} extrapolated volume of distribution
  - V_p plasma volume
  - V_{ss} steady-state volume of distribution
  - V_t tissue volume
  - V_{max} maximum rate of the elimination process
- ***X*** : amount of drug
  - X_0 dose (or initial dose) of drug
  - X_1, X_2 amount of drug at different times
  - X_c amount of drug in central compartment
  - X_d daily dose of drug
  - X_p amount of drug in peripheral compartment

QU: Add MDRP and MIC?