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Essay

From pharmacokinetics to pharmacodynamics – Are we ready for 3D software?☆



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ABSTRACT

The relationship between the dose and plasma concentration of a drug is determined by pharmacokinetics. However, difficulties arise when more than one drug is administered simultaneously. There is currently a gap in the teaching model when trying to convey the significance of pharmacodynamic interactions. In this article the authors reflect on the importance of developing a software that simplifies the pharmacokinetic concepts of two drugs, turning them into one single variable in space as a function of time. Together with depth of anesthesia monitoring and the pain control variables, this model will bring pharmacokinetics and pharmacodynamics together and provide a teaching tool for improved understanding of these concepts.

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De la Farmacocinética a la Farmacodinámica, estamos listos para los software 3D?

RESUMEN

La relación entre la dosis y la concentración plasmática de un fármaco está determinada por la farmacocinética, sin embargo se presentan dificultades cuando hay más de un medicamento administrado de forma simultánea. En la actualidad, hay un vacío en el modelo de enseñanza cuando se pretende difundir la importancia de las interacciones farmacodinámicas. En el presente artículo los autores hacen una reflexión sobre la importancia de poder

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construir un software que simplifique los conceptos farmacocinéticos de dos medicamentos, convirtiéndolos en una sola variable de espacio en función del tiempo. Este modelo permitiría, junto con la monitoria de la profundidad anestésica y las variables de control del dolor, acoplar la farmacocinética a la farmacodinámica, y brindaría una herramienta de educación para la comprensión de estos conceptos.

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Introduction

At present, simulation in medicine is becoming increasingly important for education and evaluation of students, residents, and specialized physicians around the world. In particular, anesthesiology is a pioneer specialty in the development and use of these tools, with positive results that impact clinical practice. Technology has experienced a 180° turn in the field of anesthesia and over the past decade, it's beginning to impact drug administration.

There are three options when administering an anesthetic agent: to use a pharmaceutical approach (mg/kg); to use a pharmacokinetic approach (predicting plasma concentrations); or with a pharmacodynamic approach (based on pain response control or depth of hypnosis). In the light of technological breakthroughs and living in the age of patient safety, administering a drug using the pharmaceutical principle is only appropriate for drugs that do not need to be infused over time or medicines for which a pharmacokinetic model is not available.¹

The administration of drugs based on the pharmacokinetic approach, with the help of a simulator or a TCI system (*Target Controlled Infusion*), would seem in principle to be the ideal tool, since we can estimate the plasma levels and the on site effects of the drug being infused.² However, the challenge is that medicines behave in one way when administered alone, but very differently when simultaneously co-administered with other drugs at the effect site. The pharmacokinetic approach guides us to establish the desired concentration, but neglects the pharmacodynamic interactions of drugs (additive effect, synergy, or under-dosing).^{3,4} Disregarding these interactions leads to unwise decision-making when determining the probability of non-response to a stimulus, since when two drugs are together in a system and interact synergistically, any change in the concentration of one drug alters the response of the other drug, based on the principle of interdependence and synergy.⁵ The ability to establish this interdependency at the time of administering anesthesia, becomes the major challenge for simulators or TCI systems.

The use of surface models to show pharmacodynamic interaction between two drugs is available for some anesthesia workstations. The main systems available in the market are: *El Anesthesia Navigator Applications Suite* (GE Healthcare, U.S.A.)⁶ and *Anesthesia Smart Pilot View* (Dräger, Germany).⁷ Both systems collect the data from the IV infusion pumps, from the patient monitor, and from the inhaled anesthesia supply system; they apply the PK/PD predictive model to the data

stored from the drugs used, helping to visualize the modeled effects of the anesthetic agents and their interactions with adjuvant medicines. Both systems show in real time the theoretical concentrations at the effect site of the IV drugs, predict, and quantify the effect of the drugs' interaction. The type of interaction may be evaluated and visualized by drawing a 3-D chart called the "response surface model".

In a publication by Cirillo et al.,⁸ the two PK/PD chart systems were compared. 60 patients were selected and divided into four groups with 15 patients each; one group per device with its control group. Both systems provided an adequate level of depth of anesthesia and reduced the use of sevoflurane, as compared against their respective control group.

Every current chart system using the PK/PD models of IV drugs has a drawback because the concentrations of IV drugs do not represent real patient measurements and the effects shown are based on published and validated pharmacokinetic models. Another weakness is that the interaction model does not use the PNR as an endpoint, which means that the anesthesiologist, despite knowing the PNR, cannot make any adjustments of changes in accordance with the anesthesia requirement.

Administering drugs based on the pharmacodynamic response (response to pain and depth of hypnosis) looks like a promising future. *Nociception level index*, *Bispectral index* and *SEDline*, are tools that enable the anesthesiologist to assess pain response and depth of hypnosis during general anesthesia. Whilst it is true that this approach for administering medications may help in intraoperative decision-making, currently there are no established parameters or targets to be used as the starting point to design the flight plan during surgery; hence, these systems are limited to introducing changes in the drugs based on a particular response, but are not designed to adjust the medication to target.

Notwithstanding the technological advancements with multiple systems that administer and predict plasma concentrations, there is still a gap in our understanding of the pharmacodynamic interactions of the drugs we administer every day.

In this scenario, each anesthesiologist just administers the medications according to his/her personal preferences, giving rise to the need of having a tool that integrates all the different ways of administering drugs in a simple, accessible, and timely manner.

The authors suggest a model to integrate the pharmacokinetic approach into a pharmacodynamic model that serves as a reference for pain and hypnosis monitors; in other words, for identifying the missing link that integrates the various

approaches to administer medications during general anesthesia or sedation.

Pharmacokinetics and pharmacodynamics software

The evolution of technology in a globalized world overwhelmingly conquers the healthcare area. The anesthesiologist environment is in itself a technological environment. This environment is conducive to the involvement of the specialist with technology in a fundamental aspect of the anesthesia process: the administration of drugs.

Currently there are a number of simulators to estimate drug concentration based on different characteristics:

TIVAtrainer

Pharmacokinetic simulation program applied to TIVA and TCI Infusion Systems. The full text may be downloaded at: http://www.eurosiva.org/TivaTrainer/tivatrainner_main.htm.

Rugloop

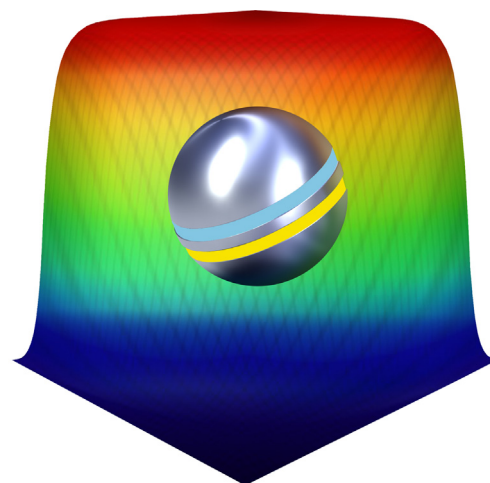
A tool developed for research and education purposes. It comprises a comprehensive database of the most commonly used IV agents with TCI systems. It is available for free download at: <http://www.demed.be/rugloopII.htm>.

AnestFusor

A program designed for the study and IV administration of anesthesia drugs or similar clinical settings. It is based on the principle of plasma drug concentration and/or site effect and may be mathematically modeled in order to accurately control the amount and rate of drug perfusion, through continues perfusion pumps. It may be downloaded at: <http://www.smb.cl/index.html>.

Similarly, there are machines able to simulate the flow of medication required to reach the target concentration in the patient. These tools have been broadly embraced by anesthesiologists, making them part of their everyday support systems. To date, few programs are able to integrate the expected behavior of the drugs with the expected or actual effects the patient presents; in other words, integrating pharmacokinetics and pharmacodynamics in a way that enables the integration not just of the various drugs, but also of the patient's response to those drugs. The current simulation systems calculate the pharmacokinetic parameters only and the closed loop systems integrate this calculation with clinical response variables but fail to consider drug interactions or the possibility to plan anesthesia focusing on the probability of non-response.⁹

It becomes then necessary to integrate all of these concepts and close the existing gap through the development of a software based on the equations of the mammillary model and the published pharmacokinetic models. This effort goes beyond converting a published model into a calculator-type interphase.



TACAN 3D TARGET CONTROLLED ANESTHESIA

Fig. 1 – The objective of 3D target controlled anesthesia (TACAN3D) would be to integrate the opioid and the hypnotic agent into one single variable – PNR – represented with the sphere (blue band = opioid and yellow band = hypnotic agent), which may be displaced in the surface model based on the analgesia or hypnosis requirements.

Source: Authors.

Proposal – TACAN 3D (target controlled anesthesia 3D) software based on the surface model

Developing a software based on pharmacokinetic models is a relatively simple task, since the mammillary model equations and the equations of the pharmacokinetic models are published, validated, and widely disseminated.¹⁰ The challenge when beginning to develop a software is mostly to succeed in designing an interphase, rather than developing a data calculator that is simply an adaptation of the published model.

Designing a software based on pharmacodynamic interactions for remifentanyl and propofol requires:

1. The equation of the multicompartment mammillary model.
2. The numerical or analytical solutions of the multicompartment model.
3. The pharmacokinetic model specific for each drug.
4. The surface model (pharmacodynamics interaction).
5. The interphase that should integrate the pharmacokinetic models for remifentanyl and propofol, the multicompartment model, and the surface model.

Integrating the above principles is the foundation for the development of a software designed to administer target controlled anesthesia (TACAN), simplifying the pharmacokinetic concepts of two drugs, merging them into one single space variable as a function of time (Fig. 1). This software shall

integrate PK/PD into a single variable: PNR (probability of non-response), that represents the pharmacodynamic interaction between the opioid and the hypnotic agent.^{11,12} Consequently, the software that represents the surface model, allows for the location in space of the reference PNRs for sedation analgesia, intubation, or a particular surgical stimulus.

Developing a 3D pharmacodynamic software for the administration of anesthesia, based on a surface model and being able to guide a 3D-target controlled anesthesia (TACAN 3D) is a research project available at the segest.com education platform.

Major 3D software objective: organize a safe flight

The purpose of the software is to provide tools to the anesthesiologist for developing his/her flight plan based on PK/PD principles. Following is a list of the fundamental software variables:

1. **Checklist:** The software should stress the importance of the checklist before any surgical procedure, led by the anesthesiologist with the goal of making sure that everything needed for the anesthesia and the surgical procedure is available.
2. **Information:** The software must be fed with the basic data of the patient: name, height (cm), weight (kg), gender and age (years), in order to estimate the ideal PNR during the anesthetic induction and the procedure, in addition to calculating the dose of the medications.
3. **Induction method:** The software shall allow the anesthesiologist to select the type of device to be used to secure the airway or if the procedure will be sedation. Based on this selection, the software suggests a PNR and a standard time of 3 min in case of intubation or laryngeal mask, and 6 min for sedation; in the latter case the purpose is to avoid a muscle stiffness syndrome.
4. **Procedure:** The software may also be fed with the surgical procedure to be performed and the painful stimulus. The software suggests a PNR in accordance with the selected stimulus and a fixed time of 10 min to reach that level: strong intensity stimulus surgeries (chest) PNR 95, high stimulus (abdomen) PNR 75, moderate stimulus (mastoid) PNR 50.
5. **Drugs for induction:** The software shall take into account the medications to be used according to the anesthetic technique.
6. **Drugs concentration:** The software has the option to select the diluent and the volume used to dissolve the medication, setting a specific concentration with a view to have the software calculate the amount of volume to be infused at each phase of the anesthetic procedure, based on the desired plasma concentrations.
7. **PNR induction:** In this module the anesthetic induction PNR interphase suggested in point 3 may be visualized. The software integrates the PK/PD models of both medications to calculate the effect site concentrations and their corresponding doses in accordance with the data of the patient. This PNR and the time suggested, based on the previously

mentioned criteria maybe modified by the anesthesiologist, in accordance with the patient's clinical conditions.

8. **PNR of the procedure:** This module shows the anesthetic maintenance PNR interphase suggested in item 4. The software integrates the PK/PD models of both medications to calculate the effect site concentrations and their corresponding doses, according to the patient's data. This PNR and the suggested time, based on the above-mentioned criteria, in accordance with the patient's clinical conditions.
9. **Stimulation:** This module comprises all the data required to start anesthesia which begins by pressing on the start button. The software has different infusion modes: 1× (real time), 2×, 5×, 10×, 30×, and 100×. In this module the anesthesiologist may change the PNR, the effect site concentrations of the opioid and the hypnotic agent, and the time to reach the PNR. These changes may be introduced according to the pain response variables and the depth of hypnosis, and are executed using the "update" key.

From pharmacokinetics to pharmacodynamics process of learning

When speaking about the ways to administer medications, remember that the pharmaceutical approach is not ideal and represents the most precarious way of administering anesthesia. When using the simulator or a TCI system that predict the concentrations of the hypnotic agent and the opioid, the pharmacodynamic interactions are neglected and the interdependence between the two drugs are not considered. For instance, if the TCI has 5 ng/mL of remifentanyl and 3 mcg/mL of propofol, where is the patient classified in a surface model? Secondly, if the decision is made to modify propofol, this change will have an impact on remifentanyl¹³; How is it affected? Whilst the pharmacokinetic simulators, as well as the TCI systems, provide data on the concentrations of the opioid and the hypnotic agent, we are totally ignorant about the pharmacodynamic interaction of these two drugs.

Using a software based on a surface model will provide information about where the patient is located in space as a function of time, for an easy understanding of the opioid – hypnotic agent interactions, in addition to offer a point of reference or a starting point for anesthesia during induction, maintenance and awakening. Such reference points may be changed in accordance with pain scores and/or hypnosis.

A 3D software of pharmacological interactions may be considered the link between the different approaches to administer the drugs, and represents a significant advancement in the learning process, understanding, comprehension, and the practical and tangible use of PK & PD during anesthesia.

Conclusion

The way of administration of anesthetic drugs has been evolving; pharmaceuticals, pharmacokinetics, and pharmacodynamics are all concepts that can be integrated with the current technology to facilitate our understanding. TACAN3D is a research project that for the first time suggests integrating the PK/PD principles into a space and time concept.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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