Population pharmacokinetics and pharmacodynamics of propofol in morbidly obese patients receiving propofol-remifentanil or propofol-epidural anaesthesia

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Jeroen Diepstraten, Simone van Kralingen, Vera H.M. Deneer, Bert van Ramshorst, Eric P.A. van Dongen, Catherijne A.J. Knibbe

Abstract

Reports on the influence of perioperative remifentanil on population pharmacokinetic and pharmacodynamics parameters of propofol are conflicting and for morbidly obese patients unexplored. In the current study we developed a population pharmacokinetic and pharmacodynamic model of propofol in twenty-six morbidly obese patients receiving propofol-remifentanil anaesthesia or propofol-epidural anaesthesia. Remifentanil was neither a covariate for the pharmacokinetic nor the pharmacodynamic parameters of propofol using the BIS as pharmacodynamics endpoint. In the final model, total body weight was a significant covariate for propofol clearance. These results suggest that there are no differences in the pharmacokinetic or pharmacodynamic parameters of propofol in morbidly obese patients receiving maintenance propofol-remifentanil or propofol-epidural anaesthesia when the BIS is used a pharmacodynamic endpoint.

Background

The dramatic increase in obesity rates across the world has augmented the obese population presenting for anaesthesia for various surgical procedures (1). Different strategies have been described for the complex anaesthesia of an obese patient. Most commonly, propofol in combination with remifentanil is used in morbidly obese patients. Alternatively, propofol anaesthesia can be combined with epidural analgesia. We reported before a pharmacokinetic-pharmacodynamic (PK-PD) model based dosing algorithm for propofol in combination with remifentanil in morbidly obese patients (2). Besides, we reported no difference in propofol maintenance dose between propofol-remifentanil anaesthesia and propofol-epidural anaesthesia in morbidly obese patients when aiming for stable Bispectral index and hemodynamic values (3). For non-obese patients, results studying the influence of remifentanil on propofol requirements are conflicting. No propofol infusion adjustments were reported when propofol was combined with remifentanil and dosing was based on target BIS values (4). In contrast, lower propofol concentrations were needed during laryngoscopy when propofol was combined with remifentanil in non-obese healthy volunteers (5). While changes in propofol dose may be caused by both PK and PD parameters, there are no studies on the influence of remifentanil on the separate PK and PD parameters of propofol in morbidly obese patients during surgery. Therefore, our aim was to develop a population PK-PD model of propofol in morbidly obese patients receiving maintenance of anaesthesia with propofol-remifentanil or with propofol-epidural anaesthesia. Bispectral index (BIS) values were used as PD endpoint.

Methods

Previously published data of a total of twenty-six morbidly obese patients scheduled to undergo bariatric surgery were used for this analysis (2, 3). Both the original study protocols were approved by the hospitals Ethics Committee and written informed consent was signed by each participating patient.

Before induction, an antecubital infusion line, an indwelling arterial blood pressure line and a 3-lead ECG were installed and a Bispectral index electrode was placed on the patient's forehead.

Twenty morbidly obese patients (group I) received either a propofol induction dose of 200 mg or 350 mg followed by an initial maintenance propofol infusion of 10 mg/kg times total body weight. Remifentanil was administrated 25 µg/h/kg based on ideal body weight (6). In six morbidly obese patients (group II), an epidural catheter was placed and anaesthesia was induced with a propofol bolus dose of 350 mg and maintained with a continuous infusion of propofol and epidural analgesia 8 ml/h of bupivacain 0.125% with 1 µg/ml sufentanil. In this group, propofol maintenance infusion was initiated at 5 mg/kg times total body weight. In both groups, propofol infusion rate was subsequently adjusted in order to keep BIS values between 40 and 60, the systolic arterial blood pressure between 80 and 160 mmHg and heart rate between 60 and 90 beats per minute (3). Whole-blood samples were collected on a regular basis for propofol analysis, mixed thoroughly and stored at 4°C until analysis by high-performance liquid chromatography with fluorescence detection at 276 nm and 310 nm (7).

Data analysis was performed by means of non-linear mixed-effects modeling using NONMEM (version VI, release 1.1; GloboMax LLC, Hanover, MD) (8) with S-plus (version 6.2; Insightful software, Seattle, WA) to visualize the data. Population pharmacokinetic (PK) and pharmacodynamic (PD) data were sequentially analysed by using the individual PK empirical Bayes estimates as an input to the pharmacodynamic model, and with use of a previously reported PK-PD model for propofol in morbidly obese patients (2). For the covariate analysis, a $p< 0.005$ was applied to evaluate the covariates in the forward inclusion (OFV decrease >7.9), while the backward deletion procedure used a stricter criterion (OFV decrease >10.8; $p<0.001$).

Results

Data of twenty-six morbidly obese patients were analysed (Table I). A three-compartment pharmacokinetic (PK) model adequately described the time course of the propofol whole blood concentrations in morbidly obese patients receiving either propofol-remifentanil or propofol-epidural anaesthesia (Figure 1). Total body weight was a major determinant for clearance (CL), reducing the objective function value with 18 points ($p<0.005$). The relationship was expressed using an allometric function $CL_i = CL_{70\ kg} \bullet (TBW_i/70)^{0.87}$ where CL_i represents clearance in the ith individual, $CL_{70\ kg}$ is the population mean value for clearance in an individual of 70 kg, TBW_i is the total body weight of the ith individual, and 70 is the standard total body weight in kilograms. No differences in mean PK parameters of propofol between patients receiving either propofol-remifentanil or propofol-epidural anaesthesia were observed as shown in Figure 2. Separate

Table I *Baseline characteristics of twenty morbidly obese patients receiving propofol-remifentanil (group I) and six morbidly obese patient receiving propofol-epidural (group II) for maintenance of anaesthesia. Data are presented as mean with standard deviation (SD).*

	Group I Propofol-Remifentanil Mean (SD)	Group II Propofol-Epidural Mean (SD)
Number	20	6
Gender (M / F)	4/16	1/5
Age (years)	45 (12)	41 (9)
Total body weight (kg)	124 (20)	145 (28)
Ideal body weight (kg)	61 (7)	65 (6)
Body mass index (kg/m²)	43 (6)	49 (9)
Lean body weight (kg) (19)	60 (9)	66 (10)

M = male; F = female.

estimation of volume of distribution or clearance for each of the two groups did not result in improved performance of the model.
The measured BIS values over time in the 26 morbidly obese patients were adequately described with a two-compartment biophase distribution model with a sigmoid E_{max} pharmacodynamic (PD) model for both regimens (Figure 1). Separate estimation of the PD parameters for each of the two groups did not result in improved performance of the model. Tested covariates did not significantly improve the PD model of propofol in morbidly obese patients. Figure 3 illustrates that there is no significant difference in mean PD parameters EC_{50}, k_{eo} and E_{max} of the groups receiving propofol-remifentanil and propofol-epidural anaesthesia.

Discussion

In our study in morbidly obese patients undergoing bariatric surgery, no differences in pharmacokinetic (PK) and pharmacodynamic (PD) parameters of propofol when combined with remifentanil or epidural anaesthesia were observed using BIS values as PD endpoint.

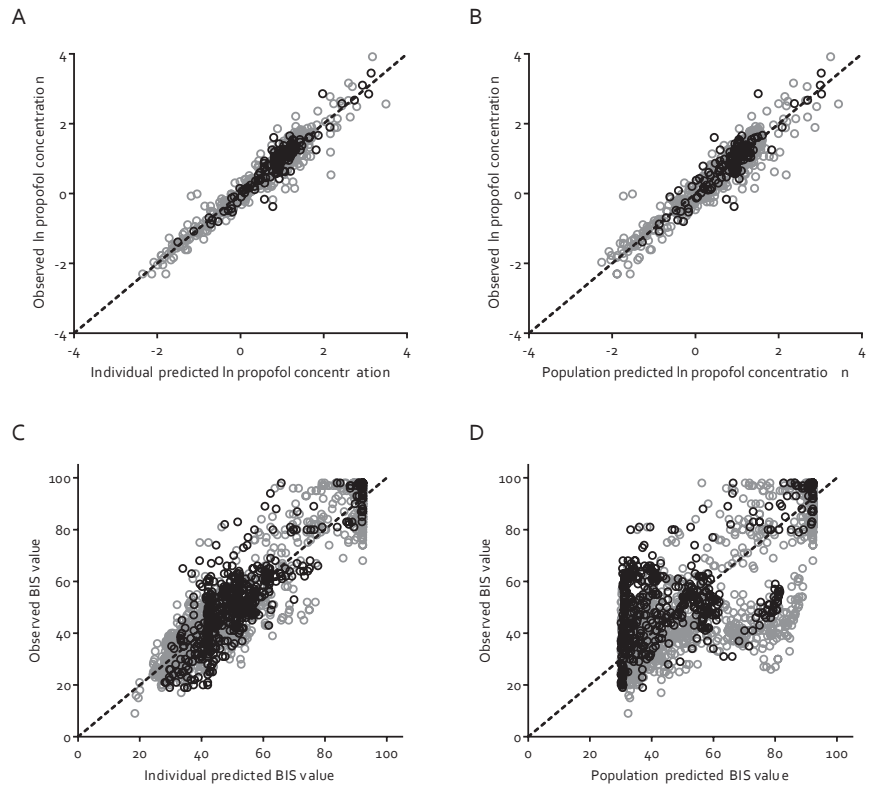

Figure 1 *Diagnostic plots for propofol pharmacokinetics (A and B) and pharmacodynamics (C and D) in morbidly patients showing individual (A and C) and population (B and D) model predictions versus observed values for final models. Morbidly obese patients receiving propofol-remifentanil anaesthesia are represented with grey open rounds and morbidly obese patients receiving propofol-epidural anaesthesia are represented with black open rounds. The dashed line represents the line of identity, x=y.*

Morbidly obese patients are at increased risk for complications during anaesthesia due to difficult intubation, positioning and diverse co-morbidities (9). Therefore, there is a need to understand the influence of excessive body weight on the PK and PD of drugs. The effect of epidural analgesia on propofol anaesthesia is rather unknown, although it cannot be excluded that epidural analgesia has a hypnotic effect (10, 11). Previously we reported no differences between propofol infusion rates and propofol concentrations when propofol dosing was based on BIS values and hemodynamic parameters in combination with remifentanil or epidural analgesia in morbidly obese patients (3). However, in non-obese patients there is debate about the influence of remifentanil on the PK of propofol and on BIS values as the effect of remifentanil is mostly evaluated in patients

with BIS values around 60 without surgical stimuli. In a study in non-obese patients, remifentanil was not found to influence the PK of propofol (12). However, the combination resulted in a reduction of BIS values during induction of anaesthesia (13, 14) and reduced propofol concentrations during extubation with the return of consciousness in a synergistic manner (15). Besides, adding remifentanil to low propofol infusion rates resulted in lower BIS values (16). In addition, lower BIS values for patients receiving higher remifentanil target concentrations were observed (17). In contrast, maintenance propofol infusion rates were not adjusted when propofol was combined with remifentanil (4) and varying the remifentanil effect-site concentration showed not to effect BIS values during target-controlled propofol infusion in non-obese patients (18). While the small sample size of patients receiving propofol-epidural anaesthesia is a limitation of the current study, our findings in morbidly obese patients are in accordance with the results in non-obese patients.

In conclusion, the present study in morbidly obese patients suggests that there are no differences in the population PK and PD parameters of propofol when combined with remifentanil or epidural anaesthesia during bariatric surgery. More data from morbidly obese patients receiving propofol-epidural anaesthesia are warranted to confirm the present results.

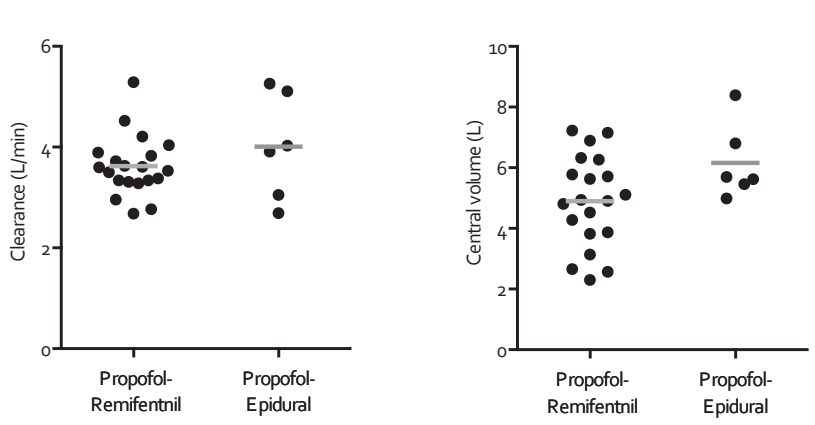

Figure 2 *Mean values (grey line) and empirical Bayes estimates for the pharmacokinetic parameters clearance (left panel) and central volume of distribution (right panel) of propofol in morbidly obese patients receiving propofol-remifentanil (n=20) or propofol-epidural anaesthesia (n=6).*

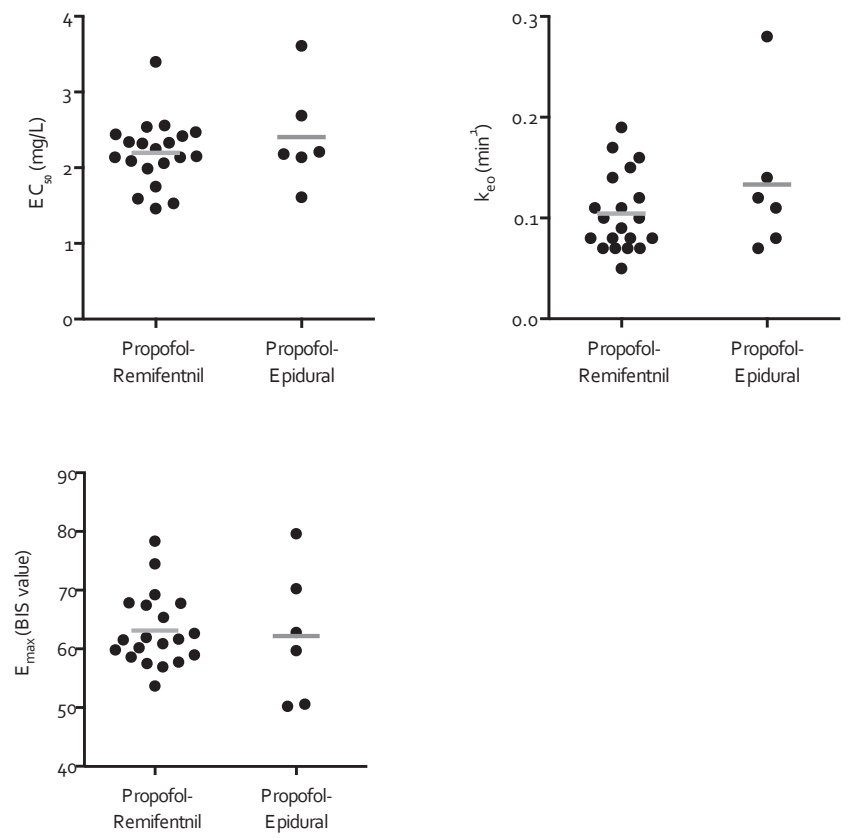

Figure 3 *Mean values (grey line) and empirical Bayes estimates for the pharmacodynamic parameters EC_{50}, k_{eo} and E_{max} of propofol in morbidly obese patients receiving propofol-remifentanil (n=20) or propofol-epidural anaesthesia (n=6).*

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