“Physiological spaces and multicompartmental pharmacokinetic models”: Fundamentals that pharmacokinetics textbooks do not tell you

Dong-Seok Yim*

Department of Clinical Pharmacology and Therapeutics, Seoul St. Mary’s Hospital, PIPET (Pharmacometrics Institute for Practical Education and Training), College of Medicine, The Catholic University of Korea, Seoul 06591, Korea

*Correspondence: D. S. Yim; Tel: +82-2-2258-7327, Fax: +82-2-2258-7876, E-mail: yimds@catholic.ac.kr

In this issue of TCP, you can see Dr. Atkinson’s article[1] on multicompartment pharmacokinetic (PK) models (tutorial section). His tutorial mentions historical, ghoulish, research efforts to measure fluid volumes in the human body and his pivotal work to reveal the physiological meaning of the PK parameters in multicompartment models. Unfortunately, most of modern pharmacokinetics textbooks do not mention the fundamental physiological relevance of PK parameters at all. However, it is evident that they cannot but reflect the human physiology that is involved when the body deals with a drug. Thus, learning the physiological meanings of PK parameters is essential to an understanding of the foundation of pharmacokinetics. As pharmacology initially branched off from physiology, fundamental PK concepts were devised by physiologists. Thus, the person who first proposed the concept of a multicompartment PK model that incorporated organ blood flow in 1937 was a Swedish physiologist Torsten Teorell.[2] It was much later that the term ‘pharmacokinetics’ was coined by Dost in 1953.[2]

Preparing for a postgraduate course using the ‘Principles of Clinical Pharmacology’ as its textbook a couple of years ago, I had the chance for the first time to read Atkinson’s crucial papers on drug distribution that were cited as references in the book. Reading his intellectually stimulating papers was a pleasure to me. At the same time, I was curious as to why this fundamental knowledge is not familiar to my colleagues, much less to graduate students. This commentary was written in order to discuss the physiological principles introduced in his tutorial so that young clinical pharmacologists may not overlook the chance to deepen their understanding of multicompartment PK: especially, the historical background and physiological implication of the concept of intercompartmental clearance (CL). Modern pharmacokinetics textbooks do not explain where the CL came from. Therein, it is presented as nothing more than a variable generated from the first-order movement of drug molecules between neighboring compartments.

Using inulin and urea as relatively small-sized molecules, he and his colleagues were able to define, initially in dogs, three-compartment models for these compounds in which the compartments corresponded to physiologic spaces.[3] This not only confirmed that transfer from the central intravascular compartment to interstitial fluid was kinetically heterogeneous, but the CL estimated from these models was used together with the free water diffusion coefficients of urea and inulin (measured in vitro) were put into the Renkin equation (below) to back-calculate the blood flow values (Q) for the two peripheral compartments. It was further shown that the sum of blood flows to two peripheral compartments approximated independently measured cardiac output (mean 97%, range: 83-113%). A critical assumption, supported by the studies of other investigators, was that the transcapillary exchange of urea and inulin was not restricted, so that the ratio of their free water diffusion coefficients was identical to the ratios of their permeability coefficient-surface area products (P/S) in the Renkin equation.[3]

\[
CL_i = Q \left(1 - e^{-P\cdotS/Q}\right)
\]

The above equation was used by Renkin to depict the distribution rate of solutes across an individual capillary in relation to capillary permeability (P), surface area (S) and the blood flow (Q). Although Renkin equations could be developed for each organ in PBPK models, the current convention is to simply assume that transfer from the intravascular space into an organ is only determined by organ blood flow. When it is applied to the whole body, the sum of blood flows to each compartment must equal cardiac output, as in Atkinson’s report.[3] The Renkin equation also implies that the sum of intercompartmental CL cannot be higher than cardiac output. Similarly, hepatic CL cannot surpass the hepatic blood flow, a well-known fact.

By now, readers will have realized how pivotal the Renkin equation is in explaining drug distribution within the framework of human physiology. This equation was originally conceptualized in 1909 by Christian Bohr[4] (Fig. 1), a Danish physiologist who first characterized pulmonary dead space, to
Commentary on Atkinson’s tutorial

Christian Bohr

First equations for O₂ diffusion between alveoli and pulmonary capillaries (1909)

Seymour Kety

Equations for time-course of blood and organ concentrations of inert gas (1951)

Eugene Renkin

Equation for CL presented: first application to pharmacokinetics in animal (1955)

Arthur J. Atkinson, Jr.

Renkin equation re-derived: applied to human pharmacokinetic data (1981)

Model pulmonary gas diffusion. Bohr was then the proponent of the “oxygen secretion theory” that alveoli secret O₂ to pulmonary capillaries. This is remembered as one of the most colorful controversies in physiology in the first decade of the 20th century. [5] In his 1909 paper, he called it the ‘specific function’ of the lung. Oddly enough, in the same article emphasizing the O₂ secretion theory, he demonstrated the mathematical steps needed to calculate the diffusion of O₂ to the pulmonary capillary, now known as the “Bohr integration.”[5]

In 1951, Seymour Kety, presented equations to describe inert gas diffusion between blood and organs based upon Bohr’s researches.[6] When you read his paper, you may easily recognize that his equations for ‘saturation’ and ‘desaturation’ of tissue gas concentrations are fundamentally identical to the equation for continuous infusion, \(C_e^{out} \cdot (1-e^{-kt})\), and that for first-order elimination, \(C_e \cdot e^{-kt}\), used in modern pharmacokinetics every day. At that time, Kety also developed the first quantitative and reproducible method for measuring human cerebral blood flow. His research career was further expanded to neuroscience and he is currently credited as the father of neuroscience and modern biological psychiatry.[7]

Four years after Kety’s report, Eugene Renkin published the equation in the currently known form, \(CL_i = Q \cdot (1 - e^{-P \cdot S/Q})\).[8] Renkin used an amputated cat hindleg connected to a perfusion device to measure the concentrations of antipyrine, urea, and sucrose in arterial and venous blood. This marks the first time that the permeability-flow equation, or Renkin equation, was used for a drug PK study. Unfortunately, the derivation of his equation \(CL_i = Q \cdot (1 - e^{-P \cdot S/Q})\) was not included in his published paper, although it is available by request from the American Documentation Institute.

In 1981, Stec and Atkinson re-derived the Renkin equation and applied it to the multicompartamental model that they used to analyze their human PK data on procainamide and its metabolite, NAPA.[9] In this derivation, they assumed that drug transfers across a capillary wall results in a homogeneous interstitial fluid drug concentration within each compartment, and that the concentration of drug in blood leaving the capillary is equal to the interstitial concentration. (In a personal communication with Atkinson, Renkin commented that their derivation process was a little simpler than the one that he used.) Therefore, the urea and inulin \(CL_i\) to each peripheral compartment essentially reflects a time-delay in the distribution process caused by the transcapillary diffusion of those molecules, in addition to the compartmental blood flow. Microscopic observations and PK studies after partial ablation of splanchnic organs[10] suggest that somatic and some splanchnic capillaries differ in their permeability. This presumably accounts for the kinetic heterogeneity (slow and fast) and differing \(CL_i\)’s in distribution to the interstitial fluid spaces of the two peripheral compartments. In another dog study on PK changes during hemodialysis,[11] the Renkin equation helped Atkinson and his colleagues conclude that blood flow to the slowly equilibrating peripheral compartment, presumably consisting primarily of skeletal muscle supplied by somatic capillaries, decreased by 90%. Thus, adverse reactions such as the intradialytic muscle cramping observed in some patients might be the result of hemodynamic changes from volume stress of hemodialysis.[11]

Thanks to the Renkin equation and clinical pharmacologists who applied it to their studies, insight has been gained into the pathophysiology of muscle cramping. This vivid example illustrates the essential role of clinical pharmacology as a bridge linking basic research to clinical medicine.

Acknowledgements

The author thanks Dr. Atkinson for his precious comments on this manuscript.
Conflict of interest
The author does not have any conflicts of interest to disclose.

References