Prospective clinical evaluation of a model-based dosing regimen for propofol anaesthesia in morbidly obese patients

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Abstract

Background
In pharmacokinetic-pharmacodynamic (PK-PD) models for morbidly obese patients, total body weight (TBW) has been reported the best size descriptor for propofol clearance using an allometric function. Most recently, a nonlinear total body weight-based dosing algorithm for maintenance of anaesthesia with propofol was developed aiming for Bispectral index (BIS) values of 40 ± 10 in morbidly obese patients with varying body weights. The present study aims at evaluating this algorithm prospectively in a clinical setting.
Methods
After induction of anaesthesia, propofol maintenance dose was started at 7 mg/kg ABW/h (ABW = adjusted total body weight = 70kg * (TBW/70)$^{0.72}$) in combination with remifentanil. BIS values, haemodynamic parameters and the number of the propofol infusion adjustments were recorded for each patient. Observed BIS values were compared with BIS values predicted by the previously published PK-PD model for propofol in morbidly obese patients.
Results
Fifty-one morbidly obese patients were included in this prospective study with a mean total body weight of 134 kg (range 95 – 210 kg). During maintenance of anaesthesia, sixty-eight percent of the observed BIS values were within the target range of 40 ± 10. Except during the first 20 minutes after induction of anaesthesia, blood pressure and heart rate were within predefined ranges. Mean difference in propofol maintenance infusion rates was -0.43 mg/min (95%CI -0.49 – -0.36) compared to the proposed model-based infusion rates. Observed BIS values were predicted without bias and with accurate precision by the previously published population PK-PD model.
Conclusion
Stable and effective maintenance of anaesthesia was achieved using the PK-PD model-derived propofol dosing algorithm in morbidly obese patients with total body weights varying between 95 and 210 kg.

Introduction

The rise in prevalence of obesity leads to a growing number of obese patients that are treated by health care services for a variety of concomitant diseases (1-2). Because morbidly obese patients have an altered body composition, are prone to desaturation and have an altered cardiovascular state (3-4), safe and effective anaesthesia of morbidly obese individuals remains a challenge (5-6). To date, the number of studies that is available to define the optimal dose for anaesthesia for each individual (morbidly) obese patient is still limited.

Propofol is widely used for maintenance of anaesthesia in both non-obese and morbidly obese patients albeit at a variety of dosing regimens (7). In two recent population pharmacokinetic-pharmacodynamic (PK-PD) models for morbidly obese patients, it was reported that total body weight (TBW) is the best size descriptor for propofol clearance when parameterised with an allometric function (8-9). Besides, no influence of body weight on the pharmacodynamics of propofol using Bispectral index (BIS) values in morbidly obese patients was found (8). Based on this population PK-PD model, it was proposed to dose propofol maintenance infusion in morbidly obese patients on an adjusted total body weight (ABW = 70kg * $(TBW/70)^{0.72}$) in order to obtain Bispectral index (BIS) values of 40 ± 10 across the entire heterogeneous population of morbidly obese patients (8).

Before this model-based dosing algorithm can be widely implemented in clinical practice, it is of interest to evaluate in a prospective clinical study whether the new PK-PD model derived dosing algorithm results in safe and effective anaesthesia in morbidly obese patients. Therefore, the aim of the present study was to prospectively evaluate the PK-PD model-based propofol maintenance dosing algorithm (8) in morbidly obese patients undergoing laparoscopic bariatric surgery in terms of BIS values and haemodynamic parameters. In addition, observed propofol infusion rates aiming for a BIS target of 40 ± 10 were compared with the proposed model-based dosing scheme and observed BIS values were compared to BIS values predicted by the previously published PK-PD model of propofol in morbidly obese patients (8).

Methods

Patients

Morbidly obese patients undergoing laparoscopic bariatric surgery were included in this prospective study in two large teaching hospitals (26 patients in Nieuwegein and 25 patients in Amsterdam). Patients were enrolled in the study if their age was between 18 and 60 years, they had an American Society of Anesthesiologists (ASA) physical status classification of II or III and their BMI was over 40 kg/m^2 at the day of inclusion. Exclusion criteria included epilepsy, pregnancy, breastfeeding and known allergy to propofol, soy bean oil or egg lecithin. The hospital ethics committees of both hospitals approved the study protocol and waived the need for informed consent as the dosing algorithm based on the previously published pharmacokinetic-pharmacodynamic (PK-PD) model (8) was considered best standard of care in these hospitals.

Anaesthetic and study procedure

Anaesthesia was standardized according to the previous study in which the model-based dosing algorithm for propofol was developed (8) and was repeated as relevant for this study. Before induction of anaesthesia, an antecubital infusion line was installed, a BIS electrode was placed on the patient's forehead and a sphygmomanometer was placed on the patients' upper arm. Unpremedicated patients received a bolus injection of 350 mg of propofol given over 60 seconds for induction of anaesthesia followed by atracurium besilate or rocuronium 50 mg and fentanyl 250 mcg (10). Thereafter, the trachea was intubated and mechanical ventilation was initiated by the anaesthesiologist. Arterial oxygen saturation and end-tidal carbon dioxide were monitored throughout the procedure. The surgical position of all patients was the anti-Trendelenburg position. Anaesthesia was maintained with propofol according to the dosing algorithm that was previously developed based on a PK-PD model in morbidly obese patients (8). For this dosing algorithm an adjusted body weight was calculated for each patient (Equation 1) (8):

Adjusted body weight (ABW) = 70kg * $(TBW/70)^{0.72}$ (Eq. 1)

According to this dosing algorithm, from 3 minutes after induction of anaesthesia onwards, the initial infusion rate of propofol was set on 7 mg/kg ABW/h for 20 minutes, followed by 6.5 mg/kg ABW/h for 20 minutes, 6 mg/kg ABW/h for 20 minutes, and 5.5 mg/kg ABW/h until the end of surgery.

Appendix 1 shows the propofol infusion rates across different time frames of anaesthesia for different total body weights.
The propofol infusion rate as initiated based on Table II could be adjusted by the attending anaesthesiologist in order to obtain a BIS value of 40 ± 10, blood pressure within ± 30% of baseline values and heart rate between 60 – 90 beats/min. Adjustments in propofol infusion rates were made with 50 – 150 mg/h at the discretion of the attending anaesthesiologist, and with preferably no more than one infusion rate adjustment per five minutes. Propofol infusion rates were increased if BIS values and haemodynamic parameters were higher than the predefined values. When BIS values and haemodynamic parameters were lower than the predefined values, propofol infusion rate was decreased. When haemodynamic parameters were lower than the predefined values and BIS values were higher or equal to the predefined range, medication to improve the haemodynamic parameters was administered and the propofol infusion rate was adjusted to bring BIS values within the predefined range. When haemodynamic parameters were higher than the predefined range and BIS value were lower than or within the predefined range, signs of inadequate anaesthesia were checked. When adequate anaesthesia was confirmed, medication to correct haemodynamics was administered. If there were signs of inadequate anaesthesia, the propofol infusion rate was adjusted (8).
During the procedure, remifentanil was dosed 25 mcg/kg/h based on ideal body weight (IBW) (11). The remifentanil infusion rate was kept constant, if possible, in order to rule out influence of remifentanil on haemodynamic parameters and BIS values. If necessary, remifentanil infusion rate adjustments could be made at the discretion of the attending anaesthesiologist. Additional fentanyl bolus doses could be administered if needed throughout the surgical procedure as judged by the attending anaesthesiologist. About 30 minutes before the anticipated end of the surgical procedure, morphine 10 mg was administered.

Descriptive data analysis
The SPSS statistical package (version 19.0 for Windows; IBM) was used for these analyses. Continuous data are expressed as the mean ± SD or as median (interquartile range) where appropriate. Observed BIS values during propofol infusion, systolic arterial blood pressure and heart rate were averaged within 5 minute time intervals for each patient. Based on these data, box plots were constructed indicating median, interquartile rage and 95% confidence intervals. The actual propofol infusion rates were subtracted from predefined infusion rates at one minute time intervals for all patients. If at any time interval from less than 75% of the patients data were available, this is indicated in the figures. In all figures time-point 0 indicates the induction of anaesthesia.

Comparison of observed BIS values with model-based predicted BIS values
Non-linear mixed-effects modeling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD, USA) with S-Plus (version 6.2; Insightful Software, Seattle, WA, USA) was used to obtain model-based BIS predictions. These model-based BIS predictions were generated for each of the participating patient on the basis of their total body weight and actual administrated propofol doses during the entire procedure using the previously published PK-PD model for propofol in morbidly obese patients (8). In predicted versus observed plot, the observed BIS values were visually compared to the individual BIS value predictions by the model. For each patient and for each BIS observation, a prediction error (PE) was calculated from which median performance error (MDPE) and the median absolute performance error (MDAPE) were calculated (Equation 2, 3 and 4) (12):

Prediction error (PE) at the j^{th} BIS observed of subject i:
$PE_{ij} = BIS_{observed} - BIS_{predicted}$ (Eq. 2)

The median PE (MDPE): MDPE reflects the bias of BIS in the i^{th} subject:
$MDPE_i$ (BIS values) = median $[PE_{ij}, j = 1, \ldots, N_i]$ (Eq. 3)

The median absolute PE (MDAPE): MDAPE indicates the BIS precision in the i^{th} subject:
$MDAPE_i$ (BIS values) = median $[|PE_{ij}|, j = 1, \ldots, N_i]$ (Eq. 4)

Results

Patients and data
A total of 51 morbidly obese patients with a mean total body weight of 134 kg (range 95 – 210 kg) and mean BMI of 45 kg/m² (range 35 – 56 kg/m²) were enrolled in this study. All demographic characteristics of all patients are provided in Table I. Clinical data of the patients are presented until 75 minutes after propofol induction dose administration, as at that time point surgery had been completed in more than 25% of the patients. In five patients, propofol infusion for maintenance of anaesthesia was started 1 minute earlier than the proposed 3 minutes after the induction dose.

Table I *Baseline characteristics of 51 morbidly obese patients. Data are presented as mean with standard deviation (SD) and associated range.*

	Mean (SD)	Range
Sex (Male / Female)	18 / 33	-
Age (years)	45 (8.3)	22.0 – 63.0
TBW (kg)	134 (22.6)	95.0 – 210.0
BMI (kg/m²)	45 (5.6)	34.9 – 56.3
LBW (kg)	68 (13.7)	47.6 – 104.6
IBW (kg)	65 (11.4)	44.2 – 88.6
ABW (kg)	111 (13.7)	87.0 – 154.0
Duration of surgery (min)	74.1 (24.9)	40.0 – 158.0
Duration of anaesthesia (min)	89.3 (24.5)	51.0 – 176.0
Time between start of propofol infusion – start surgery (min)*	10.3 (4.0)	0.0 – 19.0
Time between stop of propofol infusion – extubation (min)	12.4 (5.8)	3.0 – 32.0
Time between end of surgery – extubation (min)**	14.6 (6.5)	7.0 – 33.0
Time between intubation – extubation (min)	97.0 (27.4)	30.0 – 189.0

** = data available of 70.6% of the patients*
*** = data available of 66.7% of the patients*
*TBW= total body weight, BMI= body mass index, LBW= lean body weight (19), IBW= ideal body weight (25), ABW= adjusted body weight (= 70kg * (TBW/70)$^{0.72}$).*

Anaesthesia

Figure 1 shows the median observed BIS values and interquartile ranges of the 51 morbidly obese patients during anaesthesia. It is shown that median and interquartile ranges were within the target BIS range of 40 ± 10 during anaesthesia from 5 until 75 minutes after induction of anaesthesia. In total, during this period 68% of the observed BIS values were within 40 ± 10.

Figure 2 shows mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) relative to baseline pressures measured at preoperative consultation over time. Overall, SBP and DBP dropped substantially during anaesthesia, particularly within the first 20 minutes after induction of anaesthesia. Afterwards, mean SBP and DBP stayed within the predefined target values of ± 30% from baseline values with average drops of 26% (95%CI 24-28) and 27% (95%CI 26-28) during period 5-75 minutes after induction of anaesthesia, respectively. Figure 2 shows that mean heart rate values were within the predefined range of 60 – 90 beats/min during the whole observation period, even though, similar to blood pressure, heart rates dropped during the first 20 minutes after induction of anaesthesia. End-tidal

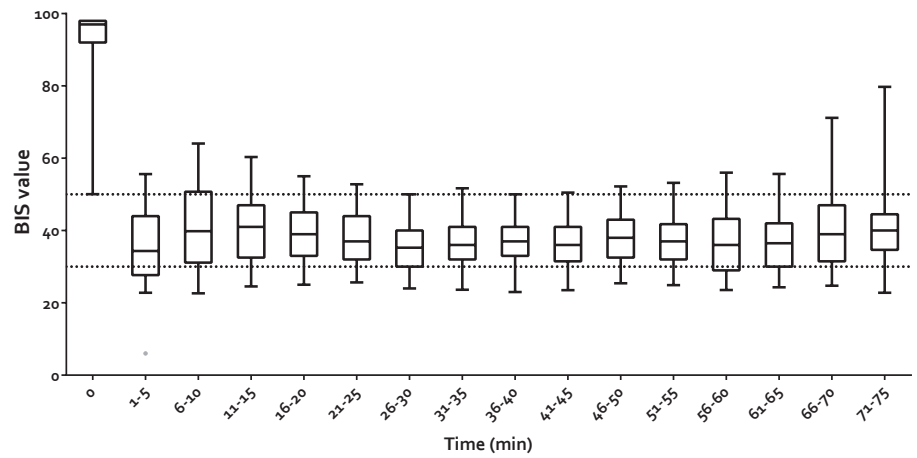

Figure 1 *Median Bispectral index (BIS) values with interquartile range (box) and 95% confidence intervals observed in time intervals of five minutes after induction of anaesthesia in 51 morbidly obese patients.*

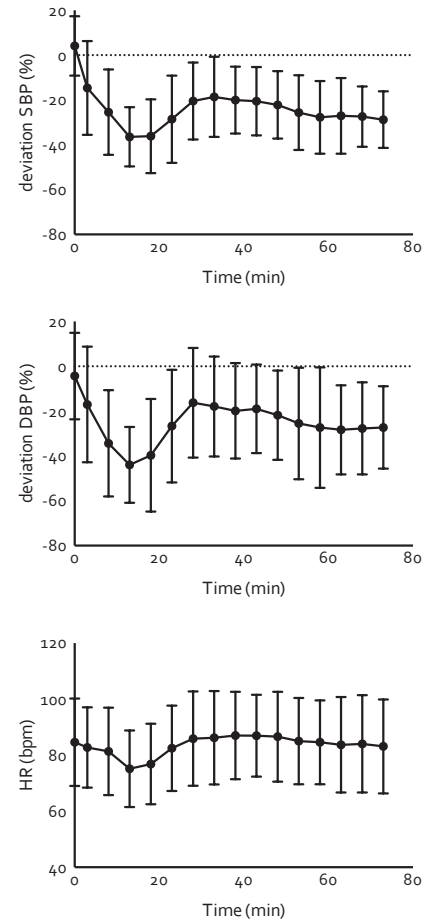

Figure 2 *Systolic blood pressure (SBP) (top panel) and diastolic blood pressure (DBP) (middle panel) at different time-points after induction of anaesthesia presented as percentage deviation from baseline values measured at preoperative consultation with standard deviations, and heart rate (HR) (bottom panel) at different time-points presented as mean with standard deviation.*

carbon dioxide measurements were not below 3.5 kPa or 26 mmHg across the observation period for all patients.
Figure 3 shows the difference between actual propofol infusion rates and proposed model-based infusion rates (Table II) from the start of the propofol maintenance infusion (at three minutes after induction of anaesthesia) until 75 minutes after the induction of anaesthesia. Overall mean difference was -0.43 mg/min (95%CI -0.49 – -0.36). It seems from this figure, that during the first ten minutes after the induction dose of 350 mg propofol, the interindividual variability in infusion rates was relatively large (Figure 3).

Table II *Proposed propofol maintenance infusion rates based on adjusted body weight (ABW) as derived from a previously published pharmacokinetic and pharmacodynamic model (8). This dosing algorithm consists of 7 mg/kg ABW*/h for 20 minutes, followed by 6.5 mg/kg ABW*/h for 20 minutes, 6 mg/kg ABW*/h for 20 minutes, and 5.5 mg/kg ABW*/h until the end of surgery.*

		7 mg/ kg ABW/ h	6,5 mg/ kg ABW/ h	6 mg/ kg ABW/ h	5,5 mg/ kg ABW/ h	5 mg/ kg ABW/ h
TBW (kg)	ABW* (kg)	Infusion rates (mL/h) using propofol 10 mg/mL				
100	90	63	59	54	50	45
105	94	66	61	56	52	47
110	97	68	63	58	53	48
115	100	70	65	60	55	50
120	103	72	67	62	57	52
125	106	74	69	64	58	53
130	109	77	71	66	60	55
135	112	79	73	67	62	56
140	115	81	75	69	63	58
145	118	83	77	71	65	59
150	121	85	79	73	67	61
155	124	87	81	74	68	62
160	127	89	83	76	70	63
165	130	91	84	78	71	65
170	133	93	86	80	73	66
175	135	95	88	81	74	68
180	138	97	90	83	76	69
185	141	99	92	85	78	70
190	144	101	93	86	79	72
195	146	102	95	88	81	73
200	149	104	97	89	82	75
205	152	106	99	91	83	76
210	154	108	100	93	85	77
215	157	110	102	94	86	79
220	160	112	104	96	88	80
225	162	114	105	97	89	81
230	165	115	107	99	91	82
235	167	117	109	100	92	84
240	170	119	110	102	93	85
245	173	121	112	104	95	86
250	175	123	114	105	96	88

** ABW = 70 * (Total body weight (=TBW)/70)$^{0.72}$*

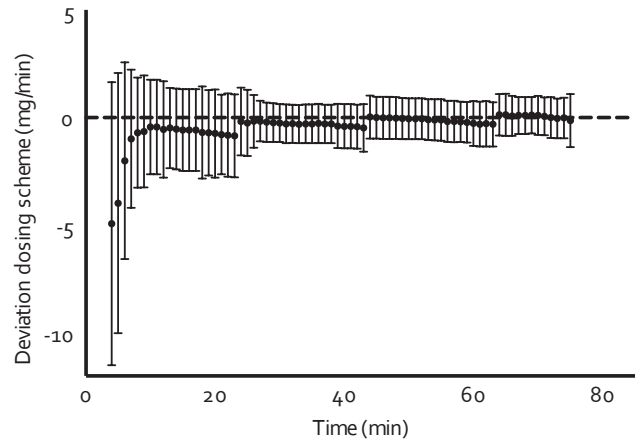

Figure 3 *Deviations in observed propofol infusion rates compared to the proposed propofol dosing algorithm as presented in Table II (mean ± SD) over time in 51 morbidly obese patients.*

Table III *Medication administered according to standardized anaesthesia protocol and additional medication presented as mean dose with standard deviation (SD).*

	Mean (SD)
Protocol medication	
Propofol bolus (mg)	362.2 (41.3)
Propofol maintenance (mg/kg/h*)	6.2 (0.54)
Remifentanil (mcg/kg/h**)	23.4 (4.8)
Fentanyl (mcg)	292.2 (77.1)
Atracurium (mg) (n=26)	54.8 (12.0)
Rocuronium (mg) (n=25)	52.2 (6.5)
Morphine (mg)	10.3 (2.8)
Additional medication (bolus doses)	
Ephedrine (mg) 0-20 min (#=27, n=22)	7.9 (2.5)
Ephedrine (mg) 21 min – end of surgery (#=18, n=11)	5.8 (1.9)
Phenylephrine 0-20 min (mg) (#=16, n=8)	0.12 (0.05)
Phenylephrine 21-end min (mg) (#=22, n=8)	0.11 (0.04)
Noradrenalin (mg) (n=5)	0.49 (0.2)

** based on model-based adjusted body weight (= 70kg * (TBW/70)$^{0.72}$)*
*** based on ideal body weight*
 # number of bolus administrations
n number of patients

Both protocol medication and additional medication that was administered during anaesthesia according to the standardised protocol are presented in Table III. Mean remifentanil dose was 23.4 mcg/kg/h (SD 4.8) based on ideal body weight (IBW) which was slightly lower than the predefined dose of 25 mcg/kg/h based on IBW (Table III). Sixty-five percent of the patients received co-medication to correct low blood pressure and/or heart rate at some time during the period of anaesthesia. In most cases, ephedrine was used to correct low blood pressures and 60% of all ephedrine doses were administered during the first 20 minutes after the start of the induction of anaesthesia.

Comparison of observed BIS values with model-based predicted BIS values
Figure 4 shows the individual predicted BIS values by the original pharmacokinetic and pharmacodynamic model (8) versus the observed BIS values of the morbidly obese patients. These plots indicate acceptable bias and adequate precision of the predictions of the BIS values. Overall performance variables were a median performance error (MDPE) -5.2 BIS points (SD 13.0) representing bias and a median absolute performance error (MDAPE) 10.5 BIS points (SD 9.3) representing precision.

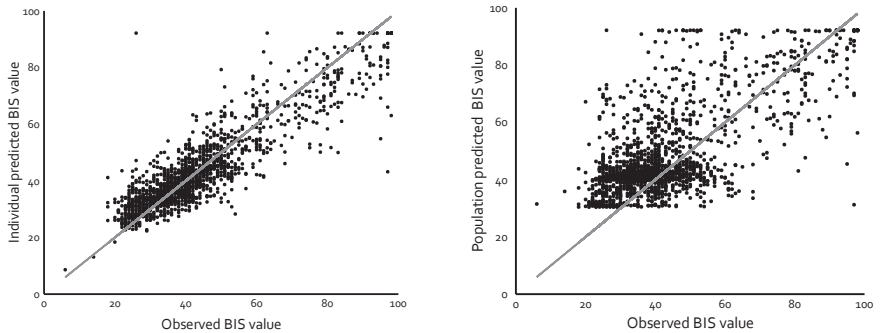

Figure 4 *Individual predicted BIS values by the original pharmacokinetic-pharmacodynamic model (8) versus the observed BIS values in the current study in fifty-one morbidly obese patients.*

Discussion

The present study prospectively evaluated a pharmacokinetic-pharmacodynamic (PK-PD) model-derived algorithm for maintenance of anaesthesia with propofol in morbidly obese patients thereby targeting on a BIS value of 40 together with stable haemodynamics. Using this propofol dosing algorithm in combination with remifentanil analgesia, effective anaesthesia was achieved with BIS values of 40 ± 10 and with haemodynamics that stayed within the predefined ranges across a wide range of total body weights from 95 to 210 kg. However, haemodynamics dropped substantially particularly within the first 20 minutes after induction of anaesthesia.
Prospective studies evaluating dosing guidelines derived from population PK-PD models on the used endpoints are scarce. The propofol dosing algorithm for morbidly obese patients evaluated in the present study was derived from a population PK-PD model in which total body weight was identified as key patient characteristic that can explain the interindividual variability of clearance of propofol in both non-obese and morbidly obese patients (8). Based on that model, when aiming for a stable BIS of 40 during maintenance of anaesthesia, an adjusted body weight (ABW); ABW = 70kg * $(TBW/70)^{0.72}$ as dosing scalar with doses reductions every 20 minutes was proposed (8). In the present evaluation of this PK-PD model-based dosing algorithm, we showed that using these propofol doses stable BIS values of 40 ± 10 were achieved in morbidly obese patients. Although the current bias and precision values for the observed BIS values were larger compared to in non-obese patients (13-14), the bias (MDPE) and precision (MDAPE) were acceptable with 10.5 (SD 9.3) and –5.2 BIS points (SD 13.0), respectively. There was also no difference in observed BIS values between the lower and higher total body weights (data not shown) indicating that the accuracy of the model is applicable for a wide range of total body weights. The present study demonstrates that PK-PD modeling in special patient groups such as morbidly obese patients can be of important value when developing evidence-based dosing algorithms for these patient groups.
In general, there may be concerns on the haemodynamic safety of propofol when used for anaesthesia in morbidly obese patients. Propofol is known to cause a decrease in systemic arterial blood pressure due to depressant effects on cardiac contractility and a reduction in venous and arteriolar systemic vascular resistance resulting in a decrease in pre- and afterload (15). While in our opinion, the risk for haemodynamic instability is reduced by dosing on adjusted body weight (Table II) instead of linear dosing on total body weight, we did observe a substantial decrease in blood

pressure over the first 20 minutes of the procedure in our study (Figure 2). Moreover, in a large number of patients additional medication to correct these haemodynamic effects were given (Table III). 20 minutes after the induction dose, the observed decrease of the haemodynamic values during propofol maintenance infusion remained within the predefined margins and there were no signs of hypoperfusion during anaesthesia. In addition, we emphasize that the decrease in observed haemodynamic values could be slightly overpredicted because of relatively high blood pressures that may be measured during preoperative consultation. As such we conclude that haemodynamic effects of propofol in morbidly obese patients are acceptable when the PK-PD model derived dosing algorithm as depicted in Table II is used for maintenance of anaesthesia.

After induction of anaesthesia, considerable variations in BIS values, blood pressures and heart rates were observed during the first 20 minutes. There is a number of possible explanations for this. First, a cause may lie in the fixed propofol induction dose of 350 mg for all morbidly obese patients. Recent study suggested to use lean body weight as dosing scalar to calculate propofol induction dose for morbidly obese patients instead of dose capping (16). This might have resulted in a lower induction dose for the less obese patients and a more stable start of anaesthesia. In an additional analysis of the present study, however, no correlation between decrease in BIS during the induction phase and lean body weight could be observed (data not shown). Second, propofol maintenance infusion was started 3 minutes after the propofol induction dose while surgery did not start in all cases. Mean time between start of surgery and start of propofol infusion was 10.3 minutes. Because start of surgery causes sympathetic activation, thereby increasing both blood pressure and heart rate (17), a delayed start of surgery and, thereby, a delayed stimulus of the sympathetic nerve system, may explain the extensive decline of blood pressure during the first minutes of propofol infusion. Therefore, before implementation, the present dosing algorithm has to be incorporated in conjugation with local practice in terms of timing of anaesthesia and start of surgery. Finally, cardiovascular consequences of obesity such as (silent) ischemic heart disease and cardiomyopathy may have aggravated the haemodynamic effects during induction of anaesthesia independent of propofol dose. Although in our study with the developed propofol dosing algorithm optimal conditions for intubation were achieved in all patients, there remains space for further improvement of the induction phase of the evaluated PK-PD model-based dosing regimen.

In our study, we decided to dose propofol based on both BIS values and hemodynamic parameters. Besides dosing based on BIS values, an alternative strategy for propofol dosing is to target to specific propofol blood concentrations using target controlled infusion techniques (TCI). La

Colla et al reported however a clinically unacceptable performance bias upon the use of total body weight as an input for the 'Marsh' model for TCI and concluded that titration on target BIS values in morbidly obese patient remains necessary (18). Although TCI can be considered an interesting approach to dose propofol for anaesthesia, it seems that the TCI systems are not yet ready for this approach in morbidly obese patients. The results of the present study show that the previously developed PK-PD model-based propofol maintenance dosing algorithm leads to stable BIS values and acceptable haemodynamics in morbidly obese patients and is ready for clinical implementation.

Conclusion

Stable and effective maintenance of anaesthesia was achieved using the PK-PD model-based propofol dosing algorithm in combination with remifentanil analgesia in morbidly obese patients varying in total body weight between 95 and 210 kg.

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