Performance of alfentanil target-controlled infusion in normal and morbidly obese female patients†

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Editor’s key points

- All alfentanil pharmacokinetic (PK) models are derived from populations with normal BMI.
- Maitre and colleagues’ alfentanil target-controlled infusion is acceptable for clinical application to morbidly obese patients.
- Maitre and colleagues’ model should be applied with caution to that population of patients, especially when high-concentration targets are applied.
- Data from this study were also accurately described by a new three-compartment model with BMI as the covariate.

Background. Available alfentanil pharmacokinetic (PK) sets for target-controlled infusion (TCI) were derived from populations with normal BMI. The performance and accuracy of the models devised by Maitre and colleagues and Scott and colleagues were evaluated in a population including morbidly obese patients.

Methods. Alfentanil TCI using Maitre and colleagues’ model was administered to 10 obese and six non-obese women (BMI 19.5–57.4 kg m$^{-2}$) undergoing laparoscopic surgery. The initial effect-site target concentration was 100 ng ml$^{-1}$. Alfentanil arterial plasma concentrations were sampled from TCI onset to 220 min after its termination. Stanpump software calculated predicted alfentanil concentrations. Data were analysed with a non-linear mixed-effect model (NONMEM, version 7.2), including calculations of the median performance error (MDPE) and the median absolute performance error (MDAPE). Scott and colleagues’ model was evaluated retrospectively.

Results. Using Maitre and colleagues’ model, MDPE and MDAPE (range) for the whole population were 13.3% and 23.9%, respectively. With Scott and colleagues’ model, MDPE and MDAPE were 30.7% and 50.1%, respectively. We created a three-compartment model with BMI as the covariate (CL), yielding MDPE 1.1% and MDAPE 30.6%.

Conclusions. Maitre and colleagues’ PK set underestimated the predicted concentrations in our mixed-weighted population, but its bias and accuracy were acceptable for clinical application. Scott and colleagues’ model was inaccurate. The NONMEM model seemed to be more accurate during the infusion and for high concentrations, but it needs to be validated in a larger population.

Keywords: alfentanil; opioids; overweight; pharmacokinetics; target-controlled infusion

Accepted for publication: 9 April 2012

Obesity induces physiological modifications that are likely to affect drug tissue distribution and elimination.1 In clinical practice, to avoid the risk of tissue drug accumulation,2 the anaesthetist has to rely on short-action substances.

Among opioids, alfentanil is useful, because of its low liposolubility and its rapid efficacy. The benefits of alfentanil target-controlled infusion (TCI) may be extended to the obese population, but the available alfentanil pharmacokinetic (PK) models were derived with data obtained from non-obese populations. Among these PK sets, Maitre and colleagues’3 and Scott and colleagues’4 models are the most used in the literature and seem to provide the best accuracy. This study was undertaken to evaluate the accuracy of Maitre and colleagues’ and Scott and colleagues’ PK sets using the alfentanil PK parameters described by Maitre and colleagues3 for morbidly obese and non-obese patients undergoing laparoscopic surgery, and to determine a PK model describing alfentanil PK parameters in this mixed population.


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Methods

This prospective study was approved by the Nice University Ethics Committee (Comité de Protection des Personnes se livrant à la Recherche Biomédicale, CIR 2003 no. 02-035), and registered with EudraCT (ref: 2011-001439-21). Written informed consent was obtained from morbidly obese patients undergoing laparoscopic bariatric surgery, and normal-weight patients (BMI <30 kg m$^{-2}$) undergoing laparoscopic surgery. Morbidly obese and non-obese female patients 18–68 yr old with ASA I or II were eligible for enrolment. Morbidly obese patients undergoing bariatric surgery had a BMI of >35 kg m$^{-2}$ in combination with a comorbidity, or a BMI of >40 kg m$^{-2}$ without any comorbidity. BMI was defined as: body weight (kg)/height$^2$ (m$^2$).

All patients underwent laboratory tests to exclude significant illness or pregnancy. Exclusion criteria were: history of alcohol abuse or illegal drug use, renal or hepatic disease, gastro-oesophageal reflux, concurrent medication included drugs known to interact significantly with opioids, or cytochrome P450.

Anaesthesia procedure

One hour before surgery, patients were premedicated with oral hydroxyzine (100 mg). After local anaesthesia (Emla\textsuperscript{®} cream, Astra, Rueil-Malmaison, France), the following blood vessels were cannulated: one forearm vein for administration of anaesthetics, a second forearm vein for fluid replacement, and a radial artery for continuous arterial pressure monitoring and blood samplings. After adequate preoxygenation, anaesthesia was induced with a propofol bolus (2.5 mg kg$^{-2}$) followed after 90 s by alfentanil in the TCI mode. Atracurium (0.6 mg kg$^{-1}$) was injected i.v. to facilitate tracheal intubation. Anaesthesia was maintained with desflurane, whose administration was adjusted to obtain the bispectral index values between 40 and 60. Muscle relaxation was monitored with a train-of-four nerve simulator.

Alfentanil was administered with a BD Pilot Anesthesia\textsuperscript{®} pump (Fresenius-Viale, Brezins, France) connected via a serial RS-232 interface to a personal computer running Stanpump\textsuperscript{®} software (SL Shafer, Department of Anesthesia, Columbia University, New York, NY, USA). The PK set for alfentanil described by Maitre and colleagues\textsuperscript{3} used the total body weight (TBW) to calculate the physiological parameters. The initial alfentanil effect-site concentration was set at 100 ng ml$^{-1}$, and then 60 ng ml$^{-1}$ 5 min later. The predicted target concentrations (effect-site and plasma) and the corresponding alfentanil infusion rate were recorded every 10 s by Stanpump\textsuperscript{®} software. During surgery, the target concentration was adjusted to mean arterial pressure (MAP) and heart rate (HR); MAP or HR variation exceeding 15% above or below baseline values induced a 10 ng ml$^{-1}$ increment in the target alfentanil concentration in the same direction; the predicted plasma concentration had to reach the predicted effect-site concentration before a new target could be requested. Alfentanil target concentration was set at 0 ng ml$^{-1}$ at pneumoperitoneum exsufflation, and Stanpump\textsuperscript{®} software was stopped after the last blood sample.

Blood sample processing and alfentanil assay

Arterial blood samples (4 ml) for alfentanil concentration measurements were obtained before a target change 1, 5, 30, 60, and 120 min after starting alfentanil infusion, and 0, 5, 10, 20, 30, 40, 50, 60, 90, 120, 180, and 220 min after its end. The corresponding predicted plasma and effect-site alfentanil concentrations of Stanpump software were recorded at the exact moment of the sampling. All blood samples were immediately heparinized and centrifuged at 4°C, and plasma was separated (3500 rpm for 10 min) and frozen (–75°C) until analysis. Plasma alfentanil concentrations were determined by high-performance liquid chromatography coupled with mass spectrometry in the single ion-monitoring mode (Département de Pharmacologie Clinique, Institut Gustave-Roussy, Villejuif, France). In accordance with the ICH guidelines, precision (repeatability and intermediate precision) of the method was evaluated. Repeatability (intra-day precision), expressed as the coefficient of variation of repeatability (CVr), was performed for each level of quality control (QC) six times and intermediate precision (interday precision), expressed as the coefficient of variation of intermediate precision (CVi), was evaluated for each level of QC over 5 days. The accuracy was measured by the deviation or bias (%) of the mean found concentration (n=6) from the actual concentration.

The CV values for repeatability (CVr) and for intermediate precision (CVi) were found between 0.8% and 4.5% and between 1.1% and 6.0%, respectively. The bias values representing the accuracy of the method were found below 4.3%.

External validation

Data were analysed using Excel 2003 (Microsoft Corporation, Seattle, WA, USA). The predictive performance of Maitre and colleagues\textsuperscript{3} PK model of alfentanil was assessed by using the prediction error (PE).

For each blood sample, the per cent PE of the predicted plasma alfentanil concentrations was calculated as follows:

$$\text{PE} = \frac{C_m - C_p}{C_p} \times 100$$

where Cm and Cp are the measured and predicted plasma alfentanil concentrations, respectively.

As recommended by Varvel and colleagues,\textsuperscript{5} intrasubject data analysis consisted of an evaluation of four indicators of predictive performance for the n subjects:

(i) The median PE (MDPE): the per cent MDPE reflects the bias of TCI in the ith subject;

$$\text{MDPE}_i(\%) = \text{median}(\text{PE}_j), \quad j = 1, \ldots, n$$
Population PK modelling

Population PK analysis was performed using a non-linear mixed effects model as implemented using NONMEM computer program (version 7.2, ICON Solutions, Dublin, Ireland). The first-order conditional estimation method was used throughout. Different structural models for alfentanil PKs were investigated: one, two, and three compartments with linear elimination. Intersubject variability of the different PK parameters was estimated with an exponential error model. Several error models (additive, proportional or both) were investigated to describe residual variability. The performance of the model was judged by both statistical and graphic methods. The minimal value of the objective function as calculated by NONMEM was also used to assess the goodness-of-fit. An increase in the goodness-of-fit is accompanied by a decrease in objective function, and this decrease is asymptotically distributed as a $\chi^2$ distribution. Furthermore, standard errors were calculated by the use of the COVARIANCE option of NONMEM. For graphic model diagnostics, the following graphs were compared: observed concentrations (depending variable, DV) vs predictions (PRED), corrected weighted residuals (CWRES) vs time, corrected weighted residuals vs PRED, individual predictions (IPRED) vs DV, and normalized predictive distribution error vs PRED or TIME. Graphics were obtained with R for Windows Software (R-2.14.1, The R Foundation for Statistical Computing).

A first analysis was performed to find the base model that best described the data. Once it was defined, the influence of each covariate on the PK parameters was tested via an upward model building. These covariates were height, body weight, lean body mass (LBM) calculated with Jammahasa-10n and colleagues’ formula, BMI, and age. The diagnostic plots described above, the change in objective function, and the change in parameter variability were noted to select those which improved the model prediction. A decrease in the objective function value (OFV) of at least 6.61 ($\chi^2$ distribution with one degree of freedom for $P<0.01$) relative to the base PK model was required for the addition of a single parameter in the model. Covariates defined as relevant during the screening step were included in a so-called ‘full model’. Then a backward elimination procedure was performed in which each covariate was removed in turn from the ‘full model’ and the difference in OFV between the full and each reduced model was examined. An increase in OFV $>7.88$ ($P<0.005$) was required to retain the covariate in the final model.

Bootstrap procedures were performed using Wings for NONMEM (www.wfn.sourceforge.net) to evaluate the 95% confidence intervals non-parametrically. One thousand bootstrapped data sets were generated by re-sampling subjects from the original data set with replacement. These data sets were analysed using the final model described previously. Finally, the 2.5th and 97.5th percentiles of the parameter estimates were taken to build the 95% bootstrap percentile confidence intervals.

Results

Ten morbidly obese and six non-obese or overweight patients were included in this study from 2004 to 2007. One non-obese patient was excluded because of a disconnection between the computer and the electric pump. No adverse effect was encountered during alfentanil administration. All patients were successfully extubated in the recovery room.

Patient characteristic data are reported in Table 1. The mean BMI for morbidly obese patients was 43 (5.6) kg m^{-2}. Alfentanil infusion duration was in mean 117 (61) min; total alfentanil dose was 5.3 (2.3) mg. Target-concentration was modified 3 (0.5) times during alfentanil infusion. The mean plasma alfentanil concentration measured at the end of the infusion was 70.9 (5.8) ng ml^{-1}.

Figure 1 shows the observed alfentanil plasma concentration vs time in obese and non-obese patients. The results of the external validation analysis are reported in Table 2. MDPE and MDAPE were calculated for obese and non-obese patients, for three periods: during and after alfentanil infusion, and for the whole study period.

Maitre and colleagues’ model

Maitre and colleagues’ model underpredicted plasma alfentanil concentrations during and after infusion in both obese and non-obese patients, and the bias differed significantly from zero. Values of MDPE for the whole population were 13.3%, and of MDAPE were 23.9%. Maitre and colleagues’ PK set performed within acceptable limits during infusion in obese patients, but only after infusion in non-obese patients. Figure 2a shows the performance error vs time in obese and
non-obese patients for Maitre and colleagues’ model. Figures 3A and 4A show the predicted vs observed plasma alfentanil concentrations and the normalized predicted distribution error vs predicted concentration for the whole period, respectively.

Scott and colleagues’ model
Scott and colleagues’ model underpredicted plasma concentrations during infusion in obese patients, and overestimated these afterwards. The model showed an overall poor performance in both obese and non-obese patients (MDPE were −30.7%, and MDAPE 50.1% for the whole population, respectively). An acceptable performance of Scott and colleagues’ model was only observed during the infusion period in non-obese patients.

NONMEM model
A three-compartment model with a first-order elimination provided a better description of the data than did a two-compartment model and was then used as the base
<table>
<thead>
<tr>
<th></th>
<th>Maitre and colleagues’ model</th>
<th>NONMEM model</th>
<th>Scott and colleagues’ model</th>
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<tr>
<td></td>
<td>MDPE</td>
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<tr>
<td>After infusion</td>
<td></td>
<td></td>
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<tr>
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<td>23.8</td>
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<tr>
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<td>7.9; 14.3</td>
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<td>Mean</td>
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<td>43.6</td>
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<td>25th; 75th percentiles</td>
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<td>5.9; 9.5</td>
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<td>23.9</td>
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<tr>
<td>25th; 75th percentiles</td>
<td>3.0; 89.6</td>
<td>7.7; 89.6</td>
<td>6.1; 9.5</td>
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The interindividual variability (IIV) was retained for clearance (CL), volume of compartment 1 ($V_1$), clearance of compartment 2 ($Q_2$), clearance of compartment 3 ($Q_3$), and volume of compartment 3 ($V_3$) and were modelled as exponential. An exponential model for the residual variability ensured a good adequacy between the observed and predicted values. During the selection process, we found that BMI was a significant factor influencing the IIV in clearance (CL). Between the base and the final model, the OFV decreased by 15 units and the intersubject variability on clearance from 61.1% to 51.1% (10.0%). None of the other covariates tested was retained. The relationship observed between BMI and CL is described in Figure 5. The final PK estimate parameters and 95% confidence intervals obtained from the bootstrap procedures are summarized in Table 3.

$h$-Shrinkage was evaluated for the parameters for which IIV was identified, since poor individual estimates of the parameter could result in distorted parameter–covariate relationship. $h$-shrinkage values were 1.06% for CL, 7.9% for $Q_2$, 4.8% for $Q_3$ and 28.7% for $V_3$, respectively.

Figure 2b shows the performance error vs time in obese and non-obese patients for the NONMEM model. Figures 3b and 4b show the predicted vs observed plasma alfentanil concentrations and the normalized predicted distribution error vs predicted concentration for the whole period, respectively.

**Discussion**

Clinical outcomes of patients anaesthetized with TCI and its accuracy should be used to select a PK set. It was shown that a mean 20–30% variation of measured concentrations above or below targeted concentrations with a maximum of 50–60% can be considered clinically acceptable. Different possible sources of variability are encountered when using a PK model for TCI, especially if patients receiving TCI do not belong to the same population as that used to develop the original PK model. In morbidly obese patients, PK changes have been reported for highly lipophilic drugs.
Only a few studies are available concerning the administration of alfentanil in the TCI mode,\textsuperscript{13–18} and ours is the first one evaluating an alfentanil TCI in a population including obese patients. However, the small number of our patients induced limitations for covariate analysis,\textsuperscript{19} and probably contributed to alter the results of Maitre and colleagues'\textsuperscript{3} and Scott and colleagues'\textsuperscript{4} PK sets performance, especially in non-obese patients (Table 2).

We selected Maitre and colleagues' PK model because it was used in all previous studies on TCI administration of alfentanil, during the intraoperative period\textsuperscript{13–16, 18} and/or for postoperative analgesia.\textsuperscript{13, 14, 17}

According to Coetzee and colleagues,\textsuperscript{10} our MDPE and MDAPE overall values of 13.3% and 23.9%, respectively, for the whole period with Maitre and colleagues' PK set would be sufficient to provide acceptable accuracy for clinical use. Our alfentanil plasma concentrations provided good residual analgesia, and according to Stanski and Hug,\textsuperscript{20} an alfentanil concentration of 100 ng ml\textsuperscript{-1} is sufficient to provide spontaneous ventilation.
Van den Nieuwenhuyzen and colleagues obtained similar results. They successfully used Maitre and colleagues’ PK set for postoperative analgesia in three different studies, and found excellent bias and accuracy values. They used Maitre and colleagues’ PK set for postoperative analgesia in three different studies, and found excellent bias and accuracy values. In their first studies, alfentanil was administered during surgery targeting plasma concentrations (400 and 150 ng ml$^{-1}$, respectively), and blood samples were collected exclusively after operation. The median values of minimal effective analgesic concentrations were in a range 43–65 ng ml$^{-1}$.

Even though no adverse effect was described in the other studies, the predictive performances of Maitre and colleagues’ PK model differed markedly. Barvais and colleagues compared nine different PK set in eight volunteers during a 4 h alfentanil infusion at 50 ng ml$^{-1}$. All PK sets, except Scott and colleagues’ model which slightly overpredicted concentrations, underestimated plasma alfentanil concentrations. Maitre and colleagues’ MDAPE was inaccurate, exceeding 50%. The authors concluded that PK models derived from patients receiving a large and rapid bolus injection were not accurate for alfentanil TCI administration, and recommended to use models derived from a slow injection. These findings were confirmed in the elderly in another study.

Others found Maitre and colleagues’ PK set to have poor predictive performance with MDPE and MDAPE values at 53% in two groups of patients, resulting in underestimations of alfentanil concentrations. The initial plasma concentration target was 100 ng ml$^{-1}$ for the first group, and the second group had sequential concentrations from 400 to 700 ng ml$^{-1}$. Arterial blood samples were collected during the intraoperative period. Those authors stopped their investigation of Maitre and colleagues’ model after 11 patients from the second group because of the poor bias and accuracy values, and pursued the study with Scott and colleagues’ PK set, which yielded better results. The authors did not find a complete explanation for the differences observed in the two PK parameter sets, but found that the inaccuracy of Maitre and colleagues’ model was high after changing the target concentration.

We observed similar results in our study, when we compared the Maitre and colleagues’ model bias and accuracy during the different periods of alfentanil infusion: performance was poorer after changing the target concentration, and at the onset of alfentanil infusion: the plot of predicted vs observed concentrations (Fig. 3A) showed a good correlation for concentrations below 110 ng ml$^{-1}$, but a lack of fit for higher concentrations for which the model

![Graph showing correlation between BMI and Clearance](image)

**Fig 5** Correlation with NONMEM model between BMI and CL.

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**Table 3** Population PK parameters of alfentanil NONMEM model (values (se)). CL, clearance; V, volume of distribution; Q, clearance of the compartment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model</th>
<th>Final model</th>
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<tbody>
<tr>
<td></td>
<td>Mean estimate</td>
<td>%SE</td>
<td>Mean estimate</td>
</tr>
<tr>
<td>CL (litre min$^{-1}$)</td>
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<td>15.3</td>
<td>—</td>
</tr>
<tr>
<td>CL (litre min$^{-1}$)</td>
<td>—</td>
<td>—</td>
<td>0.245</td>
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<tr>
<td>V₁ (litre)</td>
<td>3.67</td>
<td>8.6</td>
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<tr>
<td>Q₂ (litre min$^{-1}$)</td>
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<td>13.7</td>
<td>1.71</td>
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<tr>
<td>Q₃ (litre min$^{-1}$)</td>
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<td>0.389</td>
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<td>V₃ (litre)</td>
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<td>0.511</td>
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<tr>
<td>$\omega_1^2V₁$</td>
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<td>—</td>
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<tr>
<td>$\omega_2^2Q₂$</td>
<td>0.573</td>
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<td>0.619</td>
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<td>$\omega_2^2V₂$</td>
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<td>Residual variability, $\sigma^2$</td>
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<td>22.7</td>
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underestimated the observed concentrations. We chose to target the alfentanil effect-site concentration, because of the difficulty of rapidly modifying the drug effect while targeting the plasma, as each increase in the effect-site target induced a consequent peak plasma alfentanil concentration.

The performance of Maitre and colleagues’ model was particularly bad at the first sample, 1 min after the start of alfentanil infusion (the only one sample realized before effect-site and plasma concentration equilibration), and some hypothesis may explain this situation. Mertens and colleagues21 compared alfentanil PKs during a continuous infusion, alone, or with a continuous infusion of propofol started 10 min before the start of alfentanil infusion: propofol altered alfentanil plasma concentrations, including the initial alfentanil plasma peak. In our study, a single propofol bolus was injected during induction 90 s before the start of alfentanil infusion, and it probably contributed to increase the initial alfentanil plasma peak. On the other hand, the technique of blood sampling may play an important role on possible artifacts: some authors recommend to evaluate PK studies of drugs using arterial samples, observing that venous concentrations are lower than arterial concentrations.10 22 conventional compartment models assume that drug added in the central compartment is instantaneously completely mixed and appears in the arterial concentration, but in practice, this is false, and this is a reason why PK models do not perform well in the first minutes.23 For drugs undergoing tissue elimination such as remifentanil, it was observed that venous sampling reflected more exactly the effect compartment concentrations.24

We also observed that Scott and colleagues’ model performed within acceptable performance in non-obese patients during alfentanil infusion. This PK set seemed to be more accurate than Maitre and colleagues’ one for high concentrations, but it did not perform with sufficient precision in obese patients, and during the post-infusion period in both populations.

These observations could explain the poor results obtained by Raemer and colleagues,15 because they used much higher alfentanil target concentrations than van den Nieuwenhuyzen and colleagues,13 14 who began blood sampling at lower alfentanil concentration.

The NONMEM population PK model seemed to be more accurate during the infusion and for high concentrations. But because of the small size of our population, it needs to be retested and validated in a larger population of patients, including men. Despite the relationship between BMI and CL, IIV observed with our model is relatively high. Maitre and colleagues devised their model based on data from 45 non-obese patients,3 and validated it for 19 non-obese patients:25 their PK–pharmacodynamic analysis identified three variability factors: age, sex, and weight.

Entering a modified weight on the TCI device system could improve the reliability of the PK set: Egan and colleagues11 showed that administering a lean-person dose of remifentanil to an obese patient induced an excessively high plasma concentration, and recommended to adjust remifentanil dose to LBM. But the problem is that existing LBM formulas or nomograms are not applicable to obese patients, because of the lack of data.26 Anaesthesiologists must find a compromise between IBW, and TBW for drug administration to obese patients. La Colla and colleagues27 described in a case report a super-obese patient in whom remifentanil was successfully administered in the TCI mode using the IBW. Servin and colleagues18 suggested an adjusted IBW formula for propofol administration, but finally, it seemed that the performance of the TCI device system was better with propofol administered using TBW.27 For sufentanil, we previously demonstrated that TCI administration using TBW was accurate for obese patients with the PK set described previously.29

Because of its pharmacological properties, alfentanil has lower clearance and far less redistribution than sufentanil; it could be administered as a function of LBM. But repeating our analyses with LBM showed no improvement for Maitre and colleagues’ model. Our results suggest that the concentration predicted by Maitre and colleagues’ model was underestimated, which may lead to overdosing alfentanil for obese patients. In conclusion, the accuracy of the PK model described by Maitre and colleagues3 for alfentanil TCI is acceptable for clinical application to morbidly obese patients, but it should be applied with caution to that population of patients, especially when high-concentration targets are applied.

Declaration of interest
None declared.

Funding
This study was fully supported by the University Hospital of Nice, as part of an incentive contract for Clinical research (CIR 2003).

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