Commentary

Landmark Publications in the Pharmaceutical Sciences: The Backstory
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Benet L Z and Galeazzi R L: Noncompartmental Determination of the Steady-State Volume of Distribution, *J Pharm Sci* 68, 1071–1074, 1979—the Backstory

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In 1967, as a young assistant professor at Washington State University, I received a call from Dr. Arnold Marcus, then the chair of the Industrial Pharmaceutical Technology Section of the Academy of Pharmaceutical Sciences, who asked if I would serve as a faculty member in the academy's January 1968 Arden House Conference on Pharmacokinetics. I answered, "Arnold, I don't know any pharmacokinetics. I never took a course in pharmacokinetics and the little reading that I've done in the pharmacokinetics literature is just cursory." Arnold replied that he was looking for someone with a good mathematical background to critique the approaches then being proposed in the field of pharmacokinetics and to lead the discussion during the last session of the course summarizing the positives and negatives of the approaches being employed, while attempting to hypothesize the future directions of the field. I accepted Arnold's offer and in late January 1968 traveled from Pullman, Washington to Harriman, New York with a suitcase full of *Journal of Pharmaceutical Sciences* issues containing pharmacokinetic papers. Obviously this was prior to copy machines and baggage fees. I felt that I learned more about pharmacokinetics than any of the attendees at the conference, and my general

impression at that time was that the discipline as practiced was much too complicated mathematically (unnecessarily) to have a major impact on drug therapy. In general the pharmacokinetic parameters in use at that time appeared to have no relationship with useful physiological and pathological processes that would allow a clinician to know how to adjust dosing under the various conditions that a patient would experience.

As a result of my participation in the 1968 Arden House Conference on Pharmacokinetics, I began a more than 40-year, and ongoing, quest to simplify the pharmacokinetic approaches and make them relevant to patient care and drug development. One year later, I published, together with graduate student Robert Ronfeld, my first paper in the field "Volume Terms in Pharmacokinetics" (1). Then, in 1971, I published a short note on the use of the general partial fraction theorem for obtaining inverse Laplace transforms in pharmacokinetic analysis (2) not realizing that Rescigno and Segre had published the use of Laplace transforms in their text in Italian in 1961, which was translated into English in 1966 (3).

Prior to the 1970s, many papers were published in the pharmacokinetic literature that presented in excruciating detail the derivation of the equations used to fit plasma/blood/urine concentration time curves. In 1972 I published "General Treatment of Linear Mammillary Models with Elimination from Any Compartment as Used in Pharmacokinetics" (4), which obviated all of these derivations and allowed investigators in one step utilizing

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input and disposition functions to write the Laplace transform of the pharmacokinetic equation and in a second step solve the equation in terms of concentration time parameters. In this 1972 paper, I did recognize the Rescigno and Segre book (3) and noted that they had authored, particularly with respect to disposition characteristics, the use of transfer functions in the derivation of pharmacokinetic models. Thus, by 1972 the mathematics of pharmacokinetics was greatly simplified. However, the use of pharmacokinetics in clinical practice and its application to drug dosing had not improved. In fact, the field became even more complicated in 1970 when chemical engineers, Ken Bischoff, Bob Dedrick and Dan Zaharko, published the first physiologically based pharmacokinetic model for the drug methotrexate (5).

In my opinion, the big breakthrough in the applicability of pharmacokinetics to drug dosing and patient care came with the publication in 1973 of "Clearance Concepts in Pharmacokinetics" (6). I have recently reviewed this development of clearance (7) in the 2010 dedicatory issue of the Journal of Pharmacokinetics and Pharmacodynamics in celebration of Professor Malcolm Rowland's 70th birthday. Clearance concepts allowed the field to develop a basic understanding and to make predictions as to how pathological and physiological changes would influence drug kinetics and drug dosing. It provided the quantitative rationale for clinical pharmacology. In addition, clearance was the first noncompartmental parameter. No pharmacokinetic model was required, as clearance could be simply calculated as the ratio of dose to the measured area under the curve.

Following publication of the clearance paper and its subsequent elaboration by Wilkinson and Shand (8), I began thinking of pharmacokinetics as having two purposes: (a) as a tool in therapeutics and (b) as a tool in defining drug disposition. Together with bioavailability, clearance served as a tool in therapeutics to define the dosing rate. As a tool in defining drug disposition, clearance was the measure of the body's ability to eliminate drug. Until the elaboration of clearance concepts in pharmacokinetics (6,8), half-life had always been considered the parameter that characterized the body's ability to eliminate drug. This difference in clearance and half-life was brought home by a 1977 publication (9) investigating longitudinally the clearance of intravenous tolbutamide in patients while they experienced acute hepatic disease and after they recovered. Surprisingly, total clearance increased for this hepatically

eliminated drug during the acute viral hepatitis evaluation, although unbound clearance was unchanged as a function of disease. Therefore, the authors recommended no change in tolbutamide dosing in acute viral hepatitis. Since total volume of distribution was also independent of disease, half-life became shorter together with the increased clearance during viral hepatitis. However, unbound volume of distribution increased during viral hepatitis and we recognized that volume of distribution was having an effect on half-life, independent of clearance.

At this time two competing, whole-body volume of distribution measures was generally employed. The first, V_{area} or V_{β} , was reported for all drugs since it could be calculated so easily. Following intravenous dosing, V_{area} was calculated as drug clearance (CL) divided by the terminal rate constant (in those days in terms of a two compartment model defined as β). For oral dosing where bioavailability (F) must be considered, CL/F divided by the terminal rate constant would yield V_{area}/F . The other whole-body volume term being considered in those days was the volume of distribution steady state (V_{ss}), which had to be defined in terms of the distribution rate constants in a multicompartment pharmacokinetic model. In therapeutics, volume of distribution will define the space available in the body in which the drug may distribute. In a disease state, it would be useful to know if drug distribution had changed. Our laboratory recognized that V_{area} would usually change when clearance changed. We hypothesized that V_{ss} would be independent of elimination processes and suggested that V_{ss} was the more appropriate parameter to determine (10). Then for the drug cefamandole, we compared the kinetics of this primarily renal eliminated cephalosporin in uremic patients undergoing hemodialysis with health volunteers (10,11). We showed that although the total body clearance of cefamandole decreased markedly in the renal failure patients, V_{ss} did not change. That is, the disease state had no effect on the distribution characteristics of the antibiotic. In contrast V_{area} did change and was not useful in defining the space available in the body in which the drug may distribute as a function of disease states. Now knowing that V_{ss} was the distribution parameter that we wished to determine for all drugs, we began to search for a noncompartmental method to allow us to determine this pharmacokinetic parameter.

During the first 6 months of 1976, I took a sabbatical at the Kantonsspital at the University of Basel in Basel, Switzerland in the laboratory of Professor Luzius Dettli. One afternoon in late

May of 1976, I received a telephone call from Dr. Renato Galeazzi, a former clinical pharmacology fellow at UCSF, who had returned to the University of Bern. Renato had read a paper in the *Journal of Clinical Endocrinology and Metabolism* by Oppenheimer et al. entitled "Determination of Common Parameters of Iodothyronine Metabolism and Distribution in Man by Noncompartmental Analysis" (12). Renato wanted to know what was this volume term that Oppenheimer and colleagues had calculated with respect to the pharmacokinetic theory he had learned at UCSF. Oppenheimer et al. had developed their approach from indicator dilution studies commonly employed in medicine using mathematical methodology based on the Stewart–Hamilton theorems for flow and volume (13,14). Perl and Samuel (15) generalized these theorems to the case of multiple input channels with partially labeled input in a study of the input rate and trace mass of body cholesterol. Oppenheimer et al. (12,16) adapted these principles to the calculation of conventionally used parameters in the study of iodothyronine metabolism and distribution. As Renato and I reviewed the publications, we recognized that this noncompartmental parameter in the Oppenheimer et al. papers (12,16) was in fact the pharmacokinetic volume of distribution steady state. I wrote to Professor Oppenheimer at the Albert Einstein College of Medicine and asked him whether he recognized that the volume term that he was calculating with his indicator dilution studies was in fact the pharmacokinetic parameter volume of distribution steady state, and if he did not recognize this, would he and his colleagues be willing for Renato and I to publish a paper showing that the noncompartmental methods utilized in indicator dilution studies would allow the determination of V_{ss} with the proviso that we would reference his work and that of his predecessors using indicator dilution studies. Dr. Oppenheimer graciously replied that he had been following classical indicator dilution techniques and applying them to endocrinology and that he was unaware of the various pharmacokinetic parameters and had no objection to our publishing our paper.

Thus, since our finding was a recognition that work in another field had relevance to the pharmacokinetic V_{ss} , we published our work as a short letter to the editor in the *Journal of Pharmaceutical Sciences* that comprised less than three printed pages (17). Yet, the paper became very influential and according to ISI is the most cited of the more than 18,000 papers to appear in

the *Journal of Pharmaceutical Sciences* since 1965. What are the reasons for this very high citation rate? First, following recognition of the importance of the noncompartmental parameter clearance (6–8), workers in the field appreciated the value of a noncompartmental method to determine the volume of distribution steady state. However, probably of more relevance was the fact that in our paper (17), we presented for the first time in the pharmacokinetic literature the interrelationship between clearance, volume of distribution steady state and mean residence time. Mean residence time (MRT) is a measure of the average time a drug molecule remains in the total body.

We were not the first to introduce mean residence time concepts into pharmacokinetics. This occurred a year prior to our 1979 publication in a paper by Yamaoka et al. (18) entitled "Statistical Moments in Pharmacokinetics." However, as noted above, we were the first to recognize that the product of the inverse of MRT and the steady-state volume of distribution, V_{ss} , yields clearance, and that these are time and dose invariant parameters for drugs exhibiting linear disposition kinetics, where elimination only occurs from the measured, central compartment, as universally utilized in pharmacokinetic analyses.

I continue to pursue understanding and simplifying pharmacokinetic approaches. Recently I have been investigating the calculation of accumulation parameters upon multiple dosing (19,20), with the recognition that much of the literature and text book approaches on this topic will not provide useful predictions. This is due to the fact that all of the earlier theory is based on half-life calculations for intravenous dosed drugs following one-compartment body models.

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