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Adaptive pharmacokinetic and pharmacodynamic modelling to predict propofol effect using BIS-guided anesthesia

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ABSTRACT

Background and objective: Propofol is widely used for hypnosis induction and maintenance of general anesthesia. Its effect can be assessed using the bispectral index (BIS). Many automatic infusion systems are based in pharmacokinetics (PK) and pharmacodynamics (PD) models to predict the response of the patient to the drug. However, all these models do not take into account intra and inter-patient variability. An adjusted intraoperative drug administration allows faster recovery and provides post-operative side-effect mitigation

Methods: BIS evolution and surgery-recorded propofol infusion data of a group of 60 adult patients (30 males/30 females) with ASA I/II physical status were used to test a real time PK/PD compartmental model. This new algorithm tunes three model parameters (c_{e50}, γ and k_{e0}), minimizing a performance function online.

Results: The error in the BIS signal predicted by the real time PK/PD model was smaller than the error measured with fixed parameter equations. This model shows that c_{e50}, γ and k_{e0} change with time and patients, given a mean (95% confidence interval) of 3.89 (3.52–4.26) mg/l, 4.63 (4.13–5.13) and 0.36 (0.31–0.4) min^{-1}, respectively.

Conclusions: The real time PK/PD model proposed provides a closer description of the patient real state at each sample time. This allows for greater control of the drug infusion, and thus the quantity of drug administered can be titrated to achieve the desired effect for the desired duration, and reduce unnecessary waste or post-operative effects.

1. Introduction

Propofol has been applied in humans since the late 1970s [1,2] for anesthetic induction and maintenance, as well as for sedation in intensive care units [3]. In addition, propofol has anxiolytic effects and neuro-protective effects at low concentration [3]. Its advantages include rapid induction, smooth maintenance, rapid recovery, and minimal side-effects [4]. However, propofol titration in the patient must be adequate during the anesthetic procedure. Propofol is generally administered according to a manual continuous infusion scheme or using a target-controlled infusion (TCI) system based on patient models [5,6]. Automatic closed-loop systems based on proportional integral derivate controllers (PID) have demonstrated to offer high performance even compared to manual infusion [7–9]. Advanced techniques in this field include the use of robust or adaptive strategies [10–12]. In any case, the success of these techniques greatly depends on the reliability of predictions of the patient evolution during the anesthesia.

The description of a physiological process can be described using many different approaches. In pharmacology, the most widely used models are compartmental ones. This is because of their ability to easily describe distribution processes and its simplicity compared to other nonparametric alternatives used in other research areas. In the field of anesthesia with propofol, these models describe both the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug in the body. PK models describe the evolution of propofol concentration in plasma based on multi-compartmental models (see Marsh et al. [13], Kataria et al. [14], Schnider et al. [15], and Schüttler et al. [16]), while PD models describe variations in propofol concentration in the effect site according to the nonlinear Hill equation [17]. PK/PD-modelling links pharmacokinetics and pharmacodynamics to establish and evaluate dose-concentration-response relationships and consequently describe and predict the effect-time courses resulting from a drug dose. PD models usually describe drug effects according to the bispectral index (BIS) [18]. BIS is a parameter that

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measures the degree of patient depth of consciousness derived from the processed electroencephalogram. Therefore, BIS monitoring is widely used to regulate the applied anesthetic drug due to its reliability and applicability, resulting in reduced infused-drug and, consequently, mitigated post-operative side-effects [19].

PK models have parameters that are determined by patient factors, such as age, weight, height and gender. Likewise, PD models depend on c_{e50} (effect-site concentration corresponding to 50% of maximal effect) and γ (concentration steepness versus response curve), obtained by different authors from different groups of patients [18]. However, high variability has been reported in these values. Current PK/PD models set parameters depending on the patient. Parameters are then maintained constant throughout the surgery process, without regard for the different reactions patients may undergo such as blood volume variations. Consequently, accuracy in the prediction of the future short-term evolution of BIS decreases and model information may be inadequate to improve drug dosage in both, TCI and model-based closed-loop systems.

To address this problem, a method for automatic tuning of model parameters (c_{e50}, γ and k_{e0}) is proposed in this study. Other previous publications have developed simpler PK/PD models looking at individualized anesthesia care [20,21]. Our aim is to improve the model predictions minimizing the deviations from the real data collected in the operating theatre. The proposed model, the real time PK/PD (RT-PK/PD) model, was validated with data obtained from 60 patients anesthetized with propofol and remifentanil during scheduled surgery. Accuracy of the RT-PK/PD model was tested according to Schnider's model for propofol. Parameters, c_{e50}, γ and $k_{e0,}$ in the RT-PK/PD model were re-calculated every minute taking into account information from the previous 10 min of simultaneous BIS and propofol infusion recordings using Sequential Quadratic Programming. With this methodology, the model takes into account the inter-patient and intra-patient variability. Thus, administration of drug can be personalized to the needs of each individual patient.

2. Methods

2.1. Clinical protocol

The study was conducted in accordance with the ethical guidelines of the HUC Medical Research Ethics Committee (Hospital Universitario de Canarias, Spain). After written informed consent, 60 adult patients (30 males and 30 females) with ASA I/II physical status (13/17 males and 17/13 females) took part in the present study. Interventions were abdominal, gynecologic and urologic laparoscopic surgery. Patient inclusion criteria were: a) had no allergy to propofol; b) were18 years of age or older; c) did not receive prior medications; d) had no neurological disorders; e) were non-obese (BMI < 30 kg/m^2); f) had normal awake BIS. The patients (males and females) were selected to be comparable in age to avoid age-related BIS differences. Fig. 1 shows their demographic features, as well as a male/female comparison.

In the clinical protocol, the first step for all patients was the administration of midazolam 0.025 mg/kg intravenously in the operating room followed by a remifentanil infusion at 0.25 μg/kg/min which was maintained throughout surgery. The clinician was able to change it between 0.15 and 0.35 μg/kg/min if heart-rate blood pressure changed over 25% from the baseline. Anesthesia was inducted with a propofol bolus of 2 mg/kg given over 25–60 s followed by rocuronium bromide 0.6 mg/kg. Anesthesia was maintained by a 1% propofol continuous infusion whose rate was controlled by an anesthesiologist trying to maintain the BIS value

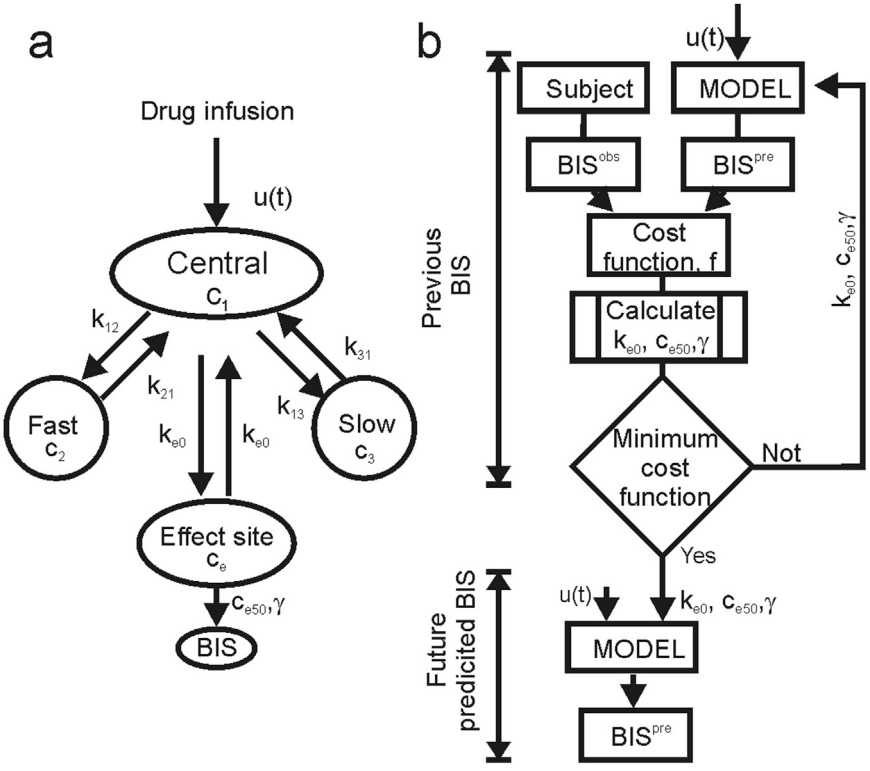

Fig. 1. Demographic features of the 60 patients taking part in this study (30 males and 30 females). The presented values are means and standard deviations. The Wilcoxon T-test was used to compare male and female patient populations: ns (not significant) $p > 0.05$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Lean body mass (LBM).