Handbook of BASIC PHARMACOKINETICS

W. A. Ritschel

SECOND EDITION

Updated 1982

Handbook of Basic Pharmacokinetics

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Preface

First Edition

Pharmacokinetics is a comparatively young discipline among the health sciences which is interrelated with biopharmaceutics, pharmacology and therapeutics. Although most of the foundation of pharmacokinetics was laid in the late fifties and early sixties, the seventies have produced wider application of pharmacokinetics, not only in drug and drug product development but also in the treatment of patients in the clinical setting. The latter application evolves into a sub-discipline: clinical pharmacokinetics.

The *Handbook of Basic Pharmacokinetics* does not claim to be a textbook in the traditional sense. Rather, it is a compilation of highlights to be taught and discussed in a formal course on pharmacokinetics. The *Handbook* serves as a guide for those who

have been exposed to the subject but who wish to refer to the material primarily for general use or for an examination, as well as for those who need a refresher. The author believes that the time is at hand when pharmacists are expected not only to have some knowledge of pharmacokinetics but to actually apply it by designing loading and maintenance doses and dosing intervals for individual patients, and by determining dosage regimen adjustment in patients with renal failure.

Pharmacokinetics is a further step toward rational and optimal therapy, preventing danger of toxicity but assuring maintenance of therapeutic drug concentration in the body. This is particularly important in the severely sick patient and in therapy with life-saving drugs, such as antibiotics, chemotherapeutics, antidiabetics, anticoagulants, etc. Furthermore, a profound knowledge of pharmacokinetics is essential in designing, testing, and evaluating bioavailability, now a major task in our profession.

The material is presented in a rather simplified and condensed manner to give the reader a quick orientation and summary. Since only basic information is given, no references are included in the text. Different concepts, theories, and approaches are used by different scientists in the field. The *Handbook* does not elaborate on these; rather, it tries to present the commonly used approaches.

The nomenclature in pharmacokinetics among individual scientists and between different countries varies widely and is often confusing. Therefore, a standard nomenclature has been used throughout the book.

Because no reference has been made to the use of computers in pharmacokinetics (and those using

such equipment would not need this handbook), only the open one-compartment model and the open two-compartment model are discussed here. This does not imply that more complex models do not exist or are not useful, only that, for practical and application purposes, these two different compartment models for intravascular and extravascular administration are the most important ones, and in most instances are quite sufficient.

The *Handbook of Basic Pharmacokinetics* evolved from undergraduate and graduate courses in biopharmaceutics and pharmacokinetics which the author has taught during the past seven years at the University of Cincinnati. It began with a steadily increasing number of handouts for the students which summarized the highlights and contained the most important facts. It further developed because students at our, as at many other institutions, participate in rounds on the floors of hospitals where they find a knowledge of pharmacokinetics essential, if they are to contribute in a meaningful way to patient care through interdisciplinary communication. It is hoped that this contribution will be a valuable tool for them.

I would like to thank the Department of Biomedical Communications of the University of Cincinnati Medical Center for assistance in preparing the figures. Further, I would like to thank the publisher for his invaluable encouragement and support.

Finally, a request to the reader and user of this book: Nothing is perfect in the world but God. However, we all should try to do our best and should seek to improve our world for the sake of mankind. The author would appreciate any con-

structive criticism, especially information to include in an eventual revised edition, and particularly would welcome data such as is contained in Appendix I, Pharmacokinetic Data on Drugs.

WOLFGANG A. RITSCHEL

Cincinnati, Fall, 1975

Second Edition

Since the appearance of the first edition of this *Handbook*, pharmacokinetics has found much wider acceptance as well as more practical applications, particularly in the clinical areas. An increasing number of papers in the medical and pharmaceutical literature include or deal with pharmacokinetics. The sub-discipline of clinical pharmacokinetics was established during that period and several new journals appeared in this subject area. Consequently, this second edition of the *Handbook of Basic Pharmacokinetics* underwent a major revision in order to conform with these developments. The chapter on biopharmaceutical data of the gastrointestinal tract was condensed and revised. The appendices 2 through 5 were deleted, since the use of pocket calculators with log and exponential functions is common practice.

Practically all chapters of the first edition have been revised, new equations and summary tables added. New topics include Michaelis-Menten kinetics, relationship between drug response and pharmacokinetics, infusion equations, physiological and pathological factors influencing drug response, etc. The Appendix on pharmacokinetic drug data was significantly expanded, as well as the section on dosage regimen determination. Both will aid

the clinical practitioner in the task of applying bedside-kinetics for optimizing drug therapy.

The author would like to thank all those colleagues who have made constructive comments and recommendations for improvement of the handbook.

Last but not least, the author thanks the publisher for the cooperation that made this revision possible. Particular tribute is given to my dear friend, the late Dr. Donald E. Francke who, only days before his sudden death, urged and encouraged the author to start with the revision.

Cincinnati, Fall, 1979 WOLFGANG A. RITSCHEL

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Definitions and Glossary

Absolute Bioavailability is the extent or fraction of drug absorbed upon extravascular administration in comparison to the dosage size administered.

Absorption of drugs is the process of uptake of the compound from the site of administration into the systemic circulation. A prerequisite for absorption is that the drug be in aqueous solution. The only relatively rare exception is absorption by pinocytosis.

Accumulation is the increase of drug concentration in blood and tissue upon multiple dosing until steady state is reached.

Apparent Partition Coefficient is the ratio of the concentrations at equilibrium between a lipoid phase (usually n-octanol) and an aqueous phase (usually buffer *p*H 7.4). The apparent partition coefficient is uncorrected for dissociation or association in either phase.

Area Under the Curve is the integral of drug blood level over time from zero to infinity, and is a measure of quantity of drug absorbed and in the body.

Biliary Recycling is the phenomenon that drugs emptied via bile into the small intestine can be reabsorbed from the intestinal lumen into systemic circulation.

Bioavailability is defined as both the relative amount of drug from an administered dosage form which enters the systemic circulation and the rate at which the drug appears in the blood stream.

Bioequivalence of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the standard when administered at the same molar dose.

Bioequivalence Requirement is a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.

Biological Half-Life of a drug is the time in hours necessary to reduce the drug concentration in the blood, plasma or serum to one half after equilibrium is reached. The biological half-life may be influenced by: dose size, variation in urinary excretion (*p*H), inter-subject variation, age, protein binding, other drugs and diseases (especially renal and liver diseases).

Loss of drug from the body as described by the biological half-life, means the elimination of the ad-

ministered parent drug molecule (not its metabolites) by urinary excretion, metabolism or other pathways of elimination (lung, skin, etc.).

Biopharmaceutics deals with the physical and chemical properties of the drug substance, the dosage form, and the body and the biological effectiveness of a drug and/or drug product upon administration, i.e., the drug availability to the human or animal body from a given dosage form, considered as a drug delivery system. The time course of the drug in the body and the quantifying of the drug concentration pattern are explained by pharmacokinetics.

Biophase is the actual site of action of drugs in the body. It is the drug-receptor interaction on molecular level or the influence of biopolymers by the presence of drug. The biophase may be the surface of a cell or within the cell, i.e., one of the organelles.

Blood Flow Rate is the speed of blood perfusion in an organ, usually expressed in ml/100 g organ weight/min. Blood flow rates may differ severalfold between rest, or immobilization, and exercise.

Blood-, Plasma- or Serum-Levels demonstrate the concentration in blood, plasma or serum upon administration of a dosage form in various routes of administration. Blood-, plasma- or serum-level curves are plots of drug concentration versus time on numeric or semi-log graph paper. Blood-, plasma- or serum-levels are obtained from blood samples by venopuncture in certain time intervals after administration of the drug product and chemical or