A Population Pharmacokinetic Model for the Simultaneous Description of Linezolid Tissue and Plasma Disposition in Healthy Volunteers and Septic Patients

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Background and Objectives

Linezolid, the first member of the oxazolidinones, has been approved for the treatment of severe infectious diseases. Treatment failure might be associated with insufficient concentrations at the site of infection. Therefore, the aim of the study was to investigate the unbound ultrafiltered plasma (UF) as well as interstitial subcutaneous (s.c.), and muscle (i.m.) tissue concentrations of linezolid in healthy volunteers and in patients with either sepsis or septic shock, applying the microdialysis sampling technique. The data was then used to develop a population pharmacokinetic model capable of simultaneously describing both unbound plasma and tissue concentrations in all individuals. Covariate analysis was performed to account for some of the observed parameter variability.

Patients and Methods

Study characteristics

Descriptive statistics of the study population is given in table 1. All individuals were treated with 600 mg linezolid bid. Healthy volunteers received the first dose as a 30 min intravenous infusion whereas all subsequent doses were administered as a tablet while patients were only dosed intravenously. Samples were taken after single dosing and at steady state over a period of 8 h, every 20 min for the first 3 h, increasing the sampling time interval to 30 min afterwards.

Table 1. Study population characteristics

Individuals		Healthy volunteers	Septic patients	Patients with septic shock	Total
Number	(male/ female)	10 (5/5)	8 (4/4)	16 (10/6)	34 (19/15)
Age (years)	median (min.-max.)	54 (41-76)	72 (53-80)	63 (51-78)	62 (41-80)
Height (cm)	median (min.-max.)	171 (157-178)	169 (156-180)	169 (149-192)	170 (149-192)
Weight (kg)	median (min.-max.)	65 (51-80)	60 (40-102)	85 (45-142)	67 (40-142)

Pharmacokinetic Data Analysis

Overall, 1176, 1168 and 1157 linezolid concentrations were available for model development in ultrafiltered plasma and s.c. and i.m. microdialysate, respectively. Analyses were performed using NONMEM, version V, level 1.1. ADVAN 6 subroutine with the FOCE interaction estimation method was applied. At first, a model for the description of UF concentrations was developed, i.e. a three-compartment model (central, peripheral, and inhibition compartment) with first-order elimination, using an additional compartment for oral input. The inhibition compartment was a hypothetical compartment To account for s.c. and i.m. data, two compartments were added which were connected to the central compartment by monodirectional rate constants and partition coefficients (PC). When estimating these parameters the parameters previously obtained for the UF model were fixed. The joint model for unbound s.c., i.m. and ultrafiltrate concentrations is presented in figure 1.

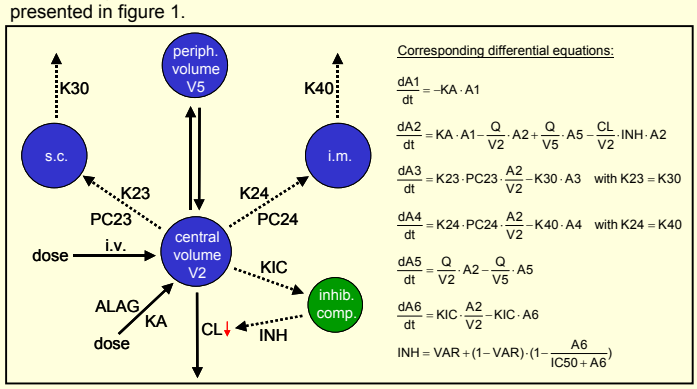

Figure 1. Model for the simultaneous description of unbound linezolid UF, i.m. and s.c. concentrations

Results

The model successfully described the UF concentration-time profiles of all subjects. The goodness of fit for the different matrices is displayed in figure 2.

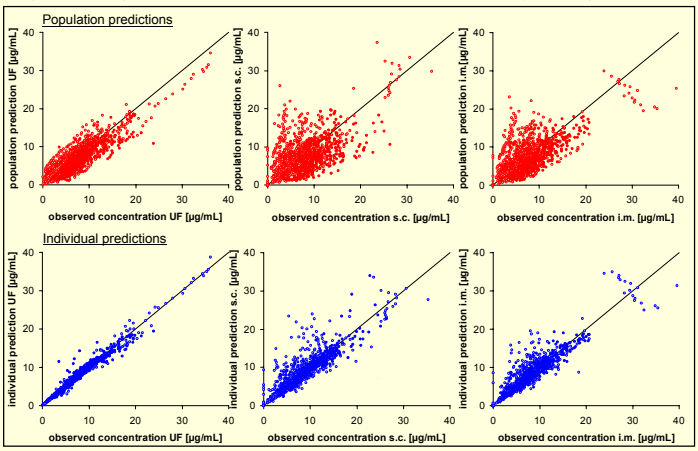

Figure 2. Goodness of fit for UF, i.m. and s.c. concentrations; upper panel: population predictions, lower panel: individual predictions; filled circles: healthy volunteers, empty circles: patients

A change in drug disposition was observed in many individuals from single to steady state dosing. This was accounted for by the introduction of an inhibition compartment by which linezolid clearance was inhibited over time. Clearance was determined to be 11.5 L/h. It could be inhibited to a value of 6.52 L/h. Total volume of distribution was 46.8 L and approximated total body water. The partition coefficient estimates close to 1 indicated a complete distribution into s.c. and i.m. tissue. However, PC23 and PC24 considerably varied intra- and interindividually, respectively. Covariate relationships were either modelled as centered around median (CAM) or as a hockey stick function (HS). An increase in creatinine clearance (CLCR), weight (WT) and thrombocytes (THRO) led to an increase in clearance (CAM). WT was also found to increase V5 (CAM). K40 was reduced when THRO increased (CAM) whereas an increase in CLCR went along with an increase in PC24 (HS). The parameters ALAG1 and K30 were fixed. For ALAG1 this was due to lacking data after oral dosing. When estimated K30 approached infinity, therefore it was fixed to a value which in simulations revealed no change in concentration-time profiles. IC50 was correlated with KIC and had to be fixed for identifiability reasons. The estimated parameters are presented in table 2.

In general, all parameters were estimated with good precision. For those parameters with standard errors larger than 50% log-likelihood profiling revealed that 95% confidence intervals did not include zero. ωVAR could not be presented as coefficient of variation as it was not coded by an exponential error model but by a code which restricted parameters to take values between 0 and 1. Thus, individual values took a u-shape (figure 3). However, a comparison of individual distributions of VAR revealed that the 95% confidence interval was reduced by the final model accounting for covariates. ωCL increased, however this can be explained by a close correlation between CL and VAR. The increase in ωKA might be due to the poor data situation after oral dosing.

Table 2. Estimated parameters for the base and the final model

		Base model		Final model	
Model		Estimate	RSE %	Estimate	RSE %
CL	[L/h]	11.1	7.8	11.5	9.1
V2	[L]	20.0	8.2	19.8	8.4
Q	[L/h]	75.0	8.6	76.8	8.2
V3	[L]	28.9	8.0	27.0	6.3
KA	[1/h]	1.81	25.9	1.85	27.9
ALAG	[h]	1.27 FIX	-	1.27 FIX	-
VAR		0.764	14.3	0.567	19.9
KIC	[1/h]	0.0019	5.2	0.0027	12.6
IC50	[mg/L]	0.1 FIX	-	0.1 FIX	-
PC23		1.05	6.4	1.05	6.4
PC24		1.03	5.4	1.07	5.9
K30	[1/h]	100 FIX	-	100 FIX	-
K40	[1/h]	12.3	17.1	13.0	14.5
Covariate influence, %					
θ_{CLCR_CL} [$]		n.a.	-	0.911	12.0
θ_{WT_CL} [$]		n.a.	-	1.13	62.7
θ_{THRO_CL} [$]		n.a.	-	0.229	47.0
θ_{WT_V5} [$]		n.a.	-	1.52	16.6
θ_{THRO_K40} [$]		n.a.	-	0.211	2.0
θ_{CLCR_PC24} [#]		n.a.	-	0.382	75.4
Interindividual variability					
ωCL	[CV%]	41.7	22.2°	49.8	40.7°
ωV2	[CV%]	40.1	22.3°	37.1	25.1°
ωV3	[CV%]	34.8	31.0°	20.5	46.2°
ωKA	[CV%]	72.4	57.1°	78.9	59.0°
ωVAR		11.8	52.5	6.36	43.7
±PC23	[CV%]	43	41.0*	44	41.0*
ωPC24	[CV%]	30	68.1*	28	71.9*
ωK40	[CV%]	77	24.7*	64	36.4*
Residual Variability					
σ proportional	[CV%]	20	4.3	20	4.2
σ additive	[mg/L]	0.01 FIX	-	0.01 FIX	-

° = Standard error given on the variance scale; n.a. = not applicable; * = covariate relationship modelled as centered around median; # = covariate relationship modeled as hockey stick function

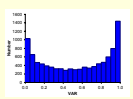

Figure 3. Individual parameter distribution of VAR in the final model

Simulations revealed that the model was able to adequately predict concentration-time profiles of linezolid in plasma. S.c. and i.m. concentrations were also well predicted. However, the median and 95% quantile were slightly overestimated. Predictions for UF, s.c. and i.m. concentrations are shown in figure 4.

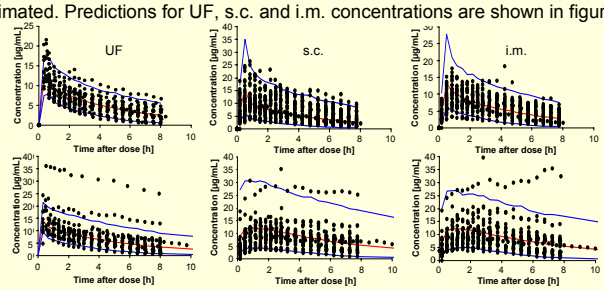

Figure 4. Predictive check for UF, s.c. and i.m. concentrations after i.v. dosing, upper panel: single dosing, lower panel: steady state

Conclusion:

Unbound linezolid pharmacokinetics in UF, s.c. and i.m. tissue of both populations were successfully described by the population pharmacokinetic modelling approach. Differences between the studied populations were not observed but could be described with the observed covariate relatioships. Linezolid displayed nonlinear elimination kinetics which were well captured by implementing an inhibition compartment. In general linezolid penetrated well into tissue fluid but displayed high variability. Overall, inclusion of covariates significantly reduced unexplained variability. In clinical practice, long time periods below the minimum inhibitory concentration of relevant pathogens might occur in lightweight individuals with high CLCR and thrombocyte values which might increase the risk of treatment failure.