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Clinical Investigation

CLINICAL INVESTIGATION

Influence of Bayesian optimization on the performance of propofol target-controlled infusion

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Abstract

Background. Target controlled infusion (TCI) systems use population-based pharmacokinetic (PK) models that do not take into account inter-individual residual variation. This study compares the bias and inaccuracy of a population-based *vs* a personalized TCI propofol titration using Bayesian adaptation. Haemodynamic and hypnotic stability, and the prediction probability of alternative PK models, was studied.

Methods. A double-blinded, prospective randomized controlled trial of 120 subjects undergoing cardiac surgery was conducted. Blood samples were obtained at 10, 35, 50, 65, 75 and 120 min and analysed using a point-of-care propofol blood analyser. Bayesian adaptation of the PK model was applied at 60 min in the intervention group. Median (Absolute) Performance Error (Md(A)PE) was used to evaluate the difference between bias and inaccuracy of the models. Haemodynamic (mean arterial pressure [MAP], heart rate) and hypnotic (bispectral index [BIS]) stability was studied. The predictive performance of four alternative propofol PK models was studied.

Results. MdPE and MdAPE did not differ between groups during the pre-adjustment period (control group: 6.3% and 16%; intervention group: 5.4% and 18%). MdPE differed in the post-adjustment period (12% vs. −0.3%), but MdAPE did not (18% vs. 15%). No difference in heart rate, MAP or BIS was found. Compared with the other models, the Eleveld propofol PK model (patients) showed the best prediction performance.

Conclusions. When an accurate population-based PK model was used for propofol TCI, Bayesian adaption of the model improved bias but not precision.

Clinical trial registration: Dutch Trial Registry NTR4518.

Key words: pharmacokinetics; drug targeting; propofol

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Editor's key points

- Target-controlled infusion (TCI) systems rely on population-based pharmacokinetic models that do not adjust for individual variation.
- Point-of-care measurement of blood propofol concentrations was used to compare population-based *vs* individualized propofol titration in a prospective clinical study of cardiac surgery patients.
- Personalized propofol titration did not improve accuracy of propofol TCI in this population.

Target-controlled infusion (TCI) is a computer-controlled drug infusion technique that aims to achieve a user-defined target drug concentration in the plasma or at the effect-site. TCI systems use multi-compartment pharmacokinetic-dynamic models to estimate the infusion rates needed to reach and maintain the desired target concentration of the respective drug.[1 2] In clinical practice, TCI technology is frequently used to administer propofol.[3] The pharmacokinetics of propofol have been extensively described.[4–6] Recently Eleveld and colleagues[7] developed a general purpose three-compartment pharmacokinetic model that has acceptable performance over a wide range of patients and volunteers and can be incorporated into TCI systems.[8 9]

All current TCI systems use population-typical values for drug distribution and clearance as the basis for further estimation in the individual patient. While this approach of using population estimates to steer drug infusions in an individual can achieve clinically acceptable anaesthetic conditions, it does retain a source of error because it does not adjust for inter-individual variability. Individuals do not exactly match calculated population typical individuals because of non-modelled residual biological variability, even if covariates such as age, sex, weight and height are included in the typical values for drug distribution and clearance.[1 10 11] Sources of intra-individual variability, such as chronopharmacokinetics, are not included in current propofol PK models.[12]

A fully patient-specific pharmacokinetic model has the potential to achieve a more precisely controlled time course of plasma concentration, but this approach suffers from practical drawbacks, mostly the lack of sufficient samples in a wide range of plasma concentrations for the individual. Bayesian forecasting provides a compromise by tailoring the starting (population) model to a more patient-individualized model on the basis of measured blood samples.[13] Individualizing pharmacokinetic models using intermittent or continuous drug concentration measurements in a Bayesian approach has been demonstrated successfully in an off-line setting.[14 15] This approach has seldom been applied in clinical practice for propofol administration because a method of fast, bedside measurement of propofol concentration has not been available. Recently, point-of-care analysis of propofol has become available (Pelorus 1500, Sphere Medical, Cambridge, UK) enabling the clinician to obtain accurate propofol blood concentration information at the bedside in less than five min.[16]

The question remains if individualization of the propofol model during TCI results in a significantly better prediction of subsequent propofol plasma concentrations. In this study, our primary aim was to compare the bias and precision of classical population-based TCI propofol *vs* personalized TCI propofol administration. We used a Bayesian approach for adjustment and individualization of the propofol pharmacokinetic model using bedside measured propofol concentrations. Secondly, we compared hypnotic and haemodynamic stability before and after the adaptation as measured by processed electroencephalography and other vital signs registered during routine clinical monitoring. Additionally, we investigated the accuracy of the applied propofol pharmacokinetic model published by Eleveld and colleagues *vs* previously published models.[7]

Methods

Study management and registration

This trial was conducted at the Department of Anaesthesiology at the University Medical Center Groningen, University of Groningen, The Netherlands, in accordance with the Declaration of Helsinki, and in compliance with Good Clinical Practice and applicable regulatory requirements. Ethics committee approval was obtained (UMCG Ethics' Committee, Groningen, The Netherlands, METc 2013/374) and the study was registered in a public registry (Dutch Trial Register, NTR4518) before the start of the study. All patients provided written informed consent before participation.

Subjects

Patients between 18 and 75 yrs of age, with a BMI between 18 and 35 kg m^{-2}, ASA Physical Status Classification of I-III, undergoing elective off-pump coronary artery bypass surgery and receiving propofol per standard clinical practice were eligible for this study. Subjects were excluded in case of neurological disease (dementia, cerebral stroke, seizures), psychiatric diseases, regular intake of benzodiazepines, antidepressants, antipsychotics or anticonvulsants, regular intake of opioids, hepatic disease (Child B or higher), pregnancy or currently nursing, overt signs of alcohol abuse, contra-indications or allergies to the drugs used in the study or expected blood loss during surgery of $>$ 2000 ml.

Study execution

This study was designed as a double-blinded, prospective, randomized controlled trial. As a result of the specific screen design of the computer software used, the anaesthetist responsible for the clinical care of the patient could be blinded to the arm in which the subject was enrolled during the whole operation. Subjects were randomized to one of the two study groups using the sealed envelope technique (60 intervention *vs* 60 control group).

All subjects in both groups received standard clinical anaesthesia care and monitoring. On arrival in the operating room, a peripheral i.v. line was inserted in the subject's non-dominant hand or forearm to deliver the required drugs and fluids. Routine vital signs monitors consisting of 5-lead electrocardiography (ECG), pulse oximetry, non-invasive blood pressure (IntelliVue MX800, Philips, Eindhoven, The Netherlands) and frontal bispectral index (BIS, Covidien, Dublin, Ireland) were connected. Before induction of anaesthesia, a catheter was placed under topical anaesthesia in the radial artery of the non-dominant hand and connected to a pressure transducer to measure continuous arterial blood pressure and to draw blood samples.

Anaesthesia was induced with a bolus dose of sufentanil and propofol TCI as part of routine clinical care. The initial plasma target concentration was set by clinician discretion and TCI was started. At loss of consciousness, rocuronium was