TOPICS IN PHARMACEUTICAL SCIENCES

D. D. BREIMER & P. SPEISER
EDITORS

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Proceedings of the 41st International Congress of Pharmaceutical Sciences of F.I.P., held in Vienna, Austria, September 7-11, 1981.

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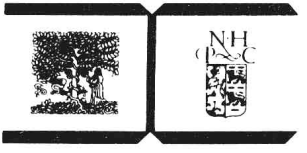

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PREFACE

This volume contains the invited papers of the 41st International Congress of Pharmaceutical Sciences of F.I.P. (Fédération Internationale Pharmaceutique or International Pharmaceutical Federation), held in Vienna, Austria, 7-11 September, 1981.

For the first time in the history of F.I.P. congresses, this annual congress was not associated with one general theme, but the emphasis was on advances in various fields of pharmaceutical sciences through specialized symposia. There were more than 2000 participants in Vienna and in addition to 34 invited papers, about 250 poster and oral communications were presented. Publishing the latter in this volume was impossible.

The topics of the seven symposia were connected with the major divisions of pharmaceutical sciences: pharmacokinetics, biopharmaceutics, pharmaceutical technology, drug analysis, medicinal chemistry (drug stability). The other two had an interdisciplinary character: "pharmaceutical aspects of anti-cancer drug treatment" and "gene manipulation, cell cultures and pharmaceutical sciences". In all symposia the state of the art and future perspectives were discussed. We are grateful to the speakers for conforming to the deadline of delivering their manuscripts so promptly. This made it possible to publish the Proceedings very shortly after the congress.

These Proceedings are dedicated to the memory of Dr. Sidney Riegelman, of San Francisco, who died on April 4, 1981. He was to have been an invited speaker at the pharmacokinetics symposium at this congress. Dr. Riegelman was a pioneer and world leader in pharmaceutical sciences. Dr. Malcolm Rowland presented the memorial address, which is also included in this volume.

D.D. Breimer and P. Speiser

Dr. Sidney Riegelman

MEMORIAL ADDRESS

by Professor Malcolm Rowland, University of Manchester

to Dr. Sidney Riegelman

It seems to me most fitting that this symposium, on Advances in Pharmacokinetics, should be dedicated to the memory of a pioneer of the subject, Dr. Sidney Riegelman, who died so tragically on 4 April, this year while scuba diving with his wife Milli, at Salt Point, California.

A graduate of pharmacy from the University of Wisconsin in 1944, receiving his Ph. D. from the same University in 1948, Sidney Riegelman spent his entire professional life in academia at the School of Pharmacy, University of California, San Francisco, first as an instructor and then as an Assistant (1950), Associate (1956) and finally full Professor of Pharmacy and Pharmaceutical Chemistry (1964). He was chairman of the Department of Pharmacy from 1967-1978, and at the time of death was Associate Dean of Research Services.

Coming from Wisconsin not unnaturally Sid's initial research interests were in physical pharmacy, studying such subjects as the properties of powders, solubilization and the optimal formulation of ophthalmic solutions. The environment of the health science complex at San Francisco did much, I suspect, however, to change his direction of research into the one for which he may best be remembered, pharmacokinetics. In the late 1950's, with pharmacokinetics still in its infancy, he examined the kinetics and factors controlling the rectal absorption of drugs. For

this classic piece of work he received the coveted Ebert Prize, considered to be the highest scientific award in American pharmacy.

Innovation and creativity are hallmarks of his numerous contributions to pharmacokinetics. Landmarks amongst them are one of the first demonstrations, with aspirin, of the importance of gut wall and hepatic metabolism in the loss of availability of orally administered drugs, the now well-known "first-pass" effect; the development of various mathematical models to assess the kinetics of absorption and the extent of distribution of drugs; the demonstration and quantitation of renal metabolism of some drugs, as well as the characterisation of non-linear aspects of the pharmacokinetics of phenytoin, propranolol, theophylline and quinidine in man. He has also made significant contributions to pharmaceutical analysis and to dermatology, constantly illustrating the importance of pharmaceutical formulation and pharmacokinetics. Without question, his studies have led to the more rational use of many drugs in clinical practice. In 1972 he founded and became editor of the Journal of Pharmacokinetics and Biopharmaceutics, a speciality journal that has done much to set the standards in the subject.

In recognition of these and other outstanding contributions he received the American Pharmaceutical Foundation Research Achievement awards in Physical Pharmacy (1968) and Pharmacodynamics (1970), and more recently the distinguished Carl Wilhelm Scheele Award from Sweden.

As chairman of the department of pharmacy (1967 - 1978), at San Francisco, he not only built up a fine faculty in biopharmaceutics and pharmacokinetics, but also was instrumental in the development and expansion of clinical pharmacy. A never failing advocate for the advancement of his profession, he nurtured clinical pharmacy through its infancy, providing sustenance, direction and constant comfort to the dedicated young staff, until clinical pharmacy could stand on its own two feet and be counted as one of the major innovations of modern pharmacy practice. Sidney Riegelman's contribution here can never be overstated.

I have had the pleasure and good fortune to have known Sidney Riegelman for the past 16 years, 10 of these working under his chairmanship. These were most delightful, informative and memorable times for me. I have

vivid memories of long hours of intensive and spontaneous discussion on a whole host of subjects, politics, economics, the arts as well as the pharmaceutical sciences, with a vibrant and enthusiastic man, warmth in his eyes and an infectious laugh. A man never shy to show his ignorance, and always willing to learn, a true student of life, living it fully with his family and sharing it with his friends, colleagues and students.

His presence at this symposium, at which he was to have been a speaker, will be sadly missed. Yet I sense that each of those speakers, who knew him personally, can, like me, still feel his warm and friendly hand on their shoulder. I have lost a dear friend, pharmacy has lost a leader.

CONTENTS

ADVANCES IN PHARMACOKINETICS

Topics in Pharmaceutical Sciences
D. D. Breimer and P. Speiser, editors

LINEAR *VS.* NONLINEAR KINETICS

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INTRODUCTION

The pharmacokinetic behavior of drugs is often characterized by parameters, such as those listed in Table 1 for a one-compartment model. These parameters summarize and permit one to predict the time-course of an observation, for example, plasma concentration or excretion rate, on administering a dose of a drug. Although the values of these parameters are subject to experimental and other sources of variability, they are not expected to vary with the dose administered when linear kinetics are followed. If the value of one, or more, of the parameters does vary with dose, the kinetics are said to show *dose-dependence* or to be *nonlinear*. Thus, nonlinear kinetics may be recognized by a consistent change with dose in the value of any one, or more, of the pharmacokinetic parameters listed in Table 1.

TABLE 1

RECOGNITION OF NONLINEAR KINETICS - CHANGE IN PARAMETER VALUE

Administration	Pharmacokinetic Parameter			Observation
	Absorption	Distribution	Elimination	
	Availability	Volume of Distribution	Renal Clearance	Blood (Plasma) Concentration
Dose[a]	Absorption Rate Constant	(Fraction Unbound in Plasma)	Extrarenal Clearance	Unbound Concentration
			(Fraction Excreted Unchanged)	Amount Excreted Unchanged

[a]Route, method of administration, and dosage form held constant.

A more appropriate method of distinguishing between linear and nonlinear kinetics is by the rule of superposition. In linear kinetics, the time-course of an observation following one dose is superimposable on that following any other dose, if the observation is normalized to the dose administered. A lack of superposition indicates *nonlinearity* or the occurrence of *dose-dependent kinetics*.

When the value of a pharmacokinetic parameter changes with time on either continuous infusion or repetitive administration of the same dose, the kinetics are said to show *time-dependence*. The mechanisms responsible for time-dependent kinetics, e.g., autoinduction and drug-induced diuresis, are often dose-dependent as well.

Table 2 lists a number of causes of dose and time dependencies and selected drugs that show such behavior. The causes are generally related to the *saturability* of the process or to the pharmacologic effect of the drug itself. A *saturable* process is one with a maximum capacity. Capacity-limited metabolism is an example of a saturable process and nephrotoxicity produced by a drug that is eliminated in the urine is an example of nonlinearity caused by an effect of the drug.

TABLE 2

EXAMPLES OF CAUSES OF AND DRUGS SHOWING DOSE- AND TIME-DEPENDENT KINETICS

Cause[a]	Drug
Absorption	
A. Saturable transport in gut wall.	Riboflavin
B. Drug comparatively insoluble	Griseofulvin
C. Saturable gut wall or hepatic metabolism on first pass	Propranolol, Salicylamide
D. Pharmacologic effect on GI motility	Metoclopramide, Chloroquine
E. Saturable gastric or GI decomposition	Some Penicillins
Distribution	
A. Saturable plasma protein binding	Phenylbutazone, Salicylate
B. Saturable tissue binding	-
C. Saturable transport into or out of tissues . . .	Methotrexate
Renal Elimination	
A. Active secretion	Penicillin G
B. Active reabsorption	Ascorbic Acid
C. Change in urine pH	Salicylic Acid
D. Saturable plasma protein binding	Salicylic Acid
E. Nephrotoxic effect at higher doses	Aminoglycosides
F. Diuretic effect	Theophylline, Alcohol
Extrarenal Elimination	
A. Capacity-limited metabolism - enzyme saturation or cofactor limitation	Phenytoin, Theophylline Salicylic Acid, Alcohol
B. Saturable biliary excretion	-
C. Enzyme induction	Carbamazepine
D. Hepatotoxic at higher doses	Acetaminophen
E. Saturable plasma protein binding	Phenylbutazone
F. Altered hepatic blood flow	Propranolol
G. Metabolite inhibition	Diazepam

[a]Hypothermia, metabolic acidosis, altered cardiovascular function, and coma are additional causes of dose and time dependencies in drug overdose.

Although nonlinear kinetic behavior may be the exception rather than the rule at therapeutic doses and concentrations, the list of drugs in Table 2 suggests that it is an important consideration in drug therapy. It is particularly pertinent to drug intoxication, where nonlinear kinetic behavior occurs more frequently.

This presentation summarizes the dose and time dependencies that we have observed in the therapeutic range with two drugs, theophylline and salicylic acid. These drugs are of special interest because they each show multiple sources of dose and time dependencies and because their dependencies tend to have opposing effects. They also exemplify some of the difficulties that are encountered in distinguishing between linear and nonlinear kinetics.

THEOPHYLLINE

Theophylline is extensively metabolized by demethylation and by oxidation to uric acid derivatives. The principal metabolites, which are excreted in the urine and which account for up to 80% of the administered dose (1, 2), are shown in Figure 1. Approximately 10% is recovered unchanged in the urine after a single dose (1-3).

Although the decline in plasma theophylline concentration with time after therapeutic doses is often described by linear kinetics (4-6), the renal clearance of this drug depends on urine flow rate (7) and the formation of 3-methyxanthine is capacity-limited (3). These observations, together with evidence of a disproportionate relationship between steady-state serum theophylline concentration and dosing rate in children (8) and a convex decline in the log concentration-time curve in case reports (9, 10) of intoxication, led us to explore further the disposition kinetics of this drug. The results of these studies are in the process of publication (11-13) and are only briefly summarized here.

The kinetics of the disposition of theophylline and its major metabolites were studied in 14 healthy adults, 24 to 32 years of age and 53 to 93 kg in weight. The plasma concentration and the urinary excretion rate were monitored after single intravenous and oral doses and in a multiple plateau study in which the concentrations of theophylline and its metabolites were maintained at essentially constant values. Plasma and urine samples were analyzed by reversed-phase high-performance liquid chromatography (14).

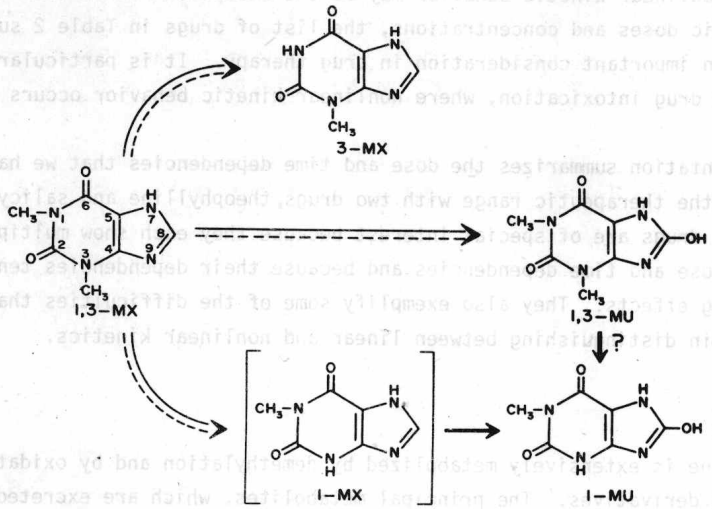

Fig. 1. The major metabolites of theophylline (1,3-dimethylxanthine, 1,3-MX) are: 1,3-dimethyluric acid (1,3-MU); 3-methylxanthine (3-MX); and 1-methyluric acid (1-MU). There is evidence to suggest that 1-methylxanthine (1-MX, in brackets) is the precusor of 1-MU, although its recovery in urine is usually not measurable. The double arrows (⟹) denote nonlinear pathways.

Dose-Dependent Metabolism

Under steady-state conditions or in situations in which elimination is rate-limited by formation, the rates of elimination and formation of each metabolite are essentially equal. Assuming that the major metabolites of theophylline, 1,3-dimethyluric acid, 3-methylxanthine, and 1-methyluric acid, are eliminated solely by renal excretion, the excretion rate of each metabolite is then a measure of the rate of its own formation. By relating the excretion rate to the plasma metabolite concentration and to the plasma theophylline concentration, the renal clearance of the metabolite and the metabolic clearance to the corresponding metabolite, respectively, are obtained.

Analysis of our data indicated that the renal clearances of the three metabolites are constant, values listed in Table 3, but that the metabolic formation clearances depend upon the concentration of theophylline.