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.

Methods

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 taken after single dosing and at steady state for a period of 8 h, every 20 min for the first 3 h, increasing the sampling time interval to 30 min afterwards.

Pharmacokinetic Data Analysis

Overall, 1176, 1168 and 1157 linezolid concentrations were available for model development in ultrafiltered plasma and s.c. and i.m. microdialysis, 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 in Plasma was added 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.

Results

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 ωA might be due to the poor data situation after oral dosing.

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.

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 relationships. Linezolid displayed nonlinear elimination kinetics which was 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.