Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development
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Springer Science+Business Media, LLC

ISBN 978-1-4757-1522-4

© 1993 Springer Science+Business Media New York

Originally published by Plenum Press, New York in 1993

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PREFACE

This volume contains the invited papers presented at the conference entitled “The Integration of Pharmacokinetic, Pharmacodynamic and Toxicokinetic Principles in Rational Drug Development” held in April, 1991. The conference was sponsored by the American Association of Pharmaceutical Scientists, the U.S. Food and Drug Administration and the American Society for Clinical Pharmacology and Therapeutics. The conference was organized with three objectives:

To identify the roles and interrelationships between pharmacokinetics, pharmacodynamics and toxicokinetics in the drug development process.

To evolve strategies for the effective application of the principles of pharmacokinetics, pharmacodynamics and toxicokinetics in drug development, including early clinical trials.

To prepare a report on the use of pharmacokinetics and pharmacodynamics in rational drug development as a basis for the development of future regulatory guidelines.

The report from this conference, a copy of which can be found on pages 249-262 of this volume, was published in mid 1992 in four leading journals of special interest to the more than 600 scientists who attended the conference. However, a great deal of information on the use of pharmacokinetics, pharmacodynamics and toxicokinetics in drug development was presented by the 25 academic, governmental and industrial scientists who made formal presentations at this unique meeting. It was strongly felt by the Editors, that this wealth of useful information would be of benefit to those in the pharmaceutical industry as well as to those in the regulatory agencies who are most concerned with the use of pharmacokinetics, pharmacodynamics and toxicokinetics in drug development. Therefore, the authors were requested to prepare formal documents of their presentations. However, it was also felt by the Editors that the volume should be more than a “conference proceedings”. Thus the 25 individual chapters have been edited, prepared in a common print type face, with references updated as necessary, and supplemented with a complete subject index, which should make the book quite useful to those interested in particular topics.

The Editors greatly appreciate the efforts of Ms. Amy Miller of the AAPS staff who has spent innumerable hours and great efforts in assuring that this volume represents a first-class contribution to the drug development literature. We also appreciate the efforts of Ms. Leah
Dible of the Department of Pharmacy at the University of California, San Francisco in assisting the Editors in reference updates and index preparation.

The Editors anticipate that the conference summary report and this volume will only be the first of the publications which emanate from the 1991 workshop as we develop and hone our skills in the use of pharmacokinetics, pharmacodynamics and toxicokinetics in rational drug development.
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CONTENTS

INTRODUCTION xv

SECTION I

INTRODUCTION
1. Rationale for the Effective Use of Pharmacokinetics and Pharmacodynamics in Early Drug Development
   Carl C. Peck 1
2. The Case for Preclinical Pharmacodynamics
   Gerhard Levy 7
3. Utility of Kinetic, Dynamic, and Metabolic Data in Nonclinical Pharmacology/Toxicology Studies
   Judi Weissinger 15

SECTION II

PRECLINICAL PHARMACOKINETIC & PHARMACODYNAMIC STUDIES
4. Pharmacokinetics and Drug Metabolism in Animal Studies (ADME, Protein Binding, Mass Balance, Animal Models)
   Glenna G. Fitzgerald 23
5. Nonclinical Considerations: Disposition of Drugs
   Martin David Green 33
6. Use of Acute Toxicity Data in the Design and Interpretation of Subchronic and Chronic Toxicity Studies
   Karl K. Rozman 39
7. Use of Pharmacokinetics and Pharmacodynamics in Preclinical Studies to Guide Dosage Escalation Schemes in Phase I Studies of Anticancer Drugs
   Jerry M. Collins 49
8. Use of Toxicokinetic Principles in Drug Development: Bridging Preclinical and Clinical Studies
   Mauricio Leal, Avraham Yacobi and Vijay K. Batra 55
SECTION III

METHODOLOGY FOR PRECLINICAL PHARMACODYNAMIC STUDIES

9. Preclinical Pharmacodynamics of Central Nervous System Active Agents
   Meindert Danhof, Jaap W. Mandema and Arendien Hoogerkamp 69

10. Preclinical Pharmacodynamics of Antihypertensives
    Robert A. Branch and Edwin K. Jackson 81

11. Preclinical Pharmacodynamics of Anxiolytics: Effects of Chronic Benzodiazepine Administration
    Lawrence G. Miller 91

12. Guidelines for Development of a New Diuretic Agent
    D. Craig Brater 97

13. Preclinical Pharmacodynamics of Anti-Inflammatory Drugs
    Asoke Mukherjee, Conrad Chen, Lucy Jean and Claude B. Coutinho 105

SECTION IV

PRECLINICAL & CLINICAL PHARMACOKINETICS

14. The Role of Pharmacokinetics in the Drug Development Process
    Leslie Z. Benet 115

15. Implementation of an Effective Pharmacokinetics Research Program in Industry
    Avraham Yacobi, Vijay K. Batra, Robert Desjardins, Robert D. Faulkner,
    Gabriela Nicolau, William R. Pool, Anita Shah and Alfred P. Tonelli 125

16. Pharmacoepidemiology, Population Pharmacokinetics and New Drug Development
    Thaddeus H. Grasela and Edward J. Antal 137

17. Assessment of Pharmacokinetic Drug Interactions in Clinical Drug Development
    Jerome J. Schentag 149

SECTION V

CLINICAL PHARMACODYNAMICS

18. Pharmacokinetic/Pharmacodynamic Models and Methods
    Davide Verotta and Lewis B. Sheiner 159

19. Pharmacokinetic and Pharmacodynamic Modeling Applied to Anesthetic Drugs
    Donald R. Stanski 179

20. Pharmacodynamic/Pharmacokinetic Relationships for Rapidly Acting Drugs (NSAIDS) in Rheumatoid Arthritis: Problems and Preliminary Solutions
    Daniel E. Furst 193
21. The Value of Plasma-Warfarin Measurement
   Robert A. O'Reilly 201

22. Clinical Pharmacodynamics of Cardiovascular Agents:
    Focus on Sudden Cardiac Death
    Dan M. Roden 207

23. The Benzodiazepines: Kinetic-Dynamic Relationships
    David J. Greenblatt 217

SECTION VI

APPLICATION OF PHARMACODYNAMICS & PHARMACOKINETICS IN
THE DRUG DEVELOPMENT PROCESS

24. The Integration of Pharmacodynamics and Pharmacokinetics in Rational Drug
    Development
    Sally Usdin Yasuda, Sorell L. Schwartz, Anton Wellstein and
    Raymond L. Woosley 225

25. Concentration-Controlled Trials: Basic Concepts, Design, and Implementation
    Lilly Sanathanan and Carl C. Peck 239

SECTION VII

SUMMARY REPORT

26. Opportunities for Integration of Pharmacokinetics, Pharmacodynamics and
    Toxicokinetics in Rational Drug Development 249

Author Index 265
Subject Index 267
INTRODUCTION

In 1962 Congress passed the Kefauver Harris Amendments to the Pure Food and Drug Act. Drugs approved by the Food and Drug Administration from 1938 to that date had been approved only on the basis of safety, i.e., 'lack of toxicity.' To be sure, the toxicity data required in NDA submissions were considerably more onerous in 1960, than in the late 30's and early 40's. But the amended law now provided that drugs henceforth approved would require proof of efficacy as well. Moreover, those drugs approved between 1938 and October 10, 1962, would be reviewed to determine whether or not they were efficacious. Those that were judged to meet the efficacy provision, were additionally required to demonstrate that they were "bioavailable". Generic versions were required, among labeling and other considerations, to establish that they were bioequivalent to the bioavailable product.

The argument of the late 60's and early 70's was over whether the new sciences of biopharmaceutics and pharmacokinetics could be employed to demonstrate product bioequivalence, or whether generic firms would have to also conduct clinical studies. Such studies were neither economically feasible nor scientifically advisable. They would require many patients, and for many drugs, differences on the order of 50 to 100% could not be detected clinically. The Agency, with academic support, opted for in vivo human bioavailability and bioequivalence studies.

Over time, thousands of such studies were conducted. But determinations of drug bioavailability/bioequivalence provide for a very limited use of the pharmacokinetic information obtained. Gradually pharmacokinetics (the study of the time course of drug and metabolite concentrations and amounts in biological fluids, tissues, and excreta) came to be routinely employed in the design of dosage regimen and drug interaction studies. Today it is especially useful in the design of dosage regimens in subpopulations which differ markedly in their physiological responses. Nevertheless, while these studies have been conducted in humans to great advantage, similar employment has not been utilized in animal toxicity studies. Toxicokinetics, which encompasses the kinetics of absorption, distribution, metabolism, and elimination of large doses of drugs in the body and the safety evaluation and assessment of adverse reactions caused by excessive drug dosage, has yet to reach its full potential. It is interesting that even at this point in time, 20 years after the discovery of the importance of drug blood levels, our animal toxicity data is still largely dose based, even when the dose may not have been completely absorbed. Pharmacodynamics, which provides an assessment on how drugs exert their therapeutic and toxic effect on the body by describing the relationship
of drug concentration to drug effect, is still an infant science. Yet we are aware that for many drugs the pharmacokinetic and pharmacodynamic effects appear to be unrelated.

The Editors, through this book, are resolved to make available all of the information presented at the AAPS/FDA/ASCPT workshop in April 1991, along with the summary document which was issued as a result. Our purpose is to take that first real public step toward the rational integration of pharmacokinetics, pharmacodynamics, and toxicokinetics. We hope that this step will encourage others to follow.