ARTICLE

Limited-Sampling Strategies for Anti-Infective Agents: Systematic Review

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ABSTRACT

Background: Area under the concentration–time curve (AUC) is a pharmacokinetic parameter that represents overall exposure to a drug. For selected anti-infective agents, pharmacokinetic–pharmacodynamic parameters, such as AUC/MIC (where MIC is the minimal inhibitory concentration), have been correlated with outcome in a few studies. A limited-sampling strategy may be used to estimate pharmacokinetic parameters such as AUC, without the frequent, costly, and inconvenient blood sampling that would be required to directly calculate the AUC.

Objective: To discuss, by means of a systematic review, the strengths, limitations, and clinical implications of published studies involving a limited-sampling strategy for anti-infective agents and to propose improvements in methodology for future studies.

Methods: The PubMed and EMBASE databases were searched using the terms "anti-infective agents", "limited sampling", "optimal sampling", "sparse sampling", "AUC monitoring", "abbreviated AUC", "abbreviated sampling", and "Bayesian". The reference lists of retrieved articles were searched manually. Included studies were classified according to modified criteria from the US Preventive Services Task Force.

Results: Twenty studies met the inclusion criteria. Six of the studies (involving didanosine, zidovudine, nevirapine, ciprofloxacin, efavirenz, and nelfinavir) were classified as providing level I evidence, 4 studies (involving vancomycin, didanosine, lamivudine, and lopinavir–ritonavir) provided level II-1 evidence, 2 studies (involving saquinavir and ceftazidime) provided level II-2 evidence, and 8 studies (involving ciprofloxacin, nelfinavir, vancomycin, ceftazidime, ganciclovir, pyrazinamide, meropenem, and alpha interferon) provided level III evidence. All of the studies providing level I evidence used prospectively collected data and proper validation procedures with separate, randomly selected index and validation groups. However, most of the included studies did not provide an adequate description of the methods or the characteristics of included patients, which limited their generalizability.

Conclusions: Many limited-sampling strategies have been developed for anti-infective agents that do not have a clearly established link between AUC and clinical outcomes in humans. Future studies should first determine if there is an association between AUC monitoring and clinical outcomes. Thereafter, it may be worthwhile to prospectively develop and validate a limited-sampling strategy for the particular anti-infective agent in a similar population.

Key words: limited-sampling strategy, anti-infectives, pharmacokinetics, therapeutic drug monitoring

RÉSUMÉ

Contexte : L'aire sous la courbe de la concentration en fonction du temps (ASC) est un paramètre pharmacocinétique qui représente l'exposition globale d'un patient à un médicament. En ce qui a trait à des agents anti-infectieux sélectionnés, les paramètres pharmacocinétiques et pharmacodynamiques, comme l'ASC/CMI (concentration minimale inhibitrice), ont été corrélés avec les résultats cliniques dans un nombre limité d'études. On peut utiliser une stratégie de prélèvements limités pour estimer la valeur des paramètres pharmacocinétiques, comme l'ASC, sans avoir à recourir aux prélèvements de sang fréquents, coûteux et peu pratiques qui sont nécessaires pour calculer directement l'ASC.

Objectif : Discuter, au moyen d'une analyse systématique, les forces, les limites et les implications cliniques des études publiées comportant une stratégie de prélèvements limités pour les agents anti-infectieux et proposer des améliorations à la méthodologie de futures études.

Méthodes : Les bases de données PubMed et EMBASE ont été interrogées en utilisant les termes « agents anti-infectieux » (« anti-infective agents »), « prélèvements limités » (« limited sampling »), « prélèvements optimaux » (« optimal sampling »), « prélèvements parcimonieux » (« sparse sampling »), surveillance de l'ASC (« AUC monitoring »), ASC abrégée (« abbreviated AUC »), prélèvements simplifiés (« abbreviated sampling ») et bayésien (« Bayesian »). Les listes de référence des articles extraits ont été examinées manuellement. Les études retenues ont été classées selon des critères modifiés du *US Preventive Services Task Force*.

Résultats : Vingt études ont satisfait aux critères d'inclusion. Six de ces études (portant sur la didanosine, la zidovudine, la névirapine, la ciprofloxacine, l'éfavirenz et le nelfinavir) ont été classées comme fournissant des données probantes de niveau I, quatre études (portant sur la vancomycine, la didanosine, la lamivudine et le lopinavir–ritonavir) ont fourni des données probantes de niveau II-1, deux études (portant sur le saquinavir et la ceftazidime) ont fourni des données probantes de niveau II-2, et huit études (portant sur la ciprofloxacine, le nelfinavir, la vancomycine, la ceftazidime, le ganciclovir, la pyrazinamide, le méropenem et l'interféron alpha) ont fourni des données probantes de niveau III. Toutes les études fournissant des données probantes de niveau I ont utilisé des données recueillies prospectivement et des méthodes de validation adéquates avec un groupe de référence et un groupe de validation distincts et choisis au hasard. Cependant, la plupart des études incluses n'ont pas fourni une description adéquate des méthodes ou des caractéristiques des patients admis, ce qui a limité leur généralisabilité.

Conclusions : Plusieurs stratégies de prélèvements limités ont été développées pour les agents anti-infectieux et elles ne comportent pas de lien clairement établi entre l'ASC et les résultats cliniques chez l'humain. Les études ultérieures devraient d'abord déterminer s'il existe un lien entre la surveillance de l'ASC et les résultats cliniques. Il pourra par la suite

s'avérer utile de développer et de valider prospectivement une stratégie de prélèvements limités pour un agent anti-infectieux particulier chez une population de patients similaire.

Mots clés : stratégies de prélèvements limités, agents anti-infectieux, pharmacocinétique, surveillance thérapeutique pharmacologique

[Traduction par l'éditeur]

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INTRODUCTION

It has been proposed that therapeutic drug monitoring is warranted when a drug exhibits a narrow therapeutic range, therapy is of sufficient duration, pharmacokinetic parameters have been correlated with clinical outcome, the pharmacodynamic response is not readily assessable, and/or the drug assay results provide more information than clinical judgement alone.[1] For a drug that is suitable for therapeutic drug monitoring, measurement of the area under the concentration–time curve (AUC) is considered a good representation of overall exposure to the drug. For selected anti-infective agents, pharmacokinetic parameters such as AUC/MIC (drug exposure relative to the bacterial minimum inhibitory concentration) and peak/MIC (peak concentration relative to the bacterial minimum inhibitory concentration) have been correlated with outcomes in animal, in vitro, and a small number of human studies.[2] In their review of pharmacokinetic and pharmacodynamic considerations for selecting agents for outpatient parenteral antimicrobial therapy, Slavik and Jewesson[2] discussed several anti-infectives for which AUC/MIC may correlate with clinical efficacy. Such agents include, but are not limited to, fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin) and quinupristin–dalfopristin.[2]

The use of AUC is limited, however, by the large number of blood samples required for its accurate determination. As many as 10 or more samples may be needed to characterize AUC in the research setting, but in clinical practice such frequent blood sampling is impractical, time-consuming, costly, and, for infants, potentially unethical. It also may not be possible to obtain blood samples frequently from elderly or critically ill patients with poor venous access.

One proposed method of reducing the cost and inconvenience of frequent sampling is the use of limited-sampling strategies. A limited-sampling strategy is a method of characterizing pharmacokinetic parameters, particularly the AUC, using relatively few blood samples, usually 3 or fewer. The methods used to develop and validate limited-sampling strategies have been reviewed elsewhere.[3-7] Briefly, these approaches are usually developed using either multiple regression analysis with a stepwise approach or population estimates with the Bayesian approach. Multiple regression analysis determines the relation between the dependent variable (usually AUC) and various independent variables (i.e., timed concentrations from serially collected blood samples). The resulting limited-sampling strategy is described as follows:

$$\text{AUC} = b + m_1C(t_1) + m_2C(t_2) + m_3C(t_3) + \ldots m_iC(t_i)$$

where $C(t)$ is the drug concentration at time t_i, b represents the y-intercept, and m_i represents the slope of the equation at time t_i.[3-7] The Bayesian method blends population estimates with data from individual patients; as such, both population and individual data are required. If population estimates are unavailable, the index data set can be used to determine them. Then, one or more timed concentrations from the validation data set are entered as individual data to predict the AUC. Equations with a high coefficient of determination (r^2) are typical candidates for a limited-sampling strategy, which is then subjected to testing with a validation data set.[3-7] Acceptable methods for validation include data splitting (ideally by randomly assigning patients to index and validation groups), cross-validation (multiple data splitting), jackknife resampling, and bootstrap resampling. Bias and the precision of limited-sampling strategies are often presented as mean prediction error and mean squared prediction error, according to the methods of Scheiner and Beal.[8] A commonly accepted range of bias and precision values is 15% to 20%. Another important requirement of a clinically useful limited-sampling strategy would be a maximum of 3 conveniently timed (e.g., obtained within 4 h after administration of a dose) concentrations.[3-7]

The objectives of this review were to critically evaluate published limited-sampling strategies for anti-infective agents, to discuss the clinical implications of these strategies as they apply to anti-infectives, and to propose improvements in methodology for future studies of limited-sampling strategies.

METHODS

The PubMed (January 1966 to December 2008) and EMBASE (January 1980 to December 2008) databases were searched to identify potential studies for review. The following search terms were used: "anti-infective agents", "limited sampling", "optimal sampling", "sparse sampling", "AUC monitoring", "abbreviated AUC", "abbreviated sampling", and "Bayesian". The reference lists of retrieved articles were also searched manually.

Studies were retrieved if the abstract described the use of limited, optimal, or sparse blood sampling for monitoring an anti-infective agent. Studies published in abstract form were excluded. Studies published in full were included if they described the development of limited-sampling strategies to predict AUC or peak concentrations for anti-infective agents in humans and were written in English. Studies conducted in

healthy volunteers or in patients without an active infection were excluded; the results of such studies cannot be extrapolated to patients with active infections because of potential differences in pharmacokinetic–pharmacodynamic parameters. Also excluded were studies that did not suggest sampling times and those that merely described a previously developed and validated limited-sampling strategy.

Included studies were classified according to their levels of evidence. Because there are no formalized criteria for determining levels of evidence for studies of limited-sampling strategies, the criteria were adapted from those developed by the US Preventive Services Task Force.[9] This adaptation has been used successfully in previous reviews of limited-sampling strategies of immunosuppressants[5] and chemotherapy agents.[6,7] Studies were classified into 4 categories (level I, II-1, II-2, or III) according to criteria presented in Table 1.[5-7,9]

RESULTS

Thirty-four studies met the initial inclusion criteria.[10-44] Fourteen of these studies[10-24] were excluded: 4 were conducted in healthy volunteers,[10-13] 1 involved volunteers with cystic fibrosis who did not have an active infection,[14] 8 did not suggest sampling times,[14-22] and 2 studied previously validated limited-sampling strategies in new populations.[23,24] Table 2 summarizes the characteristics of the included studies[25-44] according to their levels of evidence. The following information was extracted from each study: level of evidence, the anti-infective agent, the population for derivation of the limited-sampling strategy, the sampling times investigated, the suggested timed samples, the equation(s) for the limited-sampling strategy, r (the correlation coefficient) or r^2, the percent bias for the validation group, the percent precision, and additional comments.

Two studies for each of the following drugs described limited-sampling strategies (Table 2): ciprofloxacin (level I and level III evidence, respectively), didanosine (level I and level II-1 evidence, respectively), nelfinavir (level I and level III evidence, respectively), vancomycin (level II-1 and level III evidence, respectively) and ceftazidime (level II-2 and level III evidence, respectively). Limited-sampling strategies were described in a single study for each of the following agents: zidovudine (level I evidence), nevirapine (level I evidence), efavirenz (level I evidence), lamivudine (level II-1 evidence), lopinavir–ritonavir (level II-1), saquinavir (level II-2 evidence), ganciclovir (level III evidence), pyrazinamide (level III evidence), meropenem (level III evidence) and alpha interferon (level III evidence).

DISCUSSION

Study Strengths and Limitations

Six studies of limited-sampling strategies were considered to present evidence of the highest quality (level I), describing strategies for didanosine,[25] zidovudine,[26] nevirapine,[27] ciprofloxacin,[28] efavirenz,[29] and nelfinavir[30] (Table 2). Each study used prospectively collected data and proper validation procedures. All 6 studies randomized pharmacokinetic data into index and validation groups, and 5 of the studies clearly randomized the pharmacokinetic data into independent data sets.[25,27-30] Each study illustrated the potential utility of limited-sampling strategies by requiring only 1 or 2 blood samples to predict AUC, with minimal bias and relatively good precision. The level I studies of didanosine and zidovudine also provided 1-sample limited-sampling strategies to predict a second pharmacokinetic parameter, maximum drug concentration (C_{max}).[25,26]

Of the level I studies, the study of a validated limited-sampling strategy for nevirapine probably provided the most

Table 1. Classification of studies of limited sampling strategies[5-7,9]

Level of Evidence	Description
Level I (evidence obtained from at least one properly randomized controlled trial)	• Used prospectively collected data • Had proper validation procedures (separate validation group, jackknife method, or bootstrap method) • Assigned data randomly into index and validation groups (not applicable when using jackknife and bootstrap methods) • Studies assumed to be prospective even if not explicitly stated by authors
Level II-1 (evidence obtained from well-designed controlled trials without randomization)	• Used prospectively collected data • Had proper validation procedures • Lacked random assignment of data into index and validation groups
Level II-2 (evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group)	• Used retrospective data • Had proper validation procedures regardless of randomization
Level III (opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees)	• Did not have proper validation procedures

Table 2. Summary of Limited-Sampling Strategies (LSS) for Anti-infective Agents

Drug and Study	Population for LSS Derivation	Sampling Times Investigated (h)*	Suggested Timed Samples (h)*	Equation	r (r^2)	Validation Group	% Bias	% Precision	Comments
Level I evidence									
Didanosine (Burger et al.[25])	45 PK curves from 30 HIV-infected adult patients	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6	For AUC: 0.75, 4 For C_{max}: 0.75	AUC = 0.25 + 1.16$C_{0.75h}$ + 5.43C_{4h} C_{max} = 0.15 + 1.00$C_{0.75h}$	AUC: r^2 = 0.93 C_{max}: r^2 = 0.79	Yes	AUC: %ME ± SE –2 ± 4 C_{max}: %ME ± SE 2 ± 5	AUC: %RMSE 16 C_{max}: %RMSE 22	Patients randomly assigned to index (n = 22) or validation data set (n = 23); multiple PK curves from the same patient included in same data set to ensure independent data sets
Zidovudine (Burger et al.[26])	83 PK curves from 62 patients	0, 10, 20, 30, 45, 60, 90, 120, 150, 180 min	30, 180 min	AUC = 0.0022 (dose) + 5.24C_{180min} + 0.39C_{30min} C_{max} = 0.0022 (dose) + 2.11C_{180min} + 0.93C_{30min}	AUC: r^2 = 0.93 C_{max}: r^2 = 0.93	Yes	AUC: %ME ± SE –4.9 ± 4.1 C_{max}: %ME ± SE 2.8 ± 5.8	AUC: %RMSE 26.6 C_{max}: %RMSE 36.5	PK curves randomly assigned to index (n = 42) or validation (n = 41) data set; unclear if data sets were independent, as PK curves (not patients) were randomized
Nevirapine (Veldkamp et al.[27])	20 HIV-infected patients	0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12	One random sample within 2–4 h after ingestion	AUC_{12h} = 11.699$C_{2–4h}$ – 4.381	r = 0.982	Yes	%ME (95% CI) 0.45 (–3.98 to 4.88)	%RMSE (95% CI) 5.89 (0 to 8.58)	Patients randomly assigned to index (n = 10) or validation (n = 10) data set
Ciprofloxacin (Payen et al.[28])	55 patients (1 day to 24 years of age) with either infections caused by multiresistant organisms (n = 35) or a *Pseudomonas* infection in the presence of cystic fibrosis (n = 20)	From 1 to 13 samples, according to dosage regimen used	1S: 12 2S: 0.5 and 12 or 1 and 12	Bayesian	NR	Yes	CL_T, ME (95% CI) 1S: 0.93 (–4.45 to 6.31) 2S: 2.27 (–1.98 to 6.53) or –1.19 (–2.74 to 0.35)	CL_T, RMSE 1S: 4.78 2S: 4.34 or 1.80	Patients randomly assigned to index (n = 37) or validation (n = 18) data set
Efavirenz (López-Cortés et al.[29])	59 PK profiles from 44 adult HIV-infected patients	0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24	12 or 16	$AUC_{0–24h}$ = 5.478 + 22.136C_{12h} $AUC_{0–24h}$ = 8.859 + 24.527C_{16h}	C_{12}: r = 0.989 C_{16}: r = 0.991	Yes	%ME (95% CI) C_{12h}: 3.0 (–2.5 to 8.5) C_{16h}: 5.6 (0.5 to 10.8)	%RMSE (95% CI) C_{12h}: 10.6 (6.6 to 14.8) C_{16h}: 10.9 (7.1 to 14.8)	Patients randomly assigned to index (n = 29) or validation (n = 30) data set

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Table 2. Summary of Limited-Sampling Strategies (LSS) for Anti-infective Agents (continued)

Drug and Study	Population for LSS Derivation	Sampling Times Investigated (h)*	Suggested Timed Samples (h)*	Equation	r (r^2)	Validation Group	% Bias	% Precision	Comments
Nelfinavir (Regazzi et al.[30])	99 HIV-infected patients	0, 1, 2, 3, 4, 5, 6, 8, 12	0, 4	$AUC_{0–12h} = 3 + 2.7C_{0h} + 6.4C_{4h}$	$r^2 = 0.92$	Yes	%ME ± SD 2.2 ± 17.8	%RMSE ± SD 12.3 ± 13.0	Patients randomly assigned to index (n = 49) or validation (n = 50) data set
Level II-1 evidence									
Vancomycin (Burstein et al.[31])	11 neonates with sepsis who received 12 courses of therapy	0.25, 0.5, 1.5, 2, 11	0.5, 11	Bayesian	NR	Monte Carlo simulation of 100 cases	CL_T: %ME (IQR) –1.7 (–16 to 8.4)	CL_T: %MAE (IQR) 11 (3.8 to 32)	Sampling times selected using D-optimality
Didanosine (Balis et al.[32])	13 HIV-infected children who received 120 mg/m^2 oral dose	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8	2S: 0.5, 1.5 3S: 0.5, 1.5, 3	2S: $AUC = 0.44C_{0.5h} + 2.78C_{1.5h} – 0.26$ 3S: $AUC = 0.41C_{0.5h} + 2.08C_{1.5h} + 2.66C_{3h} – 0.19$	2S: $r^2 = 0.97$ 3S: $r^2 = 0.96$	Yes: 7 children who received 180 mg/m^2 oral dose	NR	NR	
Lamivudine (Mueller et al.[33])	10 HIV-infected children who received 10 mg/kg dose	0, 0.5, 1, 1.5, 2, 4, 6, 8	2, 6	$AUC = 2.51C_{2h} + 6.46C_{6h} + 0.97$ (dose)	$r^2 = 0.973$	Yes: 8 children who received 2 mg/kg dose	NR	NR	
Lopinavir–ritonavir (Alexander et al.[34])	81 HIV-infected patients	0, 1, 2, 4, 6, 8, 10, 12	2, 6	C_{max}: $0.182C_{2h} + 0.552C_{6h} + 1.105$ AUC: $0.246C_{2h} + 0.716C_{6h} + 1.191$	C_{max}: $r^2 = 0.891$ $AUC_{0–12h}$: $r^2 = 0.957$	Yes: 25 HIV-infected patients	%bias C_{max}: –0.17 $AUC_{0–12h}$: –4.70	RMSE C_{max}: 0.055 $AUC_{0–12h}$: 0.047	Six patients were in both index and validation groups; data presented for lopinavir only, as there were no adequate estimates of ritonavir PK parameters
Level II-2 evidence									
Ceftazidime (Vinks et al.[35])	17 patients with cystic fibrosis receiving continuous IV infusions of ceftazidime	0, 10, 20, 30, 40, 50, 60 min, 1.5, 2, 3, 4, 6, 8 h or 0, 30, 40, 50, 60 min, 1.5, 2.5, 4, 6, 8 h	0.33, 1.58, 3.25, 6.39	Bayesian	$r^2 = 0.63$	Yes: 31 patients with cystic fibrosis	ME –2.46	RMSE 6.76	Sampling times selected by computer program to generate D-optimal times

Table 2. Summary of Limited-Sampling Strategies (LSS) for Anti-infective Agents (continued)

Drug and Study	Population for LSS Derivation	Sampling Times Investigated (h)*	Suggested Timed Samples (h)*	Equation	r (r^2)	Validation Group	% Bias	% Precision	Comments
Saquinavir (Dickinson et al.[36])	34 HIV-infected patients treated bid with saquinavir (1000 mg) – ritonavir (10) mg	0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12	2S: 2, 6 3S: 2, 4, 6	2S: $AUC_{0-12h} = 5.023C_{2h} + 5.776C_{6h} - 1304.768$ 3S: $AUC_{0-12h} = 3.359C_{2h} + 1.559C_{4h} + 4.87C_{6h} - 1109.702$	2S: $r^2 = 0.972$ 3S: $r^2 = 0.985$	Yes	2S: –0.4 (95% CI –6.7 to 5.8) 3S: 1.6 (95% CI –1.8 to 4.7)	2S: 11.7 3S: 6.4	Patients randomly assigned to index (n = 17) and validation (n = 17) data sets
Level III evidence									
Ganciclovir (Preston and Drusano[37])	43 patients: 26 with CMV retinitis and 17 shedding CMV into urine	0.5, 1, 2, 3, 4, 6, 8, 12, 15, 24	0.5, 1, 2, 3, 8	NR	NR	No	NR (reported only bias and precision of MAP-Bayesian analysis relative to traditional, 2-stage analysis)	NR	Descriptive statistics only comparing 10-point data set with 2-, 3-, 4-, and 5-point data sets (selected by D-optimal design); mean and median clearance values similar
Ceftazidime (Kashuba et al.[38])	23 adult patients with Gram-negative respiratory or skin and soft-tissue infections	0, 0.5, 1, 2, 4, 6, 8, 12, 18, 24	CrCl < 30 mL/min per m^2: 0.583, 4.5, 11.5, 24 CrCl ≥ 30 mL/min per m^2: 0.583, 3, 7, 16	NR	NR	No	NR	NR	Only 5 patients had full 10-point data set; concentrations determined by D-optimality with efficiency of 0.991 for steady state values in patients with CrCl ≥ 30 mL/min per m^2
Nelfinavir (Regazzi et al.[39])	18 HIV-infected patients	0, 1, 2, 3, 4, 6, 8	6	$AUC_{0-8h} = 9.41 \times C_{6h}$	r = 0.97	No	NR	NR	
Pyrazinamide (Perlman et al.[40])	48 HIV-infected patients with tuberculosis infection	2, 6, 10	2	NR	r = 0.92	No	NR	NR	
Meropenem (Ariano et al.[41])	12 patients with febrile neutropenia	End of infusion and 1, 2, 4, 6, 8	0.5, 1, 2, and either 4 or 6 h (depending on renal function)	NR	Distribution CL: r = 0.80	No	NR	NR	Described similarity of CL_T between sparse data obtained through D-optimality design and full data sets

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Table 2. Summary of Limited-Sampling Strategies (LSS) for Anti-infective Agents (continued)

Drug and Study	Population for LSS Derivation	Sampling Times Investigated (h)*	Suggested Timed Samples (h)*	Equation	r (r^2)	Validation Group	% Bias	% Precision	Comments
Vancomycin (Andrés et al.[42])	79 adult hospital inpatients	0, 2	0	Bayesian	r = 0.94	No	ME (95% CI) –0.54 (–1.1 to 0.02)	MAE (95% CI) 1.74 (1.33 to 2.15)	
Ciprofloxacin (Forrest et al.[43])	29 acutely ill patients from 2 clinical trials	0, 0.5, 1, 2, 3, 4, 6, 8, 11	0.25–0.5, 2.5, 11	Bayesian	r = 0.99	No	%ME ± SD 0.03 ± 3.0 SD	%MAE ± SD 2.0 ± 1.8	
Alpha interferon (Chatelut et al.[44])	27 patients with chronic hepatitis C	0, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32	8, 20	Bayesian	r^2 = 0.987	No	%ME (95% CI) 3.5 (–3.3 to 10.3)	%RMSE (95% CI) 7.7 (0 to 11.2)	Data from only 7 randomly selected patients in the study population were used to validate LSS against full data set

1S = 1 sample, 2S = 2 samples, 3S = 3 samples, AUC = area under the concentration–time curve, C_{xh} = concentration at x hours, C_{xmin} = concentration at x minutes, CI = confidence interval, CL = clearance, CLT = total clearance, C_{max} = maximum plasma concentration, CMV = cytomegalovirus, CrCl = creatinine clearance, IQR = interquartile range, %MAE = mean absolute prediction error, MAP = maximum a posteriori probability, %ME = mean prediction error, NR = not reported, PK = pharmacokinetic, r = correlation coefficient, r^2 = coefficient of determination, RMSE = root mean squared error, SD = standard deviation, SE = standard error.
*Unless specified otherwise.

flexibility and convenience for clinical use.[27] In that study, all 14 sampling data points were used to determine a 1-sample (i.e., a random sample between 2 and 4 h after dosing) limited-sampling strategy that predicted the AUC with minimal bias and good precision.[27] This single "random" sample would be a convenient method for future research to determine if the AUC for nevirapine correlates with clinical outcome. A distinctive strength of the efavirenz study was that concomitant medications were accounted for in the randomization scheme.[29] Of the level I studies, the nelfinavir trial had the largest sample size, with random assignment of 99 HIV-infected patients to the index (n = 49) and validation (n = 50) groups.[30]

Five anti-infective agents were each studied in 2 separate trials, as described in Table 2.[25,28,30-32,35,38,39,42,43] Classification according to level of evidence is important when there are discrepant results between studies for suggested sampling times to characterize pharmacokinetic parameters. As a general guideline, clinicians may choose to place more weight on results of studies classified as having a higher level of evidence. For example, although the 2 ceftazidime studies suggested 2 different 4-point sampling strategies to characterize AUC, one study had level II-2 evidence[35] and the other had level III evidence.[38] The 2 didanosine studies also yielded discordant limited-sampling strategies.[25,32] Although this may have been due to differences in the populations studied (adults versus children), one study had level I evidence and the other level II-1 evidence. The 2 studies that described limited-sampling strategies for ciprofloxacin also produced discordant results.[28,43] The level III study required an additional sample at 2.5 h to best characterize total clearance.[43] However, when restricted to only 2 samples, the selected times were similar to those suggested in the level I study.[28] The 2 nelfinavir studies were difficult to compare, as they characterized 2 different pharmacokinetic parameters ($AUC_{0–12h}$ and $AUC_{0–8h}$) and provided level I and level III evidence, respectively.[30,39] The 2 vancomycin studies also developed limited-sampling strategies for prediction of different parameters (clearance and concentration), but again were classified as providing level II-1 and level III evidence, respectively.[31,42]

In general, the studies identified in this systematic review had small sample sizes, the methods and patient populations were not well described, and a variety of methods were used to determine optimal sampling times (Table 2). Two studies[37,41] did not report bias or precision for the variations in sampling times used in development of the limited-sampling strategy; instead, only descriptive statistics of clearance were provided. Methods for determining the sampling times to be used in the limited-sampling strategies included arbitrarily selecting times[43] and use of software to obtain D-optimal times.[31,35,37,38] Use of a computer software program to determine optimal sampling times may yield times that are impractical, as was the case for one ceftazidime study.[35]

One study, considered to report level I evidence, randomized data from 83 pharmacokinetic curves into separate index

and validation groups, but it is unclear if the 2 groups represented 2 independent sets of patients, as the data were obtained from only 62 patients.[26] The study also did not provide information about the baseline characteristics of the patients, so it was assumed that the "patients" who "ingested their usual morning dose" were receiving zidovudine therapy for HIV and were not volunteers.[26] It would be difficult to apply this limited-sampling strategy in practice, as little is known about the underlying population that was studied. It has been previously shown that a limited-sampling strategy for a drug cannot always be extrapolated to a population other than the one studied. For example, a limited-sampling strategy for didanosine was evaluated in 13 HIV-infected children in a study with level II-1 evidence,[32] but the recommended equations did not reliably predict the AUC in a study of HIV-infected adults.[25] In addition to the expected differences in pharmacokinetics between adults and children, this discrepancy might also have resulted from a difference in the rigour of the evaluations.

Three studies, all considered to present level I evidence, did not report concomitant medications or medical conditions, which limits the generalizability of their findings.[25,27,28] In studies of antiretroviral agents, which have numerous potential pharmacokinetic interactions, it would be important to note concomitant antiretrovirals and other medications. In the studies with level I evidence that were identified in this review, patients were prospectively and randomly assigned to index and validation groups, but because the studies were small, it is possible that not all characteristics were balanced between the groups.

A ciprofloxacin study of level I evidence (n = 55) included 20 patients with cystic fibrosis, all less than 25 years of age.[28] Given the pharmacokinetic characteristics specific to patients with cystic fibrosis, such as increased clearance, as well as the pharmacokinetic differences across pediatric and adolescent age groups, it would be desirable to develop and validate a limited-sampling strategy in a study of patients with cystic fibrosis within a narrower age range. The ciprofloxacin study[28] also used 4 different sets of sampling times, ranging from 1 to 13 samples, and selected times on the basis of the dosing regimen used. It would be preferable to characterize a full pharmacokinetic profile for several patients with similar characteristics, all of whom received the same dose, and to attempt validation for all possible combinations of sampling times, to obtain the most precise and least biased limited-sampling strategy. A level I study of a limited-sampling strategy for efavirenz exemplified proper validation procedures, in that patients were randomly assigned to 3 different sets of index and validation groups according to concomitant interacting medications.[29] However, that study also assessed only 3 single sampling times in its evaluation. Although full pharmacokinetic profiles were obtained, the reason for the authors' choice of 3 time points (8, 12, and 16 h) to estimate the AUC and trough (at 24 h) was not stated.[29]

A study of nelfinavir-treated patients, which had level I evidence, provided some baseline comparative information on comorbid conditions between index and validation groups; it also had a more complete evaluation of sampling times than the other level I studies.[30] However, little information on concomitant medication was provided, and, as discussed below, the use of nelfinavir has now fallen out of favour.

Clinical Implications

It is difficult to draw conclusions from the limited-sampling strategies that have been described in the literature to date, given their methodologic flaws and limitations. As well, discrepancies in results between studies may be attributable to the differences between the patient subpopulations being studied. For example, in addition to pathophysiologic parameters (e.g., age, sex, disease states), results for limited-sampling strategies may vary according to dosing schedules, drug bioavailability, and other pharmacokinetic parameters such as elimination half-life. More importantly, there is a lack of evidence supporting the need for therapeutic drug monitoring for the majority of anti-infectives for which limited-sampling strategies have been developed. In other words, even if clinical efficacy and AUC are related, a limited-sampling strategy may be of limited clinical utility. For example, concentrations of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz are not routinely monitored in practice, because clinicians are able to monitor efficacy and toxicity clinically and the evidence related to therapeutic drug monitoring for these agents is conflicting.[45] Therapeutic drug monitoring of the nucleoside reverse transcriptase inhibitors, such as didanosine, stavudine, zidovudine, and lamivudine, is also not routine practice.[46,47] These agents require intracellular activation, and the intracellular concentration of active drug does not correlate well with the plasma concentration of the parent compound.

Although correlation between pharmacokinetic–pharmacodynamic data and microbiological cure has been demonstrated in vitro and in animal models, there are limited prospective human data correlating pharmacokinetic–pharmacodynamic parameters with clinical outcomes. For the ß-lactam anti-infectives, such as ceftazidime and meropenem, which were included in this review, it appears that time above MIC (t > MIC) is actually the pharmacokinetic–pharmacodynamic parameter that correlates best with microbiological and clinical efficacy.[2] The t > MIC parameter represents the time that the antibiotic concentration remains above a certain threshold concentration, usually a concentration 4 to 5 times greater than the MIC. These data are again based largely on animal and in vitro data. However,, if t > MIC is the parameter that correlates best with efficacy, as has been traditionally thought for the time-dependent ß–lactams, determining the AUC would not be required. Therefore, limited-sampling strategies for the ß-lactam anti-infectives would not be necessary.

Two studies included in this review describe limited-sampling strategies for vancomycin. Although vancomycin peak and trough concentrations have been routinely monitored for years, there are limited human data to support an association between concentration and efficacy or toxicity.[48] The AUC/MIC has been correlated with improved outcome in animal models and one human study, but other unpublished human data indicate no relationship between the pharmacokinetic–pharmacodynamic parameters and efficacy.

Plasma concentrations of protease inhibitors may be associated with efficacy and toxicity. However, 2 of the protease inhibitors included in studies of limited-sampling strategies may now be less frequently used in practice. It is now known that ethyl methanesulfonate, an animal carcinogen and teratogen, is released in small amounts during the manufacturing of nelfinavir.[47] This has led to an advisory against using nelfinavir in pregnancy and withdrawal of the drug from the market in some countries. Saquinavir may also be used less frequently than other protease inhibitors because of a greater "pill burden" and the requirement for twice-daily dosing.[47] In addition, the efficacy and toxicity of these agents can be monitored clinically, on the basis of viral load, CD4 count, physical symptoms, and laboratory parameters, as is the case of the NNRTIs. This may limit the utility of therapeutic drug monitoring for these agents.

Data also suggest that AUC/MIC and peak/MIC may be correlated with the efficacy of the fluoroquinolones.[2] These data have been derived mostly from animal and in vitro modelling, but a few retrospective and observational human studies support these findings as well. However, therapeutic drug monitoring is not routine practice for the fluoroquinolones, because the efficacy and toxicity of these drugs can be monitored clinically.

Suggestions for Future Studies

To date, AUC/MIC has been suggested to correlate with clinical efficacy for a limited number of anti-infective agents (e.g., fluoroquinolones, quinupristin–dalfopristin).[2] Ideally, limited-sampling strategies would be developed only for those drugs for which the need for therapeutic drug monitoring has been clearly demonstrated. Alternatively, any limited-sampling strategies that are developed should be assessed to determine if their use results in better clinical outcomes than usual practice (i.e., no monitoring). Optimally, limited-sampling strategies should be prospectively evaluated in a large number of patients randomly assigned to either an index group or a validation group, to determine the validity of the model. Blood sampling in the index group would need to be sufficient to adequately characterize the AUC. Then, all possible combinations of limited sampling at convenient times, using 3 or fewer samples, would be tested to determine the optimal sampling times to characterize AUC or other pharmacokinetic parameters. In addition, the characteristics of the included patients should be clearly outlined to establish generalizability. If it is desirable to use the limited-sampling strategy in a population other than the one studied, the method must first be validated in the new population.

Conclusions

To our knowledge, this is the first systematic review of limited-sampling strategies for anti-infective agents. The findings indicate that although a number of such strategies have been developed, the important link between limited-sampling strategies and clinical outcomes has not yet been established. Despite the identification of 6 level I studies in this review, it is difficult to draw conclusions from the majority of studies of limited-sampling strategies that have been reported in the literature to date, given their methodologic flaws and the limited data correlating pharmacokinetic–pharmacodynamic monitoring with clinical outcomes of anti-infective therapy. Future studies should first determine if monitoring pharmacokinetic–pharmacodynamic parameters yields better predictions of efficacy and/or toxicity of an anti-infective agent than no monitoring at all. Once an association between AUC monitoring and clinical outcomes has been clearly established, it may be worthwhile to prospectively develop and evaluate a limited-sampling strategy for the particular anti-infective agent in a similar population.

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