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Optimal Design of Perturbations For Individual Two-Compartment Pharmacokinetic Analysis

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Abstract

We consider the optimal design of pharmacokinetic studies in patients that receive intermittent hemodialysis and intravenous antibiotic. Hemodialysis perturbs the pharmacokinetic system, providing additional opportunity for study. Designs that allocate measurements to occur exclusively during hemodialysis are shown to be viable alternatives to conventional designs, where all measurements occur outside of hemodialysis. Furthermore, hybrid designs with both conventional and intradialytic measurements have nearly double the efficiency of conventional designs. Convex optimal design and Monte Carlo techniques were used to simultaneously optimize hemodialysis event characteristics and sampling times, accounting for population pharmacokinetic heterogeneity. We also present several related methodological innovations.

Introduction

Individual pharmacokinetic analysis is used to guide the management of drugs that exhibit widely variable kinetics in certain patient populations. In such cases, the use of “standard” dosing regimen can result in subtherapeutic or toxic drug concentrations. However, conventional pharmacokinetic study designs are costly in personnel, laboratory, and patient resources. In particular, the patient must endure the discomfort of repeated phlebotomy, and is more susceptible to infection and anemia. To mitigate the costs and risks, a mature literature has developed for the purpose of optimizing the frequency and timing of serial sampling, so that fewer samples are needed to yield an accurate estimate of individual pharmacokinetics (D’Argenio, 1981; Kong and Gonin, 2000; Gagnon and Leonov, 2004; Wang et al., 2012; Foo et al., 2012; Jelliffe, 2012). As a result, optimal sampling time techniques have been widely adopted.

The conventional pharmacokinetic study is a type of “challenge-response” experiment, wherein the system is disrupted, or *challenged* by injecting drug. The resultant physiologic distribution and elimination of drug, or *response* is informative about the underlying pharmacokinetic system. However, in clinical and research settings, there are additional opportunities to experimentally disrupt a pharmacokinetic system, and thereby garner additional information. We present evidence that the type and specific characteristics of such perturbations (e.g., intensity, duration, frequency) affect the relative amounts of information learned. Hence, we argue that experimental perturbations are useful in the study of individual pharmacokinetics, and demonstrate their amenability to optimal experimental

design. While the optimal frequency and timing of pharmacokinetic samples are the subject of an extensive literature (see Fedorov and Leonov, 2013, Chapter 7, and references therein), the optimal design of serial experimental perturbations is not well studied.

Many drugs exhibit kinetics that are well approximated by compartmental linear differential equation models (Bischoff and Dedrick, 1970). A compartmental model represents a *responsive* physiologic system, and can therefore model the concentration of drug under experimental perturbations. In conventional pharmacokinetic analysis, just the initial perturbation (i.e., resulting from the introduction of drug) is considered, although any number of subsequent perturbations can be modeled.

Though many types of perturbations are possible in the clinical environment, we evaluate a specific challenge characterized by intermittent exogenous elimination of drug from the blood. This type of challenge occurs routinely in the medical setting for patients receiving intermittent hemodialysis, and is readily modeled using compartmental methods. A sequence of such perturbations can be treated as part of the pharmacokinetic study design. In combination with statistical models for population (between-subject) and measurement (within-subject) uncertainty, the amount of information attained by such an experiment can be quantified and optimized by carefully selecting the characteristics of experimental perturbations. For a broad population, the resulting optimal designs offer significantly greater information regarding individual pharmacokinetics.

Methods

Pharmacokinetic & Statistical Models

Without loss of generality, we focus on the open two-compartment model. The model is visualized as a directed graph (Figure 1), with nodes that represent compartments, and edges that represent drug injection, intercompartmental distribution, and elimination. The two-compartment model is formally expressed as a system of two coupled ordinary differential equations, as follows

$$\frac{dc_1}{dt} = -k_{12}c_1 + k_{21}c_2 - k_{10}c_1 + \frac{k_R}{v_1} - \frac{k_D}{v_1}c_1 \quad (1)$$

$$\frac{dc_2}{dt} = k_{12}c_1 - k_{21}c_2 \quad (2)$$

where c_1 and c_2 represent drug concentration ($\text{mg}\cdot\text{L}^{-1}$) in the central (blood) and peripheral compartments, respectively. The central compartment volume is given by v_1 . The rate of drug injection in the central compartment is denoted k_R ($\text{mg}\cdot\text{h}^{-1}$). The expression $\frac{k_R}{v_1}$ formalizes the notion of intravenous infusion. The parameters k_{12} and k_{21} represent the rates (h^{-1}) of drug distribution between the compartments. The rate k_{10} (h^{-1}) and clearance k_D ($\text{L}\cdot\text{h}^{-1}$) represent endogenous and exogenous (i.e., hemodialysis) mechanisms of drug

elimination, respectively. In clinical settings, drug dosing and hemodialysis events are intermittent. Hence, in these equations, the parameters k_R and k_D are discrete (on/off) functions of time. Each parameter must take a nonnegative value. Solutions for c_1 and c_2 are found by integrating equations 1 and 2 in pieces that correspond to the periods of time where k_R and k_D are constant. Hence, this linear non-homogeneous system yields a piecewise analytic solution (see Online Supplement: Two-compartment Model Solution).

For a sequence of drug concentration measurements $\{y_1, \dots, y_n\}$ at times $\{t_1, \dots, t_n\}$, the statistical model is

$$\log y_i = \log c_1(t_i, k_D, \beta) + \varepsilon_i \quad (3)$$

where $c_1(t_i, k_D, \beta)$ is the solution to equation 1 at time t_i , β is the four-element vector of individual pharmacokinetic parameters $\{v_1, k_{10}, k_{12}, \text{ and } k_{21}\}$, and ε_i is a random variable with mean zero and standard deviation σ . The dialytic clearance function k_D is assumed to be known, but not fixed. That is, k_D may be experimentally modified. The dosing function k_R is assumed to be known and fixed, and is therefore omitted from the expression above. In studies of individual pharmacokinetics, β can be estimated by minimizing the sum of squared deviations

$$\hat{\beta} = \arg \min_{\beta \in \mathcal{B}} \sum_{i=1}^n [\log y_i - \log c_1(t_i, k_D, \beta)]^2, \quad (4)$$

where $\mathcal{B}$ is the space of possible (nonnegative) values that β can take, and $\hat{\beta}$ is the *nonlinear least-squares* estimate of β .

Target Drug & Population

Piperacillin is a beta-lactam antibiotic that is administered by intravenous infusion. Several authors have found that a one- or two-compartment model offers adequate approximation to piperacillin kinetics in patients with severe renal insufficiency (Thompson et al., 1981; Giron et al., 1981; De Schepper et al., 1982; Manley et al., 2000).

Francke et al. (1979) and Johnson et al. (1992) reported that, on average, 38% and 48% of piperacillin was dialyzed over the course of 4.0 and 3.2 hours, respectively. In addition, Francke et al. (1979) discovered that the blood concentration of piperacillin recovers by 33%, on average, after the conclusion of hemodialysis. The two-compartment model predicts that by initiating and then halting the flow of dialysate (i.e., by specifying a “square wave” pattern for k_D), the central compartment can experience a transient influx of drug (see Online Supplement: Dialytic Clearance). We believe this is the first demonstration of such theoretical and empirical concordance.

A random effects framework (Davidian and Giltinan, 2003) was used to model and simulate population (between-subject) pharmacokinetic variability. For v_1 , k_{10} , k_{12} , and k_{21} , represented as a four-element vector β , between-subject variability was modeled as follows

$$\beta = \beta_0 e^b \quad (5)$$

where β_0 is the population median and b is four-element vector of normal random variables with mean zero and covariance matrix Σ_0 .

The pharmacokinetics of beta-lactams are widely variable in patients with critical illness (Sime et al., 2012). Estimates of pharmacokinetic variability among patients with renal disease are themselves widely variable (Francke et al., 1979; Giron et al., 1981; Johnson et al., 1992; Manley et al., 2000). Although there is weak evidence of statistical dependence among the elements of β (Roberts et al., 2010), estimates of their covariation are generally omitted from the piperacillin literature. For the purposes of design optimization and simulation, we assume that the elements of β are mutually independent (diagonal Σ_0) with 25% coefficient of variation. In order to assess the robustness of optimization and simulation results to deviations from these assumptions, we also consider a scenario where the covariance matrix for b is instead a random variable Σ having a Wishart distribution with diagonal mean matrix Σ_0 and $\nu = 4$ degrees of freedom (i.e., the smallest value of ν that ensures positive definite Σ).

The population medians for parameters v_1 , k_{10} , k_{12} , and k_{21} were fixed at 10, 0.35, 3.5, and 1.5, respectively. These specific parameter values were selected to represent a typical patient with severe renal insufficiency (Thompson et al., 1981; De Schepper et al., 1982). For simulation purposes, the within-subject coefficient of variation was evaluated at 2.5%, 5.0%, and 10.0%. Variability in the resulting concentration-time kinetics was encompassing of that reported in the literature. The value of the dialytic clearance function k_D was fixed at 15 L·h⁻¹ while in dialysis, and zero otherwise.

Design Space

In conventional pharmacokinetic analysis, blood samples are drawn at one or more times during a single dosing cycle, with no additional pharmacological perturbation. Samples are generally more frequent just before or during drug administration, and less frequent afterward. For example, De Schepper et al. (1982) sampled immediately before and after drug administration by intravenous bolus injection over three minutes, and again at 5, 10, 20, 30, 60, and 90 minutes, and 2, 3, 4, 6 and 8 hours afterward.

In an *intradialytic* design, samples are collected exclusively during hemodialysis. A typical hemodialysis session has duration between three and four hours, and is repeated every 48 hours. The intradialytic design assumes that drug has been administered at a known time, dose, and route beforehand. The pharmacokinetic system is then perturbed by the initiation of dialysis, and may be further perturbed by halting and resuming the flow of dialysate, causing the drug concentration in blood to fluctuate. In addition to the arrangement of

sampling times, the lengths of time between starting, halting, and resuming dialysis are amenable to optimal design. The drug dose, infusion length and route, dosing cycle, and dialysis schedule are also potential design features. However, clinical and practical considerations often override their utility for this purpose.

We evaluated study designs that encompass two consecutive eight-hour dosing cycles. Each cycle began with administration of 3g piperacillin by intravenous infusion over one-half hour. The first cycle was uninterrupted, and hemodialysis was initiated halfway through the second cycle. The cumulative dialysis time (excluding the pause) was three hours (Figure 2). The set of all possible conventional sampling times included every whole minute boundary of the first dose cycle (labeled “Conventional Period” in Figure 2). The set of all possible intradialytic sample times included every whole minute boundary between the start and end of dialysis (labeled “Intradialytic Period” in Figure 2). The *hybrid* set of sample times included all possible conventional and intradialytic sample times.

The lengths of time between the start, pause, and resumption of dialysis, denoted $D = \{d^+, d^-\}$, were each allowed to take values 0.25, 0.50, 0.75, and 1.00 hours. The possibility of uninterrupted dialysis ($d^+ = d^- = 0$) was also considered, bringing the count of all possible dialysis challenges to 17. Hence, the intradialytic sampling period was 3.00, 3.25, 3.50, 3.75, or 4.00 hours in length, depending on the value of d^+ . The dialytic clearance function k_D is uniquely determined by the values of d^+ and d^- , such that k_D is equal to zero before and after dialysis ($t_j < 12$ hours and $t_j - 12 + 3 + d^-$ hours), when dialysis is paused ($12 + d^+ - t_j < 12 + d^+ + d^-$ hours), and otherwise equal to a fixed positive quantity ($15 \text{ L}\cdot\text{h}^{-1}$, or $250 \text{ mL}\cdot\text{min}^{-1}$).

We sought designs consisting of exactly 12 unique sample times among the $8 \cdot 60 + 1 = 481$ whole minute boundaries in the conventional sampling period and $3 \cdot 60 + 1 = 181$ (at

minimum) in the intradialytic period. Hence, there were more than $\binom{481+181}{12} \cdot 17$ possible combinations of sample times and dialysis challenges, or more than 10^{26} discrete experimental designs.

Initial drug concentrations within the central and peripheral compartments were computed using an “initialization” simulation consisting of four consecutive and uninterrupted dosing cycles that were otherwise identical to those described above. The first cycle was drug naïve, whereas the last cycle represented an approximate steady-state. The central and peripheral drug concentrations at the end of the fourth cycle were taken as initial values. Hence, the dosing cycles that encompass the conventional and intradialytic sampling periods represent the final two in a 48-hour dialysis cycle.

Design Optimality

In order to compare intradialytic, conventional, and hybrid designs, the corresponding subsets of designs were optimized separately using a two-stage approach. In the first stage, the mature theory of convex optimal design was used to identify optimal continuous designs and their discrete approximations, and to evaluate the robustness of the latter to uncertainty about the distribution of β . In the second stage, a Monte Carlo simulation method was used

to further evaluate the variability of parameter estimates (and other pharmacokinetic summaries) that arise under the efficient discrete designs.

Continuous Optimal Designs—The size of the discrete design space prohibits direct enumeration of all possible designs. In convex optimal design theory, discrete design spaces are made continuous by allowing certain aspects of designs to vary continuously. Such designs are often impossible to implement. However, for many of the most popular optimality criteria, an optimal continuous design can be identified efficiently (see Fedorov and Leonov, 2013). A discrete design can then be selected to approximate the optimal continuous design. Discrete approximations of optimal continuous designs are generally not optimal in the space of discrete designs, but are often very efficient.

Since the dialysis challenge design $D = \{d^+, d^-\}$ interacts with the set of possible intradialytic sample times, a divide-and-conquer approach was used to simultaneously optimize the location of sample times and dialysis challenge characteristics. To identify an optimal continuous design, *conditionally optimal* designs were first identified by conditioning on each of the 17 dialysis challenges. The most optimal among the conditionally optimal designs was taken as the optimal continuous design.

To represent continuous and discrete designs in this framework, let ξ be a collection of weights (W) with corresponding sample times (T), and the lengths of time (D) between the start, pause, and resumption of dialysis:

$$\xi = \begin{Bmatrix} W \\ T \\ D \end{Bmatrix} = \begin{Bmatrix} w_1, \dots, w_M \\ t_1, \dots, t_M \\ d^+, d^- \end{Bmatrix}.$$

For continuous designs, the weights w_j are bounded and normalized such that $0 \leq w_j \leq 1$ for all $j = 1 \dots M$, and $\sum w_j = 1$. For conventional designs, $M = 481$ is the count of all possible conventional sample times. For intradialytic and hybrid designs, $M = (181 + 60d^+ + 1)$ and $M = (481 + 181 + 60d^+ + 1)$ are the counts of all possible intradialytic and hybrid sample times, respectively. While continuous designs have normalized weights, discrete designs have nonnegative integer weights. Hence, for discrete designs, each w_j represents the count of samples that occur at time t_j , and $N = \sum w_j$ is the total number of samples. Discrete designs of size N are denoted ξ_N .

A linear combination of two continuous designs is defined by summing the corresponding weights

$$\alpha\xi + \alpha'\xi' = \begin{Bmatrix} \alpha W + \alpha' W' \\ T \\ D \end{Bmatrix}, \quad (6)$$

where α and α' are scalars. Operation 6 is only defined for designs ξ and ξ' with identical sample times $T = T'$ and dialysis challenge characteristics $D = D'$.

We sought designs that were robust to population pharmacokinetic variability. In particular, we selected designs that optimizes the population averaged D-optimality criterion (Fedorov, 1972), or more compactly, the ED-optimality criterion (Pronzato and Walter, 1985). A design is D-optimal if it minimizes the D-optimality criterion

$$\Psi_D(\xi, \beta) = \log |I(\xi, \beta)^{-1}|, \quad (7)$$

where $|I(\xi, \beta)^{-1}|$ is the determinant of the inverse *information matrix* given design ξ and parameter β :

$$I(\xi, \beta) = \sum_{j=1}^M w_j \mu(t_j, k_D, \beta) = \sum_{j=1}^M w_j \frac{\partial \log c_1(t_j, k_D, \beta)}{\partial \beta} \frac{\partial \log c_1(t_j, k_D, \beta)}{\partial \beta^T}. \quad (8)$$

The D-optimality criterion is attractive in studies of individual pharmacokinetics due to its intuitive relationship with the nonlinear least-squares estimator $\hat{\beta}$, defined by expression 4. Under mild conditions (Fedorov and Leonov, 2013, Section 1.4), the distribution of $\hat{\beta}$ is approximately normal with mean β and variance $V[\hat{\beta}] = \sigma^2 I(\xi, \beta)^{-1}$, where estimates $\hat{\sigma}^2$ and $\hat{\beta}$ are substituted for the unknown parameters σ^2 and β when it is necessary to estimate the value of $V[\hat{\beta}]$. Hence, an approximate $100(1 - \alpha)\%$ confidence ellipsoid for β is given by

$$\left\{ \beta : (\beta - \hat{\beta})^T I(\xi, \hat{\beta}) (\beta - \hat{\beta}) \leq \hat{\sigma}^2 \chi_{p, \alpha}^2 \right\} \quad (9)$$

where $\chi_{p, \alpha}^2$ is the $100(1 - \alpha)\%$ percentile of the χ^2 distribution with $p = 4$ degrees of freedom. The ellipse volume is inversely proportional to the square root of $|I(\xi, \beta)^{-1}|$. Hence, a D-optimal design assures the confidence ellipsoid with smallest volume.

Designs that are D-optimal for a particular value of β are said to be *locally* D-optimal. In contrast, optimality criteria that account for uncertainty in β are said to be *robust*. The ED-optimality criterion accounts for uncertainty by averaging the D-optimality criterion over a specified prior distribution for β . In the current context, the prior distribution for β represents population pharmacokinetic variability. A design is ED-optimal if it minimizes the ED-optimality criterion:

$$\Psi_{ED}(\xi) = E_{\beta} [\log |I(\xi, \beta)^{-1}|], \quad (10)$$

where E_{β} denotes the expected value with respect β . The *relative ED-efficiency*

$$R_{ED}(\xi, \xi') = (\Psi_{ED}(\xi) / \Psi_{ED}(\xi'))^{(1/p)}$$

is a relative measure of ED-optimality for competing designs, where $p = 4$ is the count of free model parameters.

Fedorov and Leonov (2013) present a generic first-order design optimization algorithm as follows. For continuous design $\xi^{(s)}$ at iteration s ,

$$\xi^{(s+1)} = (1 - \alpha^{(s)})\xi^{(s)} + (\alpha^{(s)})\xi^m \quad (11)$$

where $\alpha^{(s)} = 1/(M + s)$ is a fixed sequence of values that determine the rate of algorithm convergence, and ξ^m is a continuous design with exactly one nonzero weight $w_m = 1$. At each iteration, the index m corresponds to the sample time t_m that maximizes a *sensitivity function*, denoted $\phi(t, \xi, \beta)$ at design $\xi^{(s)}$. The sensitivity function quantifies the reduction in an optimality criterion that results from a small increase in the weight associated with sample time t , and a corresponding decrease in the weights associated with all other times to ensure that the weights remain standardized. For the ED-optimality criterion, the sensitivity function is

$$\phi_{ED}(t, \xi) = \int \phi_D(t, \xi, \beta) F(d\beta) = \int \text{tr}[\mu(t, k_D, \beta) I(\xi, \beta)^{-1}] F(d\beta) \quad (12)$$

where $\mu(t, k_D, \beta)$ is the information contribution at time t (equation 8), and $F(d\beta)$ is the population distribution of β (equation 5). The expression under the integral sign is the sensitivity function of the D-optimality criterion. See Fedorov and Leonov (2013), Sections 2.24, 2.5, 3.2, and 5.2, for additional details.

Rather than directly compute the integral in equation 12, we adapted the approach of Pronzato and Walter (1985) to implement a stochastic version of algorithm 11 where, at each iteration, β' was randomly selected according to F , and m corresponds to the sample time t_m that maximizes the D-optimality sensitivity function $\phi_D(t, \xi^{(s)}, \beta')$. Equal weights were initially specified for each sample time. The stochastic algorithm was then applied over 10000 iterations. The algorithm pseudo-code is as follows:

1. initialize $\xi^{(0)}$, set $W^{(0)} = 1/M$ elementwise, then for $s = 0, 1, \dots, 10000$,
2. randomly select β' according to F
3. identify $m \in 1 \dots M$ such that $\phi_D(t_m, \xi^{(s)}, \beta')$ is maximized
4. compute $\xi^{(s+1)} = (1 - \alpha^{(s)})\xi^{(s)} + (\alpha^{(s)})\xi^m$

The continuous design at the final iteration was taken as the optimal continuous design. Under mild conditions, the stochastic version of the algorithm converges almost surely.

Specifically, equality 12 must be valid and the sequence of step sizes must satisfy $\sum_s \alpha^{(s)} = \infty$ and $\sum_s (\alpha^{(s)})^2 < \infty$ (Bottou, 1998).

The optimality of continuous designs can be assessed using one of several equivalent criteria, which are given by well-known “equivalence theorems” in the optimal experimental design literature (Fedorov and Leonov, 2013). For ED-optimality, one such criterion is that the value of the ED-sensitivity function is nowhere larger than the number of free model parameters, which is four in the current context. In order to evaluate this equivalence criterion, the ED-sensitivity function was approximated by averaging the D-sensitivity function over 10000 samples from the population distribution of β .

Efficient Discrete Designs—Although the continuous optimal design framework is needed to overcome the combinatorial complexity of discrete designs, the latter is often required for practical implementation. In many cases, an apportionment or “rounding” method can be used to approximate an optimal continuous design. For finite sample size N and continuous design ξ , the apportionment method prescribes that, for each $j \in 1, \dots, M$, the nearest integer to $w_j N$ is the discrete weight corresponding to time t_j (Pukelsheim, 2006). Of course, the apportionment method does not ensure that the N sample times will be unique, which is a practical constraint for the problem at hand. Even if the uniqueness constraint were relaxed, the apportionment method can perform poorly when N is smaller than the count of nonzero continuous weights, which is often the case for nearly ED-optimal continuous designs.

In order to overcome these deficiencies in the apportionment method, and to satisfy the uniqueness constraint, we developed an alternative discretization algorithm consisting of three steps. The first step is to apply the apportionment method for a large sample size $N^* \gg N$, where N is the target sample size, and N^* is selected to ensure that the apportioned design achieves a specified relative ED-efficiency. For our purposes, $N^* = 100$ ensured greater than 99% ED-efficiency, relative to the nearly optimal continuous design. The second and third steps satisfy the uniqueness and sample size constraints, respectively. In the second step, duplicate sample times are discarded. Note that this step can result in fewer than N sample times. However, when there are at least N nonzero continuous weights, this can be remedied by increasing the value of N^* . In the final step, sample times are discarded in a sequentially ED-efficient manner until exactly N sample times remain. In order to compactly write the algorithm pseudo-code, define the following function $\psi_{ED}(\xi_n, m) = \Psi_{ED}(\xi_n - \xi^m)$, where ξ^m has exactly one nonzero weight $w_m = 1$. This function computes the value of the ED-optimality criterion that results from discarding a single observation at time t_m from discrete design ξ_n . For continuous design ξ , target sample size N , and sequence of discrete designs ξ_s the algorithm pseudo-code is as follows:

1. initialize ξ_{N^*} with weights $W_{N^*} = \lfloor W + 1/2 \rfloor$ elementwise, set $s = \sum_j \mathbb{I}(W_{N^*} > 0)$
2. set $W_s = 1$ if $W_{N^*} > 0$ else set $W_s = 0$, elementwise
3. while $s > N$, do the following
 - identify $m \in 1 \dots M$ such that $\psi_{ED}(\xi_s, m)$ is maximized

- set $\xi_{s-1} = \xi_s - \xi^m$
- set $s = s - 1$

The three-step discretization algorithm was used to compute efficient discrete designs for the conventional, intradialytic, and hybrid design subsets. The three-step method performs well in the current application. However, neither it nor the apportionment method guarantee optimality of the resulting discrete design. This is a reflection of the difficulty in optimizing discrete designs, and is considered acceptable since the efficiency loss due to discretization can be directly computed (i.e., using the relative ED-efficiency metric). Hence, a discretized design (or discretization algorithm) may be rejected when it does not yield acceptable ED-efficiency relative to a corresponding continuous design.

Design Assessment

In order to assess the robustness of efficient discrete designs to uncertainty about the population distribution of β , the ED-optimality criterion was re-computed by specifying additional uncertainty in the distribution of b . In the revised calculations, b was multivariate normal distributed with mean zero and *random* covariance matrix Σ , where Σ had a Wishart distribution with diagonal mean matrix Σ_0 and $\nu = 4$ degrees of freedom. In order to emphasize dependence on Σ , equation 10 is rewritten as follows:

$$\Psi_{ED}(\xi, \Sigma) = E_{\beta|\Sigma} [|I(\xi, \beta)|]$$

The revised ED-optimality criterion, denoted $\Psi'_{ED}(\xi)$, is given by

$$\begin{aligned}\Psi'_{ED}(\xi) &= E_{\Sigma} [E_{\beta|\Sigma} [|I(\xi, \beta)|]] \\ &= E_{\Sigma} [\Psi_{ED}(\xi, \Sigma)].\end{aligned}$$

Hence, $\Psi'_{ED}(\xi)$ may be interpreted as the average ED-optimality associated with design ξ under a variety of deviations from Σ_0 .

Each efficient discrete design was further evaluated using a Monte Carlo simulation technique. Experimental data ($n = 12$) were simulated for 10000 subjects by combining the measurement error and population variability models, jointly characterized by expressions 3 and 5, respectively, where e_i was further specified to be normally distributed. For each simulated subject, a nonlinear least-squares method was used to estimate the two-compartment model parameters v_1 , k_{10} , k_{12} , and k_{21} . Given these estimates, we also estimated (1) the fraction of time that drug concentration in blood was greater than a minimum inhibitory level of $64 \text{ mg}\cdot\text{mL}^{-1}$ (denoted %T>MIC), and (2) the area under the concentration-time curve (AUC) for the combined conventional and intradialytic dosing cycles (16h total). These two quantities are important in clinical assessments of drug exposure. The three efficient discrete designs were compared by computing the associated bias and root-mean-squared-error (RMSE) for estimates of each model parameter, %T>MIC, and AUC.

Results

ED-Optimality

Figure 3 illustrates the optimized continuous conventional, hybrid, and intradialytic designs and the corresponding approximate ED-sensitivity function, which demonstrate *near* ED-optimality (i.e., the sensitivity function is nearly everywhere less than the number of free model parameters). The discrete hybrid design included both conventional and intradialytic sample times. The conventional times concentrated around the dose administration period, at 7, 8, 9, 10, 44, 45, and 46 minutes following the start of IV infusion (note that the IV infusion was completed at minute 30). The optimal dialytic challenge was characterized by a 30 minute initial dialysis period, followed by a 60 minute pause. However, the discrete hybrid design with no pause in dialysis was just 3% less ED-efficient. The intradialytic sample times occurred at 27, 28, 29, and 30 minutes following the start of dialysis, and at the end of dialysis. Note that no sample times occurred during the pause in dialysis.

The discrete conventional design consisted of sample times at 4, 10, 11, 12, 42, 43, 44, 105, 106, 107, 108, minutes, and at 8 hours following the start of IV infusion. This design was 44% less efficient than the discrete hybrid design. For comparison purposes, we also evaluated the (non-optimal) discrete design reported by De Schepper et al. (1982), excluding the 6 hour time, so that the remaining 12 times are more comparable with the efficient discrete design. This design was 53% less efficient than the discrete hybrid design, and just 15% less efficient than the discrete conventional design.

The dialytic challenge associated with the discrete intradialytic design was characterized by a 60 minute initial dialysis period (i.e., 30 minutes longer than the discrete hybrid design), followed by a 60 minute pause. The sample times occurred at the start of dialysis, 8, 9, 37, 38, and 39 minutes afterward, 12, 13, and 14 minutes into the pause of dialysis, at the resumption of dialysis, six minutes afterward, and at the end of dialysis. The discrete intradialytic design was 48% less efficient than the discrete hybrid design, but just 7% less efficient than the discrete conventional design.

Discretization of optimal continuous designs resulted in loss of efficiency. However, each approximation was more than 90% ED-efficient. Table 1 lists the values of the ED-optimality criterion associated with each discrete design, the ED-efficiencies relative to the discrete hybrid design, and the ED-efficiencies relative to the continuous design (i.e., the discretization efficiency). Table 2 catalogs a series of discrete designs, including the twelve-sample designs evaluated here and corresponding nine-sample and six-sample designs. The latter were derived by extending the third step of the discretization algorithm, which discards sample times in a sequentially ED-efficient fashion. The nine-sample and six-sample designs were not evaluated further.

Using the alternative sensitivity analysis criterion $\Psi'_{ED}(\xi)$, the discretize conventional, intradialytic, and hybrid designs were 1%, 13%, and 2% *larger* more efficient, respectively. Although the average ED-optimality under a variety of deviations in Σ_0 was greater for each design, the difference was much larger in magnitude for the intradialytic design. This

suggests that the intradialytic design may be more sensitive than the conventional or hybrid designs to assumptions about the distribution of β .

Simulation

For 2.5% and 5.0% within-subject coefficient of variation, the discrete hybrid design demonstrated the smallest bias and root mean square error for each kinetic parameter and AUC. For 10% error variance, the discrete hybrid design showed the smallest bias for all parameters except k_{12} and %T>MIC, and the smallest RMSE for all parameters except k_{12} . The discrete intradialytic design showed the smallest bias and RMSE for k_{12} . Table 3 lists the detailed results of simulation.

In a fraction of simulations, there was insufficient information to uniquely identify nonlinear least squares estimates of the four kinetic parameters (i.e., the estimates were not “estimable”). In such cases, the determinant of the observed information matrix was near (i.e. within floating point precision) or equal to zero. The discrete hybrid design was associated with the fewest such simulations. For 2.5%, 5.0% and 10.0% measurement error respectively, the kinetic parameters were not identifiable in 0.31%, 0.69% and 2.19% of samples simulated under the discrete hybrid design, 0.6%, 1.17% and 4.58% for the discrete conventional design, 0.43%, 1.89% and 8.65% for the discrete intradialytic design.

Discussion

These results demonstrate that intradialytic study of piperacillin kinetics may be viable as an alternative or supplement to conventional pharmacokinetic designs in patients with severe renal insufficiency. As an alternative, the intradialytic design is somewhat less efficient than the conventional design. However, efficient hybrid designs consisting of both conventional and intradialytic measurements are especially powerful, nearly doubling the ED-efficiency of efficient conventional designs. These findings were robust to uncertainty about population pharmacokinetic heterogeneity, and were further supported by Monte Carlo simulation.

Intradialytic designs have several added practical advantages. First, the sampling period is generally shorter (3–4 hours) than that associated with conventional designs (8–24 hours). Secondly, samples may be collected directly from the dialysis apparatus, thereby reducing or eliminating the need for phlebotomy. Finally, it may be possible to use drug concentration in dialysate as a surrogate for blood, thereby eliminating the need to draw blood.

The results of simulation suggest that some parameters are more sensitive than others with respect to (within-subject) error variability. In particular, the RMSE associated with the estimate of k_{12} increased dramatically at the 10% error variance level. It is also notable that the efficient intradialytic design offered the most precise estimate of k_{12} at that level.

In a small fraction of simulations, the two-compartment model parameters were not estimable. When this occurs, it may be possible to restrict the model parameterization to an estimable subset. As a first step, the intercompartmental distribution rates k_{12} and k_{21} can be set equal, thereby reducing the count of free parameters to three. If the remaining parameters are not identifiable, then the intercompartmental distribution rate can be set equal to zero.

The resulting model is identical to a one-compartment model with two free parameters: compartment volume v_1 and elimination rate k_{10} .

This work makes some limiting assumptions that warrant additional discussion. First, we have assumed that dialytic elimination of piperacillin is a first-order process (proportional to blood concentration), and that the associated rate parameter k_D is known and constant. In practice, k_D must be estimated by alternative means. When precise estimates are not available, the efficiency associated with intradialytic measurement may be blunted.

Second, realistic investigation of optimal design is significantly hampered by uncertainty about population pharmacokinetic variability. Specifically, studies that report estimates of population kinetics for piperacillin generally omit details regarding the (between-subject) covariability in pharmacokinetic parameters. In the current study, we assumed that the between-subject covariability is negligible. Although the efficient discrete designs are robust to deviations from this assumption, the computed ED-optimality criterion may not be fully representative of the target population. Improved reporting of population pharmacokinetic variability is needed.

Although we consider a somewhat narrow clinical scenario, the techniques presented here are extensible within and beyond the context of pharmacokinetic analysis. Dosing characteristics such as the amount, frequency, and route of administration, and other types of perturbations (e.g., chemical, mechanical, radiological, etc) are all potential study design aspects. Extensions of the two-compartment model (e.g., nonlinear Michaelis–Menten kinetics), and other types of model and biological phenomena (e.g., Hodgkin-Huxley model of electrical activity in excitable cells) are candidates for this type of design optimization. We hope that this work broadens the domain of optimal design applications in pharmacokinetic analysis, and more generally to applications involving dynamic biomathematical models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The two-compartment model as a directed graph, where c_1 and c_2 represent drug concentration in compartments 1 and 2, respectively. The volume of compartment 1 is denoted v_1 (not pictured). The parameters k_R , k_{12} , k_{21} , k_{10} and k_D are rates that characterize drug injection, intercompartmental distribution, and elimination, respectively.

Figure 2.

Conventional and intradialytic sampling periods. The horizontal bars above the figure delineate the periods of time that include all possible conventional or intradialytic sample times. The black line and solid gray region within the figure represent the range of typical blood concentrations of piperacillin that result from repeated dosing and dialysis in a population with severe renal insufficiency. The vertical bars filled with angled lines correspond to periods of IV drug infusion or dialytic drug removal. The symbols d^+ and d^- represent the lengths of time between the start, pause, and resumption of dialysis.

Figure 3.

Continuous ED-optimized designs and corresponding sensitivity functions for each of the conventional, hybrid, and intradialytic design subsets. Vertical lines represent continuous design weights for each possible sample time. Curved lines represent the corresponding sensitivity functions. Dashed horizontal lines mark the sensitivity function value (4.0) associated with the ED-optimality equivalence criterion. Vertical bars filled with angled lines correspond to periods of IV drug infusion or dialytic drug removal, respectively. The lengths of time d^+ and d^- for the hybrid and intradialytic designs are indicated by the widths of the initial dialysis period and the dialysis intermission.

Table 1

ED-optimality criterion values for the discrete hybrid, conventional, and intradialytic designs. The “Hybrid” field lists the ED-efficiencies relative to the discrete hybrid design. The “Discretization Efficiency” field lists the ED-efficiencies relative to the corresponding continuous optimal design (i.e., the loss in efficiency due to discretization).

Design	ED-Opt.	Hybrid	Discretization Efficiency
Hybrid	$6.8e^{-3}$	100%	92%
Conventional	$6.5e^{-4}$	55%	90%
Intradialytic	$4.8e^{-4}$	52%	91%
De Schepper et al. (1982)	$2.9e^{-4}$	45%	—

Table 2

Efficient conventional, hybrid, and intradialytic discrete designs for sample sizes 12, 9 and 6. All sample times are listed in minutes relative to the start of the first of two 30-minute infusions separated by eight hours (480 minutes). For the hybrid and intradialytic designs, the dialysis event begins four hours after the start of the second infusion. The quantities d^+ and d^- are the lengths of time in minutes of the initial dialysis period and the dialysis intermission, respectively.

Design	d^+, d^-	Size	Sample Times
Hybrid	60, 60	12	7, 8, 9, 10, 44, 45, 46, 747, 748, 749, 750, 960
Hybrid	60, 60	9	8, 9, 10, 44, 45, 748, 749, 750, 960
Hybrid	60, 60	6	8, 9, 44, 748, 749, 960
Conventional	—, —	12	4, 10, 11, 12, 42, 43, 44, 105, 106, 107, 108, 480
Conventional	—, —	9	10, 11, 12, 42, 43, 106, 107, 108, 480
Conventional	—, —	6	10, 11, 42, 106, 107, 480
Intradialytic	30, 60	12	720, 728, 729, 757, 758, 759, 792, 793, 794, 840, 846, 960
Intradialytic	30, 60	9	720, 728, 729, 758, 759, 792, 793, 840, 960
Intradialytic	30, 60	6	720, 729, 758, 792, 840, 960

Table 3

Bias and root mean square error (RMSE) associated with each kinetic parameter, and the two clinically informative parameters %T>MIC and AUC, for 10,000 simulations under each efficient discrete design, and for three values of within-subject coefficient of variation.

Error	Criteria	Design	k_{10}	v_1	k_{12}	k_{21}	%T>MIC	AUC
2.5%	Bias	Hybrid	0.003	-0.005	0.078	0.001	-0.005	-0.215
		Conventional	0.005	-0.026	0.132	0.007	-0.009	-0.552
	RMSE	Intradialytic	0.005	0.042	0.122	0.009	0.000	0.848
		Hybrid	0.033	0.903	0.803	0.158	0.132	18.821
		Conventional	0.042	1.088	0.992	0.236	0.219	19.972
		Intradialytic	0.052	1.609	1.118	0.202	0.142	27.608
5%	Bias	Hybrid	0.013	-0.010	0.407	0.004	-0.012	0.128
		Conventional	0.022	-0.066	0.697	0.017	-0.028	-2.321
	RMSE	Intradialytic	0.024	0.163	0.610	0.028	0.011	4.991
		Hybrid	0.091	1.850	2.807	0.318	0.251	37.273
		Conventional	0.126	2.212	3.861	0.506	0.441	40.285
		Intradialytic	0.151	3.346	3.889	0.445	0.282	54.604
10%	Bias	Hybrid	0.084	0.034	2.487	-0.020	-0.041	3.995
		Conventional	0.100	-0.202	2.927	0.016	-0.111	-5.289
	RMSE	Intradialytic	0.084	0.585	1.824	0.167	0.032	27.084
		Hybrid	0.351	3.731	10.125	0.650	0.498	78.971
		Conventional	0.378	3.900	10.309	0.883	0.875	81.385
		Intradialytic	0.366	6.252	8.184	3.186	0.555	111.176