Pharmacokinetics

Edited by
E. Gladtke und G. Heimann

Gustav Fischer Verlag · Stuttgart · New York

Pharmacokinetics

A 25 year old discipline
Symposion Nov. 10th – 11th 1978, Cologne

Edited by
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127 Figures and 72 Tables

Gustav Fischer Verlag · Stuttgart
New York · 1980

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Wir danken der Bayer AG für die finanzielle Unterstützung der Drucklegung.
We are indebted to the Bayer AG, GFR, for supporting the publication

CIP-Kurztitelaufnahme der Deutschen Bibliothek

Pharmacokinetics / hrsg. von E. Gladtke u. G. Heimann. – Stuttgart, New York : Fischer, 1980.
ISBN 3-437-10646-5

NE: Gladtke, Erich [Hrsg.]

Satz: Bauer & Bökeler Filmsatz KG, Denkendorf
Druck: Offsetdruckerei Karl Grammlich, Pliezhausen
Einband: Großbuchbinderei Cl. Maier, Leinfelden-Echterdingen
Printed in Germany

Preface

25 years of pharmacokinetics, this anniversary was the reason to organize an international symposium to summarize the progress in this new scientific field.
It was surprising that most of the invited guests followed the call at once. All of them reported results and aspects from their recent activities. By this a synopsis was performed demonstrating what happens in pharmacokinetics now.
It was a great pleasure for F. H. DOST, who was present enjoying the symposium as well as for all participants, to see the evolution from the first »Blutspiegel« to the complicated new models and conceptions.
F. H. DOST introduced the name of »Pharmacokinetics«. For a long time pharmacokinetics seemed to develope to a more confusing matter. Now we tend to simplify and compress the subject to become understandable and practicable again.

E. Gladtke · G. Heimann

Köln, 11. July 1980 (70th birthday of F. H. DOST)

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25 Years Pharmacokinetics

L. DETTLI

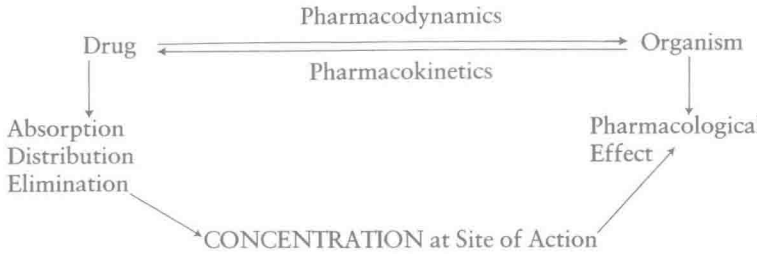
More than 400 years ago the famous physician THEOPHRASTUS PARACELSUS coined the following words: «Alle Dinge sind Gift und nichts ist ohne Gift; nur die Dosis machts, daß ein Ding kein Gift sei.» This statement may be considered the birth certificate of pharmacology in the sense of a quantitative scientific discipline, because for the first time it is clearly stated that the pharmacological effect of a bio-active substance depends quantitatively on the *dose*. After a long period of time without further progress and starting with the work of SCHMIEDEBERG in the 19th century it took a century for pharmacologists to confirm and extend the idea of PARACELSUS by the fundamental statement that the bio-activity of a substance depends on its *concentration* at the site of action and on its *intrinsic activity*. The most important break-through during this long process was the introduction of the *law of mass action* originally formulated by Guldberg and Waage in 1867 (10). Using this law the pharmacologist postulates that *molecular dispersion* is a prerequisite of drug action. This simple statement opened up the possibility to analyse pharmacodynamic events by the powerful intellectual tools of physico-chemistry and resulted in the development of a new theory which is now known under the name of *receptor theory* (1).

Although the receptor theory must be considered one of the most sophisticated biological theories it is evident that one link of the chain is missing. When we assume that both the drug and the organism are molecular systems it appears highly improbable that the administration of a drug results in a unidirectional pharmacodynamic action of the drug on the organism according to the following scheme:

$$\text{Drug} \xrightarrow{\text{Pharmacodynamics}} \text{Organism}$$

A far more satisfying assumption is the mutual *interaction* between drug and organism. The action of the organism on the drug may be summarised by the terms *absorption, distribution* and *elimination*. When these processes which are the object of *pharmacokinetics* are taken into consideration the organism is converted to an open system with respect to the drug.

It follows that the drug concentration at the site of action and consequently the pharmacological effect is a function of time controlled by both the pharmacodynamic and the pharmacokinetic characteristics of the agent, as symbolised in the following scheme:



The medical profession early recognized the basic importance of pharmacodynamics because traditionally physicians are primarily interested in the action of drugs on patients. This is possibly the reason why the practical significance of pharmacokinetics was not recognized for many years in pharmacology and clinical medicine. In 1953 however a book was published entitled *«Der Blutspiegel»* (3). In this monograph the term «pharmacokinetics» was coined and defined as the discipline describing mathematically the time course of drug concentrations in the organism. In addition, one-dose and multiple-dose pharmacokinetics in the open first-order compartment model were described so exhaustively that not much had to be added up to the present time. In summarizing, *«Der Blutspiegel»* introduced a new discipline, pharmacokinetics. It is for this reason, that the title of this report reads *«25 Years Pharmacokinetics»*. Curiously enough this monumental work was not written by a team of specialized mathematicians and pharmacologists, but by one single individual, FRIEDRICH HARTMUT DOST, a practising physician and professor of pediatrics at the University of Giessen, Federal Republic of Germany.

Fig. 1: F. H. Dost

Fig. 2: E. Krueger-Thiemer

In his book DOST compiled from the whole world literature an astonishing wealth of clinically useful pharmacokinetic information, indicating that many important contributions to the field had been made before his time. For example, in 1932 WIDMARK published his monograph on the elimination kinetics of ethyl alcohol (24) introducing in this way the concept of zero-order kinetics. In a small section consisting of a few lines Widmark described the elimination of acetone using a first-order model. It is interesting to note that WIDMARK's description of alcohol elimination based on a zero-order model which is only exceptionally useful in pharmacokinetics was immediately accepted in forensic medicine throughout the world, whereas the almost universally applicable principle of first-order kinetics went unnoticed although GEHLEN in 1933 argued based on similar lines of thought (7). The next mile-stone on the arduous way were two fundamentally important papers of TEORELL (19,20), where the open first-order two-compartment model was introduced into pharmacokinetics. From the view-point of the history of science one of the most remarcable publications is the monograph *«Dosis und Wirkung»* (5) published in 1949 by H. DRUCKREY from the Laboratory of Experimental Surgery in Freiburg, Federal Republic of Germany, and the electrical engineer K. KUEPFMUELLER. Although this book went practically unnoticed, the modern reader may find it in the most recent concepts of theoretical pharmacokinetics such as the application of analogue computers and the combination of receptor theory with pharmacokinetic equations. During the same years C. LAPP in France published several papers on drug kinetics. He introduced the term «hémicrèse» which is equivalent to the biological half-life (12).

After the publication of DOST's monograph little progress was made during the late fifties. In the next decade however, the situation changed dramatically. In 1960 E. KRUEGER-THIEMER published his classical paper on drug dosage in chemotherapy in the Journal of the American Pharmaceutical Association (11). Up to the present day this paper represents the only existing rational drug dosage theory. KRUEGER-THIEMER introduced the relative dosage interval, $\varepsilon = \tau/t_{1/2}$, a term of utmost clinical importance, because based on ε the extent of drug accumulation and the correct ratio, R^*, between loading dose and maintenance dose can be calculated in a relatively simple way. Furthermore, KRUEGER-THIEMER used the law of mass action to calculate drug plasma protein binding. In 1961 there appeared the first review article on pharmacokinetics (13). The author was the eminent pharmaceutical scientist E. NELSON from the New York State University, Buffalo, USA. In the same year the mathematician A. RESCIGNO and the pharmacologist G. SEGRE both of them collaborators of E. BECCARI (2) from the Institute of Pharmacology in Torino (Italy), published a book entitled «*La Cinetica dei Farmaci e dei Traccianti Radioattivi*» (15). The fundamental significance of this monograph cannot be overemphasized because in principle the authors discussed in it practically all problems of importance in modern pharmacokinetics including highly complex multicompartment systems, saturation kinetics, application of computers etc. Since the book was originally written in the Italian language its importance was hardly recognized until an English translation was published in 1966 (16). In the same year 1961 the word «*Biopharmaceutics*», a term originally coined by G. LEVY, one of the world's leading pharmacokineticists, appeared for the first time in a review article prepared by J. G. WAGNER (23).

In 1962 the first congress on pharmacokinetics was held in Borstel near Hamburg (6). For the first time the leading European and American kineticists were able to exchange ideas at this symposium organized by E. FREERSKEN (Borstel, Federal Republic of Germany), L. DETTLI (Basel, Switzerland), E. KRUEGER-THIEMER (Borstel) and E. NELSON (Buffalo, USA). The following years witnessed a rapid progress in the development of pharmacokinetics. On the one hand, pharmacokinetics was more and more recognized as an important discipline by the drug manufacturers, by clinicians and by drug authorities. On the other hand, several leading scientists in the field developed well equipped and specialized centers of pharmacokinetic research. Their teaching activities resulted in the development of pharmacokinetic «schools». Examples are E. R. GARRETT (Gainesville, Fla), G. LEVY (Buffalo, N.Y.), J. G. WAGNER (Ann Arbor, Mich.), S. RIEGELMANN (San Francisco), R. BECKETT (London). When considering this list of the worlds leading pharmacokinetisists two facts appear noteworthy: On the one hand, pharmacokinetics which originally developed in continental Europe was now practically an anglo-saxon discipline. During the following years this tendency increased even more because in 1969 E. KRUEGER-THIEMER died suddenly and a few years later F. H. DOST retired from academic activity. In other words, continental Europe had lost its teachers and pioneers in pharmacokinetics. On the other hand it should be noted that all leading founders of pharmacokinetic «schools» were professional pharmaceutical scientists. This preponderance of the pharmaceutical sciences was undoubtedly due to the development of modern drug legislation which considered the recently discovered possibility of generic inequivalence. As a consequence, a quantitative characterisation of bio-availability was soon one of the central themes in drug regulation and resulted in the rapid development of a subdiscipline of pharmacokinetics, ***biopharmaceutics.***

The anglo-saxon trend in pharmacokinetics is mirrored by the text-books published during these years. Except for a small volume dealing with elementary clinical pharmacokinetics (9) by E. GLADTKE and H. VON HATTINGBERG (both of them pupils of DOST) and the second revised edition of DOST's classical monograph(4) no text-book on pharmacokinetics

was published outside the English speaking world. In contrast, several important textbooks were published in the United States: «*Biopharmaceutics and Relevant Pharmacokinetics*» (1971) and «*Fundamentals of Clinical Pharmacokinetics*» (1975) by J. G. WAGNER (21,22), «*Pharmacokinetics*» (1975) by M. GIBALDI & D. PERRIER (8), and «*Biopharmaceutics and Pharmacokinetics*» (1971) by R. E. NOTARI (14). In 1973 S. RIEGELMAN, L. Z. BENET and M. ROWLAND founded the first journal devoted exclusively to drug kinetics, the *Journal of Pharmacokinetics and Biopharmaceutics*, and in 1976 appeared the first issue of the *Journal of Clinical Pharmacokinetics* edited by G. S. AVERY in New Zealand.

It is only recently that continental Europe recovered from the loss of its pioneers in pharmacokinetics. On the one hand, several leading American pharmacokinetisists such as E. R. GARRETT, J. G. WAGNER, L. Z. BENET, M. GIBALDI, and others organized a series of seminars mainly in the German speaking countries, which greatly contributed to a better understanding of modern pharmacokinetics. On the other hand many young European scientists had the opportunity to work in leading pharmacokinetic centers in the United States. In addition, under the pressure of modern drug regulation several pharmacokinetic research centers were established in pharmaceutical firms and one of the worlds leading pharmacokinetic research teams developed at the University of Nijmegen under the leadership of the pharmacologist A. VAN ROSSUM.

How about future trends in pharmacokinetics? In the opinion of the author the following topics appear of immediate interest:

1. Most pharmacokinetic experiments of the past have been conducted using healthy volunteers. This is reasonable in order to establish reliable base-lines. However, in the daily practice drugs are administered to sick patients. Therefore the question has to be answered how disease states and other individual variables influence pharmacokinetics.

2. The starting point of KRUEGER-THIEMER'S work was the elucidation of the correlations between molecular structure and physico-chemical parameters of the drug on the one hand and its pharmacokinetic and pharmacodynamic characteristics on the other. The solution of this problem would greatly improve the predictive power of pharmacokinetics and would contribute to the development of better drugs. The work of J. K. SEYDEL (18) and others is a contribution to this end.

3. Most present-day pharmacokinetic models are of an abstract nature without biological meaning. Their biological interpretation is an urgent problem.

4. We all agree with C. DOLLERY who stated that pharmacokinetics is the servant rather than the master of therapeutics. In this context a better understanding of the relations between pharmacokinetics and pharmacodynamics is desirable. The theoretical bases to solve this problems can be found in the work of E. R. GARRET and G. LEVY and in an impressing volume recently published by A. VAN ROSSUM entitled «Kinetics of Drug Action» (17) a book testifying convincingly to the remarkable progress of pharmacokinetic thinking in continental Europe.

5. The development of pharmacokinetics in its early days was mainly an intuitive process. In contrast, during recent years the development of the discipline was characterized by the introduction of highly sophisticated algorithms and computer technology. The inherent danger of this development is an unsurmountable intellectual gap between the servant and its master, i.e. between pharmacokinetics and clinical medicine. Professional pharmacokineticists should therefore undertake every effort to find a language which is both of clinically sufficient accuracy and understandable to the physician. On the other hand, physicians should consider the following words of the philosopher Sir BERTRAND RUSSELL emphasizing the necessity of sophistication in any highly developed scientific discipline: «A certain freedom from the strictures of sustained formality tends to promote the development

of a discipline in its early stage, even if this means the risk of a certain amount of error. Nevertheless, there comes a time in the development of any field when standards of rigor have to be tightened.»

Aided by the Swiss National Science Foundation

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Gladtke/Heimann (Hrsg.), Pharmacokinetics
Gustav Fischer Verlag · Stuttgart · New York · 1980

The Use of Stable Isotopes in Clinical Pharmacokinetics

H. J. DENGLER, M. EICHELBAUM, and G. VON UNRUH

Whereas in *biochemistry* metabolic pathways consisting of both synthesis and metabolic transformation of a given substance are of concern, in *xenobiotics* it is the fate of a foreign compound administered to the organism which has to be discovered in all its details. In this context «foreign» means that a chemical is synthesized either by human skill in the laboratory or produced in a living organism different from that to which it is administered. Most drugs therefore are typical examples of xenobiotics or «foreign substances». Beside the quantification of the unchanged compound, for instance the drug, in the various body fluids, one of the main problems involved is to identify a molecule as being derived from the molecular species originally incorporated into the body. It is for that purpose that tagging a label to the substance administered offers enormous advantages as the recovery of that label in a chemically different substance identifies it as a metabolite provided that certain experimental precautions have been observed.

There is no doubt that during the last two decades the use of drugs labelled with radioisotopes, mostly ^{3}H, ^{14}C and ^{35}S, was most successful and added tremendously to our knowledge of drug metabolism and – probably to a lesser extent – to pharmacokinetics. As pointed out earlier (Dengler, 1969) radioisotopes have particularly two properties which predispose them for these studies, 1. the unspecificity and 2. the high sensitivity of the analytical detection. In addition, the high specific activity which can be achieved nowadays and the most powerful instrumentation (scintillation spectrometry) permitting studies with very low doses and therefore practically no toxicology problem rendered them almost ideal tools for the study of drug disposition in *in vitro* systems. In clinical studies, however, the main disadvantage is the possible risk of radiation. Even worse is the great difficulty to explain it properly to the persons involved in such studies, let them be healthy volunteers or patients in order to obtain not only informed but understanding consent. In many countries legislation aimed to protect the patient against the unwanted side effects of radiation has definitely restricted the use of radioactive isotopes in human studies. Lately the argument of the unrivalled analytical sensitivity has also been challenged as for instance radioimmunoassay and receptor binding assay opened up similar ranges of detection limit formerly accessible to radioisotope techniques only. It is also often not understood that the use of radiolabelled drugs in pharmacokinetic studies makes by no means the development of specific analytical methods unnecessary (with all the requirements regarding specificity, accuracy, etc.) as the so-called «^{14}C- and ^{3}H-kinetics» can never replace information on individual chemical entities, either the unchanged drug or a metabolite. Therefore, even allowing the final detection method being simple and sensitive the specificity has to be ensured by foregoing separation steps.