

Table of contents :

Cover	
Half Title	
Title Page	
Copyright Page	
Dedication	
Contents	
List of Figures	
1. Introduction to Pharmacokinetics	
1.1. Introduction	
1.2. Pharmacokinetics and Its Related Fields	
1.2.1. Biopharmaceutics	
1.2.2. Pharmacokinetics	
1.2.3. Clinical Pharmacokinetics	
1.2.4. Pharmacodynamics	
1.2.5. Population Pharmacokinetics	
1.2.6. Toxicokinetics	
1.2.7. Pharmacogenetics	
1.3. Application of the Pharmacokinetic Principles in the Biomedical Fields	
1.3.1. Design and Evaluation of Dosage Forms	
1.3.2. Evaluation of Generic Drug Products	
1.3.3. Pharmacological Testing	
1.3.4. Toxicological Testing	
1.3.5. Evaluation of Organ Function	
1.3.6. Therapeutic Drug Monitoring	
1.4. The Blood Drug Concentration-Time Profile	
1.5. Linear and Nonlinear Pharmacokinetics	
1.5.1. Linear Pharmacokinetics	
1.5.2. Nonlinear Pharmacokinetics	
1.6. Pharmacokinetic Modeling	
1.6.1. Compartmental Modeling	
1.6.2. Physiological Modeling	
1.6.3. Population Pharmacokinetic Modeling	
1.6.4. Noncompartmental Data Analysis Approach	
1.6.5. Pharmacokinetic-Pharmacodynamic Modeling	
1.7. Pharmacokinetic Simulations	
1.8. Essential Graphical, Mathematical, and Statistical Fundamentals Used in Pharmacokinetics	
1.8.1. Graphs	
1.8.2. Curve Fitting	
1.8.3. Determination of the Straight-Line Parameters	
1.8.3.1. Graphical Determination of the Straight-Line Parameters	
1.8.3.2. The Least Squares Method	
1.8.4. Application of Basic Calculus Principles in Pharmacokinetics	
2. Drug Pharmacokinetics Following Single Intravenous Bolus Administration: Drug Distribution	
2.1. Introduction	
2.2. Drug Distribution	
2.2.1. The Rate and Extent of Drug Distribution	
2.3. The Volume of Distribution	
2.4. Drug Distribution after Single IV Bolus Drug Administration	
2.5. Drug Protein Binding	
2.5.1. Effect of Changing the Plasma Protein Binding	
2.5.2. Determination of Plasma Protein Binding	
2.6. Drug Partitioning to Blood Cells	
2.7. Summary	

3. *Drug Pharmacokinetics Following Single IV Bolus Administration: Drug Clearance*
 - 3.1. *Introduction*
 - 3.2. *Drug Clearance*
 - 3.2.1. *The Total Body Clearance*
 - 3.2.2. *Physiological Approach to Drug Clearance*
 - 3.2.3. *The Plasma Drug Concentration-Time Profile*
 - 3.3. *Total Body Clearance and Volume of Distribution Are the Independent Pharmacokinetic Parameters*
 - 3.4. *Determination of the Total Body Clearance*
 - 3.5. *Summary*
4. *Drug Pharmacokinetics Following Single IV Bolus Administration: The Rate of Drug Elimination*
 - 4.1. *Introduction*
 - 4.2. *Drug Elimination*
 - 4.3. *The Kinetics of the Drug Elimination Process*
 - 4.3.1. *Zero-Order Elimination*
 - 4.3.1.1. *The Zero-Order Elimination Rate Constant*
 - 4.3.1.2. *The Half-Life In Zero-Order Elimination*
 - 4.3.2. *First-Order Elimination*
 - 4.3.2.1. *The First-Order Elimination Rate Constant*
 - 4.3.2.2. *Determination of the First-Order Elimination Rate Constant*
 - 4.3.2.3. *The Half-Life in First-Order Drug Elimination*
 - 4.4. *The Mathematical Expressions for Plasma Drug Concentrations after Single IV Bolus Dose when the Elimination Process Follows First-Order Kinetics*
 - 4.5. *The Relationship between the First-Order Elimination Rate Constant, Total Body Clearance, and Volume of Distribution*
 - 4.6. *The Area under the Drug Concentration-Time Curve*
 - 4.7. *Calculation of Pharmacokinetic Parameters after Single IV Bolus Dose*
 - 4.8. *The Effect of Changing the Pharmacokinetic Parameters on the Plasma Drug Concentration-Time Profile after Single IV Bolus Dose*
 - 4.8.1. *Dose*
 - 4.8.2. *Volume of Distribution*
 - 4.8.3. *Total Body Clearance*
 - 4.9. *Summary*
5. *Drug Absorption Following Extravascular Administration: Biological, Physicochemical, and Formulation Considerations*
 - 5.1. *Introduction*
 - 5.2. *The Drug Absorption Process*
 - 5.2.1. *The Absorption Barriers*
 - 5.2.2. *Mechanisms of Drug Absorption*
 - 5.2.2.1. *Passive Diffusion*
 - 5.2.2.2. *Carrier-Mediated Transport*
 - 5.2.2.3. *Paracellular*
 - 5.2.2.4. *Other Mechanisms*
 - 5.3. *Molecular and Physicochemical Properties Affecting Drug Absorption*
 - 5.3.1. *Molecular Structure Features Affecting Drug Absorption*
 - 5.3.2. *The Physicochemical Drug Properties*
 - 5.3.2.1. *Drug Solubility*
 - 5.3.2.2. *Drug Dissolution Rate*
 - 5.3.3. *Drug Stability*
 - 5.4. *Physiological Factors Affecting Drug Absorption After Different Routes of Administration and Formulation Strategies to Accommodate These Factors*
 - 5.4.1. *Parenteral Drug Administration*
 - 5.4.2. *Oral Drug Administration*
 - 5.4.3. *Rectal Drug Administration*

- 5.4.4. *Intranasal Drug Administration*
- 5.4.5. *Pulmonary Drug Administration*
- 5.4.6. *Transdermal Drug Administration*
- 5.5. *Integration of the Physical, Chemical, and Physiological Factors Affecting Drug Absorption*
- 5.5.1. *The Biopharmaceutics Classification System*
- 5.5.2. *The Biopharmaceutics Drug Disposition Classification System (BDDCS)*
- 5.6. *Summary*

References

6. Drug Pharmacokinetics Following Single Oral Drug Administration: The Rate of Drug Absorption

- 6.1. *Introduction*
- 6.2. *Drug Absorption after Oral Administration*
- 6.2.1. *Zero-Order Drug Absorption*
- 6.2.2. *First-Order Drug Absorption*
- 6.3. *The Plasma Concentration-Time Profile After Single Oral Dose*
- 6.4. *Determination of the Absorption Rate Constant*
- 6.4.1. *The Method of Residuals*
- 6.4.1.1. *Lag Time*
- 6.4.1.2. *Flip-Flop of k_a and k*
- 6.4.2. *Wagner-Nelson Method*
- 6.4.2.1. *Application of the Wagner-Nelson Method*
- 6.5. *Summary*

References

7. Drug Pharmacokinetics Following Single Oral Drug Administration: The Extent of Drug Absorption

- 7.1. *Introduction*
- 7.2. *Causes of Incomplete Drug Bioavailability*
- 7.2.1. *The First-Pass Effect*
- 7.2.2. *The GIT Drug Transporters*
- 7.2.3. *Intestinal Drug Metabolism*
- 7.3. *The Rationale for Bioavailability Determination*
- 7.4. *Determination of the Drug In Vivo Bioavailability*
- 7.4.1. *Drug Bioavailability*
- 7.4.1.1. *Absolute Bioavailability*
- 7.4.1.2. *Relative Bioavailability*
- 7.4.2. *Calculation of the Drug Bioavailability*
- 7.4.3. *Determination of the Drug Bioavailability from Urinary Excretion Data*
- 7.5. *In Vivo Bioavailability Basic Study Design*
- 7.6. *Calculation of the AUC Using the Linear Trapezoidal Rule*
- 7.7. *The Effect of Changing the Pharmacokinetic Parameters on the Plasma Drug Concentration-Time Profile after Single Oral Dose*
- 7.7.1. *Dose*
- 7.7.2. *Bioavailability*
- 7.7.3. *Total Body Clearance*
- 7.7.4. *Volume of Distribution*
- 7.7.5. *Absorption Rate Constant*
- 7.8. *Summary*

References

8. Bioequivalence

- 8.1. *Introduction*
- 8.2. *General Definitions*
- 8.3. *Regulatory Requirement for Bioequivalence*
- 8.4. *Criteria for Requesting a Waiver of the In Vivo Bioequivalence Determination*
- 8.5. *Approaches for Demonstrating Product Bioequivalence*
- 8.5.1. *In Vivo Pharmacokinetic Studies*

- 8.5.2. *In Vitro Test Predictive of In Vivo Human Bioavailability*
- 8.5.3. *Acute Pharmacodynamic Effect*
- 8.5.4. *Comparative Clinical Studies*
- 8.5.5. *In Vitro Dissolution Testing*
- 8.6. *Pharmacokinetic Approach to Demonstrate Product Bioequivalence*
 - 8.6.1. *Planning for the In Vivo Bioequivalence Study*
 - 8.6.2. *Selection of the Reference Drug Product*
 - 8.6.3. *In Vitro Testing of the Study Products*
 - 8.6.4. *In Vivo Bioequivalence Study Design*
 - 8.6.4.1. *Basic Principles*
 - 8.6.4.2. *Ethical Approval*
 - 8.6.4.3. *The Study Subjects*
 - 8.6.4.4. *Number of Volunteers*
 - 8.6.4.5. *Drug Administration*
 - 8.6.4.6. *Experimental Protocol*
 - 8.6.4.7. *Collection of Blood Samples*
 - 8.6.4.8. *Analysis of Bioequivalence Study Samples*
 - 8.6.4.9. *Pharmacokinetic Parameter Determination*
 - 8.6.4.10. *Statistical Analysis*
 - 8.6.4.11. *Documentation and Reporting*
- 8.7. *Special Issues Related to Bioequivalence Determination*
 - 8.7.1. *Multiple-Dose Bioequivalence Studies*
 - 8.7.2. *Food-Effect Bioequivalence Studies*
 - 8.7.3. *Drugs with Long Half-Lives*
 - 8.7.4. *Determination of Bioequivalence from the Drug Urinary Excretion Data*
 - 8.7.5. *Fixed-Dose Combination*
 - 8.7.6. *Measuring Drug Metabolites in Bioequivalence Studies*
 - 8.7.7. *Highly Variable Drugs*
 - 8.7.8. *Drugs Following Nonlinear Pharmacokinetics*
 - 8.7.9. *Endogenous Substances*
 - 8.7.10. *Enantiomers versus Racemates*
 - 8.7.11. *Narrow Therapeutic Range Drugs*
 - 8.7.12. *Oral Products Intended for the Local Effect of the Drug*
 - 8.7.13. *First Point C_{pmax}*
 - 8.7.14. *Biological Products*

8.8. *Summary*

References

- 9. *Drug Pharmacokinetics during Constant Rate IV Infusion, the Steady-State Concept*
 - 9.1. *Introduction*
 - 9.2. *The Steady State*
 - 9.3. *The Time Required to Achieve Steady State*
 - 9.3.1. *Changing the Drug Infusion Rate*
 - 9.4. *Loading Dose*
 - 9.5. *Termination of the Constant Rate IV Infusion*
 - 9.6. *Determination of the Pharmacokinetic Parameters*
 - 9.6.1. *Total Body Clearance*
 - 9.6.2. *Elimination Rate Constant*
 - 9.6.3. *Volume of Distribution*
 - 9.7. *Dosage Forms with Zero-Order Input Rate*
 - 9.8. *The Effect of Changing the Pharmacokinetic Parameters on the Plasma Drug Concentration-Time Profile during Constant Rate IV Infusion*
 - 9.8.1. *Infusion Rate*
 - 9.8.2. *Total Body Clearance*
 - 9.8.3. *Volume of Distribution*

9.8.4. Loading Dose

9.9. Summary

10. Steady State during Multiple Drug Administration

10.1. Introduction

10.2. The Plasma Drug Concentration-Time Profile during Multiple Drug Administration

10.3. The Time Required to Achieve Steady State

10.4. The Loading Dose

10.4.1. IV Loading Dose

10.4.2. Oral Loading Dose

10.5. The Average Plasma Concentration at Steady State

10.6. Drug Accumulation

10.7. Controlled Release Formulations

10.8. The Effect of Changing the Pharmacokinetic Parameters on the Steady-State Plasma Drug Concentration during Multiple Drug Administration

10.8.1. Dosing Rate

10.8.2. Total Body Clearance

10.8.3. Volume of Distribution

10.8.4. Absorption Rate Constant

10.9. Dosing Regimen Design

10.9.1. Factors to Be Considered

10.9.1.1. The Therapeutic Range of the Drug

10.9.1.2. The Required Onset of Effect

10.9.1.3. The Drug Product

10.9.1.4. Progression of the Patient Disease State

10.9.2. Estimation of the Patient Pharmacokinetic Parameters

10.9.3. Selection of Dose and Dosing Interval

10.9.3.1. Multiple Controlled Release Oral Formulation

10.9.3.2. Multiple IV or Fast-Release Oral Formulations

10.9.4. Selection of the Loading Dose

10.10. Summary

11. Renal Drug Excretion

11.1. Introduction

11.2. Studying Drug Elimination through a Specific Pathway

11.3. The Renal Excretion of Drugs

11.4. Determination of the Drug Renal Excretion Rate

11.4.1. Experimental Determination of the Renal Excretion Rate

11.4.2. The Drug Renal Excretion Rate-Time Profile

11.5. The Renal Clearance

11.6. The Cumulative Amount of the Drug Excreted in Urine

11.7. Determination of the Pharmacokinetic Parameters from the Renal Excretion Rate Data

11.7.1. The Elimination Rate Constant and Half-Life

11.7.2. The Renal Excretion Rate Constant

11.7.3. The Volume of Distribution

11.7.4. The Renal Clearance

11.7.5. The Fraction of Dose Excreted Unchanged in Urine

11.7.6. Bioavailability

11.8. The Effect of Changing the Pharmacokinetic Parameters on the Urinary Excretion of Drugs

11.8.1. Dose

11.8.2. The Total Body Clearance

11.8.3. The Renal Clearance

11.9. Summary

References

12. Metabolite Pharmacokinetics

12.1. Introduction

12.2. Drug Metabolism

12.2.1. Metabolizing Enzymes

12.2.2. Formation of Active Metabolites

12.2.3. Formation of Toxic Metabolites

12.2.4. Metabolic Activation of Prodrugs

12.3. Metabolite Pharmacokinetics

12.4. A Simple Model for Metabolite Pharmacokinetics

12.4.1. Metabolite Concentration-Time Profile

12.5. The General Model for Metabolite Kinetics

12.6. Determination of the Metabolite Pharmacokinetic Parameters

12.6.1. Metabolite Elimination Rate Constant, $k(m)$

12.6.2. Fraction of the Parent Drug Dose Converted to a Specific Metabolite, f_m

12.6.3. Metabolite Clearance, $CL(m)$

12.6.4. Metabolite Volume of Distribution, $V_d(m)$

12.6.5. Metabolite Formation Clearance, $f_m CLT$

12.7. Steady-State Metabolite Concentration during Repeated Administration of the Drug

12.8. Metabolite Pharmacokinetics after Extravascular Administration of the Parent Drug

12.9. Kinetics of Sequential Metabolism

12.10. The Effect of Changing the Pharmacokinetic Parameters on the Drug and Metabolite Concentration-Time Profiles after Single IV Drug Administration and during Multiple Drug Administration

12.10.1. Drug Dose

12.10.2. Drug Total Body Clearance

12.10.3. Drug Volume of Distribution

12.10.4. Fraction of the Drug Dose Converted to the Metabolite

12.10.5. Metabolite Total Body Clearance

12.10.6. Metabolite Volume of Distribution

12.11. Summary

References

13. Nonlinear Pharmacokinetics

13.1. Introduction

13.2. Causes of Nonlinear Pharmacokinetics

13.2.1. Dose-Dependent Drug Absorption

13.2.2. Dose-Dependent Drug Distribution

13.2.3. Dose-Dependent Renal Excretion

13.2.4. Dose-Dependent Drug Metabolism

13.2.5. Other Conditions That Can Lead to Nonlinear Pharmacokinetics

13.3. Pharmacokinetics of Drugs Eliminated by Dose-Dependent Metabolism, Michaelis-Menten Pharmacokinetics

13.3.1. Michaelis-Menten Enzyme Kinetics

13.3.2. The Pharmacokinetic Parameters

13.3.3. Drug Concentration-Time Profile after Administration of a Drug Which Is Eliminated by Single Metabolic Pathway That Follows Michaelis-Menten Kinetics

13.3.3.1. After Single IV Bolus Administration

13.3.3.2. During Multiple Drug Administration

13.4. Determination of the Pharmacokinetic Parameters for Drugs with Elimination Process that Follows Michaelis-Menten Kinetics

13.4.1. The Volume of Distribution

13.4.2. The Total Body Clearance

13.4.3. The Half-Life

13.5. Oral Administration of Drugs that Are Eliminated by a Process that Follows Michaelis-Menten Kinetics

13.6. Determination of the Michaelis-Menten Parameters and Calculation of the Appropriate Dosage Regimens

13.6.1. *Mathematical Method*
13.6.2. *The Direct Linear Plot*
13.6.3. *The Linear Transformation Method*
13.7. *Multiple Elimination Pathways*
13.8. *The Effect of Changing the Pharmacokinetic Parameters on the Drug Concentration-Time Profile*
13.8.1. *The Dose*
13.8.2. *The V_{max}*
13.8.3. *The K_m*
13.9. *Summary*
References
14. *Multicompartment Pharmacokinetic Models*
14.1. *Introduction*
14.2. *Compartmental Pharmacokinetic Models*
14.3. *The Two-Compartment Pharmacokinetic Model*
14.4. *The Parameters of the Two-Compartments Pharmacokinetic Model*
14.4.1. *Definition of the Pharmacokinetic Parameters*
14.4.2. *The Mathematical Equation That Describes the Plasma Concentration-Time Profile for Drugs That Follow Two-Compartment Pharmacokinetic Models*
14.5. *Determination of the Two-Compartment Pharmacokinetic Model Parameters*
14.5.1. *The Method of Residuals*
14.5.2. *Determination of the Other Model Parameters*
14.5.2.1. *Volume of the Central Compartment, V_c*
14.5.2.2. *The Area under the Plasma Concentration-Time Curve, AUC*
14.5.2.3. *The Total Body Clearance, CLT*
14.5.2.4. *The First-Order Elimination Rate Constant from the Central Compartment, k_{10}*
14.5.2.5. *The First-Order Transfer Rate Constant from the Peripheral Compartment to the Central Compartment, k_{21}*
14.5.2.6. *The First-Order Transfer Rate Constant from the Central Compartment to the Peripheral Compartment, k_{12}*
14.5.3. *Determination of the Volumes of Distribution for the Two-Compartment Pharmacokinetic Model*
14.5.3.1. *The Volume of Distribution at Steady State, V_{dss}*
14.5.3.2. *The Volume of Distribution during the Elimination Phase, $V_{d\beta}$*
14.6. *Pharmacokinetic Behavior of Drugs that Follow the Two-Compartment Pharmacokinetic Model*
14.6.1. *Oral Administration of Drugs that Follow the Two-Compartment Pharmacokinetic Model*
14.6.2. *Constant Rate IV Administration of Drugs That Follow the Two-Compartment Pharmacokinetic Model*
14.6.3. *Multiple Administration of Drugs That Follow the Two-Compartment Pharmacokinetic Model*
14.6.4. *Renal Excretion of Drugs That Follow the Two-Compartment Pharmacokinetic Model*
14.7. *Effect of Changing the Pharmacokinetic Parameters on the Concentration-Time Profile of Drugs That Follow Two-Compartment Pharmacokinetic Model*
14.7.1. *Dose*
14.7.2. *Total Body Clearance*
14.7.3. *Volume of the Central Compartment*
14.7.4. *The Hybrid Distribution and Elimination Rate Constants*
14.7.5. *The Inter-Compartmental Clearance*
14.8. *The Three-Compartment Pharmacokinetic Model*
14.9. *Compartmental Pharmacokinetic Data Analysis*
14.9.1. *Construction of the Compartmental Model*
14.9.2. *Mathematical Description of the Model*
14.9.3. *Fitting the Model Equation to the Experimental Data*
14.9.4. *Evaluation of the Pharmacokinetic Model*
14.10. *Summary*

References

15. Drug Pharmacokinetics Following Administration by Intermittent Intravenous Infusions

15.1. Introduction

15.2. The Drug Concentration-Time Profile after Administration by Intermittent IV Infusions

15.2.1. After the First Dose

15.2.2. After Repeated Administration Before Reaching Steady State

15.2.3. At Steady State

15.3. The Effect of Changing the Pharmacokinetic Parameters on the Steady-State Plasma Concentration during Repeated Intermittent IV Infusions

15.3.1. Dose

15.3.2. Infusion Time

15.3.3. Total Body Clearance

15.3.4. Volume of Distribution

15.4. Application of the Pharmacokinetic Principles for Intermittent IV Infusion in Clinical Practice

15.4.1. Pharmacokinetic Characteristics of Aminoglycosides

15.4.2. Guidelines for Aminoglycoside Plasma Concentration

15.4.3. The Extended-Interval Aminoglycoside Dosing Regimen

15.5. Individualization of Aminoglycoside Therapy

15.5.1. Estimation of the Patient Pharmacokinetic Parameters

15.5.1.1. Estimation of the Patient Pharmacokinetic Parameters Based on the Patient Information

15.5.1.2. Estimation of the Patient's Specific Pharmacokinetic Parameters from Aminoglycoside Blood Concentrations

15.5.2. Determination of the Dosing Regimen Based on the Patient's Specific Parameters

15.5.2.1. Selection of the Dosing Interval (τ)

15.5.2.2. Selection of Dose

15.5.2.3. Selection of the Loading Dose

15.6. Summary

References

16. Physiological Approach to Hepatic Clearance

16.1. Introduction

16.2. The Organ Clearance

16.3. Hepatic Extraction Ratio

16.4. Intrinsic Clearance

16.5. Systemic Bioavailability

16.6. The Effect of Changing Intrinsic Clearance and Hepatic Blood Flow on the Hepatic Clearance, Systemic Availability, and Drug Concentration-Time Profile

16.6.1. Low Extraction Ratio Drugs

16.6.1.1. Assume that the Drug CL_{int} Increases to Double Its Original Value Due to Enzyme Induction and Q Stays the Same

16.6.1.2. Assume that Q Decreases by 50% (i.e., New $Q = 0.75$ L/min) without Affecting CL_{int}

16.6.2. High Extraction Ratio Drugs

16.6.2.1. Assume that the Drug CL_{int} Increases to Double Its Original Value Due to Enzyme Induction and Q Stays the Same

16.6.2.2. Assume that Q Decreases by 50% (New $Q = 0.75$ L/min) without Affecting CL_{int}

16.7. Protein Binding and Hepatic Extraction

16.8. Summary

References

17. Pharmacokinetics in Patients with Eliminating Organ Dysfunction

17.1. Introduction

17.2. Patients with Renal Dysfunction

17.2.1. Dosing Regimens in Renal Dysfunction Patients Based on the Creatinine Clearance

17.2.2. A General Approach for Calculation of Dosing Regimens in Renal Dysfunction Patients

17.3. Patients Receiving Renal Replacement Therapy

17.3.1. The Principle of Dialysis

17.3.2. *Factors Affecting the Drug Clearance during Dialysis*

17.3.3. *Dose Adjustment during Dialysis*

17.4. *Patients with Hepatic Insufficiency*

17.4.1. *Pharmacokinetic and Pharmacodynamic Changes in Hepatic Dysfunction*

17.4.2. *Dose Adjustment in Hepatic Dysfunction*

17.5. *Other Patient Populations*

17.6. *Summary*

References

18. *Noncompartmental Approach in Pharmacokinetic Data Analysis*

18.1. *Introduction*

18.2. *The Principles of Noncompartmental Data Analysis Method*

18.3. *The Mean Residence Time after IV Bolus Administration*

18.3.1. *Calculation of the AUC*

18.3.2. *Calculation of the AUMC*

18.4. *The MRT after Different Routes of Administration*

18.4.1. *The MRT after Extravascular Administration*

18.4.2. *The MRT after Constant Rate IV Infusion*

18.5. *Other Pharmacokinetic Parameters that Can Be Determined Using the Noncompartmental Approach*

18.6. *Determination of the MRT for Compartmental Models*

18.7. *Summary*

References

19. *Pharmacokinetic-Pharmacodynamic Modeling*

19.1. *Introduction*

19.2. *Pharmacokinetic-Pharmacodynamic Modeling*

19.2.1. *The Pharmacokinetic Model*

19.2.2. *Measuring the Response*

19.2.3. *The Pharmacodynamic Model*

19.2.3.1. *The Fixed Effect Model*

19.2.3.2. *The Linear Model*

19.2.3.3. *The Log-Linear Model*

19.2.3.4. *The Emax Model*

19.2.3.5. *The Sigmoid Emax Model*

19.3. *Integrating the Pharmacokinetic and Pharmacodynamic Models*

19.3.1. *Direct Response versus Indirect Response*

19.3.2. *Direct Link versus Indirect Link*

19.3.3. *Time-Variant versus Time-Invariant*

19.4. *Direct Link PK/PD Models for Drugs with Direct Response*

19.5. *Indirect Link PK/PD Models for Drugs with Direct Response*

19.5.1. *The Effect Compartment Approach*

19.6. *PK/PD Models for Drugs with Indirect Response*

19.7. *Other PK/PD Models*

19.8. *The PK/PD Modeling Process*

19.8.1. *Stating the Objectives, Proposing the Model and Designing the Study*

19.8.2. *Initial Data Exploration and Data Transformation*

19.8.3. *Refining and Evaluation of the PK/PD Model*

19.8.4. *Validation of the PK/PD Model*

19.9. *Applications of the PK/PD Modeling in Drug Development and Clinical Use of Drugs*

19.10. *Summary*

References

20. *Pharmacogenetics: The Genetic Basis of Pharmacokinetic and Pharmacodynamic Variability*

20.1. *Introduction*

20.2. *Gene Structure*

20.3. *Genetic Background Information*

- 20.3.1. *Gene Variants, Alleles*
- 20.3.2. *Polymorphisms*
- 20.3.3. *Gene Nomenclature*
- 20.3.4. *Genotype versus Phenotype*
- 20.3.5. *Monogenic versus Polygenic*
- 20.3.6. *Homozygous versus Heterozygous Genotype*
- 20.4. *Genetic Polymorphism in Pharmacokinetics*
 - 20.4.1. *Cytochrome P450 Enzymes*
 - 20.4.2. *Thiopurine Methyltransferase (TPMT)*
 - 20.4.3. *N-acetyltransferase*
 - 20.4.4. *UDP-Glucuronosyltransferase (UGT)*
 - 20.4.5. *Drug Transporters*
- 20.5. *Genetic Polymorphism in Pharmacodynamics*
- 20.6. *Implementation of Pharmacogenetic Testing in Clinical Practice*
 - 20.6.1. *Pharmacogenetic Training for Healthcare Providers*
 - 20.6.2. *The Pharmacogenetic Tests*
 - 20.6.3. *Interpretation of the Pharmacogenetic Test Results*
 - 20.6.4. *Guidelines for Applying the Pharmacogenetic Testing*
 - 20.6.5. *Enablers for the Implementation of Pharmacogenetics in Clinical Practice*
- 20.7. *Summary*

References

21. Therapeutic Drug Monitoring

21.1. Introduction

21.2. General Principles of Initiation and Management of Drug Therapy

21.2.1. The Use of Therapeutic Drug Monitoring in the Management of Drug Therapy

21.3. Drug Blood Concentration versus Drug Dose

21.4. The Therapeutic Range

21.5. Drug Candidates for Therapeutic Drug Monitoring

21.5.1. Drugs with Low Therapeutic Index

21.5.2. Drugs with Large Variability in Their Pharmacokinetic Behavior

21.5.3. Drugs Used in High-Risk Patients or Patients with Multiple Medical Problems

21.6. Determination of the Drug Concentration in Biological Samples

21.6.1. The Biological Samples

21.6.2. The Time of Sample

21.6.3. The Measured Drug Moiety

21.6.4. The Analytical Technique

21.7. Establishing a Therapeutic Drug Monitoring (Clinical Pharmacokinetic) Service

21.7.1. Major Requirements

21.7.2. Dosage Regimen Recommendation

21.7.2.1. Determination of the Initial Dosing Regimen

21.7.2.2. Determination of the Patient's Specific Pharmacokinetic Parameters

21.7.2.3. Calculation of the Dosage Requirements Based on the Patient's Specific Pharmacokinetic Parameters of the Drug

21.7.3. The Pharmacoeconomics of Therapeutic Drug Monitoring

21.8. Summary

References

22. Pharmacometric Applications in Drug Development and Individualization of Drug Therapy

22.1. Introduction

22.2. Pharmacometric Applications during the Preclinical Phase of Drug Development

22.2.1. Physiologically Based Pharmacokinetic Models

22.2.1.1. Physiologically Based Pharmacokinetic Model Development

22.2.1.2. Applications of the PBPK Models

22.3. Pharmacometric Applications during the Clinical Phases of Drug Development

22.3.1. Population Pharmacokinetic Analysis

22.3.1.1. *Data Consideration for Population Analysis*
22.3.1.2. *The Population Pharmacokinetic Models*
22.3.1.3. *Statistical Analysis and Parameter Estimation*
22.3.1.4. *Model Evaluation and Diagnostics*
22.3.1.5. *Reporting of the Population Pharmacokinetic Analysis Results*
22.3.1.6. *Application of Population Pharmacokinetic Analysis in Drug Development*
22.3.1.7. *Application of Population Pharmacokinetic Analysis for Drug Use Decisions in Drug Labeling*
22.4. *Pharmacometric Applications in Clinical Drug Use*
22.4.1. *Model-Based Therapeutic Drug Monitoring*
22.4.1.1. *Model Development*
22.4.1.2. *Monitoring Drug Concentration*
22.4.1.3. *Dosage Regimen Design*
22.5. *Summary*
References
23. *Answer for the Practice Problems*
Chapter 1
Chapter 2
Chapter 3
Chapter 4
Chapter 6
Chapter 7
Chapter 9
Chapter 10
Chapter 11
Chapter 12
Chapter 13
Chapter 14
Chapter 15
Chapter 16
Chapter 17
Chapter 18
Glossary
Index