A physiologically-based model to predict individual pharmacokinetics and pharmacodynamics of remifentanil

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ABSTRACT

Remifentanil based anesthesia is nowadays spread worldwide. This drug is characterized by a rapid onset of the analgesic effects, but also by a rapid onset of the side effects. For this reason, the knowledge of the remifentanil concentration in the human body is a key topic in anesthesiology. The aims of this work are to propose and validate a physiologically based pharmacokinetic model capable to predict both the pharmacokinetics and pharmacodynamics of remifentanil, and to take into account the inter-individual differences among the patients (such as height and body mass). The blood concentration of remifentanil has been successfully simulated and compared with experimental literature data. The pharmacodynamics, in terms of effect of remifentanil on minute ventilation and electroencephalogram, has been implemented in this model. Moreover, the remifentanil concentration in various organs and tissues is predicted, which is a significant improvement with respect to the traditional compartmental models. The availability of the model makes possible the prediction of the effects of remifentanil administration, also accounting for individual parameters.

1. Introduction

Remifentanil is widely used both as induction and maintenance agent in anesthesia (Freeman et al., 2015), and in the intensive care unit for postoperative pain management and analgosedation (Mattia et al., 2006). Remifentanil is a fentanyl derivative, with an ester bond which undergoes rapid hydrolysis by non-specific tissue and plasma esterases (Thompson and Rowbotham, 1996). Different attempts have been made to evaluate in vitro the hydrolysis rate of remifentanil, and to determine the influence of operating parameters, such as the effect of the temperature on degradation, the effect of the enzymes origin (Piazza et al., 2016), and the type of enzyme responsible of the hydrolysis (Davis et al., 2002). Due to its quick esterase metabolism, remifentanil is characterized by an ultra-short duration of action (Duthie, 1998). The main metabolic product of the ester hydrolysis is a carboxylic acid derivative (GR90291), which is eliminated mainly by the kidneys, and is certainly less potent than remifentanil and alfentanil (Hoke et al., 1997).

Due to the increasing interest of the scientific community on remifentanil properties, its pharmacokinetics has been widely studied (Egan, 1995). These studies allow determining the main pharmacokinetic parameters, such as the volume of distribution, which represents

the theoretical volume necessary to contain the same drug concentration observed in plasma, and the clearance, which is the volume of plasma from which a substance is completely removed per unit of time.

Mathematical modeling has been extensively used during the last decades as a valid tool to describe the drug concentration evolution in the human body after a drug administration (Grassi et al., 2011; Lamberti, 2015). In case of the modeling of remifentanil administrations, a compartmental approach is usually adopted. Compartmental models schematize the human body into one or more interacting compartments. The simplest approach is a one-compartment pharmacokinetic model (Hoke et al., 1998), in which the remifentanil concentration depends on the drug infusion rate and on the metabolic rate of remifentanil, which is metabolized in GR90291. A two-compartments infusion model can also be used to determine the concentration profiles of remifentanil and its metabolite (Hoke et al., 1997). A more complex approach is the three compartmental modeling, in which the body is schematized into three compartments: a central one, simulating the plasma, and two peripheral compartments simulating organs and tissues either highly or scarcely perfused by blood (Cascone et al., 2013).

In the last decades, in order to describe the ADME (Absorption, Distribution, Metabolism, and Excretion) phenomena, which determine

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the drug's fate once it is administered, several pharmacokinetic (PK) models have been proposed. In order to build a PK model, two main approaches can be followed: the 'empirical' approach and the 'mechanistic' approach (Lamberti et al., 2016). Usually in the empirical PK modeling the number of compartments, in which the body is schematized, is limited and they are related to different portions of the body. Despite the parameters in these models are often not corresponding to physiological variables, two of the main advantages are their simplicity and the reduced number of parameters. On the other side, the mechanistic PK models are based on a realistic compartmental structure reflecting the real physiology, and the compartments are interconnected by a mass flow scheme. These models are usually identified as "physiologically based pharmacokinetic" (PBPK) models, and they have been extensively used for several studies (Bischoff, 1987; Brown et al., 1997; McDougal, 1991). The PBPK models are based on the hypothesis that the body (human or animal) features can be described by an adequate number of interacting compartments, which simulate the anatomical and physiological functions of the organs and tissues they represent. These models are founded on the mechanistic concept that the drug transport is carried on by the blood circulation system.

This paper proposes and validates a PBPK model that describes the pharmacokinetics and pharmacodynamics of remifentanil administered intravenously by either infusion or bolus, and takes into account the inter-individual differences in the effect of that administration.

2. Materials and methods

2.1. Model description

Fig. 1 shows the model scheme used in this study. The boxes in the figure represent the compartments in which the human body is divided. The model features eight compartments: three of them represent the gastrointestinal (GI) tract (stomach, small, and large intestine), and interact with the gastrointestinal circulatory system compartment, which simulates the circulatory system around the GI tract. The other five compartments represent the liver, the plasma, the poorly perfused tissues/organs, and the highly perfused tissues/organs. The last two

compartments reproduce tissues and organs that are (i) scarcely perfused by blood, such as skin, adipose tissue, bones, and muscles, and (ii) highly perfused ones, such as kidneys, brain, and spleen. In Fig. 1, dashed arrows represent the administration routes, which can be alternatively intra-venous (IV) or oral (per os, PO). The continuous arrows are the connections between the compartments, which represent the drug distribution pattern, and the red arrows are the drug excretion routes, which can be due to elimination or metabolization of the drug. The drug concentration evolution along the human body can be described by mass balance equations, one for each compartment, together with the appropriate initial conditions. The equations set was proposed by (Di Muria et al., 2010) and refined by (Abbiati et al., 2016). The version proposed here is a full version of the model, named PBPK, whereas in (Abbiati et al., 2016) a simplified version has been used, mPBPK. The present set is:

$$\frac{dC_{GL}(t)}{dt} = \frac{PO(t)}{V_{GL}} - F_{GL}(t) \tag{1}$$

$$\frac{dC_{SIL}(t)}{dt} = -C_{SIL}(t) \cdot k_{A,SIL} + F_{GL}(t) \cdot \frac{V_{GL}}{V_{SIL}} - F_{SIL}(t) + C_{GICS}(t) \cdot \frac{k_{CA,SIL}}{R} \cdot$$
$$\frac{V_{GICS}}{V_{SIL}} \tag{2}$$

$$\frac{dC_{LIL}(t)}{dt} = -C_{LIL}(t) \cdot k_{A,LIL} + F_{SIL}(t) \cdot \frac{V_{SIL}}{V_{LIL}} - F_{E,LIL}(t)$$
$$+ C_{GICS}(t) \cdot \frac{k_{CA,LIL}}{R} \cdot \frac{V_{GICS}}{V_{LIL}} \tag{3}$$

$$\frac{dC_P(t)}{dt} = -C_P(t) \cdot \left(\frac{k_{P-PT}}{R} + \frac{k_{P-HO}}{R} + \frac{Q_{HA}}{V_P} + \frac{Q_{PV}}{V_P} \right) + C_{PT}(t) \cdot k_{PT-P} \cdot \frac{V_{PT}}{V_P}$$
$$+ C_L(t) \cdot \frac{Q_{HV}}{V_P} + C_{HO}(t) \cdot k_{HO-P} \cdot \frac{V_{HO}}{V_P} - C_P(t) \cdot \frac{k_E^P}{R} - C_P(t) \cdot \frac{CL_K}{V_P}$$
$$+ \frac{IV(t)}{V_P} \tag{4}$$

$$\frac{dC_{PT}(t)}{dt} = -C_{PT}(t) \cdot (k_{PT-P} + k_E^T) + \frac{C_P(t)}{R} \cdot k_{P-PT} \cdot \frac{V_P}{V_{PT}} \tag{5}$$
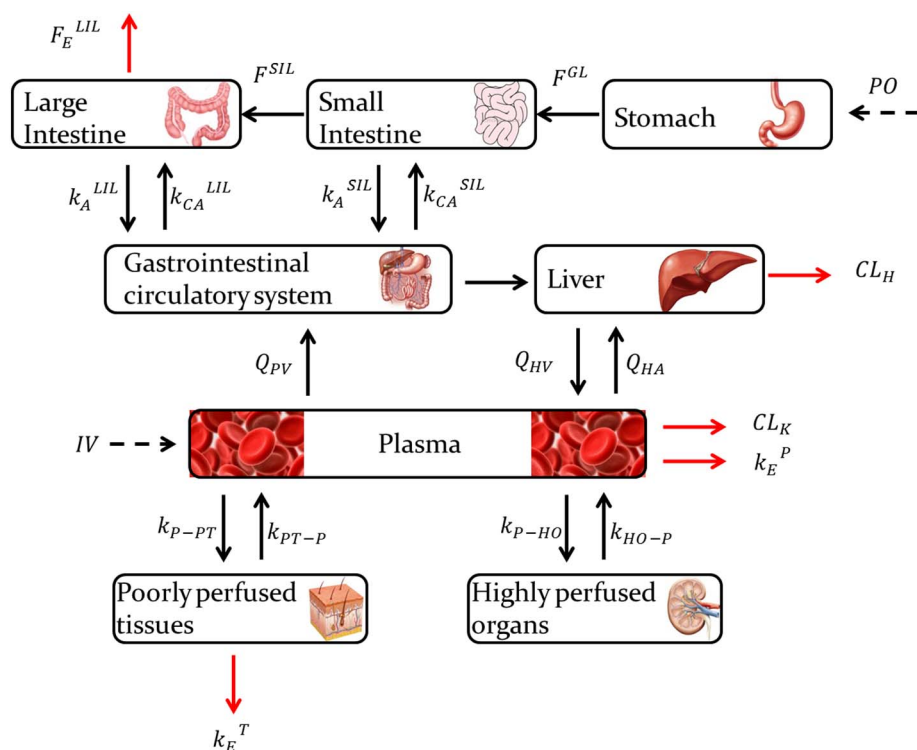

Fig. 1. Schematic of the PBPK model proposed. The boxes represent the compartments of the model, the black arrows the interactions among the compartments. The two dashed arrows (IV and PO) represent the two possible administration routes, the red arrows the excretion routes from the body. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)