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Original Article

Performance of TCI Propofol Using the Schnider Model for Cardiac Surgery on Cardiopulmonary Bypass–A Pilot Study

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Objective: This pilot study aimed to evaluate the performance of target-controlled infusion (TCI) of propofol using the Schnider pharmacokinetic model in patients undergoing cardiac surgery requiring cardiopulmonary bypass.
Design: This was a prospective pharmacokinetic study.
Setting: A tertiary care hospital.
Participants: This study is comprised of 10 patients, aged between 46 and 81, who underwent elective cardiac surgery requiring the use of cardiopulmonary bypass.
Interventions: Anesthetic technique was standardized. Hypnosis was maintained using TCI of propofol, titrated to achieve a bispectral index of 30 to 60. Calculated plasma propofol concentrations were recorded at 5 time points in total, before, during, and after cardiopulmonary bypass. Blood propofol concentration was measured at each of these time points.
Measurements and Main Results: The prediction errors and absolute prediction errors were calculated for each sample. From these, the median prediction error (MDPE) and its absolute value (MDAPE) were derived. Agreement between predicted and measured propofol concentrations was assessed using a Bland–Altman plot. Mean prediction errors were also compared pre-, on, and post-bypass using the generalized linear latent and mixed model. The MDPE and MDAPE were both found to be 45%, indicating significant bias toward under-prediction in the Schnider pharmacokinetic model. This bias was increased at an average propofol concentration of 4.5 μg/mL and above. A significant decrease in mean prediction error was noted while on bypass (45.6%, 95% confidence intervals 9.2–82.1).
Conclusions: The performance of the Schnider pharmacokinetic model for TCI propofol was poor, with a tendency toward under-prediction of blood propofol concentration, especially at higher average concentrations of propofol. While mitigating the risk of awareness, the risk of other adverse effects like hypotension and cardiorespiratory depression is increased. Patients should therefore be adequately monitored, and predicted plasma propofol concentrations taken in context with other patient parameters. A lower target concentration of propofol is probably sufficient to maintain an adequate depth of anesthesia as measured by BIS.

Key Words: target-controlled infusion; TCI; propofol; Schnider model; pharmacokinetic model; cardiopulmonary bypass

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THE ADMINISTRATION OF PROPOFOL using target-controlled infusions (TCI) for total intravenous anesthesia (TIVA) is a popular technique for anesthesia. There is a large body of evidence for the safety and efficacy of TCI.[1,2] Modern open TCI systems allow propofol to be used with a choice of pharmacokinetic models and effect-site or plasma targeting. At the authors' institution, which is a large tertiary center supporting a wide range of adult surgical specialties, the authors' experience using the Schnider pharmacokinetic model on Fresenius Kabi Injectomat TIVA Agilia syringe pumps has

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been largely positive. There is some evidence recommending the Schnider model over others such as the Marsh model.[3]

In spite of solid clinical experience, there were lingering concerns about the accuracy of TCI in patients undergoing cardiopulmonary bypass (CPB). This is a barrier to adoption because, unlike inhalational anesthetics, continuous measurement of propofol concentration is not yet possible. The commonly used models by Marsh and Schnider are derived from studies in healthy volunteers, which calls into question whether the estimated concentrations are accurate under CPB, where significant alterations to pharmacokinetics and pharmacodynamics are introduced by the bypass circuit, hypothermia, concomitant drug administration, and alterations in cardiac output and regional blood flow.

The authors undertook this pilot study to begin to address these concerns, to characterize the magnitude of prediction error in these patients, and to generate hypotheses for further studies.

Methods

Approval for this study was obtained from the authors' Institutional Review Board. Waiver of informed consent was granted as remnant samples were used and no patient identifiers were collected. Ten patients presenting for elective coronary artery bypass graft surgery with or without valve replacement were recruited for this study. The small convenience sample was chosen for this pilot study to use available resources within the department. As this was a pilot study in a relatively unexplored area, the authors hoped that the results would enable them to uncover trends and formulate hypotheses for future studies. Patients who were at least 21 years old, required CPB for their surgery and had ejection fraction of at least 50% on preoperative echocardiography were selected for the study. Anesthesia was administered by a single cardiac anesthesiologist. Patients with known allergy to anesthetic drugs and constituents, obesity (body mass index [BMI] > 35 kg/m^2), severe physiological impairments, chronic use of sedatives or opioids, and history of alcohol or illicit drug use were excluded from the study.

No pre-medications were given. Continuous monitoring of the 5-lead electrocardiogram, pulse oximetry and bispectral index (BIS) was initiated in the operating room before induction of anesthesia. A single non-invasive blood pressure reading was obtained prior to placement of an arterial line. After local anesthetic infiltration, a 20-G arterial line was placed in the radial artery for continuous monitoring of blood pressure, and for drawing the blood samples used to measure propofol concentrations. A triple-lumen central venous catheter was then inserted in the right internal jugular vein under ultrasound guidance for the continuous monitoring of central venous pressure, and for drug administration.

Anesthesia was induced with a 100 μg bolus of fentanyl, followed by propofol via target-controlled infusion, using the Schnider pharmacokinetic model on the Fresenius Kabi Injectomat TIVA Agilia syringe pump. The initial target effect-site concentration of propofol was 5 μg/mL. For muscle relaxation, a bolus dose of 0.5 to 0.6 mg/kg of atracurium was given, followed by an infusion at a rate of 0.3 to 0.6 mg/kg/h. The trachea was then intubated and the lungs were ventilated. Anesthesia was maintained using target-controlled infusion of propofol, adjusted by the anesthesiologist to keep the BIS between 30 and 60. These values were chosen because they have been shown not to be associated with awareness during cardiac surgery,[4] and also to take into account the expected decrease in BIS during hypothermic CPB.[5] Up to 1.5 mg/kg of morphine was given in titrated boluses throughout the case for analgesia.

Intraoperatively, hypertension (defined as a 20% increase in mean arterial pressure [MAP] for more than 1 minute) was managed by an intravenous infusion of glyceryl trinitrate, starting at 5 μg/min, increasing by steps of 5 μg/min every 3 to 5 minutes up to 20 μg/min, and then increasing by 10 μg/min every 3 to 5 minutes as needed. Propofol infusion was increased stepwise by an effect-site concentration of 0.1 μg/mL if the BIS was more than 60. Hypotension (defined as a 20% decrease in MAP for more than 1 minute) was managed with phenylephrine, 50-to-100 μg, or ephedrine, 5-to-10 mg. Propofol infusion was decreased stepwise by an effect-site concentration of 0.1 μg/mL if BIS was less than 30. Tachycardia (defined as heart rate above 90 bpm or a 30% increase from baseline for more than 1 minute) was managed by esmolol, 50 mg. Bradycardia (defined as heart rate below 60 bpm or a 30% decrease in baseline for more than 1 minute) was managed by a 0.6 mg bolus of atropine.

The CPB circuit was set up using the Stockert S5 Heart Lung Machine. The circuit was primed with 1 L of Ringer's lactate, 0.5 L of gelofusine, mannitol, 0.25 L, 8.4% sodium bicarbonate, 50 mL, and heparin, 5,000 IU. Excess priming solution was then discarded to make up a total priming volume of 1,300 or 1,400 mL. For patients less than 75 kg, a total prime volume of 1,300 mL was used. For patients above 80 kg, a total prime volume of 1,400 mL was used. For patients between 75 to 80 kg, the perfusionist could use either 1,300 mL or 1,400 mL.

Five milliliters of arterial blood was drawn at each of 5 time points where blood gas analyses were performed during the course of surgery:

1. 5 minutes before starting CPB
2. 15 minutes after starting CPB
3. 60 minutes after starting CPB
4. 20 minutes after rewarming
5. After coming off CPB

To avoid variation due to incomplete mixing in vivo, the samples were collected when the TCI system was at steady state between changes in target concentration. At these points, the calculated plasma and effect-site concentrations matched the target effect-site concentration set on the TCI pump. At each time point, the authors also recorded the patient's parameters, including MAP, heart rate, temperature, and BIS.

Propofol concentration in each blood sample was measured at the Analytical Toxicology laboratory at the Health Sciences

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