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Predictive performance of computer-controlled infusion of remifentanil during propofol/remifentanil anaesthesia

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Background. The predictive performance of the available pharmacokinetic parameter sets for remifentanil, when used for target-controlled infusion (TCI) during total i.v. anaesthesia, has not been determined in a clinical setting. We studied the predictive performance of five parameter sets of remifentanil when used for TCI of remifentanil during propofol anaesthesia in surgical patients.

Methods. Remifentanil concentration–time data that had been collected during a previous pharmacodynamic interaction study in 30 female patients (ASA physical status I, aged 20–65 yr) who received a TCI of remifentanil and propofol during lower abdominal surgery were used in this evaluation. The remifentanil concentrations predicted by the five parameter sets were calculated on the basis of the TCI device record of the infusion rate–time profile that had actually been administered to each individual. The individual and pooled bias [median performance error (MDPE)], inaccuracy [median absolute performance error (MDAPE)], divergence and wobble of the remifentanil TCI device were determined from the pooled and intrasubject performance errors.

Results. A total of 444 remifentanil blood samples were analysed. Blood propofol and remifentanil concentrations ranged from 0.5 to 11 $\mu g\ ml^{-1}$ and 0.1 to 19.6 $ng\ ml^{-1}$ respectively. Pooled MDPE and MDAPE of the remifentanil TCI device were –15 and 20% for the parameter set of Minto and colleagues (*Anesthesiology* 1997; **86**: 10–23), 1 and 21%, –6 and 21%, and –6 and 19% for the three parameter sets described by Egan and colleagues (*Anesthesiology* 1996; **84**: 821–33, *Anesthesiology* 1993; **79**: 881–92, *Anesthesiology* 1998; **89**: 562–73), and –24 and 30% for the parameter set described by Drover and Lemmens (*Anesthesiology* 1998; **89**: 869–77).

Conclusions. Remifentanil can be administered by TCI with acceptable bias and inaccuracy. The three pharmacokinetic parameter sets described by Egan and colleagues resulted in the least bias and best accuracy.

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Remifentanil is a synthetic μ-opioid analgesic characterized by a rapid onset of action as a result of its short blood–effect site equilibration half-time, and a rapid offset of action as a result of its large clearance by blood and tissue esterases. These characteristics make remifentanil ideally suited for target-controlled infusion (TCI). Although remifentanil TCI devices are not commercially available, they are being used for research purposes. To ensure optimal predictive performance of the TCI device, it is essential to use the most appropriate pharmacokinetic parameter set. The predictive performance of the available pharmacokinetic parameter sets of remifentanil, when applied to target-controlled infusion during total i.v. anaesthesia, has not been determined in a clinical setting. In total i.v. anaesthesia, remifentanil is frequently combined with propofol. Because propofol and remifentanil are both short-acting anaesthetic agents, this is a promising combination. At present, the influence of propofol on the bias and inaccuracy

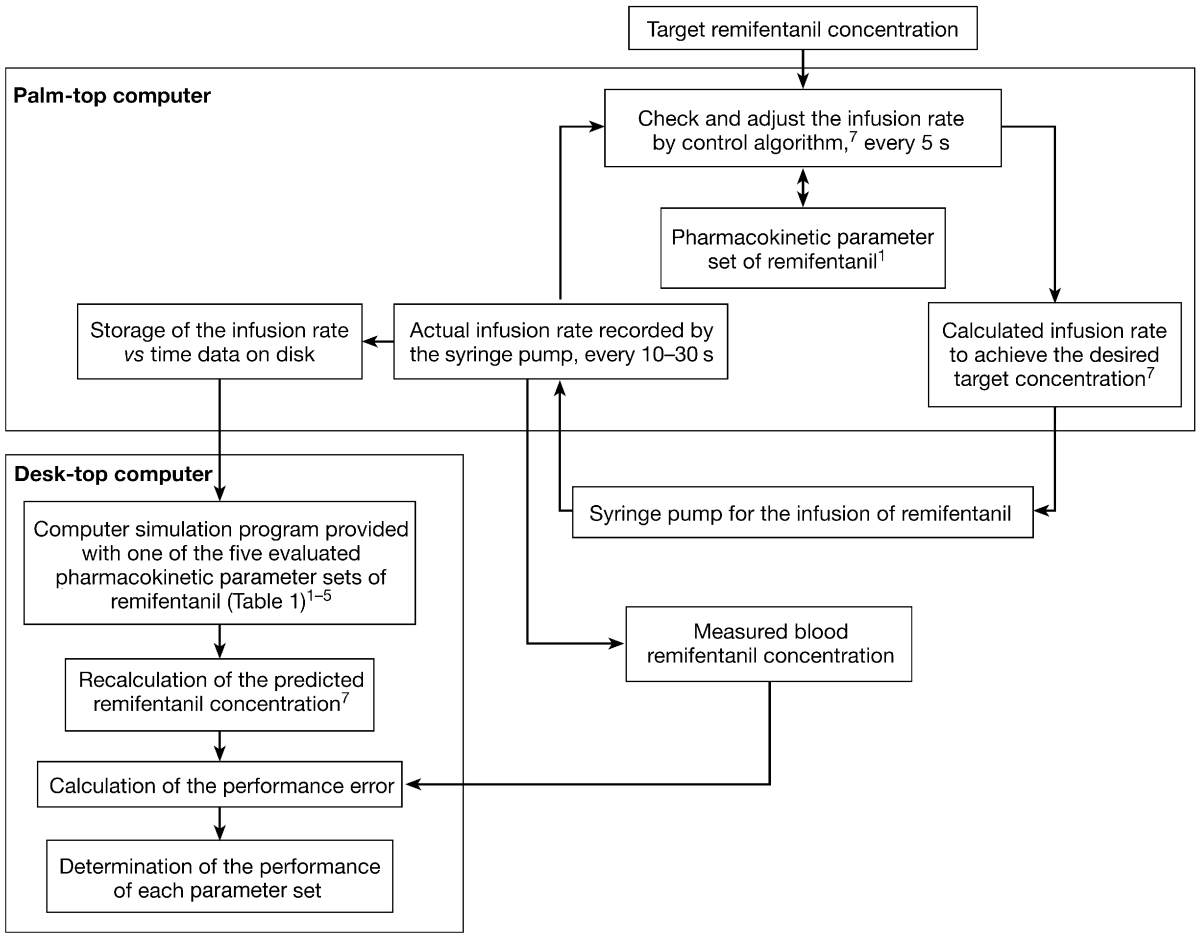


Fig 1 Flow chart describing the methods used in the study.

of a TCI of remifentanil is unknown. We therefore studied the predictive performance of five remifentanil parameter sets[1–5] applied for TCI of remifentanil during propofol anaesthesia in surgical patients and explored the influence of propofol blood concentration on the remifentanil performance error.

Methods

Patients and study design

The concentration–time data used in this study were gathered during a pharmacodynamic interaction study described elsewhere.[6] In the present study, 30 female patients (ASA I or II, aged 20–65 yr) undergoing lower abdominal surgery received a target propofol concentration of 2, 4 or 6 μg ml^{-1} in combination with a TCI of remifentanil. Whereas the target propofol concentration was maintained constant during the entire surgical procedure, the target remifentanil concentration was changed in response to the presence or absence of signs of inadequate anaesthesia.

Materials

A palm-top computer was provided with three-compartment pharmacokinetic data for remifentanil[1] to control a syringe pump for the infusion of remifentanil using the algorithm described by Hull[7] (Fig. 1). The same computer, provided with three-compartment pharmacokinetic data for propofol,[8] was used to control another syringe pump for the infusion of propofol. The control algorithm checked and adjusted the infusion rates every 5 s. Every minute the infusion rate–time data for remifentanil and propofol were stored on disk in the palm-top computer. The infusion rate–time data for each patient were entered off-line into a computer simulation program that calculated the predicted remifentanil concentrations when provided with one of the five evaluated pharmacokinetic parameter sets for remifentanil (Table 1).[1–5] Lean body mass (a covariate in three out of the five evaluated pharmacokinetic parameter sets of remifentanil) was calculated as:[1]

$$\text{Lean body mass (females)} = 1.07 \times \text{weight} - 148 \times (\text{weight}/\text{height})^2 \quad (1)$$

For each measured blood remifentanil concentration, five predicted remifentanil concentrations corresponding to five

pharmacokinetic parameter sets were thus obtained, and the performance of each parameter set was then determined.

Blood samples and assays

As described previously,[6] arterial blood samples for determination of propofol and remifentanil concentrations in whole blood were collected at laryngoscopy, intubation, skin incision, the opening of the peritoneum, at awakening, and 6 min after a predicted target remifentanil concentration had been achieved during the intraoperative period.

Samples for the determination of blood propofol concentrations were transferred to test tubes containing potassium oxalate and stored at 4°C. Propofol concentrations in blood were measured at our laboratory at the Leiden University Medical Centre by reversed-phase high-performance liquid chromatography.[9] The limit of quantitation was 110 ng ml^{-1}. The intra-assay coefficients of variation at plasma concentrations of 0.46, 2.33, 4.66 and 13.54 ng ml^{-1} were all <5.0%. The corresponding inter-assay coefficients of variation were <3.7%. Propofol assays were carried out within 12 weeks.

Samples for the determination of the blood remifentanil concentration were collected into tubes containing sodium heparin and immediately transferred to tubes containing 50% citric acid (to inactivate esterases) before freezing at –20°C. The assay method was based on tandem mass spectrometry detection (LC-MS/MS) with a quantitation limit of 0.1 ng ml^{-1}. The intra-assay coefficients of variation at plasma concentrations of 0.1, 0.2, 30 and 50 ng ml^{-1} were 10.0, 7.8, 2.5 and 2.7% respectively. The corresponding inter-assay coefficients of variation were 2.1, 9.0, 3.8 and 3.7%.[10] The remifentanil analyses were performed by a commercial laboratory (Analytico, Breda, The Netherlands).

Analysis

From each remifentanil pharmacokinetic parameter set, micro-constants were determined using standard equations (Table 2). These were introduced, along with the volume of the central compartment, into a computer simulation program in an Excel spreadsheet for the off-line calculation[7] of the predicted remifentanil concentration (*Cp*) for each time when a remifentanil blood sample was obtained from a patient. In order to correct for the fact that delivery performance of a TCI pump is never ideal,[11 12] *Cp* was calculated on the basis of the delivery system record of the

Table 1 Characteristics of the five studies examining the pharmacokinetics of remifentanil. Data are mean (SD), range or frequency

	Minto[1]	**Egan**[2]	**Egan**[3]	**Egan**[4]	**Drover**[5]
No. of subjects	65 volunteers	10 volunteers	10 volunteers	19 patients	40 patients
Age (yr)	20–85	28.5 (4.8)	28 (4)	38.2 (7.3)	55
Weight (kg)	45–106	83.5 (11.2)	79 (12)	88.7 (28.6)	71.8
Height (cm)	156–193	183.7 (5.8)	176 (8)	170.3 (9.3)	166.3
Gender (M/F)	38/27	10/0	10/0	8/16	20/20
Dosage scheme	1–8 μg kg^{-1} min^{-1} for 4–20 min	2–3 μg kg^{-1} min^{-1} for 20 min	1–8 μg kg^{-1} min^{-1} for 20 min	7.5–10 μg kg^{-1} in 1 min	TCI up to 20 ng ml^{-1}
Sampling site	Arterial	Arterial	Arterial	Arterial	Arterial
Sampling period (min)	240	240	240	360	60
Additional drugs	G, S, P, M	G, S, M	G, P, M	G, V, Mi, T, N, I, F	P, S, Ne, A, N, I, Mo or E

G=glycopyrrolate; S=succinylcholine; P=pancuronium; M=metoclopramide; V=vecuronium; Mi=midazolam; T=thiopental; N=nitrous oxide; I=isoflurane; F=fentanyl; Ne=neostigmine; A=atropine; Mo=morphine; E=epidural lidocaine 2%.

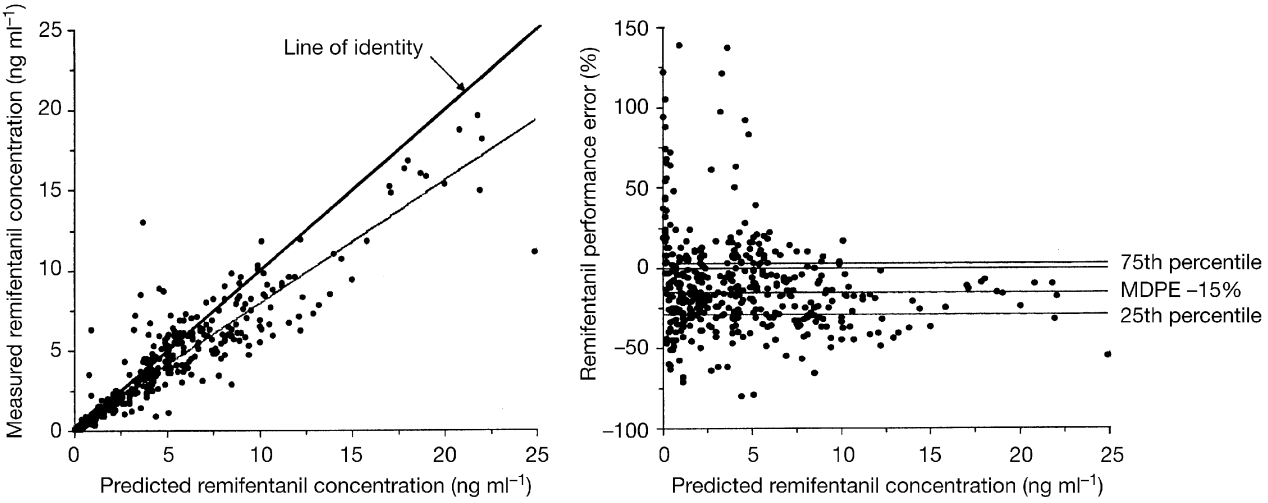
Table 2 Central volume of distribution and the micro-rate constants for the five evaluated remifentanil pharmacokinetic parameter sets. V_1 is the central volume of distribution; k_{10}, k_{12}, k_{21}, k_{13} and k_{31} are micro-rate constants

Parameter	**Minto**[1]	**Egan**[2]	**Egan**[3]	**Egan**[4]	**Drover**[5]
V_1 (litre)	5.1–0.0201(age–40)+0.072(LBM–55)	7.6	7.1	(0.121×LBM)–0.0713	0.128(LBM–50)+3.79
k_{10} (min^{-1})	[2.6–0.0162(age–40)+0.0191(LBM–55)]/V_1	0.3847	0.3955	[(0.0185×LBM)+1.88]/V_1	[0.0389(LBM–50)+2.34]/V_1
k_{12} (min^{-1})	[2.05–0.0301(age–40)]/V_1	0.2569	0.3234	1.04/V_1	1.14/V_1
k_{21} (min^{-1})	$k_{12}V_1$/[9.82–0.0811(age–40)+0.108(LBM–55)]	0.2066	0.1468	$k_{12}V_1$/[0.165×LBM)–0.0713	$k_{12}V_1$/6.87
k_{13} (min^{-1})	[0.076–0.00113(age–40)]/V_1	0.0128	0.0222	–	–
k_{31} (min^{-1})	$k_{13}V_1$/5.42	0.0205	0.0155	–	–

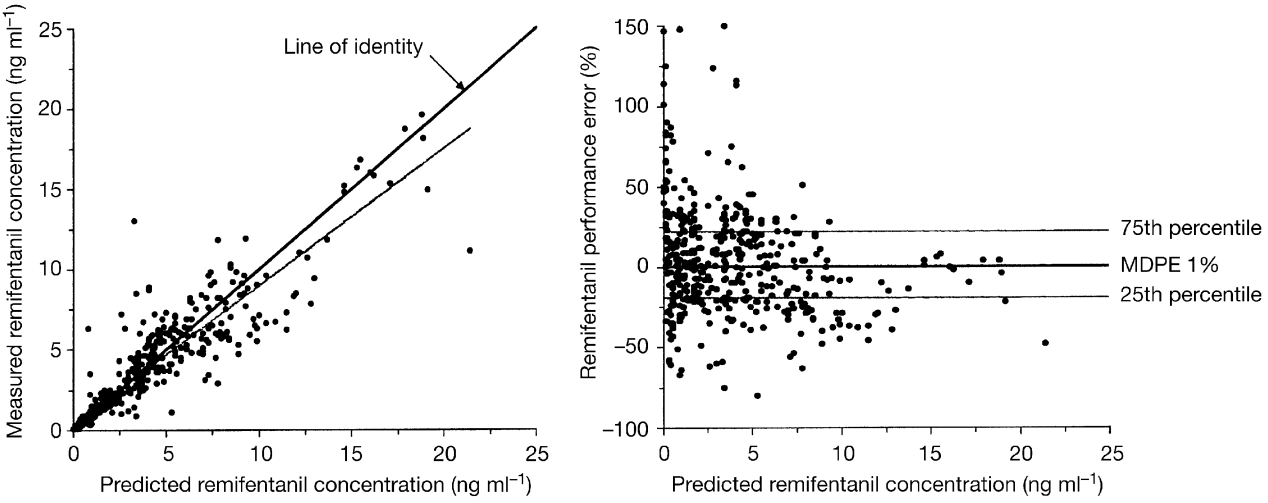
LBM=lean body mass.

Fig 2 (Left panels) Regression analysis (dashed lines) of predicted (*Cp*) *vs* measured (*Cm*) blood concentrations of remifentanil. Thick lines indicate identity. (Right panels) Plots of remifentanil performance error in relation to the predicted blood concentration of remifentanil. Thin lines indicate median performance error (MDPE) and the interquartile range of the MDPE. Predicted blood concentrations of remifentanil were calculated using the remifentanil pharmacokinetic parameters set of Minto and colleagues[1] (upper panel: $Cm=0.76Cp+0.36$; $r=0.93$), Egan and colleagues[2] (middle panel: $Cm=0.86Cp+0.42$;$r=0.91$) and Egan and collaegues[3] (lower panel: $Cm=0.86Cp+0.35$; $r=0.92$).

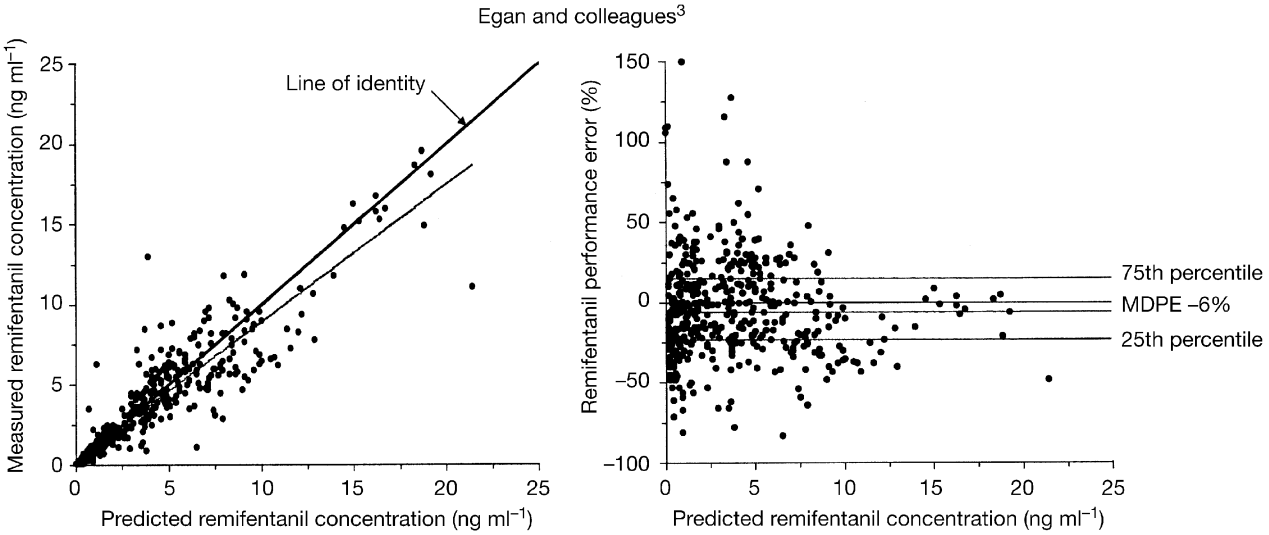
Minto and colleagues[1]



Egan and colleagues[2]



Egan and colleagues[3]



infusion rate–time profile actually used for each individual (as opposed to that which should have been given).[13]

The predictive performances of five pharmacokinetic parameter sets of remifentanil, when applied for TCI, were evaluated by examining the performance error (PE).[14] For each blood sample the PE was calculated as:

$$PE_{ij}\ (\%)=[(Cm_{ij}-Cp_{ij})/Cp_{ij}]\times 100 \quad (2)$$

where Cp_{ij} is the predicted blood remifentanil concentration in sample j from patient i, and Cm_{ij} is the measured blood concentration of remifentanil in that sample. Subsequently, the intrasubject bias (i.e. direction and size of deviation from target) and inaccuracy (i.e. size of the typical miss) of each system was assessed by determination of the median performance error ($MDPE_i$),

$$MDPE_i\ (\%)=\text{median}\{PE_{ij},\ j=1,\ldots,N_i\} \quad (3)$$

and the median absolute performance error ($MDAPE_i$),

$$MDAPE_i\ (\%)=\text{median}\{|PE|_{ij},\ j=1,\ldots,N_i\} \quad (4)$$

where N_i is the number of blood samples for individual i.

Divergence,[14] a measure of the expected systematic time-related changes in performance, was calculated for individual i as the slope obtained from linear regression of that individual's $|PE|_{ij}$ s against time:

$$\text{Divergence}_i\ (\%h^{-1}) = 60\times\frac{\sum_{j=1}^{N_i}|PE_{ij}|\times t_{ij}-\left(\sum_{j=1}^{N_i}|PE_{ij}|\right)\times\left(\sum_{j=1}^{N_i}t_{ij}\right)/N_i}{\sum_{j=1}^{N_i}(t_{ij})^2-\left(\sum_{j=1}^{N_i}t_{ij}\right)^2/N_i} \quad (5)$$

where t_{ij} is the time (in min) at which blood sample ij was collected and PE_{ij} and N_i are as described earlier.

Wobble, a measure of the total intra-individual variability in PE,[14] which is directly related to the ability to achieve stable drug concentrations with the computer-controlled infusion pump, was calculated for the ith individual as

$$\text{Wobble}_i\ (\%)=\text{median}\{|PE_{ij}-MDPE_i|,\ j=1,\ldots,N_i\} \quad (6)$$

where $MDPE_i$ is the median PE in individual i.

The influence of blood propofol concentration on remifentanil PE determined for the pharmacokinetic data set of Minto and colleagues,[1] which was implemented on the TCI device in this study, was explored by linear regression analysis.

The pooled bias and inaccuracy of each system were assessed by determination of the MDPE and MDAPE over all 444 blood samples. Furthermore, the pooled divergence and wobble were calculated from all 444 PEs of all patients. When the 95% confidence interval of the pooled MDPE included zero, it was concluded that the bias was not significant.

Data are presented as mean (SD) unless stated otherwise.

Results

The mean age, weight, height, lean body mass, and duration of anaesthesia in the 30 patients were 37 (20–65) yr, 66.9 (11.1) kg, 1.66 (0.09) m, 47.5 (6.0) kg and 192 (59) min. A total of 444 samples were available for determination of blood remifentanil and propofol concentrations. The median number of blood samples taken from each patient for remifentanil determination was 15 (range 5–20). Blood remifentanil concentrations ranged from 0.1 to 19.6 ng ml^{-1}. The measured blood propofol concentration remained reasonably stable throughout the surgical procedure in all patients. Blood propofol concentrations ranged from 0.5 to 11 μg ml^{-1}. Mean blood propofol concentrations ranged from 1.6 to 8.7 μg ml^{-1} among individuals.

The measured blood concentrations of remifentanil were lower than those predicted on the basis of the initially used pharmacokinetic parameter set of Minto and colleagues.[1] Visual inspection of the predicted *vs* measured blood remifentanil concentration plots (Figs 2 and 3) showed significant overprediction of the blood remifentanil concentration by the pharmacokinetic parameter sets of Minto and colleagues[1] and Drover and Lemmens[5] compared with the three parameter sets described by Egan and colleagues.[2–4] As a result of the relatively unbiased prediction of the blood remifentanil concentration by the three parameter sets of Egan and colleagues[2–4], the PEs were evenly distributed around a range of –6 to 1% when plotted against the predicted concentration (Figs 2 and 3, right panels), whereas the more negatively biased predictions by the parameter sets of Minto and colleagues[1] and Drover and Lemmens[5] were distributed around –15 and –24%, respectively.

The interquartile ranges (i.e. 25th to 75th percentile) of the pooled PEs were –29 to 3%, –19 to 22%, –23 to 15%, –21 to 13% and –32 to –2% for the parameter sets described by Minto and colleagues,[1] Egan and colleagues[2–4] and Drover and Lemmens[5] respectively.

In Figure 4, the percentage PEs are plotted against time.

The individual MDPE, MDAPE, divergence and wobble values calculated from individual data analysis are plotted in Figure 5. In keeping with visual inspection of the data, the individual and pooled bias (i.e. MDPE) and inaccuracy (i.e. MDAPE) of the parameter sets of Egan[2–4] were smaller compared with the two parameter sets of Minto and colleagues[1] and Drover and Lemmens[5] (Table 3). Because the 95% confidence interval of the pooled MDPE of the parameter set of Minto and colleagues,[1] two of the parameter sets of Egan and colleagues[3 4] and the parameter set of Drover and Lemmens[5] did not include zero, it was concluded that significant bias had occurred with these sets. Only one of the parameter sets of Egan[2] showed no bias.

The time-related changes in PE (i.e. divergence) were comparable between the pharmacokinetic parameter sets

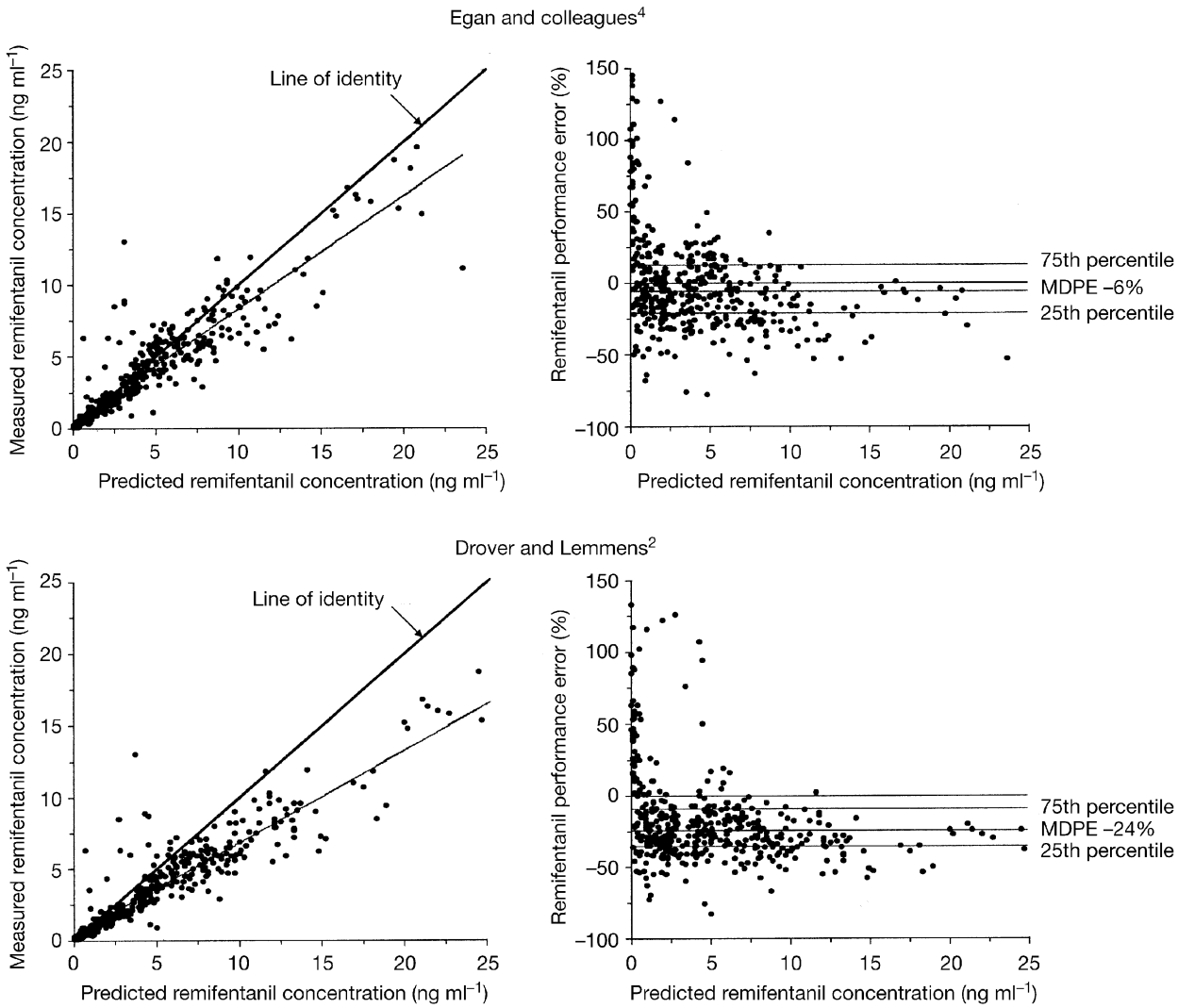


Fig 3 (Left panels) Regression analysis (dashed lines) of predicted (*Cp*) *vs* measured (*Cm*) blood concentration of remifentanil. Thick lines indicate identity. (Right panels) Plot of the remifentanil performance error in relation to predicted blood concentration of remifentanil. Thin lines indicate the median performance error (MDPE) and the interquartile range of the MDPE. Predicted blood concentrations of remifentanil were calculated using the remifentanil pharmacokinetic parameters set of Egan and collaegues[4] (upper panel: $Cm=0.79Cp+0.47$; $r=0.92$) and Drover and Lemmens[5] (lower panel: $Cm=0.64Cp+0.45$; $r=0.93$).

Table 3 Pooled bias [MDPE (95% confidence interval)], inaccuracy [MDAPE (95% confidence interval)], divergence and wobble (95% confidence interval) of the remifentanil infusion system calculated from the pooled data of all patients. *Significant bias: 95% confidence interval of MDPE did not include zero

Parameter	Minto[1]	Egan[2]	Egan[3]	Egan[4]	Drover[5]
MDPE (%)	–15 (–17 to –12)*	1 (–2 to 4)	–6 (–9 to –1)*	–6 (–9 to –3)*	–24 (–27 to –23)*
MDAPE (%)	20 (18 to 22)	21 (19 to 22)	21 (18 to 23)	19 (17 to 21)	30 (28 to 31)
Divergence (% h^{-1})	5	6	3	8	6
Wobble (%)	16 (14 to 17)	21 (19 to 22)	19 (17 to 21)	17 (15 to 19)	12 (11 to 14)

and ranged from 3 to 8% h^{-1}, meaning that the over-prediction increased slightly with time (see also Fig. 4).

The total intra-individual variability in PE (i.e. wobble), a measure that is directly related to the ability to achieve stable drug concentrations with the TCI system, was acceptable for all five parameter sets (range 12–21%).

Linear regression analysis demonstrated no influence of blood propofol concentration on the remifentanil PE (Fig. 6).

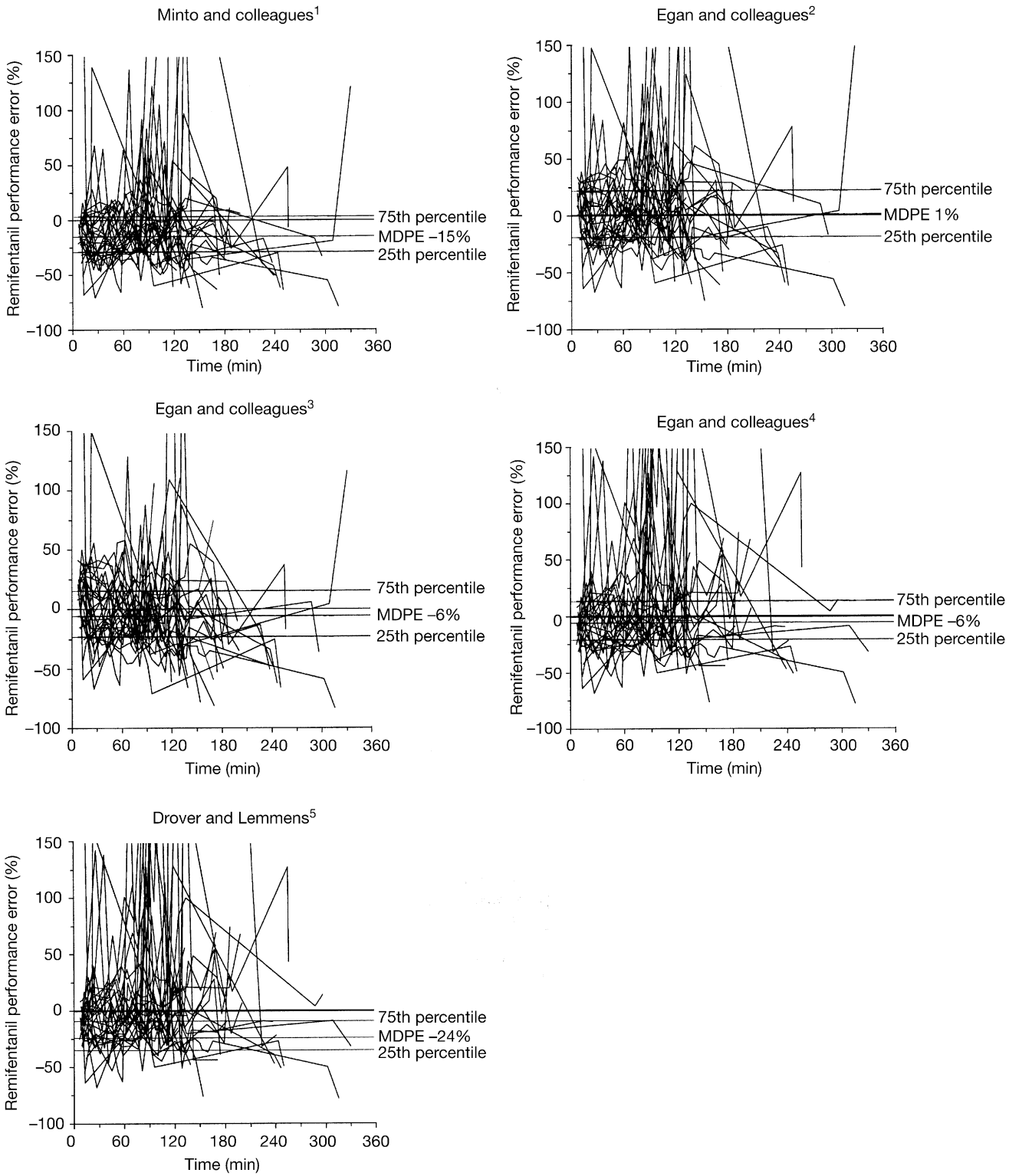


Fig 4 Percentage performance error *vs* time for all 30 patients. Predicted blood concentrations of remifentanil were calculated using the remifentanil pharmacokinetic parameter set of Minto and colleagues[1] (upper left), Egan and colleagues[2] (upper right), Egan and colleagues[3] (middle left), Egan and collaegues[4] (middle right) and Drover and Lemmens[5] (lower left). The dashed lines indicate the median performance error (MDPE) and its interquartile range. Most of the very high performance errors are a result of misprediction of very low measured blood concentrations of remifentanil (0.1–0.2 ng ml^{-1}) and thus lack clinical significance.

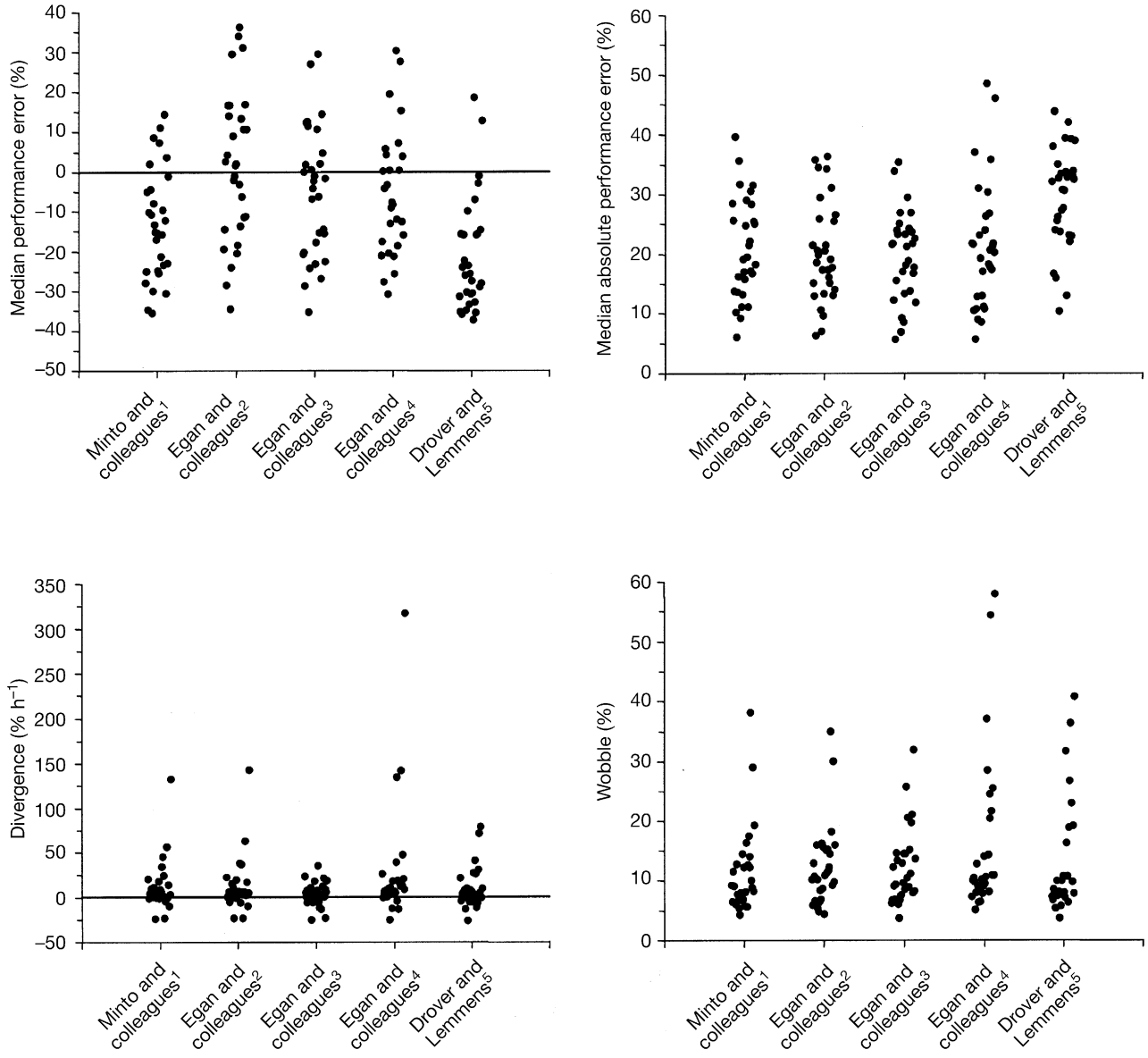


Fig 5 Median performance error (upper left), median absolute performance error (upper right), divergence (lower left) and wobble (lower right) for all 30 patients. The pharmacokinetic parameter set used to calculate the predicted blood remifentanil concentrations is indicated below the *x*-axis.

Discussion

The aim of this study was to evaluate the predictive performance of the available remifentanil pharmacokinetic parameter sets when applied in TCI of remifentanil during total i.v. anaesthesia in combination with propofol. The study demonstrated that the pharmacokinetic parameter set used initially, described by Minto and colleagues,[1] resulted in significant overprediction of the measured remifentanil concentration by 15%, with an inaccuracy of 20%. The use of the three pharmacokinetic parameter sets described by Egan and colleagues[2–4] resulted in the best prediction of the measured blood concentration of remifentanil; one of these sets exhibited no significant bias. No correlation was found between blood propofol concentration and the PE of remifentanil.

It should be emphasized that the true performance, i.e. the mismatch between the target remifentanil concentrations and the remifentanil concentrations actually measured, could only be determined for the data set of Minto and colleagues that had been implemented in the TCI system. Had we implemented one of the other data sets, the actually achieved (measured) concentrations would have been somewhat different. However, the true performance of that data set determined in this way would, in all likelihood, be very similar to the expected performance calculated on the basis of the volumes per unit of time actually delivered, as done in this study, because in the relatively narrow

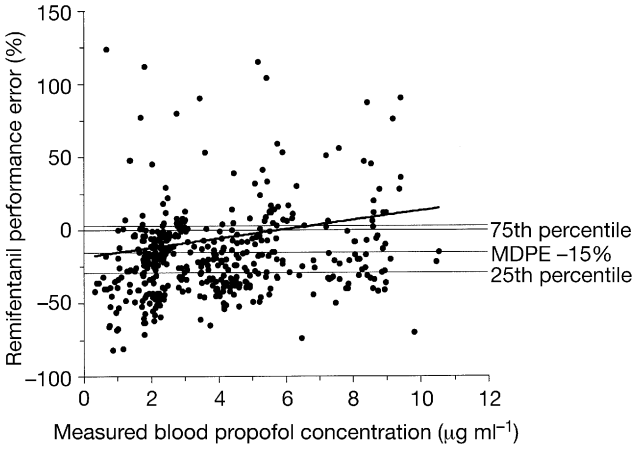


Fig 6 Regression analysis (line) of measured blood propofol concentration (C_{prop}) *vs* the remifentanil performance error (PE_{rem}). Thin lines indicate the median performance error (MDPE) and its interquartile range. Remifentanil performance errors were calculated using the remifentanil pharmacokinetic parameters set of Minto and colleagues[1] ($PE_{rem}=3.16C_{prop}-18.4$; $R^2=0.02$).

clinical concentration range the PEs of remifentanil are independent of the absolute remifentanil concentration.

The accuracies of the evaluated parameter sets (MDAPE) ranged from 19 to 30%. With the exception of the parameter set of Drover and Lemmens,[5] these were comparable with the median absolute weighted residual (MDAWR),[14] a measure of accuracy of a parameter set in its original study population. The MDAPE found in our study and the reported MDAWR in the original publications were 20 *vs* 15.3% for the set of Minto and colleagues,[1] 21 *vs* 15.9%, 21 *vs* 14.8% and 19 *vs* 23.1% for the three sets of Egan and colleagues,[2–4] and 30 *vs* 9.7% for the parameter set of Drover and Lemmens.[5] The observed bias (MDPE) of the evaluated parameter sets, when applied in TCI, was predominantly negative. In our study one of the parameter sets described by Egan[2] achieved an unbiased performance.

The pharmacokinetics of remifentanil is linear (i.e. independent of dose or infusion rate) over a large dose range.[2 15 16] Because remifentanil is cleared rapidly, most of the interindividual variability in concentration during a continuous infusion will reflect variability in metabolic clearance.[1] In population pharmacokinetic models, an attempt has been made to explain and thereby reduce the interindividual variability of the pharmacokinetic parameters by the introduction of covariates into the model.[17] In the pharmacokinetic parameter set of Minto and colleagues[1] that was implemented in the TCI device in our study, the coefficient of variation in Cl_1 in their model without covariates was 23%. The coefficient of variation for Cl_1 was 14% when the covariates age and lean body mass were included in their final model. Age and lean body mass therefore accounted for 9% of the interindividual variability. The source of the remaining 14% variability remains unknown. Considering the coefficient of variation for Cl_1 of 14%, the MDAPE (a measure of the typical error) of 20% calculated for the parameter set of Minto and colleagues[1] in our study is in line with what may be expected. The reported coefficients of variation for Cl_1 reported by Egan[2 3] and Drover and Lemmens[5] were 12, 10 and 23% respectively.

To achieve the most accurate prediction of blood concentrations of remifentanil, one should use a pharmacokinetic parameter set that has been determined in a population that most resembles the actual patients who receive the drug. The blood remifentanil samples evaluated in our study were obtained during abdominal surgery in mechanically ventilated female patients and in the presence of propofol. Our study population therefore differed from those described in the original publications in which the evaluated parameter sets were determined (Table 1).

The MDPEs of the evaluated pharmacokinetic parameter sets, when used for TCI, differed between the five parameter sets and were predominantly negative. As follows from equation (1), a negative prediction error will result from *Cm* being lower than *Cp*. Because remifentanil is cleared rapidly, most of the variability in concentration during a continuous infusion will reflect variability in metabolic clearance.[1]

The primary metabolic pathway of remifentanil is hydrolysis by non-specific blood and tissue esterases, resulting in formation of the carboxylic acid metabolite GI-90291. Approximately 90% of remifentanil can be recovered as the acid metabolite.[18] Hydrolysis in blood, liver and kidneys each accounted for only 1% of the systemic clearance of remifentanil in male Beagle dogs, whereas muscle, intestine and brain had the largest tissue clearance rates of the tissues examined.[19] The *in vitro* half-life of remifentanil in human blood at 37°C is approximately 60 min.[20] The rapid metabolism of remifentanil is therefore more likely to be explained by hydrolysis of remifentanil in tissues than by hydrolysis in blood. In a study on the influence of arterial *vs* venous sampling on remifentanil pharmacokinetics, Hermann and colleagues[21] demonstrated the importance of tissue metabolism in the pharmacokinetics of remifentanil. They used a pharmacokinetic model in which a one- or two-compartment venous model was linked to the central arterial compartment of a standard three-compartment, open, linear mammillary model to describe the time courses of arterial and venous remifentanil concentration data simultaneously. Elimination occurred from both the arterial and the venous central compartment. They suggest that differences between subjects in extraction ratios across the sampling site could lead to added variability in concentrations and estimated pharmacokinetic parameters. According to this study, increased tissue perfusion or decreased tissue transit time will thus lead to increased clearance of remifentanil from the blood. Indeed, Duthie and colleagues[16] found a direct relation between remifentanil clearance and cardiac output, indicating that the tissues eliminating remifentanil clear the drug better when blood is perfused to them. In contrast, during

haemorrhagic shock with low cardiac output and low mean arterial pressure, remifentanil elimination clearance and central volume were reduced in pigs.[22]

Tissue perfusion is the most important determinant of remifentanil tissue clearance and tissue clearance is the most important process determining remifentanil elimination clearance, which is the most important parameter determining the pharmacokinetics of remifentanil. This is influenced by sex and the conditions during surgery (i.e. mechanical ventilation, abdominal surgery, increased protein binding and/or the presence of propofol). These factors may explain the differences in PE between the five pharmacokinetic parameter sets.

When remifentanil is administered during propofol anaesthesia to ASA I–II adult patients using a TCI device driven by the pharmacokinetic parameter sets determined by Minto and colleagues[1] or Drover and Lemmens,[5] one should be aware that a considerable bias may exist. In the presence of propofol the actual measured remifentanil concentration, and thus the actual effect site concentration, may be 15% lower than predicted by the TCI device. This can be especially important when following remifentanil dosing guidelines, as mentioned in the literature on blood remifentanil concentrations associated with a particular effect. With the set of Egan and colleagues,[2] on the other hand, an unbiased predictive performance can be achieved.

In conclusion, remifentanil can be administered by TCI with acceptable bias and inaccuracy. The use of the pharmacokinetic parameter sets of Egan and colleagues[2–4] resulted in the best precision and accuracy in ASA I–II female patients. No correlation was found between blood propofol concentration and the PE of remifentanil. Although the parameter set of Egan and colleagues[2] performed best in our population, we believe that a population pharmacokinetic parameter set like that of Minto and colleagues[1] may prove beneficial in more heterogeneous groups of patients.

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