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ARTICLE

Pharmacometric and statistical considerations for dose optimization

Palang Chotsiri[1] | **Prasert Yodsawat**[1] | **Richard M. Hoglund**[1,2] | **Julie A. Simpson**[2,3] | **Joel Tarning**[1,2]

[1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

[2]Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health, Oxford University, Oxford, UK

[3]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia

Correspondence
Joel Tarning, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand.
Email: joel@tropmedres.ac

Abstract

The probability of target attainment (PTA) is a common metric in drug dose optimization, but it requires a specific known target concentration threshold. Such target thresholds are not always available for some treatments, and patient and disease groups, particularly when treating children. This study performed pharmacokinetic and pharmacokinetic-pharmacodynamic (PKPD) simulations to explore different statistical approaches for determining the optimal dose for unknown PK and PKPD targets. To determine an optimal dose, PK and PKPD outcomes in typical patients with a standard adult dosing regimen were simulated and set as the reference profile, and compared to simulated outcomes for different dosing regimens in the population of interest. Statistical distances between the empirical cumulative distribution functions of the outcomes from all possible dosing regimens were calculated and compared to the reference profile. An optimal dose for known PK and PKPD target outcomes was selected to maintain the outcome above the assigned target, while optimal dosing in a population of interest with an unknown target was selected to generate equivalent PK and PKPD outcomes as the typical population. All of the dose optimization methods with commonly used PK and PKPD models and covariates were implemented as an open source freely available Shiny web-application. The developed pharmacometric method for dose optimization in populations with known and unknown target levels were robust and reproducible, and the implementation of a freely accessible Shiny web-application ensures widespread use and could be a useful tool for dose optimization in populations of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

A general goal of pharmacometric modeling and simulation is dose optimization. An optimal dose is selected to maintain the pharmacokinetic and/or pharmacodynamic outcome parameters above a pre-defined target threshold (e.g., time above the minimum inhibitory concentration; $T > \text{MIC}$) known as probability of

target attainment (PTA). Such pre-defined PK and/or PKPD targets are not always available, especially in pediatric dosing.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is an accurate, unbiased methodology for assigning an optimal dose for drugs with an unknown target threshold? How can this methodology be implemented for a user-friendly uptake by pharmacometricians and clinical pharmacologists?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

When a pre-defined PK or PKPD target outcome is not available, we propose that several possible PK or PKPD targets (e.g., exposure, C_{max}, $T>MIC$) at different doses should be evaluated in a population of interest (e.g., pediatric patients) and compared to that expected in a reference population (e.g., adult patients) receiving an efficacious dose. The dose that results in equivalent target(s) for the most appropriate PK or PKPD measures should be assigned as an optimal dose. Currently, there is no standard, unbiased methodology to evaluate this. We evaluated different statistical measures to compare the distance between the distribution of PK or PKPD target outcomes. The recommended optimal dose in the population of interest was the dose with the minimum statistical distance compared to the reference population. The methodology was implemented in a user-friendly freely available web-application.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The proposed methodology provides an unbiased way to determine an optimized dose in a population of interest (e.g., pregnant women and children), based on achieving the most equivalent pharmacological outcome compared with a reference population. This approach should maximize the overall treatment outcome, balancing the risks of sub-therapeutic exposures and toxicity of the available dose strengths. The user-friendly web-application can also be used to evaluate the need for different tablet strengths and how regional and/or country-level differences in available products can impact the risk of underdosing and adverse events.

INTRODUCTION

Dose selection and dose optimization are related concepts in drug development and clinical practice, but they occur at different stages and focus on different aspects of determining an appropriate drug dose. Dose selection involves choosing an initial dose or range of doses to evaluate based on preclinical and early clinical data. Dose optimization is one of the most challenging problems in clinical practice, and often defined as an iterative process of refining the clinical dose to achieve the best therapeutic outcomes with minimal adverse effects. Pharmacokinetic (PK) and/or pharmacokinetic-pharmacodynamic (PKPD) studies aim to optimize the dose in both the clinical and post-marketing phases. In separate target populations such as children, pregnant women, elderly, severely ill patients, or individuals with a specific genetic polymorphism, the dose might need to be optimized due to altered PK and/or PKPD profiles. In infectious diseases treatments, finding the optimal dose also plays an important role in minimizing the development of pathogen resistance.

Therapeutic responses in a target population depend on the dosing regimen, that is, a fixed/flat dosing regimen for all individuals may produce highly variable PK and PD responses, while an individualized dosing regimen can result in the desired response in each patient.[1] Dose banding is a simplified individualized dosing regimen where patients are allocated to a dose group according to their clinical and/or demographic characteristics, for example, weight or age bands. PK or PKPD models and in silico simulations can be important tools to generate optimal dosing regimens in specific populations. Drugs given intra-venously or intra-muscularly can be accurately administered, whereas oral treatments are limited by available drug tablet strengths. Some drug tablets are administered as half or quarter tablets to get as close as possible to the ideal dosing recommendation. To give an exact amount of an oral drug, the tablet(s) need to be crushed

and mixed with water and an exact volume of the mixture measured for administration, which is not practical in some clinical settings. Access to potable clean water is limited in some countries and administration of an exact volume of a mixture might be practically difficult to control in small children.

For many drugs, such as antimicrobial drugs, the optimal dosing is commonly defined by the drug's total exposure (i.e., area under the curve; AUC) and in some cases peak drug concentrations (C_{MAX}). Additional information on the PKPD target, such as a minimum inhibitory concentration (MIC), can refine the dose selection. Typically used exposure-, concentration-, and time-dependent PKPD measures include the drug exposure over the MIC (fAUC/MIC), maximum drug concentration over the MIC (fC_{MAX}/MIC), and time of the drug concentration above the MIC ($T>$MIC), respectively. Optimal dosing can be directly determined by the proportion of patients who can maintain the PK or PKPD outcome above the pre-defined target, namely the proportion of target attainment (PTA). Unfortunately, the PK or PKPD target is not always available and sometimes difficult to determine in the population of interest. In some cases, especially in the field of neglected tropical diseases, the exact drug mechanism of action is still unknown and the target PK and/or PKPD outcomes have not been well established when the drug is marketed. In such cases, optimal dose assignment is commonly based on an *equivalent* PK or PKPD outcome compared with the standard dose in a reference population (i.e., in adult patients). To date, there is no standard statistical methodology to determine the *equivalent* PK or PKPD outcomes between the population of interest and the reference population.

In this study, we describe and summarize the most commonly used method to determine the optimal dose for a known PK target outcome (i.e., using PTA) and propose statistical approaches for dose optimization when the PK or PKPD target outcomes are unknown. Several hypothetical and real-world examples are tested and presented. A freely accessible web-application was developed for the implementation of the dose optimization methods.

METHODS

Pharmacokinetic models and simulations

The dose optimization methods were evaluated for hypothetical and real-world scenarios (Table 1). The methodology for dose optimization can be divided into two types, that is, known and unknown PK or PKPD targets. The overall methodological framework is presented in Figure 1. A simple one-compartment disposition model with a transit absorption model was used for all hypothetical scenarios. Between-subject variabilities (BSV) were implemented on all PK parameters and set to 10%. The BSV was purposely set to a relatively low value of 10% as it was implemented uniformly on all parameters, while most literature commonly present a somewhat higher BSV of 30%–50% in specific parameters. This assumption was also evaluated with a sensitivity analysis. Dose selection for anti-malarial drugs was used as a real-world example. PK and PKPD models and their parameter estimates were set according to published literature. Details of the models, parameters, and optimization outcomes for each scenario are provided in Supplementary Information S1. Simulations of the drug concentration versus time profiles for each model were implemented in R version 4.2.3, using rxode2 and mlxR packages for solving differential equations.[2,3]

Dose optimization for a known PK target

For the known target, PTAs for each possible dose were calculated. Known targets can be either PK parameters (e.g., C_{MAX}, AUC, and C_{trough}) or PKPD parameters (e.g., fC_{MAX}/MIC, fAUC/MIC, AUC above MIC, and $T>$MIC). The choice of the known target depends on the mechanism of action for the specific drug-disease scenario under investigation. A PTA of each possible dose can be determined by simulating the PK and/or PKPD profiles in the target population. The lowest dose that can maintain the PK or PKPD outcome above the known PTA threshold is assigned to be an optimal dose (Scenario 1 and 6). Additionally, for a PK model that includes patient characteristics such as body weight, this methodology can be applied iteratively for each body weight group (Scenario 2 and 7).

Dose optimization for an unknown PK or PKPD target

The drug mechanism of action or PK target outcome is sometimes unknown and only a standard dosing regimen in an adult reference population is known. Dosing regimens for other population groups, for example, pregnant women or children, are usually scaled linearly or allometrically by the individual's body weight. However, for many drugs, dose assignment based on a simple body weight scaling still result in sub-therapeutic drug exposures indicating that the PK is influenced by other factors than just difference in body weight between the investigated group and the reference population.[4,5] In order to determine the optimal dose in a specific population, an equivalent drug exposure (for exposure-dependent drugs) to the reference

TABLE 1 Summary of simulated scenarios and examples used in this investigation.

Scenarios	Optimized drug	Tablet strength (mg)	PK model	Covariate model	PK outcomes	Target	Ref.
1	Hypothetical	300	One-compartment model	Categorical	$AUC_{0\text{-}48h}$	≥10 h·ng/mL	
2	Hypothetical	300	One-compartment model	Allometry	$AUC_{0\text{-}48h}$	≥10 h·ng/mL	
3	Hypothetical	300	One-compartment model	Categorical	C_{MAX}, $AUC_{0\text{-}48h}$, and $T>MIC$	Equivalent to 1200 mg in 60 kg subject	
4	Hypothetical	300	One-compartment model	Allometry	C_{MAX}, $AUC_{0\text{-}48h}$, and $T>MIC$	Equivalent to 1200 mg in 60 kg subject	
5	Hypothetical	300	One-compartment model	Allometry and maturation effects	C_{MAX}, $AUC_{0\text{-}48h}$, and $T>MIC$	Equivalent to 1200 mg in 60 kg subject	
6	Chloroquine	500	PK: Two-compartment model PD: Direct effect linear model	Healthy volunteer	Maximum ΔQTc	<30 ms <60 ms	[12]
7	Piperaquine	320, 160	Three-compartment model	Allometry and maturation effects	Day-7 conc.	≥30 ng/mL (venous)	[13]
8	Dihydroartemisinin	40, 20	One-compartment model	Allometry and pregnancy	$AUC_{0\text{-}12h}$	Equivalent to 120 mg in 60 kg subject	[15]
9	Primaquine	15, 5	Drug-metabolite model	Allometry and maturation effects	$AUC_{0\text{-}48h}$	Equivalent to 30 mg in 60 kg subject	[17]

Note: The pharmacokinetic parameters and modeling details for each scenario are presented in Supplementary Information S1.

population would maximize the chance of a similar clinical response of the drug, similar to the concept of the bioequivalent criteria.

To quantify the similarity of an outcome parameter between two populations, distributions of the outcome parameter of both populations can be compared visually and by using a statistical measure (example in Figure 2). Probability density functions (PDFs) were transformed into empirical cumulative distribution functions (ECDFs), and the distance between the two ECDFs was used to determine the level of similarity (or equivalence) of the two populations. Several statistical calculations can be used to determine the distance between two ECDFs, that is, a horizontal distance, a vertical distance, and an area-based distance. All statistical calculations evaluated to determine the distance between two ECDFs are provided in Appendix A.

In the present work, PK models with a categorical covariate were investigated (Scenario 3 and 8). For a PK model with continuous covariates, this methodology was applied iteratively (Box 1) and the optimal dosing regimen was assigned (Scenario 4, 5, and 9). For all hypothetical scenarios, three PK/PKPD outcomes were considered, including C_{MAX}, AUC_{LAST}, and $T>MIC$, representing drug concentration-, exposure-, and time-dependent effects, respectively. Also, the mean ratio of the outcome parameters compared to the reference population was calculated, and the proportion within the bioequivalent criteria (i.e., 80%–125%) presented,

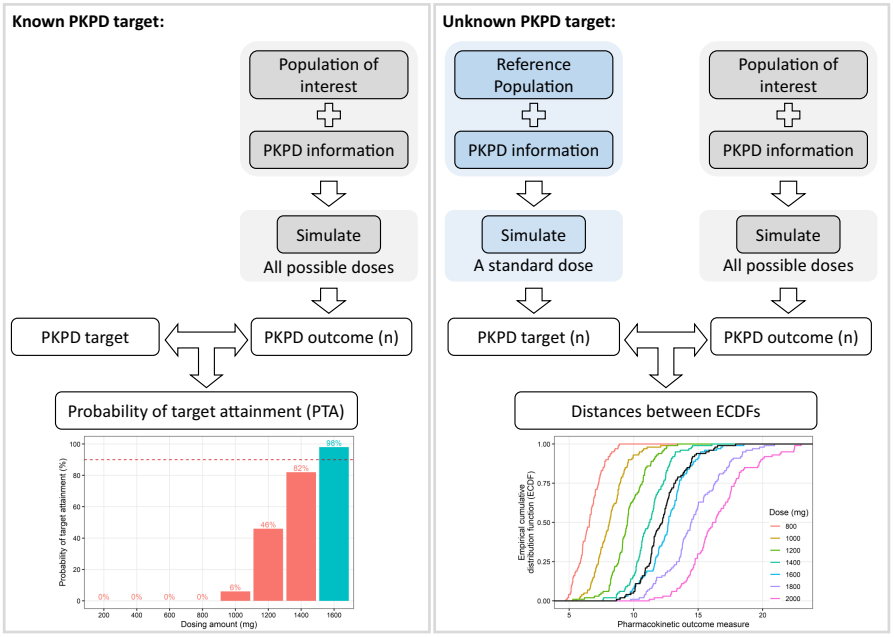

FIGURE 1 Methodological frameworks of dose optimization for known PK or PKPD targets (left panel) and unknown PK or PKPD targets (right panel). Dose optimization of known targets is determined by the probability of the target attainment (PTA), whereas dose optimization of the unknown targets is based on the distance between the ECDF of the target profile in a reference population after a standard dose (solid black line) and ECDF of each possible dose in the population of interest (solid color lines). The dose with the minimum distance to the target profile will be assigned as an optimal dose.

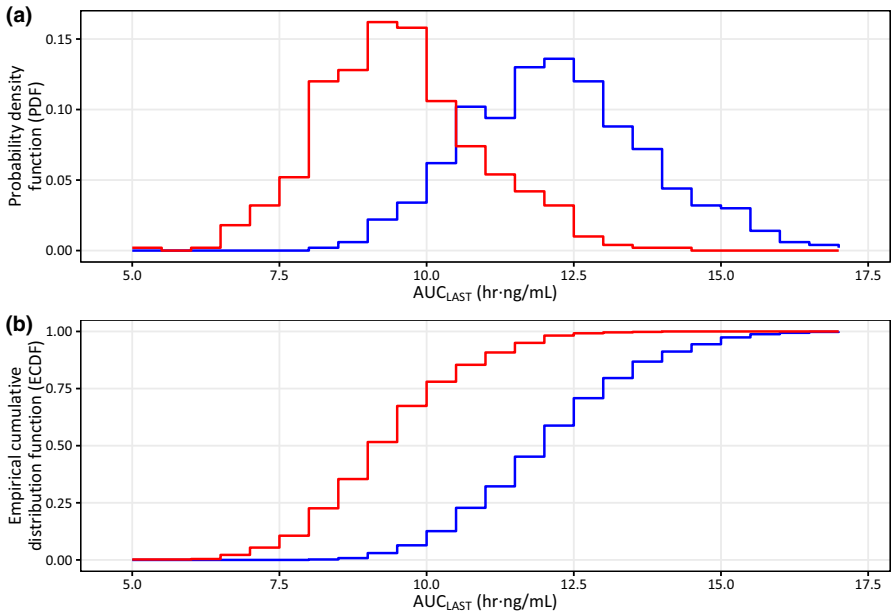

FIGURE 2 Probability density function (a) and empirical cumulative distribution function (b) of AUC_{LAST} between a reference population (blue lines) and a population of interest (red lines).

BOX 1 Algorithm for an optimal dosing design of a continuous covariate (i.e., body weight) for an unknown pharmacokinetic target

PK_tar ← Target PK outcome in a reference population receiving a standard dose

Body_weight ∈ (5 to 80 kg)

Possible_dose ∈ (0.5 × n × tablet_strength)

For (i in each Body_weight) **Do (**

For (j in each Possible_Dose) **Do (**

Calculate the PK outcomes (N subjects) of Body_weight = i, dose = j

Compare the distribution of the PK_ij with the PK_tar

Calculate a distance† between the ECDFs of PK_ij and the ECDF of PK_tar

)

The optimal dose will assign to the dose with lowest distance

)

†The distance between two ECDFs can be calculated using the following statistics: t statistic, Wilcoxon statistics, Kolmogorov–Smirnov statistics, Kuiper statistics, Cramér-von Mises statistics, Anderson-Darling statistics, Wasserstein distance statistics, and DTS statistics.

as well as the proportion of outcome parameters above the 10th percentile of the reference population.

Dose optimization when more than one patient covariate influences the PK profile

Population PK studies in children commonly conclude that more than one patient characteristic alters the PK profile. Patient body weight and age as allometry and enzymatic maturation effects, respectively, are often identified to be important determinants in pediatric studies.[6,7] Therefore, the relationship between these covariates needs to be carefully considered since the demographic and anthropometric parameters are highly correlated in children. When the reported PK model consists of more than one covariate, simulations of the distribution of each covariate independently do not maintain the correlation between the covariates. Therefore, resampling individuals from a survey database can maintain the population characteristics and capture more accurate covariate relationships. In this simulation study, resampling of individual covariates was performed using two large datasets, the National Health and Nutritional Examination Survey (NHANES III) from the US CDC (n = 47,804)[8] and the Severe Malaria African Children (SMAC) network (n = 25,733).[9,10]

Sensitivity analysis of the unknown target dose optimization

The derived optimal dose was evaluated based on an ideal dose for a basic pharmacokinetic measure of drug exposure

$$\mathrm{AUC} = \frac{F \cdot \mathrm{Dose}}{\mathrm{CL}}$$

where AUC is the area under the concentration-time curve, F is the oral bioavailability, and CL is the elimination clearance.

A standard dose in a reference population was assigned to be 200 mg, and the population of interest had a doubling of the drug absorption (i.e., 100% increase in relative bioavailability) compared to that of the reference population. In order to maintain the same AUC as the reference population, an ideal optimal dose for the population of interest is 100 mg. For determining the sensitivity of the assigned dosing regimen, the derived dosing regimen was varied by ±20% and ±50%. The sensitivity analysis was conducted using a basic one-compartment PK model with first-order absorption (CL = 100 L/h, volume of central compartment (V_C) = 400 L, absorption rate constant (K_A) = 0.5 h^{-1}). The bioavailability in the reference population and the population of interest was fixed to 1 and 2, respectively. The impact of inter-individual variability on bioavailability was evaluated (i.e., from 20% to 100%), while it was assumed that no other PK parameters had any inter-individual variability. Different numbers of simulated individuals were evaluated (i.e., 10–500 individuals). Dose optimization simulations were performed 100 times in order to determine the sensitivity of the proposed methodology.

Examples of dose optimization in real-world problems

Examples of real-world problems were focused on dose optimization of antimalarial drugs, including chloroquine, piperaquine, dihydroartemisinin, and primaquine. Of these four antimalarial drugs, only chloroquine and piperaquine have pre-defined exposure target outcomes. All simulation details are summarized in Table 1 and presented in full in the Supplementary Information S1.

Chloroquine (Scenario 6)

Chloroquine dose optimization was based on the cardiotoxicity outcome, that is, prolonged QTc intervals. Chloroquine dosing should not result in a QTc prolongation above 60 ms according to the E14 guideline.[11] A population PKPD model for chloroquine, based on a study in healthy volunteers, was implemented to simulate concentration-time profiles and resulting QTc prolongations in subjects weighing 60 kg after receiving the 3-day standard oral treatment dose.[12] A QTc prolongation of 30 and 60 ms was judged to be clinically acceptable and set as the target outcome. The PTA of each possible dose (using currently available tablet strengths) was assessed, and the maximum dose that resulted in at least 95% of patients showing a QTc prolongation below 30 and 60 ms was assigned as an optimal dose. An arbitrary PTA of 95% was chosen as QT prolongation is a relative risk for potentially fatal cardiovascular adverse events, and 60 ms should not be seen as absolute cut-off associated with adverse events. This PTA can of course be altered to fit the specific investigation and risk assessment appropriately.

Piperaquine (Scenario 7)

Piperaquine dose optimization was based on the day-7 concentration PK target. A population PK model for piperaquine, based on a large pooled individual patient data meta-analysis, was selected for the dose optimization simulations.[13] Body weight implemented as an allometric function and age as an enzymatic maturation function were reported as significant covariates in the final PK model. Virtual subjects were sampled, with replacement, from a large database of 47,804 individuals (NHANES III) containing both children and adults; that is, a total of 500 individuals were selected per each kg of body weight (5–80 kg), in order to generate virtual healthy pediatric subjects with a clinically plausible combination of body weight and age (Figure S5.5). These virtual healthy pediatric subjects were used for all dose optimization simulations of piperaquine chemoprophylaxis. Day-7 concentrations were simulated and compared with a predefined target venous plasma concentration above 30 ng/mL.[14] PTA was assessed separately for each body weight group of patients at different doses, using currently available tablet strengths. The dosing amount resulting in more than 75% target attainment in each body weight group was assigned as the optimal piperaquine dose for that group of patients.[4] An arbitrary PTA of 75% was highlighted as a suitable target for therapeutic efficacy in order to balance the risk of adverse events vs. therapeutic efficacy, and the actual PTA associated with each dosing evaluated was calculated and presented if a different PTA is more appropriate to use in a specific investigation.

Dihydroartemisinin (Scenario 8)

A PK or PKPD target has not been established for dihydroartemisinin, the most important antimalarial drug today. Therefore, dihydroartemisinin exposures ($AUC_{0\text{-}12h}$) in typical adult patients receiving a standard treatment (120 mg) were set as the PK target outcome. A clinical trial in pregnant women with malaria showed that the bioavailability of dihydroartemisinin was reduced by 37.5% in the second and third trimester compared to non-pregnant female patients.[15] Dihydroartemisinin exposures in pregnant women weighing 60 kg were simulated at different doses, using the currently available tablet strengths, and compared to the target exposure in non-pregnant adult patients weighing 60 kg after receiving standard dosing. Distances between the target exposure's ECDF and the exposure's ECDFs from different doses in pregnant women were compared. The smallest distance was assigned as an optimal dihydroartemisinin dose in pregnant women.

Primaquine (Scenario 9)

Primaquine can be administered for several reasons, for example, as a radical cure in patients with *Plasmodium vivax* and *P. ovale* malaria infections, and as a transmission-blocking drug in patients with *P. falciparum* infections. A daily primaquine dose of 0.5 mg/kg is the recommended dose for radical cure for *vivax* malaria.[16] A clear PK target of primaquine is unknown and its PK properties in children are not well established. Here, a population PK model and parameter estimates from a healthy volunteer study were used.[17] Body weight and enzymatic maturation effect on the PK parameters was also implemented. A pediatric population was generated by sampling with replacement from a large dataset of 25,733 African children with severe malaria (SMAC); that is, $n = 500$ pediatric patients were selected per each kg of body weight (5–40 kg), in order to generate patients for dose optimization simulations.[9] Primaquine exposures ($AUC_{0\text{-}48h}$) in typical adult patients (i.e., 54 kg and 20 years) administered a standard oral primaquine dose of 30 mg were set as the PK target. PK profiles were simulated for all children at different dosing regimens, using currently available tablet strengths. Each body weight group of patients was compared to the

reference population by the distance method described above. The optimal primaquine dose, in each body weight group, was assigned to the dose with the smallest distance in exposure ECDF to the target exposure ECDF.

Web-application implementation and code

The developed dose optimization methodology was also implemented as an open access web-based user interface using the R Shiny package.[18] All implementation details and simulation options can be found in the Supplementary Information S2. Data and source code for the simulated scenarios and for the developed dose optimization web-application are available from the authors upon reasonable request.

RESULTS

Detailed results for each scenario are presented in the Supplementary Information S1.

Dose optimization for a known PK or PKPD target

When the PK or PKPD target is well established, dose optimization can be based on the PTA of the specific PK or PKPD outcomes. The PTA can be adjusted according to the purpose of the analysis, that is, the PK or PKPD outcome should be above an efficacy target (e.g., MIC level) or it should be below the toxicity target (e.g., QTc prolongation). Dose optimization using the PTA can be applied to PK models with both categorical and continuous covariates. For a continuous covariate such as body weight, it can be grouped and optimized iteratively by each unit of the covariate (see Scenario 2 and 7).

Dose optimization for an unknown PK or PKPD target

Distances between two ECDFs of potential PK or PKPD target were shown to be an efficient methodology for determining an optimal dose in the population of interest. The hypothetical example used C_{MAX}, AUC_{LAST}, and $T>MIC$ as the potential PKPD outcomes which represented drugs with concentration-, exposure-, and time-dependent effects (Scenario 3–5). This distance between two ECDFs can be applied to PKPD models with categorical or continuous covariates. Using different target parameters produced different optimal doses, highlighting the importance of exploring different PKPD targets when the key target for a drug is unknown. Optimal dose banding assignments, using a PKPD model with continuous covariates, were evaluated for all statistic measures and generated slightly different results. This can be explained by the stochasticity of the simulation, and a small step size of the covariate (e.g., 1-kg step size).

Dose optimization for more than one covariate effect

Pharmacometric simulations based on fully parameterized distributions and correlations of all covariates are ideal, but this information is not always available, and the relationship between covariates is often nonlinear and complex. Resampling patients of interest from large survey datasets (e.g., NHANES III or SMAC) can retain the inter-relationships between covariates (i.e., the correlation between body weight and age) and generate biologically and clinically relevant simulations (Figures S5.1, S5.5, and S9.1). Scenarios 5, 7, and 9 present the dose optimization results using resampling of the covariates, age, and body weight from the NHANES III and SMAC datasets, respectively. In the example scenarios, the population PK model has both body weight as an allometric function and age as an enzymatic maturation effect. Therefore, the dose optimization can be based either on individual's body weight or age, depending on the importance of each covariate effect and clinical feasibility. One of the datasets or a combination of both were used depending on the specific patient population needed, that is, malaria patients (SMAC), healthy subjects (NHANES III), or a combination of both (SMAC and NHANES III).

Statistical sensitivity of the unknown target dose optimization

The sensitivity of the developed dose optimization methodology (i.e., ability to statistically differentiate between a target dose and an altered dose) was evaluated for an unknown PKPD target by deriving and comparing ECDF distance at different conditions. Distances between ECDFs were sensitive to (1) the relative difference between available tablet strengths, (2) the distribution variance of the target outcome (i.e., inter-individual variability in model parameters), and (3) the size of the simulated population. To evaluate the sensitivity of the proposed dose optimization methodology, we fixed the dose in the population of interest to ±50% (i.e., half tablet) or ±20% (i.e., the bioequivalence criteria) compared

to that in the reference population, and then evaluated the impact of a varying degree of inter-individual variability in model parameters and the impact of varying number of simulated patients. All statistical measures evaluated showed similar results of increased sensitivity with increasing number of simulated patients and decreasing inter-individual variability in parameter estimates (Figure 3). The statistical measures that used one or two surrogate points (Kolmogorov–Smirnov, Kuiper, and *t*-statistic) from each ECDF showed a lower level of sensitivity compared to the other statistical measures. All statistics showed a high sensitivity when the relative difference in available tablet strengths was larger (i.e., ±50%). Larger numbers of patients need to be simulated when the relative difference in available tablet strengths is smaller and when the inter-individual variability in model parameters increases.

Web-application

The suggested dose optimization procedures were implemented as a Shiny web-application and it can be accessed via https://pharmacology.shinyapps.io/dose_optimization/. All basic PK models (i.e., one-, two-, and three-compartment models) with the first-order absorption or transit-absorption were implemented with different covariates models (i.e., no covariate, body weight as an allometric function, age maturation effect, and a combination of both). Known and unknown target PK or PKPD outcomes were included in the developed web-application.

DISCUSSION

The PTA is commonly used for dose optimization when the target PK or PKPD outcomes are available. However, not all drugs have an established PK or PKPD target. Several drugs do not have a well-known mechanism of action or its PK target thresholds. Dosing recommendations are often based on the best possible guess, such as weight-based normalized dose or body surface area normalized dose. Therefore, this study proposes a methodology in order to inform the optimal dose in the population of interest when the PK or PKPD target is unknown.

For antibiotics with a bactericidal activity, the PK target can be defined around the MIC value[19] (e.g., $T>$MIC, AUC above MIC, *f*AUC/MIC, and fC_{MAX}/MIC), which needs to be determined from in vitro experiments and based on the mechanism of action of the specific drug evaluated. A dose that can maintain a high percentage of PTA can be assigned as the optimal dose. On the other hand, for drugs without any prior information on their mechanism of action or an established PK target, the optimal dose in the population of interest is the dose that can maintain an equivalent PK outcome as the standard

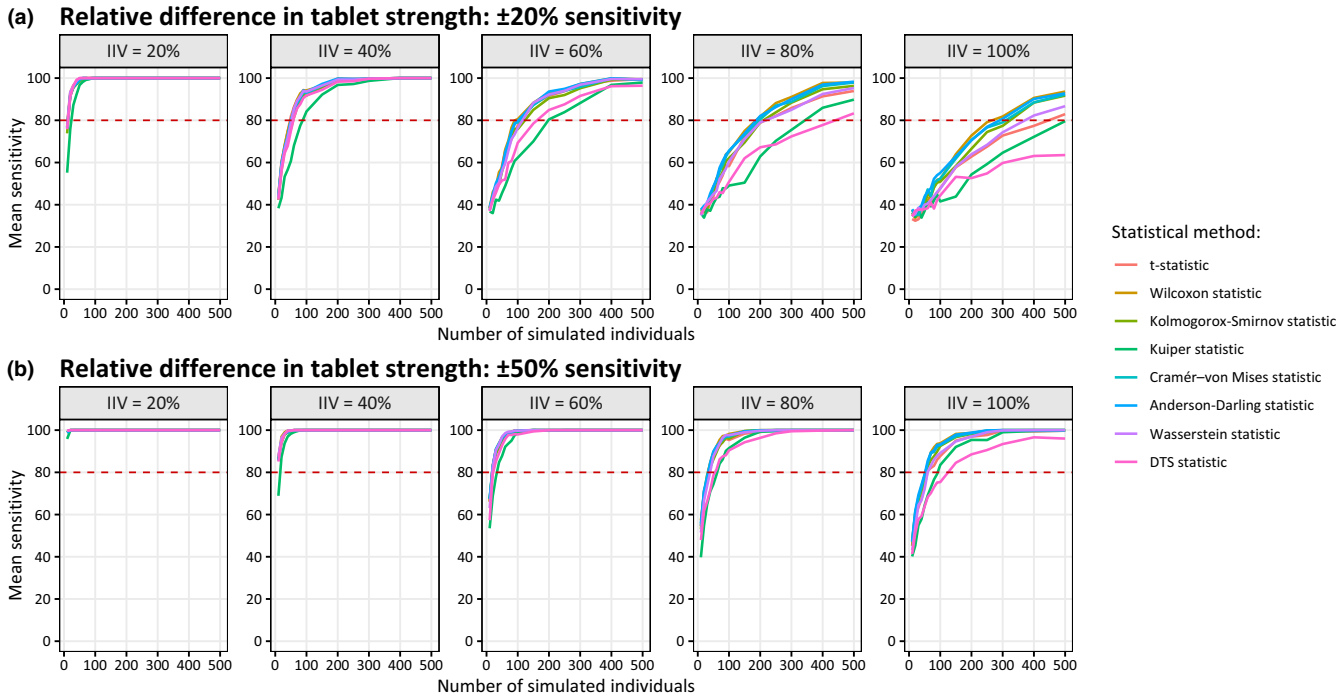

FIGURE 3 Statistical sensitivity of dose optimization for an unknown target outcome, stratified by different levels of the possible tablet strengths, that is, ±20% (a) and ±50% (b). Each panel shows a different level of inter-individual variability (from 20% to 100%) in underlying model parameters. Colored lines represent the different statistical calculations for the distance between two ECDFs.

dose in the reference patient population. To date, there is no standard approach for determining the level of equivalence between the PK outcomes from the reference patient population and the patient population of interest. This study recommends that the statistical distance between two ECDFs for multiple PK targets could be used to guide the optimal dose for the patient population of interest.

Distance statistics between ECDFs were calculated to determine the optimal dosing regimen. Of the available measurements, the area-based distance (i.e., Wasserstein distance statistics) or distance statistics calculated from all observations (i.e., Wilcoxon, Cramér–von Mises, and Anderson-Darling) are recommended because these measures consider the whole distribution of the PK parameter. Distances which are calculated by using only one or few surrogate numbers for the whole distribution (i.e., *t*-statistics, Kolmogorov–Smirnov statistics, Kuiper statistics) tend to be less sensitive toward the individuals with extreme parameter estimates. To obtain a robust dose optimization, a large number of individuals should be simulated when there is large inter-individual variability in the PK parameters. In adults and older children, the PK or PKPD outcome of weight-based dose selection was less varied compared to the age-based dose selection, which can be explained that the enzymatic maturation factor dominates during the early age while the allometric scaling of body weight dominates afterward. Both age-based and weight-based dose selection should be considered in young children in order to determine which is the most appropriate dose. Nevertheless, using both weight- and age-based dose optimization would be better but practically difficult.

In this study, we applied the proposed dose optimization procedures (i.e., the distances between ECDFs) for antimalarial drugs using unknown PK and PKPD target outcomes. For antimalarial drugs with known target outcomes, the standard methodology (i.e., PTA) was applied. For chloroquine dose optimization (Scenario 6), the dose optimization was based on a PKPD cardiotoxicity model.[12] The QTc prolongation of <30 and <60 ms were set as the target outcome. Approximately, 80% of simulated individuals assigned the standard chloroquine dose (600 mg daily for 3 days) had a QTc prolongation between 30 and 60 ms, which agrees with the published data.[12] When we considered 60 ms as the QTc prolongation target for toxicity, the optimal safe dose should be below 1050 mg (i.e., 97.8% of individuals have QTc prolongation below 60 ms). This methodology can allow us to determine a safe dose range in a particular population. Another example of a known PK target is piperaquine (Scenario 7), recommended as a day-7 venous plasma concentration target above 30 ng/mL.[14] Dose optimization of piperaquine according to the proportion of target attainment chosen in this study agreed with the WHO malaria treatment guideline[16] (Table S7.1). For dose optimization of dihydroartemisinin in pregnant women (Scenario 8) and primaquine in children (Scenario 9), we evaluated the scenario of an unknown PK target. In pregnant women, bioavailability of dihydroartemisinin has been shown to be reduced by 37.5%.[15] The standard dihydroartemisinin dose in a typical patient (60 kg) is 120 mg. All statistical distances of the target exposure ($AUC_{0\text{-}12h}$) agreed and showed that the most equivalent dose in pregnant women was assigned to be 180 mg. Primaquine dosing recommendations differ by malaria species. For the treatment of *P. vivax* or *P. ovale* infections, it can be prescribed as standard dose once daily for 14 days or high dose once daily for 7 days. For *P. falciparum* infections, it can be prescribed as a single low dose to prevent disease transmission. Here, dose optimization of primaquine in children was conducted with the assumption of allometrically scaled body weight and an enzymatic age-maturation factor.[17] Weight-based dose optimization showed an equivalent exposure compared to the reference adult patient population. Only a few body weight groups (i.e., the body weight at the border of each dosing bands) had predicted exposures outside the bioequivalence criteria.

The application of using the distance between the ECDF for comparing doses when the PK or PKPD target is unknown was presented for a population PK model. However, this approach can easily be applied for any type of PK or PKPD models, as well as physiologically based pharmacokinetic (PBPK) models or target-mediated drug disposition (TMDD) models.

This study has some limitations. Dose optimization suggested by the proposed methodology is based on population PK models. It aims to reduce the variabilities of the target PK outcome according to the dosing option, that is, available tablet's strength. It does not aim to optimize the individual dosing regimen. The optimal dose assigned by this proposed methodology might not provide a bioequivalent dosing regimen to the reference population, but it provides the most similar dose to the reference population according to the available dosing options. This dose optimization methodology is based on a single PK or PKPD outcome and for one particular drug dose optimization. If the mechanism of action of the drug of interest is unknown, it requires, at least, the knowledge of what is the possible driver for efficacy (e.g., concentration-dependent action, exposure-dependent action, or time-dependent action). Additionally, several tablet formulations are fixed-dose combinations, and therefore, information on PKPD interactions of the combined drugs is needed for dose optimization. Dihydroartemisinin-piperaquine, for example, is formulated as a fixed-dose combination, but the dose

optimization method presented is based on either piperaquine (Scenario 7) or dihydroartemisinin (Scenario 8). Furthermore, this optimization method does not accommodate the combination of two target parameters (e.g., reaching the target outcome and not exceeding the toxicity threshold). Drug adherence and forgiveness might change with dosing and were not considered in this study, but they could be included in future work in order to reflect real-world applications of dose optimization. Other areas of further development are to include additional patient populations to draw covariate relationships from, and to include dose optimization for, drug combination therapies and to optimize dosing based on multiple PK or PKPD targets. For the web-application, it was initially designed for general use, with simulations based on simple PK models and covariates, with the aim of expanding it to include more complex scenarios. For more complex PKPD models and specific dose optimization scenarios, users can still apply the overall methodology for their study's objectives.

CONCLUSIONS

Dose optimization in a specific population is a fundamental pharmacometric protocol performed in all phases of drug development. This study evaluated several statistical measures for determining the optimal dose in a patient population of interest, focusing on drugs in current clinical use. For the known PK and PKPD target outcomes, the PTA approach is recommended. For unknown PK and PKPD targets, this analysis recommends evaluating multiple targets using distance-based statistics of the ECDFs of the outcome PK or PKPD parameters between a typical patient population receiving the standard dosing regimen and a patient population of interest at a range of available doses. An optimized dose in the patient population of interest is the dosing scenario that achieves an equivalent target outcome as the typical population. This developed dose-optimizing methodology was also implemented as a freely available web-application (https://pharmacology.shinyapps.io/dose_optimization/).

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. P.C., R.M.H., J.A.S., and J.T. designed the research. P.C. and P.Y. performed the research. P.C., R.M.H., J.A.S., and J.T. analyzed the data. P.Y. contributed analytical tools.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

ORCID

Palang Chotsiri https://orcid.org/0000-0003-3839-9777
Prasert Yodsawat https://orcid.org/0000-0002-0176-0170
Richard M. Hoglund https://orcid.org/0000-0002-5322-912X
Julie A. Simpson https://orcid.org/0000-0002-2660-2013
Joel Tarning https://orcid.org/0000-0003-4566-4030

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

Several statistical methods can be used to determine the distance between two distributions. In this appendix, we categorize the distance between two ECDFs by way of statistical calculations, that is, a distance along the *x*-axis, a distance along the *y*-axis, and an area between two ECDFs. Ideally, when two distributions are exactly the same, all of these statistical distance calculations will be 0. However, detailed calculations and interpretations of each statistic are somewhat different.

A horizontal distance between two ECDFs

t-statistic is a basic statistical method based on the difference of the means ($\overline{X}$) of two distributions, standardized by using the standard deviation (SD). Assumptions of the *t*-statistic are based on a normal distribution and equal variance. The *t*-statistic between two distributions was calculated according to the following expression:

$$t = \frac{\overline{X_1} - \overline{X_2}}{\mathrm{SD}}$$

Wilcoxon statistic is a non-parametric test calculated from a summation of the sample ranks (R_i) in the combined distribution adjusted by its sign. Wilcoxon statistic considers all values from two distributions. However, it is simplified by using each value's rank. The Wilcoxon statistic between two distributions can be calculated using the following expression:

$$W = \sum_{i=1}^{N} \mathrm{sgn}\left(x_{2,i} - x_{1,i}\right) \cdot R_i$$

A vertical distance between two ECDFs

Kolmogorov–Smirnov statistic is determined by one maximum distance along the *y*-axis of two ECDFs. It can be calculated using the following expression:

$$\mathrm{KS} = \max_{x \in \mathbb{R}} \left| \hat{F}(x) - \hat{E}(x) \right|$$

Kuiper statistic is an extended version of the Kolmogorov–Smirnov statistics; it uses two distances, that is, the maximum and minimum distances between two ECDFs. It can be calculated as follows:

$$\mathrm{Kuiper} = \max_{x \in \mathbb{R}} \left| \hat{F}(x) - \hat{E}(x) \right| + \min_{x \in \mathbb{R}} \left| \hat{F}(x) - \hat{E}(x) \right|$$

Cramér–von Mises statistic is based on a summation of all distances of two ECFDs along the *y*-axis.

$$\mathrm{CVM} = \sum_{x \in X} \left| \hat{F}(x) - \hat{E}(x) \right|$$

Anderson-Darling statistic extended the Cramér–von Mises statistic by using each sample's deviation to weight the distance.

$$\mathrm{AD} = \sum_{x \in X} \frac{\left|\widehat{F}(x) - \widehat{E}(x)\right|}{\widehat{D}(x) \cdot \left(1 - \widehat{D}(x)\right)}$$

An area-based distance between two ECDFs

Wasserstein distance statistic is a distance between two ECDFs calculated based on the area.

$$\mathrm{wass} = \int_{-\infty}^{\infty} \left|\widehat{F}(x) - \widehat{E}(x)\right| \mathrm{d}x$$

DTS statistic was developed based on the Wasserstein distance statistic.[20] It is defined as an area between two ECDFs and weighted by the deviation of each sample's deviation from the shared distribution.

$$\mathrm{DTS} = \int_{-\infty}^{\infty} \frac{\left|\widehat{F}(x) - \widehat{E}(x)\right|}{\widehat{D}(x) \cdot \left(1 - \widehat{D}(x)\right)} \mathrm{d}x$$