Galeno - Modeling and Control for Personalized Drug Administration

Interaction Model

Propofol + Remifentanil

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The most common models for the effect concentration of a drug are compartmental systems.

A system is a set of interconnected elements that are dependent on each other and form a unit that has specific characteristics and functions. Each system admits states that are defined as a set of variables capable to describe the system in any instant of time. Systems can be classified as continuous or discrete-time systems according to the continuous or discrete nature of the time-line over which their variables are defined. Also, systems can be classified as open, closed or isolated. An open system can exchange matter or energy with its surroundings, while a closed system can only exchange energy, but not matter with its surroundings. In contrast, an isolated system cannot exchange neither energy nor matter.

Compartmental systems are widely used to model the pharmacodynamics and pharmacokinetics of intravenously administered drugs. A compartmental system is a system that has a finite number of homogeneous, well-mixed subsystems, called compartments that exchange material among them and with the environment. These models are based on the principle of mass conservation.

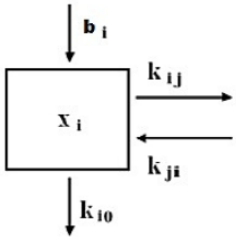

Figure 1 - Representation of a compartment.

Fig. 1 represents a compartment, in this case compartment i; here b_i represents the input rate (the drug infusion rate to a patient if we consider the specific case of anesthesia), x_i is the concentration of material in the compartment i, k_{ij} represents the rate of mass transfer from compartment i to compartment j, and k_{i0} represents the rate of material output from compartment i to the environment. The input to compartment i, is given by $b_i.u$, where u is the total system input. This input, the state x_i and all the rate constants are assumed to be non-negative. At each time instant t, the variation $\dot{x}(t)$ is the concentration of material in compartment i.

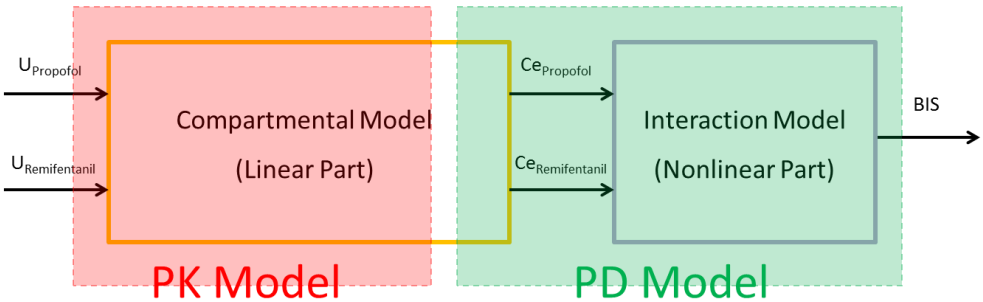

Figure 2 - Wiener model for the interacion model of propofol and remifentanil

Compartmental Model (Linear Part)

The compartmental model describing the linear part of the two drugs, propofol and remifentanil, are described through a 3-compartmental model (Figure 2), according to the literature described in the Marsh or Schnider models for propofol, and Minto model for remifentanil.

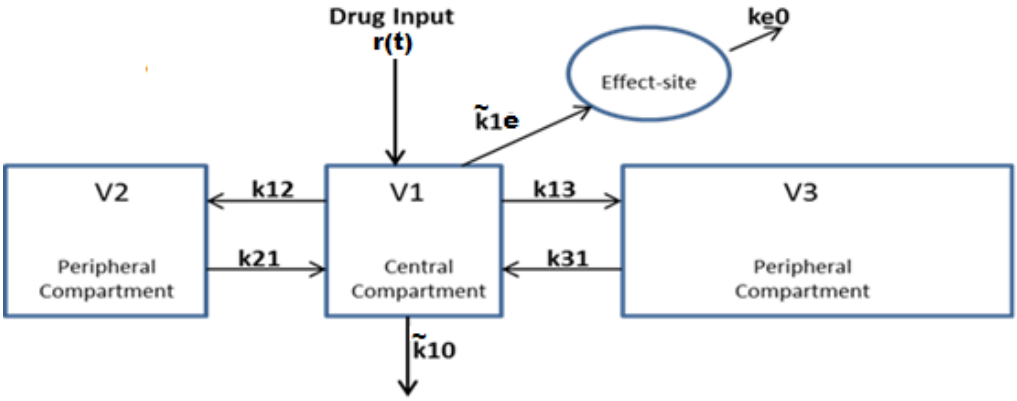

Figure 3 - Compartmental Model of the Marsh Model for Propofol.

Interaction Model (Nonlinear Part)

The objective of the interaction model is to describe the relationship between the drug effect concentrations of propofol and remifentanil and the corresponding BIS value obtained.

First the concentrations are normalized to their respective potencies (EC_{50p} and EC_{50r} for propofol and remifentanil respectively), i.e. the effect concentrations at half the maximal effect:

$$U_{prop} = \frac{Ce_p(t)}{EC_{50p}}$$

$$U_{remi} = \frac{Ce_r(t)}{EC_{50r}}$$

where Ce_p and Ce_r are the respective effect concentrations of propofol and remifentanil. To describe the additive interaction, the "effective" concentration is the sum of the individual concentrations normalized, so the BIS can be described as:

$$BIS = BIS_0\left(1 - \frac{U_{prop} + U_{remi}}{1 + U_{prop} + U_{remi}}\right)$$

where BIS_0 is the BIS value at zero concentrations (maximal value measured by the BIS monitor, usually is equal to 97.7 due to monitor restriction). Deviation from a purely additive interaction is modeled by changing the potency of the drug mixture depending on the ratio of the interacting drugs:

$$\theta = \frac{U_{prop}}{U_{prop} + U_{remi}}$$

By definition, θ ranges from 0 (remifentanil only) to 1(propofol only). Thus, the concentration-response relationship for any ratio of the two drugs regardless of the type of interaction can be described as:

$$BIS = BIS_0\left(1 - \frac{\left(U_{prop} + U_{remi}\right)/U_{50(\theta)}^{\gamma}}{1 + \left(U_{prop} + U_{remi}\right)/U_{50(\theta)}^{\gamma}}\right)$$

where γ is the stepness of the concentration-response relation, and $U_{50(\theta)}$ is the number of units (U) associated with 50% of maximum effect at ratio θ. According to [1] $U_{50(\theta)}$ can be described as:

$$U_{50(\theta)} = 1 - \beta_{2.U50}\theta + \beta_{2.U50}\theta^2$$

Bibliography

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[2] - Minto et al, ”**Appendix 1: Review of Common Drug Interaction Models "**, Drug Interaction Models in Anesthesia: Web Supplement, 2000.

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