Is the expected performance of a target-controlled-infusion system influenced by the population analysis method

D J Eleveld (1), J K G Wietasch (2), J H Proost (1), S Guzy (3), A Hoeft (4)

1) Research Group for Experimental Anesthesiology and Clinical Pharmacology, Department of Anesthesiology, University Medical Center Groningen, The Netherlands; (2) Department of Anesthesiology, University Medical Center Groningen, The Netherlands; (3) POP-PHARM; XOMA; (4) Department of Anesthesiology and Intensive Care medicine, University of Bonn, Germany;

EXPERIMENTAL ANESTHESIOLOGY
RESEARCH GROUP
CLINICAL PHARMACOLOGY

University Medical Center Groningen

Introduction

Target-controlled infusion (TCI) systems calculate the intravenous drug rate required to rapidly achieve a desired drug concentration using a pharmacokinetic (PK) model. In the past, NONMEM[1] was the only widely available population PK analysis method and all propofol PK parameter set in existing literature were determined using this method. Recently, a number of population analysis methods have been described in the literature, potentially providing 'better' population PK parameter sets. The purpose of this investigation was to estimate the degree to which differences in TCI performance may be expected depending on the population analysis method used. We used NONMEM[2], MCPEM[3] and Multifit[4] software packages to estimate the population PK model for propofol when used in combination with sufentanil. We estimated the performance of TCI systems based on the results of each of the methods as well as propofol PK parameter sets from existing literature.

Methods

After institutional review board approval and written informed consent, fifty-six patients undergoing elective cardiac surgery included in the study. Propofol infusion rates were adjusted to maintain bi-spectral index values of 50±10. Sufentanil infusion rates were adjusted to maintain heart rate and blood pressure appropriate for the surgical procedure. Arterial blood samples for determination of propofol plasma concentrations were taken. We used a mammillary 3-compartmental model to describe patient PK characteristics. To evaluate the expected TCI system performance of the PK parameter sets produced by the population analysis methods we performed simulations of a TCI system. Target plasma concentration was 5 μg/ml and simulation time was 2 hours.

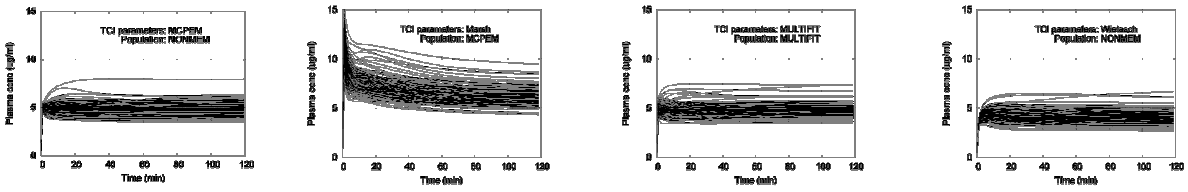
$$PE = \frac{C_{simulated} - C_{target}}{C_{target}} \times 100\%$$

$$MdPE = \frac{1}{\sum_{i=1}^{M} N_i} \times \sum_{i=1}^{M} \left(N_i \times Median(PE_i) \right) \qquad MdAPE = \frac{1}{\sum_{i=1}^{M} N_i} \times \sum_{i=1}^{M} \left(N_i \times Median(|PE_i|) \right)$$

Results

PK population estimation was performed on 1239 samples from 56 individuals receiving 60 bolus doses and 2398 infusions. Figures show time course of plasma sufentanil concentration for 100 TCI system simulations with various combinations of populations and TCI controller parameters.

PK population	*V1* (l)	cv	*V2* (l)	cv	*V3* (l)	cv	*Cl10* (l/min)	cv	*Cl12* (l/min)	cv	*Cl13* (l/min)	cv	Residual (%)
NONMEM (naive pool)	5.79	-	12.0	-	700	-	1.40	-	0.89	-	0.58	-	13.4%
NONMEM	5.59	0%	11.1	54%	628	80%	1.44	18%	0.85	0%	0.56	35%	7.3%
MCPEM	5.70	16%	11.3	47%	640	84%	1.41	17%	0.83	48%	0.54	35%	5.5%
MULTIFIT	5.71	17%	10.6	51%	638	72%	1.45	17%	0.99	32%	0.57	30%	6.0%
Previously published													
Marsh[5]	15.96	-	32.50	-	203	-	1.90	-	1.79	-	0.67	-	
Schneider[6]	3.99	-	17.64	-	222	-	1.76	-	1.20	-	0.78	-	
Wietasch[7]	3.31	28%	10.10	14%	152	0%	1.22	22%	0.91	87%	0.53	54%	



Discussion

Small differences in TCI system MdPE values were found between the methods but the MdAPE values were very similar. On average, the parameter sets from the methods investigated provided essentially equal expected TCI system performance error.

Conclusions

Even though each of the population analysis methods provides different PK parameter estimates they do not significantly influence the expected performance of propofol TCI systems.

Expected TCI system performance

Each performance evaluation consists of 10000 TCI system simulations.

	PK population							
TCI parameters	NONMEM		MCPEM		Multifit		All populations	
	MdPE	MdAPE	MdPE	MdAPE	MdPE	MdAPE	MdPE	MdAPE
NONMEM	-1.9%	12.4%	0.5%	12.1%	-2.4%	11.7%	-1.3%	12.1%
MCPEM	-3.7%	12.6%	-1.3%	12.3%	-4.7%	11.9%	-3.2%	12.2%
Multifit	-0.7%	12.4%	1.7%	12.5%	-1.4%	11.6%	-0.1%	12.2%
NONMEM (pool)	-2.0%	12.7%	0.3%	12.2%	-3.0%	11.6%	-1.5%	12.2%
Marsh[5]	27.9%	29.3%	30.8%	31.9%	26.7%	28.0%	28.5%	29.7%
Schnider[6]	20.6%	22.8%	23.2%	24.7%	19.3%	21.2%	21.0%	22.9%
Wietasch[7]	-17.5%	19.0%	-15.3%	17.3%	-18.2%	19.2%	-17.0%	18.5%

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