

Clinical Pharmacokinetics Concepts and Applications

third edition

MALCOLM ROWLAND, Ph.D.
Department of Pharmacy
University of Manchester
Manchester, England

THOMAS N. TOZER, Ph.D.
School of Pharmacy
University of California
San Francisco, California

A Lea & Febiger Book



Williams & Wilkins

BALTIMORE • PHILADELPHIA • HONG KONG
LONDON • MUNICH • SYDNEY • TOKYO

A WAVERLY COMPANY

1995



Executive Editor: Donna Balado
 Developmental Editors: Frances Klass, Lisa Stead
 Production Manager: Laurie Forsyth
 Project Editor: Robert D. Magee

Copyright © 1995
 Williams & Wilkins
 Rose Tree Corporate Center
 1400 North Providence Road
 Building II, Suite 5025
 Media, PA 19063-2043 USA



All rights reserved. This book is protected by copyright. No part of this book may be reproduced in any form or by any means, including photocopying, or utilized by any information storage and retrieval system without written permission from the copyright owner.

Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

Printed in the United States of America

First Edition 1980

Library of Congress Cataloging-in-Publication Data

Rowland, Malcolm.
 Clinical Pharmacokinetics : concepts and applications / Malcolm
 Rowland, Thomas N. Tozer. — 3rd ed.
 p. cm.
 "A Lea & Febiger Book."
 Includes bibliographical references and index.
 ISBN 0-683-07404-0
 1. Pharmacokinetics. 2. Chemotherapy. I. Tozer, Thomas N.
 II. Title.
 [DNLM: 1. Pharmacokinetics. 2. Drug Therapy. QV 38 R883c 1994]
 RM301.5.R68 1994
 615.7—dc20
 DNLM/DLC
 for Library of Congress

94-26305
 CIP

The Publishers have made every effort to trace the copyright holders for borrowed material. If they have inadvertently overlooked any, they will be pleased to make the necessary arrangements at the first opportunity.

95 96 97 98
 1 2 3 4 5 6 7 8 9 10

Reprints of chapters may be purchased from Williams & Wilkins in quantities of 100 or more. Call Isabella Wise, Special Sales Department, (800) 358-3583.

DIUM
 QV38
 R883c
 19.75

CONTENTS

Definitions of Symbols	xi
1. Why Clinical Pharmacokinetics?	1
SECTION I. ABSORPTION AND DISPOSITION KINETICS	
2. Basic Considerations	11
3. Intravenous Dose	18
4. Extravascular Dose	34
SECTION II. THERAPEUTIC REGIMENS	
5. Therapeutic Response and Toxicity	53
6. Constant-Rate Regimens	66
7. Multiple-Dose Regimens	83
SECTION III. PHYSIOLOGIC CONCEPTS AND KINETICS	
8. Movement Through Membranes	109
9. Absorption	119
10. Distribution	137
11. Elimination	156
12. Integration With Kinetics	184
SECTION IV. INDIVIDUALIZATION	
13. Variability	203
14. Genetics	220
15. Age and Weight	230
16. Disease	248
17. Interacting Drugs	267
18. Concentration Monitoring	290
SECTION V. SELECTED TOPICS	
19. Distribution Kinetics	313
20. Pharmacologic Response	340
21. Metabolite Kinetics	367
22. Dose and Time Dependencies	394
23. Turnover Concepts	424
24. Dialysis	443
SELECTED READING	463
APPENDIX I. ADDITIONAL CONCEPTS AND DERIVATIONS	
A. Assessment of <i>AUC</i>	469
B. Estimation of Elimination Half-Life From Urine Data	473

ix

C. Estimation of Absorption Kinetics From Plasma Concentration Data478
D. Mean Residence Time485
E. Amount of Drug in Body on Accumulation to Plateau490
F. Distribution of Drugs Extensively Bound to Plasma Proteins494
G. Blood to Plasma Concentration Ratio502
H. Estimation of Creatinine Clearance Under Nonsteady-State Conditions504

APPENDIX II. ANSWERS TO PROBLEMS507

INDEX586

WHY CLINICAL PHARMACOKINETICS?

Those patients who suffer from chronic ailments such as diabetes and epilepsy may have to take drugs every day for the rest of their lives. At the other extreme are those who take a single dose of a drug to relieve an occasional headache. The duration of drug therapy is usually between these extremes. The manner in which a drug is taken is called a *dosage regimen*. Both the duration of drug therapy and the dosage regimen depend on the therapeutic objectives, which may be either the cure, the mitigation, or the prevention of disease. Because all drugs exhibit undesirable effects, such as drowsiness, dryness of the mouth, gastrointestinal irritation, nausea, and hypotension, successful drug therapy is achieved by optimally balancing the desirable and the undesirable effects. To achieve optimal therapy, the appropriate "drug of choice" must be selected. This decision implies an accurate diagnosis of the disease, a knowledge of the clinical state of the patient, and a sound understanding of the pharmacotherapeutic management of the disease. Then the questions How much? How often? and How long? must be answered. The question How much? recognizes that the magnitudes of the therapeutic and toxic responses are functions of the dose given. The question How often? recognizes the importance of time, in that the magnitude of the effect eventually declines with time following a single dose of drug. The question How long? recognizes that a cost (in terms of side effects, toxicity, economics) is incurred with continuous drug administration. In practice, these questions cannot be divorced from one another. For example, the convenience of giving a larger dose less frequently may be more than offset by an increased incidence of toxicity.

In the past, the answers to many important therapeutic questions were obtained by trial and error. The dose, interval between doses, and route of administration were selected, and the patient's progress followed. The desired effect and any signs of toxicity were carefully noted, and if necessary, the dosage regimen was adjusted empirically until an acceptable balance between the desired effect and toxicity was achieved. Eventually, after considerable experimentation on a large number of patients, reasonable dosage regimens were established (Table 1-1), but not without some regimens producing excessive toxicity or proving ineffective. Moreover, the above empirical approach left many questions unanswered. Why, for example, does tetracycline have to be given every 6 to 8 hours to be effective, while digoxin can be given once daily? Why must oxytocin be infused intravenously? Why is morphine more effective given intramuscularly than when given orally? Furthermore, this empirical approach contributes little, if anything, toward establishing a safe, effective dosage regimen of another drug. That is, our basic understanding of drugs has not been increased.

To overcome some of the limitations of the empirical approach and to answer some of the questions raised, it is necessary to delve further into the events that follow drug administration. *In vitro* and *in vivo* studies show that the magnitude of the response is a function of the concentration of drug in the fluid bathing the site(s) of action. From these observations the suggestion might be made that the therapeutic objective can be achieved by maintaining an adequate concentration of drug at the site(s) of action for the duration

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.