Poster

[P25-1] P25-1: Anti-infective drugs (1): Aminoglycosides and beta-lactams

Chair: Andrew McLachlan, Australia

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[P25-1-4] External evaluation of amikacin population pharmacokinetic models in Japanese adult patients

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Background

Amikacin is an aminoglycoside commonly used for the treatment of life-threatening Gram-negative infections. Although amikacin population pharmacokinetic (popPK) models were published, their predictive performance was not evaluated in Japanese adult patients. To find suitable popPK models is important for individualizing amikacin therapy based on therapeutic drug monitoring(TDM). This study thus aimed to compare and externally evaluate amikacin popPK models by applying them to a new patient cohort in order to assess their predictive performance.

Methods

Eight popPK models were obtained from the literature(Philip 1980, Lacarelle 1987, Abbott Corporation 1993, Bressolle 1996, Tod 1998, Romano 1998, Romano 1999 and Jang 2011). Predictive performance of the models was evaluated using an independent dataset of 454 concentration-time points from 318 Japanese adult patients who received intravenous amikacin in Funabashi General Hospital, Chiba, Japan. Predictive performance was assessed by comparison of predictions to observations, calculation of bias and imprecision, and use of simulation-based diagnostics.

Results

Calculated metrics showed bias from 38% underprediction bias (Romano 1998 model) to 44% overprediction (Philip model). Tod model performed best in all evaluations : mean errors(ME) ranging from -3.36 to 3.40 mg/L, root mean square errors (RMSE) ranging from 4.72 to 8.33 mg/L, average fold error (AFE) ranging from 0.35 to 1.00 and absolute average fold error (AAFE) ranging from 1.00 to 2.89. Tod and Abbott Corporation methods only showed no significant bias (deltaME [95% confidence interval (CI)]:0.34 [−0.11 to 0.80]). Romano 1998, Tod, Jang and Lacarelle methods were not significantly different because delta MSE (95% CI) value were 2.39 (−3.17 to 8.83), 2.43 (−3.12 to 9.43) and, −0.19 (−5.74 to 5.39), respectively. These prediction results were supported by the simulation-based diagnostics.

Conclusions

Published popPK models showed low accuracy, poor precision and trueness, although Tod model performed better. Therefore, none of the eight models showed clinically acceptable predictive performance for routine dosage adjustment in Japanese adult patients. These findings suggest that knowledge of typical pharmacokinetic behaviors and patient information of covariate values are not sufficient, and TDM with

measuring drug concentration is thus needed for precisely predicting amikacin pharmacokinetics.