IMPROVING THE PERFORMANCE OF THE 'MINTO' REMIFENTANIL PHARACOKINETIC MODEL BY INCORPORATING DATA FROM OBESE SUBJECTS

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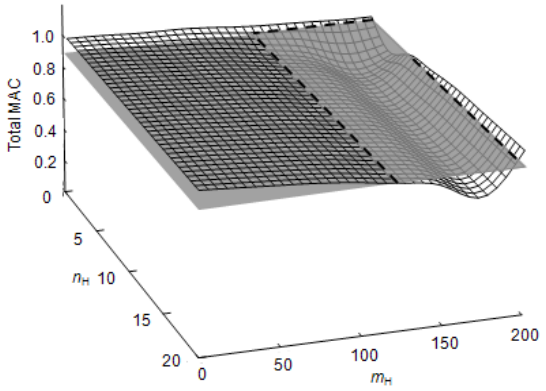
Introduction: For remifentanil target-controlled infusion (TCI) or pharmacokinetic simulation, the 'Minto' pharmacokinetic parameter set (1) has been commonly used. However, the model has potential problems: (a) the original dataset does not include truly obese subjects and, (b) the lean body mass (LBM) covariate implemented in this model was calculated using a flawed method at high values of total body weight (TBW). Recently, improved LBM (JanLBM) calculation methods have been reported (2,3), and the scientific foundation supporting allometric body mass scaling in biologic modeling has been established.(4) We hypothesized that incorporating data from obese subjects, improved LBM calculations and allometric scaling would improve the performance of the Minto pharmacokinetic model. The aim of this study was test this hypothesis using historical datasets for model building and validation.

Method: Eighty-nine subjects' drug administration and time vs concentration data for pharmacokinetic analysis were obtained from the authors.(1,5) Nonlinear regression techniques were used to construct two pharmacokinetic models characterizing remifentanil's disposition, one model using the "JanLBM" and another using "allometrically standardized TBW" as covariates. The prospective performances of the models were assessed using separate historical pharmacokinetic data sets from 125 subjects obtained from the authors.(6-9) Measures of accuracy and bias were computed using techniques described by Varvel and Shafer.(10)



Results: 2336 data points for model building and 1957 data points for the prospective validation of the models were analyzed. The final model parameters and performance measures are shown in the table.

Conclusion: Our hypothesis was confirmed. While all the models performed well, new models addressing the shortcomings of the Minto model performed slightly better in terms of accuracy and bias. An important limitation of this analysis is the relative shortage of extremely obese subjects' pharmacokinetic data in the validation dataset. It is possible that validation data sets including more obese subjects may demonstrate a greater improvement in the new models.

References:

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Population models

	Minto	improved Minto	Obara (JanLBM scaled)	Obara (allometric TBW scaled)
V1 (L)	5.1 - 0.0201*(age - 40) + 0.072*(LBM - 55)	Replace LBM in Minto's model with JanLBM	5.15 + 0.0316*(JanLBM - 57)	3.82 + 1.13*(TBW / 70)
V2 (L)	9.82 - 0.0811*(age - 40) + 0.108*(LBM - 55)		12.8	12.3
V3 (L)	5.42		7.78	7.65
CL1 (L/min)	2.6 - 0.0162*(age - 40)+0.0191*(LBM - 55)		2.71 – 0.0127*(age – 38) + 0.0214*(JanLBM – 57)	1.66 – 0.0136*(age – 38) + 0.939*(TBW / 70)$^{0.75}$
CL2 (L/min)	2.05 - 0.0301*(age-40)		0.13	0.127
CL3 (L/min)	0.076 - 0.00113*(age-40)		1.07	1.08
MDPE			0.049	0.037
MDAPE			0.258	0.25

Model Validation

	Minto	Improved Minto	Obara (JanLBM scaled)	Obara (allometric TBW scaled)
MDPE	-0.119	-0.14	-0.102	-0.076
MDAPE	0.219	0.227	0.205	0.205

MDPE = median prediction error; MDAPE = median absolute prediction error; LBM = James' lean body mass; JanLBM = Janmahsatian's lean body mass; TBW = Total body weight (kg)

Acknowledgment: We thank the investigators from prior studies for making their data available (Ref. 6, 7, 9 and 1).