Drug and Chemical Toxicology/9

DRUG TOXICOKINETICS

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DRUG TOXICOKINETICS

DRUG AND CHEMICAL TOXICOLOGY

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About the Series

Toxicology has come a long way since the ancient use of botanical fluids to eliminate personal and political enemies. While such means are still employed (often with more potent and subtle materials), toxicology has left the boiling-pots-and-vapors atmosphere of the "old days" and evolved into a discipline that is at the forefront of science. In this process, present-day toxicologists have adopted a variety of techniques from other scientific areas and developed new skills unique to the questions asked and the studies being pursued. More often than not, the questions asked have never been thought about before, and only through the advances made in other disciplines (for example, in analytical chemistry) were the needs for answers raised. The compounding concerns of society for public safety, the maintenance of environmental health, and the improvement of the welfare of research animals have expanded the boundaries in which toxicologists work. At the same time, society has spotlighted toxicology as the science that will offer the hope of safety guarantees, or at least minimal and acceptable risks, in our everyday chemical encounters.

This Drug and Chemical Toxicology series was established to provide a means by which leading scientists may document and communicate important information in the rapidly growing arena of toxicology. Providing relevant and forward-looking subjects with diverse and flexible themes in an expedited and prompt publication format will be our goal. We will strive in this vehicle to provide fellow toxicologists and other knowledgeable and interested parties with appropriate new information that can be promptly applied to help answer current questions.

Drug Toxicokinetics is a state-of-the-art work. It explains basic principles and their present and future application in drug design, discovery, and development. It looks to a future with safer and more effective pharmaceuticals.

Frederick J. Di Carlo
Frederick W. Oehme

FOREWORD

We have come a long way since 1922, when C. P. Sherwin proposed the chemical defense hypothesis stating that living organisms generally convert foreign substances to more water-soluble, and thus more readily excretable, metabolites [1]. Sherwin, who studied under Thierfelder in Tubingen, was the "German Connection" for the small drug metabolism community in America [2]. For reviews published in 1933 and 1935 [3,4], he used the durable title "Detoxication Mechanisms," a term that he probably derived from Neumeister's *entgiftung* [5]. R. T. Williams adopted *Detoxication Mechanisms* for the title of his classic volumes in 1947 and 1959 [6] and furthered acceptance of the chemical defense hypothesis.

But there was a serious problem: Not all metabolites are innocuous. In 1950 Boyland suggested that aryl oxide intermediates might be responsible for the carcinogenicity of their parent compounds [7], and in 1968 Jerina et al. demonstrated that naphthalene-1,2-epoxide is a reactive intermediate formed in the metabolism of naphthalene [8]. Metabolite identification increased explosively with the development of remarkable chromatographic and spectrometric instrumentation. New reactive metabolic intermediates were discovered and introduced into toxicology. Considerable research focus shifted from pharmacology to toxicology, and from pharmacokinetics to toxicokinetics, the latter being defined as the rates of absorption, tissue distribution and redistribution, enzymic and non-enzymic biotransformation, and excretion as related to toxicologic endpoints [9]. Gradually, the euphemism "side effect" was replaced by "toxicity."

Today toxicokinetics is maturing and moving to center stage in toxicology. Since "the dose makes the poison," we need to focus on the de-

livery of that dose to critical biological sites so that we can understand the molecular events producing toxicities and learn how to intervene. To achieve these objectives, it is clear that toxicokinetics will require close collaboration between pharmacokineticists and toxicologists.

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PREFACE

Toxicokinetics is emerging as a new and important discipline in drug discovery and development. It represents a combination of two disciplines, pharmacokinetics and toxicology, which are in themselves relatively new and rapidly evolving in terms of technology and scope.

It has become widely recognized that it is important to understand drug disposition when administration is at toxicological doses just as when it is at pharmacological or therapeutic doses. Similarly, the metabolic transformation of compounds in toxicity species has to be understood in order to provide adequate and informed comparisons of their effects in both toxicity and pharmacology studies in humans.

Toxicokinetics is uniquely different from pharmacokinetics in that it represents the study of drug absorption, distribution, metabolism, and excretion at doses that are far greater than those normally used in a pharmacologic screen or in therapy. Transport systems and metabolizing enzymes become saturated, protein binding may change, and the overall response of physiological systems may change due to the greater concentrations of compounds in the body at toxicologic doses. It is no longer sufficient simply to administer a drug at toxicological doses and note the events that occur. Just as interest in scientific and regulatory circles has shifted from consideration of dose–response relationships to drug concentration–response relationships, so in toxicology emphasis is shifting to concentration–effect considerations.

In order to address the many concepts in this rapidly changing area, we have invited experts from a wide spectrum of disciplines and backgrounds to contribute state-of-the-art concepts and technologies to this book. Each author is a recognized expert in his or her field and they thus collectively provide a wealth of experience in disciplines that are

either directly or closely related to toxicokinetics. This book will assist and guide those who are involved in this important discipline. We have attempted to cover a range of topics, from basic considerations of saturable and nonsaturable pharmacokinetics to practical considerations of specific therapeutic areas and a projection of the evolving nature of toxicokinetics in the future. The overall purpose of this book is to bring together various aspects of toxicokinetics with an emphasis on practical applications. Thus we designed this work as a "manual" or "textbook" rather than dwelling on basic concepts. This approach is essential in order to familiarize toxicologists and drug metabolism scientists with toxicokinetic principles and facilitate the application of these in drug development.

Development of this book took significant professional effort and resources by the contributors. In addition, numerous colleagues helped to bring it to its final form. We thank particularly Ms. Theresa Davis, who carried the administrative responsibilities and kept the whole thing together.

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NOMENCLATURE

A	Amount of drug in the body
ACAT	Acyl-coenzyme A cholesterol transferase
ACE	Angiotensin converting enzyme
ADHD	Attention deficit hyperactivity disorder
ADME	Absorption, distribution, metabolism, and excretion
ALT	Alanine aminotransferase
A_{ss}	Amount of drug in the body at steady state
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
Au	Quantity of unchanged drug cleared in urine
AUC	Area under drug concentration versus time curve in blood, plasma, etc.
BID	Drug dosing twice each day
BLQ	Below limit of quantitation
BSA	Body surface area
BUN	Blood urea nitrogen
C	Concentration of drug in blood, plasma, etc.
C_0	Concentration of drug in blood, plasma, etc., immediately following a rapid intravenous dose
CBER	Center for Biologics Evaluation and Research (US FDA)
CDER	Center for Drug Evaluation and Research (US FDA)
cDNA	Cyclic DNA
C-HUS/TTP	Hemolytic uremic syndrome complicated with thrombocytopenia
Cl_m	Metabolic clearance
Cl_p	Plasma clearance
Cl_r	Renal clearance

C_{max}	Maximum drug concentration in blood, plasma, etc.
C_{min}	Minimum drug concentration in blood, plasma, etc., during repeated drug dosing
CNS	Central nervous system
CSA	Clinical studies application (European Community)
CSF	Cerebrospinal fluid
C_{ss}	Concentration of drug in blood or plasma at steady state
D	Dose of a drug
d	Membrane thickness
DNA	Deoxyribonucleic acid
ϵ	Ratio of drug dosing interval to elimination half-life
EC	Extracellular
EGF	Epidermal growth factor
ESRF	End-stage renal failure
F	Fraction of administered drug that is systemically available
FDA	United States Food and Drug Administration
FGF	Fibroblast growth factor
fu	Fraction of unbound drug in plasma
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLC	Gas liquid chromatography
GLP	Good laboratory practice
GSH	Glutathione
Hct	Hematocrit
HDL	High-density lipoprotein
HPLC	High-performance liquid chromatography
HMG CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HTE	Human time equivalent
HUS	Hemolytic uremic syndrome
IC	Intracellular
ICH-1	First International Conference on Harmonization
IgG	Immunogammaglobulin
IM	Intramuscular
IND	Notice of claimed investigational exemption for a new drug (USA)
IP	Intraperitoneal
IV	Intravenous
k_0	Zero-order rate constant
K_f	Glomerular ultrafiltration coefficient

K_m	Michaelis constant drug concentration at which elimination rate is one-half the maximum when Michaelis kinetics are operative
k_p	Red blood cell plasma partition coefficient
LD_{10}	Drug dosage that is lethal to 10% of an animal species
LDL	Low-density lipoprotein
MAA	Marketing Authorization Application (European Community)
MAO	Monoamine oxidase
MEC	Minimum effective drug concentration
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NAT	*N*-acetyltransferase
NCE	New chemical entity
NDA	New Drug Application (US FDA)
NED	No effect dose
NOAEL	No observable adverse effect level
NOEL	No observable effect level
NSAID	Nonsteroidal anti-inflammatory drug
ΔP	Glomerular transcapillary hydraulic pressure gradient
PAF	Platelet activating factor
PAS	Periodic acid-Schiff reaction
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PFR	Plasma flow rate
PLA	Product license application for biologicals (US FDA, CBER)
PO	Oral route (per os)
Q	Blood flow rate
QC	Quality control
QD	Drug dosing once each day
R	Drug accumulation factor with repeated dosing
RBF	Renal blood flow
RPN	Renal papillary necrosis
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
RSD	Relative standard deviation
Safety margin	Ratio of animal no observed toxic effect exposure level to human clinical exposure level
SOP	Standard operating procedure
τ	Dosing interval
$t_{1/2}$	Elimination half-life

t_{max}	Time of maximum drug concentration
t_{min}	Time of minimum drug concentration in blood or plasma during repeated drug dosing
tRNA	Transfer RNA
TV	Tissue volume
V	Drug distribution volume in the body
V_{max}	Maximum rate of drug elimination
W	Body weight