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Drug Interaction Between Propofol and Remifentanil in Individualised Drug Delivery Systems

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Abstract: Optimal and safe control of drug delivery systems with continuous infusion protocol is of key importance to avoid over-dosing or under-dosing of the patient. Advanced model based control techniques are able to predict and regulate the amount of drugs given to the patient but they rely heavily on patient model. This paper discusses and investigates the effects of synergistic drug interaction between Propofol (hypnotic) and Remifentanil (opioid) and its requirements on the robustness and stability of the closed loop system.

Keywords: drug delivery systems, interaction modeling, personalized healthcare

1. INTRODUCTION

Individualised drug delivery systems during general anesthesia represent an important step forward in clinical practice. The anesthesiologist has to provide specific care during surgery or maintenance for the three main components of general anesthesia (i.e. neuromuscular blockade, hypnosis and analgesia) (Absalom et al. (2011); Struys et al. (2003); Bailey and Haddad (2005)). In order to achieve adequate levels of anesthesia the anesthesiologists must adjust several parameters. An overview of the inputs and the outputs of the anesthesia paradigm is depicted in figure 1.

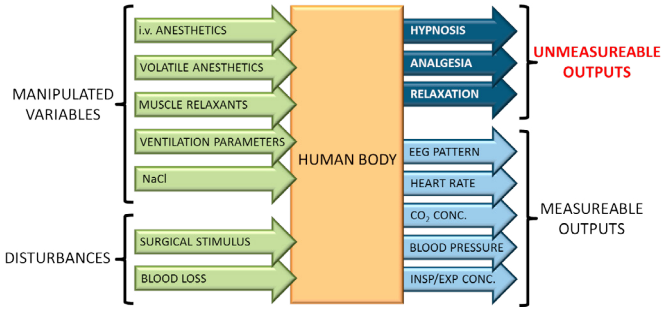

Fig. 1. Oversimplified overview of the anesthesia paradigm.

Nowadays, in clinical practice, open-loop systems such as target controlled infusion systems are used. The open-loop control strategies rise inaccuracies in drug delivery due to the fact that they are based on generic population models which obviously diverge from the real patient response. The role of the anesthesiologist is to tackle this difference by adequately changing the drug infusion rates. To ease the burden of this crucial role, a solution may be given by introducing model based closed-loop control techniques. These strategies are based on the availability of a patient model and then the role of the anesthetist will be freed of some regular tasks so that he can focus more on the state of the patient. From the patient-individualized control point of view, pharmacodynamics models capture the inter- and intra-patient variability and pose most challenges for control (i.e. highly nonlinear characteristic) (Schnider et al. (1998, 1999)). This is mainly due to the nonlinearity introduced by the multiple drug interaction model and significant unmeasurable disturbances present in the system (noxious stimuli). A solution for optimal control strategy of general anesthesia has not yet been found. Closed-loop control strategies for depth of anesthesia (DOA) regulatory systems are nowadays investigated by several research groups worldwide, and a brief overview is given below, within the physical limits of this paper.

Neuromuscular blockade (NMB) level is measured from the electromyography signal obtained by electrical stimulation. Control of NMB is done my means of continuous infusion of a muscle relaxant. During the last two decades several automatic control strategies for NMB have been developed (Teixeira et al. (2014)).

Quantification of the hypnotic agent can be done by means of availability of various indexes which are derived from signals such as electroencephalogram (EEG). For instance, bispectral (BIS) index is derived form EEG and it has been shown to have a high sensitivity and specificity to measure the drug effect (Struys et al. (2003)). Currently, BIS signal is used as a reference for closed loop purposes (Ionescu et al. (2008)).

The third component, i.e. analgesia, is still to be demystified (Ionescu et al. (2014)). An accurate and objective measurement of the patient's response to analgesic drug is still lacking. However, when BIS is known, a suitable

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interaction model between hypnotics and analgesics might be helpful to simultaneously control both components of depth of anesthesia.

Various interaction models between intravenous hypnotics and analgesics have been described (Bouillon et al. (2004)). Pharmacodynamic (PD) response surface models have been developed to quantitatively describe the relationship between two (or more) drug concentrations with their corresponding combined clinical drug effect. Until now, these interaction models have not been effectively used in closed-loop control of depth of anesthesia.

The role of this paper is to illustrate the degree of nonlinearity present in case of inter- or intra- patient variability and how it affects the performance of the closed loop system. For this purpose, we make use of the PD model for synergy between Propofol (hypnotic drug) and Remifentanil (opioid drug) and simulate various situations. Closed loop control elements are enumerated and motivated.

The structure of the paper is the following: *Section 2* describes the hypnotic and opioid agents. In this section the pharmacokinetic and pharmacodynamics of the two drugs are presented. This is followed by *Section 3* where the interaction between the hypnotic and opioid agents is analyzed. In this section some simulation results are presented and discussed. *Section 4* focuses on the control problem in general anesthesia. In this section an overview of the state of the art is presented and the importance of drug interaction in developing an optimal control strategy for general anesthesia is tackled.

2. HYPNOTIC AND OPIOID AGENTS

Before discussing the PD properties of the hypnotic and opioid drug a schematic representation of a three compartmental model is presented in figure 2.

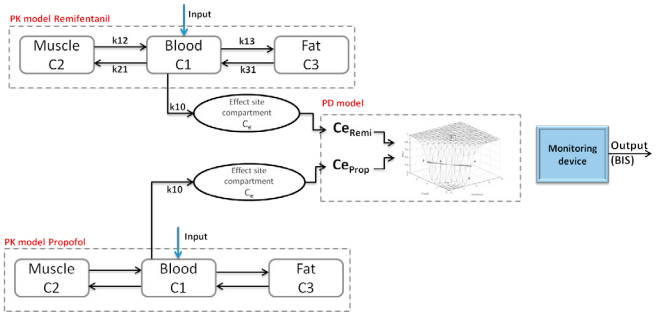

Fig. 2. A schematic representation of a three compartmental PK-PD model of the patient.

In this figure $k12$, $k21$, $k13$, $k31$, $k1e$ represent the inter-compartmental rate constants, $k10$ represents the clearance rate from compartment 1. Concentrations in each compartment are denoted by C_1 - compartment 1, C_2 - compartment 2, C_3 - compartment 3, C_e - effect site compartment.

During general anesthesia the patient receives a hypnotic drug (eg. Propofol) to ensure loss of consciousness and absence of post-operative recall of events occurred during surgery. Additionally, the patient receives a dose of opioid drug (eg Remifentanil) to ensure the absence of pain. Some reasons why Remifentanil is increasingly used in combination with Propofol in todays clinical practice are listed below:
i) recently released sophisticated drug delivery systems such as target-controlled infusion (Egan and Shafer (2003)) allow for precise titration and safe administration in patients with very narrow therapeutic margin;
ii) some new clinical applications are currently growing, such as Remifentanils use as the sole agent for sedation during painful procedures in patients breathing spontaneously, or as the analgesic component in intensive care sedation;
iii) simultaneously, Remifentanil has permitted important scientific research, leading to better understanding of post-operative hyperalgesia and acute tolerance to the analgesic action of opioids.

Remifentanil equilibration half-time between plasma and the effect compartment has been modelled using continuous EEG and is fast (0.1-1.5 min) (Glass et al. (1994)). Transfer to central nervous system competes with distribution processes and time to peak effect should be considered instead. During intravenous administration, the PK properties of Propofol are characterized by an initial distribution half-life of 2 - 8 min, with the slow distribution half-life ranging from 30 - 70 min. This depends on several factors such as: method of administration (i.e. bolus or infusion dosing) age, disease, body weight, gender, etc. (Gepts et al. (1988); Shafer and Varvel (1991); Schnider et al. (1998, 1999); Kirkpatrick et al. (1988)). These properties make these two drugs ideal candidates for continuous infusion DOA regulatory systems.

Propofol concentration for loss of consciousness is reduced by 25% in the presence of Remifentanil (i.e. 6 ng/ml) (Nieuwenhuijs et al. (2003); Manyam et al. (2006); Albertin et al. (2006); Bouillon et al. (2004); Kern et al. (2004); Drover et al. (2004); Mertens et al. (2003); Fechner et al. (2003)). Hence, a synergistic interaction with hypnotics is present in the reaction of Remifentanil. The minimal hypnotic concentration required to control noxious stimuli is markedly reduced (50-60%) when a lower concentration of opioid is added (Manyam et al. (2006)). Intermediate opioid concentrations allow a further reduction in hypnotic requirement of 15-20%. The combination which allows the quickest recovery is shifted towards high Remifentanil, low hypnotic concentrations. Typically, Remifentanil concentrations must be above 8 ng/ml for laryngoscopy or incision. This synergistic interaction is also observed for the hypnotic effect, but is of a lower magnitude. Without opioid, the hypnotic concentration required for loss of consciousness is lower than the one to prevent response to noxio us stimuli.

3. DRUG-INTERACTION ANALYSIS

In clinical practice the anesthesiologist takes advantage of the synergy between drugs. One such advantage is given by the fact that the therapeutic goals of the anesthetic drugs can be achieved faster and with less toxicity. Another advantage is that when combination of drugs is used, also a faster recovery is achieved in comparison to the case when individual drugs in higher doses are administered (**?**). The