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Population Pharmacokinetic Models of Remifentanil in Korean Healthy Volunteers Using Nonlinear Mixed Effects Model and Machine Learning Methods

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Objective: The primary objective of this study was to develop optimal pharmacokinetic models of remifentanil using nonlinear mixed effects model and machine learning methods. The secondary objective was to compare the performance of multiple machine learning methods with that of the dominant pharmacokinetic modeling method, a nonliner mixed effects model, in predicting blood concentration of remifentanil.

Methods: Pharmacokinetic data were collected during a study involving the zero-order infusion of remifentanil into healthy volunteers. Pharmacokinetic models were constructed using the nonlinear mixed effects model as implemented by NONMEM, artificial neural networks, support vector machines, and multi-method ensembles. Models were assessed using goodness?)of?]fit statistics and error measurement, and performance was compared using paired t-tests.

Results: An ensemble, the mean of the artificial neural network and NONMEM predictions, achieved minimal error and the highest correlation coefficient. The support vector machine produced the highest error and the lowest correlation coefficient. Paired t-tests indicate that there is insufficient evidence that the predicted values of the artificial neural network, the support vector machine, and two multi?]method ensembles differ from the actual measured values at ??=.05.

Conclusions: Consistent with previous literature, the artificial neural network predicted blood concentrations more accurately than a nonlinear mixed effects model created with NONMEM. However, an ensemble method combining the artificial neural network and NONMEM predictions outperformed either method alone. The results indicate a potential advantage of ensembles in improving accuracy and reducing variance of pharmacokinetic models.

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