

Concepts in Clinical

Pharmacokinetics

Fifth Edition

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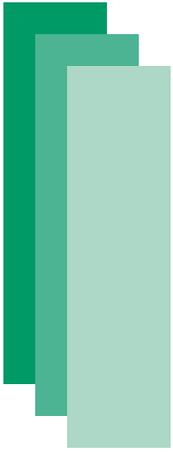
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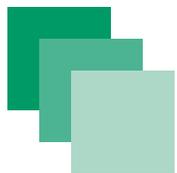
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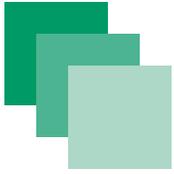
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Preface

For the individual pursuing the study of pharmacokinetics, whether a student just entering the world of pharmacy or the seasoned practitioner, the mathematical equations required for drug dosing may be quite intimidating. This, compounded with the terminology of this science, may make a course in pharmacokinetics a considerable challenge. In this fifth edition of *Concepts in Clinical Pharmacokinetics*, we continue to focus on the fundamental pharmacokinetic concepts. These concepts, along with mathematical equations, are broken down to their simplest forms, and a step-by-step approach is adopted to explain the “how to” of this discipline. We believe that such an approach allows the student to gain a 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 as well as to a valuable appendix containing equations used to dose specific drugs.

The reader will also find that each chapter has been revised and updated with additional clinical correlates throughout. Clinical correlates help the reader to link fundamental kinetic models to specific clinical applications. Clinical correlates highlight either a mathematical or clinical point, helping the reader avoid making simple mistakes.

In this new edition we have also expanded coverage of renal function assessment, comparing creatinine clearance estimates to the modification of diet in renal disease glomerular filtration rates estimates for drug dosing. Cases have been revised to reflect important new clinical concepts for aminoglycosides, vancomycin, and digoxin, and discussion points have been added for these cases.

The design elements from the previous edition have been maintained, with the addition of an equation circumscription tool used to “call out” specific equation components for further explanation. As in each of our previous four editions our goal remains the same—to provide the student or practitioner with the concepts and clinical applications needed for a better understanding of this complicated yet useful subject.

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Abbreviations

- α : distribution rate constant for two-compartment model
- AUC: area under plasma drug concentration versus time curve
- AUMC: area under the (drug concentration \times time) versus time (moment) curve
- β : terminal elimination rate constant
- C: concentration
- \bar{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
- $Cl_{P \rightarrow mX}$: formation clearance for a given metabolite X
- $Cl_{P \rightarrow m1}$: 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
- e : base of natural logarithm
- F : fraction of drug absorbed that reaches systemic circulation (bioavailability)
- F_p : fraction of unbound drug in plasma
- F_t : fraction of unbound drug in tissue
- F_{m1} : fraction of metabolite m_1 formed from a single dose of the parent drug
- 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 = $1/2 V_{max}$)
- 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 : blood flow
- Q_h : hepatic blood flow
- 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
- $T^{1/2}$: half-life

xii Abbreviations

$t_{90\%}$: 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