

Kinetics of drug action in disease states: towards physiology-based pharmacodynamic (PBPD) models

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Abstract Gerhard Levy started his investigations on the “Kinetics of Drug Action in Disease States” in the fall of 1980. The objective of his research was to study inter-individual variation in pharmacodynamics. To this end, theoretical concepts and experimental approaches were introduced, which enabled assessment of the changes in pharmacodynamics per se, while excluding or accounting for the confounding effects of concomitant changes in pharmacokinetics. These concepts were applied in several studies. The results, which were published in 45 papers in the years 1984–1994, showed considerable variation in pharmacodynamics. These initial studies on kinetics of drug action in disease states triggered further experimental research on the relations between pharmacokinetics and pharmacodynamics. Together with the concepts in Levy’s earlier publications “Kinetics of Pharmacologic Effects” (Clin Pharmacol Ther 7(3): 362–372, 1966) and “Kinetics of pharmacologic effects in man: the anticoagulant action of warfarin” (Clin Pharmacol Ther 10(1): 22–35, 1969), they form a significant impulse to the development of physiology-based pharmacodynamic (PBPD) modeling as novel discipline in the pharmaceutical sciences. This paper reviews Levy’s research on the “Kinetics of Drug Action in Disease States”. Next it addresses the significance of his research for the evolution of PBPD modeling as a scientific discipline. PBPD models contain specific expressions to characterize in a strictly quantitative manner processes on the causal path between exposure (in terms of

concentration at the target site) and the drug effect (in terms of the change in biological function). Pertinent processes on the causal path are: (1) target site distribution, (2) target binding and activation and (3) transduction and homeostatic feedback.

Keywords Biophase distribution · Receptor theory · Dynamical systems analysis · Disease systems analysis

Introduction

Gerhard Levy started his investigations in the series “Kinetics of Drug Action in Disease States”, in the fall of 1980. At that time it was well-established that multiple factors including certain diseases, changes in physiology, concomitant use of other drugs and environmental factors can have profound effects on the pharmacokinetics of drugs [1]. Also, the awareness of large inter-individual variation in pharmacokinetics had led to the introduction of therapeutic drug concentration monitoring in clinical practice as the basis for individualized optimization of drug dosage, yielding plasma concentrations in a pre-defined therapeutic range [2–4]. In this practice it was implicitly assumed that inter-individual variation in pharmacodynamics is small. However, limited information was available on variation in pharmacodynamics (i.e. drug concentration–effect relations). A review of the literature revealed that there are many examples of altered drug response as result of disease, but that in general it was not possible to determine the mechanism of this altered response in terms of changes in pharmacokinetics, pharmacodynamics or a combination of both. In other words, the magnitude and the underlying mechanisms of inter-individual variation in pharmacodynamics were largely unknown. It were these observations that that

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Kinetics Of Drug Action In Disease States

Jens-Uwe Peters



Kinetics Of Drug Action In Disease States:

Kinetics of Drug Action in Disease States, 2002 **Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development** A. Yacobi, J. P. Skelly, Vinod P. Shah, L. Z. Benet, 2013-11-11 Proceedings of a conference sponsored by the American Association of Pharmaceutical Scientists the U S Food and Drug Administration and the American Society for Clinical Pharmacology and Therapeutics held in Arlington Virginia April 24 26 1991 **The In Vivo Study of Drug Action** Christoffel Jos van Bortel, N. H. G. Holford, M. Danhof, 1992 Pharmacodynamics is the oldest in vitro element of pharmacology and the youngest in vivo element However over the last decade there has been significant progress in understanding the kinetics of drug action in vivo and pharmacodynamics now ranks with pharmacokinetics in the content of clinical pharmacology journals The purpose of this book is to link theory and practice of in vivo pharmacodynamic studies This presents a major challenge due to the multi faceted nature of the kinetics of drug actions The first step involves identification of those effects which represent the actions of a drug using mathematical models in combination with classical receptor theory Subsequently these effects must be quantified in a precise and reproducible manner and the pharmacokinetics of the drug and its active metabolites must be accurately described Finally realistic models must be developed which identify the site of action and can describe and predict the time course of drug action under physiological and pathological conditions As in the development of most sciences the theory is in advance of the practice **Handbook of Pharmacokinetic/Pharmacodynamic Correlation** Hartmut Derendorf, Guenther Hochhaus, 2019-06-04 First published in 1995 Combining the established disciplines of pharmacokinetics PK the relationship between drug concentration and time and pharmacodynamics PD the relationship between drug effects and concentration this handbook examines the relevant relationship between drug effects and time **The Effect of Disease States on Drug Pharmacokinetics** American Pharmaceutical Association, 1976 **Cumulated Index Medicus**, 1977 **Polypharmacology in Drug Discovery** Jens-Uwe Peters, 2012-01-20 An essential outline of the main facets of polypharmacology in drug discovery research Extending drug discovery opportunities beyond the one drug one target philosophy a polypharmacological approach to the treatment of complex diseases is emerging as a hot topic in both industry and academic research Polypharmacology in Drug Discovery presents an overview of the various facets of polypharmacology and how it can be applied as an innovative concept for developing medicines for treating bacterial infections epilepsy cancer psychiatric disorders and more Filled with a collection of instructive case studies that reinforce the material and illuminate the subject this practical guide Covers the two sided nature of polypharmacology its contribution to adverse drug reactions and its benefit in certain therapeutic drug classes Addresses the important topic of polypharmacology in drug discovery a subject that has not been thoroughly covered outside of scattered journal articles Overviews state of the art approaches and developments to help readers understand concepts and issues related to polypharmacology Fosters interdisciplinary drug discovery research by embracing computational

synthetic in vitro and in vivo pharmacological and clinical aspects of polypharmacology A clear road map for helping readers successfully navigate around the problems involved with promiscuous ligands and targets Polypharmacology in Drug Discovery provides real examples in depth explanations and discussions and detailed reviews and opinions to spark inspiration for new drug discovery projects Yaffe and Aranda's Neonatal and Pediatric Pharmacology Jacob V. Aranda,2020-11-05 The premier comprehensive textbook in the field Yaffe and Aranda s Neonatal and Pediatric Pharmacology Fifth Edition provides an authoritative overview of all aspects of drug therapy in newborns children and adolescents It offers evidence based guidelines for safe effective and rational drug therapy including specific recommendations for all major drug classes and diseases Now in a vibrant two color format this fully revised reference is an indispensable resource for pediatricians neonatologists pediatric residents and fellows in different pediatric subspecialties including neonatal medicine and pediatric critical care Trauma Anesthesia Charles E. Smith,2015-04-09 Trauma patients present a unique challenge to anesthesiologists since they require resource intensive care often complicated by pre existing medical conditions This fully revised new edition focuses on a broad spectrum of traumatic injuries and the procedures anesthesiologists perform to care for trauma patients perioperatively surgically and post operatively Special emphasis is given to assessment and treatment of co existing disease including surgical management of trauma patients with head spine orthopedic cardiac and burn injuries Topics such as training for trauma including use of simulation and hypothermia in trauma are also covered Six brand new chapters address pre hospital and ED trauma management imaging in trauma surgical issues in head trauma and in abdominal trauma anesthesia for oral and maxillofacial trauma and prevention of injuries The text is enhanced with numerous tables and 300 illustrations showcasing techniques of airway management shock resuscitation echocardiography and use of ultrasound for the performance of regional anesthesia in trauma **Drug Actions** Mutschler,Hartmut Derendorf,1995 The most highly acclaimed pharmacology and toxicology text reference used in Europe is now available in English This excellent translation of Mutschler s Arzneimittelwirkungen combines a clear informative narrative with 255 figures 261 diagrams and 198 tables to appeal to both new students and experts in pharmacy pharmacology and therapeutics Drug structure and activity relationships are emphasized as an important dimension that is sometimes lacking in other pharmacology texts Drug Actions is organized into three major sections covering general drug action and dosing principles specific drug therapeutics and toxicology The first section provides an integrated overview of basic principles in pharmacology with chapters addressing pharmacokinetics pharmacodynamics drug side effects drug interactions chronopharmacology rational and irrational drug combinations as well as drug developments and drug trials The second section systematically describes specific drug actions with pharmacology clinical indications standard doses side effects and contraindications described for each approved drug category The third section addresses toxicology where specific drug toxicities are identified and treatment options for accidental and drug associated poisoning are presented

Topics covered include environmental occupational and nutritional exposure to toxins **Pharmacokinetics of Drugs**

Peter G. Welling, Luc P. Balant, 2012-12-06 The author of this Foreword has recently retired after spending 25 years in academia and 15 years in the pharmaceutical industry Most of this time has been spent following and hopefully in some instances contributing to advancement of the discipline of pharmacokinetics During the last 40 years pharmacokinetics has grown from a fledgling in the 1950s to an adult in the 1990s The late development of the discipline of pharmacokinetics relative to other disciplines such as chemistry bio chemistry and pharmacology probably stems both from general ignorance of the importance of the time course of concentration effect relationships in drug therapy and from our technical inability to do anything about it had we been more enlightened Just as the end of the historical dark ages had to await the beginning of the Carolingian revival so the end of the pharma co kinetic dark age had to await the discovery of adequate analytical methods and also an intellectual leap of faith to accept that drug action is in some way dependent on receptor site occupancy and therefore on drug con centration The recent evolution of pharmacokinetics has occurred in three phases which may be identified as those of discovery stabilization and rationaliz ation The discovery phase which occurred in the 1950s and 1960s esta blished the mathematics and concepts of modern pharmacokinetics and sought areas of application ranging from model independent methods through compartment approaches to complex physiological models *Drug Delivery to the Brain*

Margareta Hammarlund-Udenaes, Elizabeth C.M. de Lange, Robert G. Thorne, 2013-12-03 The development of new CNS drugs is notoriously difficult Drugs must reach CNS target sites for action and these sites are protected by a number of barriers the most important being the blood brain barrier BBB Many factors are therefore critical to consider for CNS drug delivery e g active passive transport across the BBB intra brain distribution and central systemic pharmacokinetics to name a few Neurological disease and trauma conditions add further complexity because CNS barriers drug distribution and pharmacokinetics are dynamic and often changed by disease trauma Knowledge of all these factors and their interplay in different conditions is of utmost importance for proper CNS drug development and disease treatment In recent years much information has become available for a better understanding of the many factors important for CNS drug delivery and how they interact to affect drug action This book describes small and large drug delivery to the brain with an emphasis on the physiology of the BBB and the principles and concepts for drug delivery across the BBB and distribution within the brain It contains methods descriptions for studying drug delivery routes and approaches of administering drugs into the brain the influence of disease and drug industry perspectives Therewith it contributes to an in depth understanding of the interplay between brain patho physiology and drug characteristics Furthermore the content is designed to be both cutting edge and educational so that the book can be used in high level training of academic and industry scientists with full references to original publications Kidney Disease and Nephrology Index , 1977-07 **Delivery Systems for Peptide Drugs** S.S.

Davis, Lisbeth Illum, E. Tomlinson, 2013-11-11 Recent years have seen enormous advances in the field of protein and peptide

engineering and a greater understanding in the way in which biological response modifiers function in the body It is now possible through the use of recombinant DNA techniques or by solid phase protein synthesis to produce significant quantities of a wide variety of regulatory agents that are therapeutically applicable The list of these response modifiers expands almost daily to include interferons macrophage activation factors neuropeptides and agents that may have potential in cardiovascular disease inflammation contraception etc Prospects to use some of these materials in medicine have reached the stage where products have either been approved by regulatory authorities or are the subject of applications as investigatory drugs or as new therapeutic agents In some uses the pertinent agent will be administered on an acute basis in the form of a simple injection as for example the use of a tissue plasminogen activator for the treatment of coronary infarct In other cases regulatory proteins and peptides are indicated for chronic therapy and here they will need to be administered by an appropriate delivery system Unfortunately the research on delivery systems for peptides and proteins has not kept pace with the rapid progress in biotechnology and consequently there are presently few systems that are entirely appropriate for the administration of macromolecular drugs according to complex dosage regimens eg intermittent and pulsed therapy Furthermore essential pharmacokinetic and pharmacodynamic data may be missing Replacement of Renal Function by Dialysis William Drukker, Frank M. Parsons, J.F. Maher, 2012-12-06 More than 50 years after Haas first human dialysis and second edition by incorporating chapters on its history 40 years after Kolfrs pioneering work a book on the and on the practical aspects present state of the art cannot be written by one person The size of the book has almost doubled partly by obviously it had to be a multi authored volume There using more illustrations The inclusion of a number of fore some overlap between chapters and even a few con colour reproductions has been made possible by a sup troversies between authors became unavoidable porting grant of the National Kidney Foundation of we deliberately avoided editorial streamlin the Netherlands which the editors gratefully acknow However ing of manuscripts leaving the authors personal style ledge We considered asking several authors to shorten their and personal opinions unaltered as much as possible We resisted this as it would have delayed the This may make the book more vivid to read and may chapters sometimes stimulate readers to study a subject in greater publishing date and would possibly have removed much detail from the literature Additionally both British and material besides being a painful task for our collea American spellings have been kept because of the inter gues

Research Awards Index ,1987 Cardiac Electrophysiology: From Cell to Bedside E-Book Douglas P. Zipes, Jose Jalife, 2009-05-06 Cardiac Electrophysiology From Cell to Bedside defines the entire state of current scientific and clinical knowledge in this subspecialty In response to the many major recent developments in the field Drs Zipes and Jalife have completely updated this modern classic making the 5th Edition the most significant revision yet From our latest understanding of ion channels molecular genetics and cardiac electrical activity through newly recognized syndromes unique needs of special patient populations and new diagnostic and therapeutic options you ll find all the state of the art guidance

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Critical Care Medicine E-Book Joseph E. Parrillo, R. Phillip Dellinger, 2018-11-12 Now completely revised to bring you up to date with the latest advances in the field Critical Care Medicine Principles of Diagnosis and Management in the Adult 5th Edition delivers expert practical guidance on virtually any clinical scenario you may encounter in the ICU Designed for intensivists critical care and pulmonology residents fellows practicing physicians and nurse practitioners this highly regarded text is clinically focused and easy to reference Led by Drs Joseph Parrillo and Phillip Dellinger the 5th Edition introduces numerous new authors who lend a fresh perspective and contribute their expertise to that of hundreds of top authorities in the field Includes new chapters on current applications of bedside ultrasound in the ICU both diagnostic and procedural mechanical assist devices and extra corporeal membrane oxygenation ECMO Contains new administrative chapters that provide important information on performance improvement and quality length of stay operations working with the Joint Commission and more Features new videos and images that provide visual guidance and clarify complex topics Keeps you up to date with expanded chapters on echocardiography in the

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Annual Report National Institute on Aging,1986 *Pharmacology for Rehabilitation Professionals - E-Book* Barbara Gladson,2010-09-28 Now fully revised and updated Dr Barbara Gladson s *Pharmacology for Rehabilitation Professionals* 2nd Edition remains your best resource for understanding how various drugs affect patients during therapeutic exercise and rehabilitation Using case studies and engaging activities it helps you apply essential pharmacology information directly to rehabilitation practice New chapters a new reader friendly design new artwork and more enhance the text and bring you up to date with both basic pharmacologic principles as well as the mechanism of action and side effects of drugs commonly seen in rehabilitation practice Helps you develop effective exercise programs by providing drug exercise interactions from a pharmacokinetics perspective You will clearly see the implications for exercise for each specific condition and medication Presents case studies in every chapter that demonstrate the effects of various drugs on the diagnosis prognosis and interventions in physical therapy so you can more easily monitor patients for adverse drug effects Features engaging activities in every chapter ranging from patient interviews to challenging real life questions helping you retain and apply what you ve learned Encourages you to use the latest research in your clinical decision making with evidence based content incorporated throughout Simplifies the complex topic of pharmacokinetics so that you will fully understand how it affects your individual patients and your care plans Guides you in using the Internet for online drug information with references to specific sites and when and how to use them to their fullest potential Discusses lifespan considerations such as age physical differences and obesity as well as the latest information on diabetes and glucose testing A new chapter on Complementary and Alternative Medicine in Pharmacology covers popular herbal and alternative products used to promote health as well as herbal remedies used during menopause and in the treatment of cancer helping you recognize the impact of herbals on your patients symptoms and response to therapy A new chapter on Drugs Affecting the Integumentary System discusses skin disorders and their pharmacological treatment prophylactic and debriding agents antiseptics and more A new chapter on Nutrition and Pharmacology provides current information on vitamins and minerals enteral and parenteral nutrition and food and drug interactions important topics that affect rehabilitation outcomes Updated drug information and new drugs are added throughout the text keeping you up to date with current pharmacological

information as it pertains to rehabilitation

Decoding **Kinetics Of Drug Action In Disease States**: Revealing the Captivating Potential of Verbal Expression

In a time characterized by interconnectedness and an insatiable thirst for knowledge, the captivating potential of verbal expression has emerged as a formidable force. Its capability to evoke sentiments, stimulate introspection, and incite profound transformations is genuinely awe-inspiring. Within the pages of "**Kinetics Of Drug Action In Disease States**," a mesmerizing literary creation penned with a celebrated wordsmith, readers attempt an enlightening odyssey, unraveling the intricate significance of language and its enduring affect our lives. In this appraisal, we shall explore the book's central themes, evaluate its distinctive writing style, and gauge its pervasive influence on the hearts and minds of its readership.

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