



PK/PD of propofol and fentanyl in patients undergoing abdominal aortic surgery – the influence of cardiac output and drug interactions



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Objectives

Pharmacokinetic (PK) and pharmacodynamic (PD) data of propofol and fentanyl, the cardiac output (CO) measurements, and the bispectral index (BIS) were available from a study of ASA physical status III patients scheduled for abdominal aortic surgery. The aim of the work was to assess the influence of CO on propofol and fentanyl PK/PD and to determine the effect of fentanyl on hypnotic effects of propofol.

Methods

After institutional approval, the data was obtained from ten patients of 50 to 75 years age and weighing between 50 and 92 kg. Propofol was administered by means of the target-controlled infusion system (Diprifusor) and fentanyl was given whenever inadequate analgesia was assessed throughout the surgery at a dose of 2–3 µg/kg. Hemodynamic measurements were done with FloTrac/Vigileo TM (Edwards, USA). The bispectral index (BIS) served to monitor the depth of anesthesia and was kept between 40 and 60.

Population nonlinear mixed-effect modeling was done using NONMEM (Version 7.2, Icon Development Solutions, Ellicott City, MD, USA) and the Intel Fortran Compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN611, <http://wfn.sourceforge.net>). The first-order conditional estimation with interaction (FOCE) method was used. The minimum value of the NONMEM objective function (MOF), typical goodness of fit diagnostic plots, and evaluation of the precision of PK parameter and variability estimates were used to discriminate between various models during the model-building process. The NONMEM data processing and plots were done in Matlab® Software version 7.0 (The MathWorks, Inc., Natick, MA, USA).

Results

A three and a two compartment model was sufficient to describe propofol and fentanyl PK. The delay of the anesthetic effect, with respect to plasma concentrations, was described by the effect compartment. The BIS index was linked to the propofol and fentanyl effect site concentrations through a synergistic E_{max} model. In this study the cardiac output has been identified as significant covariant influencing fentanyl disposition (elimination and distribution clearance). The effects of CO on propofol PK were less evident and could not be supported by the present data.

Conclusions

The population PK/PD model was successfully developed to describe the time course and variability of propofol and fentanyl concentrations and BIS index. The effects of CO on fentanyl PK and interactions between fentanyl and propofol were observed in the study.

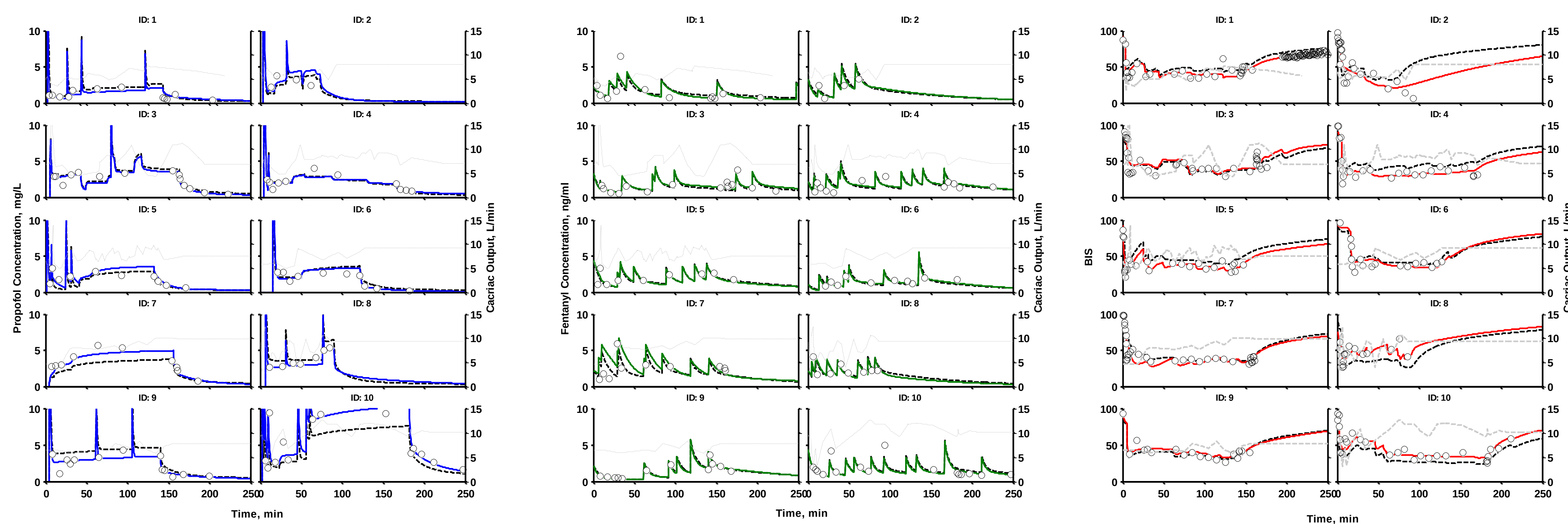


Figure 2. Plot of observed (open circle), population predicted (solid line) and individual predicted (broken line) propofol/fentanyl concentrations and BIS versus time for the final PK/PD model. The gray broken line indicates cardiac output measurements.

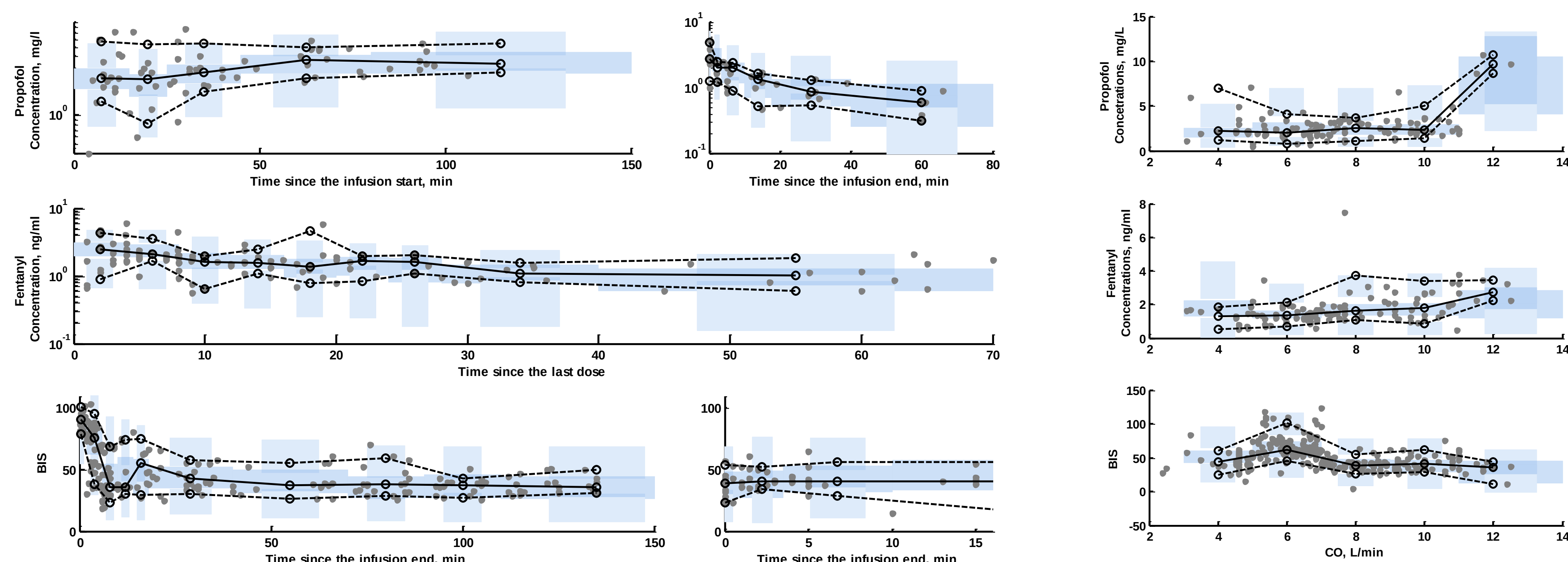


Figure 4. The prediction corrected visual predictive check plots (pcVPC) for propofol/fentanyl concentrations and BIS measurements. The pcVPC plots show the simulation-based 95% confidence intervals around the 10th, 50th, and 90th percentiles of the PD data in the form of blue (50th) and light blue (10th and 90th) areas. The corresponding percentiles from the prediction corrected observed data are plotted in black color. The prediction corrected raw data is presented as gray closed symbol.

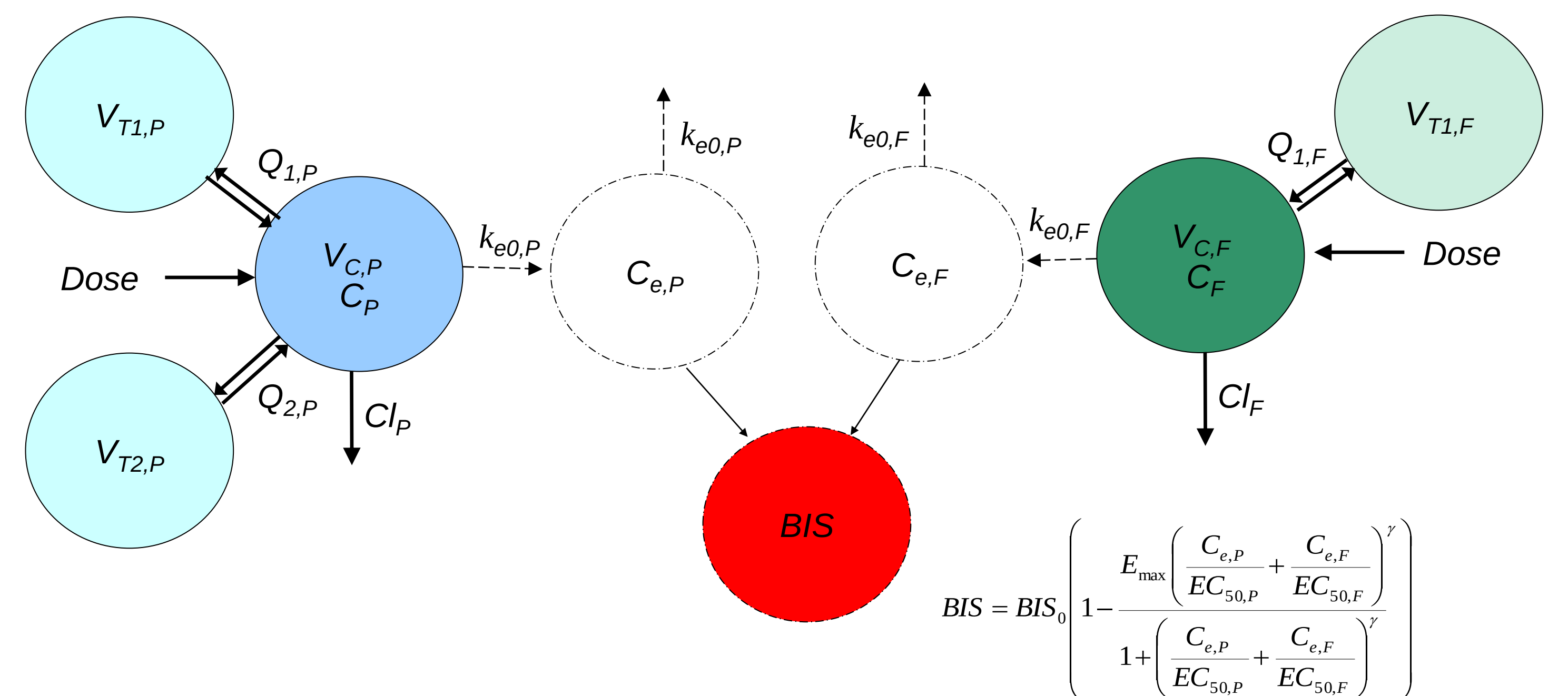


Figure 1. Diagram of PK/PD model of propofol/fentanyl.

Table 1. Summary of the final population PK/PD parameters and inter-subject and residual error variance estimates of propofol. The bootstrap estimates (n=100) are given for comparison.

Parameter [unit]	θ , Estimate	ω^2 (%CV), Estimate	θ , Bootstrap Estimate Median (5th-95th percentile)	ω^2 (%CV), Bootstrap Estimate Median (5th-95th percentile)
$V_{C,P}$, [L]	4.01 (29.4)	-	3.9 [2.01 - 7.84]	-
CL_P , [L/min]	1.88 (9.6)	24.7 (31.9) [5.7%]	1.72 [0.0188 - 2.19]	36.8 (0.244-244)
$Q_{1,P}$, [L/min]	0.725 (36.0)	80.1 (83.2) [14.7%]	1.26 [0.523 - 2.33]	41.5 (0.774-112)
$V_{1,P}$, [L]	109 (9.7)	-	147 [86 - 2188]	-
$Q_{2,P}$, [L/min]	1.81 (45.6)	86.7 (80.3) [20.7%]	1.9 [0.956 - 3.8]	57.3 (0.836-120)
$V_{2,P}$, [L]	17.4 (26.2)	-	15.5 [9.99 - 21.4]	-
$V_{C,F}$, [L]	44.8 (27.2)	-	44.2 [24.6 - 65.0]	-
$CL_F \cdot (CO/6.5)$, [L/min]	1.44 (13.4)	18.2 (56.2) [25.6%]	1.46 [0.994 - 1.72]	18.2(0.2-33.5)
$Q_{1,F} \cdot (CO/6.5)$, [L/min]	4.07 (30.2)	73.7 (43.3) [15.5%]	4.33 [2.71 - 6.16]	64.6 (3.16-91.3)
$V_{1,F}$, [L]	130 (20.2)	-	132 [103 - 205]	-
BIS_p , []	93.1 (3.7)	-	94.3 [87.9 - 99.9]	-
E_{MAX} , []	1 fixed	-	1 fixed	-
$EC_{50,F}$, [ng/ml]	4.76 (60.1)	74.4 (85.6) [16.3%]	4.35 [2.08 - 19.96]	63.5 (0.837-120.6)
$EC_{50,P}$, [mg/L]	3.25 (26.8)	69.7 (45.7) [3.52 %]	3.29 [2.26 - 5.89]	61.4 (35.2-85.9)
γ , []	1 fixed	-	1 fixed	-
$k_{e0,P} = k_{e0,F}$ [1/min]	0.192 (33.3)	84.7 (66.4) [5.3%]	0.191 [0.140 - 0.293]	74.8 (27.2-120.0)
Residual variability				
$\sigma^2_{prop,P}$, %	31.1 (11) [7.5%]		30.1 [0.254 - 0.350]	
$\sigma^2_{prop,F}$, %	38.7 (11.6) [3.8%]		36.8 [0.306 - 0.462]	
$\sigma^2_{add,BIS}$, []	8.43 (13.5) [4.0%]		8.82 [6.88 - 10.3]	

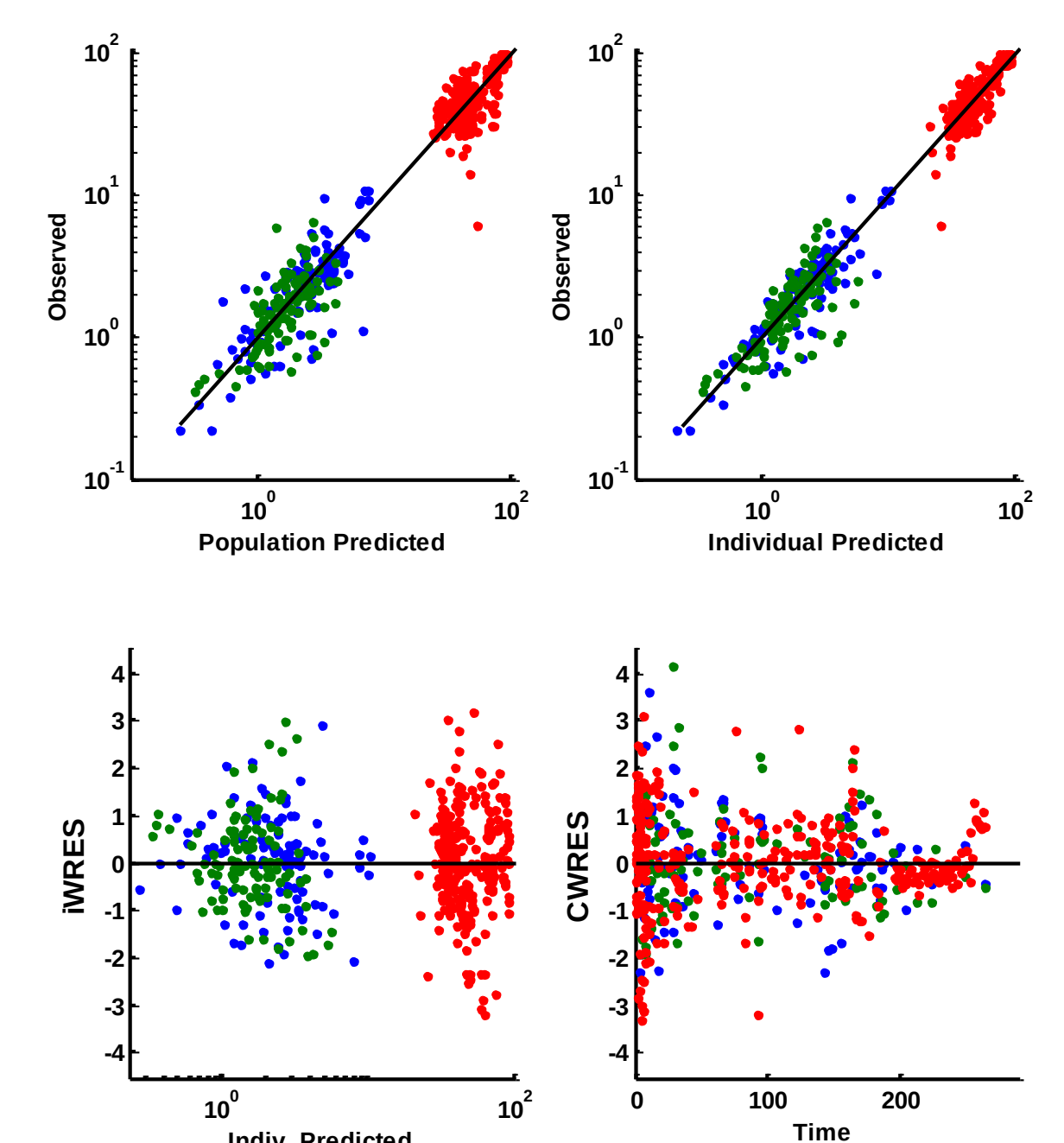


Figure 3. Goodness of fit plots for the final PK/PD model.

Table 2. The decrease in objective function value (OFV) after inclusion of CO effect on the propofol and fentanyl clearance parameters.

Key modeling steps, Equations	ΔOFV
Fentanyl: $CL_F \cdot (CO/6.5), Q_{1,F} \cdot (CO/6.5)$	- 5.21
Propofol : $CL_P \cdot (CO/6.5), Q_{1,P} \cdot (CO/6.5), Q_{2,P} \cdot (CO/6.5)$	+ 3.23

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