

# Collaborative Pharmacokinetic–Pharmacodynamic Research for Optimization of Antimicrobial Therapy

Seunghoon Han<sup>1,2</sup>

<sup>1</sup>Department of Pharmacology, and <sup>2</sup>PIPET (Pharmacometrics Institute for Practical Education and Training), College of Medicine, The Catholic University of Korea, Seoul, Korea

The individualization of antimicrobial therapy has long been of major interest to infectious disease physicians [1]. Individualization of dosage regimens includes consideration of the patient's demographics, disease conditions, and pathogenic factors (e.g. microbes and their minimum inhibitory concentration [MIC] against antimicrobials) to ensure efficacy and avoid significant toxicity [1, 2]. In addition, precise use of antimicrobial agents, with regard to indication and treatment duration, may reduce the development of resistant microbes. To establish individualized therapeutic strategies, it is essential to characterize and understand the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents in various clinical scenarios [2-4]. Thus, most clinicians treating infectious diseases are more familiar with the PK–PD concept of antimicrobial agents and studies have primarily focused on these issues, compared to other areas of pharmacotherapy.

However, our current knowledge of each agent's PK–PD in the Korean population is limited unfortunately, particularly for vulnerable populations (e.g. children, the elderly and severely ill patients) [5]. Many current drug labels and prescription guidelines used in Korea were established based on clinical

evidence from the West or Japan, where population demographics and clinical characteristics that influence PK characteristics may differ from those in Korea [6, 7]. Moreover, the PK–PD properties and recommended dosage regimens for each agent are characterized for only a few indications and pathogens, so the application for many clinical usages is dependent upon the clinician's experience. Thus, it is clear that additional clinical PK–PD studies, which are efficiently designed with regard to both sampling and data analysis, should be initiated within the Korean population toward a goal of improving antimicrobial therapies with Korean-specific dosage regimens.

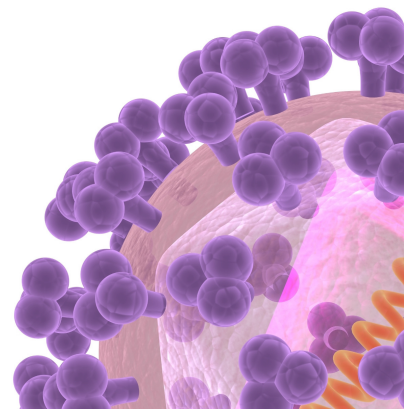
In this issue of *Infection & Chemotherapy*, Kim *et al.* [8] present an example of patient-based PK research using mixed-effects modeling techniques. Based on the author's prior experience with similar designs, the establishment of a multidisciplinary research team should be considered a critical precondition for conducting successful collaborative research. From the study design to the interpretation of results, both clinical and pharmacological aspects of antimicrobial therapy should be considered together. Since participant enrollment and

**Corresponding Author :** Seunghoon Han, MD, PhD  
Department of Pharmacology, College of Medicine, The Catholic University of Korea,  
222 Banpo-daero, Seocho-gu, Seoul 06591, Korea  
Tel: +82 2 2258 7326; Fax: +82 2 2258 7876  
E-mail: waystolove@catholic.ac.kr

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data acquisition are non-trivial challenges, study goals should be clearly defined according to the clinical needs. In addition, a minimalist design should be used to achieve the study objectives, along with pharmacologic knowledge on procedures (e.g. blood sampling) that may cause participant discomfort. During the period of data collection, continuous feedback between clinicians and clinical pharmacologists will allow reevaluation of the study design, such as whether it is applicable in the current clinical setting and whether resulting data are consistent with the study goals. Timely modifications of the study design (e.g. type of data obtained, target population and/or sampling strategies) may improve the likelihood of producing clinically meaningful results. Accordingly, data interpretation should focus on answering specific questions about antimicrobial therapy such as, 'Should the dose be reduced for patients with estimated glomerular filtration rates less than 60 mL/min/1.73 m<sup>2</sup> and if so, by what amount?'. Active and productive discussions throughout the research process are the key to understanding each other's areas of expertise and enabling the development of clinically applicable outcomes.

In respect to both minimizing patient risk and quantitative interpretation, mixed-effects modeling and simulation should be an essential element of PK-PD research. Mixed-effects modeling is a powerful technique for interpreting sparse data that minimizes the number of samples needed to achieve PK objectives [9]. In contrast, traditional analytic methods such as non-compartmental analysis require dense sampling for which each individual represents a single observation toward summarizing drug concentration; this is inadequate for fulfilling current clinical needs. In addition, by incorporating explainable (*i.e.* covariates) or unexplainable between-subject variabilities (*i.e.* random effects), some models suffice for suggesting adequate dosing regimens for patient-specific conditions. Once an acceptable model is built, the input of various factors such as patients' demographics (e.g. weight, age) and disease status (e.g. estimated renal function, sepsis, and edema) to the model may simulate the expected drug concentrations based on time after a specific dosage. Thus, the simulated drug concentration level can be assessed along with MIC level using known efficacy parameters (the clinically observable PD parameter, e.g. time>MIC, area under the time-free concentration curve/MIC) to calculate the probability of target attainment. Various dosage regimens (*i.e.* dosing amounts and frequencies) may also be compared in this context. Through such procedures, PK study outcomes in actual patients with various characteristics can become a practical guide for clinicians toward determining dosage regimens. In

addition, model and parameter values in the therapeutic drug monitoring algorithm can be replaced with Korean population-specific information, improving predicted concentration accuracy. Thus, the modeling-simulation technique can be optimized by quantitatively assessing PK (and even PD) characteristics within the Korean population, including the explainable versus random variability within that population.

Optimization of antimicrobial therapy against multidrug-resistant bacteria, or reusing old antibiotics for specific infections, is a rapidly growing issue in the field of infectious diseases. As is the case in many clinical disciplines, in order to provide the best treatment to our patients we must generate the evidence-basis that will support clinical practice through collaborative and quantitative PK-PD studies. To maximize the impact of such efforts, with limited time and resources, and to overcome the limits of current sporadic and case-specific research, a nationwide approach should be prioritized. This approach may include drug type, patient characteristics, and pathogen specifics. Using systematic research to establish practical and evidence-based practice guidelines, we may solve our current problem. In addition, through such national prioritization and experience, we may also establish a platform to manage problems that may arise in the future.

## Conflicts of Interest

No conflicts of interest.

## ORCID

Seunghoon Han

<http://orcid.org/0000-0002-9976-5120>

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