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Feasibility of closed-loop co-administration of propofol and remifentanil guided by the bispectral index in obese patients: a prospective cohort comparison†

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Editor's key points

- Closed-loop controlled drug administration of propofol and remifentanil was used as an unbiased method for the determination of anaesthetic requirements in morbidly obese and lean patients.
- Under the studied conditions, this study concludes that propofol doses in obese and lean patients were nearly identical when expressed as a function of total body weight.
- Remifentanil doses were similar when expressed in terms of ideal body weight.

Background. We used an automated bispectral index (BIS)-guided dual-loop controller to determine propofol and remifentanil requirements during general anaesthesia in obese and lean surgical patients.

Methods. Obese patients, BMI>35 kg m^{-2}, and lean patients (<25 kg m^{-2}) having laparoscopic procedures were prospectively evaluated in this multicentre single-blind study. The automated controller targeted BIS between 40 and 60 by adjusting propofol and remifentanil administration. Propofol and remifentanil consumptions were calculated using both total body weight (TBW) and ideal body weight (IBW). Results are expressed as medians (inter-quartile range).

Results. Thirty obese [BMI=43 (40–49) kg m^{-2}] and 29 lean [BMI=23 (21–25) kg m^{-2}] patients completed the study. BIS was between 40 and 60 during 84 (69–91)% *vs* 85 (78–92)% of the anaesthetic time, $P=0.46$. The amount of propofol given during induction [1.2 (1.1–1.6) *vs* 1.3 (1.0–1.7) mg kg^{-1}, $P=0.47$] and maintenance [5.2 (4.1–6) *vs* 5.3 (4.7–6.4) mg kg^{-1} h^{-1}, $P=0.39$] calculated using TBW was similar between the two groups. The dual-loop controller delivered half as much remifentanil to the obese patients during induction [1.0 (0.8–1.6) *vs* 2.2 (1.5–2.7) μg kg^{-1}, $P<0.001$] and maintenance [0.12 (0.07–0.16) *vs* 0.25 (0.17–0.29) μg kg^{-1} min^{-1}, $P<0.001$] calculated using TBW. But when remifentanil consumption was calculated using IBW, the amounts were similar during induction at 2.2 (1.6–3.5) *vs* 2.0 (1.6–3.0) μg kg^{-1} IBW, $P=0.48$, and during maintenance at 0.26 (0.16–0.34) *vs* 0.27 (0.18–0.33) μg kg^{-1} min^{-1}, $P=0.50$.

Conclusions. The amount of propofol–remifentanil administered by the controller is consistent with current knowledge, propofol is best dosed using TBW whereas remifentanil is best dosed using IBW.

Clinical trial registration. NCT00779844.

Keywords: anaesthesia; bispectral index; closed-loop; i.v. anaesthetics; obesity; propofol; remifentanil

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A growing fraction of the world's population is obese[1] and obese patients are considered as high anaesthetic risk patients.[2] Optimizing i.v. anaesthetic titration represents a challenge for the clinician because of obesity-related modifications in drug pharmacokinetics (PK) and possibly pharmacodynamics (PD).[3] Dosing propofol based on actual or total body weight (TBW) may result in excessive drug administration[4] during maintenance, whereas dosing based on ideal body weight (IBW) may result in inadequate drug administration during induction.[5] It is similarly unclear how best to approach remifentanil dosing in obese patients.

One approach to dosing is to conduct PK analyses in the obese and then introduce a weight-specific PK model in target-controlled infusion (TCI) systems. For lean patients, the PK model of Schnider and colleagues[6] for propofol is used in routine practice. But for obese patients, this PK model overestimates propofol

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clearance during maintenance because of a paradoxically decreased value of lean body mass calculated by the James[7] formula which appears to be flawed at high values of TBW.[8 9] For remifentanil, the lean body mass used in the PK model of Minto and colleagues[10] is calculated using the same formula.[7] The lean body mass is an important covariate of several PK parameters in the Minto and colleagues model,[10] in particular the central volume, the rapid peripheral volume of distribution, and the metabolic clearance were underestimated with the consequence that remifentanil is underdosed in obese patients.[11 12] Finally, for obese patients, specific propofol PK models have been developed[13] with age integrated as a relevant covariate.[14] The PK model of Minto can similarly be improved by calculating the true value of lean body mass using the formula of Janmahasatian and colleagues[12 15] or by calculating 'fictitious height'.[11] However, one difficulty with an isolated PK approach is that PD factors may also vary in lean or obese patients.[16]

An alternative strategy is to titrate drug administration to a direct measure of hypnotic effect, for example, frontal electrocortical activity as determined by the bispectral index (BIS).[17 18] Moreover, the BIS change is sensitive for detecting the deficit of antinociception: noxious stimuli may cause electro-cortical activation such as haemodynamic change allowing the titration of analgesia.[19] We have developed and validated a dual closed-loop controller that automatically co-administers propofol and remifentanil solely guided by the BIS.[20] The closed-loop system has a cascade structure including a proportional-integral-derivative controller which steers a TCI system. Recently, the controller was used as an unbiased method for the determination of anaesthetic requirements in surgical patients,[21–23] and this reproducible method has the potential to accurately determine anaesthetic requirements in obese patients.

We thus used our BIS-guided dual-loop controller to determine propofol and remifentanil requirements during induction and maintenance of general anaesthesia in obese and lean surgical patients. In particular, we evaluated propofol and remifentanil consumption when the same controller was used in both groups without modification of the PK models or weight adjustment methods.

Methods

Our prospective two-centre, single-blind, cohort comparison with adaptive matching was approved by the French Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, Boulogne Billancourt, France, N° 08 03 11). It was also approved by the French National Regulatory Office (Agence Française de Sécurité Sanitaire des Produits de Santé, N° A80314-53). This study was registered at ClinicalTrials.gov (NCT00779844). Written informed consent was obtained from participating patients.

We enrolled adults undergoing elective upper-abdominal or bariatric laparoscopic procedures expected to last >60 min requiring general anaesthesia with tracheal intubation without combined regional anaesthesia. All were ASA physical status I–III. Exclusion criteria included psychiatric illness, supraspinal neurological disorders, a pacemaker, symptomatic gastro-oesophageal reflux, expected difficult airway management, or planned awake fibreoptic intubation. Obese patients were enrolled at the Hôpital Européen Georges Pompidou (Paris, France) and lean patients were enrolled at the Hôpital Foch (Suresnes, France).

Patients with a BMI >35 kg m^{-2} were enrolled in the obese group. Matched patients with a BMI<25 kg m^{-2} were enrolled in the lean group. The matching criteria were age ($\pm$10 yr) and sex. A preliminary analysis reported that the sex ratio was one male for four females for the obese patients and one male for one female in lean patients undergoing elective upper-abdominal laparoscopic procedures. Thus, we decided to enrol one lean man for each obese man, and two lean women and one lean man for every three obese women allowing the inclusion of one lean patient within 30 days after the inclusion of one obese patient.

Procedures

No premedication was used except for 150 mg of cimetidine in the obese patients. Propofol and remifentanil were administered by identical closed-loop automated systems. Automated control was used during induction and throughout maintenance of general anaesthesia. TBW was set in the TCI systems of the controller using the PK model of Schnider and colleagues[6] for propofol and the PK model of Minto and colleagues[10] for remifentanil in both groups.

The controller modifies the calculated effect-site drug concentrations using the TBW in both groups according to intraoperative BIS variations (Covidien, Dublin, Ireland). The dual-loop assumption is that small fluctuations of BIS are related to the intensity of noxious stimuli.[19] Small variations in BIS thus provoked changes only to remifentanil; but when the variation was large, both remifentanil and propofol were modified. The controller has previously been validated in lean patients in a randomized controlled study.[20] Details of the controller are provided in the Appendix. All investigators received a full day of training in the use of the automated controller at the Hôpital Foch, and were able to override the automated system if necessary, or to switch between automated and manual control.

Upon arrival in the operating theatre, a dedicated i.v. cannula was inserted and routine monitoring started. Neuromuscular function at the adductor pollicis was monitored after loss of consciousness. Before induction, a BIS electrode (Zip Prep, Covidien) was positioned on the patient's forehead and connected to either an A-2000 XP (version 3.11) BIS monitor or a BIS M-Module (GE-Healthcare S/5™, Helsinki, Finland).

Before induction, patients were pre-oxygenated with 100% oxygen through a face mask. In obese patients, a PEEP at 10 cm H_2O was applied until end-tidal oxygen saturation >92% was obtained. In both groups, investigators chose the initial propofol effect-site target concentration according to their clinical judgement; in contrast, the initial remifentanil effect-site