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Predictive Accuracy of Target-controlled Propofol and Sufentanil Coinfusion in Long-lasting Surgery

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Background: **The predictive accuracy of target concentration infusions of propofol has been documented only for less than 4 h, and no prospective study of sufentanil target controlled infusion is available. The authors investigated the predictive accuracy of pharmacokinetic models for propofol and sufentanil coadministered during long-lasting surgery.**

Methods: **Ten patients, American Society of Anesthesiologists physical status I and II, were studied during extended cervicofacial surgery. Target controlled infusion of propofol and sufentanil was administered during surgery using decisional algorithms, taking into consideration pain assessment, hemodynamic changes, and peroperative blood losses. Intrasubject data analysis included calculation of performance error, median performance error, median absolute performance error, divergence, and wobble.**

Results: **The range of plasma target concentrations was 2–5 μg/ml for propofol and 0.2–1 ng/ml for sufentanil. Median performance error was −12.1% for propofol and −10% for sufentanil. The wobble values were 11.6% and 22.3% for propofol and sufentanil, respectively. The pharmacokinetic sets used slightly overpredicted the concentrations, with negative values of divergence of 2.92% and 0.22% units/h for propofol and sufentanil, for a mean infusion period of 762 min.**

Conclusions: **This prospective study demonstrates the predictive accuracy of the pharmacokinetic model for sufentanil infusion and confirms that for propofol during long-lasting surgery using standardized rules for the management of target controlled infusion and blood loss replacement.**

COMPUTER-ASSISTED target controlled infusion (TCI) of intravenous anesthetic drugs has been investigated for its ability to achieve targeted blood concentrations of selected drugs.[1,2] In the majority of the TCI studies dealing with predictive accuracy of a pharmacokinetic model, the drug was infused for only a limited period; long-term infusions have not been studied.[3–5] Moreover, no prospective study has evaluated the predictive accuracy of prolonged coinfusion of propofol and sufentanil.

The main goal of this study was to evaluate the predictive accuracy of a combined TCI of propofol and sufentanil in adult patients scheduled for long-lasting surgery.

Materials and Methods

Anesthetic Procedure

This study was approved by the Institutional Committee of Human Ethics. Informed consent was obtained from 10 nonobese adult patients with American Society of Anesthesiologists status I and II (seven men and three women) and age 36–69 yr. None of the patients had a history of cardiovascular, respiratory, neurologic, hepatic, or kidney dysfunction. All of the patients underwent the same prolonged type of cervicofacial surgery for extended tumor and multiple lymph node resection. This population included six pharyngo-laryngectomies, two transmandibular buccopharyngectomies, one orbital tumor with hemifacial resection, and one tumor of the acoustic meatus with partial temporal bone resection.

The patients were premedicated with intramuscular

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midazolam (0.1 mg/kg) 30–60 min before their arrival in the operating room. After noninvasive monitor placement, the following blood vessels were cannulated: a forearm vein for administration of anesthetics and other drugs; a femoral vein for fluid administration, blood, or plasma replacement; a femoral artery for the continuous monitoring of blood pressure and blood sampling; and a subclavian vein for monitoring the central venous pressure. Hartmann solution was infused at a rate of 80 ml/h in addition to blood and fluid replacement as indicated by the clinical context. All fluids were warmed to 37–40°C.

Heart rate, mean arterial pressure, and mean central venous pressure were noted before induction and strictly repeated on a regular basis thereafter.

Patients received total intravenous anesthesia with a combination of propofol and sufentanil TCI using the pharmacokinetic sets of Marsh *et al.*[6] and Gepts *et al.*,[7] respectively (table 1). To control the propofol and sufentanil TCI, we used Toolbox, the software elaborated in the Department of Computer Science of the Erasmus Medicine School of the Free University of Brussels.[8] Two Pilot C pumps (Becton Dickinson Inc., Franklin Lakes, NJ) were driven through the two serial ports of a portable personal computer.

Table 1. Pharmacokinetic Parameters Used for Target Controlled Infusions of Propofol (Marsh *et al.*[6]) and Sufentanil (Gepts *et al.*[7])

Parameters	Propofol	Sufentanil
V_1 (l/kg)	0.228	0.21
K_{10} (min^{-1})	0.119	0.0645
K_{12} (min^{-1})	0.112	0.1086
K_{21} (min^{-1})	0.055	0.0245
K_{13} (min^{-1})	0.0419	0.0229
K_{31} (min^{-1})	0.0033	0.0013

Sufentanil infusion was started to produce within 60 s a 0.5-ng/ml plasma concentration. One minute later, the propofol infusion was initiated to achieve a plasma target propofol concentration of 3 μg/ml; this was increased to 4 μg/ml when needed to achieve uncon-

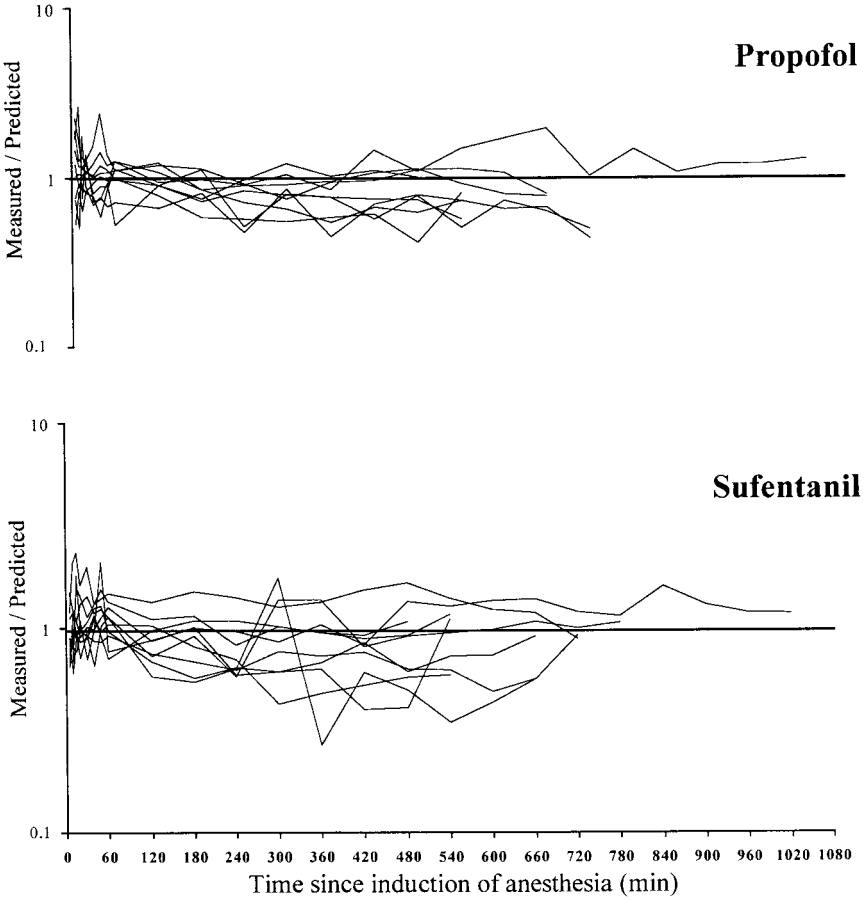

Fig. 1. Ratio of measured to predicted arterial plasma propofol and sufentanil concentrations on a semilogarithmic scale plotted for each patient over time. Equality between measured and predicted concentrations is reflected by a ratio equal to 1. The graphs permit visual assessment of bias and inaccuracy of both pharmacokinetic sets and time-related errors.

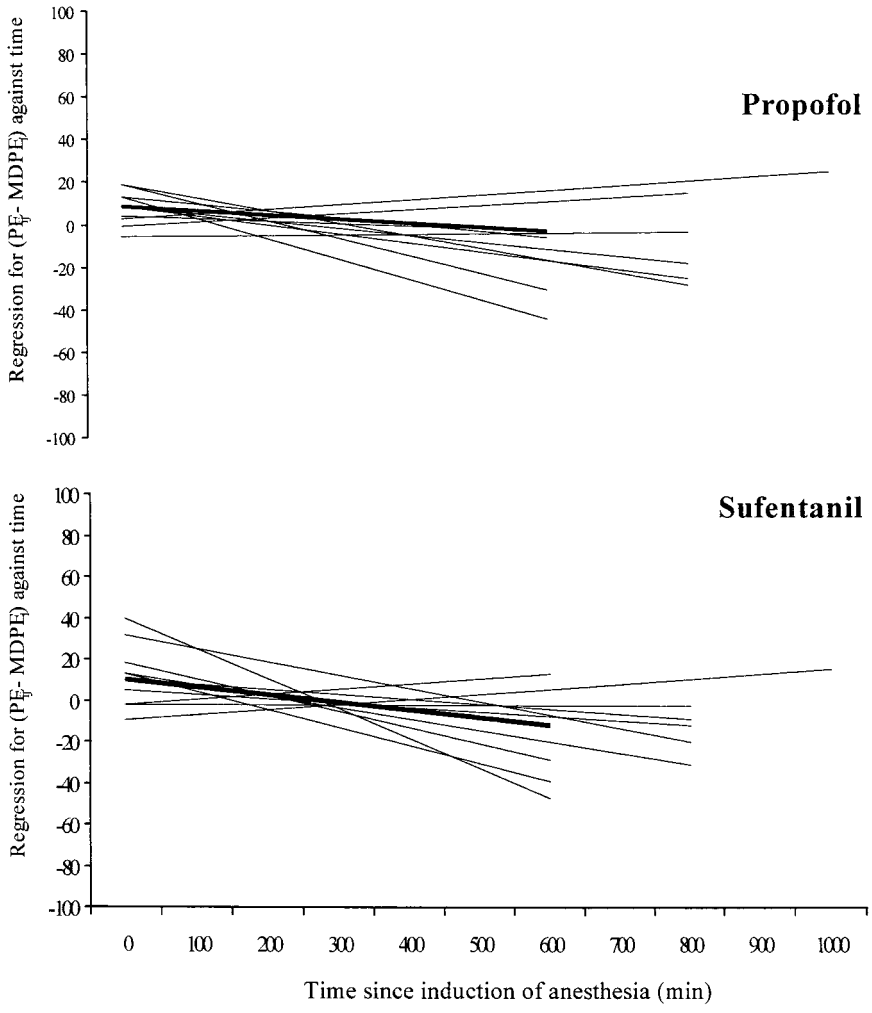

Fig. 2. Individual linear regression of the (PE_{ij} − $MDPE_i$) over time. Tendency of the percentage performance errors (PE) in each patient and in the population (thick line) to increase or decrease over time. A positive slope indicates progressive widening of the gap between measured and predicted concentrations, whereas a negative slope reveals that the measured concentrations converge to the predicted values.

sciousness. A bolus dose of atracurium 0.5 mg/kg was then administered intravenously to facilitate tracheal intubation. No additional atracurium was given thereafter. After intubation, patients were ventilated with an air–oxygen mixture (40% oxygen), with maintenance of end-tidal carbon dioxide pressure between 32 and 35 mmHg.

Anesthesia management was standardized according to decisional algorithms. The volumes of peroperative and postoperative blood losses were noted. When hypovolemia occurred, 10–25 ml/kg serum albumin 4% was used as colloid to maintain mean arterial pressure and mean central venous pressure within acceptable values. If hemoglobin blood measurement (Instrumentation Laboratory co-oximeter; Lexington, MA) was less than 90 g/l, 10–20 ml/kg of packed erythrocytes was transfused to the patient to restore the selected threshold level of hemoglobin.

Measurement of Propofol and Sufentanil Blood Concentrations

Arterial blood samples were drawn every 5 min for 20 min, every 10 min for the next 40 min, and hourly up to the end of the surgery. When propofol or sufentanil target concentrations were changed, additional samples were drawn, approximately 2–3 min after the change. With the TCI pump delivering at the maximum speed of 15 ml/min, we expected the plasma concentration to have reached the new steady state.

For propofol, 3 ml of blood was allowed to clot in a tube prepared with silicon and was placed in a refrigerator (4°C) until analysis. The measurements of propofol concentrations were performed by high-performance liquid chromatography with fluorescence detection.[9] The limit of detection was 0.001 μg/ml, and the range of quantification was 0.002–10 μg/ml.

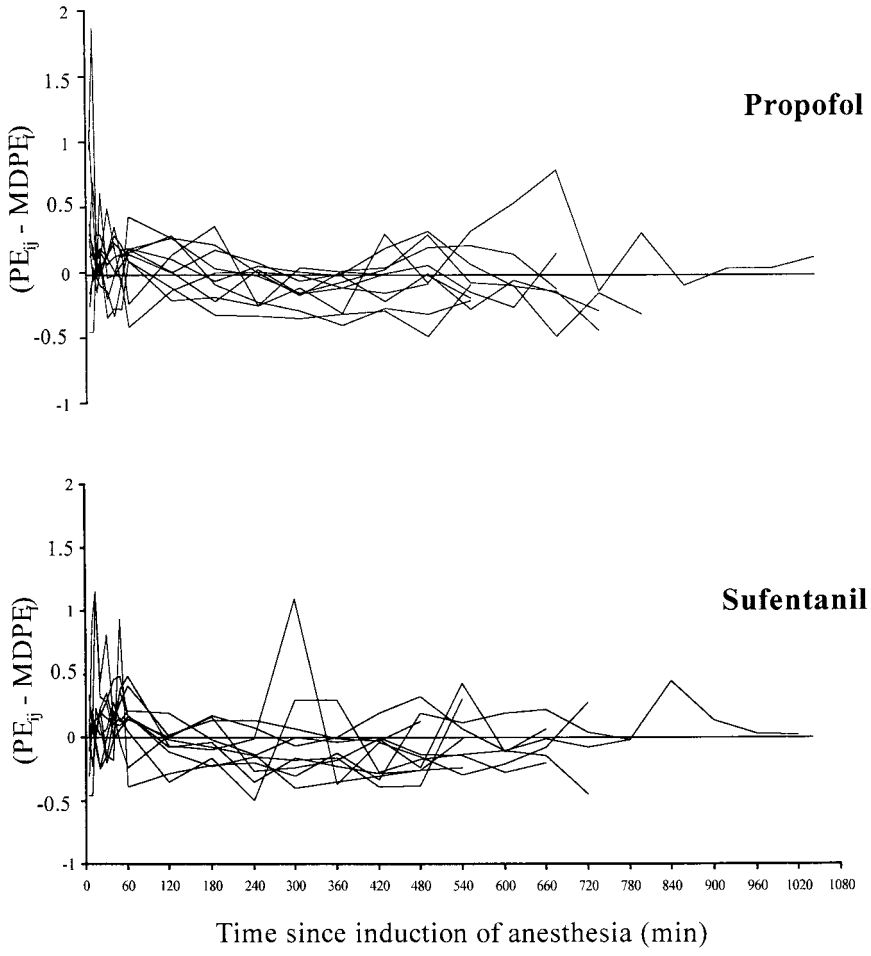

Fig. 3. Variation of each patient's measured performance error (PE) over time. The ordinate represents the difference between the PE and the median prediction error (MDPE) for each patient ($PE_{ij} - MDPE_i$).

For sufentanil, blood samples (4 ml) were immediately centrifuged in the operating room, and separated plasma was frozen (−27°C) for storage until time of analysis. Plasma sufentanil concentrations were determined by radioimmunoassay[10] (Janssen Research Foundation, Beerse, Belgium). The limit of detection was 0.02 ng/ml and the interassay coefficient of variation was 8.5–10.5% for a concentration range of 0.05–10 ng/ml.

Predictive Accuracy Analysis

Data were analyzed using SyStat 5.0 (Systat Incorporation; Hallogram Publishing Inc., Aurora, CO). We used descriptive statistics, including means, 95% confidence intervals, medians, and 10th and 90th percentiles. For each sample, the percentage performance error (PE) of the predicted propofol and sufentanil plasma concentrations were calculated according to the recommendations[3,11]:

$$PE = (Measured - Predicted)/Predicted \times 100$$

PE is an indication of the bias of the achieved concentrations, and the absolute value of PE (|PE|) is a measure of the precision (inaccuracy).

Intrasubject Data Analysis. Intrasubject data analysis consisted in an evaluation, according to Coetzee *et al.*[3] and Varvel *et al.*[11] of four indicators of predictive performance for the n subjects.

Median Performance Error. The percentage median prediction error (MDPE) reflects the bias of the TCI in the ith subject.

$$MDPE_i = \text{median } \{PE_{ij}, j = 1,\ldots, N_i\}$$

where N_i is the number of PE values obtained for the ith subject.

Median Absolute Performance Error. The percentage median absolute prediction error (MDAPE) indicates the inaccuracy of TCI in the ith subject.

$$MDAPE_i = \text{median } \{|PE|_{ij}, j = 1,\ldots, N_i\}$$

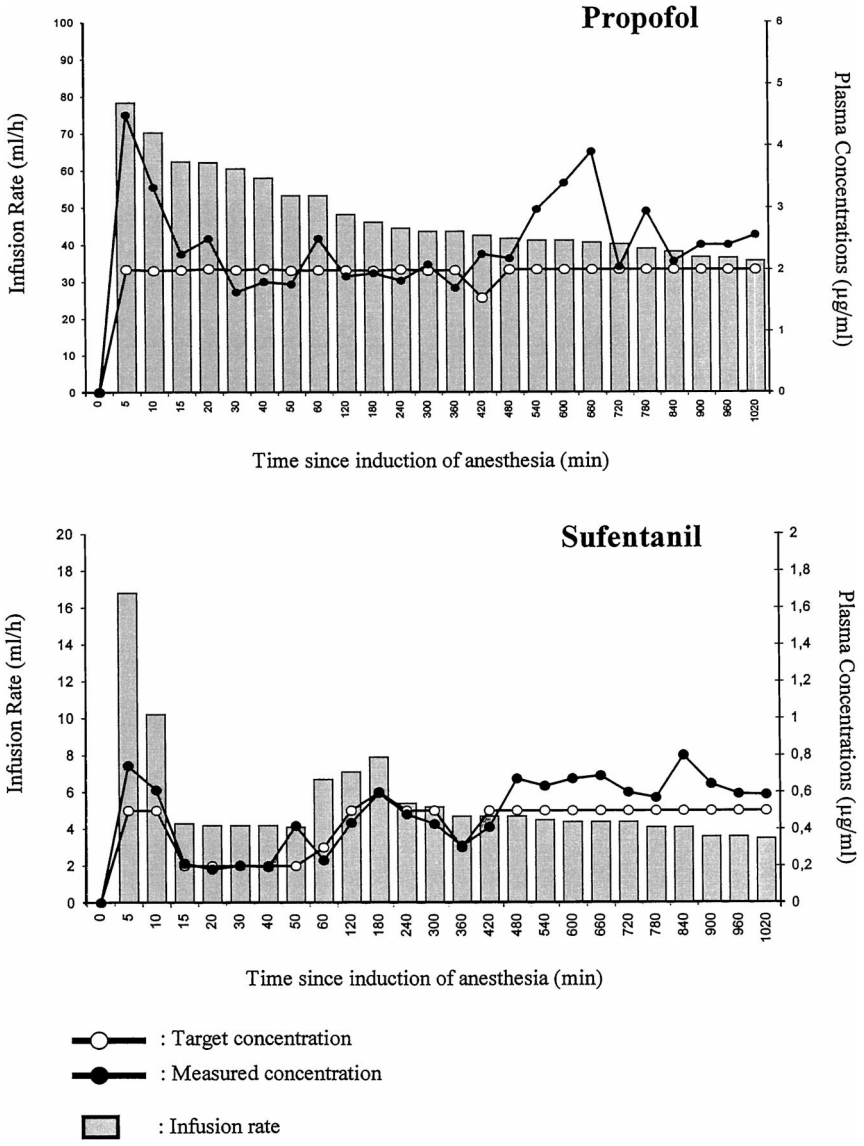

Fig. 4. Illustration of time evolution of infusion rate and plasma concentration for propofol and sufentanil observed in the patient presenting the most prolonged infusion time (1,020 min). The left axis represents the infusion rate, and the right axis the plasma concentration of the drugs. The white dotted line represents the target concentration, and the black dotted line represents the measured concentration. Grey rectangles represent the flow rates as they were applied.

Divergence. The divergence[3,11] for the ith individual is defined as the slope of the linear regression equation of the absolute value of the percentage PE (|PE|) against time expressed in units of percentage divergence per hour. A positive value indicates an increasing widening of the gap between predicted and measured concentrations, whereas a negative value conveys a convergence of the measured to the predicted values.

Wobble. Wobble[3,11] represents an index of the time-related changes in performance and measures the intrasubject variability in PEs. In the ith subject the percentage wobble is calculated as follows:

$$\text{wobble}_i = \text{median}\ \{|PE_{ij} - MDPE_i|,\ j = 1,\ldots, N_i\}$$

Intersubject Data Analysis. Figures 1–5 show the performances of each model over time. Figure 1 shows measured values divided by the predicted values plotted over time. These graphs provided a means to visually assess the extent of bias and precision in both groups. Figure 2 shows plots of the regression lines for $PE_{ij} - MDPE_i$ on time and illustrates how the errors in each patient tended to differ over time from that patient's own $MDPE_i$. Figure 3 shows plots of $(PE_{ij} - MDPE_i)$ over time (where $j = 1,\ldots N_i$ in the ith subject) and illustrates the magnitude of the terms used to estimate the wobble_i of each patient. It is the median of these absolute values that provides the wobble_i of each patient. Once each

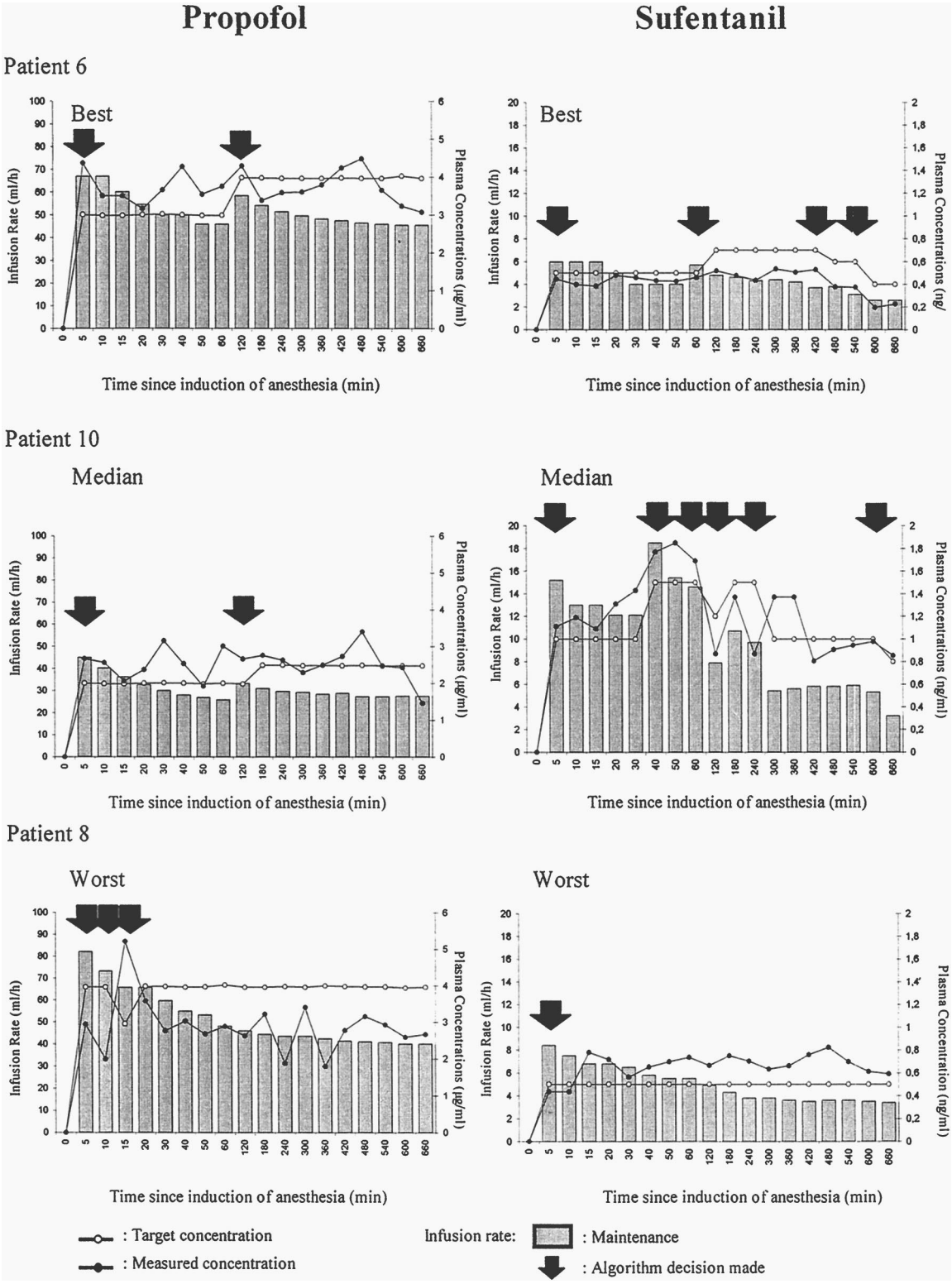
Propofol
Sufentanil
Patient 6
Best
Best
Infusion Rate (ml/h)
Plasma Concentrations (µg/ml)
Plasma Concentrations (ng/
Time since induction of anesthesia (min)
Time since induction of anesthesia (min)
Patient 10
Median
Median
Infusion Rate (ml/h)
Plasma Concentrations (µg/ml)
Plasma Concentrations (ng/ml)
Time since induction of anesthesia (min)
Time since induction of anesthesia (min)
Patient 8
Worst
Worst
Infusion Rate (ml/h)
Plasma Concentrations (µg/ml)
Plasma Concentration (ng/ml)
Time since induction of anesthesia (min)
Time since induction of anesthesia (min)
: Target concentration
: Measured concentration
Infusion rate:
: Maintenance
: Algorithm decision made

Fig. 5. Illustration of time evolution of infusion rate and plasma concentration for propofol and sufentanil observed in the best, median, and worst patients, limited to the first 660 min. The left axis represents the infusion rate, and the right axis represents the plasma concentration of the drugs. The white dotted line represents the target concentration, and the black dotted line represents the measured concentration. Grey rectangles represent the flow rates applied, and black arrows indicate modifications of target concentration indicated by an algorithm decision.

patient's wobble has been obtained, the wobble of the model is derived by calculating their average. Figure 4 shows patient data with the most prolonged infusion time (1,020 min), providing the infusion rate and the target and measured concentrations for propofol and sufentanil. Figure 5 shows the results from the individual patients exhibiting the best, median, and worst performances, illustrating the adequacy of both models (as judged by the measured/predicted ratio, PE-MDPE, and divergence trends).

Results

Demographic data are summarized in table 2. The ranges of applied target concentrations was 2– 5 μg/ml for propofol and 0.2–1 ng/ml for sufentanil. Table 3 shows the results of the four calculated indicators (MDPE, MDAPE, divergence, and wobble) of predictive performance for the pharmacokinetic sets during a mean period of 762 min. MDPE and divergence did not differ statistically from zero as their 95% confidence intervals include 0.

Figure 1 shows that there was no systematic overprediction of the concentrations of both drugs, especially during the initial 60 min, and in some patients the sufentanil model underpredicted the measured concentrations. Figure 2 illustrates that the tendency for the error to range in the negative values and from ith patient's own $MDPE_i$ is comparable and similar for both drugs. The wobble analysis (fig. 3) showed a similar degree of variation from each patient's $MDPE_i$ over time for the two drugs. Figure 4 allows the comparison between the calculated and measured plasma concentrations in parallel with the infusion rate recorded on the pump. Figure 5 is a two-panel plot (one for each drug) from the patients presenting the best, median, and worst performance of the propofol and the sufentanil pharmacokinetic models. These patients were selected on the basis of their measured/predicted ratio (fig. 1), divergence (fig. 2), and PE-$MDPE_i$ (fig. 3). The target concentrations for propofol and sufentanil were modified two, two, and three times, respectively, for propofol and four, six, and one times, respectively for sufentanil in each patient.

Finally, in agreement with the anesthesia management standardization, the patients received, on average, 6.2 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} (range, 6–6.6 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}) of crystalloid (Hartmann solution), 4.1 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} (range, 4–4.3 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}) of colloid (serum albumin 4%), and 1.9 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} (range, 1.8–2.1 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}) of packed erythrocytes, respectively. All of the subjects were transfused at least one time to maintain hemoglobin more than 90 g/l during surgery.

Because infusion was long, drug accumulation on time could be suspect. Probably, in relation to the relatively small range of measured concentrations (2–5 μg/ml for propofol and 0.2–2 ng/ml for sufentanil), the variance analysis shows that the errors distribution seemed to be dose-independent. This rejects any possible relation between the prediction errors and the dose of the delivered drug.

Table 2. Demographic Data

Variable	Mean ± SD (Range)
Age (yr)	66 ± 11 (36–69)
Body weight (kg)	49 ± 21 (42–75)
Duration of infusion (min)	762 ± 28 (540–1,020)
Duration of surgery (min)	721 ± 31 (520–1,010)
Total dose of propofol (mg/kg)	40 ± 11 (32–58)
Total dose of sufentanil (μg/kg)	6 ± 1 (5–7.5)

Discussion

The study was designed to investigate prospectively the pharmacokinetics of long-term TCI coadministration

Table 3. Indices of Predictive Accuracy and Their 95% Confidence Intervals for the Two Pharmacokinetic Sets

	Propofol[6]	Sufentanil[7]
MDPE	−12.1 (−40.1–37.6)	−10.0 (−35–32.8)
MDAPE	22.1 (6.6–42.8)	20.7 (8.2–39.4)
PE p10	−57.9 (−9.2–−88.3)	−45.6 (−7.6–−115)
PE p90	40.4 (8.1–76.4)	35.3 (12.6–65.5)
Wobble	11.6 (3.8–33.8)	22.3 (5.2–43.7)
Divergence	−2.92 (−6.14–25.08)	−0.22 (−5.08–23.1)

Divergence is expressed in units/h.

MDPE = median performance error; MDAPE = median absolute performance error; PE p10 = 10th percentile of performance error; PE p90 = 90th percentile of performance error.

of propofol and sufentanil in strictly standardization clinical conditions. It was also designed to interfere as little as possible with the pharmacokinetic of the drugs. For this we considered (1) the selection of a surgery interfering poorly with drug metabolism and pharmacokinetics and (2) the anesthesia management standardization and the guidelines dealing with the replacement of blood volume losses in agreement with the present consensual rules.[12,13]

Pharmacokinetic Model Performances

Several models have been proposed and validated for their ability to predict drug concentration in the plasma compartment for short-term studies. Our main goal was to validate those in such a long-term study, this having not been performed previously for propofol and sufentanil. We expected the same order of magnitude of the error or even greater. We would not have been surprised to observe increasing divergence over time between measured and predicted concentrations. Of course, we suspected that the use of the decisional algorithm had contributed to the patient's homeostasis and so had contributed to the reduction of percentage prediction error on a sample measurement for a given patient. Compartment pharmacokinetic models are useful to predict theoretical drug concentrations in the central compartment[14] when the targeted plasma concentrations are restricted to values less than 5 μg/ml for propofol[15] and 1 ng/ml for sufentanil.[7] The pharmacokinetic parameter sets were selected from the literature. For propofol, according to Coetzee *et al.*,[3] the modification by Marsh *et al.*[6] of the model by Gepts *et al.*[16] was selected. For sufentanil, the multidose model of Gepts *et al.*[7] was chosen. In comparison to the results reported by Coetzee *et al.*,[3] arterial propofol concentrations revealed greater bias (MDPE −12.1% in comparison to −7%) but is not statistically significant. The results showed slightly greater inaccuracy (MDAPE 22.1% instead of 18.2%), whereas divergence is smaller (−2.92 *vs.* 6.5%) and also not statistically significant. Finally, wobble is of the same order of magnitude (11.6 *vs.* 10%). Because results with regard to sufentanil were lacking, we simply obtained results as good as those obtained for propofol (MDPE −10%, MDAPE 20.7%), except for wobble, which is the worst (22.3% instead of 10%), and divergence, which is even better (−0.22% compared with 6.5%) and also not statistically significant.

There is no agreement in the literature about the corrections of the pharmacokinetic parameters for age and sex. For propofol, several investigators[14,17,18] reported influence of age or sex on the parameters, whereas the results of others[19–21] are not as clear. Results for sex and age simply do not exist for sufentanil presently. Pharmacokinetic interactions between propofol and opioids (fentanyl, alfentanil) have been regularly studied[22–26] using an opioid bolus dose[22,24,25] or infusion.[26,27] These results are not homogeneous as significant interactions were described[22,23,26] concerning the propofol pharmacokinetic parameters when alfentanil is coadministered. On the contrary, the coadministration of propofol and fentanyl, in the conditions described by Gill *et al.*,[24] are not accompanied by an alteration in the propofol pharmacokinetic model.

Surgery Selection

All patients underwent the same prolonged cervicofacial surgery. This kind of procedure does not induce major pharmacokinetic perturbations[1,27] or extremely painful stimuli.[27–31] Moreover, surface or nonmajor surgery required, in general, lower anesthetic drugs concentrations.[21,32] Lengthy surgical procedures do not automatically imply difficult changes to manage in the macrophysiologic parameters (cardiovascular, hepatic, and renal) controlled. Shafer *et al.*[21] and Björkman *et al.*[33] demonstrated that no substantial interference with the pharmacokinetics of propofol and opioids was observed when cardiac output was maintained in a physiologic range of values. This would correspond to the conditions in the present study and can be considered as acceptable. Furthermore, it was important to obtain usual, and not too-high, propofol target concentrations during the study, because the quality of prediction of different pharmacokinetic models is poorer for high values of blood concentrations.[15] Blood losses were essentially external throughout the surgical field and therefore more simple to observe and quantify.

It must be emphasized that, in this such topographically restricted surgery, the prevention of relevant heat loss and plasma hypovolemia seemed more simple to manage compared with plastic surgery or peripheral vascular surgery, where large skin areas are frequently exposed to room temperature.

Conclusion

In conclusion, the selected pharmacokinetic parameter sets, those of Marsh *et al.*[6] for propofol and Gepts *et al.*[7] for sufentanil, proved to be accurate for predicting plasma concentrations during prolonged surgery (6–17 h) with an

acceptable MDPE, wobble, and divergence and without any important time influence. These results represent a major point of the study, particularly for the sufentanil TCI, because these notions were until now lacking in the literature. Finally, the models could be used to predict propofol and sufentanil blood concentrations, providing that standardized rules for the management of TCI and volume replacement could be applied.

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