
Pharmacodynamics and Drug Development Perspectives in Clinical Pharmacology

Edited by

Neal R. Cutler

California Clinical Trials, Beverly Hills, California, USA

John J. Sramek

California Clinical Trials, Beverly Hills, California, USA

Prem K. Narang

Pharmacia Adria, Clinical Pharmacology/Pharmacokinetics, Columbus, Ohio, USA

JOHN WILEY & SONS

Chichester · New York · Brisbane · Toronto · Singapore

DOCKET
A L A R M

Find authenticated court documents without watermarks at docketalarm.com.

Copyright © 1994 by John Wiley & Sons Ltd,*
Baffins Lane, Chichester,
West Sussex PO19 1UD, England
Telephone:
National Chichester (0243) 779777
International +44 243 779777

*except Chapter 12 which is in the public domain.

All rights reserved.

No part of this book may be reproduced by any means,
or transmitted, or translated into a machine language
without the written permission of the publisher.

Other Wiley Editorial Offices

John Wiley & Sons, Inc., 605 Third Avenue,
New York NY 10158-0012, USA

Jacaranda Wiley Ltd, 33 Park Road, Milton,
Queensland 4064, Australia

John Wiley & Sons (Canada) Ltd, 22 Worcester Road,
Rexdale, Ontario M9W 1L1, Canada

John Wiley & Sons (SEA) Pte Ltd, 37 Jalan Pemimpin #05-04
Block B, Union Industrial Building, Singapore 2057

Library of Congress Cataloging-in-Publication Data

Pharmacodynamics and drug development: perspectives in clinical
pharmacology / edited by Neal R. Cutler, John J. Sramek and Prem K.
Narang.

p. cm.

Includes bibliographical references and index.

ISBN 0 471 95052 1

I. Drugs—Physiological effect. I. Cutler, Neal R. II. Narang,
Prem K. III. Sramek, John J.

[DNLM: 1. Pharmacology, Clinical. QV 38 P5318 1994]

RM300.P48 1994

615'.7—dc20

DNLM/DLC

for Library of Congress

94-6103
CIP

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0 471 950 521

Typeset in 10/12 pt Plantin by

Mathematical Composition Setters Ltd, Salisbury, Wiltshire

Printed and bound in Great Britain by

Bookcraft (Bath) Ltd, Midsomer Norton, Avon

phar

BM
300

ASK3689

Contents

428
1994

QV
38
D5316d
1994

List of Contributors	x
Foreword <i>Leslie Z. Benet</i>	xiii

I OVERVIEW OF PHARMACODYNAMICS

1 Basic Pharmacodynamic Concepts and Models <i>Robert J. Wills</i>	3
2 Simultaneous Pharmacokinetic/Pharmacodynamic Modeling <i>Wayne A. Colburn and Michael A. Eldon</i>	19
3 Factors Influencing Variability in Kinetics and Dynamics <i>Prem K. Narang and Ronald C. Li</i>	45
4 Population-Based Approaches to the Assessment of Pharmacokinetics and Pharmacodynamics <i>Joseph C. Fleishaker and Edward J. Antal</i>	73
5 General Perspectives on the Role of Metabolites in Pharmacokinetics and Pharmacodynamics <i>Randall D. Seifert</i>	89
6 Enantioselectivity in Drug Action and Drug Metabolism: Influence on Dynamics <i>Heyo K. Kroemer, Annette S. Gross and Michel Eichelbaum</i>	103
7 Regulatory Perspective: The Role of Pharmacokinetics and Pharmacodynamics <i>Lawrence Lesko and Roger L. Williams</i>	115

II APPLICATION OF PHARMACODYNAMICS IN SELECTED THERAPEUTIC DOMAINS

8 Theoretical Models for Developing Anxiolytics <i>P. V. Nickell and Thomas W. Uhde</i>	133
9 Pharmacodynamics of Antidepressants <i>Karon Dawkins, Hussein K. Manji and William Z. Potter</i>	157

- | | | |
|----|---|-----|
| 10 | Pharmacodynamics of Antipsychotic Drugs in Schizophrenia
<i>John J. Sramek and George M. Simpson</i> | 181 |
| 11 | Pharmacodynamic Models Useful in the Evaluation of Drugs for Cognitive Impairment
<i>Michael F. Murphy, Klaudius R. Siegfried, F. Jacob Huff and Neal R. Cutler</i> | 201 |
| 12 | Alzheimer's Disease: Assessment of Cholinomimetic Agents
<i>Scott A. Reines</i> | 225 |
| 13 | Antihypertensive Drugs
<i>L. Michael Prisant and Albert A. Carr</i> | 241 |
| 14 | Pharmacodynamics of Calcium Antagonist Drugs
<i>Darrell R. Abernethy and Nabil S. Andrawis</i> | 253 |
| 15 | Agents in Congestive Heart Failure
<i>Edmund V. Capparelli</i> | 267 |
| 16 | Antiarrhythmic Drugs
<i>Janice B. Schwartz</i> | 291 |
| 17 | Antibiotic Pharmacodynamics
<i>John C. Rotschafer, Karla J. Walker, Karl J. Kelly and Christopher J. Sullivan</i> | 315 |
| 18 | Pharmacodynamics of Antineoplastic Agents
<i>Gary L. Rosner and Mark J. Ratain</i> | 345 |
| 19 | Controlling the Systemic Exposure of Anticancer Drugs: The Dose Regimen Design Problem
<i>David Z. D'Argenio and John H. Rodman</i> | 363 |
| 20 | Virology and Antiviral Drug Development
<i>Michael A. Amantea, James R. Minor and Stephen E. Straus</i> | 379 |

III FRONTIERS IN PHARMACODYNAMICS: INSIGHT FROM MOLECULAR APPROACHES

- | | | |
|----|--|-----|
| 21 | α-Adrenoceptors and their Subtypes: Pharmacological Aspects
<i>P. A. van Zwieten</i> | 409 |
|----|--|-----|

CONTENTS	vii
22 Muscarinic Receptors: Pharmacological Subtypes, Structure, Function and Regulation <i>Lin Mei, William R. Roeske and Henry I. Yamamura</i>	435
23 Serotonin Receptor Subtypes <i>Dolan B. Pritchett</i>	457
Index	475

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.