Abstract: Purpose: Aim of this study was to evaluate maintenance of anesthesia using propofol with continuous Bispectral Index (BIS)-monitoring in morbidly obese patients receiving propofol-remifentanil and propofol-epidural anesthesia.

Methods: In the first group in ten morbidly obese patients receiving remifentanil analgesia, a propofol infusion was started at 10 mg/kg/hr and modified by aiming at BIS values between 40-60 together with predefined hemodynamic parameters.

In the second group, the propofol dose resulting from the first group was prospectively evaluated in a matched cohort of six morbidly obese patients receiving propofol-epidural analgesia aiming for the same BIS and hemodynamic parameters.

In both groups, propofol concentration and infusion rates, BIS and hemodynamic values were collected.

Results: In the propofol-remifentanil group (Body Mass Index (BMI) 39-60 kg/m²), the mean propofol infusion rate that corresponded to the predefined BIS and hemodynamic parameters was 4.8 mg/kg/hr (SD 1.5). On this basis, a maintenance dose of 5 mg/kg/hr was started in the propofol-epidural group (BMI 38-58 kg/m²). In this second group, the mean propofol infusion rate that corresponded to predefined BIS and hemodynamic parameters was 5.0 mg/kg/hr (SD 0.6). Between the two groups, there was no difference in the propofol concentration-BIS relation.

Conclusion: Using both BIS and hemodynamic parameters as an endpoint, a maintenance dose of propofol of 4-6 mg/kg/hr is proposed for maintenance of anesthesia in morbidly obese patients undergoing bariatric surgery either in combination with remifentanil or epidural analgesia. There was no difference in propofol concentration-BIS relation in morbidly obese patients receiving propofol-remifentanil or propofol-epidural anesthesia.

Key words: Morbid obesity ; propofol ; Bispectral Index ; anesthesia.

INTRODUCTION

Although propofol is an intravenous anesthetic commonly used for anesthesia in morbidly obese patients, specific guidelines for this special population of which body weights are still increasing are conflicting (1-5). Recent available literature also includes target controlled infusion (TCI) using total body weight or adjusted body weight, in which it was reported that both strategies lead to performance error in predicted propofol concentrations using TCI (4). Even though this difference between target and predicted propofol concentrations is also seen in non-obese patients (6), the manufacturer of TCI does not support the use of this device in morbidly obese patients, which implies that propofol should be titrated on clinical end-points, such as processed-EEG values such as the Bispectral Index (BIS) together with hemodynamic parameters (4).

However, the exact dose in mg per kg per hour that is actually required in morbidly obese patients for maintenance of anesthesia, particularly in view of the increasing body weights of this category of patients and varying co-analgesics, is unknown.

Aim of this study was to derive a dosing advice for propofol in mg/kg/hr on a total body weight basis for maintenance of anesthesia in morbidly obese patients undergoing bariatric surgery, either combined with remifentanil or epidural analgesia.

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Primary endpoints to evaluate propofol dosing were BIS values, systolic blood pressure and heart rate.

Secondary endpoint of this study was to evaluate the propofol concentration–BIS relation in morbidly obese patients receiving propofol-remifentanil or propofol-epidural anesthesia. For this study, one group received propofol-remifentanil anesthesia and the other group received propofol-epidural anesthesia. In the first group, the required propofol dose in mg/kg/hr for maintenance of propofol-remifentanil anesthesia in morbidly obese patients was assessed by aiming at predefined BIS values and hemodynamic parameters after an initial infusion rate of 10 mg/kg/hr.

Then a second study was performed in which the resulting propofol dose from the first group was evaluated using both predefined BIS and hemodynamic parameters in a matched population of morbidly obese patients receiving propofol-epidural anesthesia.

In both cohorts propofol concentrations were measured and linked to BIS values in order to study the propofol concentration – BIS relation.

METHODS

Patients group I

After approval of the study by the ethics committee of the St. Antonius Hospital, ten morbidly obese patients undergoing laparoscopic gastric banding or gastric bypass surgery were prospectively studied. Inclusion criteria were: age between 18 and 60 years, American Society of Anesthesiologists (ASA) physical status classification II or III, a Body Mass Index (BMI) of over 35 kg/m² at inclusion together with an indication for weight-reducing surgery, and normal renal and hepatic function. Exclusion criteria were: pregnancy, breast feeding, epilepsy, contraindications for placement of an epidural catheter and known allergy for propofol, soybean oil, egg lecithin or levobupivacain. Written informed consent was obtained in all patients.

Induction and maintenance of anesthesia in group I

Unpremedicated patients received an induction dose of propofol 350 mg, administered as a bolus injection using a TIVA pump (Asena TCI & TIVA, Alaris medical systems). An indwelling arterial blood pressure line, an infusion line, a Bispectral Index (BIS) monitor (Model DSC-XP, Aspect Medical Systems) and a 3-lead ECG were installed before induction of anesthesia. After administration of propofol, fentanyl 250 µg and atracurium 50 mg intravenously were given according to routine clinical practice in our hospital. Hereafter, patients were intubated and mechanically ventilated.

After induction of anesthesia, continuous infusions of propofol, atracurium and remifentanil were administered to maintain anesthesia. The infusion rate of propofol was initially 10 mg/kg/hr on a total body weight basis, and was subsequently adjusted in order to obtain BIS values between 40 and 60 with acceptable hemodynamics (see also Bispectral Index monitoring and Hemodynamic monitoring). The infusion rate of atracurium was 0.3 mg/hr times total body weight and the infusion rate of remifentanil was 25 µg/hr times ideal body weight (7). Ideal body weight was calculated by the following formula: Male: 50 + ((2.3*length in inches)-60)), female: 45.5 + ((2.3*length in inches)-60)). The remifentanil infusion rate was maintained constant throughout the procedure, in order to exclude any influence of changes in remifentanil concentrations on BIS values or hemodynamic parameters. Hydration status was standardized for all patients.

Evaluation of all parameters was done from 10 minutes after induction of anesthesia onwards to exclude any influence of the agents used for induction of anesthesia on these parameters and evaluation stopped at 90 minutes after induction of anes-
Induction and maintenance of anesthesia in group II

An epidural catheter was placed at the interspace of approximately thoracic vertebrae 8 and 9 and topped with 10 ml of levobupivacain 0.25%, after which an infusion rate of epidural analgesia was started at 8 ml/hr 0.125% bupivacain with 1 μg/ml sufentanil. Unpremedicated patients received an induction dose of propofol 350 mg, administered as a bolus injection using a TIVA pump (Asena TCI & TIVA, Alaris medical systems). An indwelling arterial blood pressure line, an infusion line, a Bispectral Index (BIS) monitor (Model DSC-XP, Aspect Medical Systems) and a 3-lead ECG were installed before induction of anesthesia. After administration of propofol, fentanyl 250 µg and atracurium 50 mg intravenously were given according to routine clinical practice in our hospital. Hereafter, patients were intubated and mechanically ventilated.

After induction of anesthesia, continuous infusions of propofol, atracurium and epidural analgesia were administered to maintain anesthesia. Based on the findings of group I, the infusion rate of propofol was initially 5 mg/kg/hr on a total body weight basis, and was subsequently adjusted in order to obtain BIS values between 40 and 60 with acceptable hemodynamics (see also Bispectral Index monitoring and Hemodynamic monitoring). The infusion rate of atracurium was 0.3 mg/hr times total body weight and the infusion rate of epidural analgesia was 8 ml/hr 0.125% bupivacain with 1 μg/ml sufentanil. Hydration status was standardized for all patients.

Evaluation of all parameters was done from 10 minutes after induction of anesthesia onwards to exclude any influence of the agents used for induction of anesthesia on these parameters and evaluation stopped at 90 minutes after induction of anesthesia in order to exclude differences between the groups.

Bispectral Index monitoring

Continuous BIS-monitoring was performed, with BIS values recorded at five-minute intervals from ten minutes after the induction dose onwards up until 90 minutes after the induction dose. During anesthesia, the aim was to maintain the BIS value between 40 and 60.

Hemodynamic monitoring

Beat-to-beat systolic arterial blood pressures and heart rates were collected during maintenance of anesthesia and were noted every minute from ten minutes after the induction dose onwards up until 90 minutes after the induction dose. During anesthesia, the aim was to maintain systolic arterial blood pressure between 80 and 160 mmHg and heart rate between 60 and 90 beats per minute.

Propofol dose adjustment

While aiming at a BIS value between 40 and 60, systolic arterial blood pressures between 80-160 mmHg and heart rate between 60-90 beats per minute, target BIS values were coupled to hemodynamic values and vice versa. This means that the infusion rate of propofol was elevated when BIS values and hemodynamic parameters were higher than the preset range. When BIS values and hemodynamic parameters were lower than the preset range the propofol infusion rate was decreased.

In general, a minimum of five minutes between changes of the infusion rate was awaited in order to achieve a steady state at the installed infusion rate.

Blood sampling and analytical methods

During the entire procedure, blood was withdrawn from the indwelling arterial line, the exact time being noted together with the actual Bispectral Index value. Blood samples were evaluated approximately at the following times: at baseline before the start of the propofol infusion for maintenance of anesthesia, 3, 7, 15, 25 and 45 minutes after the start of the propofol infusion, just before and 15 minutes after dose adjustment, just before discontinuation of the propofol infusion, and 1, 3, 5, 7,
10, 20, 30 minutes after stopping the infusion. Whole-blood samples for propofol analysis were mixed thoroughly and stored at 4°C until analysis by HPLC with fluorescence detection (9). With this method, the coefficients of variation for the intra-assay and inter-assay precision were less than 3.7% and 9.8%, respectively, over the concentration range from 0.05 to 5.0 mg/L and the limit of quantification was 0.05 mg/L.

Follow up

Patients were asked whether they remembered anything from the peri-operative process (awareness) at the moment of discharge from the recovery room.

Statistical analysis

Mean propofol infusion rates, BIS values, systolic arterial blood pressures and heart rates were obtained by calculating the mean value of all patients at five-minute intervals and for propofol concentrations at ten minutes intervals. Hereafter, mean values for propofol infusion rates, BIS values, systolic arterial blood pressures, heart rates and propofol concentrations were calculated for three time periods; 10-30 minutes, 30-60 minutes and 60-90 minutes after induction of anesthesia.

The SPSS statistical package (version 16.0 for Mac; SPSS, Chicago, IL) was used for the statistical analyses. Continuous data are expressed as the mean ± SD or as the median (interquartile range) where appropriate. Categorical data were analyzed by 2 and continuous data by Student’s t-test or rank tests where appropriate. For all tests, p ≤ 0.05 was considered significant. A univariate multi-level linear regression analysis was used to study the propofol concentration - BIS relation and to assess differences between the two groups. Multilevel modeling allows for the examination of variability in outcomes between individuals as well as between higher-level units. Imputation of propofol concentrations was applied for missing data at some time-points (8.8%).

RESULTS

Group I

Patient characteristics

Table 1 shows the baseline characteristics of ten morbidly obese patients receiving propofol-remifentanil anesthesia. Two patients underwent laparoscopic gastric bypass surgery and eight patients underwent laparoscopic banding. All patients were classified as ASA physical status II.

Propofol infusion rates

Figure 1 (left panel) shows the mean propofol infusion rate expressed in mg/kg/hr versus time in all ten patients receiving propofol-remifentanil anesthesia from ten minutes after the induction dose onwards, which is the result of an initial propofol dose of 10 mg/kg/hr with subsequent dose adjustments in order to aim at a BIS of 40-60, systolic arterial blood pressure of 80-160 mmHg and heart rate between 60-90 beats/min. Mean propofol infusion rates and corresponding standard deviations were calculated for three time periods: 10-30 minutes, 30-60 minutes and 60-90 minutes after induction of anesthesia are summarized in Table 2.

The overall mean propofol infusion rate was 4.8 mg/kg/hr (SD 1.5), and therefore the infusion rate for group II was started at 5 mg/kg/hr.

### Table 1

Baseline characteristics of ten morbidly obese patients receiving propofol-remifentanil anesthesia (group I) and six morbidly obese patients receiving propofol-epidural (group II) for maintenance of anesthesia. Values are expressed as median (interquartile range), mean (SD) or number (%)

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (38-55)</td>
<td>45 (32-52)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female</td>
<td>4 (80%)</td>
<td>4 (67%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.66 (0.07)</td>
<td>1.72 (0.07)</td>
<td>0.11</td>
</tr>
<tr>
<td>Total body weight (kg)</td>
<td>125 (20)</td>
<td>138 (22)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ideal body weight (kg)</td>
<td>58 (8)</td>
<td>65 (8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>48 (10)</td>
<td>47 (7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>69 (63-91)</td>
<td>120 (93-146)</td>
<td>0.05</td>
</tr>
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</table>
Bispectral Index

Figure 2 upper left panel shows Bispectral Index (BIS) values versus time in all ten patients receiving propofol-remifentanil for maintenance of anesthesia from ten minutes after the induction dose onwards, which are observed following an initial propofol dose of 10 mg/kg/hr with subsequent dose reductions in order to aim at a BIS of 40-60, systolic arterial blood pressure of 80-160 mmHg and heart rate between 60-90 beats/min. Mean BIS values and corresponding standard deviations between 10-30 minutes, 30-60 minutes and 60-90 minutes after induction of anesthesia are shown in Table 2. None of the patients showed signs of inadequate anesthesia (wide pupils and/or sweating).
Figure 2 middle and lower left panels show systolic arterial blood pressure and heart rate, respectively, in patients receiving propofol-remifentanil for maintenance of anesthesia from ten minutes after the induction dose onwards, which are observed following an initial propofol dose of 10 mg/kg/hr with subsequent dose adjustments in order to aim at a BIS of 40-60, systolic arterial blood pressure of 80-160 mmHg and heart rate between 60-90 beats/min. Mean values and standard deviation of systolic arterial blood pressure and heart rate are summarized in Table 2. None of the patients needed medication to control hemodynamic parameters.

Propofol concentrations

Figure 3 (left panel) shows mean propofol concentrations versus time in ten patients receiving propofol-remifentanil for maintenance of anesthesia from ten minutes after the induction dose onwards. Mean propofol concentrations and corresponding standard deviations between 10-30 minutes, 30-60 minutes and 60-90 minutes after induction of anesthesia are summarized in Table 2.

Follow up

None of the patients reported awareness postoperatively.

Group II

Patient characteristics

Table 1 shows the baseline characteristics of six morbidly obese patients receiving propofol-epidural anesthesia. Five patients underwent laparoscopic gastric bypass surgery and one patient underwent open gastric bypass surgery. All patients were classified as ASA physical status II.

Table 2

<table>
<thead>
<tr>
<th>Number of patients (n)</th>
<th>Group I</th>
<th>Group II</th>
<th>p-value</th>
<th>Study I</th>
<th>Study II</th>
<th>p-value</th>
<th>Study I</th>
<th>Study II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-30</td>
<td>30-60</td>
<td>60-90</td>
<td>0.33</td>
<td>4.8 (0.8)</td>
<td>0.001</td>
<td>4.1 (0.5)</td>
<td>0.33</td>
<td>4.0 (0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>5.1 (0.6)</td>
<td>5.0 (0.8)</td>
<td>5.0 (0.8)</td>
<td>0.33</td>
<td>6.9 (1.2)</td>
<td>0.001</td>
<td>6.9 (1.2)</td>
<td>0.33</td>
<td>6.9 (1.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.06</td>
<td>0.001</td>
<td>4.7 (0.5)</td>
<td>0.001</td>
<td>4.7 (0.5)</td>
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<td>0.001</td>
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<tr>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>0.001</td>
<td>110 (4)</td>
<td>0.001</td>
<td>110 (4)</td>
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<td>110 (4)</td>
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<tr>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.001</td>
<td>75 (4)</td>
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<td>75 (4)</td>
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</tr>
<tr>
<td>3.02 (0.43)</td>
<td>3.06 (0.94)</td>
<td>0.001</td>
<td>2.99 (0.89)</td>
<td>0.81</td>
<td>2.99 (0.89)</td>
<td>0.001</td>
<td>2.99 (0.89)</td>
<td>0.81</td>
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</tr>
<tr>
<td>4.02 (0.61)</td>
<td>3.06 (0.94)</td>
<td>0.001</td>
<td>2.99 (0.89)</td>
<td>0.81</td>
<td>2.99 (0.89)</td>
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<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>3.7 (2)</td>
<td>0.001</td>
<td>3.7 (2)</td>
<td>0.001</td>
<td>3.7 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>0.001</td>
<td>42 (10)</td>
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<td>42 (10)</td>
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<td>42 (10)</td>
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<tr>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>108 (4)</td>
<td>0.001</td>
<td>108 (4)</td>
<td>0.001</td>
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<td>&lt; 0.001</td>
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<tr>
<td>2.46 (1.05)</td>
<td>2.84 (0.6)</td>
<td>0.21</td>
<td>2.46 (1.05)</td>
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<td>2.46 (1.05)</td>
<td>0.21</td>
<td>2.46 (1.05)</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

BIS = Bispectral Index, SBP = systolic blood pressure, HR = heart rate.
Propofol infusion rates

Figure 1 (right panel) shows the propofol infusion rates expressed in mg/kg/hr versus time in six patients receiving propofol-epidural anesthesia from ten minutes after the induction dose onwards, which are the result of an initial propofol dose of 5 mg/kg/hr with subsequent dose adjustments in order to aim at a BIS value of 40-60, systolic arterial blood pressure of 80-160 mmHg and heart rate between 60-90 beats/min. Mean propofol infusion rates and corresponding standard deviations between 10-30, 30-60 minutes and 60-90 minutes after induction of anesthesia are summarized in table 2. The overall mean propofol infusion rate was 5 mg/kg/hr (SD 0.1).

Bispectral Index

Figure 2 upper right panel shows Bispectral Index (BIS) values versus time for six patients receiving propofol-epidural maintenance of anesthesia from ten minutes after the induction dose onwards, which are observed following an initial propofol infusion rate of 5 mg/kg/hr with subsequent dose adjustments in order to aim at a BIS value of 40-60, systolic arterial blood pressure of 80-160 mmHg and heart rate between 60-90 beats/min. One patient was administered midazolam 5 mg intravenously approximately 30 minutes before induction during placement of the epidural catheter. Mean BIS values and corresponding standard deviations between 10-30, 30-60 and 60-90 minutes after induction of anesthesia are summarized in table 2. None of the patients showed signs of inadequate anesthesia (wide pupils and/or sweating).

Hemodynamic monitoring

Figure 2 middle en lower right panels show the hemodynamic parameters in the six patients receiving propofol-epidural anesthesia for maintenance of anesthesia from ten minutes after the induction dose onwards, which are observed following an initial propofol dose of 5 mg/kg/hr with subsequent dose adjustments in order to aim at a systolic arterial blood pressure between 80-160 mmHg and heart rate between 60-90 beats/minute. Mean values and standard deviation of systolic arterial blood pressure and heart rate are summarized in table 2.

None of the patients needed medication to control hemodynamic parameters.

Propofol concentrations

Figure 3 (right panel) shows mean propofol concentrations versus time in six patients receiving propofol-epidural anesthesia for maintenance of anesthesia from ten minutes after the induction dose onwards. Mean propofol concentrations and corresponding standard deviations between 10-30, 30-60 and 60-90 minutes after induction of anesthesia are summarized in table 2.

Follow up

None of the patients reported awareness postoperatively.

Comparison between group I and II

As shown in table 1, there were no significant differences in patient characteristics between the patients of group I or group II. Table 2 shows that propofol infusion rates were significantly different between the propofol-remifentanil and propofol-epidural groups at 10-30 minutes after induction and at 60-90 minutes after induction (p < 0.001 and p = 0.001 respectively). Between 10-30 minutes after induction, propofol infusion rates were higher in the propofol-remifentanil group (p < 0.001), while between 60-90 minutes these propofol infusion rates were lower (p = 0.001). The higher propofol infusion rate at 10-30 minutes after induction of anesthesia was a result of the study design, as the propofol-remifentanil group started with a higher infusion rate than the propofol-epidural group (10 mg/kg/hr versus 5 mg/kg/hr, respectively). In accordance with these results, propofol concentrations were higher in the propofol-remifentanil group between 10-30 min after induction of anesthesia (p = 0.001), even though thereafter there were no differences in propofol concentrations between the two groups. BIS values were lower in the propofol-remifentanil group compared to the propofol-epidural group at all time points (p < 0.001). Systolic arterial blood pressures were significantly lower in the propofol-remifentanil group from 30 minutes after induction onwards (p < 0.001). Heart rate was not significantly different between the two cohorts studied.

Figure 4 shows the propofol concentrations and corresponding BIS values for all patients in both the propofol-remifentanil and the propofol-epidural group from ten minutes after the induction of anesthesia onwards. The figure includes 220 propofol-BIS values from the patients receiving propofol-remifentanil and 120 values from the
patients receiving propofol-epidural anesthesia. The univariate multi-level linear regression analysis showed no significant effect for “group” in the relation between propofol concentrations and BIS values (p = 0.224).

**DISCUSSION**

The current study evaluated maintenance of anesthesia with propofol using continuous BIS and hemodynamic monitoring in morbidly obese patients undergoing bariatric surgery. Although it has been proposed repeatedly to use total body weight as a basis for propofol maintenance dosing in morbidly obese patients (1-3), the exact dose in mg per kg per hour is still unknown, particularly in view of the increasing body weights of this category of patients and varying co-analgesics. Recently, a study on target controlled infusion (TCI) based on total body weight versus adjusted body weight reported that both strategies lead to performance error in predicted propofol concentrations (4), which implies that propofol should be titrated on clinical end-points, such as the Bispectral Index (BIS) together with hemodynamic parameters. This makes our study the first study that evaluated maintenance dosing of propofol in mg/kg/hr on a total body weight basis in morbidly obese patients by using clinical end-points. In our study, the propofol dose that resulted from the first titration group of patients receiving propofol-remifentanil anesthesia was subsequently studied in a second group in six matched morbidly obese patients receiving propofol-epidural anesthesia. Even though study numbers were small, our findings suggest that the same maintenance dose of propofol can be used for propofol-remifentanil anesthesia or propofol-epidural anesthesia, being 4.9 mg/kg/hr on a total body weight basis.

Even though the initial infusion rate (10 mg/kg/hr) in the propofol-remifentanil group (group I) was within the range of the manufacturers’ recommendations (4-12 mg/kg/hr) (10), initial Bispectral Index (BIS) values and hemodynamics were relatively low (Fig. 2, left panels). Therefore, in accordance with the titration protocol, propofol infusion rates were reduced, finally revealing a maintenance dose of 4.8 mg/kg/hr when co-administered with remifentanil to maintain adequate anesthesia (BIS target range 40-60) and achieve acceptable hemodynamics (target systolic arterial blood pressures 80-160 mmHg). In group II the infusion rate of propofol was thus started at an infusion rate of 5 mg/kg/hr. As shown in figure 1 (right panel), mean propofol rates were 3-7 mg/kg/hr, which resulted in acceptable BIS-values and hemodynamics when used in combination with epidural analgesia. While this dose is in agreement with the ten morbidly obese patients receiving propofol-remifentanil (Fig. 1, left panel) of group I, our infusion rates seem to be slightly lower compared to those of a previous report in which it was proposed that propofol infusion for maintenance of anesthesia in morbidly obese patients should be dosed as in non-obese patients (6 mg/kg/hr) (1). This small difference may be explained by the fact that in that study, conclusions were based on the pharmacokinetics of propofol alone and BIS values or other anesthetic measures were not evaluated. The results of our study revealed that propofol infusion rates in morbidly obese patients when combined with remifentanil should be slightly lower compared to non-obese patients when dosed on total body weight (7-8 mg/kg/hr) (11). It seems, therefore, that our study does add relevant information to a limited set of available evidence on how to dose propofol in morbidly obese patients when using propofol-remifentanil or propofol-epidural anesthesia, as in our study propofol was titrated on anesthetic end-

![Fig. 4. — Bispectral Index (BIS) values versus propofol concentration for the propofol-remifentanil group (square, solid line) (n = 10) and propofol-epidural group (circle, dotted line) (n = 6) from ten minutes after induction onwards. Y = 89.6 (95 CI 84.0-95.2); slope : -13.3 (95% CI -14.3 to -12.3); effect of group : -3.9 (-10.4 to 2.6).](image-url)
points (e.g. BIS and hemodynamic parameters) and propofol concentrations were measured.

We found in this study that there is no difference in propofol maintenance dose when analgesia is provided with remifentanil or an epidural, based on both BIS and hemodynamic measurements. While it is generally accepted that there is a pharmacodynamic interaction between remifentanil and propofol, studies on the opioid-propofol interaction, measured using BIS values, are conflicting. Some conclude there is a deeper level of sedation when an opioid is co-administered with propofol, which, though, is not reflected by a lower BIS (12-14). In contrast, earlier reports (15-17) did show an influence on the BIS when remifentanil was given during anesthesia with propofol. An explanation for the results of the studies that did not show an effect on the BIS is that hypnotics affect the EEG by an action on the cerebral cortex, whereas opioids exert their analgesic action through an inhibition of subcortical structures, including the spinal cord. These last structures may not be integrated in the Bispectral Index monitor. The studies that did show a decrease in BIS when an opioid is administered can be explained by the decrease in blood pressure and heart rate when an opioid is co-administered, leading to a reduction of cerebral blood flow and thus a decrease in BIS, but not an actual hypnotic effect (17). Besides, it can not be excluded that epidural analgesia produces a hypnotic effect (18-19). While in our study we found no difference in overall propofol infusion rates or propofol concentration – BIS relation between the propofol-remifentanil and propofol-epidural group, these aspects of the BIS when studying the interaction between propofol and remifentanil should be kept in mind.

A limitation of the study is the small number of patients included, especially in the propofol-epidural group. However, patients were stratified for body weight in the propofol-remifentanil group and therefore a large range in body weight was studied. In addition, the patients in the propofol-epidural group were matched to the six body weight groups of the propofol-remifentanil population, which potentially improves the validity of the results. Finally, propofol dose was titrated on both predefined BIS values and hemodynamic parameters resulting in a propofol dose that corresponds to a certain window in parameters that are routinely measured. In addition to the evaluation of BIS values and hemodynamics, propofol concentrations were measured allowing for evaluation of propofol concentrations in the two groups.

Another limitation, in particular for the comparison between the two groups, is the fact that both groups started at different propofol infusion rates. The question is whether these two limitations of a small sample size and varying starting doses may have influenced the final results. While overall propofol infusion rates were similar in both groups, there were differences in infusion rates and propofol concentrations as a result of the study design. When the time frame 30-60 minutes was considered in which almost all patients could still be evaluated and the influence of the initial propofol infusion rate can be neglected, propofol infusion rates and concentrations were similar (4.7 versus 5.0 mg/kg/hr and 2.99 versus 3.06 mg/L, for group I and group II respectively) while BIS values and systemic arterial blood pressures were significantly lower in the propofol-remifentanil group (group I). However, as the actual difference in BIS values and blood pressures were low (37 versus 42 and 110 versus 120), we think that our conclusion that the influence of remifentanil is similar to that of epidural analgesia for propofol dosing is still justified.

Other limitations of the study were the small age range, no inclusion of patients with cardiac dysfunction or of super-obese patients, which would require a larger study. In case such large scale data are available, it seems important to perform a full pharmacokinetic-pharmacodynamic analysis using NONMEM instead of linear regression analysis, as by using that approach all BIS values can be evaluated on the basis of the pharmacokinetic analysis, even when at a specific time point the propofol concentration is not available.

In conclusion, in morbidly obese patients receiving propofol-remifentanil and propofol-epidural anesthesia, based on both BIS values and hemodynamic parameters, a maintenance dose of propofol of 4-6 mg/kg/hr on a total body weight basis is proposed for maintenance of anesthesia. As there was no difference in propofol concentration-BIS relation between morbidly obese patients receiving propofol-remifentanil anesthesia and those receiving propofol-epidural anesthesia, we conclude that BIS values are influenced to the same extend by adding remifentanil compared to epidural analgesia to propofol anesthesia. Awaiting larger studies in morbidly obese patients to confirm the present results, dose-adjustment by titration on BIS values and hemodynamic parameters upon the initial start of the maintenance infusion remains important.
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References