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Review

A Methodological Review on the Pharmacokinetic/Pharmacodynamic Integration of Antibacterial Drugs

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Abstract: Inappropriate application of antimicrobial agents can result in resistance by bacteria to drugs and changes in bacterial ecology. In particular, the emergence of multi-drug resistant bacteria seriously affects the antibacterial efficacy of drugs, which threatens the health and lives of humans and animals. Pharmacokinetic/Pharmacodynamic (PK/PD) models can be used to analyze the relationship between PK and PD data and the antibacterial effect. PK/PD models provide valuable guidance for optimization of dosage regimens, development of new drugs, setting of susceptibility breakpoints, and analyses of resistant mutants. The main models of PK/PD integration are *in vitro* PK/PD, *ex vivo* PK/PD, and *in vivo* PK/PD. Each of these models has its own advantages and disadvantages. Hence, knowing how to choose the appropriate PK/PD model has a huge influence on obtaining accurate PK/PD data. In this review, we describe the commonly used PK/PD methods. In this way, we provide a reference for optimizing drug regimens and preventing and controlling drug-resistant bacterial infections.

Keywords: *Antibacterial drugs, PK/PD integration model, Multi-drug resistance, Dosage regimen optimization, In vivo PK/PD model*

Antibakteriyel İlaçların Farmakokinetik/Farmakodinamik Entegrasyonu Üzerine Metodolojik Bir İnceleme

Öz: Antimikrobiyal ajanların uygun olmayan şekillerde kullanımı, bakterilerin ilaçlara direncine ve bakteri ekolojisinde değişikliklere neden olabilir. Özellikle çoklu ilaca dirençli bakterilerin ortaya çıkması, ilaçların antibakteriyel etkinliğini ciddi şekilde etkilemekte ve bu durum insan ve hayvanların sağlığını ve yaşamını tehdit etmektedir. Farmakokinetik/Farmakodinamik (PK/PD) modeller, PK ve PD verileri ile antibakteriyel etki arasındaki ilişkiyi analiz etmek için kullanılabilmektedir. PK/PD modelleri, dozaj rejimlerinin optimizasyonu, yeni ilaçların geliştirilmesi, duyarlılık sınır değerlerinin belirlenmesi ve dirençli mutantların analizleri için değerli rehberlik sağlarlar. PK/PD entegrasyonunun temel modelleri *in vitro* PK/PD, *ex vivo* PK/PD ve *in vivo* PK/PD'dir. Bu modellerin her birinin kendine göre avantajları ve dezavantajları vardır. Bu nedenle, uygun PK/PD modelinin nasıl seçileceğinin bilinmesi, doğru PK/PD verilerinin elde edilmesinde büyük bir etkiye sahiptir. Bu derlemede, yaygın olarak kullanılan PK/PD yöntemlerini açıklamaktayız. Böylelikle, ilaç rejimlerini optimize etmek ve ilaca dirençli bakteriyel enfeksiyonları önlemek ve kontrol etmek için bir referans sağlamaktayız.

Anahtar sözcükler: *Antibakteriyel ilaçlar, PK/PD entegrasyon modeli, Çoklu ilaç direnci, Dozaj rejimi optimizasyonu, In vivo PK/PD modeli*

Introduction

With the large-scale and intensive development of the animal-breeding industry, there is a risk of disease outbreaks. Hence, antimicrobial drugs are used to prevent and treat animal infections. However, inappropriate application of antimicrobial agents (e.g., inappropriate treatment course or selection of antimicrobial) can result in resistance by bacteria to drugs and changes in bacterial ecology. In particular, the emergence of multi-drug resistant bacteria

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seriously affects the antibacterial efficacy of drugs, which threatens the health and lives of humans and animals. Therefore, solving these problems is extremely important [1-3].

The most common approaches to resolve drug resistance in bacteria is to develop new veterinary drugs and optimize drug regimens. However, the speed of research and development of new drugs cannot keep pace with the mutation rate of drug-resistant bacteria. Therefore, optimization of drug regimens is a practical and reliable method to deal with the threat of drug-resistant bacteria.

An integrated pharmacokinetic/pharmacodynamic (PK/PD) model can be used to evaluate the interaction between drugs, hosts, and pathogens. This can be achieved by analyzing the relationship between PK, PD, and PK/PD parameters and the antibacterial effect, as well as predicting the values needed to elicit different antibacterial effects. Hence, PK/PD is an important method for optimizing dosage regimens [4-6].

At present, PK/PD integration model were classified to *in vitro* PK/PD, *ex vivo* PK/PD, and *in vivo* PK/PD, such as *in vitro* peristaltic model, *ex vivo* time-kill model, and *in vivo* tissue cage (TC) model. Each of these models has advantages and disadvantages. Hence, knowing how to choose an appropriate PK/PD model has a major influence on the obtained PK/PD data.

In this review, we introduced the commonly applied PK/PD methods and we this review can provide a reference for optimizing drug regimens and preventing and controlling drug-resistant bacterial infection.

Basic Concepts of PK

PK is the study of the absorption, distribution, metabolism, and elimination of drugs in the host. The main PK parameters are maximum concentration of a drug in plasma (C_{max}), time to reach C_{max} of a drug in plasma (T_{max}), time the drug concentration needs to decrease by 50% (elimination half-life ($T_{1/2\beta}$), area under the concentration-time curve (AUC), the volume of drug in the body cleared per unit time (clearance), the proportion of a drug which enters the circulation when introduced into the body and is able to have an active effect (bioavailability).

Basic Concepts of PD

PD is the study of the biochemical and physiologic effects of drugs. PD parameters describe the action of the drug upon the body and pathogens.

In terms of antibiotic therapy, the important parameters are the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), mutant prevention concentration (MPC), post-antibacterial effect (PAE), growth rate, and kill rate.

The MIC is the lowest concentration of an antimicrobial agent that will inhibit the visible growth of a micro-organism after overnight incubation. The MBC is the lowest concentration of a antimicrobial drug that will prevent the growth of an organism. The MPC can be defined as the MIC of the least susceptible single-step mutant. The PAE refers to a period of time after complete removal of an antibiotic during in which there is no growth of the target organism. The growth rate is the speed at which the number of organisms in a population increases. The kill rate is defined as the reduction of organisms numbers after interacted with antibacterials.

Basic Concepts of PK/PD Models

A PK/PD model can guide dosage regimens using PK/PD parameters which connect PK data to PD data.

The commonly applied PK/PD indices are AUC/MIC, C_{max}/MIC, %T > MIC (the percentage of drug concentration above the MIC during dosing intervals), AUC/MPC, C_{max}/MPC, and %T > MPC (the percentage of drug concentration above the MPC during dosing intervals) [7,8].

Usually, the antibacterial effect (E) is expressed by the clinical effect before and after treatment, or the change of the number of bacteria (colony forming units, CFU). In general, according to the change of bacteria population, the antibacterial effect is divided into a bacteriostatic effect (E = 0), bactericidal effect (E = -3), and eradication effect (E ≥ -4). PK/PD integration aims to establish the concentration-time-effect relationship by analyzing the relationship between PK/PD parameters and E by linear or sigmoidal formulae, and then calculating PK/PD indices for achieving different antibacterial effects.

According to the best-fitting PK/PD parameters to E, drugs are often classified into three categories [9]: (i) concentration-dependent drugs; (ii) time-dependent drugs with long PAE; (iii) time-dependent drugs with short PAE *(Table 1)*.

The antibacterial activity of concentration-dependent drugs is closely related to the drug concentration exposed to bacteria. The drug regimen requires a high dose to make the drug concentration in tissue or plasma 10-12-times higher than the MIC [10].

The antibacterial activity of time-dependent drugs is dependent upon the percentage of time the drug concentration is above the MIC during the dosing interval. Therefore, shortening the dosing interval and increasing the administration duration can ensure the required percentage of drug concentration above the MIC reaches a bactericidal effect (%T> MIC ≥ 50%) [11]. PK/PD parameters can also reflect the influence of a drug

Table 1. Classification of antibacterial drugs based on PK/PD indices			
Classification	**Antibacterial Drugs**	**PK/PD Indices**	**Activity**
Concentration-dependent	Aminoglycosides, fluoroquinolones amphotericin B, metronidazole, colistin, rifamycins	C_{max}/MIC or AUC/MIC	Primarily bactericidal
Time-dependent with short PAE	Macrolides with short half-life (erythromycin), penicillins, carbapenems, cephalosporins	%T > MIC	Primarily bactericidal
Time-dependent with prolonged PAE	Macrolides with long half-life (azithromycin, tulathromycin), clindamycin, ketolides	AUC/MIC or %T > MIC	Primarily bacteriostatic
Co-dependent	Tetracycline Glycopeptides	AUC/MIC or %T > MIC	Bacteriostatic Bactericidal

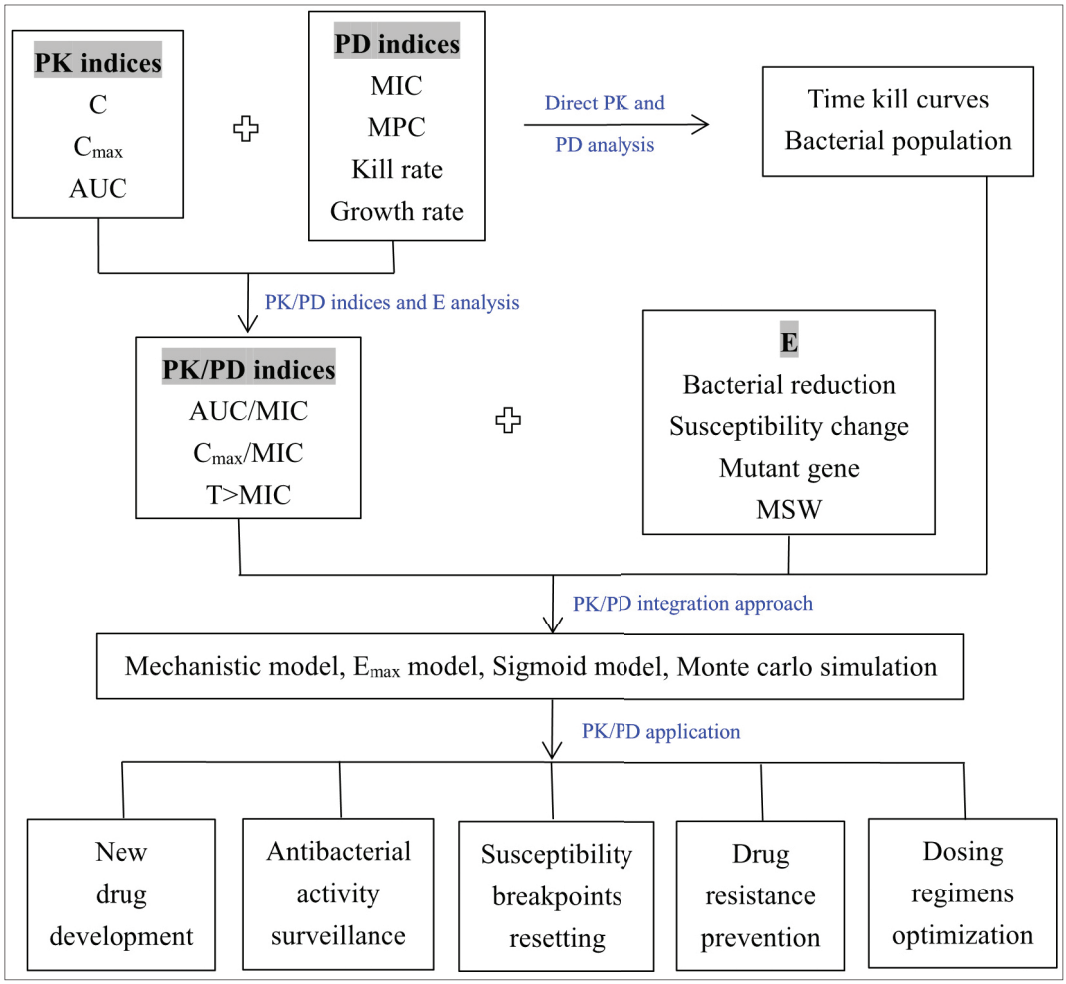

Fig 1. Process and application of PK/PD integration

regimen on the resistance of mutant bacteria. For example, the analysis of relationships between mutation frequency and PK/PD parameters based on the MPC can keep the PK/PD indices away from the resistant mutation concentration when designing the drug regimen [12]. After Monte Carlo simulation, the obtained PK/PD breakpoint (CO_{PD}) is combined to the epidemiological breakpoint (E_{coff}) or wild-type breakpoint (COWT), and clinical tipping point (CO_{CL}) to reset the susceptibility breakpoint for monitoring of bacterial sensitivity [13,14]. PK/PD integration had been used widely in several fields, and the general process and application is shown in *Fig. 1*. The commonly applied methods for PK/PD study are listed in *Table 2*.

In Vitro PK/PD Models

Static Concentration Time-Kill Curves (SCTKCs)

A SCTKC is the basic method to study the antibacterial activity of drugs and the cornerstone for developing new antibacterial agents and optimizing dose regimens. A SCTKC can be acquired by counting the bacterial population in different drug concentrations (based on

Table 2. *Classification, methods, and application of PK/PD models*

Basic Classification	Common Methods	Application
In vitro PK/PD model	Static concentration time-kill curves	Tube model
	Dynamic concentration time-kill curves	Peristaltic-pump model, Hollow-fiber model
Ex vivo PK/PD model	Tissue-cage model	Pig, calf, rabbit, sheep, goat, camel
	Serum	Most animals
	Other body fluids	Uterine fluid, ileum content, pulmonary epithelial lining fluid
In vivo PK/PD model	Animal-organ infection model	Murine, duck, chicken
	Tissue-cage infection model	Pig, calf, rabbit
	Microdialysis-based PK/PD model	Mice

different folds of the MIC) at different time points [15]. This method can directly reveal the kill rate, antibacterial effect, and recovery of bacteria. A traditional SCTKC related only to the MIC cannot reflect the detail of antibacterial activities. Therefore, two optimized SCTKC methods are applied commonly to study PK/PD integration.

One model is the kill rate-based SCTKC [16-18]. The kill rate is a PD parameter (containing the MIC and SCTKC) which represents the difference between the growth rate and death rate. The value of the kill rate is the slope of a SCTKC during different periods. This model directly reflects the antibacterial characteristic of drugs, and also can divide drugs into concentration-dependent and time-dependent types. Ferro et al.[16] studied the relationship between antibacterial concentrations and the kill rate of several antibiotics against two types of rapidly growing mycobacteria by sigmoid E_{max} fitting. The highest kill rates appeared at 24-27 h for *Mycobacterium abscessus*, and the highest E_{max} was 0.0427/h, 0.0231/h, and 0.0142/h for amikacin, clarithromycin, and cefoxitin, respectively. For *Mycobacterium fortuitum*, the highest kill rate appeared at 3-24 h and the highest E_{max} of amikacin was 0.1933/h. Cheah et al.[17] compared the difference between a kill rate-based SCTKC model with a PD metrics-free SCTKC model by analyzing the antibacterial activity of different drugs against six strains of *Acinetobacter baumannii*. They showed that both models had identical dose-response relationships. However, the kill rate-based SCTKC approach exhibited 10-times faster killing by colistin than doripenem, and the bacterial regrowth for colistin was 3-h earlier than that for doripenem. This kill rate-based model could provide a detailed framework to distinguish the antibacterial characteristics of drugs and to optimize dosage regimens. Zhang et al.[18] studied the relationship between the kill rate and doxycycline concentration against *Mycoplasma gallisepticum* at different times. Doxycycline exhibited time-dependent antibacterial activity, and the best-fitting time period was 0-48 h ($R^2 = 0.986$) and the highest kill rate was 0.11/h after PK/PD analyses.

The other model for SCTKC is to add several PD parameters with the MIC for more detailed PK/PD integration [19-21]. Nolting et al.[19] applied a modified E_{max}-model for PK/PD fitting by describing the changes in the *Escherichia coli* population over time under different piperacillin concentrations. In this model, several PD parameters were considered: maximum kill effect (K_{max}), normal growth rate (K), initial bacterial count (N), and delayed bacterial growth constant. Regoes et al.[20] established a PK/PD model comprising four PD parameters: maximum growth rate in a drug-free medium (ψ_{max}); minimum growth rate in a contained drug medium (ψ_{min}); the slope of drug concentration and kill rate (k); MICs for different bacteria (zMIC). After analyzing these PD parameters to drug concentrations (a), they showed that the higher the value of k, the greater was the antibacterial effect as identified by the MIC. Compared with use of MIC alone, this modified SCTKC-based PK/PD model containing multiple PD parameters could guide the design of the dosage regimen in more detail and more precisely.

Dynamic Concentration Time-Kill Curves

Dynamic concentration time-kill curves can simultaneously acquire dynamic antibacterial concentrations and bacterial populations in the same central compartment for PK/PD fitting by simulating the *in vivo* antibacterial PK characteristics [22]. Therefore, this model needs sophisticated equipment. The commonly used models are peristaltic model and hollow-fiber model.

A basic peristaltic model comprises one reserve compartment (containing blank medium), one central compartment (containing the drug, bacteria, and medium), and one elimination compartment (to collect the waste medium) [23]. A peristaltic pump is applied to connect each compartment and make the medium flow in turn to simulate *in vivo* antibacterial PK based on real PK data (e.g., elimination rate constant and absorption rate constant). Vadday et al.[24] applied this model to analyze the PK/PD integration of two candidate spectinamide drugs (1445 and 1599) against *Mycobacterium bovis* BCG. They showed that 1445 exhibited time-dependent antibacterial activity and the best-fit PK/PD parameter was T > MIC ($R^2 = 0.910$). For 1599, concentration-dependent antibacterial activity was

observed, and the best-fit PK/PD parameter was fC_{max}/MIC (R^2 = 0.827). However, this basic model could not prevent the loss of bacteria from the central compartment, which may affect the antibacterial effect for slow-growing bacteria and collection of mutant strains. Hence, a modified model was applied. Meletiadis et al.[25] developed a new peristaltic model for PK/PD integration. They added a dialysis tube made of semipermeable cellulose membrane which could allow free diffusion of the drug, but not bacteria. Zhang et al.[18] applied this modified model to study the PK/PD of doxycycline against *Mycoplasma gallisepticum*, and the value of %T >MIC for 0-$\log_{10}$ reduction, 2-$\log_{10}$ reduction, and 3-$\log_{10}$ reduction was 32.48%, 45.68%, and 54.36%, respectively. Nevertheless, this model also had limitations. For instance, because the pore of the semipermeable cellulose membrane was small, rapid growth of bacteria could block it, which could reduce the interaction between the drug and medium. This phenomenon could result in bacterial death because of a lack of nutrients after long-term incubation. Therefore, suitable pathogens and culture duration are needed for application of this model.

Hollow-fiber models are of small size and sophisticated build quality. The central chamber contains thousands of hollow fiber tubes which can prevent bacterial loss and are often used to simulate antibacterial PK characteristics according to a multi-compartment model [26]. Jacobsson et al.[27] established a hollow-fiber infection model to study the PK/PD of zoliflodacin against susceptible and resistant *Neisseria gonorrhoeae*. A dose <1 g/day could result in treatment failure and lead to drug-resistant mutations *(gyrB)* in bacteria. A dose >2 g/day could eradicate this effect for both strains. Bhagunde et al.[28] applied a hollow-fiber infection model to study the PK/PD of relebactam against imipenem-resistant *Pseudomonas aeruginosa*. *f*AUC/MIC was the best-fitting PK/PD parameter for an antibacterial effect, and *f*AUC/MIC = 7.5 mg·h/L could produce a 2-$\log_{10}$ reduction.

The advantages of these *in vitro* time-kill-related PK/PD models are that they are simple, economical, easy to operate, and reflect antibacterial activity directly. Upon optimization of PD parameters, these models can guide the development of new drugs and optimization of dosage regimens. The disadvantage of these *in vitro* time-kill-related PK/PD models is that the antibacterial effect does not reflect the influence of the host on drugs and pathogens.

Ex Vivo PK/PD Models

Ex vivo PK/PD integration has been employed to study the antibacterial effect (time-kill curves and MIC) of drugs against pathogens in biological matrices (serum, tissue fluid, inflammatory exudates). After drug administration, the matrix is collected at different time points and divided equally into two samples. One sample is applied to detect the drug concentration for PK study. The other sample is added logarithmic pathogenic bacteria for time kill curves study. The PK/PD parameter used is AUC_{24h}/MIC (the antibacterial concentration in the matrix multiplied by 24 h and divided by the MIC).

A serum sample can be collected readily, so has been applied widely for *ex vivo* PK/PD [29,30]. Li et al.[29] studied the *ex vivo* PK/PD of ceftiofur against *Haemophilus parasuis* in porcine serum. They documented that the values of AUC_{24h}/MIC to produce bacteriostatic, bactericidal, and clearance effects were 36.006 h, 71.637 h, and 90.619 h, respectively. Lee et al.[30] studied the *ex vivo* PK/PD of levofloxacin against *Escherichia coli* in broiler chickens. Levofloxacin showed concentration-dependent antibacterial activity against a clinical isolate of *E. coli* (MIC = 0.125 μg/mL) and the predicted dosage to produce a bactericidal response and bacterial eradication was 2.9 mg/kg/day and 4.3 mg/kg/day, respectively. However, the serum samples reflect the changes in drug concentration and cytokines in the systemic circulation, which are different to the changes in target tissues. Hence, it is more rational to use samples collected from target tissues (e.g., tissue fluid).

To acquire tissue fluid, a TC model in animals is used commonly. The TC can be cylindrical or spherical. Cylindrical TCs are smaller, can collect less tissue fluid, and are often used in tight-skin animals (e.g., pigs) [31]. Spherical TCs are larger in volume, can obtain more tissue fluid, and are often used for loose-skin animals (e.g., goats, camels) [32,33]. This model is established by surgery to implant the sterile TC between skin and muscle. About 4-weeks later, granulation tissue surrounds the TC and secretes tissue fluid into the cage. Zhang et al.[34] applied a porcine TC model and studied the PK/PD of cefquinome against *E. coli* ($MIC_{90} \leq$ 0.50 μg/mL). The AUC_{24h}/MIC to produce bactericidal and eradication effects was 35.01 h and 44.28 h, respectively. The TC model has been applied to study many antibacterial drugs and pathogens. However, this model has some disadvantages. For instance, this model is not suitable for the study of poorly absorbed drugs because such drugs have difficulty reaching the systemic circulation. Also, intracellular pathogens cannot be applied to this model because the TC sample is extracellular fluid.

In addition to the *ex vivo* PK/PD models described above, other matrix samples have been studied. Maan et al.[35] investigated the PK/PD of aditoprim against *Trueperella pyogenes* in the uterine fluid of cattle. They documented an AUC_{24h}/MIC to produce bacteriostatic, bactericidal, and clearance effects to be 2904 h, 13047 h, and 21970 h, respectively. Lei et al.[36] applied the content of porcine ileum to study *ex vivo* PK/PD of marbofloxacin against *E. coli*. They revealed the AUC_{24h}/MIC to produce bacteriostatic, bactericidal, and clearance effects to be 16.26 h,

23.54 h, and 27.18 h, respectively. Luo et al.[37] applied the fluid from pulmonary epithelial linings to study the *ex vivo* PK/PD of ceftiofur against *Streptococcus suis*, and provided abundant reference data for the design of dosage regimens.

Compared with the *in vitro* model, the *ex vivo* PK/PD model can reflect (at least in part) the effects between drugs, the host (e.g., immune factors, defense factors) and pathogenic bacteria. Such information provides detailed understanding of the influence of body substances on pathogenic bacteria. In addition, the *ex vivo* PK/PD model requires fewer/less damage to animals and lower costs, and is an important supplement to the *in vitro* PK/PD model. However, the *ex vivo* PK/PD model has limitations. For example, although this model applied *in vivo* PK data, but the PD was still acquired from static drug concentrations which not synchronized with the absorption and elimination of drugs in the host.

In Vivo PK/PD Models

This model applies *in vivo* PK and PD data for PK/PD integration. It can be used to analyze the interaction between drugs, pathogens, and the host. The most commonly used model types are the animal-organ infection model (AOIM) and tissue-cage infection model (TCIM).

AOIM

The AOIM is the most commonly applied *in vivo* PK/PD model. The basic research approach involves division into four stages. First, an infection model in a target organ is established to fit the linear relationship between the dose and drug concentration in plasma by administrating a different antibacterial dose on one occasion. Second, the antibacterial effect is calculated after therapy for 24 h at different intervals and dosages by dose fractionation. Third, an extrapolation approach is applied to acquire the drug concentrations of each dose during 24 h for calculation of PK/PD parameters. Finally, a sigmoid inhibitory E_{max} formula is used to analyze the relationships between PK/PD parameters and antibacterial effect, and to guide regimen design.

The AOIM has been established in mouse thighs, mouse lungs, chicken lungs, and duck lungs [38-40]. Xiao et al.[38] applied a duck-lung infection model to study the PK/PD of florfenicol against *P. multocida*. The AUC_{24h}/MIC to produce a bactericidal effect was 108.19 h and 54.30 h against the strains 0825Y1 and 0901J1, respectively, and the recommended dose was 52 mg/kg after Monte Carlo simulation. Zhang et al.[39] established a chicken-lung infection model to study the PK/PD of danofloxacin against *Mycoplasma gallisepticum* and analyzed the relationships between PK/PD parameters and resistant mutant genes. Li et al.[41] applied a mouse-lung infection model to study the PK/PD of nemonoxacin against *Streptococcus pneumoniae*. The AUC_{24h}/MIC was 8.6 h, 23.2 h, and 44.4 h to reach a bacteriostatic effect, 1-log_{10} reduction, and 2-log_{10} reduction, respectively. Watanabe et al.[42] used a mouse-thigh infection model to study the PK/PD of teicoplanin against *Staphylococcus aureus*. The $fAUC_{24h}$/MIC to produce a bacteriostatic effect and 1-log_{10} reduction was 54.8 h and 76.4 h, respectively.

The antibacterial effect of the AOIM is the result of the interaction between the host, bacteria, and drugs in the target organ, which is similar to clinical treatment. However, the AOIM has three main shortcomings. First, the PK data are obtained from plasma and are meant to represent the target organ. Some researchers have studied the relationships between plasma and target-organ values, but the target-organ data were not applied extensively. The other deficiency is that the PK data was consist with plenty of independent animals which may be influenced from the difference of animals physical condition. Third, the antibacterial effect is defined as the change in the final bacterial population 0 h and 24 h after treatment, which does not reflect the dynamic change in bacterial populations.

TCIM

After the TC model has been established, a certain concentration of bacteria solution (10^8-10^{10} CFU/mL) is injected and incubation permitted for a period of time. When the bacterial population stabilizes at 10^6-10^8 CFU/mL, then the TCIM has been established. After a series of dose regimens have been administrated, the TC fluid is removed at different time points for measurement of drug concentrations and bacterial populations. Finally, the relationships between PK/PD parameters and the antibacterial effect are analyzed to guide the design of the dosage regimen. This model realizes PK/PD integration at the same location and reflects the interactions between the host, drugs and bacteria. Hence, this infection model has been used widely for PK/PD integration and been established in pigs, rabbits, and cows [43-45]. Cao et al.[44] applied a calf TCIM to study the PK/PD of marbofloxacin against *P. multocida*. The AUC_{24h}/MIC to produce a 1.5-log_{10} reduction and 3-log_{10} reduction was 18.6 h and 50.65 h, respectively. Xiong et al.[46] applied a rabbit TCIM to study the relationship between the PK/PD parameters of cefquinome against mutant strains of *S. aureus*. They revealed that resistant *S. aureus* were selected and enriched if %T > MPC < 58% or %T > MIC_{99} ≥ 70%.

The TCIM has two main limitations. First, this model is based on a local infection between skin and muscle, which is not the target organ for all pathogens. Therefore, the obtained results are different from those after a systemic infection. Second, TC fluid is a component of extracellular fluid, which is suitable for most bacterial growth. Hence,

this model is not applicable for the study for cell-growing microorganisms (e.g., *Mycoplasma* species).

Microdialysis-Based PK/PD Model

Microdialysis is a microsampling technique based on dialysis. It permits sampling of low quantities, is associated with little damage to tissue, and enables continuous sampling and real-time monitoring of drug concentrations. The basic constituents of a microdialysis system are a micro-control pump, microsyringe, inlet line, microdialysis probe, outlet line, and collection tube. The microdialysis probe comprises a semipermeable membrane. The levels of substances either side of the semipermeable membrane can be balanced by passive transport. The micro-control pump is used to make the perfusate flow slowly through the dialysis membrane and bring-out the dialysate. After detected the drug concentration in the dialysis, the concentration in organ was converted by *in vivo* recovery. This method is very important for acquisition of the PK parameters of target organs (site of bacterial infection), so it has been applied for PK studies. Bernardi et al.[47] used microdialysis to investigate the penetration of tobramycin from the plasma to the lungs in rats. Yang et al.[48] employed microdialysis to study the PK of florfenicol in pig lungs. Zhang et al.[49] applied microdialysis to study the influence of body status on cefquinome PK in mouse thighs. Hence, microdialysis technology has important applications in PK/PD research, especially for the AOIM, because PK parameters in target organs can be obtained continuously to allow more precise PK/PD integration. Studies on the PK/PD integration of antibacterial agents using microdialysis have been reported rarely. Zhang et al.[50] established a mouse-thigh microdialysis infection model to study the PK/PD of cefquinome against *Actinobacillus pleuropneumoniae*. The %*f*T >MIC to produce a 1-$\log_{10}$ reduction, 2-$\log_{10}$ reduction, and 3-$\log_{10}$ reduction was 36.11%, 52.96%, and 82.68%, respectively. Microdialysis could have broad application prospects in PK/PD integration.

Conclusions and Recommendation

There is an increasing prevalence of drug resistance and slowing down of new-drug development because of the expense of research and development. Hence, PK/PD models can be used to guide optimization of dosage regimens which can prolong the life of antibacterial drugs, increase the antibacterial effect, and prevent the emergence and spread of resistant bacteria. Various PK/PD models have their own advantages and disadvantages, so the selection of an appropriate PK/PD model has a huge influence on obtaining accurate results. With the development and application of new technologies, more accurate PK/PD results will be obtained to guide appropriate use of clinical drugs.

Availability of Data and Materials

Not applicable.

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Competing Interest

The authors declare that they have no conflict of interest.

Author's Contributions

HW and LZ contributed to the methodology, software use, validation, and writing. LZ and JH contributed to the supervision.

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