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Predictive performance of 'Servin's formula' during BIS®-guided propofol-remifentanil target-controlled infusion in morbidly obese patients

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Background. The aim of this study was to assess the predictive performance of 'Servin's formula' for bispectral index (BIS)-guided propofol-remifentanil target-controlled infusion (TCI) in morbidly obese patients.

Methods. Twenty patients (ASA physical status II–III, age 32–64 yr) undergoing bilio-intestinal bypass surgery, were recruited. Anaesthesia was induced by using a TCI of propofol with an initial target plasma concentration of 6 $\mu g\ ml^{-1}$, then adapted to maintain stable BIS values ranging between 40 and 50. A TCI of remifentanil was added to achieve pain control and haemodynamic stability. For propofol, weight was corrected as suggested by Servin and colleagues. With ideal body weight (IBW) corrected according to formula suggested by Lemmens and colleagues. For remifentanil, weight was corrected according to IBW. Arterial blood samples for the determination of blood propofol concentrations were collected at different surgical times. The predictive performance of propofol TCI was evaluated by examining performance accuracy.

Results. Median prediction error and median absolute prediction error were −32.6% (range −53.4%; −2.5%) and 33.1% (10.8%; 53.4%), respectively. Wobble median value was 5.9% (2.5%; 25.2%) while divergence median value was $-1.5\%\ h^{-1}$ (-7.7; $33.8\%\ h^{-1}$).

Conclusion. Significant bias between predicted and measured plasma propofol concentrations was found while the low wobble values suggest that propofol TCI system is able to maintain stable drug concentrations over time. As already suggested before, a computer simulation confirmed that the TCI system performance could be significantly improved when total body weight is used.

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Obesity is a chronic illness of multifactorial aetiology which is defined as BMI>30 kg m^{-2}.[1] The kinetic behaviour of many drugs is different in obese patients compared with non-obese patients, depending on factors related both to obesity and drug used.[2 3] Both fat and lean body mass increase in the obese individual, although there is a relative decrease in lean body mass and water content. Blood flow per gram of fat tissue is reduced in obese compared with non-obese subjects.[4–7] Highly lipophilic substances[2 3 8] can therefore show significant increases in apparent volume of distribution (VD) in obese individuals relative to normal-weight individuals. The total volume of the central compartment (where drugs are first distributed) is somewhat increased by obesity, as is resting cardiac output;[6 9] in contrast, extracellular volume is reduced on a volume/weight basis.[10] Hepatic[9] and renal[11] clearances are usually unaffected or increased in these individuals. These changes can have marked effects on the dosage of highly lipophilic drugs, such as propofol and sodium thiopentale.

Propofol is a short-acting intravenous anaesthetic with an excellent recovery profile.[12] The introduction of target-controlled infusion (TCI) systems gives the further potential for improving both speed and accuracy in achieving and maintaining a desired level of anaesthesia.[13 14]

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Remifentanil is a selective μ-opioid receptor agonist providing intense analgesia of rapid onset and ultra short duration, with a very short blood/effect-site equilibration half-time.[15]

Despite its high lipophilicity, propofol has been recommended to be scaled to lean body mass,[16] at least for induction dose. However, the matter of dosing schemes and scaling doses of drugs, especially for patients weighing more than ideal body weight (IBW), has already been emphasized.[17]

At present, there is no agreement between anaesthetists on the optimal weight input to set when using a TCI system in obese patients, but the formula for weight correction suggested by Servin and colleagues[18] has been successfully used for propofol anaesthesia in obese patients, with no evidence of propofol accumulation.

The aim of this study was to assess the performance of Servin's weight correction formula during propofol TCI in morbidly obese patients undergoing bilio-intestinal bypass surgery.

Materials and methods

After Ethics Committee approval and written informed consent was obtained, 20 patients (ASA physical status II–III, aged 32–64 yr) undergoing elective bilio-intestinal bypass surgery, were prospectively studied. Patients with ASA physical status >III, aged <20 or >65 yr, with a history of alcohol or drug abuse, were excluded.

Patients fasted for 8 h before surgery and received no premedication. After arrival in the operating room two 18-gauge i.v. cannulas were placed on the forearm, and Ringer's lactate solution 6 ml kg^{-1} was infused. A radial artery catheter was inserted for both arterial blood sampling and invasive arterial blood pressure monitoring. Standard monitoring was used throughout the study, including electrocardiography, heart rate (Lead II) and pulse oximetry. In all patients the bispectral index (BIS) was also monitored using an EEG monitor (BIS XP for monitor A 2000; Aspect Medical Systems Inc., Natick, MA, USA). To improve predictive performance, all patients were intubated awake by means of a flexible fibreoptic bronchoscopic technique facilitated by a target-controlled effect-site concentration of remifentanil set at 2.5 ng ml^{-1} and maintained until the first surgical stimulus was performed. Then, the target concentration was adjusted in order to ensure haemodynamic stability, identified by heart rate and mean blood pressure between ±20% of the basal values. After awake fibreoptic endotracheal intubation, general anaesthesia was started using a TCI system to administer propofol, with the target plasma concentration initially set at 6 μg ml^{-1}. After 2 min this target was reduced at 4 μg ml^{-1} then adapted to the need of each patient to maintain stable BIS values ranging between 40 and 50. Ventilation was assisted with a 50% oxygen in air mixture and mechanically controlled using a Cato-Dräger (Dräger, Lubeck, Germany) anaesthesia workstation set to maintain an end-tidal partial pressure of carbon dioxide ranging between 32 and 35 mm Hg. cis-Atracurium was used for neuromuscular block.

Propofol was administered using a TCI system (Diprifusor, Fresenius, Italy). The pharmacokinetic data set used by the TCI system consists of a three-compartment pharmacokinetic model that incorporates the parameters introduced by Marsh and colleagues.[14]

For propofol TCI, weight was corrected according to the formula suggested by Servin and colleagues[18] (Equation 1), with IBW estimated according to the formula suggested by Lemmens and colleagues[19] (Equation 2).

$$\text{Corrected body weight} = \text{ideal body weight (IBW)} + \{0.4 \times [\text{Total body weight (TBW)} - \text{IBW}]\}. \quad (1)$$

$$\text{Ideal body weight (IBW)} = 22 \times \text{height}^2 (\text{m}). \quad (2)$$

Remifentanil was administered using a pharmacokinetic model-driven computer-assisted continuous infusion system allowing to achieve and maintain constant target effect-site concentrations. The system consisted of an Acer TravelMate 518TX computer connected to a Graseby 3500 infusion pump (Sims Graseby Limited, Waterford, Herts, UK) using the Rugloop I software (designed by Tom De Smet and Michel Struys, Department of Anaesthesia, University Hospital, Ghent, Belgium, v. 1.3). The pharmacokinetic parameters used in the computer-assisted continuous infusion for administration of remifentanil were based on the model described by Minto and colleagues.[20 21] For remifentanil TCI weight was corrected according to formula suggested by Lemmens and colleagues[19] (Equation 2).

During the maintenance of anaesthesia, the blood target concentration of propofol was adapted to each patient's need, with a BIS value maintained between 40 and 50 while the effect-site concentration of remifentanil was titrated to maintain the heart rate and blood pressure within ±20% of baseline values.

Arterial blood samples (5 ml) for the determination of blood propofol concentrations were collected before the start of the infusion (T_0), plasma-effect site equilibrium (T_1), opening of the peritoneum (T_2), bowel resection (T_3), colecisto-jejunal anastostomosis (T_4), ileum-jejunal anastomosis (T_5), closing of peritoneum (T_6) and last skin stitch (T_7).

Analytical approach

Propofol (2,6-diisopropylphenol) was provided by AstraZeneca (Mereside, UK). Thymol, used as internal standard (IS), was obtained from Riedel-deHaen (Sigma-Aldrich, Seelze, Germany). Cyclohexane, 2-propanol, trifluoroacetic acid (TFA) and tetramethylammonium hydroxide were obtained from Fluka (Buchs, Switzerland). HPLC-grade acetonitrile and methanol were supplied by VWR (Darmstadt, Germany).

HPLC system Gold from Beckman (Palo Alto, CA, USA) was equipped with a Shimadzu fluorescence detector

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RF-551 (λec=276 nm, λem=310 nm). Hypersil ODS column (100×4.0 mm; 3 μm) protected by guard column Hypersil ODS (4×4.0 mm; 5 μm) (Agilent Technologies, USA) were used. The mobile phase was the same as reported by Plummer and colleagues.[22] Flow rate was 0.4 ml min^{-1} and the run totally lasted 8 min.

Propofol and thymol solutions were prepared immediately prior to running. The drugs were diluted in methanol to an appropriate working concentration of 0.83 and 0.02 mg ml^{-1} for propofol and IS, respectively. Blood samples were collected, stored and prepared as recommended by Plummer and colleagues.[22]

Linearity was assessed by adding known amounts of propofol to the blood samples in the final concentration ranges of 0–8.2 μg ml^{-1}. Linear regression analysis obtained by plotting the area ratio of propofol/IS against the known concentration of the anaesthetic yielded: Y=0.0977 (±0.0979)+0.414 (±0.023)×(±SE), r=0.995. Analytical recovery, tested in the same concentration ranges as for linearity, was 97.2%.

The lowest level of detection of propofol in blood found with a S/N ratio of 3 was 25 ng ml^{-1}. Coefficient of variation (CV%) values ranged from 0.9% to 6.8% and from 1.2% to 9.9% for within- and between-day, respectively.

Statistical analysis

The predictive performance of TCI of propofol was evaluated by examining the performance error (PE).[23] For each blood sample PE was calculated. Subsequently, the intrasubject bias (i.e. direction and size of deviation from predicted concentration) and inaccuracy (i.e. size of the typical miss) were assessed by determination of median performance error ($MDPE_i$) and median absolute performance error ($MDAPE_i$).

Divergence, a measure of the expected systematic time-related changes in performance (that is, the tendency towards the narrowing or the widening over time of the gap between measured and calculated concentrations in a given subject) was calculated as the slope obtained from linear regression of that individual's $|PE|_{ij}$s against time.

Wobble, a measure of the total intra-individual variability in PEs, which is directly related to the ability to achieve stable drug concentrations, was calculated as the median value of the absolute differences between the individual PEs at each sampling time and the MDPE for that patient.

Finally, we performed the same calculations following computer simulation of TCI (TivaTrainer v. 5.1, Leiden, The Netherlands) according to TBW instead of Servin weight formula correction.

Data are presented as mean (SD) or number (%) or median (25th–75th percentile).

For reference on the mathematical processes involved in data analysis, we refer to Varvel and colleagues.[23]

The difference between MDPE, MDAPE, divergence and wobble value obtained from collected samples and those obtained from computer simulation was tested using the Mann–Whitney U-test.

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA).

Results

Six men and 14 women were included in this study. Patient characteristic data, as well as BMI and IBW, are presented in Table 1. Eight samples were taken from each patient for determination of propofol plasma concentrations. A total of 160 samples were available for determination of blood propofol concentrations.

Blood propofol concentration ranged from 1.2 to 6.2 μg ml^{-1} among individuals, and remained reasonably stable throughout the surgical procedure in all patients (Fig. 1). Median values and interquartile ranges of both predicted and measured propofol plasma concentrations in addition to mean times of blood sample collection are presented in Table 2.

Measured blood propofol concentrations were lower than those predicted on the basis of the pharmacokinetic parameter set of Marsh and colleagues[14] and employing the weight adjustment formula suggested by Servin and colleagues.[18] Visual inspection of the predicted *vs* measured blood propofol concentration plot suggests significant overprediction of the blood propofol concentration (Figs 1 and 2).

PEs were distributed around a range of −69.5% to 55% when plotted against the predicted concentrations, with a median value of −32.5%. The interquartile range of the pooled PEs was −42.4% to −15.63% (Fig. 3). In Figure 4, the pooled PEs are plotted against time.

Individual MDPE, MDAPE, divergence and wobble are summarized in Table 3. MDPEs, a measure of the intrasubject bias (i.e. direction and size of deviation from target concentration), ranged from −53.4% to −2.5%, with a median value of −32.6% and an interquartile range of −39.7% to −15.7% (Table 3), negative values suggesting a significant overestimation (see also Figs 1 and 2). In Figure 5, the patient with the best agreement between measured and predicted concentrations (i.e. lowest MDPE) and the patient with the worst agreement between measured

Table 1 General design of the study. Data are presented as mean (SD), mean (range) or frequency

Characteristics	Values
No. of subjects	20
Age (yr)	47 (32–64)
Weight (kg)	140 (30)
Height (cm)	168 (12)
BMI (kg m^{-2})	49.1 (7.4)
IBW	61.1 (9.9)
Gender (M:F)	6:14
ASA physical status (II:III)	6:14
Sampling period (min)	159.3 (22.4)

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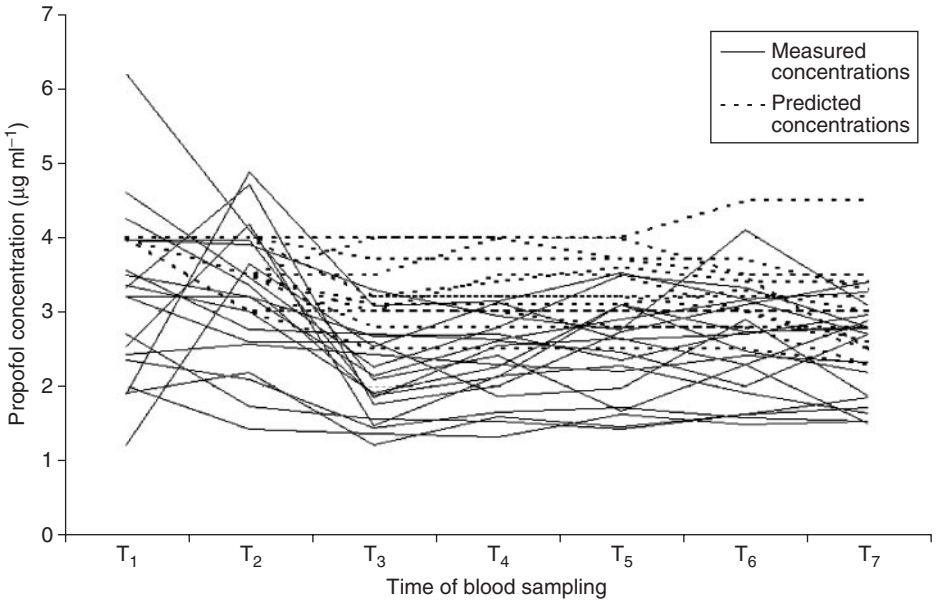

Fig 1 Plot of each patient's propofol plasma concentrations *vs* sampling times. Thick lines represent measured values, whereas broken lines represent predicted values.

Table 2 Predicted *vs* measured propofol concentrations at T_0, T_1, T_2, T_3, T_4, T_5, T_6 and T_7, and sampling times. Data are presented as median (25th percentile; 75th percentile)

Sampling period	Time (min)	Propofol		*P*-value
		Predicted concentration (μg ml^{-1})	Measured concentration (μg ml^{-1})	
T_0	0.0 (0.0)	0.0 (0.0:0.0)	0.0 (0.0:0.0)	
T_1	7.0 (8.1)	4.0 (4.0:4.0)	3.3 (2.4:3.7)	<0.05
T_2	21.9 (8.2)	3.5 (3.4:4.0)	3.2 (2.5:3.9)	=0.0527
T_3	40.7 (8.4)	3.2 (3.0:4.0)	2.0 (1.6:2.6)	<0.001
T_4	52.6 (8.8)	3.6 (3.1:4.0)	2.3 (2.0:2.6)	<0.001
T_5	69.4 (10.2)	3.7 (3.1:4.0)	2.4 (1.9:2.8)	<0.001
T_6	99.8 (12.9)	3.5 (3.0:4.0)	2.4 (1.8:3.0)	<0.001
T_7	159.3 (22.4)	3.3 (2.8:4.0)	2.5 (1.7:2.8)	<0.001

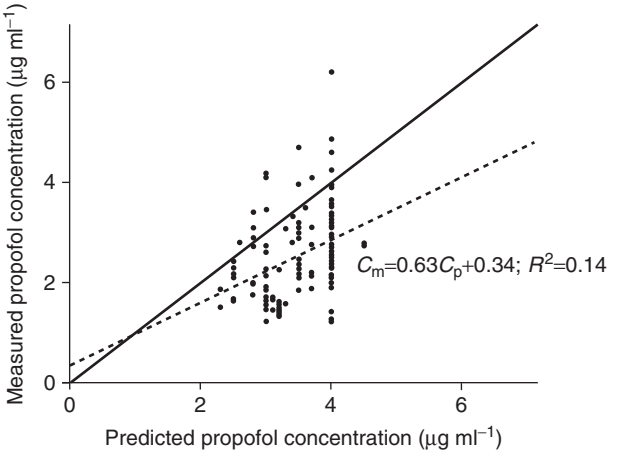

Fig 2 Regression analysis (broken line) of predicted (C_p) *vs* measured (C_m) blood concentration of propofol. Solid line indicates identity. Predicted blood propofol concentration was calculated using the propofol pharmacokinetic set of Marsh and colleagues[14] and setting a weight corrected according the formula suggested by Servin and colleagues[18] (C_m=0.63C_p+0.34; R^2=0.14).

and predicted concentrations (i.e. greatest MDPE) are depicted.

MDAPEs, a measure of inaccuracy (i.e. size of the typical miss), ranged from 10.8% to 53.4%, with a median value of 33.1% and an interquartile range of 20.7% to 39.7% (Table 3).

Wobble values (a measure of total intra-individual variability in PEs) ranged from 2.5% to 25.2%, with a median value of 5.9% and an interquartile range of 5.2% to 13% (Table 3). Wobble can also be desumed from Figure 6, which depicts the difference between PEs and MDPEs for every patient at each time of blood sampling.

Divergence values (i.e. time-related changes in PEs) ranged from −7.7 to 33.8% h^{-1}, with a median value of −1.5% h^{-1} and an interquartile range of −3.9 to 2.5% h^{-1} (Table 3), meaning that the overprediction decreased slightly with time for most patients. This mild convergence of measured values to predicted ones is also inferable by Figure 7, which represents the trends of each individual patient's ratios between measured and predicted concentrations at each sampling time.

Table 4 shows median values and interquartile ranges of plasma propofol concentrations predicted by the infusion pump compared with that predicted following computer simulation of the same infusion schemes as those used in real patients, by using TBW instead of Servin correction formula for weight setting. When using TBW, plasma propofol concentrations (i.e. PEs) would have been significantly higher, and they would not have been statistically

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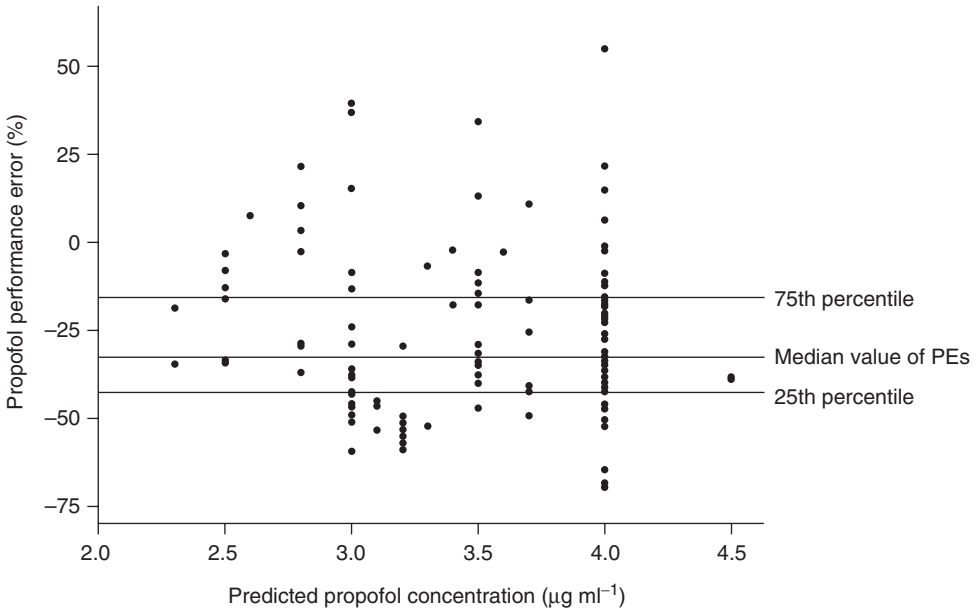

Fig 3 Plot of the propofol performance errors in relation to predicted blood propofol concentration. Soild lines indicate the median value of the pooled PEs, 25th and 75th percentile values.

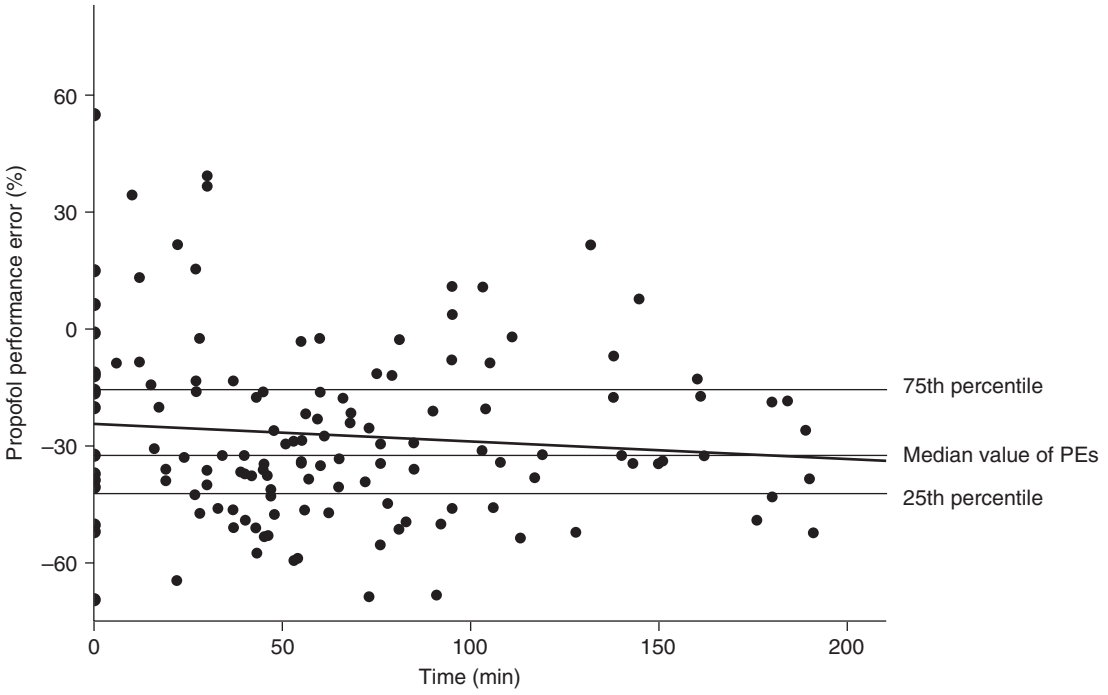

Fig 4 Percentage performance errors *vs* time. Predicted blood propofol concentration were calculated using the propofol pharmacokinetic set of Marsh and colleagues[14] and setting a weight corrected according to the formula suggested by Servin and colleagues.[18] Thin lines indicate the median value of the pooled PEs, 25th and 75th percentile values. Thick line indicates regression analysis of PEs *vs* time (PE=−0.05Time−24.17; R^2=0.1).

different (apart from T_3 samples) from those predicted by the TCI infusion set.

In Table 3 are also summarized MDPE, MDAPE, divergence and wobble values obtained following the aforesaid computer simulation. When using TBW, MDPE resulted significantly higher and MDAPE significantly lower compared with those calculated when Servin formula was used (P=0.003 and 0.03, respectively), whereas no significant differences were observed in divergence and wobble values.

Discussion

Different pharmacokinetic models have been proposed and validated for their ability to predict drug concentration in

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plasma and effect-site compartment. Performance of pharmacokinetic set proposed by Marsh and colleagues[14] has been evaluated in different clinical settings,[24–26] but it has not yet been clarified in morbidly obese patients. Performance of TCI is undoubtedly influenced by intersubject variability, which arises from many different possible sources. In particular, as far as our case is concerned, patients could not belong to the same population the original pharmacokinetic model was tested on during its development.[27] In moderately obese patients, kinetic differences have been reported for opioids, such as remifentanil[28] or sufentanil.[29] Consequently, applying to obese patients a model derived from a population of normal-weight individuals could lead to errors or inaccuracies.[28]

Different standard definitions of overweight have been suggested.[1 29] Traditionally, obesity has been defined as body weight >30% above IBW on standard height–weight tables. Currently, it is usually defined in terms of BMI. In this study, all patients were morbidly obese (BMI >35 kg m^{-2}).[1]

The aim of this study was to assess the performance of Servin's formula when used to set the weight on a propofol TCI system incorporating Diprifusor® in morbidly obese patients undergoing bilio-intestinal bypass surgery.

The choice to associate remifentanil and propofol, although reasonable from a clinical standpoint, could be considered a drawback of our study, as Mertens and colleagues[30] suggested an interdependence between the kinetics of opiates and propofol. This interrelationship is most likely because of the haemodynamic changes associated with the use of both drugs. The vasodilator and possible negative inotrope effects of propofol, in particular, could have major consequences on arterial blood pressure, heart rate and cardiac output. These changes, in turn, could affect the delivery and the redistribution of drugs to tissues. The titration of remifentanil perfusion to match the patients' requirements and to achieve haemodynamic stability can avoid the great shifts in cardiac output that are probably the basis of the observations made by Mertens and colleagues.[30]

The model proposed by Minto and colleagues[21] was chosen for remifentanil and TCI was programmed at a body weight adjusted to IBW. In the absence of any final evidence on predictivity, we chose to use the formula proposed by Lemmens and colleagues[19] to calculate IBW because, as suggested in their study, yields weight values that are midway between values obtained with other published formulas.

Marsh's pharmacokinetic set as incorporated in the Diprifusor® system was chosen for propofol,[14] and propofol TCI was set including patients' body weight corrected as suggested by Servin.[18] Why choose Servin's weight adjustment? Truly, our situation and environment were different from those described by Servin and colleagues. First of all, they proposed that formula at a time when no

Table 3 MDPE, MDAPE, wobble and divergence values obtained following computer simulation by using total body weight (TBW) compared with those obtained from sample analysis, when Servin correction formula was used (Servin). Data are presented as median (25th percentile;75th percentile)

Parameter	TBW	Servin	*P*-value
MDPE (%)	−6.21 (−26; 7)	−32.6 (−39.7; −15.7)	0.003
MDAPE (%)	23.6 (9.33; 29.88)	33.1 (20.7; 39.7)	0.03
Wobble (%)	7.96 (6; 16.7)	5.9 (5.2; 13)	0.465
Divergence (% h^{-1})	−1.8 (−8.2; 3.34)	−1.5 (−3.9; 2.5)	0.194

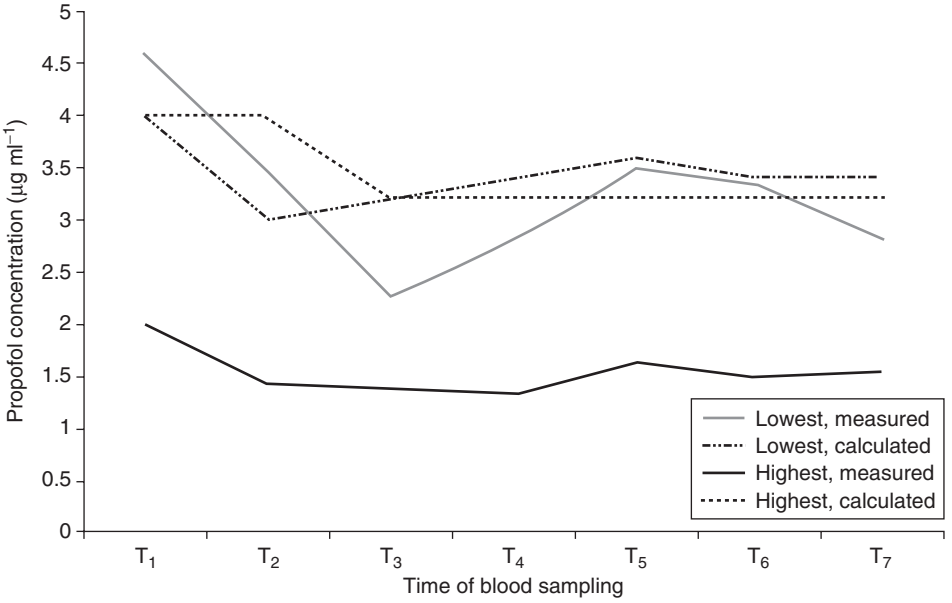

Fig 5 Plot of blood propofol concentrations of the patient with the lowest MDPE and the patient with the greatest MDPE *vs* times of sampling. Soild lines represent measured values whereas broken lines represent predicted values.

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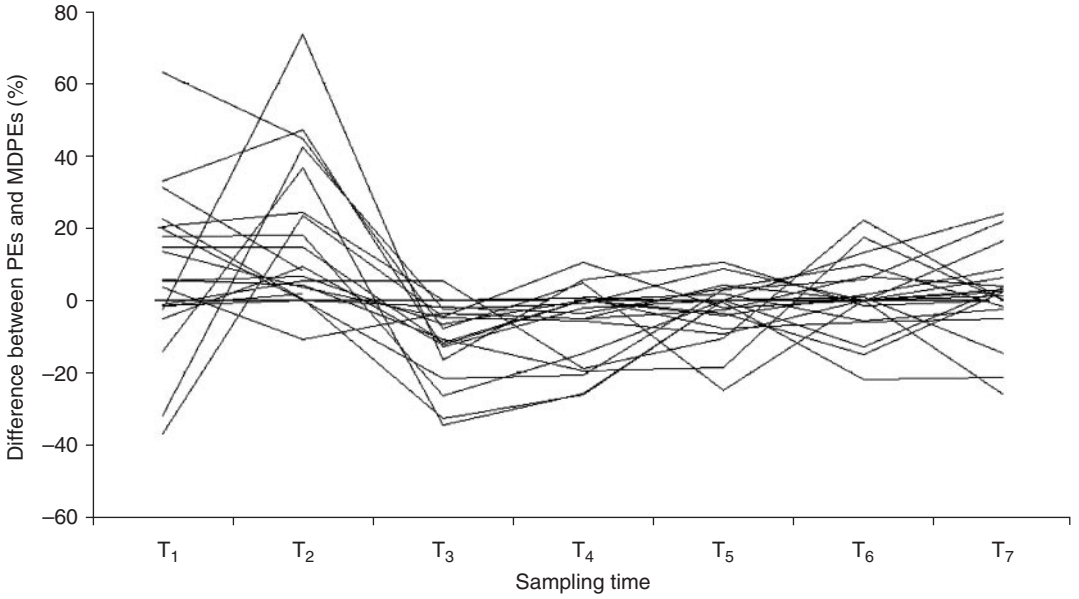

Fig 6 Plot of the difference between PEs and MDPEs for every patient at each sampling time.

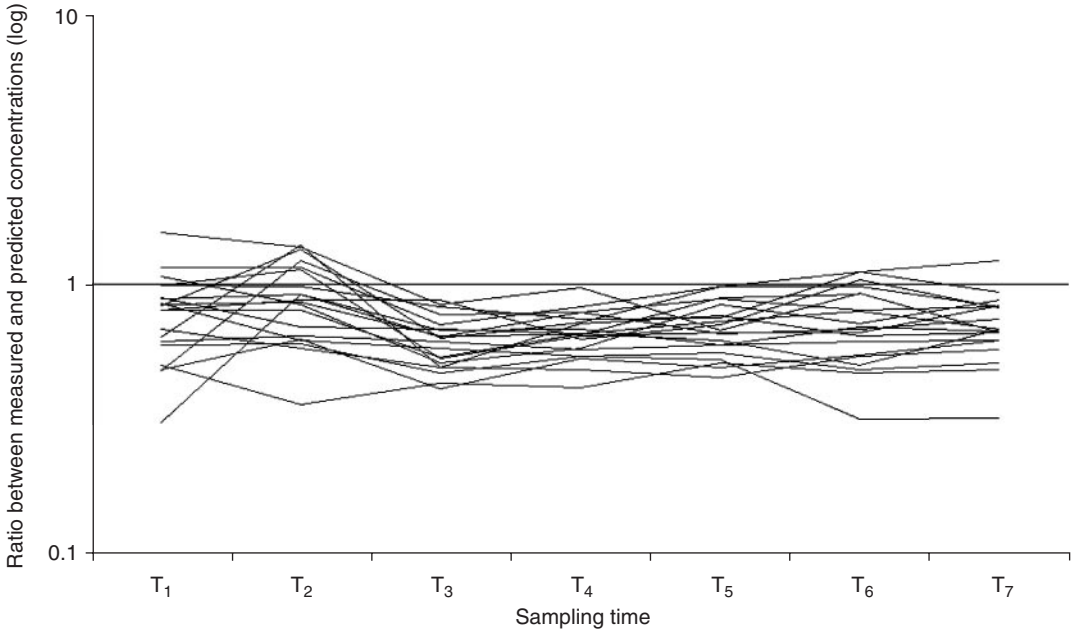

Fig 7 Plot of each individual patient's ratios between measured and predicted concentrations at each sampling time. The scale of the ordinate is logarithmic.

propofol pharmacokinetics data in obese were available. In addition, as far as anaesthetic procedure is concerned, our patients were not premedicated and we used remifentanil instead of N_2O and fentanyl.

Thus, the choice of this correction formula may appear arbitrary, also because, at present, there is no agreement between anaesthetists on the optimal weight input to set when using a TCI system in obese patients. On the one hand, Gepts and colleagues[31] suggest the application of the formula proposed by Servin in obese patients. On the other hand, Servin had already suggested that propofol should be dosed according to TBW. Other groups state that LBM should be used instead of TBW, but they performed their studies using the pharmacokinetic set of Schnider.[32] Schuttler and colleagues[33] performed a population pharmacokinetic modelling for propofol taking into account weight, height, age and gender. Weight was a significant covariate for all clearances and compartmental volumes, but the best fit was achieved with power functions with exponents <1.

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Table 4 Predicted propofol concentration by the TCI *vs* predicted plasma propofol concentrations obtained from computer simulation when setting TBW in the TCI infusion system at T_0, T_1, T_2, T_3, T_4, T_5, T_6 and T_7, and sampling times. Data are presented as median (25^{th} percentile;75^{th} percentile)

Sampling period	Time (min)	Propofol		*P*-value
		Predicted concentration ($\mu g\ ml^{-1}$)	Predicted concentration ($\mu g\ ml^{-1}$) computer simulation (TBW)	
T_0	1.0 (0.0)	0.0 (0.0:0.0)	0.0 (0.0:0.0)	
T_1	7.0 (8.1)	4.0 (4.0:4.0)	4.0 (2.9:4.9)	=0.9
T_2	21.9 (8.2)	3.5 (3.4:4.0)	4.6 (3.1:5.1)	=0.07
T_3	40.7 (8.4)	3.2 (3.0:4.0)	2.5 (1.8:3.3)	<0.05
T_4	52.6 (8.8)	3.6 (3.1:4.0)	3.0 (2.3:3.7)	=0.05
T_5	69.4 (10.2)	3.7 (3.1:4.0)	4.4 (2.5:3.9)	=0.17
T_6	99.8 (12.9)	3.5 (3.0:4.0)	3.3 (2.1:3.9)	=0.47
T_7	159.3 (22.4	3.3 (2.8:4.0)	3.1 (2.1:3.8)	=0.49

Furthermore, Bouillon and Shafer[17] suggest that, when we are unsure of the real relationship between anthropometric parameters and pharmacokinetics, especially for patients weighing more than their IBW, a reasonable approach would be to scale dose to IBW plus some fraction of the difference between TBW and IBW. This kind of weight correction may resemble Servin's formula at a first glance, but, although very similar, it is a non-linear function, whereas Servin's formula is a linear function.

Propofol, although highly lipophilic, does not accumulate in obese patients. Therefore, in theory it should be possible to calculate the maintenance dose of propofol on the basis of TBW, without incurring a significant risk of accumulation. However, by setting TBW on a TCI device, large doses of propofol are administered in a short time, and a concrete risk of major haemodynamic side-effects is present.

Considering that Servin's weight correction formula has shown good haemodynamic stability and no evidence of accumulation in obese patients during propofol continuous infusion, we decided to evaluate its predictive performance when using a propofol TCI system.

Hypnosis and analgesia were indeed continuously monitored throughout the study by maintaining BIS values between 40 and 50 and heart rate and blood pressure within ±20% of baseline values.

In our series of patients a significantly higher target plasma concentration seems to be required to maintain an adequate level of hypnosis, compared with non-obese patients. This is probably not because of different pharmacodynamics in morbidly obese patients. Servin and colleagues[18] reported that their patients opened their eyes at a blood propofol concentration of about 1 $\mu g\ ml^{-1}$, similar to the awakening concentration identified by Shafer and colleagues in non-obese subjects.[34] Furthermore, there is good agreement in terms of awakening concentrations between those found by Kakinohana[35] and Saijo[36] in obese patients and those reported by Casati and colleagues[37] in non-obese individuals. Measured blood concentrations required for hypnosis are, therefore, similar to those measured in normal patients. The gap between predicted and measured concentrations required to obtain hypnosis (Cp_{50}) lies in the marked overprediction of the infusion algorithm (see Figs 1 and 2) caused by the use of this particular kind of weight adjustment.

Performance of propofol infusion systems incorporating Marsh model[14] has been evaluated in different clinical trials, as by Swinhoe and colleagues during major surgery,[27] Barvais and colleagues[25] during cardiac surgery and Coetzee and colleagues[26] during orthopaedic or gynaecological surgery.

None of these studies involved obese patients. Anyway, compared with their results, the bias we found was consistently larger, with a median value of percentage median performance errors (MDPEs) of −32.6% *vs* +16.2%, +21.2% and −1%, respectively. Coetzee reported a small overprediction, with an MDPE of −1%. Swinhoe and Barvais, on the contrary, found the algorithm underpredicted real plasma concentrations, yielding MDPEs of +16.2% and +21.2%, respectively.

Our results showed slightly greater inaccuracy in obese patients compared with normal patients, with a median value of MDAPE of 33.1% *vs* 29%, 24.1%, and 23%, respectively.

Divergence in our series resulted higher than calculated by Swinhoe and colleagues,[24] with a median value of divergence of $-1.5\%\ h^{-1}$ *vs* $-7.6\%\ h^{-1}$. Negative values, as obtained in most of the patients (12 out of 20), indicate a progressive thinning of the gap between predicted and measured concentrations. The more negative value obtained by Swinhoe and colleagues. suggests that convergence of the measured to the predicted values is more pronounced for normal patients. Finally, the median value of wobble (5.9%) resulted similar to that measured by Coetzee and colleagues,[26] but significantly lower compared with Swinhoe and colleagues,[24] suggesting a lower intrasubject variability in morbidly obese patients. Glass and colleagues[13] suggested that the performance of a TCI system is clinically acceptable if both the bias in the *i*th subject (MDPE) is no greater than 10–20% and the inaccuracy of TCI (MDAPE) in the *i*th subject is within 35%.

Considering these limits, performance of propofol TCI using Marsh model in obese patients should not be acceptable. In our case, however, even though inaccuracies were found, adequate anaesthesia was obtained because BIS®-guided administration of propofol was used. Indeed, the low wobble and divergence values we obtained from our analysis suggest that pharmacokinetic parameters fit well even in obese patients, even if real plasma concentration are lower than those predicted, at least as long as the ability to maintain stable drug concentrations over time is concerned. This ability allows the anaesthesiologist to maintain a stable level of hypnosis even in obese patients.

Overall, these data suggest that this partial lack of performance is not because of the Marsh model itself, but

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rather to an excessive underestimation by the formula used to correct body weight.

This weight correction technique, when applied to the Diprifusor® TCI system, is unable to reliably support the prediction algorithm. The result is a marked overprediction of the plasma drug concentration that could lead to potentially serious errors, especially if the procedure is conducted without monitoring the level of consciousness or if high doses of opioids are required to blunt the haemodynamic response to surgical stimuli.

Starting from this point, we decided to recalculate plasma propofol concentration by using a TCI simulation software and test what the performance would have been if TBW had been used instead of Servin weight correction formula. Our results indicated that, when using an unadjusted Marsh pharmacokinetic set, predictive performance would have been much better, with a median value of −6.21% MDPE and a median value of 23.6% MDAPE, both acceptable according to Glass and colleagues.[13] Wobble and divergence values were not significantly different from those obtained with Servin formula, confirming the goodness of Marsh pharmacokinetic set independently of the weight set.

These results are not surprising, because, even if this pharmacokinetic set has never been tested in morbidly obese patients, already in 1993 Servin and colleagues concluded in their study that initial VD was not modified in obese patients, while total body clearance and VD at steady state were correlated to TBW.

In conclusion, we showed the existence of a significant bias between predicted and measured plasma propofol concentrations during propofol TCI in morbidly obese patients when Servin weight correction formula is used for the weight implemented in the TCI system. As already suggested by Servin and colleagues, a computer simulation confirmed that the TCI system performance could be significantly improved when TBW is used.

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