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Clinical testing of propofol geriatic dose for sedation designed via *in silico* trial

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ABSTRACT

The geriatric population shows significant physiological changes due to aging and the multiple co-morbidities that they often present. Conventionally the propofol sedation dose for patients older than 65 years is 80% of the adult dose. We performed an *in silico* trial for elderly population and the results showed that the necessary simulated dose of propofol was lower than the conventional dose; therefore, a clinical trial was implemented to test three different propofol doses, two of them lower than the conventional dose, during a pacemaker implantation. The clinical trial showed that there was no clinical difference between the effects of the doses. A BIS monitor was used to measure the level of sedation, which proved to be adequate and well maintained by all patients. All the patients maintained an acceptable level of sedation, measured by a BIS monitor. Since propofol has some dose-dependent secondary effects, the use of lower doses, especially the ones designed for this age group, helps to avoid them.

1. Introduction

Sedation is a drug-induced depression of consciousness used to help the patient tolerate unpleasant procedures. There are several depths of sedation, as shown in Table 1. **Minimal sedation** or anxiolysis allows the patient to respond to verbal stimulation, while the cognitive functions may be impaired. **Moderate sedation** has as main characteristics a purposely response to verbal commands from the patient and an unaffected cardiovascular function; usually spontaneous ventilation is adequate at this sedation stage. During **deep sedation** the patient cannot be easily aroused but responds purposefully to painful stimulation. The ventilatory function may be impaired but the cardiovascular function is usually maintained [1].

Propofol is an intravenous short-acting anesthetic agent used for sedation, induction and maintenance of general anesthesia. Usually it can induce hypnosis within 40 seconds once it has been injected [2], and it presents several advantages over inhaled anesthesia, like less post-anesthetic nausea, rapid induction and emergence [3]. Propofol is infused via pump during the maintenance phase to maintain a stable plasma concentration because it has a short half-life of the blood–brain equilibration, approximately 1 to 3 minutes [2]. This feature also allows the physicians to evaluate rapidly the cognitive state of the patient because of fast emergence.

In the clinical practice, the anesthesiologist calculates the propofol dose according to the regime given by pharmaceutical companies. Those regimens are based mostly on the patient's weight. During the surgical procedure the

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Table 1 – BIS values correlated to clinical observations, depth of anesthesia and EEG.

BIS	Depth of anesthesia	Clinical observations	EEG
100–90	Awake	Responsive patient	β waves (14–30 Hz)
90–80	Minimal sedation	Anxiolysis allows the patient to respond to verbal stimulation	α waves (9–13 Hz)
80–70	Moderate sedation	Patient responds purposefully to verbal commands	α waves (8–10 Hz)
70–60	Deep sedation	Patient cannot be easily aroused but responds to painful stimulation	θ waves (4–8 Hz)
60–40	General anesthesia	Patient does not respond to any surgical stimulation	δ waves (1–3 Hz)

anesthesiologist can adjust the dose based on the patient's response and his own clinical experience; however, there is a large inter-patient variability of the parameters that can lead to a possible under- or over-dosing responsible for perioperative awareness or prolonging delay of recovery [4]. The inter-patient becomes evident when comparing different age groups (from children to elderly people). It has been well established that age and weight are significant covariates of the pharmacokinetic model of propofol [5].

In the elderly (population older than 65 years) the anesthesia presents more risks compared to younger people because they do not only present age-related physiological changes, but also changes related to the multiple co-morbidities they often show [6]. The weight-normalized dose for the elderly is always lower than for adults [5], plus there are at least four important aspects to consider when administrating a propofol anesthesia or sedation to the this group of people. For example:

1. Propofol is highly protein bounded, and since protein is lower in the elderly, their clinical response can be intensified because a great amount of unbounded propofol would circulate freely [6].
2. The increased distribution volume of propofol due to a fat distribution change in the elderly will prolong the propofol action because of the high lipid solubility it has [7].
3. A propofol bolus into contracted blood volume will produce higher initial plasma concentration [6].
4. Propofol sensitivity is increased in the elderly population [8].

Propofol has a dose-dependent decreasing effect on the heart contractibility, and consequently blood pressure is reduced [9]; for example, a 2–5 *mg/kg* dose administered in bolus can decrease up to 30% the blood pressure, and therefore it is necessary to use the minimal effective dose to avoid the secondary events, mainly in the geriatric population.

A common surgical procedure in older persons is the pacemaker implantation; it is indicated to patients with bradycardia (low heart rate), which induces low blood pressure and poor tissue oxigenation. A pacemaker is an implantable electronic device that helps maintain an adequate heart rate by prompting the heart to beat at a normal rate with an electrical stimulation. There is no international consensus on the anesthesia technique needed for the pacemaker implantation, so the selection is made by a medical committee in each hospital [10]. Since it is a short procedure, moderate sedation with local anesthesia is often used, and the conventional sedation dose of propofol for geriatric patients is 20 to 60 *μg/kg/min*; it represents 80% of the adult dose [2,11].

A tool used by the anesthesiologists is the anesthesia monitor, which offers an indirect measurement of the depth of the anesthesia based on the analysis of electroencephalogram (EEG). The use of the anesthesia monitors allows the physician to individualize the dose of drugs administered to the patient in order to minimize the secondary effects that every drug has [12]. There are several anesthesia monitors, like BIS Vista Monitor by Medtronic (Dublin, Ireland), NeuroSense Monitor by CleveMed (Cleveland, USA), and Entropy Monitor by General Electric (Connecticut, USA). This study considers the BIS Monitor to measure the hypnosis level as feedback for a Proportional Derivative Controller (PI) used in the *in silico* trial to calculate the propofol dose, and for the clinical trial because it is the one that offers the most clinical information about the benefits of a monitored anesthesia according to the UK Agency for Healthcare Research and Quality, and the US National Institute for Health and Care Excellence [13,14].

BIS was designed to correlate with hypnotic clinical endpoints (sedation, lack of awareness, and memory) and to track changes in the effects of anesthetics on the brain [15]. The BIS Monitor displays a number between 0 and 100 based on the analysis of the real-time EEG. A 0 BIS value indicates an isoelectric EEG signal, while a 100 value indicates a fully awake patient. The values between 90 and 60 are considered sedation, whereas values between 40 and 60 are considered as an adequate general anesthesia, as can be seen in Table 1.

In this study we propose an 8.3 *μg/kg/min* propofol dose for pacemaker implantation procedure for patients older than 65 years, based on a simulation of this specific age group. The BIS target considered is $BIS_t = 70$ for moderate sedation. The dose was validated in a pilot clinical study.

2. Mathematical model

The dynamic of a drug can be described by a pharmacokinetic–pharmacodynamic (PK–PD) model. The pharmacokinetics describes the drug distribution in the body, and the pharmacodynamics part describes the effect the drug has with respect to its concentration in blood. There are several models for propofol dynamics; in this study, we considered the Schnider PK–PD [8,16] because it is the most complete model, since it considers age, weight, height and lean body mass as covariates [17].

The pharmacokinetics model is shown in Eq. (1) [16], while the pharmacodynamics are described in Eq. (2) [8]. The plasma–effect-site equilibration rate constant (K_{e0}) relates the pharmacokinetics and pharmacodynamics of a given drug. For propofol, it was originally considered $K_{e0} = 0.456$, but the observations of Sepúlveda and Mora concluded that age is also an important covariate for K_{e0}; this relation is shown in Eq. (3) [17]. The relationship between propofol and BIS is shown in Eq. (4).