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Assessment of pharmacodynamic surrogates in response to the treatment of skin and skin structure infections in children

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We characterised the pharmacokinetic-pharmacodynamic (PK-PD) profile for linezolid and cefadroxil with respect to treatment response rates in children with skin and skin structure infections (SSIs). In linezolid-treated subjects, response rates were consistent with a PK profile which generates a predicted PD profile that equals or exceeds the "optima" for most pathogens. In contrast, the cefadroxil data suggest a response rate which is inconsistent with optimal plasma PD surrogates but perhaps consistent with the tissue PD profile.

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Introduction

Uncomplicated bacterial skin and skin structure infections (SSIs) are common in children, accounting for up to 18% of paediatric outpatient clinic visits[1]. The Gram-positive organisms *Staphylococcus aureus* and *Streptococcus pyogenes* are the most frequently isolated pathogens, causing approximately 70% and 30% of outpatient paediatric SSIs, respectively[2]. The β-lactam antibiotics, primarily the cephalosporins (e.g. cefadroxil) and the penicillinase-resistant penicillins, remain the standard for the empirical treatment of uncomplicated paediatric SSIs. In children with infections caused by resistant pathogens, the oxazolidinones (e.g. linezolid) offer a potential alternative.

The efficacy of antimicrobial therapy for SSIs, as in other infections, is guided by a complex interaction between the pharmacokinetic profile of the drug, the physicochemical and biochemical characteristics of the local environment, the susceptibility of the infecting organisms under the local growth conditions and the host immune system. Pharmacodynamic (PD) surrogates,

which link together these various determinants of efficacy, have been proposed as a tool for predicting and optimising response to treatment. The most frequently referenced surrogates link attainable plasma drug concentrations with *in vitro* estimates of pathogen susceptibility. For the β-lactams and the oxazolidinones, the percent of time that the plasma or tissue concentration exceeds the minimum inhibitory concentration (T > MIC) has been closely linked to therapeutic response (i.e. time-dependent killing). Specifically, in animal models, optimal response occurs with a plasma T>MIC of 50–60% and 40% for the cephalosporin[3,4] and oxazolidinone[5] antibiotics, respectively. It is unclear, however, whether these aforementioned PD optima are useful in determining response to peripheral compartment infections such as SSIs in children. The purpose of this exploratory investigation was to characterise the pharmacokinetics of linezolid and cefadroxil in children with SSIs, to predict the PD profile and to determine whether these parameters are consistent with clinical outcome observed in a larger phase III clinical trials[6].

Methods

Subjects

Data from a limited subset of patients (n=2 linezolid, n=6 cefadroxil) drawn from a multi-centre clinical study[6] (n=499) were examined. Eligibility criteria were identical to those of the larger clinical study and have been previously described[6]. The study protocol was approved by the Investigational Review Board and/or Independent Ethics Committee of each participating institution. All subjects were enrolled via written informed parental/guardian consent and by assent when appropriate (i.e., ≥ 7 years of age). In order to enrich the data for linezolid as only two subjects in the phase III SSIs study had plasma concentration-time profiles, pharmacokinetic data from a similar population of healthy subjects (n=14) in a previous paediatric study conducted by our group were also included[9].

Study design

The study was a steady-state evaluation of the pharmacokinetics of cefadroxil and linezolid in the fasting state. Subjects were randomised to 10–21 days of oral antimicrobial therapy with either linezolid (10 mg/kg 12 hourly, maximum 600 mg/dose) or cefadroxil (15 mg/kg 12 hourly, maximum 500 mg/dose). Study medication was provided by the sponsor (Pharmacia Corporation, Kalamazoo, MI, USA) as an oral suspension (linezolid 100 mg/5mL, cefadroxil 125 mg/5mL) for children aged 5–11 years and as a solid dosage form (linezolid 600 mg tablets, cefadroxil 500 mg capsules) for children aged 12–17 years. Compliance with the assigned therapeutic regimen was monitored as part of the larger phase III clinical trial[6].

Sample collection and analysis

Steady-state pharmacokinetic evaluation was performed on day 7 via repeated blood sampling over 12 hours. All subjects were inpatients during the entire 12 h post-dose sampling period. Venous blood samples (1.5 mL each) for determination of linezolid and cefadroxil plasma concentrations were collected from an indwelling catheter into glass tubes containing EDTA. Blood samples were collected immediately before drug administration and at 2, 3, 4, 6, 8 and 12 hours after the dose. Samples were transported to the laboratory on ice where the plasma was separated by centrifugation (3,000 rpm × 10 minutes) and subsequently stored in polypropylene tubes at –70°C until analysis.

Linezolid plasma concentrations were determined using a validated high-performance liquid chromatographic assay with tandem mass spectrophotometric detection (LC/MS/MS) as described previously[7]. An 8-point standard curve using the ratio of active compound to internal standard was prepared daily in drug-free human plasma and was used to calculate all plasma linezolid concentrations. The assay had a range of linearity from 1 to 250 ng/ml (r^2>0.998) and a limit of quantification of 1 ng/ml. Cefadroxil plasma concentrations were determined by high performance liquid chromatography with ultraviolet detection using a modification of the methods of Lindgren et al[8]. A 7-point standard curve using the peak height ratio of active compound to internal standard (cephradine) was prepared daily and used to calculate plasma cefadroxil concentrations. The range of linearity for this assay ranged from 0.5 to 50 microg/ml (r^2 > 0.99) and the limit of quantification of 0.5 microg/ml. All linezolid and cefadroxil assays were performed in duplicate and the resultant average concentration was used in the pharmacokinetic analyses.

Pharmacokinetic, pharmacodynamic and statistical analysis

Pharmacokinetic analyses were conducted using Kinetica® Version 3.0 (InnaPhase, Philadelphia, PA). Individual C_{max} and T_{max} were obtained directly from the plasma concentration *vs.* time data. The free (i.e. pharmacologically active) plasma concentrations were also calculated using estimates of plasma protein binding for both drugs[10].

The area under the plasma concentration *vs* time curve (AUC_{0-12}) was determined by the log-linear trapezoidal rule. Extrapolation of the AUC to infinity ($AUC_{0-\infty}$) was calculated by summation of $AUC_{0-12} + Cp_{12}/\lambda_z$, where Cp_{12} is the projected (i.e. from the apparent terminal elimination phase) plasma drug concentration at 12 hours and λ_z is the apparent terminal elimination rate constant. Apparent total body clearance (Cl/F) and apparent steady state volume of distribution (Vd_{ss}/F) were calculated from the $AUC_{0-\infty}$ using standard non-compartmental techniques.

Previously reported mean plasma (linezolid), serum (cefadroxil) and skin blister concentration *vs* time data in adults were used to estimate tissue λ_z and to calculate the serum/plasma:skin blister ratio[11,12]. For cefadroxil, these values (which reflect single-dose administration) were accumulated to steady-state using the accumulation factor $1–e^{-(\lambda z)(\tau)}$, where τ is the dosing interval. Individual linezolid and cefadroxil tissue C_{max} were then predicted using observed plasma values and steady-state tissue concentration *vs* time profiles were simulated[11,12]. The percent of the dosing interval where the measured plasma (total and free) and simulated tissue concentrations exceeded the MIC_{90} (% $T >$ MIC) were then calculated using established MIC_{90} values for pathogens commonly encountered in uncomplicated paediatric SSIs[13,14] given that study-specific MIC_{90} data were not available. Previously reported cure rates (clinical and microbiological) from the larger clinical study[6] were assumed to reflect therapeutic response associated with antimicrobial therapy.

Demographic data (subjects and historical linezolid controls) were compared between treatment groups using a two-tailed, unpaired Student's *t*-test. The level of significance for all statistical tests was α=0.05. All analyses were performed using SPSS® for Windows Version 9 (SPSS, Chicago, IL).

Results

Eight subjects (*n*=2 linezolid, *n*=6 cefadroxil) completed this pharmacokinetic evaluation. The demographic variables for these subjects were similar between treatment groups ($P > 0.05$) and are provided in Table 1. Both linezolid and cefadroxil were well tolerated in the larger clinical study, with similar rates of adverse events noted between groups[6].

The pharmacokinetic parameter estimates for the two linezolid-treated subjects are shown in Table 1. The mean ± SD (range) of values for λ_z, oral steady-state C_{max} derived from the historical controls (*n*=14) were 0.28 ± 0.11 h^{-1} (0.15–0.61), 15.3 ± 4.1 microg/ml (11.1–27.5). The estimated linezolid tissue λ_z and plasma:skin blister fluid ratio values were 0.12 h^{-1} and 0.90, respectively. In subjects receiving linezolid, the predicted peak tissue concentration for subjects in the SSIs and historical control groups were 7.0–15.8 microg/ml and 13.7 ± 3.8 (9.9–24.6) microg/ml, respectively. Predicted trough linezolid concentrations in tissue were 2.3–5.3 and 4.6 ± 1.2 (3.3–8.3) in the SSIs and historical control groups, respectively. Composite measured plasma and simulated tissue concentration *vs.* time curves for linezolid are shown in Figure 1.

Table 1 Summary of demographic, pharmacokinetic and pharmacodynamic parameters

	Linezolid		Cefadroxil	
Number of subjects	2		6	
Age (yr)	8.2–12.7*		7.9 ± 2.6 (5.0–11.6)†	
Weight (kg)	34.9–52.6		30.7 ± 14.2 (18.2–48.9)	
Dose (mg/kg)	10–11.4		13.4 ± 2.3 (10.2–15.0)	
Pharmacokinetics				
C_{max} (mg/L)	7.8–17.5		17.1 ± 5.14 (12.1–25.8)	
T_{max} (h)	2–4		2 ± 0 (2)	
$AUC_{0-\infty}$ (mg*h/L)	108.1–144.4		48.8 ± 17.6 (34.5–80.9)	
λ_z (h^{-1})	0.09–0.14		0.48 ± 0.04 (0.43–0.56)	
Half-life (h)	4.9–7.5		1.44 ± 0.13 (1.2–1.6)	
CL/F (L/h/kg)	0.08–0.09		0.29 ± 0.06 (0.18–0.38)	
Vd_{ss}/F (L/kg)	0.63–1.16		0.93 ± 0.19 (0.66–1.24)	
C_{12} predicted (mg/L)	3.8–4.2		0.12 ± 0.10 (0.05–0.31)	
Pharmacodynamics				
	Plasma (total)	**Tissue**	**Plasma (total)**	**Tissue**
$\%T > MIC_{90} = 0.13$			99.7 ± 10.4 (89.8–100)[c]	100 ± 0 (100)
$\%T > MIC_{90} = 2$	77.7 ± 28.1 (30.6–100)[a,b]	100 ± 0 (100)		
$\%T > MIC_{90} = 4$	49.7 ± 17.3 (20.5–93.4)[c]	100 ± 25 (51–100)	32.5 ± 7.8 (25.4–46.2)[a]	54.7 ± 14.9 (37.4–76.5)
$\%T > MIC_{90} = 8$			18.9 ± 7.6 (11.2–31.6)[b]	26.4 ± 14.9 (9.2–8.2)

* Data represented as individual patient values

† Data represented as mean ± SD (range)

Cmax, observed peak plasma concentration; T_{max}, observed time of C_{max}; $AUC_{0-\infty}$, area under the plasma concentration vs. time curve extrapolated to infinity; Cl/F, apparent plasma clearance, Vd_{ss}/F, apparent steady state volume of distribution; C_{12} predicted, predicted concentration at 12 hours

MIC data derived from references 12, 13. Values represent the MIC_{90} for the agent against [a] MSSA, [b] GAS and [c] MRSA

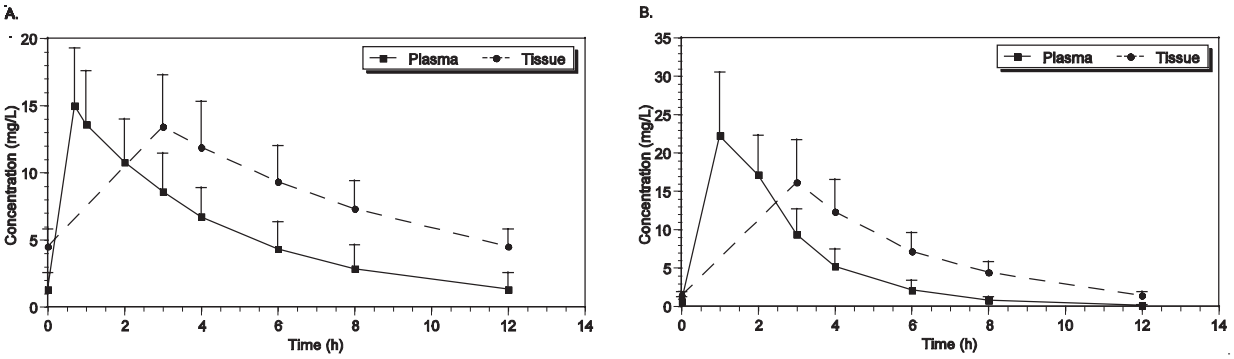

Figure 1 Composite steady-state measured plasma and simulated tissue concentration *vs* time data for (A) linezolid and (B) cefadroxil

The cefadroxil plasma pharmacokinetic profile observed in our study was consistent with that previously reported in paediatric patients[15-17]. However, T_{max} was slightly delayed compared with previously published estimates in similar aged children (e.g. 2 h observed *vs* 1 h reported)[15-17]. The estimated cefadroxil tissue λ_z and serum:skin blister fluid ratio values were 0.27 h^{-1} and 0.73, respectively. Predicted peak tissue concentration for all subjects was 16.2 ± 5.5 micrg/ml (10.0–26.0 microg/ml). The predicted trough concentrations in tissue were 1.40 ± 0.47 microg/ml. Composite measured plasma and simulated tissue concentration *vs* time curves for cefadroxil are shown in Figure 1.

The predicted PD surrogates for linezolid (calculated using composite of SSIs and healthy control data) and cefadroxil in plasma and tissue are shown in Table 1. In both plasma and tissue fluid, steady state concentrations of linezolid (total) reflected an apparent adequate % *T* > MIC (i.e. ≥ 40%) against *S. pyogenes* and *S. aureus*, including those strains that are methicillin-resistant. However, when the free (i.e. pharmacologically-active) concentration was used, this PD surrogate was below the suggested optima for methicillin-resistant *S. aureus*. The calculated PD surrogates for cefadroxil (total and free) were below the suggested optima (i.e. ≥ 50–60%) for all *S. aureus* isolates in plasma and for methicillin-resistant strains in tissue, thereby suggesting the possibility of inadequate therapy.

As previously reported, the rates of clinical cure (intent-to-treat) in the larger Phase III study were similar between both treatment groups (88.7% and 86.2% in linezolid- and cefadroxil-treated subjects, respectively)[6]. Pathogen eradication rates (intent-to-treat) were also comparable among microbiologically-evaluable subjects with infections due to susceptible strains of *S. aureus* (89.4% *vs* 85.5%) and *S. pyogenes* (89.2% *vs* 96.3%) treated with linezolid and cefadroxil, respectively.

Discussion

PD surrogates that integrate population or patient-specific pharmacokinetic information with pathogen susceptibility data have been shown to predict clinical response in patients receiving antimicrobial therapy. For antimicrobials that exhibit time-dependent bacterial killing (e.g., β-lactams, oxazolidinones) several clinical studies have confirmed that the % *T* > MIC is an appropriate PD endpoint and have established target "PD optima" for this surrogate[3-5]. In studies of upper respiratory tract infection, the highest bacterial eradication rates for the β-lactams are observed when the *T* > MIC exceeds 40–50% of the dosing interval[4]. Similarly, cure rates with cefuroxime drop from greater than 90% to approximately 75% when the T > MIC falls below 40%[18,19]. Consequently, these PD "optima" have been integrated into the design of targeted antimicrobial dosing regimens as demonstrated in a previous study in neutropaenic patients where an overall efficacy rate of 65% was observed following continuous infusion cefamandole as compared with 21% efficacy in patients receiving intermittent administration[20].

To investigate whether the proposed PD surrogates may be useful in the determination of therapeutic response in the treatment of paediatric SSIs, we characterised the pharmacokinetic-pharmacodynamic profile in a sub-group of children with uncomplicated SSIs and examined outcome in a larger paediatric population participating in a phase III trial of efficacy and safety. It should be noted, however, that concentration–time data were available for only two linezolid-treated subjects in this multi-centre clinical trial. Although the plasma pharmacokinetics in these subjects are comparable to those previously reported in healthy controls, it is possible that the physiological alterations associated with an active SSI may impact the pharmacokinetic-pharmacodynamic profile. Consequently, the

calculated PD surrogates derived from composite data (i.e. SSIs and historical control) may not truly reflect that in subjects with active SSIs.

The proposed PD surrogate (i.e. % *T* >MIC) for cefadroxil did not appear to be a marker of either clinical or microbiological cure for infections caused by *S. aureus* using either the total or free (i.e. pharmacologically-active) plasma concentrations irrespective of phenotypic resistance pattern. Specifically, approximately 85% of patients achieved clinical and/or microbiological cure for methicillin-susceptible strains of *S. aureus* despite projected % T > MIC values in plasma that ranged from 25 to 46% (mean 33%) and 22 to 42% (mean 29%) for total and free concentrations, respectively. This observation suggests that the PD optima for the cephalosporins in paediatric SSIs might be less stringent than those established for other infectious processes caused by susceptible bacteria. Furthermore, it is possible that other clinical endpoints (e.g., time to clinical and/or microbiological cure) may serve as a better correlate with this particular PD surrogate for cephalosporins in paediatric SSIs. Alternatively, the historical MIC_{90} data for *S. aureus* used in this analysis may have been more conservative than those actually present in our subjects. In this case, our calculations would have underestimated the true % *T* > MIC and therefore, predicted values may be higher than expected.

It is also possible that PD "optima" established using plasma concentration profiles for an antibiotic may not be appropriate for infections located in deep peripheral compartments (e.g. loculated infections) and/or for highly protein bound drugs where diffusion and persistence of active drug could be more limited. Hence, antimicrobial exposure at the tissue level may be the more important correlate of clinical response in such instances. As illustrated by our simulated tissue concentration-time profile for cefadroxil, the predicted percent of the dosing interval that was greater than the MIC for selected pathogens ranged from 37 to 77% (mean 55%), thereby achieving the proposed "optima" for this antimicrobial agent. These simulations were performed using data derived from the skin blister fluid model in healthy adults, however, and may not be directly applicable to children with an active SSI. The tissue PD estimations in this investigation are therefore at best exploratory. Given that direct measurement of antimicrobial concentrations in tissue is neither feasible nor practical in children, however, PD modelling methods such as those utilised in this investigation are necessary to offer insight into optimal PD surrogates.

In summary, currently accepted PD "optima" for the cephalosporins in plasma (i.e. *T* > MIC for at least 50-60% of the dosing interval) does not appear to be a good correlate of therapeutic response to staphylococcal SSIs when only the plasma concentrations of a drug such as cefadroxil are considered. In contrast, the % T > MIC in the tissue may serve as a better correlate for clinical outcome. It appears that the proposed PD optima for linezolid and presumably, other oxazolidinones, may be useful as a marker of clinical outcome in children with SSIs caused by susceptible pathogens. Alternatively, the treatment response rates associated with this antimicrobial class may be so consistent such that the PK/PD profile is irrelevant. Finally, apparent discordance between PD optima based on plasma concentration data and therapeutic outcome can, in certain instances, be explained by considering the pharmacokinetics of the drug at the site of infection (i.e. in the tissue). The factors that influence antimicrobial exposure at any extravascular site of infection (e.g. protein binding, extent and rate of distribution) and the resulting pharmacokinetic-pharmacodynamic profile should be recognised and considered in both the selection of antimicrobial therapy and the clinical evaluation of response to same. PD modeling methods such as those utilised in this investigation are also necessary to offer insight into optimal PD surrogates.

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