External validation of pharmacokinetic population model of alfentanil in obese patients

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INTRODUCTION

- Alfentanil is a short-acting opioid, used in anesthesia with a target controlled infusion (TCI).
- Pharmacokinetic model used derived from normal weight patients.
- External validation with a dataset of obese patients.
- Proposition of another model to compare the obtained results.

Table1. Demographic data

Variable	Mean	+/- SD	Range
Age (yr)	42.9	12.3	18 to 68
Weight (kg)	98.0	29.5	50.0 to 145.0
Duration of alfentanil infusion (min)	116.9	60.8	7.2 to 212.0
Total alfentanil dose (mg)	5.3	2.3	1.3 to 7.9

METHOD

- Administration of alfentanil to ten obese patients undergoing laparoscopic gastroplasty and five normal patients undergoing surgery (Table1).
- The predicted alfentanil target concentrations were calculated by Stanpump software.
- Plan of sampling of blood: at 1 and 5 minutes after the start of infusion and at 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 180, 220 and 300 minutes after the definitive stop of infusion.
- Determination of concentrations with a gas chromatography method.
- Pharmacokinetic analysis was made by using a non linear mixed-effect population model.
- Data analysis included calculation of performance error (PE), median performance error (MDPE) and median absolute performance error (MDAPE).

RESULTS

- Model of Maitre et al. [1], with three compartments and two covariates : age (clearance and k31) and sex (volume of distribution of the central compartment) (Table2).
- Our three compartments model has included two covariates : age (k12) and weight (k13) (Table2).
- The pharmacokinetic parameters of our model were listed in Table3.
- Validation of our model by an internal method : bootstraping and GoF plots (Graphics1 and 2).

Graphic1. Normalized predictive distribution errors (npde) versus time (min).

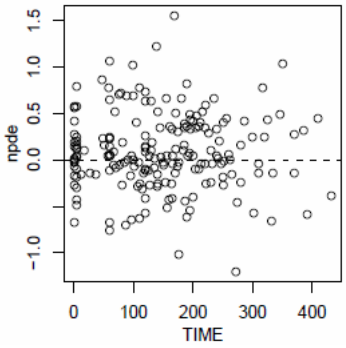

Table2. Accuracy of pharmacokinetic models.

	INFUSION		AFTER INFUSION		WHOLE PERIOD	
%	Maitre	Our model	Maitre	Our model	Maitre	Our model
MDPE	29.9	-5.3	39.8	-10.7	11.3	-7.7
Range	-47.7 to 225.7	-58.4 to 74.6	-98.7 to 350.4	-81.5 to 263.2	-98.7 to 350.4	-81.5 to 263.2
MPE	53.8	-3.1	20.1	5.1	28.3	3.1
95% CI	34.1 to 73.5	-10.5 to 4.3	9.3 to 30.9	-5.3 to 15.5	18.6 to 38.0	-5.0 to 1.2
MDAPE	34.9	9	25.1	31.8	26	25.2
Range	0.6 to 225.7	0.6 to 74.6	0.6 to 350.4	0.02 to 263.2	0.6 to 350.4	0.02 to 263.2
MAPE	59	18.6	45.9	46.7	49.1	39.9
95% CI	40.7 to 77.4	13.5 to 23.7	37.4 to 54.3	39.6 to 53.8	41.3 to 56.9	34.1 to 45.7

Graphic2. Normalized predictive distribution errors (npde) versus predicted concentrations (PRED).

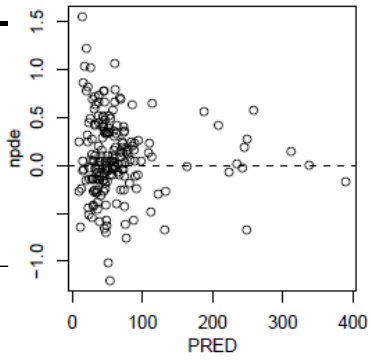

Table3. Final estimates for population pharmacokinetic parameters of alfentanil in obese patients.

Parameters	NONMEM Estimates	(+/- SE)	95% CI
CL (L/min)	0.273	0.120	0.210 to 0.341
K12 (min^{-1}) Age ≤ 40 yr	1.410	0.096	1.110 to 1.910
K12 (min^{-1}) Age > 40 yr	0.822	0.202	0.524 to 1.540
K21 (min^{-1})	0.320	0.168	0.228 to 0.400
K13 (kg/min)	3.96E-03	0.231	2.26E-03 to 6.63E-03
K31 (min^{-1})	2.01E-02	0.168	1.36E-02 to 2.61E-02
V (L)	1.550	0.113	0.893 to 2.060
Interindividual variability of CL (%)	47.5	43.0	24.9 to 65.1
Interindividual variability of K31 (%)	32.1	25.6	21.7 to 40.5
Residual intraindividual variability (%)	14.8	28.1	10.5 to 18.4

CONCLUSION

- The model of Maitre et al. [1] underestimated the predicted concentrations which may lead to an overdosage of alfentanil.
- Our model, including body weight, improves considerably the values of high concentrations (during infusion).
- We suggest to use our model for obese patients when delivering alfentanil with target controlled infusion.

Reference: [1] Maitre et al. Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 1987