Comparing two-sample log-linear exposure estimation with Bayesian model-informed precision dosing of tobramycin in adult patients with cystic fibrosis

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Background

Dosing of tobramycin in patients with cystic fibrosis (CF) to manage acute pulmonary exacerbations is challenging due to its high pharmacokinetic (PK) variability and narrow therapeutic window. The gold standard for tobramycin dosing is the two-sample log-linear regression (LLR) method. Bayesian model-informed precision dosing (MIPD) may allow for exposure estimation with fewer samples; however, the relative accuracies of these two methods in CF patients is unknown.

Methods

This retrospective analysis included 50 adult patients with CF receiving tobramycin therapy at Brigham and Women's Hospital from 2015 to 2022. Tobramycin concentration predictions made using LLR or Bayesian estimation with two population PK models (the Hennig and Alghanem models) were compared to measured values. Simulations assessed the impact of sample timing and area under the concentration-time curve (AUC) estimation accuracy. Concentration-time curves were simulated using popPK models, and either LLR or Bayesian estimation was used to estimate AUC. To account for model misspecification, estimation was performed with either regular or flattened Bayesian priors. Prediction error was quantified using normalized root mean square error (nRMSE), mean percent error (MPE), and accuracy, defined individually for each type of exposure.

Results

The two-sample LLR method predicted peak concentrations with higher accuracy (73.5% vs 55.0% Hennig and 45.0% Alghanem), lower MPE (3.0% vs 22.5% Hennig and 33.4% Alghanem), and lower nRMSE (23.5% vs 33.8% Hennig and 40.7% Alghanem). Bayesian methods better predicted trough concentrations, with similar accuracy (92.9% Hennig and 92.0% Alghanem vs 92.6% LLR), lower MPE (-8.5% Hennig and -14.6% Alghanem vs -19.6% LLR), and nRMSE (68.8% Hennig and 73.7% Alghanem vs 96.9% LLR). Bayesian MIPD with flattened priors and two tobramycin samples at 1- and 10-hours post-dose estimated AUC with an accuracy of 74.9% (Hennig) and 83.9% (Alghanem), compared to 78.9% by LLR. With one sample at 6 hours, accuracy drops to 74.9% Hennig and 75.8% Alghanem.

Conclusions

Bayesian MIPD with flattened priors with a single sample at 6 hours was comparable to two-sample LLR in estimating tobramycin AUC, showing the potential for reduced sampling strategies.

Key Words: tobramycin, cystic fibrosis, population pharmacokinetic model, Bayesian estimation, two-sample log-linear regression