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Paper Poster Session
PK/PD of agents against Gram-positives

Population pharmacokinetics of linezolid as it applies to therapeutic drug monitoring: a comparison of ten approaches

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Background: Linezolid (LNZ) Therapeutic Drug Monitoring (TDM) has been studied before, but there are no reports on comparing the accuracy and precision of published pharmacokinetic (PK) models at forecasting LNZ concentrations . The goal of this study was to compare the bias and precision of ten published population equations at predicting future LNZ concentrations.

Material/methods: LNZ levels were collected as part of TDM programs. LNZ was administered by intermittent or continuous infusion and via the oral route. Ten linear and mixed linear and non-linear population equations with one to multiple compartments were coded into Individually Designed Optimum Dosing Strategies (ID-ODS™) online. Up to fifteen levels were predicted per patient. For models with covariate relationship, a change in PK parameters - as a result of a change in physiologic variables - were allowed to improve the predictive performance of the equations. The mean prediction error (ME) and mean squared prediction error (MSE) and their 95% confidence intervals (95%CI) were calculated to measure absolute, while Δ ME and Δ MSE and their 95% CI to measure relative bias and precision, respectively.

Results: 179 LNZ levels in 54 patients were analyzed. The models studied showed MEs in predicting serum concentrations that ranged from a mean (95% CI) % difference of -5.94 (-7.16, -4.72) mg/L to 6.44 (5.07, 7.82) mg/L, while MSEs that ranged from 62.61 (40.25, 84.97) mg/L^2 to 127.92 (92.63, 163.21) mg/L^2 . The one compartment model by Tsuji et al. was found to be numerically most accurate and precise. When compared to the model by Tsuji et al., the formulas by Polk and Abe et al. showed non-significantly different Δ MEs for bias, while the equations by Matsumoto, Boak and Abe et al. resulted in non-significantly different Δ MSEs for precision. The comparison of the rest of the approaches relative to the Tsuji method showed mostly negative values of Δ MEs and Δ MSEs that ranged from 13.51 (2.05, 24.97) mg/L^2 to 65.30 (26.55, 104.05) mg/L^2 .

Conclusions: Eight of the ten equations evaluated here are likely to under-predict total LNZ concentrations coupled with variable magnitudes of precision. When compared to the observed concentrations, the model by Tsuji et al. ranked the highest at accurately and precisely predicting LNZ

concentrations. The calculated results by the Abe et al. dosing approach also led to non-significantly different accuracy and precision as compared to the results based on the Tsuji method. Either one of these two competing and best performed models thus may be adapted into a TDM program focusing on the optimal dosing of LNZ.