Biopharmaceutics and Clinical Pharmacokinetics

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FOURTH EDITION

LEA & FEBIGER • Philadelphia • London • 1991

Lea & Febiger
200 Chester Field Parkway
Malvern, Pennsylvania 19355-9725
U.S.A.
(215) 251-2230
1-800-444-1785

Lea & Febiger (UK) Ltd.
145a Croydon Road
Beckenham, Kent BR3 3RB
U.K.

Library of Congress Cataloging-in-Publication Data

Gibaldi, Milo.
Biopharmaceutics and clinical pharmacokinetics / Milo Gibaldi.—
4th ed.
p. cm.
Includes bibliographical references.
ISBN 0-8121-1346-2
1. Biopharmaceutics. 2. Pharmacokinetics. I. Title
[DNLM: 1. Biopharmaceutics. 2. Pharmacokinetics. QV 38 G437b]
RM301.4.G53 1990
615'.7—dc20
DNLM/DLC
for Library of Congress 90-5614
CIP

First Edition, 1971
Reprinted 1973, 1974, 1975
Second Edition, 1977
Reprinted 1978, 1979, 1982
Third Edition, 1984
Reprinted 1988
Fourth Edition, 1991
First Spanish Edition, 1974
First Japanese Edition, 1976
Second Japanese Edition, 1981
Second Turkish Edition, 1981

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Introduction to Pharmacokinetics

Advancements in biopharmaceutics have come about largely through the development and application of pharmacokinetics. Pharmacokinetics is the study and characterization of the time course of drug absorption, distribution, metabolism, and excretion, and the relationship of these processes to the intensity and time course of therapeutic and toxicologic effects of drugs. Pharmacokinetics is used in the clinical setting to enhance the safe and effective therapeutic management of the individual patient. This application has been termed *clinical pharmacokinetics*.

DISTRIBUTION AND ELIMINATION

The transfer of a drug from its absorption site to the blood, and the various steps involved in the distribution and elimination of the drug in the body, are shown in schematic form in Figure 1–1. In the blood, the drug distributes rapidly between the plasma and erythrocytes (red blood cells). Rapid distribution of drug also occurs between the plasma proteins (usually albumin but sometimes α_1-acid glycoproteins and occasionally globulin) and plasma water. Since most drugs are relatively small molecules they readily cross the blood capillaries and reach the extracellular fluids of almost every organ in the body. Most drugs are also sufficiently lipid soluble to cross cell membranes and distribute in the intracellular fluids of various tissues. Throughout the body there is a distribution of drug between body water and proteins or other macromolecules that are dispersed in the body fluids or are components of the cells.

The body can be envisioned as a collection of separate compartments, each containing some fraction of the administered dose. The transfer of drug from one compartment to another is associated with a rate constant (k). The magnitude of the rate constant determines how fast the transfer occurs.

The transfer of drug from blood to extravascular fluids (i.e., extracellular and intracellular water) and tissues is called *distribution*. Drug distribution is usually a rapid and reversible process. Fairly quickly after intravenous (iv) injection, drug in the plasma exists in a distribution equilibrium with drug in the erythrocytes, in other body fluids, and in tissues. As a consequence of this dynamic equilibrium, changes in the concentration of drug in the plasma are indicative of changes in drug level in other tissues including sites of pharmacologic effect (bioreceptors).

The transfer of drug from the blood to the urine or other excretory compartments (i.e., bile, saliva, and milk), and the enzymatic or biochemical transformation *(metabolism)* of drug in the tissues or plasma to metabolic products, are usually irreversible processes. The net result of these irreversible steps, depicted in Figure 1–1, is called *drug elimination*. Elimination processes are responsible for the physical or biochemical removal of drug from the body.

The moment a drug reaches the bloodstream, it is subject to both distribution and elimination. The rate constants associated with distribution, however, are usually much larger than those related to drug elimination. Accordingly, drug distribution throughout the body is usually complete while most of the dose is still in the body. In fact, some drugs attain distribution equilibrium before virtually any of the dose is eliminated. In such cases, the body appears to have the characteristics of a single compartment.

This simplification, however, may not be applied to all drugs. For most drugs, concentrations in plasma measured shortly after iv injection reveal a

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