Remifentanil pharmacokinetics: a fractional order modeling approach

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Summary. This paper presents a first attempt in using fractional calculus to model Remifentanil pharmacokinetics. Remifentanil is a opioid characterized by a fast time of action. Its pharmacokinetic and pharmacodynamics properties makes Remifentanil a very interesting molecule in the field of anesthesia. However a complete and versatile pharmacokinetic description of Remifentanil still lacks. A three-compartmental model using fractional calculus has been developed to describe the PK of Remifentanil when a bolus injection is used.

Introduction

The standard modeling strategy which has been commonly used to describe the relationships between anesthetic inputs and patient output indicators (or effects) is that of compartment models. Pharmacokinetic (PK) compartment models are widely used as means of predicting the disposition of drug in the body by modeling the simultaneous diffusion of drug through body tissues and the drug flow blood. Most drugs are characterized by models containing a central compartment, which typically has a drug concentration corresponding to that of the blood, and peripheral compartments that represent groupings of internal organs and fatty tissues of the body. A virtual effect compartment may be included, typically consisting of a nonlinear pharmacodynamic (PD) model plus a first order linear time invariant system that is used to reflect the time-lag in the patient response to anesthesia (see [1, 2] for details).

Fractional calculus plays an important role in modeling many phenomena in physics, chemistry, but also in the engineering area [3, 4]. In the field of medicine fractional-order calculus is an emerging tool for pioneering steps [5]. This research field promises to serve a whole range of applications with a large impact on the progress of science and welfare. The last decades have shown an increased interest of the research community to employ parametric model structures of fractional-order for analyzing nonlinear biological systems [6, 7]. However, the theoretical concepts of fractals, chaos and multi-scale analysis have not yet been employed in the field of anesthesia, where the electrical activity of the brain is altered by the effects of hypnotic and analgesic drugs. Initial attemps have been done by our group and the work presented in this paper is their sequel [8, 9].

Modelling

In the three compartmental modeling, three compartments describe the fate of a drug once administered: the central compartment, which represents the plasma; the highly perfused compartment, which represents the organs and tissues highly perfused by the blood; and the scarcely perfused compartment, which represents the organs and tissues scarcely perfused by blood. A schematic of the model is shown in figure 1. Using the pharmacokinetic model proposed in [8, 9], fractional calculus has been used to show drug concentration profile of Remifentanil in each compartment (1)-(2).

$$\tau_1^{n_1-1} D_t^{n_1} q_1(t) = K_{21} q_2(t) + K_{31} q_3(t) - K_{12} q_1(t) - K_{01} q_1(t) + U(t) \tag{1}$$

$$\tau_2^{n_2-1} D_t^{n_2} q_2(t) = K_{12} q_1(t) - K_{21} q_2(t); \tau_3^{n_3-1} D_t^{n_3} q_3(t) = K_{13} q_1(t) - K_{31} q_3(t) \tag{2}$$

where: τ_1, τ_2 and τ_3 represent the characteristic times for compartment 1, respectively compartment 2 and 3. The introduction of τ leads to the dimensional homogeneity of fractional rate equations. Considering the initial conditions $q_2(0) = d_2 = 0$, $q_3(0) = d_3 = 0$ and $q_1(0) = d_1 = bolus\ injection$. After multiplying (1) and (2) with $\tau_1^{-n_1+1}$, $\tau_2^{-n_2+1}$ and $\tau_3^{-n_3+1}$ redefining the model coefficients and assuming $n_1 = n_2 = n_3 = n$ for maintaining the mass balance, the model becomes:

$$D_t^n q_1(t) = k_{21} q_2(t) - k_{12} q_1(t) - k_{01} q_1(t); D_t^n q_2(t) = k_{12} q_1(t) - k_{21} q_2(t) - k_{02} q_2(t) \tag{3}$$

$$D_t^n q_3(t) = k_{13} q_1(t) - k_{31} q_3(t) - k_{03} q_3(t) \tag{4}$$

with: $\tau_1^{n_1-1} = \tau_2^{n_2-1} = \tau_3^{n_3-1}$, $k_{12} = K_{12}/\tau^{n_1-1}$, $k_{02} = K_{02}/\tau^{n_2-1}$, $k_{21} = K_{21}/\tau^{n_1-1}$, $k_{01} = K_{01}/\tau^{n_1-1}$, $k_{31} = K_{31}/\tau^{n_3-1}$ and $k_{03} = K_{03}/\tau^{n_3-1}$
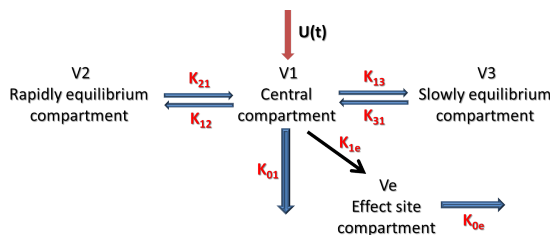

Figure 1: Three-compartment model representing the basic pharmacokinetic processes that occur after intravenous drug administration. U, dosing scheme as a function of time; k_{01}, rate constant reflecting all processes acting to irreversibly remove drug from the central compartment; K_{12}, K_{13}, K_{21}, K_{31} and K_{1e} represent the inter-compartmental rate constants; $V1$, represents the volume of the central compartment, $V2$ and $V3$ represent the volume of the peripheral compartments (respectively muscle and fat).

Results and discussions

In this paper we consider a three-compartmental model as the one depicted in figure 1. Assuming that the $q_i(t) = v_i c_i$, for $i = 1,2,...,$ denote the amount of a drug in a specific compartment. Therefore, c_i is the concentration of a drug, given by $c_i = q_i/v_i$ and v_i is the volume of compartment i. K_{ij} represents the given constants of elimination from compartment i to compartment j. The first compartment represents the place where the drug is applied (plasma), second compartment represents the target organ (muscle) and the third compartment represents the fat. The central compartment that represents the blood and it has a volume, the peripheral compartment represents the muscle and is assumed to reach steady-state equilibrium quickly. The second peripheral compartment with volume V_3 represents the fatty tissues. It is assumed that the infused drug will mix immediately in the volume space of the central compartment (e.g., the heart for the intravenous injections and the lung for inhaled anesthetics). The drug concentration in the central compartment then decreases due to metabolic clearance and distribution to other compartments. From figure 2, we can conclude that the order of the
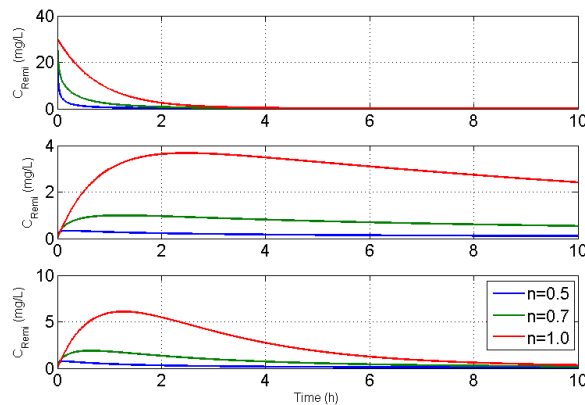

Figure 2: Remifentanil concentration profile in compartment blood, muscle and fat.

derivatives n determines the decay of the numerical solution. Notice that for $n < 1$, the decrease of the amount in compartment 1 (plasma) is faster than in the integer order model ($n = 1.0$). This is a very important property of the fractional-order model that can be used to capture inter-patient variability. In our simulation study, the value for k_{12} and k_{21} are calculated as follows: $k_{12} = \frac{k_{01}}{v_1}, k_{21} = \frac{k_{02}}{v_2}, k_{31} = \frac{k_{03}}{v_3}$ where v_1 is the volume of blood, v_2 is the muscle volume, v_3 is the fat volume and k_{01}, k_{02}, k_{03} represent the clearance for the three compartments. The blood volume is $v_1 = 4.27$ and the fat volume is $v_3 = 40L$ while v_2 and and clearances are calculated as follows: $v_2 = 18.9 - 0.391(age - 53)$, $k_{01} = 1.89 + 0.0456 * (weight - 77) - 0.0681 * (lbm - 59) + 0.0264 * (height - 77)$, $k_{02} = 1.29 - 0.024 * (age - 53)$, $k_{03} = 0.595 - 0.007 * (age - 53)$.

Conclusions

From the results obtained in this paper we can conclude that fractional calculus is a useful tool in pharmacokinetics and pharmacodynamics, especially for modeling datasets. The degree of resistance of the patient to the drugs has a great influence on the amount of drugs necessary during surgery to maintain an adequate level of unconsciousness and analgesia. The information gathered from this can be used to adapt the patient rates for Propofol as well for Reminfentanil. In this way, a improvement of patient's safety, comfort and the possibility of avoiding the cases of overdoses and awareness during surgery can be avoided. The model captures the individual patient response and gives information to the anesthesiologist regarding the necessary dose of drug to obtain the desired level of anesthesia.

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