BJA

British Journal of Anaesthesia, ■ (■): 1–8 (2018)

doi: 10.1016/j.bja.2018.04.045
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Population pharmacokinetic analysis of propofol in underweight patients under general anaesthesia

J. H. Park[1,#], S. M. Choi[2,#], J. H. Park[3], K. H. Lee[3], H. J. Yun[4], E. K. Lee[5], B. M. Choi[4,*,†] and G. J. Noh[4,6]

[1]Department of Anaesthesiology and Pain Medicine, Hangang Sacred Heart Hospital, Hallym University College of Medicine, Seoul, South Korea, [2]University of Ulsan College of Medicine, Seoul, South Korea, [3]Department of Anaesthesiology and Pain Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea, [4]Department of Anaesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea, [5]Department of Statistics, Ewha Womans University, Seoul, South Korea and [6]Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

*Corresponding author. E-mail: byungmoonchoi7@gmail.com

[#] Contributed equally to this work as first authors.
[†] Principal Investigator.

Abstract

Background: The modified Marsh and Schnider pharmacokinetic models for propofol consistently produce negatively and positively biased predictions in underweight patients, respectively. We aimed to develop a new pharmacokinetic model of propofol in underweight patients.

Methods: Twenty underweight (BMI<18.5 kg m^{-2}) patients aged 20–68 yr were given an i.v. bolus of propofol (2 mg kg^{-1}) for induction of anaesthesia. Anaesthesia was maintained with a zero-order infusion (8 mg kg^{-1} h^{-1}) of propofol and target-controlled infusion of remifentanil. Arterial blood was sampled at preset intervals. A population pharmacokinetic analysis was performed using non-linear mixed effects modelling. The time to peak effect (t_{peak}, maximally reduced bispectral index) was measured in 28 additional underweight patients receiving propofol 2 mg kg^{-1}.

Results: In total, 455 plasma concentration measurements from the 20 patients were used to characterise the pharmacokinetics of propofol. A three-compartment mammillary model well described the propofol concentration time course. BMI and lean body mass (LBM) calculated using the Janmahasatian formula were significant covariates for the rapid peripheral volume of distribution and for the clearance of the final pharmacokinetic model of propofol, respectively. The parameter estimates were as follows: V_1(L)=2.02, V_2(L)=$12.9^{(BMI/18.5)}$, V_3(L)=139, Cl (L·min^{-1})=$1.66^{(LBM/40)}$, Q_1 (L·min^{-1})=1.44, Q_2 (L·min^{-1})=0.87+0.0189×(LBM−40). The median t_{peak} of propofol was 1.32 min (n=48).

Conclusions: A three-compartment mammillary model can be used to administer propofol via target effect-site concentration-controlled infusion of propofol in underweight patients.

Clinical trial registration: KCT0001760.

Keywords: pharmacokinetics; propofol; underweight

Editorial decision: 20 May 2018; **Accepted:** 20 May 2018

Editor's key points

- Body mass has a strong influence on the pharmacokinetics of propofol.
- The Marsh and Schnider models perform poorly in underweight patients.
- Arterial propofol concentrations were measured to develop a new pharmacokinetic model for underweight patients.
- In this model, V2 (rapid peripheral volume of distribution) and metabolic clearance were functions of BMI and lean body mass, respectively.

Low body mass index (BMI) can result from malnutrition, underlying health conditions such as malignancy, and psychological factors in adults.[1,2] 'Low body weight' is a term used to simply describe that a person's weight is low, whereas the definition of 'underweight' usually refers to a person whose weight is low for their height (BMI<18.5 kg m^{-2}).[3] In a previous study, about 2.4% of patients undergoing major intra-abdominal cancer surgery were underweight.[4]

The modified Marsh model and the Schnider model are two models commonly used to administer propofol via target-controlled infusion (TCI),[5] and these two models alone have been embedded in the commercially available TCI pumps in Korea. In our previous study, the predictive performance of these two models in the target effect-site concentration (*Ce*) range of 2–6 μg ml^{-1} was evaluated in underweight patients.[6] The pooled median (95% confidence interval) biases and inaccuracies at a target *Ce*≤3 μg ml^{-1} were −22.6% (−28.8% to −12.6%) and 31.9% (24.8–36.8%) for the modified Marsh model. These values at *Ce*≥4 μg ml^{-1} were 19.8% (12.9–25.7%) and 36.2% (31.4–39.7%) for the Schnider model.[6] The clinically acceptable range for pooled inaccuracies in pharmacokinetic predictions of propofol is approximately 20–30%.[7–9] Those of the modified Marsh and Schnider models failed to meet these criteria within a specific target *Ce* range. Also, the modified Marsh and Schnider models consistently produced negatively and positively biased predictions, respectively. This may suggest that use of the modified Marsh and Schnider models can lead to inadvertent underdosing and overdosing of propofol in underweight patients. In another retrospective study of ours, general anaesthesia was maintained at a propofol target *Ce* of 2.5–3 μg ml^{-1} using the modified Marsh model, and the amount of i.v. midazolam and mean infusion rate of remifentanil during anaesthesia were significantly higher in underweight patients than in normal weight patients.[10] Unfortunately, the Eleveld model, performed for a wide range of patient groups and clinical conditions,[11] showed similar predictive performance to the modified Marsh and Schnider models.[6]

The aim of this study was to develop a new pharmacokinetic model for TCI of propofol to underweight patients. In addition, the time to peak effect for calculating the blood brain equilibration rate constant (k_{e0}) was measured in another a second underweight patients group.

Methods

Investigation drug

Propofol, formulated in a mixture of medium- and long-chain triglycerides (Propofol-MCT/LCT 1%, Freefol-MCT®; Daewon Pharmaceutical Co Ltd, Seoul, Korea), was used in this study.

Patient population

This prospective clinical trial was conducted from September 2015 to April 2016. The study protocol was approved by the Institutional Review Board of Asan Medical Centre (2015–0957, Seoul, Korea) and registered on an international clinical trials registry platform (http://cris.nih.go.kr; KCT0001760). Twenty ASA physical status 1 or 2 underweight patients who were undergoing elective surgery were enrolled in the pharmacokinetic model building. The patient exclusion criteria included a known allergy to propofol, a preoperative haemoglobin level <9 g dl^{-1}, clinically significant laboratory findings, and evidence of pregnancy.

Procedure

All of the patients fasted from midnight on the day of surgery, without premedication. Once in the operating theatre, they were monitored using pulse oximetry, electrocardiography, end-tidal carbon dioxide partial pressure, NIBP (Carescape™ Monitor B850; GE Healthcare, Chicago, IL, USA), and the bispectral index (BIS® monitor; Covidien, Boulder, CO, USA). All data were recorded continuously until the end of anaesthesia. A 20-gauge angiocatheter was placed in the radial artery for frequent blood sampling. During pre-oxygenation using a face mask with oxygen 100%, lidocaine 20 mg was i.v. administered before propofol injection. Subsequently, an i.v. bolus of propofol 2 mg kg^{-1} was given to patients. Five minutes later, a zero-order infusion of propofol was started at a rate of 8 mg kg^{-1} h^{-1} until the end of surgery and remifentanil was administered via target *Ce*-controlled infusion using the Minto model.[12] If necessary, midazolam was administered to maintain BIS values less than 60 during anaesthesia maintenance. The target *Ce* of remifentanil was titrated to maintain stable haemodynamics (systolic BP>80 mm Hg and heart rate>45 beats min^{-1}) within the range of 2–20 ng ml^{-1}. Tracheal intubation was facilitated by administration of rocuronium 0.6 mg kg^{-1}. The patients were then ventilated with oxygen in air (1:2), and the ventilation rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35–45 mm Hg. If necessary, ephedrine was administered to maintain stable haemodynamics. Infusions of propofol and remifentanil were terminated at the onset of skin suture. Neuromuscular block was antagonised via the administration of neostigmine and glycopyrrolate at the end of surgery.

Blood sampling and plasma concentration assay

Arterial blood samples (5 ml) were obtained at preset intervals: 0, 0.5, 1, 1.5, 3, and 5 min after a bolus dose of propofol; 5, 10, 20, 40, 60, 90, and 120 min after continuous infusion of propofol; and 0, 5, 10, and 30 min and 1, 2, 6, 12, and 24 h after discontinuation of propofol infusion. Additionally, arterial blood samples were also obtained at the time to loss of responsiveness (LOR) and recovery of responsiveness (ROR). Time to LOR was determined every 5 s after the bolus injection of propofol via the loss of response to a verbal command (open your eyes). Time to ROR was assessed every 30 s after discontinuation of propofol via the eyes opening in response to a verbal command.[13] Each blood sample was collected in a tube containing ethylenediaminetetraacetic acid and centrifuged for 10 min at 252 × *g*; the plasma was stored at −70°C until required for the assay. Plasma concentrations of propofol were analysed using ultrafast lipid chromatography (Shimadzu, Kyoto, Japan)